Genomics of schizophrenia and pharmacogenomics of antipsychotic drugs

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ABSTRACT

Antipsychotic drugs are the neuroleptics currently used in the treatment of schizophrenia (SCZ) and psychotic disorders. SCZ has a heritability estimated at 70% - 90%; and pharmacogenomics accounts for 60% - 90% variability in the pharmacokinetics and pharmacodynamics of psychotropic drugs. Personalized therapeutics based on individual genomic profiles in SCZ entails the characterization of 5 types of gene clusters and their related metabolomic profiles: 1) genes associated with disease pathogenesis; 2) genes associated with the mechanism of action of drugs; 3) genes associated with drug metabolism (phase I and II reactions); 4) genes associated with drug transporters; and 5) pleiotropic genes involved in multifaceted cascades and metabolic reactions. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single-nucleotide polymorphisms in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment. Approximately 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4. About 10% - 20% of Western populations are defective in genes of the CYP superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the trigenic cluster integrated by the CYP2D6 + CYP2C19 + CYP2C9 genes. Efficacy and safety issues in the pharmacological treatment of SCZ are directly linked to genetic clusters involved in the pharmacogenomics of antipsychotic drugs and also to environmental factors. Consequently, the incorporation of pharmacogenomic procedures both to drugs under development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system disorders.

Keywords: Genomics; Antipsychotic Drugs; Schizophrenia

1. INTRODUCTION

Central nervous system (CNS) disorders are the third greatest problem of health in developed countries, representing 10% - 15% of deaths after cardiovascular disorders (25%) and cancer (20%). CNS disorders pose several challenges to our society and the scientific community: 1) they represent an epidemiological problem and a socio-economic, psychological and family burden; 2) most of them have an obscure/complex pathogenesis; 3) their diagnosis is not easy and lacks specific biomarkers; and 4) their treatment is difficult and inefficient. In terms of economic burden, approximately 10% - 20% of direct costs are associated with their pharmacological treatment, with a gradual increase in parallel with the severity of the disease [1,2].

Approximately 127 million Europeans suffer brain disorders. The total annual cost of brain disorders in Europe is about €386 billion, with €135 billion in direct medical expenditures (€78 billion, inpatients; €45 billion, outpatients; €13 billion, pharmacological treatment), €179 billion in indirect costs (lost workdays, loss of productivity, permanent disability), and €72 billion in direct non-medical costs. Mental disorders represent €240 billion (62% of the total cost, excluding dementia), followed by neurological diseases (€84 billion, 22%) [3].

Common features in CNS disorders include the following: 1) polygenic/complex disorders in which genetic, epigenetic and environmental factors are involved; 2) deterioration of higher activities of the CNS; 3) multifactorial dysfunctions in several metabolomic networks leading to functional damage to specific brain circuits;

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and 4) accumulation of toxic proteins in the nervous tissue in cases of neurodegeneration [1,2].

Our understanding of the pathophysiology of CNS disorders has advanced dramatically during the last 30 years, especially in terms of their molecular pathogenesis and genetics. Drug treatment has also made remarkable strides, with the introduction of many new drugs; however, improvement in terms of clinical outcome has fallen short of expectations, with up to one third of patients continuing to experience clinical relapse or unacceptable medication-related side-effects in spite of efforts to identify optimal treatment regimens. Potential reasons to explain this historical setback might be that: 1) the molecular pathology of brain disorders is still poorly understood; 2) drug targets are inappropriate, not fitting into the real etiology of the disease; 3) most treatments are symptomatic, but not anti-pathogenic; 4) the genetic component of CNS disorders is poorly defined; and 5) the understanding of genome-drug interactions is very limited [2,4-6].

The pharmacological management of CNS disorders is an issue of special concern due to the polymedication required to modulate the symptomatic complexity of brain disorders. The introduction of novel procedures into an integral genomic medicine protocol in CNS disorders is an imperative requirement for clinical practice and drug development in order to improve diagnostic accuracy (disease-specific biomarkers) and to optimize therapeutics (pharmacogenomics) [7-12]. A growing body of fresh knowledge on the pathogenesis of CNS disorders, together with data on neurogenomics and pharmacogenomics, is emerging in recent times. The incorporation of this new armamentarium of molecular pathology and genomic medicine to daily medical practice, together with educational programs for the correct use of drugs, must help to: 1) understand brain pathogenesis; 2) establish an early diagnosis; and 3) optimize therapeutics either as a preventive strategy or as a formal symptomatic treatment [2,5,6,13,14].

Schizophrenia (SCZ) is a typical paradigm of mental disorder with a prevalence of 1% and a high socioeconomic impact in our society. SCZ and related disorders are highly heritable but cannot be explained by currently known genetic risk factors. SCZ has a heritability estimated at 70% - 90% [1,15-17]. Several neurobiological hypotheses have been postulated as responsible for SCZ pathogenesis: polygenic/multifactorial genomic defects, intrauterine and perinatal environment-genome interactions, neurodevelopmental defects, dopaminergic, cholinergic, serotonergic, GABAergic, neuropeptidergic and glutamatergic/NMDA dysfunctions, seasonal infection, neuroimmune dysfunction, and epigenetic dysregulation. The dopamine hypothesis of SCZ has been one of the most enduring ideas in psychiatry. Initially, the emphasis was on the role of hyperdopaminergia in the etiology of SCZ, but it was subsequently reconceptualized to specify subcortical hyperdopaminergia with prefrontal hypodopaminergia [18]. Carlsson's hypothesis postulates that the positive and negative symptoms of SCZ are due to failure of mesolimbic and mesocortical projections consequent on hypofunction of the glutamate N-methyl-D-aspartate (NMDA) receptor. The emergence of positive symptoms (hallucinations), and synapse regression involves molecules such as neuregulin and its receptor ErbB4, which have been implicated in SCZ [19]. While multiple theories have been put forth regarding the origin of SCZ, by far the vast majority of evidence points to the neurodevelopmental model in which developmental insults as early as late first or early second trimester lead to the activation of pathologic neural circuits during adolescence or young adulthood, leading to the emergence of positive or negative symptoms. There is evidence from brain pathology (enlargement of the cerebroventricular system, changes in gray and white matters, and abnormal laminar organization), genetics (changes in the normal expression of proteins involved in early migration of neurons and glia, cell proliferation, axonal outgrowth, synaptogenesis, and apoptosis), environmental factors (increased frequency of obstetric complications and increased rates of schizophrenic births due to prenatal viral or bacterial infections), and gene-environmental interactions (a disproportionate number of SCZ candidate genes are regulated by hypoxia, microdeletions and microduplications, the overrepresentation of pathogen-related genes among SCZ candidate genes) in support of the neurodevelopmental model [20]. Dean [21] reviewed evidence to assess the hypothesis that SCZ is a human-specific disorder associated with the need for highly complex CNS development. Changes in the size of the frontal lobe, increases in numbers of specific cell types, changes in gene expression and changes in genome sequence all seem to be involved in the evolution of the human CNS. Human-specific changes in CNS development are wide-ranging. The modification in CNS structure and function that has resulted from these changes affects many pathways and behaviors that also appear to be affected in subjects with SCZ. Therefore, there is evidence to support the hypothesis that SCZ is a disease that develops due to derangements to human-specific CNS functions that have emerged since our species diverged from non-human primates.

Antipsychotic drugs (neuroleptics) represent the primary pharmacological treatment for schizophrenia and psychotic disorders worldwide. The proportion of treatment-resistant patients is estimated to be 20% to 40%, and the treatment of patients with schizophrenia who fail to respond to antipsychotics is a major challenge in psychiatry [22]. Studies reported during the past 20 years

have demonstrated that the efficacy and safety of anti-psychotics are closely related to the pharmacogenomic profiles of schizophrenic patients [1,17,22].

2. GENES INVOLVED IN PHARMACOGENOMICS

The genes involved in the pharmacogenomic response to drugs in CNS disorders may fall into five major categories: 1) genes associated with CNS pathogenesis (disease-specific genes); 2) genes associated with the mechanism of action of drugs; 3) genes associated with drug metabolism; 4) genes associated with drug transporters; and 5) pleiotropic genes involved in multifaceted cascades and metabolic reactions [2]. The therapeutic outcome (efficacy and safety) is the result of the interplay of drugs with these different categories of gene products and epigenetic factors to reverse or modify the phenotypic expression of a given disease [23]. Pharmacogenomics accounts for 30% - 90% variability in pharmacokinetics and pharmacodynamics.

2.1. Pathogenic Genes

Over 6000 genes distributed across the human genome have been screened for associations with CNS disorders during the past 30 years [1,24]. Studies of many candidate genes potentially associated with a particular CNS disorder could not be replicated in different settings, cohorts, and geographical contexts due to methodological problems, sample selection and multi-ethnic genetic variation. In the case of SCZ and related disorders, over 200 genes have been associated with psychotic disorders [1,7] (**Figure 1**, **Table 1**).

2.2. Genes Associated with the Mechanism of Action of Drugs

Most genes associated with the mechanism of action of CNS drugs encode receptors, enzymes, and neurotransmitters (**Tables 1** and **2**) on which psychotropic drugs act as ligands (agonists, antagonists), enzyme modulators (substrates, inhibitors, inducers) or neurotransmitter regulators (releasers, reuptake inhibitors) [25].

2.3. Genes Involved in Drug Metabolism

Drug metabolism includes phase I reactions (*i.e.* oxidation, reduction, hydrolysis) and phase II conjugation reactions (*i.e.* acetylation, glucuronidation, sulphation, methylation). The principal enzymes with polymorphic variants involved in phase I reactions are the following: Cytochrome P450 monooxygenases (CYP3A4/5/7, CYP-2E1, CYP2D6, CYP2C19, CYP2C9, CYP2C8, CYP2B6, CYP2A6, CYP1B1, CYP1A1/2), epoxide hydrolase, esterases, NQO1 (NADPH-quinone oxidoreductase), DPD (dihydropyrimidine dehydrogenase), ADH (alcohol dehydrogenase), and ALDH (aldehyde dehydrogenase); and major enzymes involved in phase II reactions include UGTs (uridine 5'-triphosphate glucuronosyl transferases), TPMT (thiopurine methyltransferase), COMT (catechol-O-methyltransferase), HMT (histamine methyltransferase), STs (sulfotransferases), GST-A (glutathione S-transferase A), GST-P, GST-T, GST-M, NAT1 (N-acetyl transferase 1), NAT2, and others. Among these enzymes, CYP2D6, CYP2C9, CYP2C19, and CYP3A4/5 are the most relevant in the pharmacogenetics of CNS drugs [14,25] (**Table 2**). Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40%

Distribution of genes potentially associated with psychosis and dementia
Number of Genes/Chromosome

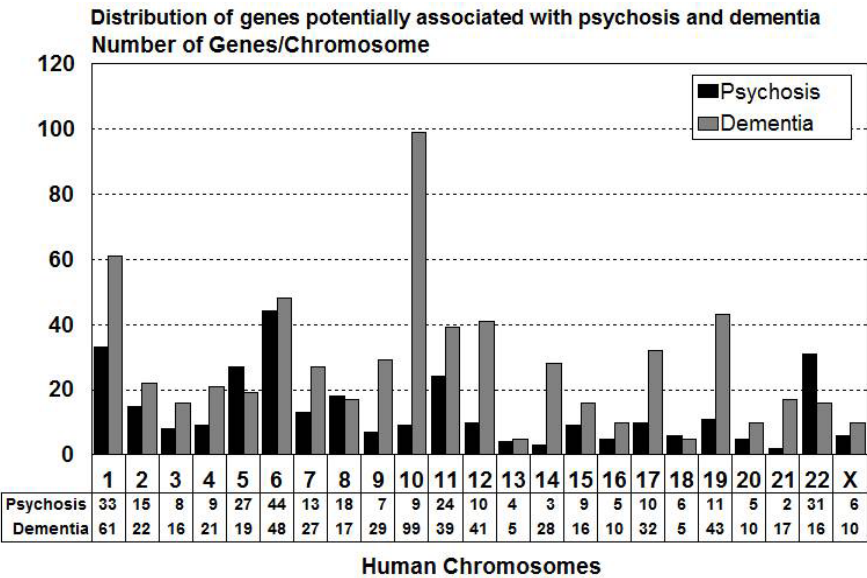| Human Chromosomes	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X
Psychosis	33	15	8	9	27	44	13	18	7	9	24	10	4	3	9	5	10	6	11	5	2	31	6
Dementia	61	22	16	21	19	48	27	17	29	99	39	41	5	28	16	10	32	5	43	10	17	16	10

Figure 1. Distribution of genes potentially associated with psychosis and dementia in the human genome.

Table 1. Genes potentially associated with schizophrenia and psychotic disorders.

Symbol	Name	Locus	SZC-Related SNPs	Other Diseases
ABCA7	ATP-binding cassette, sub-family A (ABC1), member 7	19p13.3		
ABCA13	ATP-binding cassette, sub-family A (ABC1), member 13	7p12.3		
ABCB1	ATP-binding cassette, sub-family A (ABC1), member 1	9q31.1	rs3858075	Atherosclerosis; Cerebral amyloid angiopathy; Colorectal cancer; Colorectal neoplasms; Coronary artery disease; Coronary disease; Dyslipidemias; Familial hypercholesterolemia; High density lipoprotein deficiency (type 1); High density lipoprotein deficiency (type 2); Hyperalphalipoproteinemia; Hypercholesterolemia; Hyperlipidemia; Kidney diseases; Tangier disease
ACE	Angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	17q23.3		Alzheimer disease; Anxiety disorders; Cardiovascular diseases; Hemorrhagic stroke; Dementia; Depression; Diabetes mellitus; Diabetic nephropathy; Hyperlipidemias; Hypertension; Hypotension; IgA glomerulonephritis; IgA nephropathy; Ischemic stroke; Major depressive disorder; Meningococcal disease; Myocardial infarction; Myophosphorylase deficiency; Preterm cardiorespiratory disease; Renal tubular dysgenesis; Severe acute respiratory syndrome; Stroke; Susceptibility to microvascular complications of diabetes I; Vascular dementia
ACSL6	Acyl-CoA synthetase long-chain family member 6	5q31	rs11743803	Acute eosinophilic leukemia; Acute myelogenous leukemia; Acute myelogenous leukemia; Myelodysplastic syndrome
ADRA1A	Adrenergic, alpha-1A-, receptor	8p21.2		
ADRA2A	Adrenergic alpha-2A, receptor	10q24-q26	rs1800544	Attention-deficit hyperactivity disorder; Hypertension Diarrhea-predominant irritable bowel syndrome; Response to methylphenidate treatment in Korean subjects with attention deficit hyperactivity disorder; Obesity; Predisposition to tobacco smoking
ADSS	Adenylosuccinate synthase	1cen-q12	rs227061; rs3102460	
AHI1	Abelson helper integration site 1	6q23.3	rs7750586; rs911507	Joubert syndrome-3
AKT1	v-akt murine thymoma viral oncogene homolog 1	14q32.32	rs3803300	Breast cancer, somatic; Colorectal cancer, somatic; Ovarian cancer, somatic
ALDH1A2	Aldehyde dehydrogenase 1 family, member A2	15q21.3	rs4646642-rs4646580	
ALDH3B1	Aldehyde dehydrogenase 3 family, member B1	11q13		
AP3M1	Adaptor-related protein complex 3, mu 1 subunit	10q22.2	rs6688	
APOE	Apolipoprotein E	19q13.2		Age-related macular degeneration; Age-related macular degeneration 1; Alzheimer disease; Amyloidosis; APOE5-associated hyperlipoproteinemia and atherosclerosis; APOE7-associated type III hyperlipoproteinemia; Apolipoproteinemia E1; Arteriosclerosis; Asthma; Atherosclerosis; Autosomal dominant type III hyperlipoproteinemia; Autosomal recessive hyperlipoproteinemia; Autosomal recessive type III hyperlipoproteinemia associated with APOE deficiency; Cardiovascular disease; Carotid stenosis; Cerebrovascular disease; Coronary arteriosclerosis; Craniocerebral trauma; Drug-induced liver injury; Dysbetalipoproteinemia; Dysbetalipoproteinemia due to APOE2; Dyslipidemias; Familial dysbetalipoproteinemias; Macular degeneration; Hypertriglyceridemia; Ischemic cerebrovascular disease; Ischemic heart disease; Ischemic stroke; Lipoprotein glomerulopathy; Lung neoplasms; Hyperlipoproteinemia (type II); Hyperlipoproteinemia (type III);

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				Hyperlipoproteinemias; Metabolic syndrome; Multiple sclerosis; Myocardial infarction; Myocardial ischemia; Neurodegenerative diseases; Psoriasis; Sea-blue histiocyte syndrome; Type III hypercholesterolemia and hypertriglyceridemia; Type III hyperlipoproteinemia; Type III hyperlipoproteinemia associated with APOE deficiency; Type III hyperlipoproteinemia associated with APOE Leiden; Type III hyperlipoproteinemia associated with APOE2; Type III hyperlipoproteinemia associated with APOE2-Fukuoka; Type III hyperlipoproteinemia associated with APOE4; Type III hyperlipoproteinemia due to APOE1-Harrisburg; Type III hyperlipoproteinemia due to APOE4-Philadelphia; Type III hyperliporpoteinemia due to APOE2-Christchurch; Type V hyperlipoproteinemia; Vascular dementia; Vascular disease
APOL1	Apolipoprotein L, 1	22q13.1		
APOL2	Apolipoprotein l, 2	22q12		
APOL4	Apolipoprotein l, 4	22q11.2-q13.2		
ARRB2	Arrestin, beta 2	17p13	rs1045280 Ser280Ser	
ARVCF	Armadillo repeat gene deleted in velocardiofacial syndrome	22q11.21		
ATM	Ataxia telangiectasia Mutated	11q22-q23	rs664143 rs227061	
AVPR1A	Arginine vasopressin receptor 1A	12q14-q15		
AVPR1B	Arginine vasopressin receptor 1B	1q32		
BDNF	Brain-derived neurotrophic factor	11p13	rs6265 Val66Met C270T	Aniridia; Anorexia nervosa; Bipolar disorder; Bulimia nervosa; Congenital central hypoventilation syndrome; Depressive disorder; Genitourinary anomalies, Lithium response; Major depressive disorder; Memory impairment; Mental retardation; Methadone response; Obesity; Obsessive-compulsive disorder; Parkinson's disease; Protection against obsessive-compulsive disorder; Tardive dyskinesia; WAGR syndrome; Wilms' tumor
BIK	BCL2-interacting killer (apoptosis-inducing)	22q13.31	rs926328; rs2235316	
BLOC1S3	Biogenesis of lysosomal organelles complex-1, subunit 3	19q13.32		
BRD1	Bromodomain containing 1	22q13.33		
C3	Complement component 3	19p13.3-p13.2		Age-related macular degeneration 9; C3 deficiency; Susceptibility to atypical hemolytic uremic syndrome 5
C4B	Complement component 4B (Chido blood group)	6p21.3		C4 deficiency
C6orf217	Chromosome 6 open reading frame 217	6q23.3	rs1475069	
C10orf26, OPAL1	Chromosome 10 open reading frame 26	10q24.32		
C22DDELS	Chromosome 22q11.2 deletion syndrome, distal	22q11.2		
CACNA1C	Calcium channel, voltage-dependent, L type, alpha 1C subunit	12p13.3	rs1006737; rs22512119	
CALR	Calreticulin	19p13.3-p13.2		
CCKAR	Cholecystokinin A receptor	4p15.1-p15.2	rs1800857; 779T/C	

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CDC42SE2	CDC42 small effector 2	5q31.1		
CFB	Complement factor B	6p21.3		Reduced risk of age-related macular degeneration; Susceptibility to atypical hemolytic uremic syndrome 4
CHAT	Choline O-acetyltransferase	10q11.2		Alzheimer disease; Congenital myasthenic syndrome associated with episodic apnea; Myasthenic syndrome; Neurodegenerative diseases; Neurotoxicity syndromes; Parkinson's disease (secondary); Peripheral nervous system diseases
CHGA	Chromogranin A (parathyroid secretory protein 1)	14q32		
CHGB	Chromogranin B (secretogranin 1)	20pter-p12		
CHI3L1	Chitinase 3-like 1 (cartilage glycoprotein-39)	1q32.1		Effect of variation in CHI3L1 on serum YKL-40 level, risk of asthma, and lung function; Susceptibility to asthma-related traits 7
CHRFAM7 A	CHRNA7 (cholinergic receptor, nicotinic, alpha 7, exons 5 - 10) and FAM7A (family with sequence similarity 7A, exons A-E) fusion	15q13.1		
CHRNA2	Cholinergic receptor, nicotinic, alpha 2 (neuronal)	8p21		Nocturnal frontal lobe epilepsy type 4
CHRNA6	Cholinergic receptor, nicotinic, alpha 6	8p11.21		
CHRNA7	Cholinergic receptor, nicotinic, alpha 7	15q14	rs3087454	
CHRNB3	Cholinergic receptor, nicotinic, beta 3	8p11.2		
CLDN5	Claudin 5	22q11.21		
CLINT1	Clathrin interactor 1	5q33.3		
CLOCK	Clock homolog (mouse)	4q12		
CLU	Clusterin	8p21-p12	rs11136000	
CMYA5	Cardiomyopathy associated 5	5q14.1	rs10043986; rs4704591	
CNP	2',3'-cyclic nucleotide 3' phosphodiesterase	17q21		
CNR1	Cannabinoid receptor 1 (brain)	6q14-q15		Alzheimer disease; Central nervous system diseases; Cocaine-related disorders; Muscle spasticity; Neurodegenerative diseases; Neurotoxicity syndromes; Substance withdrawal syndrome
CNR2	Cannabinoid receptor 2 (macrophage)	1p36.11		
CNTNAP2	Contactin associated protein-like 2	7q35		Cortical dysplasia focal epilepsy syndrome; Autism (susceptibility); Pitt-Hopkins-like syndrome
COMT	Catechol-O-methyltransferase	22q11.21	rs4680; rs6267; rs737865 rs7378-rs4680-rs165599 rs2075507 rs362204	Anxiety disorders; Autistic disorder; Bipolar disorder; Depressive disorder; DiGeorge syndrome; Migraine; Mood disorders; Nervous system diseases; Panic disorder; Obsessive-compulsive disorder; Parkinson's disease; Prostatic neoplasms Susceptibility to panic disorder
CPLX2	Complexin 2	5q35.2	rs3822674	
CRP	C-reactive protein, pentraxin-related	1q21-q23		Atherosclerosis; Cardiovascular disease; Cerebrovascular disease; Coronary disease; Diabetes mellitus (type 2); Heart diseases; Heart failure; Heart injuries; Hepatocellular carcinoma; Inflammation; Lung neoplasms; Lupus erythematosus; Malaria; *Pasteurellaceae* infections; Stroke; Systemic lupus erythematosus; Thrombosis
CSF2RA	Colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)	Xp22.32 and Yp11.3		Acute M2 type myeloid leukemia; Pulmonary alveolar proteinosis

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CSF2RB	Colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)	22q13.1		Pulmonary alveolar proteinosis
CSMD1	KIAA1890 Cub and Sushi multiple domains 1	8p23.2		
CTL4	cytotoxic T-lymphocyte-associated protein 4	2q33	rs231779; rs16840252	
CTSK	cathepsin K	1q21		Pycnodysostosis
CYBB	Cytochrome b-245, beta polypeptide	Xp21.1		
CYP1A2	Cytochrome P450, family 1, subfamily A, polypeptide 2	15q24.1		Experimental liver cirrhosis; Experimental liver neoplasms; Experimental neoplasms; Gastric adenocarcinoma; Gastrointestinal neoplasms; Hepatocellular carcinoma; Leflunomide-induced toxicity; Methemoglobinemia; Myocardial infarction; Liver diseases; Neoplasms; Susceptibility to tobacco addiction; Tardive dyskinesia; Tobacco use disorder
CYP3A4/5	Cytochrome P450, family 3, subfamily A, polypeptide 4/5	7q21.1		Acute hypoxia; Acute lymphoblastic leukemia; Acute myeloid leukemia; Age-related metabolism variation; Alcoholism; Allergic rhinitis; Alveolar echinococcosis; Antiplatelet drug resistance; Antiretroviral-antineoplastic drug interactions; Atherosclerosis; Azoospermia; Balkan endemic nephropathy; Barrett's metaplasia; Benign prostate hyperplasia; Bile acid metabolism; Bladder cancer; Blood pressure; Brain tumors; Breast cancer; Breast neoplasms; Cancer; Celiac disease; Cerebrotendinous xanthomatosis; Cholestasis; Cholesterol homeostasis; Chronic hepatitis C; Cirrhosis; Colon adenoma; Colorectal cancer; Colorectal liver metastases; Crohn's disease; Cushing's syndrome; Cystic fibrosis; Depression; Depressive disorder; Diabetes mellitus (type 2); Diffuse panbronchiolitis; Drug-induced liver injury; Drug-virus interaction; Ehrlichiosis; Endometrial cancer; Epilepsy; Erectile dysfunction; Esophageal squamous cell carcinoma; Food-drug interactions; Gastric tumors; Gingival hyperplasia; Glucocorticoid-induced hypertension in children with acute lymphoblastic leukemia; Headache; *Helicobacter pylori*; Hepatic steatosis; Hepatitis; Hepatitis B infection; Hepatocellular tumors; Hodgkin's disease; Hodgkin's lymphoma; Hypertension; Hypothermia; Inflammatory bowel diseases; *Lactobacillus rhamnosus*; Leukemia; Liver cancer; Liver diseases; Liver neoplasms; Lung cancer; Lung neoplasms; Lymphocytes; Malaria; Menopause; Menstruation; Metabolic syndrome; Metabolic syndrome X; Migraine; Multiple myeloma; Myocardial infarction; Myocardial ischemia; Nasopharyngeal carcinoma; Neuropathic pain; Non-alcoholic fatty liver disease; Non-small cell lung cancer; Non-small cell lung carcinoma; Onychomycosis; Osteomalacia; Osteonecrosis; Osteosarcoma; Ovarian cancer; Ovarian neoplasms; Oxidative stress; Parkinson's disease; Porphyrias; Precocious puberty; Pregnancy; Pregnancy complications; Primary biliary cirrhosis; Proctitis; Prostate cancer; Prostatic hyperplasia; Prostatic neoplasms; QT interval prolongation; Renal cancer; Renal cell carcinoma; Rhabdomyolysis; Schizophrenia; Squamous cell carcinoma of the larynx and hypopharynx; Stroke; T-cell lymphomas; Testicular germ cell cancer; Thalassemia; Torsades de pointes; Tuberculosis; Veno-occlusive disease; Venous thromboembolism; Venous thrombosis
DAAM2	Dishevelled associated activator of morphogenesis 2	6p21.2		

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DAO	D-amino-acid oxidase	12q24	rs2111902; rs3741775; rs3918346; rs4623951; rs3918347-rs4964770; rs3825251-rs3918347-; rs4964770	
DAOA	D-amino acid oxidase activator	13q34	rs3916971; rs778293; rs2391191 (M15); rs778293; rs3918342	
DBH	Dopamine beta-hydroxylase (dopamine beta-monooxygenase)	9q34	rs1108580	
DDR1	Discoidin domain receptor tyrosine kinase 1	6p21.3	rs4532	Attention-deficit hyperactivity disorder; Autistic disorder; Bipolar disorder; Mental disorders; Nicotine dependence
DGCR2	DiGeorge syndrome critical region gene 2	22q11.21	rs2073776	
DGCR6	DiGeorge syndrome critical region gene 6	22q11		
DISC1	Disrupted in schizophrenia 1	1q42.1	rs3737597; rs821616; rs6675281; rs821597	Susceptibility to schizoaffective disorder
DISC2	Disrupted in schizophrenia 2 (non-protein coding)	1q42.1		Association of lipid-lowering response to statins in combined study populations
DKK4	Dickkopf homolog 4 (Xenopus laevis)	8p11.2-p11.1		
DNMT3B	DNA (cytosine-5-)-methyltransferase 3 beta	20q11.2	rs6119954; rs2424908	
DPYSL2	Dihydropyrimidinase-like 2	8p22-p21		
DRD1	Dopamine receptor D1	5q35.1		
DRD2	Dopamine receptor D2	11q23	rs1799732; rs2283265; rs12364283; rs1076560; rs1079597 (Taql-B); rs6277; rs1801028; rs6275; rs6277; rs11608185	Alcoholism; Myoclonic dystonia; Myoclonus-dystonia syndrome; Obesity; Parkinson's disease; Substance withdrawal syndrome; Tardive dyskinesia
DRD3	Dopamine receptor D3	3q13.3	rs6280	Autistic disorder; Hereditary essential tremor 1; Nicotine addiction; Parkinson's disease; Susceptibility to essential tremor; Tardive dyskinesia
DRD4	Dopamine receptor D4	11p15.5	rs1805186; 120-bp TR; rs1800955; rs4646983; rs4646984	Attention-deficit hyperactivity disorder; Autonomic nervous system dysfunction; Novelty-seeking personality trait; Parkinson's disease; Personality disorders; Protection against Parkinson's disease; Psychotic disorders; Tobacco use disorder
DRD5	Dopamine receptor D5	4p16.1	$(CT/GT/GA)_n$ $(CA)_n$	Primary benign blepharospasm; Primary cervical dystonia; Susceptibility to attention-deficit hyperactivity disorder

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DTNBP1	Dystrobrevin binding protein 1	6p22.3	rs104893945; rs2619522; rs7758659; rs1047631; rs1474605; rs2005976; rs2619539; rs760666; rs2619528; rs2619538; rs875462; rs3213207; rs760761; rs1011313; rs1018381; rs2619538 (SNPA); rs3213207 (P1635)	Bipolar disorder; Major depressive disorder; Hermansky-Pudlak syndrome; Hermansky-Pudlak syndrome 7
EGF	Epidermal growth factor	4q25		Renal hypomagnesemia 4
ERBB3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	12q13	rs773123	Lethal congenital contractural syndrome 2
ERBB4	v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	2q33.3-q34		
ESR1	Estrogen receptor 1	6q25.1		
FABP7	Fatty acid binding protein 7, brain	6q22-q23		
FADS2	Fatty acid desaturase 2	11q12.2		
FAS	Fas (TNF receptor superfamily, member 6)	10q24.1		Association of IFIH1 and other autoimmunity risk alleles with selective IgA deficiency; Autoimmune lymphoproliferative syndrome; Autoimmune lymphoproliferative syndrome, type IA; Burn scar-related somatic squamous cell carcinoma
FGF1	Fibroblast growth factor 1 (acidic)	5q31		
FGF17	Fibroblast growth factor 17	8p21		
FGFR1	Fibroblast growth factor receptor 1	8p12		
FMO3	Flavin containing monooxygenase 3	1q24.3		Familial adenomatous polyposis; Trimethylaminuria
FOLH1	Folate hydrolase (prostate-specific membrane antigen) 1	11p11.2		
FOXP2	Forkhead box P2	7q31		Speech-language disorder-1
FTO	Fat mass and obesity associated	16q12.2	rs9939609	
FXYD2	FXYD domain containing ion transport regulator 2	11q23		Renal hypomagnesemia-2
FXYD6	FXYD domain containing ion transport regulator 6	11q23.3	rs11544201 rs10790212-rs11544201	
FYN	FYN oncogene related to SRC, FGR, YES	6q21	rs6916861; rs3730353	
FZD3	Frizzled homolog 3 (Drosophila)	8p21		

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GABBR1	Gamma-aminobutyric acid (GABA) B receptor, 1	6p21.31		
GABRB1	Gamma-aminobutyric acid (GABA) A receptor, beta 1	4p12		
GABRB2	Gamma-aminobutyric acid (GABA) A receptor, beta 2	5q34	rs1816072	
GABRG2	Gamma-aminobutyric acid (GABA) A receptor, gamma 2	5q34		Childhood absence epilepsy; Childhood absence epilepsy 2; Familial febrile convulsions 8; Generalized epilepsy with febrile seizures plus; Generalized epilepsy with febrile seizures plus, type 3; Severe myoclonic epilepsy of infancy; Susceptibility to childhood absence epilepsy 2
GAD1	Glutamate decarboxylase 1 (brain, 67 kDa)	2q31		Autosomal recessive symmetric spastic cerebral palsy
GAD2	Glutamate decarboxylase 2 (pancreatic islets and brain, 65 kDa)	10p11.23		
GC	Group-specific component (vitamin D binding protein)	4q12-q13		Susceptibility to Graves' disease 3
GCLM	Glutamate-cysteine ligase, modifier subunit	1p22.1		Susceptibility to myocardial infarction
GJA8	Gap junction protein, alpha 8, 50 kDa	1q21.1		Cataract-microcornea syndrome; Nuclear progressive cataract; Nuclear pulverulent cataract; Zonular pulverulent cataract 1
GLS	Glutaminase	2q32-q34		
GLUL	Glutamate-ammonia ligase	1q31		
GNB1L	Guanine nucleotide binding protein (G protein), beta polypeptide 1-like	22q11.2		
GRIA1	Glutamate receptor, ionotropic, AMPA 1	5q31.1		
GRIA4	Glutamate receptor, ionotrophic, AMPA 4	11q22		
GRID1	Glutamate receptor, ionotropic, delta 1	10q22	rs3814614; rs10749535; rs11201985	
GRIK3	Glutamate receptor, ionotropic, kainate 3	1p34-p33	rs6691840	
GRIK4	Glutamate receptor, ionotropic, kainate 4	11q22.3	rs4935752; rs6589846; rs4430518	Bipolar disorder; Depression
GRIK5	Glutamate receptor, ionotropic, kainate 5	19q13.2		
GRIN1	Glutamate receptor, iono-tropic, N-methyl D-aspartate 1	9q34.3		
GRIN2B	Glutamate receptor, ionotropic, N-methyl D-aspartate 2B	12p12	rs1019385 rs7301328	
GRIN2D	Glutamate receptor, ionotropic, N-methyl D-aspartate 2D	19q13.1-qter		
GRM3	Glutamate receptor, metabotropic 3	7q21.1-q21.2		
GRM4	Glutamate receptor, metabotropic 4	6p21.3		

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Gene	Description	Locus	Polymorphism	Associated conditions
GRM7	Glutamate receptor, metabotropic 7	3p26.1-p25.1	rs12491620; rs1450099	
GPR109A	G protein-coupled receptor 109A	12q24.31		
GPR109B	G protein-coupled receptor 109B	12q24.31		
GSK3B	Glycogen synthase kinase 3 beta	3q13.3	$(CAA)_n$ repeat polymorphisms; -1727 A/T	Alzheimer disease; Bipolar disorder; Cancer; Colonic neoplasms; Colorectal neoplasms; Diabetes (type 2); Diabetes mellitus; Depression; Insulin resistance; Lithium sensitivity; Major depression; Myeloid/lymphoid or mixed lineage leukemia; Neurodegenerative diseases; Parkinsonian disorders; Tauopathy
GSTM1	Glutathione S-transferase mu 1	1p13.3	GSTM1*0	Acute lymphoblastic leukemia; Acute myeloid leukemia; Acute promyelocytic leukemia; Adverse drug reactions to azathioprine; Aflatoxin-related hepatocarcinogenesis; Aplastic anemia; Autism; Autistic disorder; Azathioprine adverse effects; Benzene toxicity; Basal cell nervous syndrome; Basal cell carcinoma; Bladder cancer; Bleomycin moderate toxicity; Breast cancer; Busulfan pharmacokinetics; Carbamazepine-induced mild hepatotoxicity; Carcinogen toxicity; Colorectal cancer; Colorectal neoplasms; Coronary artery disease; Cytochrome P450 1A1 gene transcription; Diabetes mellitus (type 2); DNA damage after exposure to hydroquinone; Diabetic nephropathy; GSTM1 methylation; Head and neck neoplasms; Hepatocellular carcinoma; Leukemia; Hydroquinone-induced DNA damage; High inducibility of cytochrome P450 1A1 gene transcription; Liver cancer; Liver neoplasms; Lung cancer; Lung neoplasms; Lymphoblastic leukemia; Mesothelioma; Methotrexate toxicity; Myelodisplastic syndrome; Myeloid leukemia; Prostate cancer; Prostatic neoplasms; Raynaud's disease; Responses to environmental and industrial carcinogens; Second primary neoplasms; Skin diseases; Systemic lupus erythematosus; Tacrine-induced hepatotoxicity; Testicular neoplasms; Thimerosal sensitization; Urinary bladder neoplasms; Troglitazone-induced liver failure
GSTP1	Glutathione S-transferase pi 1	11q13		
GSTT1	Glutathione S-transferase theta 1	22q11.23		
GULP1	GULP, engulfment adaptor PTB domain containing 1	2q32.3-q33	rs2004888	
GWA 10q2613			rs17101921	
GWA 11p141			rs1602565	
GWA 16p1312			rs71992086	
GWA_10q26.13			rs17101921	
GWA_11p14.1			rs1602565	
GWA_16p13.12			rs7192086	
HINT1	Histidine triad nucleotide binding protein 1	5q31.2		
HLA-A	Major histocompatibility complex, class I, A	6p21.3		
HLA-B	Major histocompatibility complex, class I, B	6p21.3		
HLA-C	Major histocompatibility complex, class I, C	6p21.3		

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HLA-DQA1	Major histocompatibility complex, class II, DQ alpha 1	6p21.3		Asthma; Celiac disease; Diabetes (type 1); Gluten-sensitive enteropathy; HLA-DQA1 differential expression; Lung adenocarcinoma; Metamizol-related agranulocytosis; Oligoarticular juvenile idiopathic arthritis; Rheumatoid arthritis; Susceptibility to onchocerciasis; Toxoplasmic encephalitis; Ximelagratan sensitivity
HLA-DQB	Major histocompatibility complex, class II, DQ beta 1	6p21.3		
HLA-DRB1	Major histocompatibility complex, class II, DR beta 1	6p21.3		
HLA-E	Major histocompatibility complex, class I,	6p21.3		Bipolar disorder
HIST1H2BJ	Histone cluster 1, H2bj	6p22.1	rs6913660	
HOMER	Homer homolog 2 (Drosophila)	15q24.3	rs17158184; rs2306428	
HP	Haptoglobin	16q22.1	Hp1/2	Anemia; Atherosclerosis; Autoimmune diseases; Breast neoplasms; Cardiovascular disease; Chronic hepatitis B; Chronic hepatitis C; Coronary atherosclerosis; Crohn's disease; Diabetic vascular disease; Dyslipidemias; Diabetes mellitus (type 1); Diabetes mellitus (type 2); Diabetic angiopathy; Diabetic nephropathy; Female genital neoplasms; Hemochromatosis; Hepatitis B; HIV infections; Hypersensitivity; Hypertension; Leukemia; Malaria; Myocardial infarction; Nasopharyngeal carcinoma; Parkinson's disease; *Pasteurellaceae* infections; Pregnancy-induced hypertension; Primary sclerosis cholangitis; Retinal detachment; Sickle cell anemia; Tuberculosis; Trachoma
HRH1	Histamine receptor H1	3p25		Allergy; Allergic contact dermatitis; Angioedema; Asthma; Atopic dermatitis; Bronchial hyperreactivity; Hypersensitivity; Inflammation; Learning disorders; Long QT syndrome; Memory disorders; Mental disorders; Perennial allergic rhinitis; Pruritus; Pulmonary eosinophilia; Respiratory hypersensitivity; Respiratory tract diseases; Rhinitis; Urticaria; Sinusitis; Skin disorders; Sneezing; Seasonal allergic rhinitis; Seizures
HSPA1B	Heat shock 70kDa protein 1B	6q21.3	rs539689	
HTR1A	5-Hydroxytryptamine (serotonin) receptor 1A	5q11.2-q13		Alzheimer disease; Antidepressant sensitivity; Anxiety disorders; Depression; Macular degeneration; Major depression; Mental disorders; Neuroleptic-related weight gain in schizophrenia; Panic disorder; Personality disorders; Psychotic disorders; Schizophrenia-related weight gain; Sudden infant death
HTR2A	5-Hydroxytryptamine (serotonin) receptor 2A	13q14-q21	rs6313; rs6314; rs6311	Alcohol dependence; Alzheimer disease; Anorexia nervosa; Antidepressant-related response; Antipsychotic-related response; Asperger's syndrome; Attention-deficit hyperactivity disorder; Autistic disorder; Bipolar disorder; Clozapine-induced weight gain; Depression; Depressive disorder; Major depression; Major depressive disorder; Memory performance; Mental disorders; Mental retardation; Migraine; Mood disorders; Neuroleptic-induced weight gain; Neuroleptic-related response; Neurotoxicity syndromes; Obsessive-compulsive disorder; Personality disorders; Pervasive child development disorders; Psychotic disorders; Substance abuse; Response to citalopram therapy in major depressive disorder; Tardive dyskinesia
HTR3A	5-Hydroxytryptamine (serotonin) receptor 3A	11q23.1		
HTR4	5-Hydroxytryptamine (serotonin) receptor 4	5q31-q33		
IDE	Insulin-degrading enzyme	10q23-q25		

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IFNG	Interferon, gamma	12q14	rs62559044	AIDS; Allergic contact dermatitis; Aortic aneurysm; Aplastic anemia; Appendicitis; Asthma; Atherosclerosis; Autistic disorder; Crohn's disease; Drug-induced liver injury; Entamebiasis; Hepatitis; Hepatitis C; Hepatocellular carcinoma; Hepatomegaly; Inflammation; Job's syndrome; Kidney angiomyolipoma; Kidney failure; Myocardial infarction; Liver neoplasms; Lupus nephritis; Multiple sclerosis; Liver cirrhosis; Liver diseases; Oral submucous fibrosis; Renal cell carcinoma; Tuberculosis; Tuberous sclerosis; Susceptibility to human immunodeficiency virus type 1
IGHA1	Immunoglobulin heavy constant alpha 1	14q32.33		
IL1A	Interleukin 1, alpha	2q14		
IL1B	Interleukin 1, beta	2q14	rs1143634 rs16944	Alzheimer disease; Ankylosing spondylitis; Arsenic poisoning; Body fat mass; Breast neoplasms; Bronchopulmonary dysplasia; Colon cancer; Colonic neoplasms; Diabetic nephropathy; Distal interphalangeal joint osteoarthritis; Entamebiasis; Experimental liver cirrhosis; Fever; Gastric cancer; Gastric cancer and *Helicobacter pylori*; Glioblastoma; IgA nephropathy; Inflammation; Inflammatory bowel disease; Lung diseases; Major depression; Major depressive disorder; Osteoporosis; Microvascular complications of diabetes; Multiple sclerosis; Nervous system diseases; Non-small cell lung cancer; Parkinson's disease; Postmenopausal osteoporosis; Primary open-angle glaucoma; Pulmonary fibrosis; Skin diseases; Stomach neoplasms; Ulcerative colitis
IL1RN	Interleukin 1 receptor antagonist	2q14.2		Arsenic poisoning; Autistic disorder; Colonic neoplams; Chagas' disease; Diabetes; Gastric cancer susceptibility after *H. pylori* infection; Generalized aggressive periodontitis; Inflammatory bowel disease; Interleukin 1 receptor antagonist deficiency; Memory disorders; Metabolic syndrome; Multiple sclerosis; Osteoarthritis; Osteoporosis; Prostatic neoplasms; Skin diseases; Stroke; Susceptibility to microvascular complications of diabetes 4; Tourette's syndrome; Ulcer
IL3	Interleukin 3 (colony-stimulating factor, multiple)	5q31.1		
IL3RA	Interleukin 3 receptor, alpha (low affinity)	Xp22.3 or Yp11.3	rs6603272	
IL4	Interleukin 4	5q31.1		Allergic contact dermatitis; Arthritis; Asthma; Atopic dermatitis; Autistic disorder; Autoimmune hypothyroidism; Bladder cancer; Chronic periodontitis; Common variable immunodeficiency; Graves' disease; Glioblastoma; Hypersensitivity; Psoriasis; Subacute sclerosing panencephalitis; Systemic lupus erythematosus; Thromboembolic stroke
IL10	Interleukin 10	1q31-q32	rs1800896; rs1800872	Acquired immunodeficiency syndrome; Alcoholic liver disease; Alzheimer disease; Appendicitis; Autistic disorder; Colitis; Coronary heart disease; Crohn's disease; Diabetes mellitus (type 1); Enterocolitis; Entamebiasis; Experimental mammary neoplasms; Graft *vs* host disease (acute); Hepatitis B; Hepatocellular carcinoma; HIV infections; Inflammatory bowel disease; Irritable bowel syndrome; Kawasaki disease; Leprosy; Lung neoplasms; Malaria; Prostate cancer; Prostatic neoplasms; Psoriasis; Rheumatoid arthritis; Severe malaria anemia; Skin carcinomas; Skin neoplasms; Squamous cell carcinoma; Sudden infant death syndrome; Systemic lupus erythematosus; Trachoma; Ulcerative colitis
IL12B	Interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40)	5q31.1-q33.1		Asthma; Atopic dermatitis; Bacillus Calmette-Guérin and *Salmonella* infection; Colorectal cancer; Crohn's disease; Diabetes mellitus (type 1); Familial atypical mycobacteriosis; Gastric cancer; Hypothermia; Leprosy; Malaria; Psoriasis; Psoriasis vulgaris; Psoriatic arthritis; *Salmonella* infection; Tuberculosis; Ulcerative colitis
IL18	Interleukin 18 (interferon-gamma-inducing factor)	11q22.2-q22.3		

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IL18R1	Interleukin 18 receptor 1	2q12		
IL18RAP	Interleukin 18 receptor accessory protein	2q12		
IPO5	Importin 5	13q32.2		
ITIH3/4	Inter-alpha (globulin) inhibitor, H3/4 polypeptides	3p21.1		
JARID2	Jumonji, AT rich interactive domain 2	6p24-p23	rs9654600; rs2235258	
KCNH2	Potassium voltage-gated channel, subfamily H (eag-related), member 2	7q36.1		Arrhythmia; Bradycardia-induced long QT syndrome; Drug-associated torsades de pointes; Long QT syndrome; Long QT syndrome 1/2; Long QT syndrome 2; Long QT syndrome 2/3; Long QT syndrome 2/5; Long QT syndrome 2/9; Nonfamiliar atrial fibrillation (AF); Schizophrenia; Short QT syndrome 1; Torsades de pointes
LEPR	Leptin receptor	1p31		Acute lymphoblastic leukemia; Diabetes; Diabetes mellitus (type 2); Glucocorticoid-induced hypertension; Hypogonadism; Impaired glucose tolerance; Low bone mineral content; Morbid obesity; Obesity; Osteoporosis; Risk of metabolic syndrome, diabetes or vascular disease
LGR4	Leucine-rich repeat containing G protein-coupled receptor 4	11p14-p13		
LTA	Lymphotoxin alpha (TNF superfamily, member 1)	6p21.3		Susceptibility to leprosy 4; Susceptibility to myocardial infarction; Susceptibility to psoriatic arthritis
MAGI1	Membrane associated guanylate kinase, WW and PDZ domain containing 1	3p14.1		
MAGI2	Membrane associated guanylate kinase, WW and PDZ domain containing 2	7q21		
MAGI3	Membrane associated guanylate kinase, WW and PDZ domain containing 3	1p12-p11.2		
MBP	Myelin basic protein	18q23		
MC5R	Melanocortin 5 receptor	18p11.2		
MCHR1	Melanin-concentrating hormone receptor 1	22q13.2		
MCHR2	Melanin-concentrating hormone receptor 2	6q16		
MCTP2	Multiple C2 domains, transmembrane 2	15q26.2		
MDGA1	MAM domain containing glycosylphosphatidylinositol anchor 1	6p21	rs11759115	
ME2	Malic enzyme 2, NAD(+)-dependent, mitochondrial	18q21		
MED12	Mediator complex subunit 12	Xq13		FG syndrome 1; Lujan-Fryns syndrome; Opitz-Kaveggia syndrome
MEGF10	Multiple EGF-like-domains 10	5q33		
MICB	MHC class I polypeptide-related sequence B	6p21.3		
MLC1	Megalencephalic leukoencephalopathy with subcortical cysts 1	22q13.33		Megalencephalic leukoencephalopathy with subcortical cysts

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MMP3	Matrix metallopeptidase 3 (stromelysin 1, progelatinase)	11q22.3		Abdominal aortic aneurysm; Breast neoplasms; Coronary arteriosclerosis; Coronary disease; Coronary heart disease; Rheumatoid arthritis; Schizophrenia
MMP9	Matrix metallopeptidase 9 (gelatinase B, 92 kDa gelatinase, 92 kDa type IV collagenase)	20q11.2-q13.1		
MOG	Myelin oligodendrocyte glycoprotein	6p22.1		
MTHFR	Methylenetetrahydrofolate reductase (NAD(P)H)	1p36.3	rs1801131; rs1801133	Abnormal spermatogenesis; Acute lymphocytic leukemia (ALL); Alzheimer disease; Autistic disorder; B-cell chronic lymphocytic leukemia; Bipolar disorder; Breast neoplasms; Budd-Chiari syndrome; Cancer; Cardiovascular diseases; Cervical intraepithelial neoplasia; Cleft lip; Cleft lip/palate; Clubfoot; Cognition disorders; Colonic neoplasms; Colorectal neoplasms; Congenital cardiac disease; Congenital heart defects; Coronary artery disease; Coronary heart disease; Coronary restenosis; Decreased viability among fetuses; Depression; Depressive disorder; Diabetic angiopathy; Down's syndrome; Endometrial neoplasms; Female infertility; Folate-sensitive neural tube defects; Follicular lymphoma; Gastric cancer; Glaucoma; Graft *vs* host disease; Homocystinuria; Homocystinuria due to deficiency of N(5,10)-methylenetetrahydrofolate reductase activity; Hyperhomocysteinemia; Hypersensitivity; Hypertension; Ischemic stroke; Liver diseases; Lower toxicity in 5-FU treatment; Lung neoplasms; Lymphoma; Major depressive disorder; Male infertility; Malnutrition; Maxillofacial abnormalities; Meningomyelocele; Metabolic diseases; Microsatellite instability; Microvascular angina; Migraine; Migraine with aura; MTHFR deficiency; Mucositis; Neoplasm metastasis; Neural tube defects; Nitrous oxide sensitivity in MTHFR deficiency; Non-Hodgkin lymphoma; Orofacial cleft 1; Precursor cell lymphoblastic leukemia-lymphoma; Pre-eclampsia; Primary open-angle glaucoma; Prostatic neoplasms; Retinal artery occlusion; Rheumatoid arthritis; Smallpox vaccine; Spinal cord diseases; Stomach neoplasms; Stroke; Sudden hearing loss; Thrombophilia; Thrombosis; Uterine cervical neoplasms
MUTED	Muted homolog (mouse)	6p25.1-p24.3		
NALCN	Sodium leak channel, nonselective	13q33.1	rs2152324	
NCAM1	Neural cell adhesion molecule 1	11q23.1		
NDEL1	NudE nuclear distribution gene E homolog (A. nidulans)-like 1	17p13.1	rs17806986	
NEFM	Neurofilament, medium polypeptide	8p21		
NEUROG1	Neurogenin 1	5q23-q31		
NOS1	Nitric oxide synthase 1 (neuronal)	12q24.2-q24.31		Susceptibility to infantile hypertrophic pyloric stenosis 1
NOS1AP	Nitric oxide synthase 1 (neuronal) adaptor protein	1q23.3	rs12742393	
NOTCH4	Notch 4	6p21.3	rs3131296	HIV-1 in humans
NPHP1	Nephronophthisis 1 (juvenile)	2q13		Joubert syndrome 4; Juvenile nephronophthisis 1; Juvenile nephronophthisis; Senior-Loken syndrome-1
NPY	Neuropeptide Y	7p15.1		Alcoholism; Anorexia nervosa; Anxiety disorders; Anxious depression; Appetite disorders; Birth weight; Cachexia; Carotid atherosclerosis; Cerebral infarction; Diabetes mellitus (type 2); Essential hypertension; Hypercholesterolemia; Hyperlipidemias; Hypertriglyceridemia; Ischemic stroke; Left ventricular hypertrophy; Myocardial infarction; Obesity; Stress
NQO2	NAD(P)H dehydrogenase, quinone 2	6pter-q12		Breast cancer susceptibility

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NR4A2	Nuclear receptor subfamily 4, group A, member 2	2q22-q23		Parkinson's disease
NRG1	Neuregulin 1	8p12	rs2439272; rs35753505; rs473376; rs10503929; rs7825588; rs6994992; rs4623364	
NRG2	Neuregulin 2	5q23-q33		
NRG3	Neuregulin 3	10q22-q23	rs7825588; rs10883866; rs10748842; rs6584400	
NRGN	Neurogranin (protein kinase C substrate, RC3)	11q24	rs12807809; rs7113041	
NRXN1	Neurexin 1	2p16.3		
NTF3	Neurotrophin 3	12p13		
NTNG1	Netrin G1	1p13.3		
NTRK3	Neurotrophic tyrosine kinase, receptor, type 3	15q25	rs999905 rs4887348	
NUMBL	Numb homolog (Drosophila)-like	19q13.13-q13.2		
OLIG2	Oligodendrocyte lineage transcription factor 2	21q22.11	rs762237; rs2834072	
OPCML	Opioid binding protein/cell adhesion molecule-like	11q25	rs3016384	Somatic epithelial ovarian cancer; Somatic ovarian cancer
OXSR1	Oxidative-stress responsive 1	3p22.2		
PALB2	Partner and localizer of BRCA2	16p12.2		
PCM1	Pericentriolar material 1	8p22-p21.3		Papillary thyroid carcinoma
PCNT	Pericentrin	21q22.3		
PDE4B	Phosphodiesterase 4B, cAMP-specific	1p31	rs910694; rs741271	
PDE4D	Phosphodiesterase 4D, cAMP-specific	5q12	rs1120303	
PDILM5	PDZ and LIM domain 5	4q22		
PDE7B	Phosphodiesterase 7B	6q23-q24	rs9389370	
PGBD1	PiggyBac transposable element derived 1	6p22.1	rs13211507	
PICALM	Phosphatidylinositol binding clathrin assembly protein	11q14	rs3851179	
PICK1	Protein interacting with PRKCA 1	22q13.1		
PIK3C3	Phosphoinositide-3-kinase, class 3	18q12.3		
PI4K2B	Phosphatidylinositol 4-kinase type 2 beta	4p15.2		
PLA2G4A	Phospholipase A2, group IVA (cytosolic, calcium-dependent)	1q25	rs10798059	Deficiency of phospholipase A2, group IV A
PLAT	Plasminogen activator, tissue	8p12		Familial hyperfibrinolysis, due to increased release of PLAT; Plasminogen activator deficiency

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PLXNA2	plexin A2	1q32.2	rs1327175; rs841865	
PPP1R1B	Protein phosphatase 1, regulatory (inhibitor) subunit 1B	17q12	rs907094	
PPP3CC	Protein phosphatase 3, catalytic subunit, gamma isozyme	8p21.3	rs10108011	
PRDX6	Peroxiredoxin 6	1q25.1	rs1295645; rs11405; rs6759; rs1046240; rs8383	
PRODH	Proline dehydrogenase (oxidase) 1	22q11.21		
PRSS16	Protease, serine, 16 (thymus)	6p21	rs6932590	
PSEN2	Presenilin 2 (Alzheimer disease 4)	1q31-q42	rs1295645	Alzheimer disease; Central nervous system diseases; Dilated cardiomyopathy; Frontotemporal dementia; Ischemic stroke; Left ventricular dysfunction; Left ventricular hypertrophy; Peripartum cardiomyopathy; Schizophrenia
PTGS2	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase	1q25.2-q25.3	rs2745557	Acute pancreatitis; Adenocarcinoma; Adenoma; Adenomatous polyposis coli; Amyotrophic lateral sclerosis; Cholangiocarcinoma; Basal cell carcinoma; B-cell chronic lymphocytic leukemia; B-cell lymphoma; Asthma; Breast neoplasms; Carcinoma; Carcinoma *in situ*; Autistic disorder; Esophageal neoplasms; Coronary artery disease; Diabetes mellitus (type 2); Drug-induced abnormalities; Duodenal ulcer; Colonic neoplasms; Colorectal neoplasms; Experimental liver cirrhosis; Glioma; Hepatocellular carcinoma; Inflammation; Intestinal polyps; Ischemic stroke; Ischemic proliferative retinopathy; Leiomyosarcoma; Kidney neoplasms; Myocardial infarction; Myocardial ischemia; Non-small cell lung carcinoma; Oral submucous fibrosis; Pancreatic neoplasms; Pituitary neoplasms; Renal cell carcinoma; Prostatic neoplasms; Inflammation; Intestinal polyps; Ischemic stroke; Ischemic proliferative retinopathy; Leiomyosarcoma; Kidney neoplasms; Myocardial infarction; Myocardial ischemia; Non-small cell lung carcinoma; Oral submucous fibrosis; Pancreatic neoplasms; Pituitary neoplasms; Renal cell carcinoma; Prostatic neoplasms; Skin diseases; Squamous cell carcinoma; Stomach neoplasms; Stomach ulcer; Tongue neoplasms; Urinary bladder neoplasms; Transitional cell carcinoma
PTPRZ1	Protein tyrosine phosphatase, receptor-type, Z polypeptide 1	7q31.3		Susceptibility to *H. pylori* infection
QKI	Quaking homolog, KH domain RNA binding (mouse)	6q26		
RNABP1	RAN binding protein 1	22q11.21	rs2238798; rs175162	
RAPGEF6	Rap guanine nucleotide exchange factor (GEF) 6	5q31.1		
RELN	Reelin	7q22	rs7341475	Lissencephaly syndrome, Norman-Roberts type
RGS4	Regulator of G-protein signaling 4	1q23.3	rs2661319 (SNP16)	
RPGRIP1L	RPGRIP1-like	16q12.2	rs9922369	COACH syndrome; Joubert syndrome 7; Meckel syndrome, type 5
RPP21	Ribonuclease P/MRP 21kDa subunit	6p22.1	rs3130375	
RTN4	Reticulon 4	2p16.3		
RTN4R	Reticulon 4 receptor	22q11.21		
SAT1	Spermidine/spermine N1-acetyltransferase 1	Xp22.1		

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SCNB	Synuclein, beta	5q35		Lewy body dementia
SCZD1	Schizophrenia disorder 1	5q11.2-q13.3		
SCZD2	Schizophrenia disorder 2	11q14-q21		
SCZD3	Schizophrenia disorder 3	6p24-p22		
SCZD6	Schizophrenia disorder 6	8p21		
SCZD7	Schizophrenia disorder 7	13q32		
SCZD8	Schizophrenia disorder 8	18p		
SCZD10	Schizophrenia disorder 10	15q15		
SCZD11	Schizophrenia susceptibility locus, chromosome 10q-related	10q22.3		
SCZD12	Schizophrenia 12	1p		
SDCCAG8	CCCAP SLSN7 Serologically defined colon cancer antigen 8	1q43		
SELENBP1	Selenium binding protein 1	1q21.3		
SFRP1	Secreted frizzled-related protein 1	8p11.21		
SH2B1	SH2B adaptor protein 1	16p11.2		
SHANK3	SH3 and multiple ankyrin repeat domains 3	22q13.3		Chromosome 22q13.3 deletion syndrome-related autism; Chromosome 22q13.3 deletion syndrome
SHMT1	Serine hydroxymethyltransferase 1 (soluble)	17p11.2		
SIGMAR1	Sigma non-opioid intracellular receptor 1	9p13.3		
SLC1A1	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	9p24		
SLC1A2	Solute carrier family 1 (glial high affinity glutamate transporter), member 2	11p13-p12		
SLC1A3	Solute carrier family 1 (glial high affinity glutamate transporter), member 3	5p13		
SLC1A6	Solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6	19p13.12		
SLC6A1	Solute carrier family 6 (neurotransmitter transporter, GABA), member 1	3p25-p24		
SLC6A3	Solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	5p15.3	rs6347	Anxiety disorders; Attention-deficit hyperactivity disorder; Bipolar affective disorder; Bipolar disorder; Brain diseases; Cocaine dependence; Cocaine-induced paranoia; Major depressive disorder; Parkinson's disease; Parkinsonian disorders; Pervasive development disorders; Protection against nicotine dependence; Susceptibility to tobacco addiction; Tic disorders; Tourette's syndrome

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SLC6A4	Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	17q11.2		Alcoholism; Alzheimer disease; Anorexia nervosa; Anxiety disorders; Anxiety-related personality traits; Attention-deficit hyperactivity disorder; Autistic disorder; Bipolar affective disorder and personality traits; Bipolar affective disorders; Bipolar disorder; Brain diseases; Chronobiology disorders; Diabetes mellitus type 2; Frontotemporal lobar degeneration; Irritable bowel syndrome; Major depressive disorder; Migraine with aura; Mood disorders; Obsessive-compulsive disorder; Pain threshold; Primary insomnia; Pulmonary hypertension; Seasonal affective disorder; Sleep disorders; Susceptibility to major depression, to attention-deficit hyperactivity disorder, to autism and rigid-compulsive behaviors; Susceptibility to obsessive-compulsive disorder; Sudden infant death; Tinnitus
SLC6A9	Solute carrier family 6 (neurotransmitter transporter, glycine), member 9	1p33		
SLC12A2	Solute carrier family 12 (sodium/potassium/chloride transporters), member 2	5q23.3		
SLC12A5	Solute carrier family 12 (potassium/chloride transporter), member 5	20q13.12		
SLC17A7	Solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 7	19q13		
SLC18A1	Solute carrier family 18 (vesicular monoamine), member 1	8p21.3	rs2270641	
SMARCA2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2	9p22.3	rs2296212; rs3793490; rs3763627	
SNAP25	Synaptosomal-associated protein, 25 kDa	20p12-p11.2		
SNAP29	Synaptosomal-associated protein, 29 kDa	22q11.21		Cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma syndrome
SOX10	SRY (sex determining region Y)-box 10	22q13.1	rs139887	PCWH; PCWH syndrome; Waardenburg syndrome, type 2E, with or without neurologic involvement; Waardenburg syndrome, type 4C; Waardenburg syndrome, type IIE; Waardenburg-Shah syndrome; Yemenite deaf-blind hypopigmentation syndrome
SP4	Sp4 transcription factor	7p15.3	rs12673091; rs12668354; rs12673091; rs3735440; rs11974306; rs1018954	
SRR	Serine racemase	17p13	rs408067	
ST8SIA2	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 2	15q26	rs4586379; rs2168351	
STX1A	Syntaxin 1A (brain)	7q11.23		
STX7	Syntaxin 7	6q23.1		
SYNGAP1	Synaptic Ras GTPase activating protein 1	6p21.3		Autosomal dominant mental retardation 5
SULT4A1	Sulfotransferase family 4A, member1	22q13.2		
SYN2	Synapsin II	3p25		

Continued

SYN3	Synapsin III	22q12.3		
SYNGR1	Synaptogyrin 1	22q13.1	rs715505	
SYT11	Synaptotagmin XI	1q21.2		
TAAR6	Trace amine associated receptor 6	6q23.2		
TAP1	Transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	6p21.3		Allergic rhinitis; Bare lymphocyte syndrome (type I); Cervical neoplasia; Dengue viral infection; Hypersensitivity pneumonitis
TARDBP	TAR DNA binding protein	1p36.22		
TBP	TATA box binding protein	6q27		Huntington disease-like-4; Parkinson's disease
TCF4	Transcription factor 4	18q21.1	rs9960767	Pitt-Hopkins syndrome; Risk of bipolar disorder
TDO2	Tryptophan 2,3-dioxygenase	4q31-q32		
TH	Tyrosine hydroxylase	11p15.5	rs6356	Segawa syndrome, recessive
TNF	Tumor necrosis factor	6p21.3	rs1800629	Acute kidney failure; Alzheimer disease; Anemia; Arsenic poisoning; Asthma; Behçet's disease; Bipolar affective disorder; Breast neoplasms; Bronchiectasis; Cerebral malaria; Chronic allograft nephropathy; Coronary artery disease; Coronary restenosis; Diaphragmatic hernia; Experimental diabetes mellitus; Experimental liver cirrhosis; Fever; Hemochromatosis; Hyperalgesia; Hypersensitivity; Hypothermia; Infection; Inflammation; Irritable bowel syndrome; *Listeria* infections; Lung diseases; Lung neoplasms; Major depressive disorder; Malaria; Microchimerism and diminished immune responsiveness; Migraine; Multiple organ failure; Oral submucous fibrosis; Pain; *Plasmodium falciparum* blood infection; Postmenopausal osteoporosis; Psoriasis; Pulmonary fibrosis; Pulmonary tuberculosis; Reperfusion injury; Respiratory hypersensitivity; Respiratory tract diseases; Rheumatic heart disease; Rheumatoid arthritis; Sepsis; Septic shock; Skin diseases; Stomach neoplasms; Stomach ulcer; Systemic lupus erythematosus; Ulcerative colitis; Vascular dementia
TP53	Tumor protein p53	17p13.1	rs1042522	Adrenal cortical carcinoma; Alzheimer disease; Bladder neoplasms; Breast neoplasms; Cervical intraepithelial neoplasia; Choroid plexus papilloma; Colonic neoplasms; Colorectal neoplasms; Esophageal cancer; Gastric cancer; Glioblastoma; Head and neck neoplasms; Hepatocellular carcinoma; Histiocytoma; Li-Fraumeni syndrome 1; Lung neoplasms; Lymphocytic leukemia; Multiple malignancy syndrome; Nasopharyngeal carcinoma; Neoplasms; Osteosarcoma; Ovarian neoplasms; Pancreatic cancer; Pancreatic carcinoma; Pancreatic neoplasms; Prostatic neoplasms; Rhabdomyosarcoma; Rheumatoid arthritis; Skin neoplasms; Telangiectasia; Thyroid carcinoma
TPH1	Tryptophan hydroxylase 1	11p15.3-p14	rs1800532	Bulimia; Cardiovascular diseases; Major depression; Obsessive-compulsive disorder; Pulmonary hypertension; Risk for suicidal behavior; Slower response to fluvoxamine
TRIM32	Tripartite motif containing 32	9q33.1		
TSNAX	Translin-associated factor X	1q42.1		
UFD1L	Ubiquitin fusion degradation 1 like (yeast)	22q11.21		
VEGFA	Vascular endothelial growth factor A	6p12		Acute myocardial infarction; Alzheimer disease; Asthma; Atherosclerosis; Biliary atresia; Bladder cancer; Bladder neoplasms; Colon cancer; Colonic neoplasms; Diabetes mellitus (type 2); Diabetic nephropathy; Diabetic retinopathy; Endometriosis; Esophageal cancer; Experimental liver cirrhosis; Gastric cancer; Glioblastoma; Liver neoplasms; Macular degeneration; Neoplasms; Non-small cell lung carcinoma; Ovarian cancer; Psoriasis; Retinopathy; Rhabdomyosarcoma; Rheumatoid arthritis; Squamous cell carcinoma

Continued

VIPR2	Vasoactive intestinal peptide receptor 2	7q36.3		
WNK3	WNK lysine deficient protein kinase 3	Xp11.22		
XBP1	X-box binding protein 1	22q12		Susceptibility to bipolar disorder; Susceptibility to major affective disorder-7
XRCC1	X-ray repair complementing defective repair In Chinese hamster cells 4	19q13.2	rs6452536 rs35260	Acute lymphoblastic leukemia; Bladder neoplasms; Breast cancer; Breast neoplasms; Gastric cancer; Mesothelioma; Non-small cell lung cancer; Occupational diseases; Prostatic neoplasms; Squamous cell carcinoma of the head and neck
XRCC4	X-ray repair complementing defective repair in Chinese hamster cells 4	5q14.2		
YWHAE	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide	17p13.3		
YWHAH	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide	22q12.3		
ZBED4	Zinc finger, BED-type containing 4	22q13.33		
ZDHHC8	Zinc finger, DHHC-type containing 8	22q11.21		
ZNF804A	ZInc finger protein 804A	2q32.1	rs1344706; rs7597593; rs1344706; rs4667000; rs1366842; rs3731834	

(Updated from Cacabelos and Martínez-Bouza [17], and Cacabelos *et al.* [1]).

Table 2. Pharmacogenomics of Neuroleptics.

Drug	Features
Aripiprazole	**Category**: Atypical antipsychotic; Arilpiperazine **Mechanism**: Full agonist: 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_6$, 5-HT receptors; partial agonist: D$_2$ and 5-HT$_{1A}$ receptors; antagonist: 5-HT$_{2A}$ receptor **Genes**: ABCB1, ADRA1A, CYP2D6, CYP3A4, DRD2, DRD3, HRH1, HTR1A, HTR1B, HTR1D, HTR2A, HTR2C, HTR7 **Substrate:** CYP2D6 (major), CYP3A4 (major)
Benperidol	**Category:** Antipsychotic, Neuroleptic; Butyrophenone **Mechanism**: Blocks postsynaptic mesolimbic dopaminergic D$_1$ and D$_2$ receptors **Genes:** DRD1, DRD2
Bromperidol	**Category:** Antipsychotic, Neuroleptic; Butyrophenone **Mechanism:** D$_2$ receptor antagonist; moderate serotonin 5-HT$_2$ receptor antagonist **Genes:** ABCB1, ADRA1A, CYP2D6, DRD2, HTR2A **Substrate:** CYP2D6 (minor), CYP3A4 (major), UGTs **Inhibitor:** CYP2D6 (moderate)
Chlorpromazine	**Category:** Phenothiazine antipsychotic; Aliphatic phenothiazine **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic D$_1$ and D$_2$ receptors; has a strong anticholinergic effect; weakly blocks ganglionic, antihistaminic and antiserotonergic receptors; blocks α-adrenergic receptors (strong); inverse agonist: 5-HT$_6$, 5-HT$_7$; antagonist: 5-HT$_{1A}$, 5-HT$_{2c}$ **Genes:** ABCB1, ACACA, ADRA1A, ADRA2A, ADRA2B, ADRA2C, BDNF, CYP1A2, CYP2D6, CYP3A4, CYP2E1, DAO, DRD1, DRD2, DRD3, FABP1, FMO1, HRH1, HTR1A, HTR1E, HTR2A, HTR2C, HTR6, HTR7, KCNE2, LEP, NPY, SCN5A, UGT1A3, UGT1A4 **Substrate:** CYP1A2 (minor), CYP2D6 (major), CYP3A4 (minor), UGT1A3, UGT1A4 **Inhibitor:** CYP2D6 (strong), CYP2E1 (weak), DAO

Continued

Clozapine	**Category:** Atypical antipsychotic; Dibenzodiazepine **Mechanism:** Antagonist of histamine H_1, cholinergic and α_1-adrenergic receptors; antagonist: 5-HT$_{1A}$, 5-HT$_{2B}$; full agonist: 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1F}$; inverse agonist: 5-HT$_6$, 5-HT$_7$ **Genes:** ABCB1, ADRA1A, ADRA1B, ADRA1D, ADRB3, APOA5, APOC3, APOD, CNR1, CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, DRD1, DRD2, DRD3, DRD4, DTNBP1, FABP1, GNAS1, GNB3, GSK3B, HLAA, HRH1, HRH2, HRH4, HTR1A, HTR1B, HTR1D, HTR1E, HTR1F, HTR2A, HTR2B, HTR2C, HTR3A, HTR6, HTR7, LPL, RGS2, SLC6A2, SLC6A4, TNF, UGT1A3, UGT1A4 **Substrate:** ABCB1, CYP1A2 (major), CYP2A6 (minor), CYP2C8/9 (minor), CYP2C19 (minor), CYP2D6 (minor), CYP3A4 (major), FMO3, UGT1A3, UGT1A4 **Inhibitor:** CYP1A2 (weak), CYP2C8/9 (moderate), CYP2C19 (moderate), CYP2D6 (moderate), CYP2E1 (weak), CYP3A4 (weak)
Droperidol	**Category:** Atypical antipsychotic; Butyrophenone **Mechanism:** Blocks dopaminergic and α-adrenergic receptors **Genes:** ABCC8, ADRA1A, ADRAB1, ADRA2A, DRD2, CHRM2, CYP2C9, CYP2C19, CYP3D6, CYP3A4, KCNE1, KCNE2, KCNH2, KCNJ11, KCNQ1, SCN5A **Substrate:** CYP2C9 (major), CYP2C19 (major), CYP2D6 (major), CYP3A4 (major)
Fluphenazine	**Category:** Typical antipsychotic; Piperazine phenothiazine **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors; inverse agonist: 5-HT$_7$; antagonist: 5-HT$_{2A}$ **Genes:** ABCB1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, DRD1, DRD2, HRH1, HTR2A, HTR7 **Substrate:** CYP2D6 (major) **Inhibitor:** CYP1A2 (weak), CYP2C9 (weak), CYP2D6 (strong), CYP2E1 (weak)
Flupenthixol	**Category:** Typical antipsychotic; Thioxanthene **Mechanism:** Blocks postsynaptic dopaminergic receptors **Genes:** DRD1, DRD2
Haloperidol	**Category:** Typical antipsychotic; Butyrophenone **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors; antagonist: 5-HT$_{2A}$, 5-HT$_{2B}$ **Genes:** ABCB1, ABCC1, ADRA1A, ADRA2A, BDNF, CHRM2, CYP1A2, CYP2C9, CYP2D6, CYP3A4, DRD1, DRD2, DRD4, DTNBP1, FOS, GRIN2B, GSK3B, GSTP1, HRH1, HTR2A, HTR2B, HTT, IL1RN, KCNE1, KCNE2, KCNH2, KCNJ11, KCNQ1, SCN5A, UGTs **Substrate:** CBR, CYP1A1 (minor), CYP1A2 (minor), CYP2C8/9 (minor), CYP2C19 (minor), CYP2D6 (major), CYP3A4 (major), UGTs **Inhibitor:** CYP2D6 (moderate), CYP3A4 (moderate)
Loxapine	**Category:** Typical antipsychotic; Dibenzoxazepine **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors; blocks serotonin 5-HT$_2$ receptors; inverse agonist: 5-HT$_{2c}$, 5-HT$_6$ **Genes:** ADRA1A, DRD1, DRD2, HRH1, HTR2A, HTR2C, HTR6, KCNE2, SCN5A, UGT1A4 **Substrate:** UGT1A4
Mesoridazine	**Category:** Typical antipsychotic; Phenothiazine **Mechanism:** Putative dopaminergic, cholinergic, and adrenergic inhibition **Genes:** ADRA1A, DRD2, CHRM2, CYP2J2, KCNE1, KCNE2, KCNH2, KCNJ11, KCNQ1, SCN5A **Substrate:** CYP2J2
Molindone	**Category:** Typical antipsychotic; Dihydroindolone **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors; has a strong anticholinergic effect; weak ganglionic, antihistaminic and antiserotonergic block; strong α-adrenergic block; antagonist: 5-HT$_{2A}$ **Genes:** ADRA1A, CYPs, DRD2,DRD3, HRH1, HTR1A, HTR1E, HTR2A, HTR2C
Olanzapine	**Category:** Atypical antipsychotic; Thienobenzodiazepine **Mechanism:** Strong antagonist of serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$, 5-HT$_7$, dopaminergic D_{1-4}, histamine H_1 and α_1-adrenergic receptors; antagonist: 5-HT$_{2A}$, 5-HT$_3$ and muscarinic M$_{1-5}$; full agonist: 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1F}$; inverse agonist: 5-HT$_{2c}$, 5-HT$_6$ **Genes:** ABCB1, ADRA1A, ADRB3, APOA5, APOC3, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, COMT, CYP1A2, CYP2C8/9, CYP2C19, CYP2D6, CYP3A4, DRD1, DRD2, DRD3, DRD4, FMO1, GNB3, GRM3, HRH1, HRH2, HTR1A, HTR1B, HTR1D, HTR1E, HTR1F, HTR2A, HTR2C, HTR3A, HTR6, HTR7, KCNH2, LEP, LEPR, LPL, RGS2, SLC6A2, TNF, UGT1A4 **Substrate:** CYP1A2 (major), CYP2D6 (major), UGT1A4 **Inhibitor:** CYP1A2 (weak), CYP2C8/9 (weak), CYP2C19 (weak), CYP2D6 (weak), CYP3A4 (weak)

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Paliperidone	**Category:** Atypical antipsychotic; Benzisoxazole **Mechanism:** Serotonin and dopamine receptor antagonist; has high affinity for α_1, D_2, H_1, and 5-HT$_{2C}$ receptors; low affinity for muscarinic and 5-HT$_{1A}$ receptors **Genes:** ABCB1, ADRA1A, ADRA1B, ADRA1D, CHRMs, CYP2D6, CYP3A4, DRD2, HRH1, HTR1A, HTR2A, UGTs **Substrate:** ABCB1, ADH, CYP2D6 (major), CYP3A4 (major), UGTs **Inhibitor:** ABCB1, CYP2D6 (moderate), CYP3A4 (moderate)
Periciazine	**Category:** Typical antipsychotic; Piperidine phenothiazine **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors; blocks α-adrenergic receptors; inverse agonist: 5-HT$_6$, 5-HT$_7$; antagonist: 5-HT$_{2A}$, 5-HT$_{2c}$ **Genes:** ADRA1A, CYP2D6, CYP3A4/5, DRD1, DRD2, DRD3, HTR2A, HTR2C, HTR6, HTR7 **Substrate:** CYP2D6, CYP3A4
Perphenazine	**Category:** Typical antipsychotic; Piperazine phenothiazine **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors **Genes:** ABCB1, CYP1A2, CYP2C8/9, CYP2C19, CYP2D6, CYP3A4, DRD1, DRD2, RGS4 **Substrate:** CYP1A2 (major), CYP2C8/9 (major), CYP2C18/19 (major), CYP2D6 (major), CYP3A4/5 (major) **Inhibitor:** CYP1A2 (weak), CYP2D6 (weak)
Pimozide	**Category:** Typical antipsychotic; Difenylbutylpiperidine **Mechanism:** Dopaminergic antagonist; antagonist: 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_7$ **Genes:** ABCB1, ADRA1A, CHRM2, CYP1A2, CYP2C19, CYP2D6, CYP2E1, CYP3A4, DRD2, HRH1, HTR1A, HTR2A, HTR7, KCNE1, KCNE2, KCNH2, KCNQ1, SCN5A **Substrate:** CYP1A2 (minor), CYP3A4 (major) **Inhibitor:** CYP2C19 (weak), CYP2D6 (strong), CYP2E1 (weak), CYP3A4 (moderate)
Pipotiazine	**Category:** Typical antipsychotic; Piperidine phenothiazine **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors **Genes:** CYP2D6, CYP3A4, DRDs **Substrate:** CYP2D6, CYP3A4
Prochlorperazine	**Category:** Typical antipsychotic; Piperazine phenothiazine **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors; strong α-adrenergic and anticholinergic block **Genes:** ABCB1, ADRA1A, CYPs, DRD1, DRD2
Quetiapine	**Category:** Atypical antipsychotic; Dibenzothiazepine **Mechanism:** Serotonergic (5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_2$), dopaminergic (D_1 and D_2), histaminergic H_1, and adrenergic (α_1- and α_2-) receptor antagonist; full agonist: 5-HT$_{1A}$, 5-HT$_{1D}$, 5-HT$_{1F}$, 5-HT$_{2A}$ **Genes:** ABCB1, ADRA1A, ADRA2A, CYP3A4, CYP2D6, DRD1, DRD2, DRD4, HRH1, HTR1A, HTR1D, HTR1E, HTR1F, HTR2A, HTR2B, KCNE1, KCNE2, KCNH2, KCNQ1, RGS4, SCN5A **Substrate:** CYP3A4 (major), CYP2D6 (minor)
Risperidone	**Category:** Atypical antipsychotic; Benzisoxazole **Mechanism:** Serotonergic, dopaminergic, α_1-, α_2-adrenergic and histaminergic receptor antagonist; low-moderate affinity for 5-HT$_{1C}$, 5-HT$_{1D}$, and 5-HT$_{1A}$ receptors, low affinity for D_1; inverse agonist: 5-HT$_{2c}$, 5-HT$_6$, 5-HT$_7$ **Genes:** ABCB1, ADRA1A, ADRA1B, ADRA1D, APOA5, COMT, CYP2D6, CYP2A4, CYP3A4, DRD1, DRD2, DRD3, DRD4, FOS, GRM3, HRH1, HTR1A, HTR1B, HTR1C, HTR1D, HTR1E, HTR1F, HTR2A, HTR2C, HTR3A, HTR6, HTR7, KCNE2, KCNH2, PON1, RGS2, RGS4, SCN5A, SLC6A2, SLC6A4 **Substrate:** ABCB1, CYP2D6 (major), CYP3A4 (minor) **Inhibitor:** ABCB1, CYP2D6 (weak), CYP3A4 (weak)
Sulpiride	**Category:** Atypical antipsychotic; Benzamide **Mechanism:** Postsynaptic D_2 antagonist **Genes:** CYP2D6, CYP3A4, DRD2 **Substrate:** CYP2D6
Thioridazine	**Category:** Typical antipsychotic; Phenothiazine **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic receptors; blocks α-adrenergic receptors (strong); inverse agonist: 5-HT$_6$, 5-HT$_7$; antagonist: 5-HT$_{2c}$ **Genes:** ABCB1, ADRA1A, CHRM2, CYP1A2, CYP2C8/9, CYP2D6, CYP2C19, CYP2E1, CYP2J2, DRD2, FABP1, HRH1, HTR6, HTR7, HTR2C, KCNE1, KCNE2, KCNH2, KCNJ11, KCNQ1, SCN5A **Substrate:** CYP1A2 (major), CYP2C19 (minor), CYP2D6 (major), CYP2J2 (major), CYP3A4 (major) **Inhibitor:** ADRA1, ADRA2, ADRBs, CYP1A2 (weak), CYP2C8/9 (weak), CYP2D6 (moderate), CYP2E1 (weak), DRD1
Thiothixene	**Category:** Typical antipsychotic; Thioxanthene **Mechanism:** Inhibits dopamine receptors; blocks α-adrenergic receptors; antagonist: 5-HT$_{2a}$ **Genes:** ADRA1A, CYP1A2, CYP2D6, DRD2, HRH1, HTR2A, KCNE1, KCNE2, KCNQ1, KCNH6, SCN5A **Substrate:** CYP1A2 (major) **Inhibitor:** CYP2D6 (weak)

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Trifluoperazine	**Category:** Typical antipsychotic; Phenothiazine **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic receptors; blocks α-adrenergic receptors **Genes:** ABCB1, ADRA1A, CYP1A2, DRD2, IL12B, UGT1A4 **Substrate:** CYP1A2 (major), UGT1A4
Ziprasidone	**Category:** Atypical antipsychotic; Benzylisothiazolylpiperazine **Mechanism:** High affinity for: D_2, D_3, 5-HT$_{2A}$, 5-HT$_{1A}$, 5-HT$_{2C}$, 5-HT$_{1D}$ and α_1-adrenergic receptors; moderate affinity for histamine H_1 receptors; antagonist: D_2, 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_{1D}$; full agonist: 5-HT$_{1B}$, 5-HT$_{1D}$; partial agonist: 5-HT$_{1A}$; inverse agonist: 5-HT$_{2c}$, 5-HT$_7$ **Genes:** ADRA1A, AOX1, CYP1A2, CYP2D6, CYP3A4, DRD2, DRD3, DRD4, HRH1, HTR1A, HTR1B, HTR1D, HTR1E, HTR2A, HTR2C, HTR7, KCNE2, KCNH2, RGS4, SCN5A **Substrate:** AOXs, CYP1A2 (minor), CYP3A4 (major), HTR1A **Inhibitor:** CYP2D6 (moderate), CYP3A4 (moderate), HTR2A, DRD2
Zuclopenthixol	**Category:** Typical antipsychotic; Thioxanthene **Mechanism:** Blocks postsynaptic mesolimbic dopaminergic receptors **Genes:** CYP2D6, DRD1, DRD2 **Substrate:** CYP2D6 (major)

Symbols: ABCB1: ATP-binding cassette, sub-family B (MDR/TAP), member 1, **ACACA:** Acetyl-Coenzyme A carboxylase alpha, **ADRA1A:** Adrenergic, alpha-1A-, receptor, **ADRA1B:** Adrenergic, alpha-1B-, receptor, **ADRB3:** Adrenergic, beta-3-, receptor, **ADRA1D:** Adrenergic, alpha-1D-, receptor, **AOX1:** Aldehyde oxidase 1, **APOA5:** Apolipoprotein A-V, **APOC3:** Apolipoprotein C-III, **APOD:** Apolipoprotein D, **BDNF:** Brain-derived neurotrophic factor, **CFTR:** Cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7), **CHRMs:** Muscarinic receptors, **CHRM1:** Cholinergic receptor, muscarinic 1, **CHRM2:** Cholinergic receptor, muscarinic 2, **CHRM3:** Cholinergic receptor, muscarinic 3, **CHRM4:** Cholinergic receptor, muscarinic 4, **CHRM5:** Cholinergic receptor, muscarinic 5, **CNR1:** Cannabinoid receptor 1 (brain), **COMT:** Catechol-O-methyltransferase, **CYP1A2:** Cytochrome P450, family 1, subfamily A, polypeptide 2, **CYP2A6:** Cytochrome P450, family 2, subfamily A, polypeptide 6, **CYP2C19:** Cytochrome P450, family 2, subfamily C, polypeptide 19, **CYP2C8:** Cytochrome P450, family 2, subfamily C, polypeptide 8, **CYP2C9:** Cytochrome P450, family 2, subfamily C, polypeptide 9, **CYP2D6:** Cytochrome P450, family 2, subfamily D, polypeptide 6, **CYP2J2:** Cytochrome P450, family 2, subfamily J, polypeptide 2, **CYP2E1:** Cytochrome P450, family 2, subfamily E, polypeptide 1, **CYP3A4:** Cytochrome P450, family 3, subfamily A, polypeptide 4, **DRDs:** Dopamine receptors, **DRD1:** Dopamine receptor D1, **DRD2:** Dopamine receptor D2, **DRD3:** Dopamine receptor D3, **DRD4:** Dopamine receptor D4, **DTNBP1:** Dystrobrevin binding protein 1, **FABP1:** Fatty acid binding protein 1, liver, **FMO1:** Flavin containing monooxygenase 1, **FOS:** FBJ murine osteosarcoma viral oncogene homolog, **GNAS:** GNAS complex locus, **GNB3:** Guanine nucleotide binding protein (G protein), beta polypeptide 3, **GRIN2B:** Glutamate receptor, ionotropic, N-methyl D-aspartate 2B, **GRM3:** Glutamate receptor, metabotropic 3, **GSK3B:** Glycogen synthase kinase 3 beta, **HLA:** Major histocompatibility complex, **HLA-A:** Major histocompatibility complex, class I, A, **HRH1:** Histamine receptor H1, **HRH2:** Histamine receptor H2, **HRH3:** Histamine receptor H3, **HRH4:** Histamine receptor H4, **HTR1A:** 5-Hydroxytryptamine (serotonin) receptor 1A, **HTR1B:** 5-Hydroxytryptamine (serotonin) receptor 1B, **HTR1D:** 5-Hydroxytryptamine (serotonin) receptor 1D, **HTR1E:** 5-Hydroxytryptamine (serotonin) receptor 1E, **HTR1F:** 5-Hydroxytryptamine (serotonin) receptor 1F, **HTR2A:** 5-Hydroxytryptamine (serotonin) receptor 2A, **HTR2B:** 5-Hydroxytryptamine (serotonin) receptor 2B, **HTR2C:** 5-Hydroxytryptamine (serotonin) receptor 2C, **HTR3A:** 5-Hydroxytryptamine (serotonin) receptor 3A, **HTR6:** 5-Hydroxytryptamine (serotonin) receptor 6, **HTR7:** 5-Hydroxytryptamine (serotonin) receptor 7 (adenylate cyclase-coupled), **HTT:** Huntingtin, **IL12B:** Interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40), **IL1RN:** Interleukin 1 receptor antagonist, **KCNE1:** Potassium voltage-gated channel, Isk-related family, member 1, **KCNE2:** Potassium voltage-gated channel, Isk-related family, member 2, **KCNH:** Potassium voltage-gated channel, subfamily H (eag-related), member 1-8, **KCNH2:** Potassium voltage-gated channel, subfamily H (eag-related), member 2, **KCNH6:** Potassium voltage-gated channel, subfamily H (eag-related), member 6, **KCNJ11:** Potassium inwardly-rectifying channel, subfamily J, member 11, **KCNQ1:** Potassium voltage-gated channel, KQT-like subfamily, member 1, **LEP:** Leptin, **LEPR:** Leptin receptor, **LPL:** Lipoprotein lipase, **NPY:** Neuropeptide Y, **PON1:** Paraoxonase 1, **RGS2:** Regulator of G-protein signaling 2, 24kDa, **RGS4:** Regulator of G-protein signaling 4, **SCN5A:** Sodium channel, voltage-gated, type V, alpha subunit, **SLC6A2:** Solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2, **SLC6A4:** Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4, **TNF:** Tumor necrosis factor (TNF superfamily, member 2), **UGT1A3:** UDP glucuronosyltransferase 1 family, polypeptide A3, **UGT1A4:** UDP glucuronosyltransferase 1 family, polypeptide A4. (Generated with data from Cacabelos [25]).

of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4 [14]. Most CYP enzymes exhibit ontogenic-, age-, sex-, circadian-, and ethnic-related differences [26]. The practical consequence of this genetic variation is that the same drug can be differentially metabolized according to the genetic profile/expression during each subject's lifespan, and that knowing the pharmacogenomic profile of an individual, his/her pharmacodynamic response is potentially predictable to some extent.

Among genes of the CYP superfamily with relevance in the metabolism of psychotropic drugs, the CYP2D6, CYP2C19, CYP2C9, and CYP3A4/5 genes deserve special attention.
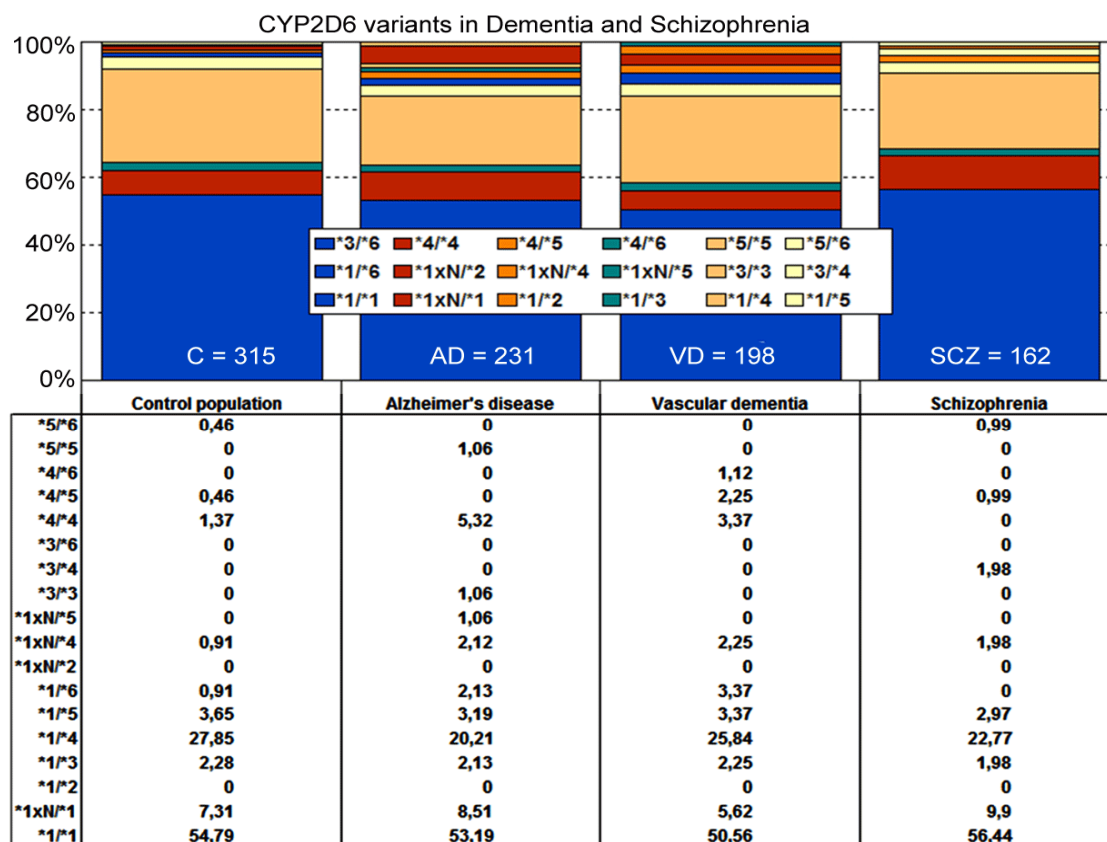
CYP2D6. CYP2D6 is a 4.38 kb gene with 9 exons mapped on 22q13.2. Four RNA transcripts of 1190 - 1684 bp are expressed in the brain, liver, spleen and reproductive system, where 4 major proteins of 48 - 55 kDa (439 - 494 aa) are identified. This protein is a transport enzyme of the cytochrome P450 subfamily IID or multigenic cytochrome P450 superfamily of mixed-function monooxygenases which localizes to the endoplasmic reticulum and is known to metabolize as many as 25% of commonly-prescribed drugs and over 60% of current psychotropics. The gene is highly polymorphic in the population. There are 141 CYP2D6 allelic variants, of which $-100C > T$, $-1023C > T$, $-1659G > A$, $-1707delT$, $-1846G > A$, $-2549delA$, $-2613 - 2615delAGA$, $-2850C > T$, $-2988G > A$, and $-3183G > A$ represent the 10 most important variants. Different

alleles result in the extensive, intermediate, poor, and ultra-rapid metabolizer phenotypes, characterized by normal, intermediate, decreased, and multiplied ability to metabolize the enzyme's substrates, respectively. P450 enzymes convert xenobiotics into electrophilic intermediates which are then conjugated by phase II enzymes to hydrophilic derivatives that can be excreted. According to the database of the World Guide for Drug Use and Pharmacogenomics [25], 982 drugs are CYP2D6-related: 371 drugs are substrates, over 300 drugs are inhibitors, and 18 drugs are CYP2D6 inducers.

Among healthy individuals, extensive metabolizers (EMs) account for 55.71% of the population, whereas intermediate metabolizers (IMs) are 34.7%, poor metabolizers (PMs) 2.28%, and ultra-rapid metabolizers (UMs) 7.31%. Remarkable interethnic differences exist in the frequency of the PM and UM phenotypes among different societies all over the world [4,27-29]. On average, approximately 6.28% of the world population belongs to the PM category. Europeans (7.86%), Polynesians (7.27%), and Africans (6.73%) exhibit the highest rate of PMs, whereas Orientals (0.94%) show the lowest rate [27]. The frequency of PMs among Middle Eastern populations, Asians, and Americans is in the range of 2% - 3%. CYP2D6 gene duplications are relatively infre-

quent among Northern Europeans, but in East Africa the frequency of alleles with duplication of CYP2D6 is as high as 29% [30]. In Europe, there is a North-South gradient in the frequency of PMs (6% - 12% of PMs in Southern European countries, and 2% - 3% PMs in Northern latitudes) [25]. In SCZ, EMs, IMs, PMs, and UMs are 58.42%, 27.72%, 3.96%, and 9.9%, respectively, with a 3% increase in the frequency of EMs, and a 7% decrease in the frequency of IMs with respect to controls in the Iberian population. In Alzheimer disease (AD), EMs, IMs, PMs, and UMs are 56.38%, 27.66%, 7.45%, and 8.51%, respectively, and in vascular dementia, 52.81%, 34.83%, 6.74%, and 5.62%, respectively (**Figures 2** and **3**). There is an accumulation of AD-related genes of risk in PMs and UMs. EMs and IMs are the best responders, and PMs and UMs are the worst responders to pharmacological treatment. Patients with depression show significant differences in the genotypic and phenotypic profiles as compared to controls and also with respect to patients with psychosis, Parkinson's disease, or brain tumors. Patients with stroke show differences as compared to patients with brain tumors, and both patients with brain tumors or with cranial nerve neuropathies differ in their CYP2D6 phenotype with regard to controls. These geno-phenotypic profiles might be important in

	Control population	Alzheimer's disease	Vascular dementia	Schizophrenia
*5/*6	0,46	0	0	0,99
*5/*5	0	1,06	0	0
*4/*6	0	0	1,12	0
*4/*5	0,46	0	2,25	0,99
*4/*4	1,37	5,32	3,37	0
*3/*6	0	0	0	0
*3/*4	0	0	0	1,98
*3/*3	0	1,06	0	0
*1xN/*5	0	1,06	0	0
*1xN/*4	0,91	2,12	2,25	1,98
*1xN/*2	0	0	0	0
*1/*6	0,91	2,13	3,37	0
*1/*5	3,65	3,19	3,37	2,97
*1/*4	27,85	20,21	25,84	22,77
*1/*3	2,28	2,13	2,25	1,98
*1/*2	0	0	0	0
*1xN/*1	7,31	8,51	5,62	9,9
*1/*1	54,79	53,19	50,56	56,44

Figure 2. CYP2D6 variants in dementia and schizophrenia. C: Controls; AD: Alzheimer disease; VD: Vascular dementia; SCZ: Schizophrenia.

CYP2D6 phenotypes in Dementia and Schizophrenia

	Control population	Alzheimer's disease	Vascular dementia	Schizophrenia
UM	7,31	8,51	5,62	9,9
PM	2,28	7,45	6,74	3,96
IM	34,7	27,66	34,83	27,72
EM	55,71	56,38	52,81	58,42

C=315 AD=231 VD=198 SCZ=162

Legend: EM, IM, PM, UM
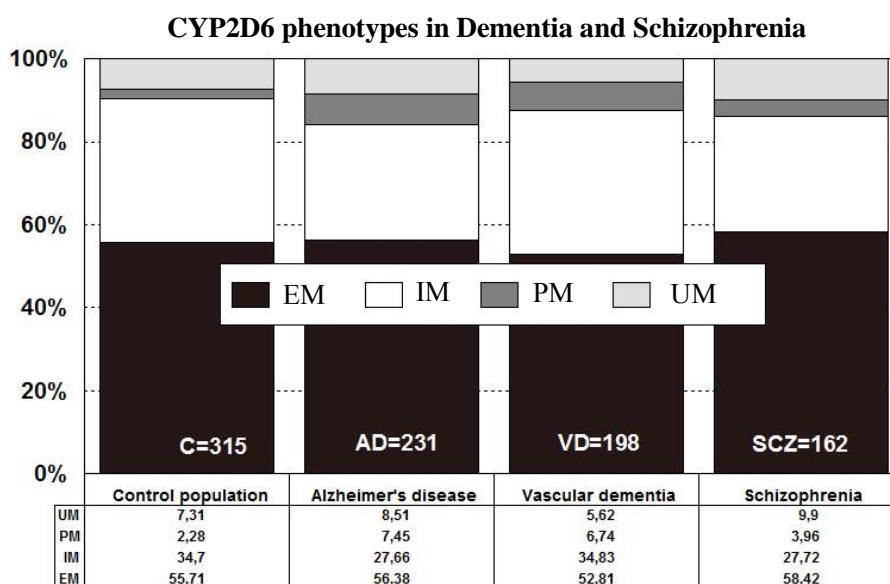
Figure 3. CYP2D6 phenotypes in dementia and schizophrenia. EM: Extensive Metabolizers; IM: Intermediate Metabolizers; PM: Poor Metabolizers; UM: Ultra-rapid Metabolizers. C: Controls; AD: Alzheimer disease; VD: Vascular dementia; SCZ: Schizophrenia.

the pathogenesis of some CNS disorders and in the therapeutic response to conventional psychotropic drugs as well [2] (**Figures 2 - 3**).

CYP2C9. CYP2C9 is a gene (50.71 kb) with 9 exons mapped on 10q24. An RNA transcript of 1860 bp is mainly expressed in hepatocytes, where a protein of 55.63 kDa (490 aa) can be identified. Over 600 drugs are CYP2C9-related, 311 acting as substrates (177 are major substrates, 134 are minor substrates), 375 as inhibitors (92 weak, 181 moderate, and 102 strong inhibitors), and 41 as inducers of the CYP2C9 enzyme [25]. There are 481 CYP2C9 SNPs. CYP2C9-*1/*1 EMs represent 60.56% of the healthy population; *1/*2 and *1/*3 IMs 18.78% and 13.62%, respectively (32.39% IMs); and *2/*2, *2/*3, and *3/*3 PMs, 3.76%, 3.28%, and 0%, respectively (7.04% PMs). No CYP2C9-*3/*3 cases have been found in the control population; however, in patients with depression, psychosis, and mental retardation the frequency of this genotype is 0.91%, 1.03%, and 1.37%, respectively (**Figure 4**). The frequency of PMs, IMs, and PMs in the control population are 60.56%, 32.39%, and 7.04%, respectively, and in SCZ are 61.86%, 32.99%, and 5.15% (**Figure 5**). Significant variation has been found in CYP2C9 genotypes among diverse brain diseases [2] (**Figures 4 - 5**).The plethora of metabolizing profiles in CNS disorders suggest a potential pathogenic role of CYP2C9 in brain pathology and a very strong role of the CYP2C9 enzyme on drugs with deleterious effects on cerebrovascular function (e.g. NSAIDs) and thromboembolic phenomena and/or bleeding (e.g. warfarin, coumarinics).

CYP2C19. CYP2C19 is a gene (90.21 kb) with 9 ex-

ons mapped on 10q24.1q24.3. RNA transcripts of 1901 bp, 2395 bp, and 1417 bp are expressed in liver cells where a protein of 55.93 kDa (490 aa) is identified. Nearly 500 drugs are CYP2C19-related, 281 acting as substrates (151 are major substrates, 130 are minor substrates), 263 as inhibitors (72 weak, 127 moderate, and 64 strong inhibitors), and 23 as inducers of the CYP2C19 enzyme [25]. About 541 SNPs have been detected in the CYP2C19 gene. The frequencies of the 3 major CYP2C19 geno-phenotypes in the control population are CYP2C19-*1/*1-EMs 68.54%, CYP2C19-*1/*2-IMs 30.05%, and CYP2C19-*2/*2-PMs 1.41%. In SCZ, EMs, IMs, and PMs represent 76.29%, 22.68%, and 1.03%, respectively (**Figure 6**). Minor variation has been reported in different brain disorders [2].

CYP3A4/5. CYP3A4 is a gene (27.2 kb) with 13 exons mapped on 7q21.1. RNA transcripts of 2153 bp, 651 bp, 564 bp, 2318 bp and 2519 bp are expressed in intestine, liver, prostate and other tissues where 4 protein variants of 57.34 kDa (503 aa), 17.29 kDa (153 aa), 40.39 kDa (353 aa), and 47.99 kDa (420 aa) are identified. The human CYP3A locus contains the three CYP3A genes (CYP3A4, CYP3A5 and CYP3A7), three pseudogenes as well as a novel CYP3A gene termed CYP3A43. The gene encodes a putative protein with between 71.5% and 75.8% identity to the other CYP3A proteins. The predominant hepatic form is CYP3A4, but CYP3A5 contributes significantly to the total liver CYP3A activity. This enzyme metabolizes over 1900 drugs, 1033 acting as substrates (897 are major substrates, 136 are minor substrates), 696 as inhibitors (118 weak, 437 moderate, and 141 strong inhibitors), and 241 as
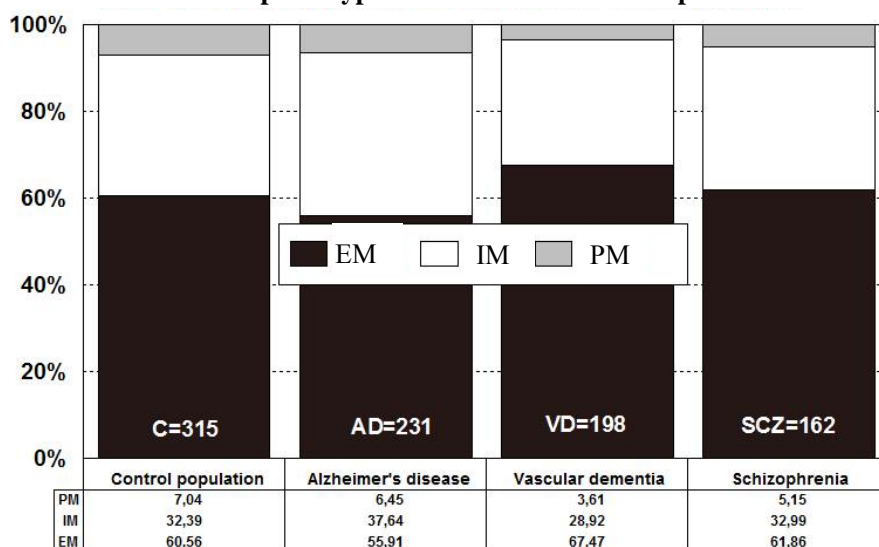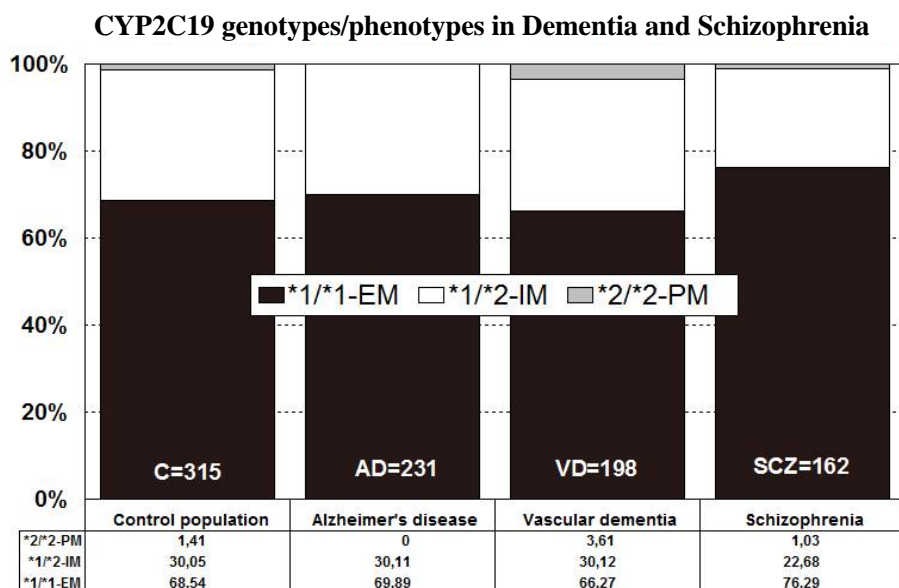
CYP2C9 genotypes/phenotypes in Dementia and Schizophrenia

	Control population	Alzheimer's disease	Vascular dementia	Schizophrenia
*3/*3-PM	0	0	0	1,03
*2/*3-PM	3,28	3,23	1,2	4,12
*2/*2-PM	3,76	3,23	2,41	0
*1/*3-IM	13,62	12,9	4,82	8,25
*1/*2-IM	18,78	24,73	24,1	24,74
*1/*1-EM	60,56	55,91	67,47	61,86
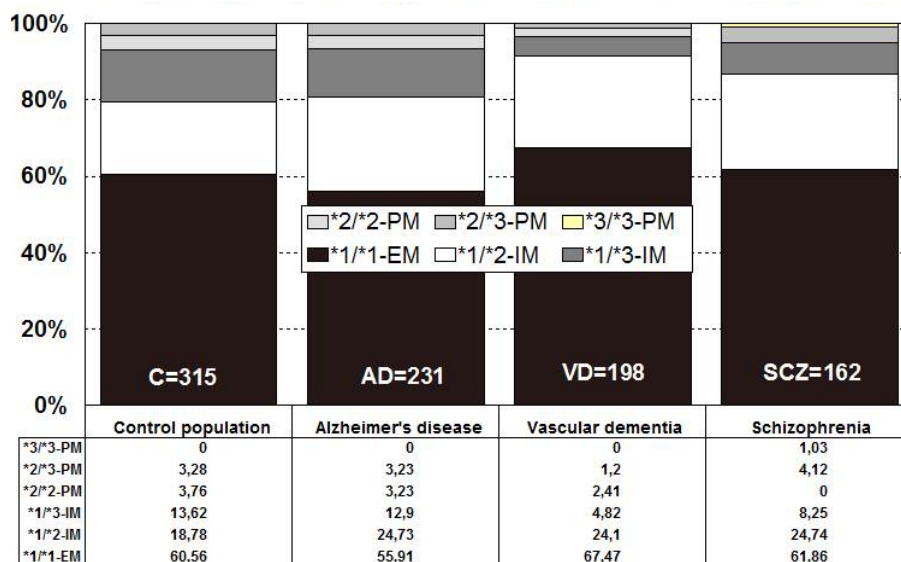
Figure 4. CYP2C9 geno/phenotypes in dementia and schizophrenia. EM: Extensive Metabolizers; IM: Intermediate Metabolizers; PM: Poor Metabolizers. C: Controls; AD: Alzheimer disease; VD: Vascular dementia; SCZ: Schizophrenia.

CYP2C9 phenotypes in Dementia and Schizophrenia

	Control population	Alzheimer's disease	Vascular dementia	Schizophrenia
PM	7,04	6,45	3,61	5,15
IM	32,39	37,64	28,92	32,99
EM	60,56	55,91	67,47	61,86

Figure 5. CYP2C9 phenotypes in dementia and schizophrenia. EM: Extensive Metabolizers; IM: Intermediate Metabolizers; PM: Poor Metabolizers. C: Controls; AD: Alzheimer disease; VD: Vascular dementia; SCZ: Schizophrenia.

inducers of the CYP3A4 enzyme [25]. About 347 SNPs have been identified in the CYP3A4 gene (CYP3A4*1A: Wild-type), 25 of which are of clinical relevance; in a Caucasian population, 82.75% are EMs (CYP3A5*3/*3), 15.88% are IMs (CYP3A5*1/*3), and 1.37% are UMs (CYP3A5*1/*1). Unlike other human P450s (CYP2D6, CYP2C19) there is no evidence of a "null" allele for CYP3A4 [2].

CYP Clustering. The construction of a genetic map integrating the most prevalent CYP2D6 + CYP2C19 + CYP2C9 polymorphic variants in a trigenic cluster yields 82 different haplotype-like profiles. The most frequent trigenic genotypes are *1*1-*1*1-*1*1 (25.70%), *1*1-*1*2-*1*2 (10.66%), *1*1-*1*1-*1*1 (10.45%), *1*4-*1*1-*1*1 (8.09%), *1*4-*1*2-*1*1 (4.91%), *1*4-*1*1-*1*2 (4.65%), and *1*1-*1*3-*1*3 (4.33%). These 82 trigenic genotypes represent 36 different pharmacogenetic phenotypes. According to these trigenic

CYP2C19 genotypes/phenotypes in Dementia and Schizophrenia

	Control population	Alzheimer's disease	Vascular dementia	Schizophrenia
*2/*2-PM	1,41	0	3,61	1,03
*1/*2-IM	30,05	30,11	30,12	22,68
*1/*1-EM	68,54	69,89	66,27	76,29

Figure 6. CYP2C19 geno/phenotypes in dementia and schizophrenia. EM: Extensive Metabolizers; IM: Intermediate Metabolizers; PM: Poor Metabolizers. C: Controls; AD: Alzheimer disease; VD: Vascular dementia; SCZ: Schizophrenia.

clusters, only 26.51% of the population show a pure 3EM phenotype, 15.29% are 2EM1IM, 2.04% are pure 3IM, 0% are pure 3PM, and 0% are 1UM2PM (the worst possible phenotype). This implies that only one-quarter of the population processes normally the drugs which are metabolized via CYP2D6, CYP2C9 and CYP2C19 (approximately 60% of the drugs of current use) [2,5,10,12].

2.4. Genes Encoding Drug Transporters

ABC genes, especially ABCB1 (ATP-binding cassette, subfamily B, member 1; P-glycoprotein-1, P-gp1; Multidrug Resistance 1, MDR1) (7q21.12), ABCC1 (9q31.1), ABCG2 (White1) (21q22.3), and other genes of this family encode proteins which are essential for drug metabolism and transport. The multidrug efflux transporters P-gp, multidrug-resistance associated protein 4 (MRP4) and breast cancer resistance protein (BCRP), located on endothelial cells lining brain vasculature, play important roles in limiting movement of substances into and enhancing their efflux from the brain. Transporters also cooperate with Phase I/Phase II metabolism enzymes by eliminating drug metabolites. Their major features are their capacity to recognize drugs belonging to unrelated pharmacological classes, and their redundancy, by which a single molecule can act as a substrate for different transporters. This ensures an efficient neuroprotection against xenobiotic invasions. The pharmacological induction of ABC gene expression is a mechanism of drug interaction, which may affect substrates of the up-regulated transporter, and overexpression of MDR transporters confers resistance to anticancer agents and CNS drugs [31,32]. Also of importance for CNS phar-

macogenomics are transporters encoded by genes of the solute carrier superfamily (SLC) and solute carrier organic (SLCO) transporter family, responsible for the transport of multiple endogenous and exogenous compounds, including folate (SLC19A1), urea (SLC14A1, SLC14A2), monoamines (SLC29A4, SLC22A3), aminoacids (SLC1A5, SLC3A1, SLC7A3, SLC7A9, SLC38A1, SLC38A4, SLC38A5, SLC38A7, SLC43A2, SLC45A1), nucleotides (SLC29A2, SLC29A3), fatty acids (SLC27A1-6), neurotransmitters (SLC6A2 (noradrenaline transporter), SLC6A3 (dopamine transporter), SLC6A4 (serotonin transporter, SERT), SLC6A5, SLC6A6, SLC6A9, SLC6A11, SLC6A12, SLC6A14, SLC6A15, SLC6A16, SLC6A17, SLC6A18, SLC6A19), glutamate (SLC1A6, SLC1A7), and others [24]. Some organic anion transporters (OAT), which belong to the solute carrier (SLC) 22A family, are also expressed at the BBB, and regulate the excretion of endogenous and exogenous organic anions and cations [33]. The transport of amino acids and di- and tripeptides is mediated by a number of different transporter families, and the bulk of oligopeptide transport is attributable to the activity of members of the SLC15A superfamily (Peptide Transporters 1 and 2 [SLC15A1 (PepT1) and SLC15A2 (PepT2), and Peptide/Histidine Transporters 1 and 2 [SLC15A4 (PHT1) and SLC15A3 (PHT2)]. ABC and SLC transporters expressed at the BBB may cooperate to regulate the passage of different molecules into the brain [34]. Polymorphic variants in ABC and SLC genes may also be associated with pathogenic events in CNS disorders and drug-related safety and efficacy complications [25].

2.5. Pleiotropic Genes

Apolipoprotein E (APOE) is a pathogenic gene in dementia and the prototypical paradigm of a pleiotropic gene with multifaceted activities in physiological and pathological conditions, including cardiovascular disease, dyslipidemia, atherosclerosis, stroke, and AD [2,6,14]. ApoE is consistently associated with the amyloid plaque marker for AD. APOE-4 may influence AD pathology interacting with APP metabolism and Aβ accumulation, enhancing hyperphosphorylation of tau protein and NFT formation, reducing choline acetyltransferase activity, increasing oxidative processes, modifying inflammation-related neuroimmunotrophic activity and glial activation, altering lipid metabolism, lipid transport and membrane biosynthesis in sprouting and synaptic remodeling, and inducing neuronal apoptosis [35].

The distribution of APOE genotypes in the Iberian Peninsula is as follows: APOE-2/2 0.32%, APOE-2/3 7.3%, APOE-2/4 1.27%, APOE-3/3 71.11%, APOE-3/4 18.41%, and APOE-4/4 1.59% (**Figure 3**). These frequencies are very similar in Europe and in other Western societies. There is a clear accumulation of APOE-4 carriers among patients with AD (APOE-3/4 30.30%; APOE-4/4 6.06%) and vascular dementia (APOE-3/4 35.85%, APOE-4/4 6.57%) as compared to controls (**Figure 7**). The distribution and frequencies of APOE genotypes in AD also differ from those of patients with anxiety, depression, psychosis, migraine, vascular encephalopathy, and post-traumatic brain injury syndrome [2,6,14] (**Figure 3**). Different APOE genotypes confer specific phenotypic profiles to AD patients. Some of these profiles may add risk or benefit when the patients

are treated with conventional drugs, and in many instances the clinical phenotype demands the administration of additional drugs which increase the complexity of therapeutic protocols. From studies designed to define APOE-related AD phenotypes, several conclusions can be drawn: 1) the age-at-onset is 5 - 10 years earlier in approximately 80% of AD cases harboring the APOE-4/4 genotype; 2) the serum levels of ApoE are lowest in APOE-4/4, intermediate in APOE-3/3 and APOE-3/4, and highest in APOE-2/3 and APOE-2/4; 3) serum cholesterol levels are higher in APOE-4/4 than in the other genotypes; 4) HDL-cholesterol levels tend to be lower in APOE-3 homozygotes than in APOE-4 allele carriers; 5) LDL-cholesterol levels are systematically higher in APOE-4/4 than in any other genotype; 6) triglyceride levels are significantly lower in APOE-4/4; 7) nitric oxide levels are slightly lower in APOE-4/4; 8) serum and cerebrospinal fluid Aβ levels tend to differ between APOE-4/4 and the other most frequent genotypes (APOE-3/3, APOE-3/4); 9) blood histamine levels are dramatically reduced in APOE-4/4 as compared with the other genotypes; 10) brain atrophy is markedly increased in APOE-4/4 > APOE-3/4 > APOE-3/3; 11) brain mapping activity shows a significant increase in slow wave activity in APOE-4/4 from early stages of the disease; 12) brain hemodynamics, as reflected by reduced brain blood flow velocity and increased pulsatility and resistance indices, is significantly worse in APOE-4/4 (and in APOE-4 carriers in general, as compared with APOE-3 carriers); brain hypoperfusion and neocortical oxygenation is also more deficient in APOE-4 carriers; 13) lymphocyte apoptosis is markedly enhanced in APOE-4 carriers; 14) cognitive deterioration is faster in APOE-4/4

	Control population	Alzheimer's disease	Vascular dementia	Schizophrenia
APOE-4/4	1,59	6,06	6,57	0,62
APOE-3/4	18,41	30,3	35,85	20,37
APOE-3/3	71,11	54,55	48,99	63,58
APOE-2/4	1,27	1,3	1,52	1,23
APOE-2/3	7,3	7,79	7,07	13,58
APOE-2/2	0,32	0	0	0,62
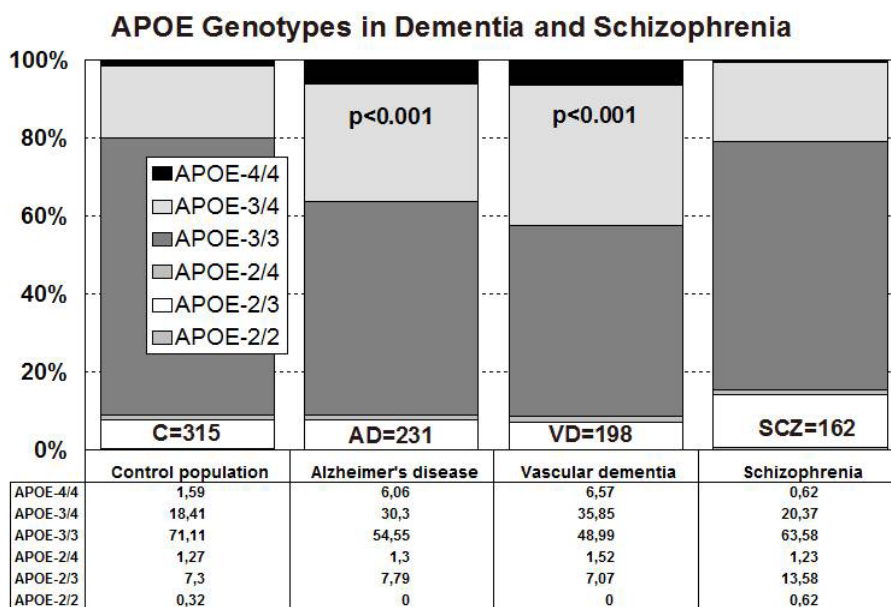
Figure 7. APOE genotypes in dementia and schizophrenia.

patients than in carriers of any other APOE genotype; 15) in approximately 3% - 8% of the AD cases, the presence of some dementia-related metabolic dysfunctions accumulates more in APOE-4 carriers than in APOE-3 carriers; 16) some behavioral disturbances, alterations in circadian rhythm patterns, and mood disorders are slightly more frequent in APOE-4 carriers; 17) aortic and systemic atherosclerosis is also more frequent in APOE-4 carriers; 18) liver metabolism and transaminase activity also differ in APOE-4/4 with respect to other genotypes; 19) hypertension and other cardiovascular risk factors also accumulate in APOE-4; and 20) APOE-4/4 carriers are the poorest responders to conventional drugs. These 20 major phenotypic features clearly illustrate the biological disadvantage of APOE-4 homozygotes and the potential consequences that these patients may experience when they receive pharmacological treatment for AD and/or concomitant pathologies [2,4-6,9-12,35].

When APOE and CYP2D6 genotypes are integrated in bigenic clusters and the APOE + CYP2D6-related therapeutic response to a combination therapy is analyzed in AD patients, it becomes clear that the presence of the APOE-4/4 genotype is able to convert pure CYP2D6*1/*1 extensive metabolizers into full poor responders to conventional treatments, indicating the existence of a powerful influence of the APOE-4 homozygous genotype on the drug-metabolizing capacity of pure CYP2D6 extensive metabolizers. In addition, a clear accumulation of APOE-4/4 genotypes is observed among CYP2D6 poor and ultra-rapid metabolizers [4,11].

3. GENOMICS OF SCHIZOPHRENIA AND PSYCHOTIC DISORDERS

3.1. Structural Genomics

Genetic studies in SCZ have revealed the presence of cytogenetic changes, chromosome anomalies and multiple candidate genes potentially associated with psychosis and related traits; and neurocognitive impairment was found to be heritable in individuals with SCZ and their relatives [36]. First-degree relatives of probands with SCZ or bipolar disorder (BD) are at increased risk of these disorders. Half-siblings have a significantly increased risk, but substantially lower than that of full-siblings. Heritability for SCZ and BD is 64% and 59%, respectively. Shared environmental effects are small but substantial (SCZ: 4.5%, 4.4% - 7.4%; BD: 3.4%, 2.3% - 6.2%) for both disorders. SCZ and BD partly share common genetic determinants [37]. Linkage analysis of SCZ in African-American families revealed that several regions show a decrease in the evidence for linkage as the definition broadens: 8q22.1 (rs911, 99.26 cM), 16q24.3 (rs1006547, 130.48 cM), and 20q13.2 (rs1022689, 81.73 cM). One region shows a substantial increase in

evidence for linkage, 11p15.2 (rs722317, 24.27 cM). These linkage results overlap two broad, previously-reported linkage regions: 8p23.3-p12, found in studies sampling largely families of European ancestry; and 11p11.2-q22.3, reported by a study of African-American families [38].

The genome-wide linkage scan analysis of 707 European-ancestry families identified suggestive evidence for linkage on chromosomes 8p21, 8q24.1, 9q34 and 12q24.1. Genome-wide significant evidence for linkage was observed on chromosome 10p12. Significant heterogeneity was also observed on chromosome 22q11.1. Evidence for linkage across family sets and analyses was most consistent on chromosome 8p21, with a one-LOD support interval that does not include the candidate gene NRG1, suggesting that one or more other susceptibility loci might exist in the region [39]. Genome-wide significant evidence for linkage for SCZ or schizoaffective disorder was found in a region on chromosome 17q21 in families of Mexican and Central American ancestry. A region on chromosome 15q22-23 showed suggestive evidence of linkage with this same phenotype [40].

The human genome is enriched in interspersed segmental duplications that sensitize approximately 10% of our genome to recurrent microdeletions and microduplications as a result of unequal crossing-over. Studies of common complex genetic disease show that a subset of these recurrent events plays an important role in autism, SCZ, and epilepsy [41]. The advent of genome-wide SNP and copy number variant (CNV) microarray technologies heralds identification of additional SCZ loci. Over 200 genes, reported in about 2400 studies, have been associated with SCZ during the past two decades; however, it is likely that over 1000 genes might be involved in SCZ pathogenesis through epistatic interaction and epigenetic phenomena. Many of these associations could not be replicated in different populations, as happens with many other multifactorial/complex disorders [42]. Data suggest that these susceptibility genes influence the cortical information processing which characterizes the schizophrenic phenotype. Aberrant postnatal brain maturation is an essential mechanism underlying the disease. Several candidate genes have been suggested, with the strongest evidence for genes encoding dystrobrevin binding protein 1 (DTNBP1), neuregulin 1 (NRG1), neuregulin 1 receptor (ERBB4) and disrupted in SCZ1 (DISC1), as well as several neurotrophic factors. These genes are involved in neuronal plasticity and also play a role in adult neurogenesis [43].

Several studies of the dystrobrevin-binding protein 1 gene (DTNBP1), neuregulin 1 (NRG1), D-amino-acid oxidase (DAO), DAO activator (DAOA, G72), and metabotropic glutamate receptor 3 (GRM3) genes have suggested an association between variants of these genes

and SCZ; however, several studies did not replicate associations of DTNBP1, NRG1, DAO, DAOA, and GRM3 gene polymorphisms and SCZ [44]. Within the last 2 years, a number of genome-wide association studies (GWAS) of SCZ and BD have been published [45-48]. These have produced stronger evidence for association to specific risk loci than had earlier studies, specifically for the zinc finger binding protein 804A (ZNF804A) locus in SCZ and for the calcium channel, voltage-dependent, L type, alpha 1C subunit (CACNA1C) and ankyrin 3, node of Ranvier (ANK3) loci in BD. The ZNF804A and CACNA1C loci appear to influence risk for both disorders, a finding that supports the hypothesis that SCZ and BD are not etiologically distinct. In the case of SCZ, a number of rare copy number variants have also been detected that have fairly large effect sizes on disease risk, and that additionally influence risk of autism, mental retardation, and other neurodevelopmental disorders. The existing findings point to some likely pathophysiological mechanisms but also challenge current concepts of disease classification [49]. A genome scan meta-analysis (GSMA) was carried out on 32 independent genome-wide linkage scan analyses that included 3255 pedigrees with 7413 genotyped cases affected with SCZ or related disorders. Suggestive evidence for linkage was observed in two single bins, on chromosomes 5q (142 - 168 Mb) and 2q (103 - 134 Mb). Genome-wide evidence for linkage was detected on chromosome 2q (119 - 152 Mb) when bin boundaries were shifted to the middle of the previous bins. The primary analysis met empirical criteria for "aggregate" genome-wide significance, indicating that some or all of 10 bins are likely to contain loci linked to SCZ, including regions of chromosomes 1, 2q, 3q, 4q, 5q, 8p and 10q. In a secondary analysis of 22 studies of European-ancestry samples, suggestive evidence for linkage was observed on chromosome 8p (16 - 33 Mb) [50]. In another GWAS, evidence was found for association to genes reported in other GWAS data sets (CACNA1C) or to closely-related family members of those genes, including CSF2RB, CACNA1B and DGKI [51].

A summary of genes (or pathological pathways) with potential effect in SCZ pathogenesis is the major goal of the present review in order to understand the complex molecular mechanisms which might be responsible for the clinical manifestations of one of the oldest diseases in the constellation of mental illness.

3.2. Genes Potentially Associated with Schizophrenia and Psychotic Disorders

ABCA13 (ATP-binding cassette, sub-family A (ABC1), member 13). The lipid transporter gene ABCA13 is a susceptibility factor for both SCZ and BD. SCZ and BD are leading causes of morbidity across all populations,

with heritability estimates of approximately 80%, indicating a substantial genetic component. Population genetics and GWAS suggest an overlap of genetic risk factors between these illnesses. Knight *et al.* [52] resequenced ABCA13 exons in cases with SCZ and controls. Multiple rare coding variants were identified, including one nonsense and nine missense mutations and compound heterozygosity/homozygosity in 6% of cases. Variants were genotyped in additional SCZ, bipolar, depression and control cohorts, and the frequency of all rare variants combined was greater than controls in SCZ and BD. The population-attributable risk of these mutations was 2.2% for SCZ and 4.0% for BD [52].

Abelson helper integration site 1 (AHI1). The Abelson helper integration site 1 (AHI1) gene locus on chromosome 6q23.3 is among a group of candidate loci for SCZ susceptibility that were initially identified by linkage followed by linkage disequilibrium (LD) mapping, and subsequent replication of the association in an independent sample. The region contains two genes, AHI1 and *C*6orf217. Both genes and the neighboring phosphodiesterase 7B (PDE7B) may be considered candidates for involvement in the genetic etiology of SCZ [53]. Of 14 SNPs tested (ATP2B2, HS3ST2, UNC5C, BAG3, PDE7B, PAICS, PTGFRN, NR3C2, ZBTB20, ST6GAL2, PIP5K1B, EPHA6, KCNH5, and AJAP1), only one (rs9389370) in PDE7B (high-affinity cAMP-specific phosphodiesterase 7B) showed significant evidence for association with SCZ in a Japanese sample [54].

The AHI1 gene is required for both cerebellar and cortical development in humans. According to Rivero *et al.* [55], while the accelerated evolution of AHI1 in the human lineage indicates a role in cognitive function, a linkage scan in large pedigrees identified AHI1 as a positional candidate for SCZ. These authors evaluated the effect of AHI1 variation on the vulnerability to psychosis in two samples from Spain and Germany. 29 SNPs located in a genomic region including the AHI1 gene were genotyped in the Ibero-German sample. rs7750586 and rs911507, both located upstream of the AHI1 coding region, were found to be associated with SCZ in the analysis of genotypic and allelic frequencies. Several other risk and protective haplotypes were also detected. Joint analysis of both ethnic samples supported the association of rs7750586 and rs911507 with the risk for SCZ.

Adenylosuccinate synthase (ADSS) and ataxia telangiectasia (ATM) genes. The blood-derived RNA levels of the adenylosuccinate synthase (ADSS) and ataxia telangiectasia mutated (ATM) genes were found to be down- and up-regulated, respectively, in schizophrenics compared with controls, and ADSS and ATM were among eight biomarker genes to discriminate schizophrenics from normal controls. ADSS catalyzes the first committed step of AMP synthesis, while ATM kinase

serves as a key signal transducer in the DNA double-strand breaks response pathway. Studies with 6 SNPs in the ADSS gene and 3 SNPs in the ATM gene did not show significant difference in the genotype, allele, or haplotype distributions in a Chinese population of SCZ patients. Using the Multifactor Dimensionality Reduction (MDR) method, interactions among rs3102460 in the ADSS gene and rs227061 and rs664143 in the ATM gene revealed a significant association with SCZ with a maximum testing accuracy of 60.4%, suggesting that the combined effects of the polymorphisms in the ADSS and ATM genes may confer susceptibility to the development of SCZ in a Chinese population [56].

Adrenergic alpha-2A, receptor (ADRA2A). Several lines of studies have shown the existence of an important inhibitory mechanism for the control of water intake involving adrenergic alpha-2A receptors. A human study using patients with SCZ demonstrated an exacerbation of polydipsia by the administration of clonidine, an ADRA2A-agonist, and a relief of polydipsia by mianserin, an ADRA2A-antagonist, suggesting the involvement of the central adrenergic system in the drinking behavior of patients with SCZ. Based on these findings Yamaguchi *et al.* [57] examined a possible association between the C-1291G polymorphism in the promoter region of the ADRA2A gene and polydipsia in SCZ using a Japanese case-control sample. No significant association between the ADRA2A C-1291G polymorphism and polydipsia was found [57].

ALDHs and retinoic acid-related genes. Vitamin A (retinol), the biologically active form of retinoic acid, has been proposed as being involved in the pathogenesis of SCZ. 18 SNPs in the regulatory and coding sequences of 7 genes involved in the synthesis, degradation and transportation of retinoic acid, ALDH1A1, ALDH1A2, ALDH1A3, CYP26A1, CYP26B1, CYP26C1 and transthyretin (TTR) have been studied in SCZ. Association analyses using both allelic and genotypic single-locus tests revealed no significant association between the risk for each of these genes and SCZ; however, analyses of multiple-locus haplotypes indicated that the overall frequency of rs4646642-rs4646580 of the ALDH1A2 gene showed a significant difference between patients and control subjects in the Chinese population [58].

Alpha- and beta-synuclein (SNCA, SNCB). Alpha-synuclein is expressed in the CNS. A high concentration of alpha-synuclein in presynaptic terminals can mimic the normal function of endogenous alpha-synuclein in regulating synaptic vesicle mobilization at nerve terminals. Beta-synuclein protein is seen primarily in brain tissue. Beta-synuclein may act as an inhibitor of alpha-synuclein aggregation, which occurs in neurodegenerative diseases, such as Parkinson's disease. Noori-

Daloii *et al.* [59] studied the changes of alpha- and beta-synucleins in SCZ patients in relation to a control group. The relative expression of alpha- and beta-synucleins showed downregulation in patients in comparison to the control group. Beta-synuclein mRNA expression in the control group was significantly higher than that in the patient group, but downregulation of alpha-synuclein gene was not significant.

Angiotensin I converting enzyme (peptidyl-dipeptidase A) 1 (ACE). ACE variants are currently associated with cardiovascular and cerebrovascular risk factors [5,10,11,35]. ACE insertion/deletion polymorphism was also associated with SCZ and BD. DD genotype and D allele distributions in bipolar patients and their first-degree relatives were significantly higher than those of SCZ patients, their relatives, and controls. In contrast, II genotype and I allele were reduced in both the patient groups and their relatives as compared with controls [60].

AP-3 complex genes. Dysbindin is a component of BLOC-1, which interacts with the adaptor protein (AP)-3 complex. Hashimoto *et al.* [61] examined a possible association between 16 SNPs in the AP3 complex genes and SCZ in Japanese patients. Nominal association between rs6688 in the AP3M1 gene and SCZ was initially found, but this association was no longer positive after correction for multiple testing, suggesting that AP3 complex genes might not play a major role in the pathogenesis of SCZ in this population [61].

APOE and cholesterol transport genes. Several studies suggest an accumulation of APOE-4 allele in SCZ [35]. Disturbances in lipid homeostasis and myelination have been proposed in the pathophysiology of SCZ and BD. Several antipsychotic and antidepressant drugs increase lipid biosynthesis through activation of the Sterol Regulatory Element-Binding Protein (SREBP) transcription factors, which control the expression of numerous genes involved in fatty acid and cholesterol biosynthesis. Quantitative PCR and immunoblotting were used to determine the level of lipid transport genes in human glioblastoma (GaMg) exposed to clozapine, olanzapine, haloperidol or imipramine. The effect of some of these drugs was also investigated in human astrocytoma (CCF-STTG1), neuroblastoma (SH-SY5Y) and hepatocellular carcinoma (HepG2) cells. Significant transcriptional changes of cholesterol transport genes (APOE, ABCA1, NPC1, NPC2, NPC1L1), which are predominantly controlled by the liver X receptor (LXR; NR1H2) transcription factor, have been detected. Stimulation of cellular lipid biosynthesis by amphiphilic psychotropic drugs is followed by a transcriptional activation of cholesterol transport and efflux pathways. Such effects may be relevant for both therapeutic effects and metabolic adverse effects of psychotropic drugs [62].

Apoptotic engulfment pathway. Apoptosis has been speculated to be involved in SCZ. The apoptotic engulfment pathway involving the MEGF10, GULP1, ABCA1 and ABCA7 genes has been investigated in SCZ. Nominally significant associations were found in GULP1 (rs2004888), ABCA1 (rs3858075) and ABCA7 genes. A significant 2-marker (rs2242436*rs3858075) interaction between the ABCA1 and ABCA7 genes and a 3-marker interaction (rs246896*rs4522565*rs3858075) amongst the MEGF10, GULP1 and ABCA1 genes were found in different samples. The GULP1 gene and the apoptotic engulfment pathway may be involved in SCZ in subjects of European ancestry and multiple genes in the pathway may interactively increase the risk of the disease [63].

Arginine vasopressin receptor 1A (AVPR1A). Arginine vasopressin (AVP) and the arginine vasopressin receptor 1A gene contribute to memory function and a range of social behaviors both in lower vertebrates and in humans. Human promoter-region microsatellite repeat regions (RS1 and RS3) in the AVPR1a gene region have been associated with autism spectrum disorders, prosocial behavior and social cognition. Prepulse inhibition (PPI) of the startle response to auditory stimuli is a largely autonomic response that resonates with social cognition in both animal models and humans. Reduced PPI has been observed in disorders, including SCZ, which are distinguished by deficits in social skills. Association studies between PPI and the AVPR1a RS1 and RS repeat regions detected association between AVPR1a promoter-region repeat length (especially RS3) and PPI. Longer RS3 alleles were associated with greater levels of prepulse inhibition. Using a short/long classification scheme for the repeat regions, significant association was also observed between all three PPI intervals (30, 60 and 120 ms) and both RS1 and RS3 polymorphisms. Longer alleles, especially in male subjects, are associated with significantly higher PPI response, consistent with a role for the promoter repeat region in partially molding social behavior in both animals and humans [64]. Molecular genetic studies of AVPR1a and oxytocin (OXTR) receptors have strengthened the evidence regarding the role of these two neuropeptides in a range of normal and pathological behaviors. Significant association has been shown between both AVPR1a repeat regions and OXTR SNPs with risk for autism. AVPR1a has also been linked to eating behavior in both clinical and non-clinical groups. Evidence also suggests that repeat variations in AVPR1a are associated with two other social domains in Homo sapiens: music and altruism. AVPR1a was associated with dance and musical cognition, probably reflecting the ancient role of this hormone in social interactions executed by vocalization, ritual movement and dyadic (mother-offspring) and group communication. Individual differences have been observed in allocation of funds in the dictator game, a laboratory game of pure altruism, associated with length of the AVPR1a RS3 promoter-region repeat [65]. Although molecular data are very limited, it might be possible that dysfunctions in these primitive neuropeptides involved in higher activities of the CNS may influence autism/SCZ pathogenesis [66].

Arrestin, beta 2 (ARRB2). Tardive dyskinesia (TD) may be associated with mediators or signaling complexes behind DRD2, such as beta-arrestin-2 (ARRB2), an important mediator between DRD2 and serine-threonine protein kinase (AKT) signal cascade. There is a significant difference in the genotype distribution of ARRB2-rs1045280 (Ser280Ser) between TD and non-TD SCZ groups; and patients with the T allele have increased risk of tardive dyskinesia [67].

BCL2-interacting killer (apoptosis-inducing) (BIK). The Bcl2-interacting killer (BIK) gene interacts with cellular and viral survival-promoting proteins, such as Bcl-2, to enhance apoptosis. The BIK protein promotes cell death in a manner analogous to Bcl-2-related death-promoting proteins, Bax and Bak. Low Bcl-2 levels and increased Bax/Bcl-2 ratio have been found in the temporal cortex of patients with SCZ. The BIK protein is suggested to be a likely target for antiapoptotic proteins. Nominal evidence for association of alleles rs926328 and rs2235316 with SCZ was found in Japanese patients; however, these associations were no longer positive after correction for multiple testing [68].

Biogenesis of lysosome-related organelles complex 1 (BLOC-1). Biogenesis of lysosome-related organelles complex 1 (BLOC-1) is a protein complex formed by the products of eight distinct genes. Loss-of-function mutations in two of these genes, DTNBP1 and BLOC1S3, cause Hermansky-Pudlak syndrome, a human disorder characterized by defective biogenesis of lysosome-related organelles. Haplotype variants within the same two genes have been postulated to increase the risk of developing SCZ. In a fly model of BLOC-1 deficiency, mutant flies lacking the conserved Blos1 subunit displayed eye pigmentation defects due to abnormal pigment granules, which are lysosome-related organelles, as well as abnormal glutamatergic transmission and behavior [69].

Brain-derived neurotrophic factor (BDNF). A variety of evidence suggests brain-derived neurotrophic factor (BDNF) as a candidate gene for SCZ. Several genetic studies have shown a significant association between the disease and certain SNPs within BDNF (specifically, Val66Met and C270T). The functional microsatellite marker BDNF-LCPR (BDNF-linked complex polymorphic region), which affects the expression level of BDNF, is associated with BD. A meta-analysis of the two most extensively studied polymorphisms (Val66Met and C270T) revealed no association in single-marker or multimarker analysis and no association of the Val66Met

polymorphism with SCZ, whereas C270T showed a trend for association in a fixed model, but not in a random model. These findings suggest that if BDNF is indeed associated with SCZ, the A1 allele in BDNF-LCPR would be the most promising candidate [70]. In a Taiwanese population no association was found between the BDNF Val66Met polymorphism and SCZ; however, this polymorphism may reduce psychopathology, in particular negative symptoms [71]. Allelic variation in the BDNF gene has been associated with affective disorders, but generally not SCZ. BDNF variants may help clarify the status of schizoaffective disorder. Patients with schizoaffective disorder and other affective disorders are significantly more likely to carry two copies of the most common BDNF haplotype (containing the valine allele of the Val66Met polymorphism) compared with healthy volunteers. When compared with SCZ patients, individuals with schizoaffective disorder are significantly more likely to carry two copies of the common haplotype [72].

Defective BDNF has been proposed as a candidate pathogenic mechanism in SCZ and dementia. BDNF transcription is regulated during the protracted period of human frontal cortex development. Expression of the four most abundant alternative 5' exons of the BDNF gene (exons I, II, IV, and VI) has been studied in RNA extracted from the prefrontal cortex. Expression of transcripts I-IX and VI-IX was highest during infancy, whereas that of transcript II-IX was lowest just after birth, slowly increasing to reach a peak in toddlers. Transcript IV-IX was significantly upregulated within the first year of life, and was maintained at this level until school age. Quantification of BDNF protein revealed that levels followed a similar developmental pattern as transcript IV-IX. *In situ* hybridization of mRNA in cortical sections showed the highest expression in layers V and VI for all four BDNF transcripts, whereas moderate expression was observed in layers II and III. Although low expression of BDNF was observed in cortical layer IV, this BDNF mRNA low-zone decreased in prominence with age and showed an increase in neuronal mRNA localization. These findings reported by Wong *et al*. [73] show that dynamic regulation of BDNF expression occurs through differential use of alternative promoters during the development of the human prefrontal cortex, particularly in the younger age groups, when the prefrontal cortex is more plastic. Alterations in BDNF processing during brain maturation cannot be neglected as a potential mechanism for prefrontal cortex dysfunction in SCZ. The levels of (pro)BDNF and receptor proteins, TrkB and p75, are altered in the hippocampus in SCZ and mood disorder and polymorphisms in each gene influence protein expression [74].

Neurodegenerative processes may be involved in the pathogenesis of tardive dyskinesia (TD), and a growing body of evidence suggests that BDNF plays a role in both the antipsychotic effects and the pathogenesis of TD. BDNF and glycogen synthase kinase (GSK)-3beta are important in neuronal survival, and thus abnormal regulation of BDNF and GSK-3beta may contribute to TD pathophysiology. Park *et al*. [75] studied the relationship between two polymorphisms, Val66Met in the BDNF coding region and −50T/C in the GSK-3beta promoter, and susceptibility to TD among a matched sample of patients having SCZ with TD, patients with SCZ without TD, and normal control subjects. PCR analysis revealed no significant difference in the occurrence of the polymorphisms among the TD, non-TD, and control subjects, but a significant interaction was observed among the groups possessing BDNF Val allele in compound genotypes. The schizophrenic subjects with the C/C GSK-3beta genotype, who carry the Val allele of the BDNF gene, are expected to have a decreased risk of developing neuroleptic-induced tardive dyskinesia [75].

Bromodomain containing 1 (BRD1). The bromodomain-containing protein 1 (BRD1) gene located at chromosome 22q13.33 has been associated with SCZ and BD susceptibility [76].

Calcium channel, voltage-dependent, L type, alpha 1C subunit (CACNA1C). Strong evidence of association at the polymorphism rs1006737 (within CACNA1C, the gene encoding the alpha-1C subunit of the L-type voltage-gated calcium channel) with the risk of BD has recently been reported in a meta-analysis of three genome-wide association studies of BD. The risk allele also conferred increased risk for SCZ and recurrent major depression with similar effect sizes to those previously observed in BD. These findings are evidence of some degree of overlap in the biological underpinnings of susceptibility to mental illness across the clinical spectrum of mood and psychotic disorders [77]. A recent meta-analysis of five case-control cohorts for major mood disorder, including over 13600 individuals genotyped on high-density SNP arrays performed by the Bipolar Disorder Genome Study (BiGS) Consortium [78] identified SNPs at 3p21.1 associated with major mood disorders (rs2251219), with supportive evidence for association observed in two out of three independent replication cohorts. These results provide another example of a shared genetic susceptibility locus for BD and major depressive disorder [78].

To identify the neural system mechanism that explains the genetic association between the CACNA1C gene and psychiatric illness, Bigos *et al*. [79] used blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) to measure brain activation in circuitries related to bipolar disorder and schizophrenia by comparing CACNA1C genotype groups among healthy subjects. The risk-associated SNP rs1006737 in

CACNA1C predicted increased hippocampal activity during emotional processing and increased prefrontal activity during executive cognition. The risk-associated SNP also predicted increased expression of CACNA1C mRNA in the human brain. The risk-associated SNP in CACNA1C maps to circuitries implicated in genetic risk for bipolar disorder and schizophrenia. According to Bigos and coworkers [79], its effects in human brain expression implicate a molecular and neural system mechanism for the clinical genetic association.

Calreticulin (CALR). Tissue-specific expression of the calreticulin (CALR) gene in the gray matter is development-dependent and coincides with the expression of psychosis phenotypes. Farokhashtiani *et al.* [80] reported instances of mutations within the core promoter sequence of the gene in schizoaffective disorder. A unique mutation at nucleotide −220 from the transcription start site, located at a conserved genomic block in the promoter region of the gene, co-occurs with the spectrum of psychoses. This mutation reverts the human promoter sequence to the ancestral type observed in chimpanzee, mouse, and several other species, implying that the genomic block harboring nucleotide −220 may be involved in the evolution of human-specific higher-order functions of the brain that are ubiquitously impaired in psychoses.

Cannabinoid receptors. Two endocannabinoid receptors, CB1 and CB2 (CNR1, CNR2), are found in the brain. The R63 allele of rs2501432 (R63Q), the C allele of rs12744386 and the haplotype of the R63-C allele of CB2 were significantly increased among patients with SCZ. A significantly lower response to CB2 ligands in cultured CHO cells transfected with the R63 allele compared with those with Q63, and significantly lower CB2 receptor mRNA and protein levels found in human brain with the CC and CT genotypes of rs12744386 compared with TT genotype were observed. Endocannabinoid function appears to be involved in SCZ. An increased risk of SCZ might be present in people with low CB2 receptor function [81].

Cathepsin K (CTSK). Recent studies associate cathepsin K with SCZ. Cathepsin K is capable of liberating Met-enkephalin from beta-endorphin (beta-EP) *in vitro*. To verify if this process might possibly contribute to the pathogenesis of SCZ, *post-mortem* brains were analyzed immunohistochemically for the presence and co-localization of cathepsin K and beta-EP. In support of a functional role of the observed formation of Met-enkephalin on the expense of beta-EP, increased numbers of cathepsin K immunoreactive cells, but diminished numbers of both beta-EP-positive cells and double-positive (cathepsin K/beta-EP) cells, were found in left and right arcuate nucleus of schizophrenics. A reduced density of beta-EP-immunoreactive neuropil (fibers, nerve

terminals) was estimated in the left and right paraventricular nucleus (PVN) of individuals with SCZ. Cathepsin K, which becomes up-regulated in its cerebral expression by neuroleptic treatment, might significantly contribute to altered opioid levels in brains of schizophrenics [82].

Cholecystokinin A receptor gene. Cholecystokinin A receptor (CCKAR) has been implicated in the pathophysiology of SCZ through its mediation of dopamine-release in the CNS. Association between the CCKAR gene and SCZ has been observed, especially between the 779T/C polymorphism and auditory hallucinations or positive symptoms of SCZ. In the Japanese population, no significant difference was observed in genotypic distributions or allelic frequencies between SCZ and controls, although there was a trend for the association between the C allele of the polymorphism and hallucination or hallucinatory-paranoid state [83].

Cholinergic receptor, nicotinic, alpha 7 (CHRNA7). Multiple genetic linkage studies support the hypothesis that the 15q14 chromosomal region contributes to the etiology of SCZ. Among the putative candidate genes in this area are the alpha7 nicotinic acetylcholine receptor gene (CHRNA7) and its partial duplication, CHRFAM7A. A large chromosomal segment including the CHRFAM7A gene locus, but not the CHRNA7 locus, is deleted in some individuals. The CHRFAM7A gene contains a polymorphism consisting of a 2 base pair (2 bp) deletion at position 497 - 498 bp of exon 6. The 2 bp polymorphism was associated with SCZ in African-Americans and in Caucasians [84]. The rs3087454 SNP, located at position −1831 bp in the upstream regulatory region of CHRNA7, was significantly associated with SCZ in African-American and non-Hispanic Caucasian case-control samples [85].

CLOCK. The clock genes have been reported to play some roles in neural transmitter systems, including the dopamine system, as well as to regulate circadian rhythms. Abnormalities in both of these mechanisms are thought to be involved in the pathophysiology of major mental illness such as SCZ and mood disorders including BP and major depressive disorder (MDD). Recent genetic studies have reported that CLOCK, one of the clock genes, might be associated with these psychiatric disorders; however, association of CLOCK with SCZ might be weak [86].

Clusterin (CLU). Clusterin (CLU) and clathrin assembly lymphoid myeloid (CALM; PICALM) protein are implicated in the function of neuronal synapses. Zhou *et al.* [87] examined whether SNPs rs11136000 within the CLU gene and rs3851179 within the CALM gene, were associated with SCZ in the Chinese population. Patients with SCZ and with family history showed a significant increase of allele C frequency in rs11136000 in

comparison to normal controls. The C allele frequency was also higher in patients with negative symptoms. In contrast, allele and genotype frequencies of rs3851179 did not show significant differences between patients and normal subjects or between patients with different symptoms.

CMYA5 (Cardiomyopathy-associated protein 5; myosprym; tripartite motif-containing protein 76, TRIM76). Chen *et al.* [88] found that in the CMYA5 gene, there were two non-synonymous markers, rs3828611 and rs10043986, showing nominal significance in both the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and MGS-GAIN (molecular genetics of schizophrenia genome-wide association study supported by the genetic association information network) samples. In a combined analysis of both the CATIE and MGS-GAIN samples, rs4704591 was identified as the most significant marker in the gene. Linkage disequilibrium analyses indicated that these markers were in low LD. CMYA5 was reported to be physically interacting with the DTNBP1 gene, a promising candidate for schizophrenia, suggesting that CMYA5 may be involved in the same biological pathway and process. In a meta-analysis of all 23 replication samples (family samples, 912 families with 4160 subjects; case-control samples, 11380 cases and 15021 controls), the authors found that the rs10043986 and rs4704591 markers are significantly associated with SCZ. Haplotype conditioned analyses indicated that the association signals observed at these two markers are independent.

CNP. 2',3'-Cyclic nucleotide 3'-phosphodiesterase (CNP), another candidate gene for SCZ, participates in oligodendrocyte function and in myelination. Five CNP SNPs were investigated in a Chinese Han SCZ case-control sample set with negative results. Factors including gender, genotype, sub-diagnosis and antipsychotic treatment were found not to contribute to the expression regulation of the CNP gene in SCZ [89].

CNTNAP2, NRXN1, and the neurexin superfamily. Heterozygous copy-number variants and SNPs of CNTNAP2 and NRXN1, two distantly related members of the neurexin superfamily, have been repeatedly associated with a wide spectrum of neuropsychiatric disorders, such as developmental language disorders, autism spectrum disorders, epilepsy, and SCZ. Homozygous and compound-heterozygous deletions and mutations via molecular karyotyping and mutational screening in CNTNAP2 and NRXN1 were identified in four patients with severe mental retardation and variable features, such as autistic behavior, epilepsy, and breathing anomalies, phenotypically overlapping with Pitt-Hopkins syndrome. With a frequency of at least 1%, recessive defects in CNTNAP2 appear to contribute significantly to severe mental retardation. As known for fly Nrx-1, the CASPR2

ortholog Nrx-IV might also localize to synapses. Overexpression of either protein can reorganize synaptic morphology and induce increased density of active zones, the synaptic domains of neurotransmitter release. Both Nrx-I and Nrx-IV determine the level of the presynaptic active-zone protein bruchpilot, indicating a possible common molecular mechanism in Nrx-1 and Nrx-IV mutant conditions [90].

Complexin-2. Because synaptic dysfunction plays a key role in SCZ, the complexin 2 gene (CPLX2) was examined by Begemann *et al.* [91] in the first phenotype-based genetic association study (PGAS) of GRAS (Göttingen Research Association for Schizophrenia). Six SNPs, distributed over the whole CPLX2 gene, were found to be highly associated with current cognition of schizophrenic subjects but only marginally with premorbid intelligence. Correspondingly, in CPLX2-null mutant mice, prominent cognitive loss of function was obtained only in combination with a minor brain lesion applied during puberty. In the human CPLX2 gene, 1 of the identified 6 cognition-relevant SNPs, rs3822674 in the 3' untranslated region, was detected to influence microRNA-498 binding and gene expression. The same marker was associated with differential expression of CPLX2 in peripheral blood mononuclear cells. Results extracted from this study suggest that cognitive performance in schizophrenic patients may be modified by CPLX2 variants modulating post-transcriptional gene expression.

COMT. The catechol-O-methyltransferase (COMT) gene, which is located in the 22q11.21 microdeletion, has been considered as a candidate gene for SCZ due to its ability to degrade catecholamines, including dopamine. Human COMT contains three common polymorphisms (A22S, A52T, and V108M), two of which (A22S and V108M) render the protein susceptible to deactivation by temperature or oxidation. The A52T mutation had no significant effect on COMT structure. Residues 22 (alpha2) and 108 (alpha5) interact with each other and are located in a polymorphic hotspot approximately 20 Å from the active site. Introduction of either the larger Ser (22) or Met (108) tightens this interaction, pulling alpha2 and alpha5 toward each other and away from the protein core. The V108M polymorphism rearranges active-site residues in alpha5, beta3, and alpha6, increasing the S-adenosylmethionine site solvent exposure. The A22S mutation reorients alpha2, moving critical catechol-binding residues away from the substrate-binding pocket. The A22S and V108M polymorphisms evolved independently in Northern European and Asian populations. While the decreased activities of both A22S and V108M COMT are associated with an increased risk for SCZ, the V108M-induced destabilization is also linked with improved cognitive function. Polymorphisms within this

hotspot may have evolved to regulate COMT activity, and heterozygosity for either mutation may be advantageous [92].

A common functional polymorphism (Val/Met) in COMT that markedly affects enzyme activity has been shown to affect executive cognition and the physiology of the prefrontal cortex in humans. The high activity Val allele slightly increases risk for SCZ through its effect on dopamine-mediated prefrontal information processing. The Val/Met polymorphism has become the most widely studied polymorphism in psychiatry [93]. No statistically significant differences were found in allele or genotype frequencies between patient and normal control subjects, although a nonsignificant over-representation of the Val allele has been detected in Han Chinese patients with SCZ. The meta-analysis of all published population-based association studies showed statistically significant evidence for heterogeneity among the group of studies. Stratification of the studies by ethnicity of the samples yielded no significant evidence for an association with the Val allele in the Asian population [94,95].

The functional SNP Val108/158Met (rs4680) and haplotypes rs737865-rs4680-rs165599 in COMT have been extensively examined for association to SCZ; however, results of replication studies have been inconsistent. Okochi *et al.* [96] performed a mutation scan to detect the existence of potent functional variants in the 5'-flanking and exon regions, and conducted a gene-based case-control study between tagging SNPs in COMT [19 SNPs including six possible functional SNPs (rs2075507, rs737865, rs4680, rs165599, rs165849)] and SCZ in the Japanese population. A meta-analysis of 5 functional SNPs and haplotypes (rs737865-rs4680-rs165599) was also carried out. No novel functional variant was detected in the mutation scan and no association was found between these tagging SNPs in COMT and Japanese SCZ. No evidence was found for an association between Val108/158Met polymorphisms, rs6267, rs165599, and haplotypes (rs7378655-rs4680-rs165599) and SCZ, although rs2075507 and rs737865 showed trends for significance in allele-wise analyses [96].

COMT impacts the regulation of dopamine neuronal activity in the brainstem, which is associated with psychosis [97]. The rs362204 polymorphism shows association with SCZ in different populations [97,98] and rs6267 showed an association with reduced risk of SCZ [99]. There is an association between the COMT gene and violent behavior in Chinese schizophrenics. The haplotypes A-A-G and G-G-A may be used to predict violent behavior in schizophrenics [100]. COMT genotype contributes to cognitive flexibility, a fundamental cognitive ability that potentially influences an individual's performance in a variety of other neurocognitive tasks. COMT genotype was significantly associated with

signal discrimination index d' in SCZ. The Val/Val genotype was associated with the highest and the Met/Met genotype with the lowest scores; heterozygous individuals displayed an intermediate performance [101]. The [oxy-Hb] increase in the Met carriers during the verbal fluency task was significantly greater than that in the Val/Val individuals in the frontopolar prefrontal cortex of patients with SCZ, although neither medication nor clinical symptoms differed significantly between the two subgroups [102].

The Val108/158Met (rs4680) SNP in the COMT gene is specifically related to impairments in executive functioning. A different genomic region composed of three SNPs (rs737865, rs4680, rs165599) within the COMT gene has been reported to be significantly associated with SCZ in Ashkenazi Jews, but not in other populations. In the Taiwanese population, the A allele of rs165599 was transmitted preferentially to the affected individuals, and significantly associated with a later age of onset, more severe delusion/hallucination symptom dimension, and poorer performance in the CPT. The triple SNP haplotypes did not reveal any significant association with SCZ or neurocognitive function [103]. According to these results, the SNP rs165599, which has been mapped to the 3'-UTR region of the COMT gene, was significantly associated with SCZ, and possibly associated with the age of onset, delusion/hallucination symptom dimension, and CPT performance. Therefore, COMT may contribute to the genetic risk for SCZ not through the Val108/158Met polymorphism, but through other variants that are situated 3' to this region [103].

Liao *et al.* [104] examined the relations of genetic variants in COMT, including rs737865 in intron 1, rs4680 in exon 4 (Val158Met) and downstream rs165599, to SCZ and its related neurocognitive functions in families of patients with SCZ. The genotypes of rs4680 were associated with both the Wisconsin Card Sorting Test (WCST) and Continuous Performance Test (CPT) performance scores in these families, but not with SCZ *per se* in either whole sample or subgroup analyses. The other two SNPs were differentially associated with the two tasks. For WCST indexes, only rs737865 exhibited moderate associations. For CPT indexes, rs737865 exhibited association for the subgroup with deficit on CPT reaction time, whereas rs165599 exhibited association for the subgroup with deficit on CPT d' as well as quantitative undegraded d'. These results suggest that COMT variants might be involved in modulation of neurocognitive functions, conferring increased risk for SCZ [104].

Some studies revealed potential epistatic effects of two intronic SNPs located in the COMT and aldehyde dehydrogenase 3B1 (ALDH3B1) genes, which conferred genetic risk to paranoid SCZ. Among the individuals carrying the rs3751082 A allele in the ALDH3B1 gene, the

rs4633 T allele in the COMT gene was associated with susceptibility to paranoid SCZ, development of hallucination, delay of P300 latency, and increased expression of the COMT gene; however, the rs4633 T allele did not show any association in the rs3751082 G/G genotype carriers [105].

CSF2RB (Colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)). CSF2RB encodes the protein which is the common β chain of the high affinity receptor for IL-3, IL-5 and CSF. It locates in the linkage region 22q13.1 of both bipolar disorder and SCZ, and is expressed in most cells. Chen *et al.* [106] carried out a large-scale case-control study to test the association between CSF2RB and three major mental disorders in the Chinese Han population. Seven SNPs were genotyped in 1140 bipolar affective disorder patients (including 645 type I bipolar affective disorder patients), 1140 schizophrenia patients, 1139 major depressive disorder patients and 1140 healthy controls. Three SNPs were found to be associated with both SCZ and major depressive disorder. Haplotype association analysis revealed one protective haplotype for SCZ and for MDD and one risk haplotype for SCZ and for MDD. These results support CSF2RB as a risk factor common to both SCZ and major depression in the Chinese Han population.

CTLA4 (Cytotoxic T-lymphocyte-associated protein 4). Some studies have reported that the cytotoxic T lymphocyte antigen-4 (CTLA-4) gene, which is related to immunological functions such as T-cell regulation, is associated with psychiatric disorders. Liu *et al.* [107] studied the relationship between CTLA-4 and three major psychiatric disorders, SCZ, major depressive disorder and bipolar disorder in the Chinese Han population. They screened 6 tag SNPs (rs231777, rs231775, rs231779, rs3087243, rs5742909, rs16840252) in the CTLA-4 gene, and found that rs231779 conferred a risk for SCZ, major depressive disorder, and bipolar disorder. rs231777 and rs16840252 had a significant association with SCZ, and rs231777 had significant association with bipolar disorder; however, after 10000 permutations, only rs231779 remained significant. These results led the Chinese authors to conclude that shared common risk factors for SCZ, major depressive disorder and bipolar disorder exist in the CTLA-4 gene in the Chinese Han population.

CYP3A4 and CYP3A5. Two-marker haplotypes covering components CYP3A41G and CYP3A53 were observed to be significantly associated with SCZ in Chinese patients [108].

D-Amino acid oxidase activator (DAOA, G72). The DAOA gene locus on chromosome 13q34 has been implicated in the etiology of SCZ. 3 SNPs (rs778294, rs779293 and rs3918342) have been identified in this region, and two of them (rs778293, rs3918342) have shown significant transmission disequilibrium and a highly significant under-transmission between haplotype CAT and SCZ. G72 is one of the most widely tested genes for association with SCZ. As G72 activates the D-amino acid oxidase (DAO), G72 is termed D-amino acid oxidase activator (DAOA). Ohi *et al.* [109] found nominal evidence for association of alleles M22/rs778293, M23/rs3918342 and M24/rs1421292, and the genotype of M22/rs778293 with SCZ, although there was no association of allele or genotype in the other five SNPs. They also found nominal haplotypic association, including M15/rs2391191 and M19/rs778294, with SCZ; however, these associations were no longer positive after correction for multiple testing, which suggests that G72 might not play a major role in the risk for SCZ in the Japanese population [109]. Association of the G72/G30 locus with SCZ and BD has been reported in several studies. The G72/G30 locus spans a broad region of chromosome 13q. One meta-analysis of published association studies shows highly significant evidence of association between nucleotide variations in the G72/ G30 region and SCZ, along with compelling evidence of association with BD [110]. This locus has been associated with panic disorder, SCZ, and BD, especially the 3 SNPs rs2391191, rs3918341, and rs1935062, with controversial results [111]. G72 is an activator of D-amino acid oxidase (DAO), supporting the glutamate dysfunction hypothesis of SCZ. G72 mRNA is poorly expressed in a variety of human tissues (e.g. adult brain, amygdala, caudate nucleus, fetal brain, spinal cord and testis) from human cell lines or SCZ/control *post-mortem* BA10 samples. The lack of demonstrable G72 expression in relevant brain regions does not support a role for G72 in modulation of DAO activity and the pathology of SCZ via a DAO-mediated mechanism. *In silico* analysis suggests that G72 is not robustly expressed and that the transcript is potentially labile [112].

Disrupted-in-schizophrenia-1 (DISC1). The disrupted-in-schizophrenia-1 (DISC1) locus is located at the breakpoint of a balanced t (1;11) (q42.1; q14.3) chromosomal translocation in a large and unique Scottish family. This translocation segregates in a highly statistically significant manner with a broad diagnosis of psychiatric illness, including SCZ, BD and major depression, as well as with a narrow diagnosis of SCZ alone. Two novel genes were identified at this locus and due to the high prevalence of SCZ in this family, they were named disrupted-in-schizophrenia-1 (DISC1) and disrupted-inschizophrenia-2 (DISC2). DISC1 encodes a novel multifunctional scaffold protein, whereas DISC2 is a putative noncoding RNA gene antisense to DISC1. A number of independent genetic linkage and association studies in diverse populations support the original linkage findings in the Scottish family and genetic evidence now impli-

cates the DISC locus in susceptibility to SCZ, schizoaffective disorder, BD and major depression as well as various cognitive traits. DISC1 is a hub protein in a multidimensional risk pathway for major mental illness [113]. Many alternatively spliced transcripts were identified, including groups lacking exon 3 (Delta3), exons 7 and 8 (Delta7Delta8), an exon 3 insertion variant (extra short variant-1, Esv1), and intergenic splicing between TSNAX and DISC1. Isoforms Delta7Delta8, Esv1, and Delta3, which encode truncated DISC1 proteins, were expressed more abundantly during fetal development than during postnatal ages, and their expression was higher in the hippocampus of patients with SCZ. SCZ risk-associated polymorphisms [non-synonymous SNPs rs821616 (Cys704Ser) and rs6675281 (Leu607Phe), and rs821597] were associated with the expression of Delta3 and Delta7Delta8 [114]. An inherited 2.07 Mb microduplication in 1q42.2 was identified in two brothers with autism and mild mental retardation in Belgium. The duplication contains seven genes, including the DISC1 gene which has been associated to SCZ, BD, autism and Asperger syndrome [115]. DISC1 regulates neuronal migration and differentiation during mammalian brain development. Enomoto *et al.* [116] reported that DISC1 interacts with the actin-binding protein girdin to regulate axonal development. Dentate granule cells (DGCs) in girdin-deficient neonatal mice exhibit deficits in axonal sprouting in the cornu ammonis 3 region of the hippocampus. Girdin deficiency, RNA interference-mediated knockdown, and inhibition of the DISC1/girdin interaction lead to overextended migration and mispositioning of the DGCs resulting in profound cytoarchitectural disorganization of the DG. These findings identify girdin as an intrinsic factor in postnatal development of the DG and provide insights into the critical role of the DISC1/girdin interaction in postnatal neurogenesis in the DG. DISC1 suppression in newborn neurons of the adult hippocampus leads to overactivated signaling of AKT, another SCZ susceptibility gene. Mechanistically, DISC1 directly interacts with KIAA1212, an AKT-binding partner that enhances AKT signaling in the absence of DISC1, and DISC1 binding to KIAA1212 prevents AKT activation *in vitro*. Multiple genetic manipulations to enhance AKT signaling in adult-born neurons *in vivo* exhibit similar defects to DISC1 suppression in neuronal development, which can be rescued by pharmacological inhibition of mammalian target of rapamycin (mTOR), an AKT downstream effector. The AKT-mTOR signaling pathway acts as a critical DISC1 target in regulating neuronal development [117].

To elucidate how DISC1 confers susceptibility to psychiatric disorders, identification of the molecules, which bind to the domain close to the translocation breakpoint in the DISC1 gene, was performed and fasciculation and elongation protein zeta-1 (Fez1), a novel DISC1-interacting protein, termed DISC1-binding zinc-finger protein (DBZ), and Kendrin were identified. The DISC1-Fez1 interaction is up-regulated by nerve growth factor (NGF) and involved in neurite extension. Transient dissociation of the DISC1-DBZ interaction by pituitary adenylate cyclase-activating polypeptide (PACAP) causes neurite extension. SNP association studies have shown the relation of the Fez1, PACAP and PACAP receptor (PAC1) genes to SCZ. In SCZ with DISC1 translocation carrier, the DISC1-Fez1 and DISC1-DBZ interaction is disrupted, and it is likely that neural circuit formation remains immature, suggesting that SCZ is a neurodevelopmental disease. The DISC1-Kendrin interaction is suggested to be involved in microtubule network formation and an association between SNPs of the Kendrin gene and bipolar disease has also been suggested in a Japanese population [118].

DISC1 interacts directly with phosphodiesterase 4B (PDE4B), an independently identified risk factor for SCZ. DISC1-PDE4B complexes are therefore likely to be involved in molecular mechanisms underlying psychiatric illness. PDE4B hydrolyzes cAMP, and DISC1 may regulate cAMP signaling through modulating PDE4B activity. There is evidence that expression of both genes is altered in some psychiatric patients. DISC1 missense mutations that give rise to phenotypes related to SCZ and depression in mice are located within binding sites for PDE4B. These mutations reduce the association between DISC1 and PDE4B, and one results in reduced brain PDE4B activity. Altered DISC1-PDE4B interaction may thus underlie the symptoms of some cases of SCZ and depression [119]. DISC1 protein binding partners include the nuclear distribution factor E homologs (NDE1 and NDEL1), LIS1, and phosphodiesterases 4B and 4D (PDE4B and PDE4D). NDE1, NDEL1 and LIS1, together with their binding partner dynein, associate with DISC1, PDE4B and PDE4D within the cell, and provide evidence that this complex is present at the centrosome. LIS1, NDEL1, DISC1, NDE1, and PDE4B are localized at synapses in cultured neurons. NDE1 is phosphorylated by cAMP-dependent protein kinase A (PKA), whose activity is, in turn, regulated by the cAMP hydrolysis activity of phosphodiesterases, including PDE4. DISC1 might act as an assembly scaffold for all of these proteins and the NDE1/NDEL1/LIS1/dynein complex might be modulated by cAMP levels via PKA and PDE4 [120].

A DISC1 haplotype, HEP3, and an NDE1 spanning tag haplotype are associated with SCZ in Finnish families. Tomppo *et al.* [121] identified three SNPs as being associated with SCZ in PDE4D (rs1120303), PDE4B (rs7412571), and NDEL1 (rs17806986). Greater significance was observed with allelic haplotypes of PDE4D, PDE4B, and NDEL1 that increased or decreased SCZ

susceptibility, highlighting the potential importance of DISC1-related molecular pathways in the etiology of SCZ and other major mental illnesses [121].

DISC1 is expressed in cranial neural crest (CNC) cells. Loss of Disc1 resulted in persistent CNC cell medial migration, dorsal to the developing neural epithelium, and hindered migration away from the region dorsal to the neural rod. The failure of CNC cells to migrate away from the neural rod correlated with the enhanced expression of two transcription factors, foxd3 and sox10. These transcription factors have many functions in CNC cells, including the maintenance of precursor pools, timing of migration onset, and the induction of cell differentiation. DISC1 functions in the transcriptional repression of foxd3 and sox10, thus mediating CNC cell migration and differentiation [122].

DISC1 is widely expressed in cortical and limbic regions. Association between the DISC1 Ser704Cys polymorphism and volumetric measurements for a broad range of fronto-parietal, temporal, and limbic-paralimbic regions was studied in Japanese patients with SCZ using magnetic resonance imaging. The Cys carriers had significantly larger volumes of the medial superior frontal gyrus and shorter insular cortex than the Ser homozygotes, but only in healthy comparison subjects. The Cys carriers tended to have a smaller supramarginal gyrus than the Ser homozygotes in SCZ patients, but not in healthy comparison subjects. The right medial superior frontal gyrus volume was significantly correlated with daily dosage of antipsychotic medication in Ser homozygote SCZ patients. These different genotype effects of the DISC1 Ser704Cys polymorphism on the brain morphology in SCZ suggest that variation in the DISC1 gene might be involved in the neurobiology of SCZ [123]. Schumacher *et al.* [124] found evidence for a common SCZ risk interval within DISC1 intron 4 - 6.

DNA methyltransferases (DNMTs). Aberrant DNA methylation may be involved in the development of SCZ. DNA methyltransferase 3B (DNMT3B) is the key methyltransferase in DNA methylation regulations. Case-control and family-based studies were performed through genotyping two tag SNPs (rs2424908 and rs6119954) covering the whole DNMT3B gene. The frequency of G allele of rs6119954 was significantly higher in SCZ. Genotype distribution of rs6119954 was significantly different between patients and controls. A haplotype-wise analysis revealed a higher frequency of the T-G (rs2424908-rs6119954) haplotype in SCZ. In the transmission disequilibrium test analysis, the G allele of rs6119954 was preferentially transmitted in the trios. According to these findings reported by Zhang *et al.* [125] in Chinese patients, DNMT3B may be a candidate gene for susceptibility to early onset SCZ. In SCZ, a

functional downregulation of the prefrontal cortex GABAergic neuronal system is mediated by a promoter hypermethylation, presumably catalyzed by an increase in DNA-methyltransferase-1 (DNMT-1) expression. This promoter hypermethylation may be mediated not only by DNMT-1 but also by an entire family of *de novo* DNA-methyltransferases, such as DNA-methyltransferase-3a (DNMT-3a) and -3b (DNMT-3b). There is an overexpression of DNMT-3a and DNMT-3b in Brodmann's area 10 (BA10) and in the caudate nucleus and putamen of SCZ brains. DNMT-3a and DNMT-1 are expressed and co-localize in distinct GABAergic neuron populations whereas DNMT-3b mRNA is virtually undetectable. Unlike DNMT-1, which is frequently overexpressed in telencephalic GABAergic neurons of SCZ, DNMT-3a mRNA is overexpressed only in layer I and II GABAergic interneurons of BA10. DNMT-1 and DNMT-3a mRNAs are also overexpressed in peripheral blood lymphocytes of SCZ patients. The upregulation of DNMT-1 and to a lesser extent that of DNMT-3a mRNA in lymphocytes of SCZ supports the concept that this readily available peripheral cell type can express an epigenetic variation of specific biomarkers relevant to SCZ morbidity [126].

Dopamine-Related Genes

DARPP-32 (PPP1R1B). Recent findings have highlighted the importance of DARPP-32 (dopamine- and cAMP-regulated phosphoprotein, 32 kDa), a key regulatory molecule in the dopaminergic signaling pathway for dopamine-related phenoltypes such as antisocial behavior, drug addiction and SCZ. Reuter *et al.* [127] reported the first study investigating the role of the DARPP-32 gene for personality. In a sample of healthy German Caucasian subjects they found a significant association between rs907094 and anger. Carriers of the T-allele showed significantly higher anger scores than participants without a T-allele. A negative association between ANGER scores and the volume of the left amygdala was also detected [127].

Dopamine beta-hydroxylase. The SNP rs1108580 A/G in DBH has been associated with SCZ [98].

Dopamine transporter (DAT; SLC6A3) 3' UTR VNTR. Dopamine has a crucial role in the modulation of neurocognitive function, and synaptic dopamine activity is normally regulated by the dopamine transporter (DAT) and catechol-O-methyltransferase (COMT). Altered dopamine function is a key pathophysiological feature of SCZ. Prata *et al.* [128] examined epistasis between the DAT 3' UTR variable number of tandem repeats (VNTR) and

COMT Val158Met polymorphisms on brain activation during executive function in SCZ. There was a significant COMT × DAT non-additive interaction effect on activation in the left supramarginal gyrus. In this region, relatively increased activation was detected only when COMT Met-158/Met-158 subjects also carried the 9-repeat DAT allele, or when, reversely, Val-158/Val-158 subjects carried the 10/10-repeat genotype. There was also a significant diagnosis × COMT × DAT non-additive interaction in the right orbital gyrus. Greater activation was only associated with a 9-repeat allele and Val-158 conjunction, and with a 10-repeat and Met-158 conjunction. COMT and DAT genes interact non-additively to modulate cortical function during executive processing, and this effect is significantly altered in SCZ, which may reflect abnormal dopamine function in the disorder [128]. The dopamine transporter plays a key role in the regulation of central dopaminergic transmission, which modulates cognitive processing. The effect of a polymorphism in the dopamine transporter gene (the variable number of tandem repeats in the 3' untranslated region) (3'UTR VNTR) on brain function during executive processing has been studied in healthy volunteers and patients with SCZ. The 10-repeat allele was associated with greater activation than the 9-repeat allele in the left anterior insula and right caudate nucleus. Insular, cingulate, and striatal function during an executive task is normally modulated by variation in the dopamine transporter gene. Its effect on activation in the dorsolateral prefrontal cortex and ventral striatum is altered in patients with SCZ. This may reflect altered dopamine function in these regions in SCZ [129].

Dopamine receptor D$_2$ (DRD2). 16 Polymorphisms from three genes, dopamine receptor D$_2$ (DRD2), COMT and BDNF, which are involved in the dopaminergic pathways, and which have been reported to be associated with susceptibility to SCZ and response to antipsychotic therapy, were investigated in SCZ. Initial significant associations of two SNPs for DRD2 (rs11608185, rs6275), and one SNP in the COMT gene (rs4680) were found, but not after correction for multiple comparisons, indicating a weak association of individual markers of DRD2 and COMT with SCZ. Multifactor-dimensionality reduction analysis suggested a two-loci model (rs6275/DRD2 and rs4680/COMT) as the best model for gene-gene interaction with 90% cross-validation consistency and 42.42% prediction error in predicting disease risk among SCZ patients [130].

Dopamine D$_4$ receptor (DRD4). Associations have been reported between the variable number of tandem repeat (VNTR) polymorphisms in exon 3 of the dopamine D$_4$ receptor (DRD4) gene and multiple psychiatric illnesses/traits. The size of allele "7R" is less frequent (0.5%) in Japanese than in Caucasian populations (20%). The most common 4R variant is considered to be the ancestral haplotype. In a gene tree of VNTR constructed on the basis of this inferred ancestral haplotype, the allele 7R has five descendent haplotypes in relatively long lineage, where genetic drift can have major influence. No evidence of association between the allele 7R and SCZ was found in the Japanese population [131]. Tardive dyskinesia (TD) is a side-effect of chronic antipsychotic medication exposure. Abnormalities in dopaminergic activity in the nigro-striatal system have most often been suggested to be involved because the agents that cause TD share in common potent antagonism of dopamine D$_2$ receptors (DRD2). A number of studies have focused on the association of dopamine system gene polymorphisms and TD, with the most consistent findings being an association between TD and the Ser9Gly polymorphism of the DRD3 gene and the TaqIA site 3' of the DRD2 gene. A haplotype containing rs3732782, rs905568, and rs7620754 in the 5' region of DRD3 was associated with TD diagnosis [132]. The DRD4 gene codes for the third member of the D$_2$-like dopamine receptor family, and the VNTR polymorphism in exon 3 of DRD4 has been associated with TD. Although the exon 3 variable number tandem repeat was not associated with TD, haplotypes consisting of four tag polymorphisms were associated with TD in males, suggesting DRD4 may be involved in TD in the Caucasian population [133].

Tyrosine hydroxylase (TH). Tyrosine hydroxylase (EC 1.14.16.2) is involved in the conversion of phenylalanine to dopamine. As the rate-limiting enzyme in the synthesis of catecholamines, tyrosine hydroxylase has a key role in the physiology of adrenergic neurons. The TH variant rs6356 A/G has been associated with SCZ [98].

Dystrobrevin binding protein 1 (DTNBP1) and dysbindin. Dystrobrevin binding protein 1, a gene encoding dysbindin protein, is a susceptibility gene for SCZ identified by family-based association analysis. A large number of independent studies have reported evidence for association between the dysbindin gene (DTNBP1) and SCZ. Up to 14 SNPs spanning the DTNBP1 locus may show association with SCZ in different studies [134]; however, a high-resolution melting

analysis (HRMA) to screen the 11 DTNBP1 exons with their corresponding DNA variants in a sample from the UK revealed no significant associations with SCZ [135]. DTNBP1 and MUTED encode proteins that belong to the endosome-localized biogenesis of lysosome-related organelles complex-1 (BLOC-1). BLOC-1 plays a key role in endosomal trafficking and as such has been found to regulate cell-surface abundance of the D_2 dopamine receptor, the biogenesis and fusion of synaptic vesicles, and neurite outgrowth. These functions are pertinent to both neurodevelopment and synaptic transmission, processes tightly regulated by selective cell-surface delivery of membrane proteins to and from endosomes. It has been proposed that cellular processes, such as endosomal trafficking, act as convergence points in which multiple small effects from polygenic genetic polymorphisms accumulate to promote the development of SCZ [136]. BLOC-1 physically interacts with the adaptor protein AP-3 complex, which is essential for vesicle or protein sorting. Dysbindin forms a complex with the AP-3 complex through the direct binding to its μ subunit. Dysbindin partially co-localized with the AP-3 complex in CA1 and CA3 of mouse hippocampus, and at presynaptic terminals and axonal growth cones of cultured hippocampal neurons. Suppression of dysbindin results in the reduction of presynaptic protein expression and glutamate release. Thus, dysbindin appears to participate in the exocytosis or sorting of the synaptic vesicle via direct interaction with the AP-3 complex [137]. Dysbindin is involved in the exocytosis and/or formation of synaptic vesicles. Proteins involved in protein localization process, including Munc18-1, were identified as dysbindin-interacting proteins [138]. A three-marker C-A-T dysbindin haplotype is associated with increased risk for SCZ, decreased mRNA expression, reduced gray matter volume in both the right dorsolateral prefrontal and left occipital cortex, poorer cognitive performance, and early sensory processing deficits [139]. 4 SNPs (rs3213207, rs1011313, rs760761, and rs2619522) have been genotyped in a large Korean SCZ sample. Haplotype analyses revealed a significant association with SCZ with the haplotypes A-C-C-C and A-C-T-A having an eminent protective effect toward SCZ. The major contribution to the difference in the haplotype distribution between patients and the controls was the rs760761 (C/T) and rs2619522 (A/C) haplotypes. No association of DTNBP1 with other clinical variables was found. This study suggests a possible protective effect of rare DTNBP1 variants in SCZ [140]. Recent studies suggest a degree of overlap in genetic susceptibility across the traditional categories of SCZ and BD. DTNBP1 has also become a focus of investigation in BD. Seven DTNBP1 SNPs: rs2743852 (SNP C), rs760761 (P1320), rs1011313 (P1325), rs3213207 (P1635), rs2619539 (P1655), rs16876571 and rs17470454,

were investigated using the SNPlex genotyping system. Significant differences in genotypic and allelic frequencies of rs3213207 and rs760761 of DTNBP1 were found between bipolar patients and controls, as well as a global haplotypic association and an association of a particular haplotype with BD [141].

ErbB4 (v-Erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)). ErbB4 is a growth factor receptor tyrosine kinase essential for neurodevelopment. Genetic variation in ErbB4 is associated with SCZ. Risk-associated polymorphisms predict overexpression of ErbB4 CYT-1 isoforms in the brain of schizophrenic patients. The molecular mechanism of association is unclear because the polymorphisms flank exon 3 of the gene and reside 700 kb distal to the CYT-1 defining exon. Tan *et al.* [142] hypothesized that the polymorphisms are indirectly associated with ErbB4 CYT-1 via splicing of exon 3 on the CYT-1 background. They identified novel splice isoforms of ErbB4, whereby exon 3 is skipped (del.3). ErbB4 del.3 transcripts exist as CYT-2 isoforms and are predicted to produce truncated proteins. Juxtamembrane (JM) splice variants of ErbB4, JM-a and JM-b respectively, are characterized by the replacement of a 75 nucleotide (nt) sequence with a 45-nt insertion, and represent four alternative exons in the gene. Novel splice variants of ErbB4 exist in the developing and adult human brain and, given the failure to identify ErbB4 del3 CYT-1 transcripts, suggest that the association of risk polymorphisms in the ErbB4 gene with CYT-1 transcript levels is not mediated via an exon 3 splicing event, according to Tan and coworkers [142].

Estrogen signaling. Estrogen signaling may be altered in the brains of people with SCZ. DNA sequence variation in the estrogen receptor (ER) alpha gene (ESR1), lower ERalpha mRNA levels, and/or blunted ERalpha signaling is associated with SCZ. The naturally-occurring truncated ERalpha isoform, Delta7, which acts as a dominant negative, can attenuate gene expression induced by the wild-type (WT) receptor in an estro-gen-dependent manner in neuronal (SHSY5Y) and non-neuronal (CHOK1 and HeLa) cells. ERalpha may also interact with NRG1-ErbB4, a leading SCZ susceptibility pathway. Reductions in the transcriptionally active form of ErbB4 comprising the intracytoplasmic domain (ErbB4-ICD) have been found in SCZ, and ERalpha and ErbB4 may converge to control gene expression. ErbB4-ICD can potentiate the transcriptional activity of WT-ERalpha at EREs in two cell lines and this potentiation effect is abolished by the presence of Delta7-ERalpha. Convergence between ERalpha and ErbB4-ICD in the transcriptional control of ERalpha-target gene expression may represent a convergent pathway that may be disrupted in SCZ [143]. Studies in Japan reported no association between ERBB3 and SCZ in the Japanese population. Li *et*

al. [144] investigated the ERBB3 gene given the putative functional nature of the gene and population heterogeneity between Asian and Caucasian. A Scottish case and control samples were sequenced with four SNPs (rs705708 at intron 15, rs2271189, rs773123, rs2271188 at exon 27), and association of rs773123, which is a nonsynonymous Ser/Cys polymorphism located seven bases downstream of rs2271189, with SCZ was detected in the Caucasian population [144].

FADS2 (Fatty acid desaturase 2). Emerging evidence suggests that SCZ might be associated with peripheral and central polyunsaturated fatty acid (PUFA) deficits. Abnormalities in fatty acid composition have been reported in peripheral tissues from drug-naïve first-episode schizophrenic patients, including deficits in ω-3 and ω-6 PUFAs, which are partially normalized following chronic antipsychotic treatment. *Post-mortem* cortical tissue from patients with SCZ also exhibits deficits in cortical docosahexaenoic acid (DHA, 22:6n − 3) and arachidonic acid (AA; 20:4n − 6) relative to normal controls, and these deficits tend to be greater in drug-free SCZ patients. Lower DHA (−20%) concentrations, and significantly greater vaccenic acid (VA) (+12.5%) concentrations, were found in the orbitofrontal cortex (OFC) (Brodmann's area 10) of SCZ patients relative to normal controls. Relative to age-matched same-gender controls, OFC DHA deficits, and elevated AA:DHA, oleic acid:DHA and docosapentaenoic acid (22:5n − 6):DHA ratios, were found in male but not female SCZ patients. SCZ patients that died of cardiovascular-related disease exhibited lower DHA (−31%) and AA (−19%) concentrations, and greater OA (+20%) and VA (+17%) concentrations, relative to normal controls that also died of cardiovascular-related disease. OFC DHA and AA deficits, and elevations in oleic acid and vaccenic acid, were numerically greater in drug-free SCZ patients and were partially normalized in SCZ patients treated with antipsychotic medications (atypical > typical) [145]. Delta-5 desaturase (FADS1), delta-6 desaturase (FADS2), elongase (HELO1 [ELOVL5]), peroxisomal (PEX19), and delta-9 desaturase (stearoyl-CoA desaturase, SCD) mRNA expression has been studied in the *post-mortem* prefrontal cortex (PFC) of patients with SCZ. FADS2 mRNA expression was significantly greater in SCZ patients relative to controls (+36%), and there was a positive trend found for FADS1 (+26%). No differences were found for HELO1 (+10%), PEX19 (+12%), or SCD (−6%). Both male (+34%) and female (+42%) SCZ patients exhibited greater FADS2 mRNA expression relative to same-gender controls. Drug-free SCZ patients (+37%), and SCZ patients treated with typical (+40%) or atypical (+31%) antipsychotics, exhibited greater FADS2 mRNA expression relative to controls. Consistent with increased delta6 desaturase activity, SCZ patients exhib-

ited a greater PUFA (product:precursor) 20:3/18:2 ratio (+20%), and a positive trend was found for 20:4/18:2 (+13%). Abnormal elevations in delta-6 desaturase (FADS2) expression in the PFC of SCZ patients are independent of gender and antipsychotic medications, and might influence SCZ pathogenesis [146].

Fat mass- and obesity-associated gene (FTO). Weight gain is one of the major adverse effects of antipsychotics. Pérez-Iglesias *et al.* [147] studied whether the fat mass and obesity-associated gene (FTO) rs9939609 variant, the SNP that has shown the strongest association with common obesity in different populations, and 3 other strong candidate genes involved in the leptin- signaling pathway including leptin, leptin receptor, and Src homology 2, influence weight gain during the first year of antipsychotic treatment. Before antipsychotic treatment, the homozygous subjects for the risk allele A of the FTO rs9939609 variant had a higher body mass index at baseline (24.2 T 3.8 kg/m^2) than the AT/TT group (22.82 T 3.3 kg/m^2); however, after 1 year of treatment with antipsychotics, the magnitude of weight increase was similar in the 3 genotypes defined by the rs9939609 variant. These results suggest that the pharmacological intervention accompanied by changes in energy intake and expenditure could suppress the genetic susceptibility conferred by the FTO genotype, with no major impact of other SNPs associated with weight gain.

FXYD6 (FXYD domain-containing ion transport regulator 6). The FXYD6 gene is located in chromosome region 11q23.3, where previous studies have shown an association with SCZ; but subsequent studies failed to replicate this finding. Zhong *et al.* [148] investigated the relationship between FXYD6 locus and SCZ in the Chinese population. Significant associations with SCZ and the marker rs11544201 and the haplotype rs10790212-rs11544201 were found, supporting that FXYD6 might be a susceptibility gene of SCZ.

Fyn (FYN oncogene related to SRC, FGR, YES). Fyn, a Src-family kinase, is highly expressed in brain tissue and blood cells. FYN participates in brain development, synaptic transmission through the phosphorylation of N-methyl-D-aspartate (NMDA) receptor subunits, and the regulation of emotional behavior. Fyn is required for the signal transduction in striatal neurons that is initiated by haloperidol. FYN abnormalities are present in patients with SCZ. A Western blot analysis revealed significantly lower levels of Fyn protein among the patients with SCZ and their relatives, compared with the level in the control group. At the mRNA level, the splicing patterns of FYN were altered in the patients and their relatives; specifically, the ratio of fynDelta7, in which exon 7 is absent, was elevated. An expression study in HEK293T cells revealed that FynDelta7 had a dominant-negative effect on the phosphorylation of Fyn's substrate. Down-

regulation of Fyn protein or altered transcription of the FYN gene might influence SCZ pathogenesis [149]. The Src family tyrosine kinase FYN plays a key role in the interaction between BDNF and glutamatergic receptor N-methyl-D-aspartate. An association was found between FYN polymorphisms and cognitive test performance in schizophrenic patients. rs706895 (-93A/G in the 5'-flanking region), rs6916861 (Ex12 + 894T/G in the 3'-UTR) and rs3730353 (IVS10 + 37T/C in intron 10) were investigated, and a significant association was found between rs6916861 T/G and rs3730353 T/C polymorphisms of the FYN gene and BD [150].

GABAergic gene expression. Prefrontal deficits in gamma-aminobutyric acid (GABA) and GABAergic gene expression, including neuropeptide Y (NPY), somatostatin (SST), and parvalbumin (PV) messenger RNAs (mRNAs), have been reported for multiple SCZ cohorts. Preclinical models suggest that a subset of these GABAergic markers (NPY/SST) is regulated by BDNF, which in turn is under the inhibitory influence of small noncoding RNAs. Subjects with SCZ show deficits in NPY and PV mRNAs. Within-pair differences in BDNF protein levels exhibit strong positive correlations with NPY and SST and a robust inverse association with miR-195 levels, which in turn are not affected by antipsychotic treatment or genetic ablation of BDNF. Prefrontal deficits in a subset of GABAergic mRNAs, including NPY, are dependent on the regional supply of BDNF, which in turn is fine-tuned through a microRNA (miRNA)-mediated mechanism [151].

Another important player in GABAergic neurotransmission is the **sodium-dependent and chloride-dependent gamma-aminobutyric acid (GABA) transporter 1 (SLC6A1)**, the target of a number of drugs of clinical importance and a major determinant of synaptic GABA concentrations. A novel 21 bp insertion in the predicted promoter region of SLC6A1 was identified. This mutation creates a second tandem copy of the sequence. Reporter assays showed that the insertion allele significantly increases promoter activity in multiple cell lines. The zinc finger transcription factor ZNF148 was found to significantly transactivate the promoter and increase expression when overexpressed but could not account for the differences in activity between the two alleles of the promoter. Copy number of the insertion sequence was associated with exponentially increasing activity of a downstream promoter, suggesting that the insertion sequence has enhanced activity when present in multiple copies. The SLC6A1 promoter genotype was found to predict SLC6A1 RNA expression in human *post-mortem* hippocampal samples. The genotyping of individuals from Tanzania suggested that the insertion allele has its origin in Africa. This relatively common polymorphism, of African origin, may prove useful in predicting clinical response to pharmacological modulators of SLC6A1 as well as GABAergic function in individuals of African descent [152].

Glutamatergic Neurotransmission

Glutamate cysteine ligase modifier (GCLM) gene. Experimental evidence shows that glutathione and its rate-limiting synthesizing enzyme, glutamate-cysteine ligase (GCL), are involved in the pathogenesis of SCZ. Genetic association was reported between two SNPs lying in noncoding regions of the glutamate cysteine ligase modifier (GCLM) gene, which specifies for the modifier subunit of GCL and SCZ. Ten sequence variations were identified, five of which were not previously described, but none of these DNA changes was within the GCLM coding sequence, and *in silico* analysis failed to indicate functional impairment induced by these variations. It is unlikely that functional mutations in the GCLM gene could play a major role in genetic predisposition to SCZ [153].

Glutamate transporter genes. Glutamatergic neurotransmission is involved in the pathogenesis of schizophrenic psychosis, in particular regarding cognitive and negative symptoms. The reported molecular mechanisms include increased glutamate transporter expression, and antipsychotic agents such as clozapine were found able to suppress the expression of these genes. The **astroglial excitatory amino acid transporter genes EAAT1** (SLC1A3) and **EAAT2** (SLC1A2) as well as the **neuronal transporter EAAT3** (SLC1A1) were suppressed by aripiprazole, while the presynaptic **vesicular glutamate transporter vGluT1** (SLC17A7) was transiently induced in hippocampal subregions and **EAAT4** (SLC1A6) was transiently suppressed in frontocortical areas. These transcriptional effects exerted by aripiprazole may counteract a glutamatergic deficit state and strengthen the neurotransmission of glutamate with positive consequences on cognitive and negative symptoms of SCZ [154].

Glutamic acid decarboxylase 2 and the glutamine synthetase genes (GAD2, GLUL). Two genes encoding glutamate metabolic enzymes, the glutamic acid decarboxylase 2 gene (GAD2) and the glutamine synthetase gene (GLUL) have been studied in Japanese patients with SCZ, including 14 SNPs in GAD2 (approximately 91 kb in size) and 6 SNPs in GLUL (approximately 14 kb in size). No significant "single-point" associations with the disease were found in any of the 20 SNPs after correction for multiple testing. Gene-gene interactions

with 6 glutamate receptor genes (GRIA4, GRIN2D, GRIK3, GRIK4, GRIK5, GRM3) did not reveal significant association, indicating that GAD2 and GLUL do not play a major role in SCZ pathogenesis and that there is no gene-gene interaction between the eight genes in the Japanese population [155]. The frequencies of GRIK3 (T928G) genotype distributions in patients with SCZ is similar to those of their relatives. The frequency of the GG genotype is significantly higher in patients than in healthy controls. GG genotype distribution in relatives is elevated compared with that in controls [156].

Glutaminase (GLS1). Genetic knockdown of glutaminase (GLS1) to reduce glutamatergic transmission presynaptically by slowing the recycling of glutamine to glutamate can produce a phenotype relevant to SCZ. GLS1 heterozygous (GLS1 het) mice showed about a 50% global reduction in glutaminase activity, and a modest reduction in glutamate levels in brain regions relevant to SCZ pathophysiology. GLS1 het mice were less sensitive to the behavioral stimulating effects of amphetamine, showed a reduction in amphetamine-induced striatal dopamine release and in ketamine-induced frontal cortical activation, suggesting that GLS1 het mice are resistant to the effects of these pro-psychotic challenges. GLS1 het mice showed clozapine-like potentiation of latent inhibition, suggesting that reduction in glutaminase has antipsychotic-like properties. These observations suggest that presynaptic modulation of the glutamine-glutamate pathway through glutaminase inhibition may provide a new direction for the pharmacotherapy of SCZ [157].

Glutamate receptor, ionotropic, delta 1 (GRID1). Recent linkage and association data have implicated the glutamate receptor delta 1 (GRID1) locus in the etiology of SCZ. The distribution of CpG islands, which are known to be relevant for transcriptional regulation, was computationally determined at the GRID1 locus, and the putative transcriptional regulatory region at the 5'-terminus was systematically tagged using HapMap data. Genotype analyses were performed with 22 haplotype-tagging SNPs (htSNPs) and two SNPs in intron 2 and one in intron 3 which have been found to be significantly associated with SCZ. Association was obtained with rs3814614, rs10749535, and rs11201985. Genetic variants in the GRID1 transcriptional regulatory region may play a role in the etiology of SCZ [158].

Glutamate carboxypeptidase II (GCPII; FOLH1). N-Acetyl aspartyl glutamate (NAAG) is an endogenous agonist at the metabotropic glutamate re-

ceptor 3 (mGluR3, GRM3) receptor and antagonist at the N-methyl D-aspartate (NMDA) receptor, both receptors important to the pathophysiology of SCZ. Glutamate carboxypeptidase II (GCPII), an enzyme that metabolizes NAAG, is also implicated in psychosis. *In situ* hybridization experiments to examine expression of mGluR3 and GCPII transcripts along the rostrocaudal axis of the human *post-mortem* hippocampus show a significant reduction of GCPII mRNA level in the anterior hippocampus in SCZ. There is a positive correlation between GCPII and mGluR3 mRNA in the CA3 of the control anterior hippocampus which is not present in SCZ, probably reflecting a disrupted functional interaction between NAAG and mGluR3 in CA3 in SCZ [159].

Group III metabotropic glutamate receptor genes, GRM4 and GRM7. Since a glutamatergic dysfunction is involved in the pathophysiology of SCZ, systematic studies on the association between glutamate receptor genes and SCZ have been performed in different populations. Shibata *et al.* [160] reported association studies of SCZ with 8 and 43 common SNPs in group III metabotropic glutamate receptor genes, GRM4 and GRM7, distributed in the entire gene regions of GRM4 (>111 kb) and GRM7 (>900 kb), respectively. Two neighboring SNPs (rs12491620 and rs1450099) in GRM7 showed highly significant haplotype association with SCZ. At least one susceptibility locus for SCZ might be located within or nearby GRM7, whereas GRM4 is unlikely to be a major susceptibility gene for SCZ in the Japanese population [160].

Glycine-and serine-related genes. Differences in the levels of the glutamate-related amino acids glycine and serine in brain/plasma between schizophrenic patients and normal subjects and changes in the plasma concentrations of these amino acids according to the clinical course have been reported. Glycine and serine metabolism may be altered in SCZ, and some genes related to the metabolism of these amino acids have been suggested to be candidate genes for SCZ. Case-control genetic association analysis of PHGDH, SHMT1, SRR, and DAO was performed, showing no association with SCZ. Only the two (rs3918347-rs4964770) and three (rs3825251-rs3918347-rs4964770) SNP-based haplotype analysis of the DAO gene showed an association with SCZ. None of the genotypes studied was associated with changes in the plasma glycine and L- and D-serine levels in SCZ [161].

NMDAR (N-Methyl D-aspartate (NMDA) receptor; GRIN1). Early postnatal inhibition of NMDAR activity in corticolimbic GABAergic in-

terneurons contributes to the pathophysiology of SCZ-related disorders [162]. Consistent with the NMDAR hypofunction theory of SCZ, in animal models in which the essential NR1 subunit of the NMDA receptor (NMDAR) was selectively elimi- nated in 40% - 50% of cortical and hippocampal interneurons in early postnatal development, dis- tinct SCZ-related symptoms emerged after adoles- cence, including novelty-induced hyperlocomotion, mating and nest-building deficits, as well as anhe- donia-like and anxiety-like behaviors. Social mem- ory, spatial working memory and prepulse inhibi- tion were also impaired. Reduced expression of glutamic acid decarboxylase 67 and parvalbumin was accompanied by disinhibition of cortical exci- tatory neurons and reduced neuronal synchrony [162]. Phosphorylation of the NR1 subunit of NMDA re- ceptors (NMDARs) at serine (S) 897 is markedly reduced in SCZ patients. Knock-in mutations (mice in which the NR1 S897 is replaced with alanine) cause severe impairment in NMDAR synaptic in- corporation and NMDAR-mediated synaptic trans- mission. Phosphomutant animals have reduced AMPA receptor (AMPAR)-mediated synaptic trans- mission, decreased AMPARGluR1 subunit in the synapse, impaired long-term potentiation, and be- havioral deficits in social interaction and sensori- motor gating, suggesting that an impairment in NR1 phosphorylation leads to glutamatergic hypofunc- tion that can contribute to behavioral deficits asso- ciated with psychiatric disorders [163].

Glutathione S-transferase GST-M1, GST-T1, and GST-P1. Data from several studies suggest that oxidative stress may play a role in the pathophysiology of tardive dyskinesia (TD). Glutathione S-transferase (GST) en- zymes exert a protecting effect on cells against oxidative stress. The GST-M1, GST-T1, and GST-P1 loci were analyzed in SCZ patients with TD and without TD. There were no significant differences in the distributions of the GST-M1, GST-T1, and GST-P1 genotypes between the TD and non-TD groups. The Ile/Ile genotype of GST-P1 had higher AIMS score compared to Ile/Val + Val/Val genotype, and MDR analysis did not show a significant interaction between the three GST gene variants and susceptibility to TD. These results suggest that GST gene polymorphisms do not confer increased susceptibility to TD in patients with SCZ but TD severity might be re- lated with GST-P1 variants [164].

Glycogen synthase kinase-3 (GSK3). Adult neuro- genesis augments neuronal plasticity, and deficient neu- rogenesis might contribute to mood disorders and SCZ and impede treatment responses. These diseases might be associated with inadequately controlled glycogen syn- thase kinase-3 (GSK3). There is a drastic 40% impair-

ment in neurogenesis *in vivo* in GSK3 alpha/beta (21A/ 21A/9A/9A) knockin mice compared with wildtype mice. Impaired neurogenesis could be due to effects of GSK3 in neural precursor cells (NPCs) or in surrounding cells that modulate NPCs. *In vitro* proliferation was equivalent for NPCs from GSK3 knockin and wild-type mice, sug- gesting an *in vivo* deficiency in GSK3 knockin mice of external support for NPC proliferation. Measurements of two neurotrophins that promote neurogenesis demon- strated less hippocampal vascular endothelial growth factor but not BDNF in GSK3 knockin mice than wild- type mice, reinforcing the possibility that insufficient environmental support in GSK3 knockin mice might contribute to impaired neurogenesis [165]. Accumulating evidence implicates deregulation of GSK3ss as a con- verging pathological event in AD and in neuropsychiatric disorders, including BD and SCZ. These neurological disorders share cognitive dysfunction as a hallmark. In rodents, increased phosphorylation of GSK3ss at serine-9 has been reported following cognitive training in two different hippocampus dependent cognitive tasks, *i.e.* inhibitory avoidance and novel object recognition task. Transgenic mice expressing the phosphorylation defec- tive mutant GSK3ss [S9A] show impaired memory in these tasks. GSK3ss [S9A] mice displayed impaired hippocampal L-LTP and facilitated LTD. Application of actinomycin, but not anisomycin, mimicked GSK3ss [S9A]-induced defects in L-LTP, suggesting that tran- scriptional activation is affected. This was further sup- ported by decreased expression of the immediate early gene c-Fos, a target gene of CREB. These data suggest a role for GSK3ss in long-term memory formation, by in- hibitory phosphorylation at serine-9 [166].

Golli-MBP. Multiple studies have reported oligoden- drocyte and myelin abnormalities, as well as dysregula- tion of their related genes, in brains of SCZ patients. One of these genes is the myelin-basic-protein (MBP) gene, which encodes two families of proteins: classic-MBPs and golli-MBPs. While the classic-MBPs are predomi- nantly located in the myelin sheaths of the nervous sys- tem, the golli proteins are more widely expressed and are found in both the immune and the nervous systems. As- sociation between six (out of 26 genotyped) SNPs has been found in Jewish Ashkenazi cohorts. Of these, three (rs12458282, rs2008323, rs721286) are from one linkage disequilibrium (LD) block which contains a CTCF bind- ing region. Haplotype analysis revealed significant "risk"/"protective" haplotypes for SCZ, suggesting that golli-MBP is a possible susceptibility gene for SCZ [167].

Growth factor signaling pathways. Evidence has accumulated that the activity of the signaling cascades of neuregulin-1, Wnt, TGF-beta, BDNF-p75 and DISC1 is different between control subjects and patients with SCZ.

These pathways are involved in embryonic and adult neurogenesis and neuronal maturation. Clinical data indicate that in SCZ the Wnt pathway is most likely hypoactive, whereas the Nrg1-ErbB4, the TGF-beta- and the BDNF-p75-pathways are hyperactive. Haplo-insuffency of the DISC1 gene is currently the best-established SCZ risk factor. Preclinical experiments indicate that suppression of DISC1 signaling leads to accelerated dendrite development in neuronal stem cells, accelerated migration and aberrant integration into the neuronal network. Increasing NRG1-, BDNF- and TGF-beta signaling and decreasing Wnt signaling also promotes adult neuronal differentiation and migration. Deviations in these pathways detected in SCZ might contribute to premature neuronal differentiation, accelerated migration and inappropriate insertion into the neuronal network. Neuronal stem cells isolated from nasal biopsies from SCZ patients display signs of accelerated development, whilst increased erosion of telomeres and bone age provide further support for accelerated cell maturation in SCZ [168].

The role of **fibroblast growth factor receptors (FGFR)** in normal brain development has been well-documented in transgenic and knock-out mouse models. Changes in FGF and its receptors have also been observed in SCZ and related developmental disorders. A transgenic th(tk-)/th(tk-) mouse model with FGF receptor signaling disruption targeted to dopamine (DA) neurons, results in neurodevelopmental, anatomical, and biochemical alterations similar to those observed in human SCZ. In th(tk-)/th(tk-) mice hypoplastic development of DA systems induces serotonergic hyperinnervation of midbrain DA nuclei, demonstrating the co-developmental relationship between DA and 5-HT systems. Behaviorally, th(tk-)/th(tk-) mice displayed impaired sensory gaiting and reduced social interactions correctable by atypical antipsychotics and a specific 5-HT$_{2A}$ antagonist, M100907. The adult onset of neurochemical and behavioral deficits was consistent with the postpubertal time course of psychotic symptoms in SCZ and related disorders. The spectrum of abnormalities observed in th(tk-)/th(tk-) mice and the ability of atypical neuroleptics to correct the behavioral deficits consistent with human psychosis suggests that midbrain 5-HT$_{2A}$-controlling systems are important loci of therapeutic action [169].

Heat shock proteins (HSPA1B). Pae *et al.* [170] investigated a group of SNPs of a set of genes coding for heat shock proteins (HSPA1A, HSPA1B and HSPA1L) and found a significant association between one HSPA1B variation and SCZ. An association between a set of variations (rs2227956, rs2075799, rs1043618, rs562047 and rs539689) within the same genes and a larger sample of schizophrenic inpatients was studied. A single variation, rs539689 (HSPA1B), was found to be marginally associated with Positive and Negative Syndrome Scale (PANSS) positive scores at discharge, and haplotype analysis revealed a significant association between improvement in PANSS scores with both A-C-G-G and A-C-G-G haplotypes. These findings support a role of heat shock proteins in the pathophysiology of SZ [170].

HOMER2. SNPs rs2306428 and rs17158184 of HOMER2 were significantly associated with SCZ in Irish samples. The protective allele at rs2306428 removes a predicted splice-enhancer binding site where HOMER2 is naturally truncated. No allelic effect of rs2306428 on neuropsychological function or on HOMER2 splicing was found [171].

IFNG (Interferon gamma). Dysregulation of the cytokine network in schizophrenia has been well documented. Such changes may occur due to disturbances in cytokine levels that are linked to polymorphisms of cytokine genes. Paul-Samojedny *et al.* [172] performed the first study to examine the association between the IFN-γ gene polymorphism and psychopathological symptoms in Polish patients with paranoid SCZ. A SNP in the IFN-γ gene (+874T/A, rs 62559044) was found to be associated with paranoid SCZ in males, but not in females. The presence of allele A at position +874 in the IFN-γ gene correlates with 1.66-fold higher risk of paranoid SCZ development in males.

3' Ig heavy chain locus enhancer HS1,2*A (IGHA1). Infectious and autoimmune pathogenic hypotheses of SCZ have been proposed, prompting searches for antibodies against viruses or brain structures, and for altered levels of immunoglobulins. Allele frequencies of the Ig heavy chain 3' enhancer HS1,2*A are associated with several autoimmune diseases, suggesting a possible correlation between HS1,2 alleles and Ig production. Levels of serum Igs and HS1,2*A genotypes have been studied in SCZ. Serum concentrations of Ig classes and IgG subclasses are higher in SCZ (80%) as compared to controls (68%). An increased frequency of the HS1,2*2A allele corresponded to increased Ig plasma levels, while an increased frequency of the HS1,2*1A allele corresponded to decreased Ig plasma levels. The transcription factor SP1 bound to the polymorphic region of both HS1,2*1A and HS1,2*2A while NF-kB bound only to the HS1,2*2A. Differences in transcription factor binding sites in the two allelic variants of the 3' IgH enhancer HS1,2 may provide a mechanism by which differences in Ig expression are affected [173].

Insulin-degrading enzyme (IDE). Insulin-degrading enzyme (IDE) is a neutral thiol metalloprotease, which cleaves insulin with high specificity. IDE also hydrolyzes Aβ, glucagon, IGF I and II, and beta-endorphin. The gene encoding IDE is located on chromosome 10q23-q25, a gene locus linked to SCZ. Insulin resistance with brain insulin receptor deficits/receptor dysfunction was re-

ported in SCZ. IDE cleaves IGF-I and IGF-II, which are implicated in the pathophysiology of SCZ, although polymorphic CA repeat in IGF1 did not show association with SCZ [174]. Brain gamma-endorphin levels, liberated from beta-endorphin exclusively by IDE, have been reported to be altered in SCZ. Studies on the expression of IDE protein in *post-mortem* brains of patients with SCZ and controls revealed a reduced number of IDE-expressing neurons and IDE protein content in the left and right dorsolateral prefrontal cortex in SCZ compared with controls, but not in other brain areas. Haloperidol might exert some effect on IDE, through changes of the expression levels of its substrates IGF-I and II, insulin and beta-endorphin. Reduced cortical IDE expression might be part of the disturbed insulin signaling cascades found in SCZ and it might contribute to the altered metabolism of certain neuropeptides (IGF-I and IGF-II, beta-endorphin) in SCZ [175].

Interleukins. SCZ has been associated with abnormalities in cytokines and cytokine receptors potentially linked to a defective immunological function in psychotic disorders. Some reports have shown that **IL-3, colony stimulating factor 2 receptor alpha (CSF2RA) and IL-3 receptor alpha (IL3RA)** are associated with SCZ. A significant association for IL3RA-rs6603272, but not for rs6645249, and a genotypic association of both polymorphisms with SCZ was found in a Chinese population. Haplotype TDT was statistically significant, with the rs6603272 (T) - rs6645249 (G) haplotype significantly associated with SCZ [176]. **Interleukin-10 (IL-10)**, an important immunoregulatory cytokine, is located on chromosome 1q31-32, a region previously reported to be linked to SCZ in genetic studies. Polymorphisms at positions −1082, −819 and −592 in the IL-10 promoter region were determined in Turkish SCZ patients, and significant differences were observed in both allelic and genotypic frequencies of the -592A/C polymorphism. GTA homozygotes (the high IL-10-producing haplotype) were more prevalent among schizophrenic patients than in controls, suggesting that the IL-10 gene promoter polymorphism may be one of the susceptibility factors to develop SCZ in the Turkish population [177].

ITIH3/4 (Inter-alpha-tryptin inhibitor, heavy chain 4), CACNA1C (Calcium channel, voltage-dependent, L type, alpha-1C subunit), and SDCCAG8 (Serologically defined colon cancer antigen 8). The Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC) highlighted 81 single-nucleotide polymorphisms (SNPs) with moderate evidence for association to schizophrenia. After follow-up in independent samples, seven loci attained genome-wide significance (GWS), but multi-locus tests suggested some SNPs that did not do so represented true associations. Hamshere *et*

al. [47] found that variants at three loci (ITIH3/4, CACNA1C and SDCCAG8) are associated with SCZ.

JARID2 (Jumonji (JMJ), at-rich interactive domain 2). An association was found of D6S289, a dinucleotide repeat polymorphism in the JARID2 gene, with SCZ and was confirmed by individual genotyping after a genome screen with 400 microsatellite markers spaced at approximately 10 cM in two DNA pools consisting of 119 SCZ patients and 119 controls recruited from a homogenous population in the Chang Le area of the Shandong peninsula of China. rs2235258 and rs9654600 in JARID2 showed association in allelic, genotypic and haplotypic tests with SCZ patients [178].

KCNH2 (Potassium voltage-gated channel, subfamily h (eag-related), member 2). Organized neuronal firing is crucial for cortical processing and this is disrupted in SCZ. A primate-specific isoform (3.1) of the ether-a-go-go-related K^+ channel KCNH2 that modulates neuronal firing has been identified. KCNH2-3.1 messenger RNA levels are comparable to full-length KCNH2-1A levels in brain but three orders of magnitude lower in heart. In hippocampus from individuals with SCZ, KCNH2-3.1 expression is 2.5-fold greater than KCNH2-1A expression. A meta-analysis of five clinical data sets shows association of SNPs in KCNH2 with SCZ. Risk-associated alleles predict lower intelligence quotient scores and speed of cognitive processing, altered memory-linked functional magnetic resonance imaging signals and increased KCNH2-3.1 mRNA levels in *post-mortem* hippocampus. KCNH2-3.1 lacks a domain that is crucial for slow channel deactivation. Overexpression of KCNH2-3.1 in primary cortical neurons induces a rapidly deactivating K^+ current and a high-frequency, nonadapting firing pattern [179].

The potassium channels are thought to have a role in modulating electrical excitability in neurons, regulating calcium signaling in oligodendrocytes and regulating action potential duration in presynaptic terminals and GABA release. Shen *et al.* [180] chose three potassium channel genes, KCNH1, KCNJ10 and KCNN3, to investigate the role of potassium channels in SCZ by genotyping 23 SNPs (9 in KCNH1, 5 in KCNJ10 and 9 in KCNN3) in a Han Chinese sample consisting of 893 SCZ patients and 611 healthy controls. No significant difference in allelic or genotypic frequency was revealed between SCZ patients and healthy individuals. According to these results, it appears that the 23 SNPs within the three potassium genes examined by Shen *et al.* do not play a major role in SCZ in the Han Chinese population.

Kynurenine pathway. Some studies of mRNA expression, protein expression, and pathway metabolite levels have implicated dysregulation of the kynurenine pathway in the etiology of SCZ and BD. A SNP in each of six genes, **TDO2 (tryptophan 2,3-dioxygenase),**

HM74 (chemokine receptor HM74/ G protein-coupled receptor 109B; GRP109B), HM74A (G protein-coupled receptor 109A; GRP109A), MCHR1 (melanin-concentrating hormone receptor 1/G protein-coupled receptor 24; GPR24), MCHR2 (melanin-concentrating hormone receptor 2), and **MC5R (melanocortin 5 receptor),** was tested for association with SCZ. An A allele in HM74 was significantly associated with SCZ and with SCZ plus BD combined. Augmentation of disease risk was found for the complex genotype HM74[A, any] + MCHR1[T, any] + MCHR2[C, any] which conferred an OR maximal for the combined diagnostic category of SCZ plus BD, carried by 30% of the cases. TDO2[CC] + MC5R[G, any] + MCHR2[GC] conferred an OR maximal for SCZ alone, carried by 8% of SCZ cases. The combined risk posed by these related, complex genotypes is greater than any identified single locus and may derive from co-regulation of the kynurenine pathway by interacting genes, a lack of adequate melanotropin-controlled sequestration of the kynurenine-derived pigments, or the production of melanotropin receptor ligands through kynurenine metabolism [181].

MAGI2 (Membrane-associated guanylate kinase, WW and PDZ domains-containing, 2). MAGI2, a large gene (~1.5 Mbps) that maps to chromosome 7q21, is involved in recruitment of neurotransmitter receptors such as AMPA- and NMDA-type glutamate receptors. Koide *et al.* [182] examined the relationship of SNP variations in MAGI2 and risk for SCZ in a large Japanese sample and explored the potential relationships between variations in MAGI2 and aspects of human cognitive function related to glutamate activity. They found suggestive evidence for genetic association of common SNPs within MAGI2 locus and SCZ.

Major histocompatibility complex (MHC). The International Schizophrenia Consortium [183] and the European SGENE-plus [184] found significant association with several markers spanning the major histocompatibility complex (MHC) region on chromosome 6p21.3-22.1. In the MHC region, the five genome-wide significant markers (MHC/HIST1H2BJ: rs6913660-C; MHC/PRSS16: rs13219354-T; MHC/PRSS16: rs6932590-T; MHC/PGBD1: rs13211507-T; MHC/NOTCH4: rs3131296-G) have risk alleles with average control frequencies between 78% and 92%. The five chromosome 6p markers, spanning about 5 Mb, cover 1.4 cM and exhibit substantial linkage disequilibrium. rs3131296 shows correlation with classical HLA alleles (HLA-A*0101, HLA-B*0801, HLA-C*0701, HLA-DRB*0301, HLA-DQA*0501, HLA-DQB*0201) [183,184]. This finding might give support to the infective-neuroimmune hypothesis of SCZ. Bergen *et al.* [48] reported a genome-wide significant association in the MHC region (rs886424). Singleton deletions were more frequent in both case groups compared with controls, whereas the largest CNVs (>500 kb) were significantly enriched only in SCZ cases. Two CNVs (16p11.2 duplications and 22q11 deletions) associated with SCZ were also overrepresented in the SCZ sample.

Malic enzyme 2. Some studies have identified a putative gene locus for both SCZ and BD in the chromosome 18q21 region. Microsatellite analyses showed evidence of association at two contiguous markers, both located at the same genetic distance and spanning approximately 11 known genes. In a corollary gene expression study, one of these genes, malic enzyme 2 (ME2), showed levels of gene expression 5.6-fold lower in anterior cingulate tissue from *post-mortem* bipolar brains. Subsequent analysis of individual SNPs in strong linkage disequilibrium with the ME2 gene revealed one SNP and one haplotype associated with the phenotype of psychosis. ME2 interacts directly with the malate shuttle system, which has been shown to be altered in SCZ and BD, and has roles in neuronal synthesis of glutamate and gamma-amino butyric acid. Genetic variation in or near the ME2 gene might be associated with both psychotic and manic disorders, including SCZ and BD [185].

Matrix metaloproteinases. Recent studies have demonstrated that matrix metalloproteinase 3 (MMP3) is a key event in associative memory formation, learning and synaptic plasticity, which are important in psychiatric disorders. Genetic variations in the MMP3 -1171 5A/6A have been studied in patients with SCZ. The frequencies of the 6A6A genotype and 6A allele distributions of MMP3 in patients with SCZ were significantly decreased when compared with controls. In contrast, in patients with SCZ, the distribution of the 5A5A genotype and 5A allele were significantly increased as compared with healthy controls. When the frequencies of genotypes or alleles in schizophrenic patients and bipolar patients were compared, 6A6A genotype and 6A allele in patients with BD-I were significantly higher than in patients with SCZ. A potential link between MMP3-1171 5A/6A variants and SCZ might be possible [186].

Matrix metallopeptidase 9 (gelatinase B, 92 kDa gelatinase, 92 kDa type IV collagenase) (MMP9). This gene plays a role in many pathological conditions such as cancer and heart disease and brain functions. It has been hypothesized that the MMP-9 gene may be associated with bipolar mood disorder. A functional −1562C/T polymorphism of the MMP-9 gene was genotyped. Patients with bipolar mood disorder had significant preponderance of T allele vs C allele of 1562C/T polymorphism of the MMP-9 gene, compared to healthy control subjects. The higher frequency of T allele compared to healthy subjects was especially evident in a subgroup of patients with BD, type II. The results may provide the first evidence for an involvement of the

MMP-9 gene in the pathogenesis of bipolar mood disorder. They may also contribute to explaining genetic connection between bipolar mood disorder and some somatic illnesses. MMP-9 may be a common susceptibility gene to major psychoses with different allelic variants occurring in bipolar illness and SCZ [187].

MCTP2 (Multiple C2 domains, transmembrane 2). The MCTP2 gene is involved in intercellular signal transduction and synapse function. Djurovic *et al.* [188] genotyped 37 tagging SNPs across the MCTP2 gene to study a possible association with SCZ in three independent Scandinavian samples, and found a possible involvement of MCTP2 as a potential novel susceptibility gene for SCZ.

Methylenetetrahydrofolate reductase (MTHFR). The frequency of homozygosity for the 677T allele of the MTHFR gene was found higher in Chinese patients with SCZ than in controls. A significant difference was observed in the plasma homocysteine levels among the different genotypes in the patient and control groups. Both elevated plasma homocysteine levels and variation in the MTHFR 677C > T gene are related to increased rates of SCZ and are risk factors for psychosis [189]. The methylenetetrahydrofolate reductase gene (MTHFR) functional polymorphism A1298C may be a risk factor for schizophrenia. Zhang *et al.* [190] found a genetic association between the MTHFR A1298C polymorphism and SCZ in the Chinese Han population.

MDGA1 (MAM domain-containing glycosylphosphatidylinositol anchor 1; glycosylphosphatidylinositol-MAM; GPIM). The structural, cytoarchitectural and functional brain abnormalities reported in patients with mental disorders may be due to aberrant neuronal migration influenced by cell adhesion molecules. MDGA1, like Ig-containing cell adhesion molecules, has several cell adhesion molecule-like domains. Kahler *et al.* [191] reported that the MDGA1 gene was a SCZ susceptibility gene in the Scandinavian population. Li *et al.* [192] investigated the association of MDGA1 with SCZ in the Chinese Han population and found that the genotype frequency of rs11759115 differed significantly between patients and controls. The C-C haplotype of rs11759115-rs7769372 was also positively associated with SCZ. rs1883901 was found to be positively associated with bipolar disorder, and the A-G-G haplotype of rs1883901-rs10807187 - rs9462343 was also positively associated with bipolar disorder.

NADPH oxidase NOX2. Sorce *et al.* [193] investigated the role of NOX2 in acute responses to subanesthetic doses of ketamine. In wild-type mice, ketamine caused rapid behavioral alterations, release of neurotransmitters, and brain oxidative stress, whereas NOX2-deficient mice did not display such alterations. Decreased expression of the subunit 2A of the NMDA re-

ceptor after repetitive ketamine exposure was also precluded by NOX2 deficiency. Neurotransmitter release and behavioral changes in response to amphetamine were not altered in NOX2-deficient mice. NOX2 is a major source of ROS production in the prefrontal cortex controlling glutamate release and associated behavioral alterations after acute ketamine exposure. Prolonged NOX2-dependent glutamate release may lead to neuroadaptive downregulation of NMDA receptor subunits. Subanesthetic doses of NMDA receptor antagonist ketamine induce schizophrenia-like symptoms in humans and behavioral changes in rodents. Subchronic administration of ketamine leads to loss of parvalbumin-positive interneurons through reactive oxygen species (ROS), generated by the NADPH oxidase NOX2. However, ketamine induces very rapid alterations, in both mice and humans.

NALCN (Sodium leak channel, nonselective). Teo *et al.* [22] screened markers for nominal significance and for statistical significance after multiple-testing correction in treatment-resistant schizophrenia and found that the most significant single nucleotide polymorphism was the rs2152324 marker in the NALCN gene (13q33.1).

Neural cell adhesion molecule 1 (NCAM1). Neural cell adhesion molecule 1 (NCAM1) is involved in several neurodevelopmental processes and abnormal expression of this gene has been associated in the pathology of SCZ and, thus, altered NCAM1 expression may be characteristic of the early stages of the illness. NCAM is a membrane-bound cell recognition molecule that exerts important functions in normal neurodevelopment including cell migration, neurite outgrowth, axon fasciculation, and synaptic plasticity. Alternative splicing of NCAM mRNA generates three main protein isoforms: NCAM-180, −140, and −120. Ectodomain shedding of NCAM isoforms can produce an extracellular 105 - 115 kDa soluble neural cell adhesion molecule fragment (NCAM-EC) and a smaller intracellular cytoplasmic fragment (NCAM-IC). NCAM also undergoes a unique post-translational modification in brain by the addition of polysialic acid (PSA)-NCAM. Both PSA-NCAM and NCAM-EC have been implicated in the pathophysiology of SCZ. mRNA expression of one of these isoforms, the 180 kDa isoform of NCAM1 (NCAM-180), was studied in the Brodmann Area (BA) 46, BA10 and BA17, of *post-mortem* samples from patients with SCZ. NCAM-180 mRNA expression was increased in BA46 from subjects with SCZ compared to controls. No differences in the expression of NCAM-180 mRNA were observed in BA10 or BA17. NCAM-180 mRNA expression is altered in a regionally-specific manner in early stages of SCZ [194]. The developmental expression patterns of the main NCAM isoforms and PSA-NCAM have been described in rodent brain and across human cortical devel-

opment. Each NCAM isoform (NCAM-180, −140, and −120), post-translational modification (PSA-NCAM) and cleavage fragment (NCAM-EC and NCAM-IC) shows developmental regulation in frontal cortex. NCAM-180, −140, and −120, as well as PSA-NCAM, and NCAM-IC all showed strong developmental regulation during fetal and early postnatal ages, consistent with their identified roles in axon growth and plasticity. NCAM-EC demonstrated a more gradual increase from the early postnatal period to reach a plateau by early adolescence, potentially implicating involvement in later developmental processes. Altered NCAM signaling during specific developmental intervals might affect synaptic connectivity and circuit formation, and thereby contribute to neurodevelopmental disorders [195].

Neuregulin (NRG1, NRG3). Chromosome 8p12 has been identified as a locus for SCZ in several genome-wide scans and confirmed by meta-analysis of published linkage data. Systematic fine mapping using extended Icelandic pedigrees identified an associated haplotype in the gene neuregulin 1 (NRG1), also known as heuregulin, glial growth factor, NDF43 and ARIA. A 290 kb core at risk haplotype at the 5' end of the gene (HAP$_{ICE}$), defined by five SNPs and two microsatellite polymorphisms, was found to be associated with SCZ in the Icelandic and Scottish populations. Analysis of the HAP$_{ICE}$ markers showed the association of a 7-marker and 2-microsatellite haplotype, different from the haplotypes associated in the Icelandic population, and overrepresented in northern Swedish control individuals. Significant association was found with 5 SNPs located in the second intron of NRG1. Furthermore, 2-, 3-, and 4-SNP windows that comprise these SNPs were also associated. One protective haplotype (0% vs 1.8%) and 1 disease risk-causing haplotype (40.4% vs 34.9%) were defined [196]. Li *et al.* [197] analyzed data from the SNP markers SNP8NRG241930, SNP8NRG243177, SNP8NRG-221132 and SNP8NRG221533, and the microsatellite markers 478B14-848, 420M9-1395. Across these studies, a strong positive association was found for all six polymorphisms. The haplotype analysis also showed significant association in the pooled international populations. In Asian populations, the risk haplotype was focused around the two microsatellite markers, 478B14-848, 420M9-1395 (haplotype block B), and in Caucasian populations with the remaining four SNP markers (haplotype block A). This meta-analysis supports the involvement of NRG1 in the pathogenesis of SCZ, but with association between two different but adjacent haplotype blocks in the Caucasian and Asian populations [197]. The promoter for the NRG1 isoform, SMDF, maps to the 3' end of the gene complex. Analysis of the SNP data-base revealed several polymorphisms within the approximate borders of the region immunoprecipitated in

ChIP-chip experiments, one of which is rs7825588. This SNP was analyzed in patients with SCZ and BD and its effect on promoter function was assessed by electromobility gel shift assays and luciferase reporter constructs. A significant increase in homozygosity for the minor allele was found in patients with SCZ, but not in BD. Molecular studies demonstrated modest, but statistically significant, allele-specific differences in protein binding and promoter function. The findings suggest that homozygosity for rs725588 could be a risk genotype for SCZ [198]. Prata *et al.* [199] tested 4 SNPs, SNP8NRG221533 (rs35753505), SNP8NRG241930, SNP8NRG243177 (rs6994992) and SNPNRG222662 (rs4623364) for allelic and haplotypic association with BD and the presence of psychotic or mood-incongruent psychotic features. Nominal allele-wise significant association for SNP8NRG-221533 was found, with the T allele being overrepresented in SCZ. This is the opposite allelic association to the original association study where the C allele was associated with SCZ. Subphenotypes were significantly associated with the SNP8NRG221533(T)-SNP8NRG241930-(G) haplotype and with the SNP8NRG221533 (T)-SNP8-NRG222662-(C)-SNP8NRG241930(G) haplotype in the case of the broader subphenotype of psychotic bipolar. This study supports the hypothesis that NRG1 may play a role in the development of BD, especially in psychotic subtypes, albeit with different alleles to previous association reports in SCZ and BD [199]. NRG1 influences the development of white matter connectivity. The cingulum bundle is a white matter structure implicated in SCZ. Abnormalities in the structural integrity of the anterior cingulum in patients with SCZ have been reported. Fractional anisotropy is reduced in the anterior cingulum in SCZ. There is interaction between genetic variation in NRG1 and diagnosis of SCZ, and patients with the T allele for SNP8NRG221533: rs35753505 have decreased anterior cingulum fractional anisotropy compared with patients homozygous for the C allele and healthy controls who were T-carriers [200]. NRG1 is one of the most researched genes associated with SCZ. Although three meta-analyses in this area have been published, the results have been inconclusive and even conflicting. Gong *et al.* [201] performed a meta-analysis of 26 published case-control and family-based association studies up to September 2008 covering 8049 cases, 8869 controls and 1515 families. Across these studies, the conclusions are as follows: 1) only SNP8NRG- 221132, 420M9-1395(0) and 478B14-848(0) showed significant association in the relatively small sample size; 2) the association analysis of case-control studies was statistically consistent with that of family studies; and 3) the matrix of coancestry coefficient suggested obvious population stratification. The study reveals that one SNP of the NRG1 gene does not contribute significantly to SCZ and that population

stratification is evident [201]. Quantitative real-time PCR was used to check the genotypes of four SNPs- rs221533 (C/T), rs7820838 (C/T), 433E1006 (A/G) and rs3924999 (C/T), located at the 510 terminus of the NRG1 gene, in 258 Chinese Han schizophrenic parent-proband trios. There was significant transmission disequilibrium in allelic transmission of C, A, T from rs221533, 433E1006, rs3924999 loci, respectively. Haplotype was analyzed at a frequency exceeding 1%. In three-marker-haplotype, C/C/G and C/C/A (rs221533, rs7820838, 433E1006) transmitted predominantly. In four-marker-haplotype (rs221533, rs7820838, 433E1006, rs3924999), C/C/G/T, C/C/A/C and C/C/A/T showed transmission disequilibrium. According to these studies, the NRG1 gene polymorphism is significantly associated with SCZ in Chinese Han, especially in the positive subtype of SCZ [202].

NRG1 is a pleiotropic growth factor involved in diverse aspects of brain development and function. In SCZ, expression of the NRG1 type I isoform is selectively increased [203]. NRG1 and ERBB4 have emerged as some of the most reproducible SCZ risk genes. The Neuregulin (NRG)/ErbB4 signaling pathway has been implicated in dendritic spine morphogenesis, glutamatergic synaptic plasticity, and neural network control. ErbB4-expressing interneurons, but not pyramidal neurons, are primary targets of NRG signaling in the hippocampus and implicate ErbB4 as a selective marker for glutamatergic synapses on inhibitory interneurons [204].

Structural brain abnormalities are present at early phases of psychosis and might be the consequence of neurodevelopmental derailment. The SNP8NRG243177 risk T allele was significantly associated, in an allele copy number-dependent fashion, with increased lateral ventricle volume in psychosis. Genotype explained 7% of the variance of lateral ventricle volume. Genetic variations of the NRG1 gene can contribute to the enlargement of the lateral ventricles described in early phases of SCZ [205].

Linkage studies have implicated 10q22-q23 as a SCZ susceptibility locus in Ashkenazi Jewish (AJ) and Han Chinese from Taiwan populations. Chen *et al.* [206] performed a peakwide association fine mapping study by using 1414 SNPs across approximately 12.5 Mb in 10q22-q23 of Ashkenazi Jews, and found strong evidence of association by using the "delusion" factor as the quantitative trait at three SNPs (rs10883866, rs10748842, and rs6584400) located in a 13 kb interval in intron 1 of NRG3. NRG3 is primarily expressed in the CNS and is one of three paralogs of NRG1 [206]. Zhang *et al.* [207] genotyped 13 SNPs within NRG3 to investigate the association between NRG3 and schizophrenia in 488 patients and 506 compared controls in Northwest China and no association was detected either in SNPs or in

haplotypes.

Neurogranin (NRGN). A marker located 3457 bases upstream of the neurogranin gene (NRGN) on 11q24 (rs128078009-T) has been associated with SCZ [208]. This marker has an average risk allele control frequency of 83%. Another NRGN SNP (rs7113041) has been reported to be associated with SCZ in Portuguese patients [209]. NRGN is expressed exclusively in brain under control of thyroid hormones, and is reduced in the prefrontal cortex of patients with SCZ. NRGN encodes a postsynaptic protein kinase substrate that binds calmodulin in the absence of calcium. NRGN is abundant in dendritic spines of hippocampal CA1 pyramidal neurons, probably acting as a calmodulin reservoir. Altered NRGN activity might mediate the effects of NMDA hypofunction implicated in SCZ pathogenesis [208].

Neuropeptide Y. It has been suggested that hypoactivity of neuropeptide Y (NPY) may be involved in the pathophysiology of SCZ. A *post-mortem* study revealed a decreased level of NPY in the brain of patients with SCZ. An increased level of NPY after antipsychotic treatment was also reported in animal brain and cerebrospinal fluid of patients. A positive association between the functional −485C > T polymorphism in the NPY gene and SCZ was reported in the Japanese population; however, more recent studies suggest that the NPY −485C > T polymorphism may not confer susceptibility to SCZ [210].

Neurotrophin receptor (NTRK-3). Based on the important role of neurotrophic factors in brain development and plasticity as well as their extensive expression in hippocampal areas, it has been hypothesized that a variation in the neurotrophin receptor 3 gene (NTRK-3) is associated with hippocampal function and SCZ. rs999905 was significantly associated with SCZ and the haplotype block that includes markers rs999905 and rs4887348 remained significant after permutation tests. The NTRK-3 gene influences hippocampal function and may modify the risk for SCZ [211].

Nitric oxide synthase (NOS). The neuronal nitric oxide synthase gene (NOS1) is located on 12q24.2-q24.31, in a susceptibility region for SCZ, and produces nitric oxide (NO) in the brain. NO plays a role in neurotransmitter release and is the second messenger of the N-methyl-D-aspartate (NMDA) receptor. It is also connected to the dopaminergic and serotonergic neural transmission systems. Therefore, abnormalities in the NO pathway are thought to be involved in the pathophysiology of SCZ. NOS1-G/G is associated with clinically significant variation in cognition. Whether this is a mechanism by which SCZ risk is increased is yet to be confirmed [212]. Several genetic studies showed an association of NOS1 with SCZ; however, results of replication studies have been inconsistent. In a replication study of NOS1 with SCZ in a Japanese sample, Okumura *et al.*

[213] selected seven SNPs (rs41279104, rs3782221, rs3782219, rs561712, rs3782206, rs2682826, and rs6490121) in NOS1 that were positively associated with SCZ in previous studies. Two SNPs showed an association with Japanese schizophrenic patients (rs3782219, rs3782206); however, these associations might have resulted from type I error on account of multiple testing [213]. In other studies no evidence was found of association with rs6490121 in NOS1 [214].

Association between markers within a region on chromosome 1q23.3, including the **NOS1AP (nitric oxide synthese 1 (neuronal) adaptor protein)** gene and SCZ has been found in a set of Canadian families of European descent, as well as significantly increased expression in SCZ of NOS1AP in unrelated *post-mortem* samples from the dorsolateral prefrontal cortex. Using the posterior probability of linkage disequilibrium (PPLD) to measure the probability that a SNP is in linkage disequilibrium with SCZ, Wratten *et al.* [215] evaluated 60 SNPs from NOS1AP in 24 Canadian families demonstrating linkage and association to this region. Two human neural cell lines (SK-N-MC and PFSK-1) were transfected with a vector containing each allelic variant of the NOS1AP promoter and a luciferase gene. Three SNPs produced PPLDs > 40%. One of them, rs12742393, demonstrated significant allelic expression differences in both cell lines tested. The allelic variation at this SNP altered the affinity of nuclear protein binding to this region of DNA, indicating that the A allele of rs12742393 appears to be a risk allele associated with SCZ that acts by enhancing transcription factor binding and increasing gene expression [215]. Findings of another study in the South American population are also consistent with a role for NOS1AP in susceptibility to SCZ, especially for the "negative syndrome" of the disorder [216].

NKCC1 and KCC2 (SLC12A2; SLC12A5). The nature of γ-aminobutyric acid neurotransmission depends on the local intracellular chloride concentration. In the CNS, the intracellular chloride level is determined by the activity of 2 cation-chloride transporters, NKCC1 and KCC2. The activities of these transporters are in turn regulated by a network of serine-threonine kinases that includes OXSR1, STK39, and the WNK kinases WNK1, WNK3, and WNK4. Arion and Lewis [217] compared the levels of NKCC1, KCC2, OXSR1, STK39, WNK1, WNK3, and WNK4 transcripts in prefrontal cortex area 9 between subjects with SCZ and healthy subjects. OXSR1 and WNK3 transcripts were substantially overexpressed in subjects with schizophrenia relative to comparison subjects. In contrast, NKCC1, KCC2, STK39, WNK1, and WNK4 transcript levels did not differ between subject groups. OXSR1 and WNK3 transcript expression levels were not changed in antipsychotic-exposed mon-

keys and were not affected by potential confounding factors in the subjects with schizophrenia. According to Arion and Lewis, in schizophrenia, increased expression levels, and possibly increased kinase activities, of OXSR1 and WNK3 may shift the balance of chloride transport by NKCC1 and KCC2 and alter the nature of γ-aminobutyric acid neurotransmission in the prefrontal cortex.

NOGO-66 receptor 1 (RTN4R). SCZ or schizoaffective disorders are quite common features in patients with DiGeorge/velo-cardio-facial syndrome (DGS/VCFS) as a result of chromosome 22q11.21 haploinsufficiency. In SCZ, genetic predisposition has been linked to chromosome 22q11, and myelin-specific genes are misexpressed in SCZ. Nogo-66 receptor 1 (NGR or RTN4R) has been considered to be a 22q11 candidate gene for SCZ susceptibility because it encodes an axonal protein that mediates myelin inhibition of axonal sprouting. The RTN4R gene encodes a subunit of the receptor complex (RTN4R-p75NTR) which results in neuronal growth inhibitory signals in response to Nogo-66, MAG or OMG signaling. RTN4R regulates axonal growth, as well as axon regeneration after injury. The gene maps to the 22q11.21 SCZ susceptibility locus and is thus a strong functional and positional candidate gene. RTN4R encodes for a functional cell surface receptor, a glycosyl-phosphatidylinositol (GPI)-linked protein, with multiple leucine-rich repeats (LRR), which is implicated in axonal growth inhibition. Three mutant alleles were detected, including two missense changes (c.355C > T; R119W and c.587G > A; R196H), and one synonymous codon variant (c.54G > A; L18L). Schizophrenic patients with the missense changes were strongly resistant to the neuroleptic treatment at any dosage. Both missense changes were absent in 300 control subjects. Molecular modeling revealed that both changes lead to putative structural alterations of the native protein [218]. RTN4R deficiency can modulate the long-term behavioral effects of transient postnatal N-methyl-D-aspartate (NMDA) receptor hypofunction. Results reported by Meng *et al.* [219] and Hsu *et al.* [220] do not support a major role of RTN4R in susceptibility to SCZ or the cognitive and behavioral deficits observed in individuals with 22q11 microdeletions; however, they suggest that RTN4R may modulate the genetic risk or clinical expression of SCZ in a subset of patients.

Neuronal cultures demonstrate that four different SCZ-derived NgR1 variants fail to transduce myelin signals into axon inhibition, and function as dominant negatives to disrupt endogenous NgR1. Mice lacking NgR1 protein exhibit reduced working memory function, consistent with a potential endophenotype of SCZ. For a restricted subset of individuals diagnosed with SCZ, the expression of dysfunctional NGR variants may contribute to in-

creased disease risk [221].

NOTCH4. The NOTCH4 gene is located within the major histocompatability complex region on chromosome 6p21.3 and sequence variants have shown association with SCZ. McDonald *et al.* [222] examined the methylation status of a region surrounding the NOTCH4 −25C/T site in leukocyte genomic DNA and human brain regions. They also studied the polymorphism status of NOTCH4 −25C/T. −25C was the only cytosine which showed methylation in any of the blood or brain samples analyzed. −25C was always fully or partially methylated in blood, was methylated in a similar pattern between SCZ and controls in the blood and was variably methylated in the brain, including completely methylated, partially methylated, subtly methylated or not methylated. −25C/T polymorphism was not associated to schizophrenia. The polymorphism and methylation analysis of NOTCH4 established that the −25C/T polymorphism and methylation status is not associated with schizophrenia, and that −25C is variably methylated in a regionspecific manner in the brain.

NRXN1 (Neurexin 1). Copy number variants (CNVs) and intragenic rearrangements of the NRXN1 (neurexin 1) gene are associated with a wide spectrum of developmental and neuropsychiatric disorders, including intellectual disability, speech delay, autism spectrum disorders (ASDs), hypotonia and schizophrenia. Schaaf *et al.* [223] performed a clinical and molecular characterization of 24 patients who underwent clinical microarray analysis and had intragenic deletions of NRXN1. 17 of these deletions involved exons of NRXN1, whereas 7 deleted intronic sequences only. The patients with exonic deletions manifested developmental delay/intellectual disability (93%), infantile hypotonia (59%) and ASDs (56%). The more C-terminal deletions, including those affecting the β isoform of neurexin 1, manifested increased head size and a high frequency of seizure disorder (88%) when compared with N-terminal deletions of NRXN1.

OLIG2 (Oligodendrocyte lineage transcription factor 2). Psychotic symptoms are common in more than 10% of patients with AD and define a phenotype with more rapid cognitive and functional decline. Oligodendrocyte lineage transcription factor 2 (OLIG2) is a regulator of white matter development and a candidate gene for SCZ [224], which may also be associated with psychotic symptoms in AD. 11 SNPs in OLIG2 previously tested for association with SCZ were tested for association with AD. Significant evidence for association of psychotic symptoms within cases was identified for the SNPs rs762237 and rs2834072 [225]. Deficits in the expression of oligodendrocyte and myelin genes have been described in numerous cortical regions in SCZ and affective disorders. mRNA expression of 17 genes expressed

by oligodendrocyte precursors (OLPs) and their derivatives, including astrocytes, have been studied in four subcortical regions (the anteroventral (AV) and mediodorsal thalamic nuclei (MDN), internal capsule (IC) and putamen (Put)). Genes expressed after the terminal differentiation of oligodendrocytes tended to have lower levels of mRNA expression in subjects with SCZ compared to controls. These differences were statistically significant across regions for four genes (CNP, GALC, MAG and MOG) and approached significance for TF. Two astrocyte-associated genes (GFAP and ALDH1L1) had higher mean expression levels across regions in SCZ. Significant positive correlations were also observed in some regions between cumulative neuroleptic exposure and the expression of genes associated with mature oligodendrocytes as well as with bipotential OLPs [226].

PALB2 (Partner and localizer of BRCA2). A genome-wide association study (GWAS) found significant association between the PALB2 SNP rs420259 and bipolar disorder (BD). The intracellular functions of the expressed proteins from the breast cancer risk genes PALB2 and BRCA2 are closely related. Tesli *et al.* [227] investigated the relation between genetic variants in PALB2 and BRCA2 and BD/SCZ in a Scandinavian case-control sample and found the BRCA2 SNP rs9567552 to be significantly associated with BD. When they combined their sample with another Nordic case-control sample from Iceland, and added results from the Wellcome Trust Case Control Consortium (WTCCC) and the STEP-UCL/ED- DUB-STEP2 study in a meta-analysis, an association between PALB2 SNP rs420259 and BD was observed. Neither the PALB2 SNP rs420259 nor the BRCA2 SNP rs9567552 were nominally significantly associated with the SCZ phenotype in the Scandinavian sample.

Pericentrin (PCNT). Pericentrin (PCNT) interacts with DISC1, BD and major depressive disorder (MDD). A significant allelic association has been found between 3 SNPs (rs3788265, rs2073376 and rs2073380) of the PCNT gene and MDD. After correction for multiple testing, 2 SNPs (rs3788265 and rs2073376) retained significant allelic associations with MDD. A significant association has also been detected between the 2 marker haplotypes (r3788265 and rs2073376) and MDD. According to these results reported by Numata *et al.* [228], genetic variations in the PCNT gene may play a role in the etiology of MDD in the Japanese population.

Peroxisome proliferator-activated receptor gamma (PPARG), PLAG2G4A, and PTGS2. Patients with SCZ have an increased risk of type-2 diabetes. The combined effects of the PLA2G4A, PTGS2 and PPARG genes were tested among 221 British nuclear families consisting of fathers, mothers and affected offspring with SCZ. A total of 10 SNPs were tested and the likeli-

hood-based association analysis for nuclear families was used to analyze the genotyping data. Eight SNPs detected across the PPARG gene did not show allelic association with SCZ; a weak association was detected at rs2745557 in the PTGS2 locus and rs10798059 in the PLA2G4A locus. The gene-gene interaction test did not show any evidence of either cis-phase interactions for the PLA2G4A and PTGS2 combinations or a trans-phase interaction for the PLA2G4A and PPARG combinations. The PPARG gene has been reported to be strongly associated with type-2 diabetes, but the results reported by Mathur *et al.* [229] did not support the hypothesis that the PPARG gene may play a role in the development of SCZ.

Phosphatidylinositol 4-kinase type-II beta (PI4K2B). Linkage of BD and recurrent major depression with markers on chromosome 4p15.2 has been identified in a large Scottish family and three smaller families. Analysis of haplotypes in the four chromosome 4p-linked families, identified two regions, each shared by three of the four families, which are also supported by a case-control association study. The candidate gene phosphatidylinositol 4-kinase type-II beta (PI4K2B) lies within one of these regions. PI4K2B is a strong functional candidate as it is a member of the phosphatidylinositol pathway, which is targeted by lithium for therapeutic effect in BD. A case-control association study, using tagging SNPs from the PI4K2B genomic region, in BD, SCZ and controls showed association with a two-marker haplotype in SCZ but not in BD (rs10939038 and rs17408391). Expression studies at the allele-specific mRNA and protein level using lymphoblastoid cell lines from members of the large Scottish family, which showed linkage to 4p15.2 in BD and recurrent major depression, showed no difference in expression differences between affected and non-affected family members. There is no evidence to suggest that PI4K2B is contributing to BD in this family but a role for this gene in SCZ has not been excluded [230].

Presenilin 2 (PSEN2). Mutations in the presenilin 1 (PSEN1) and PSEN2 genes are major causative factors for AD [35]. Presenilins are a group of proteins playing an important role in the Notch, ErbB4 and Wnt signaling pathways which might also be associated with SCZ and/or psychotic symptoms in dementia. The gene coding for presenilin 2 (PSEN2) is located on 1q31-q42 and adjacent to a balanced translocation t (1; 11) (q42; q14.3) that was found to co-segregate within family members of patients with SCZ. Five functional SNPs (rs1295645, rs11405, rs6759, rs1046240 and rs8383) present in the coding regions of the PSEN2 gene were tested in 410 patients with SCZ and 355 controls in a Chinese Han population. Association analysis showed a weak association for rs1295645, and the rs1295645-T allele was in-

volved in increased risk of SCZ. The T-C-T-T-T haplotype also showed association with increased risk of SCZ. Analysis of gene expression demonstrated that PSEN2 mRNA levels in peripheral leukocytes were significantly lower in SCZ than in controls and that expression levels of the PSEN2 gene were significantly correlated to its genotypes. Analysis of clinical profiles showed an association between the PSEN2 gene and some clinical phenotypes scored using the PANSS. The PSEN2 gene may be a novel candidate involved in the development of certain psychotic symptoms in SCZ [231].

Proline dehydrogenase/proline oxidase (PRODH). Significant associations have been shown for haplotypes comprising three PRODH SNPs: 1945T/C, 1766A/G, and 1852G/A, located in the 3' region of the gene, suggesting a role of these variants in the pathogenesis of SCZ. Studies on prepulse inhibition (PPI), verbal and working memory, trait anxiety and schizotypy indicate that CGA carriers exhibit attenuated PPI and verbal memory together with higher anxiety and schizotypy compared with noncarriers [232].

Quaking homolog, KH domain RNA binding (QKI). Chromosome 6q26 includes a susceptibility locus for SCZ in a large pedigree from northern Sweden. Aberg *et al.* [233] fine-mapped a 10.7 Mb region, included in this locus, using 42 microsatellites or SNP markers, and found a 0.5 Mb haplotype, within the large family that is shared among the majority of the patients (69%). A gamete competition test of this haplotype in 176 unrelated nuclear families from the same geographical area as the large family showed association to SCZ. The only gene located in the region, the quaking homolog, KH domain RNA binding (mouse) (QKI), was investigated in human brain autopsies. Relative mRNA expression levels of two QKI splice variants were clearly downregulated in schizophrenic patients. The mouse homolog is involved in neural development and myelination [233]. Disturbed QKI mRNA expression is observed in the prefrontal cortex of patients, and some of these changes correlate to treatment with antipsychotic drugs. In human astrocytoma (U343) and oligodendroglioma (HOG) cell lines treated with five different antipsychotic drugs including haloperidol, aripiprazole, clozapine, olanzapine and risperidone, haloperidol treatment doubled QKI-7 mRNA levels in U343 cells after 6 hours. The effect was dose-dependent, and cells treated with ten times higher concentration responded with a five-fold and three-fold increase in QKI-7, 6 and 24 hours after treatment, respectively. QKI-7 mRNA expression in human astrocytes is induced by haloperidol, at concentrations similar to plasma levels relevant to clinical treatment of SCZ [234].

RANBP1 (RAN-binding protein 1). Smooth pursuit eye movement (SPEM) disturbance is proposed as one of the most consistent neurophysiological endophenotypes

in SCZ. Cheong *et al.* [235] examined the genetic association of RANBP1 polymorphisms (22q11.21) with the risk of SCZ and with the risk of SPEM abnormality in schizophrenic patients in a Korean population. No RANBP1 polymorphisms were associated with the risk of schizophrenia; however, a common haplotype, RANBP1-ht2 (rs2238798G-rs175162T), showed significant association with the risk of SPEM abnormality among schizophrenic patients.

Reelin (RELN). Reelin is a large secreted protein of the extracellular matrix that has been proposed to participate to the etiology of SCZ. The reelin gene (RELN) encodes a secretory glycoprotein critical for brain development and synaptic plasticity. *Post-mortem* studies have shown lower reelin protein levels in the brains of patients with SCZ and BP compared with controls. In a genome-wide association study of SCZ, the strongest association was found in a marker within RELN, although this association was seen only in women. RELN is also associated with BP in women [236]. Several authors successfully replicated SCZ linkage on chromosome 7q22 in different populations and demonstrated that an intragenic short tandem repeat (STR) allele of the regional RELN gene is associated with multiple cognitive traits representing central cognitive functions regarded as valid endophenotypes for SCZ. There is association between RELN intragenic STR allele and working memory, impaired cognitive functioning and more severe positive and negative symptoms of SCZ [237]. Reelin plays a pivotal role in neurodevelopment. Excessive RELN promoter methylation and/or decreased RELN gene expression have been described in SCZ and autism. Temporocortical tissue (Brodmann's area 41/42) of postpuberal individuals is heavily methylated, especially at CpG positions located between −131 and −98 bp. Sex hormones thus seemingly boost DNA methylation at the RELN promoter. This physiological mechanism might contribute to the onset of SCZ and the worsening of autistic behaviors during the puberal period [238]. During development, reelin is crucial for the correct cytoarchitecture of laminated brain structures and is produced by a subset of neurons named Cajal-Retzius. After birth, most of these cells degenerate and reelin expression persists in postnatal and adult brain. In hippocampal cultures, reelin is secreted by GABAergic neurons displaying an intense reelin immunoreactivity (IR). Secreted reelin binds to receptors of the lipoprotein family on neurons with punctate reelin IR. Blocking protein secretion rapidly and reversibly changes the subunit composition of N-methyl-D-aspartate glutamate receptors (NMDARs) to a predominance of NR2B-containing NMDARs. Addition of recombinant or endogenously secreted reelin rescues the effects of protein secretion blockade and reverts the fraction of NR2B-containing

NMDARs to control levels. The continuous secretion of reelin is necessary to control the subunit composition of NMDARs in hippocampal neurons. Defects in reelin secretion could play a major role in the development of neuropsychiatric disorders, particularly those associated with deregulation of NMDARs such as SCZ [239]. Reelin is down-regulated in the brain of schizophrenic patients and of heterozygous reeler mice (*rl*/+). The behavioral phenotype of *rl*/− mice, however, matches only partially the SCZ hallmarks. Homozygous reeler mutants (*rl/rl*) exhibit reduced density of parvalbumin-positive (PV+) GABAergic interneurons in anatomically circumscribed regions of the neostriatum. The striatal regions in which *rl/rl* mice exhibited decreased density of PV+ interneurons are either unaltered (rostral striatum) or equally altered (dorsomedial and ventromedial intermediate striatum, caudal striatum) in *rl*/+ mice. Reelin haploinsufficiency alters the density of PV+ neurons in circumscribed regions of the striatum and selectively disrupts behaviors sensitive to dysfunction of these targeted regions [240]. Brain abnormalities in +/*rl* are similar to the psychotic brain and include a reduction in glutamic acid decarboxylase 67 (GAD67), dendritic arbors and spine density in cortex and hippocampus, and abnormalities in synaptic function including long-term potentiation (LTP). RELN and GAD67 promoters are hypermethylated in GABAergic neurons of psychotic *post-mortem* brain and DNA methyltransferase 1 (DNMT1) is up-regulated. Hypermethlyation of RELN and GAD67 promoters can be induced by treating mice with methionine, and these mice display brain and behavioral abnormalities similar to +/*rl* [241,242].

Selenium binding protein 1 (SELENBP1). The SELENBP1 gene was found to be up-regulated in both peripheral blood cell and brain tissue samples from SCZ patients. One of four haplotype-tagging SNPs and two different two-marker haplotypes showed nominally significant evidence for association with SCZ in Han Chinese patients living in Taiwan [243].

Serine racemase. D-Serine is an important NMDAR modulator. The D-serine synthesis enzyme serine racemase (SRR) has been found to be defective in SCZ. Mice with an ENU-induced mutation that results in a complete loss of SRR activity exhibit dramatically reduced D-serine levels. Mutant mice displayed behaviors relevant to SCZ, including impairments in prepulse inhibition, sociability and spatial discrimination. Behavioral deficits were exacerbated by an NMDAR antagonist and ameliorated by D-serine or the atypical antipsychotic clozapine. Expression profiling revealed that the SRR mutation influenced several genes that have been linked to SCZ and cognitive ability. Transcript levels altered by the SRR mutation were also normalized by D-serine or clozapine treatment. Analysis of SRR genetic variants in

humans identified a potential association with SCZ. Aberrant Srr function and diminished D-serine may contribute to SCZ pathogenesis [244].

Serotonin 6 (5-HT6) receptors (HTR6). Genetic alterations in serotonin 6 (5-HT6) receptors might be associated with the pathophysiology of SCZ. Kishi *et al.* [245] conducted an association study of the HTR6 gene (rs1805054 (C267T)) in Japanese patients and found no significant associations between the tagging SNPs in HTR6 and SCZ. In a meta-analysis of rs1805054, drawing data from five studies, rs1805054 was not associated with SCZ.

Serotonin (5-Hydroxytryptamine (5-HT)) transporter (SLC6A4). Serotonin (5-hydroxytryptamine (5-HT)) transporter (SLC6A4) is known to influence mood, emotion, cognition and efficacy of antidepressants, particularly that of selective serotonin reuptake inhibitors. Atypical antipsychotics exert their effects partially through serotonergic systems, and hence, variation in 5-HT uptake may affect antipsychotic action mediated through the serotonergic system. The genetic roles of five polymorphisms of SLC6A4, including those of the widely studied 44 base pair variable number of tandem repeat (VNTR) in the promoter region of SLC6A4 (the serotonin transporter gene-linked polymorphic region: 5HTTLPR) and a VNTR polymorphism (STin2) in the second intron, have been studied in SCZ. Significant allelic and genotypic associations with rs2066713, 5HTTLPR and STin2 polymorphisms have been detected. A haplotype linking these three risk alleles, 5HTTLPR/S-rs2066713/C-STin2/12-repeat, was also significantly associated with SCZ in a South Indian population [246]. A common polymorphism STin2 VNTR in the 5-HTT gene has been extensively investigated in genetic association studies. Lin *et al.* [247] conducted a case-control study of the association between STin2 VNTR and three tagging SNPs in 5-HTT and SCZ in the Han Chinese population and no association was found in the single locus, but haplotype-based analyses revealed significant association between two haplotypes with SCZ [247]. A 44 base pair insertion ("l")/deletion ("s") polymorphism (called 5-HTTLPR) in the 5' promoter region of the human serotonin transporter gene modulates expression and has been associated to anxiety and depressive traits in otherwise healthy individuals. In individuals with SCZ it seems to modulate symptom severity, acting as a disease modifying gene. In dominant models, the 5-HTTLPR genotype accounted for a significant portion of the variance in SCID depression and SANS negative symptoms (about 5%). The l allele was associated with greater psychopathology and the s allele was associated with greater anxiety and depression levels. Allelic variation may have different consequences for personality traits or psychiatric symptoms depending on epistasis or epigenetic context [248]. The serotonin transporter-linked polymorphic region (5-HTTLPR) short allele confers a general sensitivity to environmental stimuli, and anger is suspected to have a direct influence on aggressive behavior in SCZ. The 5-HTTLPR gene was associated with aggression and/or anger-related traits in SCZ; however, there was no significant difference in the distribution of the 5-HTTLPR genotype/alleles between the aggressive and nonaggressive patients. Aggressive patients carrying the s allele exhibited more anger-related traits than those with the l/l homozygotes, but this difference was not significant after correction for multiple testing. 5-HTTLPR predisposes aggressive patients to exhibit more anger-related traits, but there is no association between 5-HTTLPR and aggressive behavior in SCZ [249].

SH2B1 (SH2B adaptor protein 1). The short arm of chromosome 16 is rich in segmental duplications, predisposing this region of the genome to a number of recurrent rearrangements. Genomic imbalances of an approximately 600-kb region in 16p11.2 (29.5 - 30.1 Mb) have been associated with autism, intellectual disability, congenital anomalies, and SCZ. A separate, distal 200-kb region in 16p11.2 (28.7 - 28.9 Mb) that includes the SH2B1 gene has been associated with isolated obesity. Bachmann-Gagescu *et al.* [250] studied the phenotype of this recurrent SH2B1-containing microdeletion in a cohort of phenotypically abnormal patients with developmental delay. Deletions of the SH2B1-containing region were identified in 31 patients. The deletion is enriched in the patient population when compared with controls, with both inherited and *de novo* events. Body mass index was ≥95th percentile in four of six patients, supporting the previously described association with obesity. Accordingly, it appears that deletions of the 16p11.2 SH2B1-containing region are pathogenic and are associated with developmental delay in addition to obesity.

SHMT1 (Serine hydroxymethyltransferase, cytosolic). NMDA receptor function affects PPI integrity and D-serine and glycine are endogenous co-agonists for the receptor. A quantitative trait loci analysis using C57BL/6 (B6) mice with better PPI performance and C3H/He (C3) with lower PPI score has been reported. Genes for both D-serine synthesizing enzyme and enzyme for reversible conversion between glycine and L-serine (SRR and SHMT1, respectively) are located in the same PPI-quantitative trait loci peak. Maekawa *et al.* [251] analyzed expression levels and genetic polymorphisms of the two genes. There were promoter polymorphisms in SHMT1, which elicit lower transcriptional activity in B6 compared to C3 conforming to the results of brain expression levels, but no functional genetic variants in SRR. SHMT1 levels were higher in schizophrenic brains compared to controls, with no changes in SRR levels. A nominal association between SHMT1 and SCZ has been suggested.

Shmt1 (SHMT1), but not Srr, is likely to be one of the genetic components regulating PPI in mice and possibly relevant to SCZ.

Sialyltransferase 8B (ST8SIA2). McAuley *et al.* [252] identified a significant bipolar spectrum disorder linkage peak on 15q25-26 using 35 extended families with a broad clinical phenotype, including bipolar disorder (types I and II), recurrent unipolar depression and schizoaffective disorder. By a fine mapping association study in an Australian case-control cohort, they found that the sialyltransferase 8B (ST8SIA2) gene, coding for an enzyme that glycosylates proteins involved in neuronal plasticity which has previously shown association to both schizophrenia and autism, is associated with increased risk to bipolar spectrum disorder. Nominal single point association was observed with SNPs in ST8SIA2 (rs4586379, rs2168351), and a specific risk haplotype was identified. Using GWAS data from the NIMH bipolar disorder and NIMH schizophrenia cohorts, the equivalent haplotype was significantly over-represented in bipolar disorder, with the same direction of effect in SCZ. Variation in the ST8SIA2 gene is associated with increased risk to mental illness, acting to restrict neuronal plasticity and disrupt early neuronal network formation, rendering the developing and adult brain more vulnerable to secondary genetic or environmental insults, according to the Australian authors [252].

Sigma non-opioid intracellular receptor 1 (Sig-1R; SIGMAR1). The sigma-1 receptor (Sig-1R) is engaged in modulating NMDA and dopamine receptors which are involved in the pathophysiology of SCZ and the mechanism of psychotropic drug efficacy. Signals, detected from prefrontal regions by 52-channel near-infrared spectroscopy (NIRS) during cognitive activation, were compared between two Sig1-R genotype subgroups (Gln/Gln individuals and Pro carriers) matched for age, gender, premorbid IQ and task performance. The prefrontal hemodynamic response of healthy controls during the verbal fluency task was higher than that of patients with SCZ. For the patients with SCZ, even after controlling the effect of medication, the [oxy-Hb] increase in the prefrontal cortex of the Gln/Gln genotype group was significantly greater than that of the Pro carriers. Clinical symptoms were not significantly different between the two Sig-1R genotype subgroups. This was the first functional imaging genetics study to implicate the association between the Sig-1R genotype and prefrontal cortical function in SCZ *in vivo* [253].

SLC6A3 (Solute carrier family 6 (neurotransmitter transporter, Dopamine), member 3; Dopamine transporter; DAT). Cordeiro *et al.* [254] reported an association between a novel SNP (rs6347) located in exon 9 of the dopamine transporter (SLC6A3) and SCZ.

SMARCA2/BRM and the SWI/SNF chromatin-remodeling complex. Chromatin remodeling may play a role in the neurobiology of SCZ. The SMARCA2 gene encodes BRM in the SWI/SNF chromatin-remodeling complex, and associations of SNPs with SCZ were found in two linkage disequilibrium blocks in the SMARCA2 gene after screening of 11883 SNPs (rs2296212) and subsequent screening of 22 genes involved in chromatin remodeling (rs3793490) in a Japanese population. A risk allele of a missense polymorphism (rs2296212) induced a lower nuclear localization efficiency of BRM, and risk alleles of intronic polymorphisms (rs3763627 and rs3793490) were associated with low SMARCA2 expression levels in the *post-mortem* prefrontal cortex. A significant correlation in the fold changes of gene expression from schizophrenic prefrontal cortex was seen with suppression of SMARCA2 in transfected human cells by specific siRNA, and of orthologous genes in the prefrontal cortex of SMARCA2 knockout mice. SMARCA2 knockout mice showed impaired social interaction and prepulse inhibition. Psychotogenic drugs lowered SMARCA2 expression while antipsychotic drugs increased it in the mouse brain. According to Koga *et al.* [255] these findings support the role of BRM in the pathophysiology of SCZ.

SOX10 (SRY-BOX 10). A SNP (rs139887) in the sex-determining region Y-box 10 (SOX10) gene, was suggested to be associated with SCZ although inconsistent results had been reported. Yuan *et al.* [256] evaluated the association between SOX10 rs139887 polymorphism and SCZ and three studies were selected for meta-analysis to determine the effect of rs139887 on SCZ. The allele and genotype frequencies were significantly different between schizophrenic patients and controls, and a significant association in allele and genotype frequencies were found in male patients, but not female patients. The C/C genotype had a significant association with an earlier age of onset in male schizophrenic patients, but not in female patients. The meta-analysis showed that the same C allele was significantly associated with SCZ.

SP4 transcription factor. The Sp4 transcription factor plays a critical role for both development and function of mouse hippocampus. Reduced expression of the mouse Sp4 gene results in a variety of behavioral abnormalities relevant to human psychiatric disorders. The human SP4 gene was examined for its association with both BD and SCZ in European Caucasian and Chinese populations respectively. Out of ten SNPs selected from human SP4 genomic locus, four displayed significant association with BD in European Caucasian families (rs12668354; rs12673091; rs3735440; rs11974306). Four SNPs displayed significant association (rs40245; rs12673091; rs1018954; rs3735440) in the Chinese population and two of them (rs12673091, rs3735440) were shared with positive SNPs from European Cauca-

sian families. Considering the genetic overlap between BD and SCZ, extended studies in Chinese trio families for SCZ revealed that SNP7 (rs12673091) also displayed a significant association. SNP7 (rs12673091) was therefore significantly associated in all three samples, and shared the same susceptibility allele (A) across all three samples. A gene dosage effect for mouse Sp4 gene in the modulation of sensorimotor gating, a putative endophenotype for both SCZ and BD, was also found. The deficient sensorimotor gating in Sp4 hypomorphic mice was partially reversed by the administration of a dopamine D_2 antagonist or mood stabilizers. Both human genetic and mouse pharmacogenetic studies support the Sp4 gene as a susceptibility gene for BD or SCZ [257].

Spermidine/Spermine N1-acetyltransferase (SSAT1; SAT1). Psychotic patients tend to show increased blood and fibroblast total polyamine levels. Spermidine/spermine N1-acetyltransferase (SSAT-1) and its coding gene (SAT-1) are the main factors regulating polyamine catabolism. No association between the SAT-1 −1415T/C SNP and SCZ was found in Spanish patients; however, a mild association between allele C and psychopathology was found in the female group [258].

Sulfotransferase 4A1 (SULT4A1). Sulfotransferase 4A1 (SULT4A1) is a novel sulfotransferase expressed almost exclusively in the brain. The gene is located on chromosome 22q13.2, a region implicated in predisposition to SCZ. A variable microsatellite region located upstream of SULT4A1 was found to be associated with an increase in SCZ risk. If functional dysregulation of SULT4A1 was involved in the etiology of SCZ, then genetic variants in the coding sequence of SULT4A1 might be identified in cases compared with controls. A mutation analysis of the coding region (exons 2 - 7) in 71 Australian SCZ cases found no mutations, either synonymous or nonsynonymous. However, intronic variants (IVS5 + 12 C > T and IVS5 + 28 G > C) were identified, the frequency of which was not statistically different between cases and controls. The lack of polymorphisms in the coding region of the SULT4A1 gene is highly unusual and, along with its high conservation between species, suggests that SULT4A1 may have an important function *in vivo*, but recent findings do not support the hypothesis that germline mutations in the coding region of SULT4A1 contribute to susceptibility to SCZ [259].

Synapsin 2-3 (SYN2, SYN3). The synapsin III gene (SYN3), which belongs to the family of synaptic vesicle-associated proteins, has been implicated in the modulation of neurotransmitter release and in synaptogenesis, suggesting a potential role in several neuropsychiatric diseases. The human SYN3 gene is located on chromosome 22q12-13, a candidate region implicated in previous linkage studies of SCZ. Four SYN3 SNPs (rs133945 (−631C > G), rs133946 (−196G > A), rs9862

and rs1056484) did not show association with SCZ in either Irish or Chinese case-control samples [260]. Studies of SYN3 mRNA expression in human brain regions as well as the methylation specificity in the closest CpG island of this gene indicate that the cytosine methylation in this genomic region is restricted to cytosines in CpG dinucleotides, and is similar in brain regions and blood, and appears conserved in primate evolution. Two cytosines (cytosine 8 and 20) localized as the CpG dinucleotide are partially methylated in all brain regions. The methylation of these sites in SCZ and control blood samples is variable. The variation in SYN3 methylation is not related to SCZ or a monozygotic twin pair discordant for SCZ and is not related to the mRNA level of SYN3a in different human brain regions [261].

Synaptogyrin 1 (SYNGR1). Synaptogyrin 1 (SYNGR1) is a transmembrane protein of neurotransmitter-containing vesicle. Suggestive association between SYNGR1 intragenic polymorphisms and SCZ has been reported in the Indian population. Rare nucleotide changes with a potential pathogenic effect have been found in Indian and Chinese SCZ patients. Evidence of association has been found for rs715505 in the Italian population [262]. Polymorphisms of the synaptogyrin 1 (SYNGR1) and synasin II (SYNII) genes have been shown to be a risk factor for BD or SCZ. A case-control study with these two genes was conducted in 506 BD patients and 507 healthy individuals from the Han Chinese population. No association was found in this study [263].

Synaptosomal-associated protein 25 kDa (SNAP-25). SNAP-25 (synaptosomal-associated protein of 25 kDa) is a plasma membrane protein that, together with syntaxin and the synaptic vesicle protein VAMP/synaptobrevin, forms the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) docking complex for regulated exocytosis. SNAP-25 also modulates different voltage-gated calcium channels, representing therefore a multifunctional protein that plays essential roles in neurotransmitter release at different steps. Recent genetic studies of human populations and of some mouse models implicate alterations in SNAP-25 gene structure, expression, and/or function in contributing directly to these distinct neuropsychiatric and neurological disorders [264]. Both reduced and excessive SNAP-25 activity has been implicated in various disease states that involve cognitive dysfunctions such as ADHD, SCZ and AD. Long-term memory is formed by alterations in glutamate-dependent excitatory synaptic transmission, which is in turn regulated by SNAP-25, a key component of the SNARE complex essential for exocytosis of neurotransmitter-filled synaptic vesicles. Excess SNAP-25 activity, restricted to the adult period, is sufficient to mediate significant deficits in the memory formation process [265].

TAPASIN. *Chlamydiaceae* species has been identified as a major factor in the pathogenesis of SCZ, suggesting defective immune responses of schizophrenic patients against this environmental factor. Immune responses against *Chlamydiaceae* species are controlled by immunogenetic factors. Successful responses against microbes depend on the presentation of immunogenic peptides by HLA molecules, which are encoded by a highly polymorphic gene system. Several HLA alleles or HLA antigens have been found to be associated with SCZ in some studies. It has been proposed that variants of these genes, which control transportation and loading of microbial peptides onto HLA molecules, could prevent clearing of immune cell infection by selection of non-immunogenic peptides for HLA presentation. To generate support for this hypothesis, Fellerhoff and Wank [266] determined in a small group of schizophrenic patients and control individuals allele frequencies of the transporter proteins TAP1/TAP2, which select the immunoproteasome-tailored peptides for transportation. Frequencies of TAPASIN alleles, which encode chaperons and may also select peptides for loading on MHC molecules, have also been studied and significant associations between SCZ and TAP1 allele frequencies as well as TAPASIN allele frequencies were found, suggesting that variants of these two genetic systems could influence SCZ. These genes belong to the family of ABC transporter proteins and may also influence the efficiency of drugs [266].

TATA box-binding protein gene (TBP). Spinocerebellar ataxia type 17 (SCA17) is a rare autosomal dominant neurodegenerative disorder with ataxia and psychotic symptoms. SCA17 is caused by an expanded polyglutamine tract in the TATA box-binding protein (TBP) gene. Ohi *et al.* [267] investigated the association between SCZ and CAG repeat length in common TBP alleles with fewer than 42 CAG repeats in a Japanese population. A higher frequency of alleles with greater than 35 CAG repeats was found in patients with SCZ compared with that in controls. A negative correlation between the number of CAG repeats in the chromosome with longer CAG repeats out of two chromosomes and age at onset of SCZ was also observed. TBP genotypes with greater than 35 CAG repeats, which were enriched in patients with SCZ, were significantly associated with hypoactivation of the prefrontal cortex measured by near-infrared spectroscopy during the tower of Hanoi, a task of executive function. These findings suggest possible associations of the genetic variations of the TBP gene with risk for SCZ, age at onset and prefrontal function [267].

TDP-43 (TAR DNA-binding protein; TARDBP). Clinical features of SCZ and BD overlap with some aspects of the behavioral variant of frontotemporal lobar degeneration. The significance of pathological 43-kDa (transactivation response) DNA-binding protein (TDP-43) for frontotemporal lobar degeneration was recently suggested. Geser *et al.* [268] studied patients with chronic psychiatric diseases, mainly SCZ, for evidence of neurodegenerative TDP-43 pathology in comparison with controls. Significant TDP-43 pathology in the amygdala/periamygdaloid region or the hippocampus/transentorhinal cortex was absent in both groups in subjects younger than 65 years but present in elderly subjects (29%) of the psychiatric patients and 29% of control subjects. Twenty-three percent of the positive cases showed significant TDP-43 pathology in extended brain scans. There were no evident differences between the 2 groups in the frequency, degree, or morphological pattern of TDP-43 pathology. The latter included subpial and subependymal, focal, or diffuse lesions in deep brain parenchyma and perivascular pathology. A new GRN variant of unknown significance (c.620T > C, p.Met207Thr) was found in one patient with SCZ with TDP-43 pathology. No known TARDBP mutations or other variants were found in any of the subjects studied. The similar findings of TDP-43 pathology in elderly patients with severe mental illness and controls suggest common age-dependent TDP-43 changes in limbic brain areas that may signify that these regions are affected early in the course of a cerebral TDP-43 multisystem proteinopathy.

Transcription factor 4 (TCF4). A marker in intron 4 of the transcription factor 4 (TCF4) on 18q21.1 (rs9960767-C) has been associated with SCZ [269]. The risk allele control frequency of this marker is about 6%. TCF4 is essential for normal brain development. Mutations in this gene were found to be responsible for Pitt-Hopkins syndrome, an autosomal-dominant neurodevelopmental disorder characterized by mental and psychomotor retardation, microcephaly, epilepsy and facial dysmorphism.

Tripartite motif protein 32 (TRIM32). Mutations in the gene encoding tripartite motif protein 32 (TRIM32) cause two seemingly diverse diseases: limb-girdle muscular dystrophy type 2H (LGMD2H) or sarcotubular myopathy (STM) and Bardet-Biedl syndrome type 11 (BBS11). TRIM32 is involved in protein ubiquitination, acting as a widely-expressed ubiquitin ligase, localized to the Z-line in skeletal muscle. TRIM32 binds and ubiquitinates dysbindin, a protein implicated in the genetic etiology of SCZ, augmenting its degradation. Small-interfering RNA-mediated knockdown of TRIM32 in myoblasts resulted in elevated levels of dysbindin. The LGMD2H/STM-associated TRIM32 mutations, D487N and R394H, impair ubiquitin ligase activity towards dysbindin and were mislocalized in heterologous cells. These mutants were able to self-associate and also co-immunoprecipitated with wild-type TRIM32 in transfected cells. D487N mutant could bind to both dysbindin

and its E2 enzyme but was defective in monoubiquitination. The BBS11 mutant P130S did not show any biochemical differences compared with the wild-type protein. TRIM32 is a regulator of dysbindin and LGMD2H/STM mutations may impair substrate ubiquitination [270].

Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase Activation Protein, Eta Isoform (YWHAH). Brain protein 14-3-3, eta isoform, or tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein 1 (YWHAH; 14-3-3-ETA) is a protein kinase-dependent activator of tyrosine and tryptophan hydroxyllases and an endogenous inhibitor of protein kinase C. The 14-3-3 protein exists in several distinct forms: beta (YWHAB), gamma (YWHAG), epsilon (YWHAE), zeta (YWHAZ), theta (YWHAQ), sigma (SFN), and eta (YWHAH). YWHAH is a positional and functional candidate gene for both SCZ and BP. This gene has previously been shown to be associated with both disorders, and the chromosome location (22q12.3) has been repeatedly implicated in linkage studies for these disorders. It codes for the eta subtype of the 14-3-3 protein family, is expressed mainly in brain, and is involved in HPA axis regulation. Five tag SNPs and the (GCCTGCA)$_n$ polymorphic locus present in this gene have been genotyped and the rs2246704 SNP was associated with BP and psychotic BP. The polymorphic repeat and two other SNPs were also modestly associated with psychotic BP [271].

Vitamin D-related genes. According to Amato *et al.* [272], many natural phenomena are directly or indirectly related to latitude. Living at different latitudes, indeed, has its consequences with being exposed to different climates, diets, or light/dark cycles. In humans, one of the best known examples of genetic traits following a latitudinal gradient is skin pigmentation. The authors investigated latitude-driven adaptation phenomena, for the first time on a wide genomic scale. They selected a set of genes showing signs of latitude-dependent population differentiation and studied whether genes associated with neuropsychiatric diseases were enriched by Latitude-Related Genes (LRGs). With this strategy, they found a strong enrichment of LRGs in the set of genes associated to SCZ, especially a set of vitamin D-related genes.

X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1) and 4 (XRCC4). Human cells fused with Chinese hamster ovary (CHO) mutant lines, defective at different genes for excision repair of DNA following ultraviolet (UV) irradiation or defective in repair following X-irradiation, produce hybrids that retain the human gene that complements the defect in the CHO line when selected under conditions that require repair. The 1893-bp open reading frame of

this gene encodes a protein of 631 amino acids, compared with the 633-amino acid polypeptide of human XRCC1, which shares 86% sequence identity with mouse proteins. An association between genetic polymorphism of XRCC1 Arg194Trp and risk of SCZ has been reported [273].

Genetic factors related to the regulation of apoptosis in schizophrenic patients may be involved in a reduced vulnerability to cancer. XRCC4 is one of the potential candidate genes associated with SCZ which might induce colorectal cancer resistance. To examine the genetic association between colorectal cancer and schizophrenia, Wang *et al.* [274] analyzed five SNPs (rs6452526, rs2662238, rs963248, rs35268, rs2386275) covering ~205.7 kb in the region of XRCC4. Two of the five genetic polymorphisms (rs6452536, rs35268) showed statistically significant differences between 312 colorectal cancer subjects without SCZ and 270 schizophrenic subjects. The haplotype which combined all five markers was the most significant. XRCC4 may be a potential protective gene towards SCZ, conferring reduced susceptibility to colorectal cancer in the Han Chinese population.

YWHAE (Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon isoform; 14-3-3 epsilon protein). YWHAE is a gene encoding 14-3-3 epsilon, which is highly conserved across species, from bacteria to humans, and binds to phosphoserine/phosphothreonine motifs in a sequence-specific manner. YWHAE has been reported to be associated with SCZ in a study based on the Japanese population. Liu *et al.* [275] conducted a genetic association analysis between common SNPs in the YWHAE gene and psychiatric diseases including SCZ, major depressive disorder and bipolar disorder in Han Chinese samples (1140 schizophrenia cases, 1140 major depressive disorder cases, 1140 bipolar disorder cases and 1140 normal controls). Of the 11 SNPs studied, 7 had previously been reported as significant in YWHAE. No association was found with SCZ, major depressive disorder or bipolar disorder. Considering the size of this sample set, these results suggest that YWHAE does not play a major role in SCZ, major depressive disorder or bipolar disorder in the Han Chinese population.

Zinc finger protein 804A (ZNF804A). Two recent genome-wide association studies reported association between SCZ and the ZNF804A gene on chromosome 2q32.1 (rs1344706, rs7597593, rs1344706) [214]. The associated SNP rs1344706 lies in approximately 30 bp of conserved mammalian sequence, and the associated A allele is predicted to maintain binding sites for the brain-expressed transcription factors MYT1l and POU3F1/OCT-6. In controls, expression is significantly increased from the A allele of rs1344706 compared with the C allele. Expression is increased in schizophrenic cases

compared with controls, but this difference does not achieve statistical significance. This study replicates the original reported association of ZNF804A with SCZ and suggests that there is a consistent link between the A allele of rs1344706, increased expression of ZNF804A and risk for SCZ [276].

ZNF804A rs1344706 is the first genetic risk variant to achieve genome-wide significance for psychosis. Following earlier evidence that patients carrying the ZNF804A risk allele had relatively spared memory function compared to patient non-carriers, Donohoe *et al.* [277] investigated whether ZNF804A was also associated with variation in brain volume. In a sample of 70 patients and 38 healthy participants they used voxel-based morphometry to compare homozygous (AA) carriers of the ZNF804A risk allele to heterozygous and homozygous (AC/CC) non-carriers for both whole brain volume and specific regions implicated in earlier ZNF804A studies (the dorsolateral pre-frontal cortex, the hippocampus, and the amygdala). Homozygous SCZ "AA" risk carriers had relatively larger gray matter volumes than heterozygous/homozygous non-carriers (AC/CC), particularly for hippocampal volumes. ZNF804A might be delineating a SCZ subtype characterized by relatively intact brain volume.

Dwyer *et al.* [278] undertook a study to identify whether rare (frequency ~0.001%) coding variants in the SCZ susceptibility gene ZNF804A are involved in this psychotic disorder. No single rare variant was associated with SCZ, nor was the burden of rare, or even fairly common, non-synonymous variants. These results do not support the hypothesis that moderately rare non-synonymous variants at the ZNF804A locus are involved in schizophrenia susceptibility.

As the first gene to have achieved genome-wide significance for psychosis, ZNF804A has predictably been a subject of intense research activity. Donohoe *et al.* [279] reviewed the evidence to date for the association between SCZ and the original risk variant rs1344706, as well as additional common and rare variants at this locus, and concluded that ZNF804A is robustly, if modestly, associated with SCZ risk.

For markers rs4667000 and rs1366842, significant differences in allele frequencies were found between cases and controls in the Chinese Han population. Analysis of haplotype rs61739290-rs1366842 showed significant association with SCZ. A meta-analysis comprised of studies that utilized sample sets of either European and/or Han Chinese origin revealed statistically significant associations for two SNPs (rs1366842, rs3731834) and SCZ.

MicroRNAs (miRNAs) are small non-coding RNAs that mainly function as negative regulators of gene expression and have been shown to be involved in schizo-phrenia etiology through genetic and expression studies. A polymorphism (rs1625579) located in the primary transcript of a miRNA gene, hsa-miR-137, was reported to be strongly associated with SCZ. Four SCZ loci (CACNA1C, TCF4, CSMD1, C10orf26) were predicted as hsa-miR-137 targets, and Kim *et al.* [280] showed that ZNF804A is also a target for hsa-miR-137.

3.3. Copy Number Variants and Cytogenetic Anomalies

The mechanisms underlying generation of neuronal variability and complexity still remain enigmatic, and represent the central challenge for neuroscience. Structural variation in the neuronal genome is likely to be a relevant feature of neuronal diversity and brain dysfunction. Large-scale genomic variations due to loss or gain of whole chromosomes (aneuploidy) have been described in cells of the normal and diseased human brain, which are generated from neural stem cells during the intrauterine period of life. In studies with more than 600,000 neural cells, it has been found that the average aneuploidy frequency is 1.25% - 1.45% per chromosome, with the overall percentage of aneuploidy tending to approach 30% - 35%, and that mosaic aneuploidy may be exclusively confined to the brain. These findings might indicate that 1) aneuploidization could be an additional pathological mechanism for neuronal genome diversification; 2) aneuploidy is involved in brain development; and 3) a link between developmental chromosomal instability and intercellular/intertissular genome diversity might be associated with pathogenic mechanisms underlying specific CNS disorders [281].

Using DNA probes for chromosomes 1, 7, 11, 13, 14, 17, 18, 21, X and Y, the mean rate of stochastic aneuploidy per chromosome is 0.5% in the normal human brain. The overall proportion of aneuploid cells in the normal brain has been estimated at approximately 10%. The overall proportion of aneuploid cells in the brain of patients with ataxia-telangiectasia was estimated at approximately 20% - 50%. A dramatic 10-fold increase of chromosome 21-specific aneuploidy (both hypoploidy and hyperploidy) was detected in the AD cerebral cortex (6% - 15% vs 0.8% - 1.8% in control). It appears that somatic mosaic aneuploidy differentially contributes to intercellular genomic variation in the brain, probably influencing brain dysfunction and neurodegeneration [282].

Brain aneuploidy was hypothesized to be involved in the pathogenesis of SCZ. In normal brains, average frequencies of stochastic chromosome 1 loss and gain were 0.3% and 0.3%, respectively, with a threshold level for stochastic chromosome gain and loss of 0.7%. Average rate of aneuploidy in SCZ brains is 0.9% for chromosome 1 loss and 0.9% for chromosome 1 gain. Signifi-

cantly increased level of mosaic aneuploidy involving chromosome 1 was revealed in brains (3.6% and 4.7% of cells with chromosome 1 loss and gain, respectively). Stochastic aneuploidy rate for chromosome 1 in SCZ brains reached 0.6% for loss and 0.5% for gain and was higher than in controls, suggesting that subtle genomic imbalances manifesting as low-level mosaic aneuploidy may contribute to SCZ pathogenesis [283].

Copy number variants (CNVs) have been identified in individual patients with SCZ and also in neurodevelopmental disorders [284]. A genome-wide survey of rare CNVs in 3391 patients with SCZ and 3181 ancestrally matched controls, using high-density microarrays, detected CNVs in less than 1% of the sample with 100 kb in length. The total burden was increased 1.15-fold in patients with SCZ in comparison with controls. Deletions were found within the region critical for velo-cardio-facial syndrome, which includes psychotic symptoms in 30% of patients. Associations with SCZ were also found for large deletions on chromosome 15q13.3 and 1q21.1 [184]. CNVs have been shown to increase the risk to develop SCZ. The best supported findings are at 1q21.1, 15q11.2, 15q13.3, 16p13.1, 16p13.11 and 22q11.2, and deletions at the gene neurexin 1 (NRXN1). In the Japanese population, as in other Western populations, there is a trend for excess of rare CNVs in SCZ; however, previously implicated association for very large CNVs (>500 kb) could not be confirmed in this population [285]. In a genome-wide search for CNVs associating with SCZ, 66 *de novo* CNVs were identified in a sample of 1433 SCZ cases and 33250 controls. Three deletions at 1q21.1, 15q11.2 and 15q13.3 showing nominal association with SCZ in the first sample (phase I) were followed up in a second sample of 3285 cases and 7951 controls (phase II). All three deletions significantly associate with SCZ and related psychoses in the combined sample [208].

There are 484 annotated genes located on 8p; many are most likely oncogenes and tumor-suppressor genes. Molecular genetics and developmental studies have identified 21 genes in this region (ADRA1A, ARHGEF10, CHRNA2, CHRNA6, CHRNB3, DKK4, DPYSL2, EGR3, FGF17, FGF20, FGFR1, FZD3, LDL, NAT2, NEF3, NRG1, PCM1, PLAT, PPP3CC, SFRP1 and VMAT1/SLC18A1) that are most likely to contribute to neuropsychiatric disorders (SCZ, autism, BD and depression), neurodegenerative disorders (Parkinson's and Alzheimer diseases) and cancer. At least seven nonprotein-coding RNAs (microRNAs) are located at 8p. Structural variants on 8p, such as copy number variants, microdeletions or microduplications, might also contribute to autism, SCZ and other human diseases including cancer [286]. A genome-wide assessment of SNPs and CNVs in 1460 patients with SCZ and 12,995 controls of European ancestry identified 8 cases and zero controls

with deletions greater than 2 Mb, of which two, at 8p22 and 16p13.11-p12.4, were novel. A further evaluation of 1378 controls identified no deletions greater than 2 Mb, suggesting a high prior probability of disease involvement when such deletions are observed in cases. Further evidence for some smaller SCZ-associated CNVs, such as those in NRXN1 and APBA2, was confirmed; however, this study could not provide strong support for the hypothesis that SCZ patients have a significantly greater "load" of large (>100 kb), rare CNVs, nor could it find common CNVs that associate with SCZ or SCZ-associated CNVs that disrupt genes in neurodevelopmental pathways [287].

Kirov *et al.* [288] investigated the involvement of rare (<1%) copy number variants (CNVs) in 471 cases of SCZ and 2792 controls that had been genotyped using the Affymetrix GeneChip 500K Mapping Array. Large CNVs >1 Mb were 2.26 times more common in cases, with the effect coming mostly from deletions, although duplications were also more common. Two large deletions were found in two cases each, but in no controls: a deletion at 22q11.2 known to be a susceptibility factor for SCZ and a deletion on 17p12, at 14.0 - 15.4 Mb. The latter is known to cause hereditary neuropathy with liability to pressure palsies. The same deletion was found in 6 of 4618 (0.13%) cases and 6 of 36,092 (0.017%) controls in the re-analyzed data of two recent large CNV studies of SCZ. One large duplication on 16p13.1, which has been previously implicated as a susceptibility factor for autism, was found in three cases and six controls (0.6% vs 0.2%). This study also provided the first support for a recently reported association between deletions at 15q11.2 and SCZ [288]. A susceptibility locus in 13q13-q14 is shared by SCZ and mood disorder, and that locus would be additional to another well-documented and more distal 13q locus where the G72/G30 gene is mapped [289].

Idiopathic generalized epilepsies account for 30% of all epilepsies. Microdeletions at 15q13.3 have recently been shown to constitute a strong genetic risk factor for common idiopathic generalized epilepsy syndromes, implicating that other recurrent microdeletions may also be involved in epileptogenesis. Five microdeletions at the genomic hotspot regions 1q21.1, 15q11.2, 16p11.2, 16p13.11 and 22q11.2 represent genetic risk to common idiopathic generalized epilepsy syndromes and other neuropsychiatric disorders [290]. Microdeletion at chromosomal position 15q13.3 has been described in intellectual disability, autism spectrum disorders, SCZ and in idiopathic generalized epilepsy [291]. The phenotypic profile of children with microdeletions of 15q13.3 includes developmental delay, mental retardation, or borderline IQ, autistic spectrum disorder, speech delay, aggressiveness, attention-deficit hyperactivity disorder,

and other behavioral problems [292]. Positive genetic linkage to the 15q13-q14 region has been found in many studies, and several association reports support this locus as a candidate region for SCZ. A candidate gene in the region, the alpha7 nicotinic receptor CHRNA7, plays a seminal role in the linked endophenotype, and is decreased in expression in the patient population. The 15q13-q14 region contains a partial duplication of the CHRNA7 gene that includes exons 5 - 10 and considerable sequence downstream. Evidence from multiple studies supports a broad region of genetic linkage around the marker D15S1360 [293].

Autism and mental retardation show high rates of comorbidity and potentially share genetic risk factors. A rare approximately 2 Mb microdeletion involving chromosome band 15q13.3 was detected in a multiplex autism family. This genomic loss lies between distal break points of the Prader-Willi/Angelman syndrome locus and was first described in association with mental retardation and epilepsy. Together with recent studies that have also implicated this genomic imbalance in SCZ, this CNV shows considerable phenotypic variability [294].

Deletions and reciprocal duplications of the chromosome 16p13.1 region have been reported in several cases of autism, mental retardation and SCZ. Ingason *et al.* [295] found a threefold excess of duplications and deletions in SCZ cases compared with controls, with duplications present in 0.30% of cases *vs* 0.09% of controls and deletions in 0.12% of cases and 0.04% of controls. The region can be divided into three intervals defined by flanking low copy repeats. Duplications spanning intervals I and II showed the most significant association with SCZ. The age of onset in duplication and deletion carriers among cases ranged from 12 to 35 years, and the majority were males with a family history of psychiatric disorders. Candidate genes in the region include NTAN1 and NDE1.

Velocardiofacial syndrome, now known as 22q11.2 deletion syndrome (22qDS), is estimated to affect more than 700 children born in the United States each year. Some clinical studies have found increased rates of SCZ in adults with 22qDS. The psychiatric disorders most commonly reported in children and adolescents with 22qDS have been attention-deficit hyperactivity disorder, oppositional defiant disorder, anxiety disorders, and major depression. Psychotic symptoms have been observed in 14% to 28% of children with 22qDS [296]. Chromosome 22q11.2 deletion syndrome (22q11DS) is associated with cognitive deficits and morphometric brain abnormalities in childhood and a markedly elevated risk of SCZ in adolescence/early adulthood. Children with 22q11DS demonstrate gray matter reductions in multiple brain regions that are thought to be relevant to SCZ. The correlation of these volumetric reductions with poor neurocognition indicates that these brain regions may mediate higher neurocognitive functions implicated in SCZ [297]. Recurrent or overlapping CNVs were found in cases at 39.3% of selected loci. The collective frequency of CNVs at these loci is significantly increased in cases with autism, in cases with SCZ, and in cases with mental retardation compared with controls in France. Individual significance was reached for the association between autism and a 350-kilobase deletion located at 22q11 and spanning the PRODH and DGCR6 genes [298]. The 22q11 deletion (or DiGeorge) syndrome (22q11DS), the result of a 1.5- to 3-megabase hemizygous deletion on human chromosome 22, results in dramatically increased susceptibility for "diseases of cortical connectivity" thought to arise during development, including SCZ and autism. Diminished dosage of the genes deleted in the 1.5-megabase 22q11 minimal critical deleted region in a mouse model of 22q11DS specifically compromises neurogenesis and subsequent differentiation in the cerebral cortex [299]. There is overwhelming evidence that children and adults with 22q11.2 deletion syndrome (22q11.2DS) have a characteristic behavioral phenotype. In particular, there is a growing body of evidence that indicates an unequivocal association between 22q11.2DS and SCZ, especially in adulthood. Deletion of 22q11.2 is the third highest risk for the development of SCZ, with a greater risk only conferred by being the child of two parents with SCZ or the monozygotic co-twin of an affected individual. Both linkage and association studies of people with SCZ have implicated several susceptibility genes, of which three are in the 22q11.2 region: catechol-o-methyltransferase (COMT), proline dehydrogenase (PRODH), and Gnb1L. In addition, variation in Gnb1L is associated with the presence of psychosis in males with 22q11.2DS. In mouse models of 22q11.2DS, haploinsufficiency of Tbx1 and Gnb1L is associated with reduced prepulse inhibition, a SCZ endophenotype [300].

Initial studies of genome-wide trinucleotide repeats using the repeat expansion detection technique suggested possible association of large CAG/CTG repeat tracts with SCZ and bipolar affective disorder [301]. Tandem repeats, particularly with long (>50 bp) repeat units, are a relatively common yet underexplored type of CNV that may significantly contribute to human genomic variation and disease risk. A bacterial artificial chromosome-based array comparative genomic hybridization (aCGH) platform screen detected an apparent deletion on 5p15.1 in two probands, caused by the presence in each proband of two low copy number (short) alleles of a tandem repeat that ranges in length from fewer than 10 to greater than 50 3.4 kb units in the population examined. Short alleles partially segregate with SCZ in a small number of families [302].

Significant familiality of incongruent psychosis was observed in patients with bipolar I disorder or schizoaffective disorder, bipolar type. Covariate linkage analysis provided three regions with genome-wide suggestive evidence for linkage on chromosomes 1q32.3, 7p13 and 20q13.31 in a European sample [303].

The advent of molecular cytogenetic technologies has altered the means by which new microdeletion syndromes are identified. Whereas the cytogenetic basis of microdeletion syndromes has traditionally depended on the serendipitous ascertainment of a patient with established clinical features and a chromosomal rearrangement visible by G-banding, comparative genomic hybridization using microarrays has enabled the identification of novel, recurrent imbalances in patients with mental retardation and apparently nonspecific features. Compared with the "phenotype-first" approach of traditional cytogenetics, array-based comparative genomic hybridization has enabled the detection of novel genomic disorders using a "genotype-first" approach. An illustrative example was the characterization of a novel microdeletion syndrome of 1q41q42. In a sample of over 10,000 patients with developmental disabilities, 7 cases were found with *de novo* deletions of 1q41q42. The smallest region of overlap is 1.17 Mb and encompasses five genes, including DISP1, a gene involved in the sonic hedgehog signaling pathway, the deletion of which has been implicated in holoprosencephaly in mice. Although none of these patients showed frank holoprosencephaly, many had other midline defects (cleft palate, diaphragmatic hernia), seizures, and mental retardation or developmental delay. Dysmorphic features are present in all patients at varying degrees. This new microdeletion syndrome with its variable clinical presentation may be responsible for a proportion of Fryns syndrome patients and adds to the increasing number of new syndromes identified with array-based comparative genomic hybridization [304].

Some other novel microdeletion syndromes have been detected with array-comparative genomic hybridization (array CGH), including the 17q21.31 deletion and 17q21.31 duplication syndromes, 15q13.3 deletion syndrome, 16p11.2 deletion syndrome, 15q24 deletion syndrome, 1q41q42 deletion syndrome, 2p15p16.1 deletion syndrome and 9q22.3 deletion syndrome [305].

Autism spectrum disorders (ASDs) are childhood neurodevelopmental disorders with complex genetic origins. Previous studies focusing on candidate genes or genomic regions have identified several CNVs associated with an increased risk of ASDs. A whole-genome CNV study on a cohort of 859 ASD cases and 1409 healthy children of European ancestry genotyped with approximately 550000 SNP markers, besides previously reported ASD candidate genes such as NRXN1 and CNTN4, several new susceptibility genes encoding neuronal cell-adhesion molecules, including NLGN1 and ASTN2, were enriched with CNVs in ASD cases compared to controls. CNVs within or surrounding genes involved in the ubiquitin pathways, including UBE3A, PARK2, RFWD2 and FBXO40, were affected by CNVs not observed in controls. Duplications 55 kb upstream of complementary DNA AK123120 were also identified. Genes involved in neuronal cell-adhesion or ubiquitin degradation that belong to important gene networks expressed within the CNS may contribute to the genetic susceptibility of ASD [306].

In another genome-wide CNVs study, through prioritization of exonic deletions (eDels), exonic duplications (eDups), and whole gene duplication events (gDups), over 150 loci harboring rare variants in multiple unrelated probands, but no controls, were identified in ASDs. Rare variants at known loci, including exonic deletions at NRXN1 and whole gene duplications encompassing UBE3A and several other genes in the 15q11-q13 region, were observed in these analyses. Strong support was likewise observed for previously unreported genes such as BZRAP1, an adaptor molecule known to regulate synaptic transmission, with eDels or eDups observed in twelve unrelated cases but no controls. MDGA2 was observed to be case-specific, and the encoded protein showed an unexpectedly high similarity to Contactin 4, which has also been linked to disease [307].

Linkage studies have identified several replicated susceptibility loci for ASDs, including 2q24-2q31, 7q, and 17q11-17q21. Association studies and mutation analysis of candidate genes have implicated the synaptic genes NRXN1, NLGN3, NLGN4, SHANK3, and CNTNAP2 in ASDs. Traditional cytogenetic approaches highlight the high frequency of large chromosomal abnormalities (3% - 7% of patients), including the most frequently-observed maternal 15q11-13 duplications (1% - 3% of patients) [308].

Cornelia de Lange syndrome (CdLS) is a multisystem congenital anomaly disorder. Heterozygous point mutations in three genes (NIPBL, SMC3 and SMC1A), encoding components of the sister chromatid cohesion apparatus, are responsible for approximately 50% - 60% of CdLS cases. Recent studies have revealed a high degree of genomic rearrangements (deletions and duplications) in the human genome, which result in gene CNVs. Duplications on chromosomes 5 or X have been identified in CdLS using genome-wide array comparative genomic hybridization. The duplicated regions contain either the NIPBL or the SMC1A genes. Junction sequence analyses revealed the involvement of three genomic rearrangement mechanisms. The patients share some common features including mental retardation, developmental delay, sleep abnormalities, and craniofacial and limb

defects. The systems affected are the same as in CdLS, but clinical manifestations are distinct from CdLS; particularly the absence of the CdLS facial gestalt. The results confirm the notion that duplication CNV of genes can be a common mechanism for human genetic diseases [309].

The rate of *de novo* mutations is of relevance to evolution and disease. Kong *et al.* [310] conducted a study of genome-wide mutation rates by sequencing the entire genomes of 78 Icelandic parent-offspring trios at high coverage, and showed that with an average father's age of 29.7, the average *de novo* mutation rate is 1.20×10^{-8} per nucleotide per generation. The diversity in mutation rate of single nucleotide polymorphisms is dominated by the age of the father at conception of the child. The effect is an increase of about two mutations per year with paternal mutations doubling every 16.5 years. According to Steffanson's group [310], father's age is estimated to explain nearly all of the remaining variation in the *de novo* mutation counts with potential repercussion on the risk of diseases such as SCZ and autism.

3.4. SNPs in Human miRNA Genes

MicroRNAs (miRNAs) are 21 - 25-nucleotide-long, non-coding RNAs involved in translational regulation. Most miRNAs derive from a two-step sequential processing: the generation of pre-miRNA from pri-miRNA by the Drosha/DGCR8 complex in the nucleus, and the generation of mature miRNAs from pre-miRNAs by the Dicer/TRBP complex in the cytoplasm. Sequence variation around the processing sites, and sequence variations in the mature miRNA, especially the seed sequence, may have profound effects on miRNA biogenesis and function. Naturally occurring SNPs can impair or enhance miRNA processing as well as alter the sites of processing. Since miRNAs are small functional units, single base changes in both the precursor elements as well as the mature miRNA sequence may drive the evolution of new microRNAs by altering their biological function. At least 24 human X-linked miRNA variants with potential influence in SCZ have been identified [311]. Individual microRNAs (miRNAs) affect moderate downregulation of gene expression. Components required for miRNA processing and/or function have also been implicated in X-linked mental retardation, neurological and neoplastic diseases, pointing to the wide-ranging involvement of miRNAs in disease. To explore the role of miRNAs in SCZ, 59 microRNA genes on the X-chromosome were amplified and sequenced in males with and without SCZ spectrum disorders to test the hypothesis that ultra-rare mutations in microRNA collectively contribute to the risk of SCZ. Feng *et al.* [312] provided the first association of microRNA gene dysfunction with SCZ. Eight ultra-rare variants in the precursor or mature miRNA were identified in eight distinct miRNA genes in 4% of analyzed males with SCZ. One ultra-rare variant was identified in a control sample. These variants were not found in an additional 7197 control X-chromosomes. Functional analyses of ectopically expressed copies of the variant miRNA precursors demonstrate loss of function, gain of function or altered expression levels. These findings suggest that microRNA mutations can contribute to SCZ [312].

At least one third of known miRNA genes are expressed in the brain. Mutations disrupting MECP2 protein lead to abnormal development of the brain and resulting behavior. MiR-130b expressed in the brain and potentially targeting MECP2 is located in the susceptibility locus for SCZ (22q11). Screening for mutations has identified a population polymorphism in the 5-upstream miR-130b gene region containing DNA elements for putative transcription factors. Genetic association analysis of 300 schizophrenics and 316 controls revealed no statistically significant association of any of the miR-130b allelic variants with SCZ [313].

For posttranscriptional gene silencing, one strand of the miRNA is used to guide components of the RNA interference machinery, including Argonaute 2, to messenger RNAs (mRNAs) with complementary sequences. Targeted mRNAs are either cleaved by the endonuclease Argonaute 2, or protein synthesis is blocked by a specific mechanism. Genes encoding miRNAs are transcribed as long primary miRNAs (pri-miRNAs) that are sequentially processed by components of the nucleus and cytoplasm to yield a mature, approx 22-nucleotide (nt)-long miRNA. Two members of the ribonuclease (RNase) III endonuclease protein family, Drosha and Dicer, have been implicated in this two-step processing. Several proteins are required for the initial nuclear processing of pri-miRNAs to the approx 60- to 70-nt stem-loop intermediates known as precursor miRNAs (pre-miRNAs). A protein complex, termed Microprocessor by Gregory *et al.* [314], is necessary and sufficient for processing pri-miRNA to premiRNAs. The Microprocessor complex comprises Drosha and the double-stranded RNA-binding protein DiGeorge syndrome critical region 8 gene (DGCR8), which is deleted in DiGeorge syndrome [314].

Identification of known miRNA targets on all human genes indicates that miRNA-346 targets SCZ susceptibility genes listed in the Schizophrenia Gene database twice as frequently as expected, relative to other genes in the genome. The gene encoding this miRNA, miR-346, is located in intron 2 of the glutamate receptor ionotropic delta 1 (GRID1) gene, which has been previously implicated in SCZ susceptibility. Expression of both miR-346 and GRID1 is lower in SCZ patients than in normal controls; however, the expression of miR-346 and GRID1 is less correlated in SCZ patients than in bipolar patients or

in normal controls [315]. Cummings *et al.* [316] genotyped 821 patients with confirmed DSM-IV diagnoses of SCZ, bipolar affective disorder I and schizoaffective disorder for the risk SNP (rs1625579) of a micro-RNA, MIR-137, and found that carriers of the risk allele had lower scores for an OPCRIT-derived positive symptom factor and lower scores on a lifetime measure of psychosis incongruity. Risk allele carriers also had more cognitive deficits involving episodic memory and attentional control. The MIR-137 risk variant may be associated with a specific subgroup of psychosis patients.

3.5. Epigenetics

Despite the promising results obtained with structural and functional genomic procedures to identify associations with disease pathogenesis and potential drug targets in CNS disorders, it must be kept in mind that allelic mRNA expression is affected by genetic and epigenetic events, both with the potential to modulate neurotransmitter tone in the CNS [317]. Epigenetics is the study of how the environment can affect the genome of the individual during its development as well as the development of its descendants, all without changing the DNA sequence, but inducing modifications in gene expression through DNA methylation-demethylation or through modification of histones by processes of methylation, deacetylation, and phosphorylation [318]. DNA methylation is an epigenetic mechanism in which the methyl group is covalently coupled to the C5 position of the cytosine residue of CpG dinucleotides, generally leading to gene silencing. DNA methylation is catalyzed by a group of enzymes known as DNA methyltransferases (DNMT). DNA methylation changes only happen during DNA replication to maintain methylation patterns on hemimethylated DNA or establish new methylation. DNMT expression generally decreases after cell division, but significant levels of DNMTs are present in postmitotic neurons. There is evidence that DNA methylation correlates with some neuropsychiatric disorders, influences neural development, plasticity, learning, and memory, and is potentially reversible at certain genomic loci. This epigenetic mechanism of gene regulation gives support to a maintenance role of DNMT to prevent active demethylation in postmitotic neurons [319]. Genomic and epigenetic changes can affect complex cognitive functions, including learning and memory, and are causative in several developmental and psychiatric disorders affecting language, social functioning and IQ [320]. DNA methylation and histone deacetylation are two major epigenetic modifications that contribute to the stability of gene expression states. Perturbing DNA methylation, or disrupting the downstream response to DNA methylation-methyl-CpG-binding domain proteins (MBDs)

and histone deacetylases (HDACs) by genetic or pharmacological means, has revealed a critical requirement for epigenetic regulation in brain development, learning, and mature nervous system stability, and has identified the first distinct gene sets that are epigenetically regulated within the nervous system [321].

Epigenetic mechanisms such as DNA methylation and modifications to histone proteins regulate high-order DNA structure and gene expression. Aberrant epigenetic mechanisms are involved in different CNS disorders (Rett syndrome, mental retardation disorders, alpha-thalassemia/mental retardation X-linked syndrome, Rubinstein-Taybi syndrome, Coffin-Lowry syndrome, Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, epilepsy, amyotrophic lateral sclerosis) and also probably in mental disorders [322].

More than 150 post-translation modifications of histones have been reported, including methylations, acetylations, ubiquitinations, SUMOylations and phosphorylations. A macro-molecular complex, called ECREM for "Epigenetic Code REplication Machinery", has been proposed as a potential mechanism involved in the inheritance of the epigenetic code. The composition of ECREM may vary in a spatio-temporal manner according to the chromatin state, the cell phenotype and the development stage. Members of ECREM, responsible for the epigenetic code inheritance, include enzymes involved in DNA methylation and histone post-translational modifications. Some of them, such as DNA methyltransferases (DNMTs), histone acetyltransferases (HATs) and histone deacetylases (HDACS, including sirtuins), have been found to be deregulated in several types of pathologies and are already targeted by inhibitors [323].

Epigenetic phenomena cannot be neglected in the pathogenesis and pharmacogenomics of CNS disorders. Studies in cancer research have demonstrated the antineoplastic effects of the DNA methylation inhibitor hydralazine and the histone deacetylase inhibitor valproic acid, of current use in epilepsy [324]. Novel effects of some pleiotropic drugs with activity on the CNS have to be explored to understand in full their mechanisms of action and adjust their dosages for new indications. Both hyper- and hypo-DNA methylation changes of the regulatory regions play critical roles in defining the altered functionality of genes (MB-COMT, MAOA, DAT1, TH, DRD1, DRD2, RELN, BDNF) in major psychiatric disorders, such as SCZ and BD [325].

Histone deacetylases (HDACs), enzymes that affect the acetylation status of histones and other important cellular proteins, have been recognized as potentially useful therapeutic targets for a broad range of human disorders. Pharmacological manipulations using small-molecule HDAC inhibitors, which may restore trans-

criptional balance to neurons, modulate cytoskeletal function, affect immune responses and enhance protein degradation pathways, have been beneficial in various experimental models of brain diseases [326].

Recent advances in SCZ research indicate that the telencephalic gamma-aminobutyric acid (GABA)ergic neurotransmission deficit associated with this psychiatric disorder is probably mediated by the hypermethylation of the glutamic acid decarboxylase 67 (GAD67), reelin and other GABAergic promoters. A pharmacological strategy to reduce the hypermethylation of GABAergic promoters is to induce a DNA-cytosine demethylation by altering the chromatin remodeling with valproate (VPA). When co-administered with VPA, the clinical efficacy of atypical antipsychotics is enhanced. VPA facilitates chromatin remodeling when it is associated with clozapine or sulpiride but not with haloperidol or olanzapine [327]. This remodeling might contribute to reelin- and GAD67-promoter demethylation and might reverse the GABAergic gene-expression downregulation associated with SCZ morbidity [328,329].

Reduction of prefrontal cortex glutamic acid decarboxylase (GAD67) and reelin (mRNAs and proteins) expression is the most consistent finding reported by several studies of post-mortem SCZ brains. The reduced GAD67 and reelin expression in cortical GABAergic interneurons of SCZ brains is the consequence of an epigenetic hypermethylation of RELN and GAD67 promoters very likely mediated by the overexpression of DNA methyltransferase 1 in cortical GABAergic interneurons. RELN and GAD67 promoters express an increased recruitment of methyl-CpG binding domain proteins. The histone deacetylase inhibitor valproate, which increases acetylated histone content in cortical GABAergic interneurons, also prevents MET-induced RELN promoter hypermethylation and reduces the methyl-CpG binding domain protein binding to RELN and GAD67 promoters. DNA hypermethylation and the associated chromatin remodeling may be critically important in mediating the epigenetic down-regulation of reelin and GAD67 expression detected in cortical GABAergic interneurons of SCZ patients [330,331].

Novel strategies in psychiatric epigenetics have been developed. With two novel approaches, it has been observed that valproic acid induced a 383% increase in GAD67 mRNA, an 89% increase in total acetylated histone 3 (H3K9, K14ac) levels, and a 482% increase in H3K9,K14ac attachment to the GAD67 promoter. Trichostatin A (TSA) induced comparable changes on all measures. Bipolar patients had significantly higher baseline levels of H3K9, K14ac compared to patients with SCZ. Subjects with clinically relevant serum levels of valproic acid (>65 μg/mL) showed a significant increase in mRNA expression. Separate approaches for examining chromatin remodeling in real clinical time provide evidence for differential epigenetic events in cultured lymphocytes isolated from patients with SCZ and bipolar depression [332].

Li *et al.* [333] examined associations of structural mutability with germline DNA methylation and with non-allelic homologous recombination (NAHR) mediated by low-copy repeats (LCRs). Combined evidence from four human sperm methylome maps, human genome evolution, structural polymorphisms in the human population, and previous genomic and disease studies consistently points to a strong association of germline hypomethylation and genomic instability. Methylation deserts, the ~1% fraction of the human genome with the lowest methylation in the germline, show a tenfold enrichment for structural rearrangements that occurred in the human genome since the branching of chimpanzee and are highly enriched for fast-evolving loci that regulate tissue-specific gene expression. Analysis of copy number variants (CNVs) from 400 human samples indicates that association of structural mutability with germline hypomethylation is comparable in magnitude to the association of structural mutability with LCR-mediated NAHR. Rare CNVs occurring in the genomes of individuals diagnosed with SCZ, bipolar disorder, and developmental delay and *de novo* CNVs occurring in those diagnosed with autism are significantly more concentrated within hypomethylated regions.

3.6. Mitochondrial DNA Mutations

Mitochondria provide most of the energy for brain cells by the process of oxidative phosphorylation. Mitochondrial oxidative phosphorylation is the major ATP-producing pathway, which supplies more than 95% of the total energy requirement in the cells. Damage to the mitochondrial electron transport chain has been suggested to be an important factor in the pathogenesis of a range of psychiatric disorders. Tissues with high energy demands, such as the brain, contain a large number of mitochondria, being therefore more susceptible to reduction of the aerobic metabolism. Mitochondrial abnormalities and deficiencies in oxidative phosphorylation have been reported in individuals with SCZ, BD, and major depressive disorder (MDD) in transcriptomic, proteomic, and metabolomic studies. The evidence includes impaired energy metabolism in the brain, detected using results of magnetic resonance spectroscopy, electron microscopy, co-morbidity with mitochondrial diseases, the effects of psychotropics on mitochondria, increased mitochondrial DNA (mtDNA) deletion in the brain, and association with mtDNA mutations/polymorphisms or nuclear-encoded mitochondrial genes. Alterations of mitochondrial oxidative phosphorylation in SCZ have been reported in several brain regions and also in platelets. Abnormal mi-

tochondrial morphology, size and density have all been reported in the brains of schizophrenic individuals [334,335]. Several mutations in mtDNA sequence have been reported in SCZ and BD patients. The rate of synonymous base pair substitutions in the coding regions of the mtDNA genome is 22% higher in the dorsolateral prefrontal cortex of individuals with SCZ compared to controls [336].

Analyses of mitochondria-related genes using DNA microarray showed significantly increased LARS2 (mitochondrial leucyl-tRNA synthetase) in the *post-mortem* prefrontal cortices of patients with BD. LARS2 is a nuclear gene encoding the enzyme catalyzing the aminoacylation of mitochondrial tRNA-Leu. A well-studied mitochondrial DNA point mutation, $3243A > G$, in the region of tRNA-Leu^{UUR}, related with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), is known to decrease the efficiency of aminoacylation of tRNA-Leu^{UUR}. The steady state level of LARS2 was examined in the transmitochondrial cybrids carrying $3243A > G$. LARS2 was upregulated in the transmitochrondrial cybrids carrying $3243A > G$. The $3243A > G$ was detected in the *post-mortem* brains of patients with BD and SCZ, who also showed higher levels of the mutation in their livers and significantly higher gene expression of LARS2. Upregulation of LARS2 is a hallmark of $324A > G$ mutation. The accumulation of $3243A > G$ mutation in the brain may have a pathophysiologic role in BD and SCZ [337].

A decreased expression of mitochondrial complex I subunit gene, NDUFV2 at 18p11, in lymphoblastoid cell lines (LCLs) from Japanese patients with BD, has been reported. No differences were found in NDUFV2 mRNA levels in LCLs of Caucasian BD patients compared with controls [338].

Park *et al.* [339] characterized Mitofilin, a mitochondrial inner membrane protein, as a mediator of the mitochondrial function of DISC1. A fraction of DISC1 was localized to the inside of mitochondria and directly interacts with Mitofilin. A reduction in DISC1 function induced mitochondrial dysfunction, evidenced by decreased mitochondrial NADH dehydrogenase activities, reduced cellular ATP contents, and perturbed mitochondrial Ca^{2+} dynamics. Deficiencies in DISC1 and Mitofilin induced a reduction in mitochondrial monoamine oxidase-A activity. The mitochondrial dysfunctions evoked by the deficiency of DISC1 were partially phenocopied by an overexpression of truncated DISC1 that is associated with SCZ in humans. DISC1 deficiencies induced the ubiquitination of Mitofilin, suggesting that DISC1 is critical for the stability of Mitofilin. The mitochondrial dysfunction induced by DISC1 deficiency was partially reversed by coexpression of Mitofilin, confirming a functional link between DISC1 and Mitofilin for the

normal mitochondrial function. DISC1 may play essential roles for mitochondrial function in collaboration with the mitochondrial interacting partner Mitofilin.

3.7. Genotype-Phenotype Correlations, Transcriptomics, Proteomics, and Metabolomics

Genotype-phenotype correlations represent a central issue in functional genomics to validate the impact of genomic factors on disease pathogenesis and phenotypic expression of disease-related genes as well as in pharmacogenetics and pharmacogenomics [4]. Phenomics, the systematic study of phenotypes on a genome-wide scale, comprises a rate-limiting step on the road to genomic discovery [340]. Novel strategies to assess genotype-phenotype correlates have been developed. For instance, by using the parallel independent component analysis (para-ICA) of Liu to analyze a multimodal data set in which each subject was characterized on 24 different SNP markers spanning multiple risk genes previously associated with SCZ, Meda *et al.* [341] detected three fMRI components significantly correlated with two distinct gene components. The fMRI components, along with their significant genetic profile (dominant SNP) correlations were as follows: 1) Inferior frontal-anterior/posterior cingulate-thalamus-caudate with SNPs from BDNF and DAT, 2) superior/middle temporal gyrus-cingulate-premotor with SLC6A4_PR and SLC6A4_PR_AG (serotonin transporter promoter; 5HTTLPR), and 3) default mode-fronto-temporal gyrus with BDNF and DAT. These results reveal the effect/influence of specific interactions, between SCZ risk genes on imaging endophenotypes representing attention/working memory and goal-directed related brain function, thus establishing a useful methodology to probe multivariate genotype-phenotype relationships [341].

Bergen *et al.* [342] tested four genes [phenylalanine hydroxylase (PAH), the serotonin transporter (SLC6A4), monoamine oxidase B (MAOB), and the gamma-aminobutyric acid A receptor beta-3 subunit (GABRB3)] for their impact on five SCZ symptom factors: delusions, hallucinations, mania, depression, and negative symptoms. The PAH 232 bp microsatellite allele demonstrated significant association with the delusions factor, and a significant association between the GABRB3 191 bp allele and the hallucinations factor was also detected [342].

Transcriptomics and gene expression studies are also helping to elucidate the role of the prefrontal cortex in SCZ and affective disorders. Owing to reciprocal connectivity, the thalamic nuclei and their cortical fields act as functional units. Chu *et al.* [343] screened the expression of the entire human genome of neurons harvested by laser-capture microdissection (LCM) from the thalamic

primary relay to dorsolateral prefrontal cortex in three psychiatric disease states as compared with controls. Microarray analysis of gene expression showed the largest number of dysregulated genes in SCZ, followed by major depression and D8, respectively. Significantly, IGF1-mTOR-, AKT-, RAS-, VEGF-, Wnt- and immune-related signaling, eIF2- and proteasome-related genes were unique to SCZ. Vitamin D receptor and calcium signaling pathway were unique to BD. AKAP95 pathway and pantothenate and CoA biosynthesis were unique to major depression [343].

Studies on the human CNS transcriptome suggest changes in pro-inflammatory pathways and myelination in SCZ, whereas changes in the proteome suggest that pathways involved in energy and metabolism may be particularly stressed. There appear to be complex changes in the expression of proposed candidate genes for SCZ such as NRG1, DISC1, RGS4 and DTNB1, and there are continued reports of alterations in central gamma-aminobutyric acidergic, dopaminergic, glutamatergic and cholinergic pathways in patients with the disorder. Data on epigenetic mechanisms and transcriptome regulation suggest that at least some changes in gene expression may be due to changes in levels of gene promoter methylation or microRNAs in the CNS of patients with SCZ [344].

SCZ is likely to be a consequence of DNA alterations that, together with environmental factors, will lead to protein expression differences and the ultimate establishment of the illness. The superior temporal gyrus is implicated in SCZ and executes functions such as the processing of speech, language skills and sound processing. Proteomics studies in the left posterior superior temporal gyrus (Wernicke's area - BA22p) revealed 11 downregulated and 14 upregulated proteins, most of them related to energy metabolism. Whereas many of the identified proteins have been previously implicated in SCZ, such as fructose-bisphosphate aldolase C, creatine kinase and neuron-specific enolase, new putative disease markers were also identified such as dihydrolipoyl dehydrogenase, tropomyosin 3, breast cancer metastasis-suppressor 1, heterogeneous nuclear ribonucleoproteins C1/C2 and phosphate carrier protein, mitochondrial precursor [345].

Genome-wide expression analysis of peripheral blood identified candidate biomarkers for SCZ. Using Affymetrix microarrays, Kuzman *et al.* [346] identified significantly altered expression of 180 gene probes in psychotic patients compared to controls. The following genes were significantly altered in patients: glucose transporter, SLC2A3 and actin assembly factor DAAM2 were increased, whereas translation, zinc metallopeptidase, neurolysin 1 and myosin C were significantly decreased. DAAM2 polymorphic variants have been found significantly associated with SCZ [346].

The repertoire of biochemicals present in cells, tissue, and body fluids is known as the metabolome. State of the art metabolomic analytical platforms and informatics tools are being used to map potential biomarkers for CNS disorders. Early findings from metabolomic studies may help to identify promising biomarkers for SCZ and many other neuropsychiatric disorders [347].

4. PHARMACOGENOMICS OF ANTIPSYCHOTIC DRUGS

4.1. Aripiprazole

Aripiprazole is an arylpiperazine atypical antipsychotic with full agonist activity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_6, 5-HT receptors, acting also as a partial agonist of D_2 and 5-HT_{1A} receptors and antagonist of the 5-HT_{2A} receptor. Aripiprazole is a major substrate of CYP2D6 and CYP3A4. Caution and personalized dose adjustment should be made in patients with the following genotypes: ADRA1A (Arg347Cys), CYP2D6 (CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*10, CYP2D6*17, CYP2D6*1xN), CYP3A4 and CYP3A5 (CYP3A4*1, CYP3A4*1B, CYP3A4*2, CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*6, CYP3A4*8, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*15, CYP3A4*17, CYP3A4*18, CYP3A4*19, CYP3A5*3), DRD2 (TaqIA RFLP (rs1800497, ANKK1), TaqIB (rs1079597), rs6277), DRD3 (Ser9Gly), HTR2A (His452Tyr, His368Tyr, Ile197Val, Ile113Val, Ala447Val, Ala363Val, Thr25Asn, A-1438G (rs6311), T102C (rs6313)), HTR2C (Cys23Ser, −759C/T), and also in ABCB1 and HTR1A mutants [25] (**Table 2**).

4.2. Benperidol

Benperidol is a butyrophenone antipsychotic which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors. Genes potentially involved in efficacy and safety might be DRD1 and DRD2 [25] (**Table 2**).

4.3. Bromperidol

Bromperidol is a butyrophenone with antagonistic activity on D_2 receptors and a moderate antagonistic activity on serotonin 5-HT_2 receptors. Bromperidol is a major substrate of CYP3A4, a minor substrate of CYP2D6, a substrate of several UGTs, and a moderate inhibitor of CYP2D6. ABCB1 (C3435T and G2677T/A), DRD2 (Taq IA RFLP and rs1800497, ANKK1), and HTR2 variants may influence its pharmacokinetics and pharmacodynamics [25] (**Table 2**).

4.4. Chlorpromazine

Chlorpromazine is an aliphatic phenothiazine antipsy-

chotic which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors, has a strong anticholinergic effect, weakly blocks ganglionic, antihistaminic and antiserotonergic receptors, strongly blocks α-adrenergic receptors, and behaves as an inverse agonist of 5-HT_6 and 5-HT_7 receptors and as an antagonist of 5-HT_{1A} and 5-HT_{2c} receptors. Chlorpromazine is a major substrate of CYP2D6, a minor substrate of CYP1A2 and CYP3A4, and a substrate of UGT1A3 and UGT1A4. This neuroleptic strongly inhibits CYP2D6 and weakly CYP2E1 and DAO. Caution and personalized dose adjustment should be made in patients with the following genotypes: ACACA (rs4072032,rs2229416 (Gln526His), rs1266175, rs12453407, rs9906543), BDNF ((GT)$_n$), CYP1A2 (C734A, G-2964A), CYP2D6 (CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*10, CYP2D6*17, CYP2D6*1xN), DRD2 (−141C Ins/Del) (rs1799732) TaqIA RFLP (rs1800497, ANKK1), TaqIB (rs1079597), TaqID (rs1800498), (Ser311Cys, rs6276 and rs6277), DRD3 (Ser9Gly), HTR2C (−759C/T in the promoter region), LEP (−2548G/A), and NPY (rs1468271). ABCB1, CFTR, CYP2A6, CYP2C9, CYP2C19, CYP2E1, CYP3A4, DAO, FABP1, FMO1, UGT1A3, and UGT1A4 variants may also influence its pharmacokinetics and pharmacodynamics [25] (**Table 2**).

4.5. Clozapine

Clozapine is a dibenzodiazepine atypical antipsychotic which acts as an antagonist of histamine H_1, cholinergic and α_1-adrenergic receptors, an antagonist of 5-HT_{1A} and 5-HT_{2B} receptors, a full agonist of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors, and an inverse agonist of 5-HT_6 and 5-HT_7 receptors. Clozapine is a major substrate of ABCB1, CYP1A2 and CYP3A4, a minor substrate of CYP2A6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6, and also substrate of FMO3, UGT1A3 and UGT1A4. This atypical antipsychotic moderately inhibits CYP2C9, CYP2C19 and CYP2D6, and weakly inhibits CYP1A2, CYP2E1 and CYP3A4. Caution and personalized dose adjustment should be made in patients with the following genotypes: APOA5 (−1131C > T, Ser19Trp), APOC3 (C1100T), APOD (rs7659), CYP1A2 (C734A, G-2964A, C1545T), DRD1 (rs4532, rs265976), DRD2 (TaqIA RFLP (rs1800497, ANKK1), Taq1B (rs1079597), rs1125394), DRD3 (Ser9Gly), DTNBP1 (rs1018381, rs760761, rs2619539, rs742105, Diplotype ACCCTC/ GTTGCC, rs742106), GNB3 (Ser275Ser), HTR1F (C267T), HTR2A (His452Tyr, His368Tyr, Ile197Val, Ile113Val, Ala447Val, Ala363Val, Thr25Asn), HTR2C (Cys23Ser), TNF (−308G > A), and UGT1A4 (Leu48Val, Leu150Leu, 43fcX22). Other polymorphic variants in the ABCB1, CNR1, CYP2A6, CYP2D6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP3A4, DRD4, FABP1, FMO3,

GSK3B, HTR3A, HRH1, HTR6, LPL, NRXN1, RGS2, and UGT1A3 genes may also influence its pharmacokinetics and pharmacodynamics [25] (**Table 2**).

4.6. Droperidol

Droperidol is a butyrophenone which blocks dopaminergic and α-adrenergic receptors. This atypical antipsychotic is a major substrate of CYP2C9, CYP2C19, CYP2D6, and CYP3A4. ABCC8, ADRA2A, ADRB1, CHRM2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, KCNE1, KCNE2, KCNQ1, KCNJ11, and KCNH2 variants influence its efficacy and safety [25] (**Table 2**).

4.7. Fluphenazine

Fluphenazine is a piperazine phenothiazine which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors and is an inverse agonist of 5-HT_7 receptors, and an antagonist of 5-HT_{2A} receptors. This typical antipsychotic is a major substrate of CYP2D6; weakly inhibits CYP1A2, CYP2C9, and CYP2E1; and strongly inhibits CYP2D6. Caution and personalized dose adjustment should be made in patients with the following CYP2D6 genotypes: CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*10, CYP2D6*17, CYP2D6*1xN. ABCB1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2E1, CYP3A4, DRD1, DRD2, HRH1, HTR2A, and HTR7 variants may also affect its pharmacokinetic and pharmacodynamic properties [25] (**Table 2**).

4.8. Flupenthixol

Flupenthixol is a thioxanthene with typical antipsychotic activity by blocking postsynaptic dopaminergic receptors. DRD1 (Ala229Thr, Arg50Ser, Ser199Ala, Thr37Arg, Thr37Pro) and DRD2 variants may affect its biopharmaceutical properties [25] (**Table 2**).

4.9. Haloperidol

Haloperidol is a butyrophenone which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors, acting also as an antagonist of 5-HT_{2A} and 5-HT_{2B} receptors. This typical antipsychotic is a major substrate of CYP2D6 and CYP3A4/5, a minor substrate of CYP1A1, CYP1A2, CYP2C8, CYP2C9, and CYP2C19, a substrate of CBR and several UGTs, and a moderate inhibitor of CYP2D6 and CYP3A4. Caution and personalized dose adjustment should be made in patients with the following genotypes: CYP2D6 (CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*10, CYP2D6*17, CYP2D6*1xN), CYP3A4 and CYP3A5 (CYP3A4*1, CYP3A4*1B, CYP3A4*2, CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*6,

CYP3A4*8, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*15, CYP3A4*17, CYP3A4*18, CYP3A4*19, CYP3A5*3), DRD2 (TaqIA RFLP (rs1800497, ANKK1)), DTNBP1 (rs909706, diplotype ACCCTC/GCCGCC), HTR2A (A-1438G (rs6311)), and IL1RN (VNTR (IL1RN*1 and IL1RN*2). ABCB1, ABCC1, ADRA2A, BDNF, CHRM2, CYP1A2, CYP2A6, CYP2C9, CYP2C19, DRD1, DRD4, FOS, GRIN2B, GSK3B, GSTP1, HRH1, HTT, KCNE1, KCNE2, KCNH2, KCNJ11, and KCNQ1 variants also affect its neuroleptic properties and side-effects [25] (**Table 2**).

4.10. Loxapine

Loxapine is a dibenzoxazepine which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors and serotonin 5-HT_2 receptors, also acting as an inverse agonist of 5-HT_{2c} and 5-HT_6 receptors. This typical antipsychotic is a substrate of UGT1A4, and DRD1, DRD2, HTR2A, and UGT1A4 variants might be able to modify its biopharmaceutical properties [25] (**Table 2**).

4.11. Mesoridazine

Mesoridazine is a phenothiazine with putative dopaminergic, cholinergic and adrenergic inhibition. This typical antipsychotic is a substrate of CYP2J2, and ADRA1A, DRD2, CHRM2, CYP2J2, KCNE1, KCNE2, KCNH2, KCNJ11, KCNQ1, SCN5A variants may affect its pharmacokinetic and pharmacodynamic properties [25] (**Table 2**).

4.12. Molindone

Molindone is a dihydroindolone which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors, has a strong anticholinergic effect, a weak ganglionic, antihistaminic and antiserotonergic blocking capacity, and a strong α-adrenergic blocking activity, also acting as an antagonist of 5-HT_{2A} receptors. Polymorphic variants in the ADRA1A, DRD2, DRD3, HRH1, HTR1A, HTR1E, HTR2A, and HTR2C genes may induce changes in proteomic byproducts leading to modifications in the biopharmaceutical properties of this typical antipsychotic [25] (**Table 2**).

4.13. Olanzapine

Olanzapine is a thienobenzodiazepine which acts as a strong antagonist of serotonergic 5-HT_{2A}, 5-HT_{2C}, and 5-HT_7 receptors, dopaminergic D_{1-4} receptors, histaminergic H_1 receptors, and α_1-adrenergic receptors. This atypical antipsychotic is also an antagonist of 5-HT_{2A}, 5-HT_3 and muscarinic M_{1-5} receptors, a full agonist of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors, and an

inverse agonist of 5-HT_{2c} and 5-HT_6 receptors. Olanzapine is a major substrate of CYP1A2, CYP2D6 and UGT1A4, and a weak inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Caution and personalized dose adjustment should be made in patients with the following genotypes: ABCB1 (C1236T, G2677T/A, C3435T), ADRB3 (Arg64Trp), APOA5 (-1131T > C, Ser19Trp), APOC3 (C1100T), COMT (Val(108/158) Met), CYP2D6 (CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*10, CYP2D6*17, CYP2D6*1xN), DRD2 (TaqIA RFLP (rs1800497, ANKK1), -141C Ins/Del (rs1799732), -241 A > G, Ser311Cys), DRD3 (Ser9Gly), GNB3 (Ser275Ser), GRM3 (rs6465084, rs274622), HTR2A (His452Tyr, His368Tyr, Ile197Val, Ile113Val, Ala447Val, Ala363Val, Thr25Asn, T102C (rs6313)), HTR2C (Cys23Ser, -759C > T), LEP (rs4731426, -1548G > A), LEPR (Gln223Arg), RGS2 (rs4606, rs1152746, rs1819741, rs1933695, rs2179652, rs2746073), SLC6A2 (G1287A, T-182C), and UGT1A4 (Leu48Val). These genotypes and other polymorphic variants in the CYP1A2, CYP2C9, CYP2C19, CYP3A4, DRD4, FMO1, KCNH2, and LPL genes are determinant for olanzapine-related pharmacological properties and/or side-effects [25] (**Table 2**).

4.14. Paliperidone

Paliperidone is a benzisoxazole which acts as a serotonin and dopamine receptor antagonist, with high affinity for α_1, D_2, H_1, and 5-HT_{2C} receptors and low affinity for muscarinic and 5-HT_{1A} receptors. This atypical antipsychotic is a major substrate of ABCB1, ADH, CYP2D6, CYP3A4, and several UGTs, and inhibits ABCB1, CYP2D6, and CYP3A4. Polymorphic variants in the ABCB1, ADRA1A, ADRA1B, ADRA1D, CYP2D6, CYP3A4, DRD2, HRH1, and HTR2A genes may affect its biopharmaceutical properties and also the manifestation of potential adverse drug reactions [25] (**Table 2**).

4.15. Periciazine

Periciazine is a piperidine phenothiazine which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors, and α-adrenergic receptors, also acting as an inverse agonist of 5-HT_6 and 5-HT_7 receptors, and an antagonist of 5-HT_{2A} and 5-HT_{2c} receptors. This typical antipsychotic is a substrate of CYP2D6 and CYP3A4. Caution and personalized dose adjustment should be made in patients with the following genotypes: CYP2D6 (CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*10, CYP2D6*17, CYP2D6*1xN), and CYP3A4 (CYP3A4*3). ADRA1A, DRD1, DRD2, DRD3, HTR2A, HTR2C, HTR6, HTR7 variants may influence its pharmacokinetic and pharmacodynamic properties [25] (**Table 2**).

4.16. Perphenazine

Perphenazine is a piperazine phenothiazine which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors. This typical antipsychotic is a major substrate of CYP1A2, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, and CYP3A4/5, and a weak inhibitor of CYP1A2 and CYP2D6. Caution and personalized dose adjustment should be made in patients with the following genotypes: ADRA1A (Arg347Cys), CYP2D6 (CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*10, CYP2D6*17), and DRD2 (−141C Ins/Del (rs1799732), TaqlA (rs1800497), TaqIB (rs1079597), rs1125394). ABCB1, CYP1A2, CYP2C9, CYP2C19, CYP3A4, DRD1, and RGS4 variants may affect its biopharmaceutical properties [25] (**Table 2**).

4.17. Pimozide

Pimozide is a diphenylbutylpiperidine with antagonistic activity on dopaminergic receptors and $5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$ and $5\text{-}HT_7$ receptors. This typical antipsychotic is a major substrate of CYP3A4, a minor substrate of CYP1A2, a weak inhibitor of CYP2C19 and CYP2E1, a moderate inhibitor of CYP3A4, and a strong inhibitor of CYP2D6. Caution and personalized dose adjustment should be made in patients with the following genotypes: ADRA1A (Arg347Cys), CYP1A2 (C734A, G-2964A), CYP2D6 (CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*10, CYP2D6*17, CYP2D6*1xN), CYP3A4 (CYP3A4*3), KCNE2 (Gln9Glu, Met54Thr,Thr8Ala), KCNH2 (Arg784Trp), KCNQ1 (Arg583Cys), and SCN5A (Gly615Glu, Leu618Phe, Phe1250Leu, Leu1825Pro). Other genes potentially involved in its metabolism and pharmacological properties are ABCB1, CHRM2, CYP2C19, CYP2E1, DRD2, KCNE1, and KCNJ11 [25] (**Table 2**).

4.18. Pipotiazine

Pipotiazine is a piperidine phenothiazine which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors. This typical antipsychotic is a substrate of CYP2D6 and CYP3A4. Different polymorphic variants in the CYP2D6, CYP3A4, and DRD genes may affect its metabolism and pharmacological properties [25] (**Table 2**).

4.19. Prochlorperazine

Prochlorperazine is a piperazine phenothiazine which strongly blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors, α-adrenergic receptors and cholinergic receptors. The metabolism and pharmacological properties of this typical antipsychotic may be affected by polymorphic variants in the ABCB1, ADRA1A, CYPs, DRD1, and DRD2 genes, as well as other genes associated with histaminergic and cholinergic neurotransmission [25] (**Table 2**).

4.20. Quetiapine

Quetiapine is a dibenzothiazepine which acts as a serotonergic ($5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, $5\text{-}HT_2$), dopaminergic (D_1 and D_2), histaminergic H_1, and adrenergic (α_1- and α_2-) receptor antagonist, and a full agonist of $5\text{-}HT_{1A}$, $5\text{-}HT_{1D}$, $5\text{-}HT_{1F}$, and $5\text{-}HT_{2A}$ receptors. This atypical antipsychotic is a minor substrate of CYP2D6 and a major substrate of CYP3A4/5. Caution and personalized dose adjustment should be made in patients with the following genotypes: ADRA1A (Arg347Cys), CYP3A4 (CYP3A4*3), HTR2A (His452Tyr, His368Tyr, Ile197Val, Ile113Val, Ala447Val, Ala363Val, Thr25Asn), KCNE2 (Gln9Glu, Met54Thr, Thr8Ala), KCNH2 (Arg784Trp), KCNQ1 (Arg583Cys), and SCN5A (Gly615Glu, Leu618Phe, Phe1250Leu, Leu1825Pro). These genotypes and other polymorphisms in the ABCB1, CYP2D6, DRD1, DRD2, DRD4, HRH1, HTR1A, HTR2B, KCNE1, and RGS4 genes are responsible for the metabolism and biopharmaceutical properties of quetiapine [25] (**Table 2**).

4.21. Risperidone

Risperidone is a benzisoxazole with serotonergic, dopaminergic, α_1-, α_2-adrenergic and histaminergic receptor antagonist activity, low-moderate affinity for $5\text{-}HT_{1C}$, $5\text{-}HT_{1D}$, and $5\text{-}HT_{1A}$ receptors, low affinity for D_1 receptors, and inverse agonist activity on $5\text{-}HT_{2c}$, $5\text{-}HT_6$, and $5\text{-}HT_7$ receptors. This atypical antipsychotic is a major substrate of ABCB1 and CYP2D6, a minor substrate of CYP3A4/5, and weakly inhibits ABCB1, CYP2D6, and CYP3A4. Caution and personalized dose adjustment should be made in patients with the following genotypes: ABCB1 (C1236T, G2677T, C3435T), COMT (rs4633, rs4680, rs737865, rs6269, rs4818, rs165599), CYP2D6 (CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*10, CYP2D6*17), DRD2 (TaqIA (rs1800497), −141C Ins/Del (rs1799732), A-241G), DRD3 (Gly9Ser (rs6280), rs167771), GRM3 (rs724226), HTR2A (His452Tyr, His368Tyr, Ile197Val, Ala447Val, Ala363Val, Thr25Asn, 102-T/C (rs6313)), HTR3A (rs1176713), and HTR6 (T267C). These genotypes and other variants in the ADRA1A, ADRA1B, APOA5, CYP3A4/5, DRD1, DRD4, FOS, HTR2C, KCNH2, RGS4, and SLC6A4 genes are responsible for the metabolism, pharmacological effects, and adverse drug events associated with risperidone administration to psychotic patients [25] (**Table 2**).

4.22. Sulpiride

Sulpiride is a benzamide with postsynaptic D_2 antagonist

activity. This atypical antipsychotic is a substrate of CYP2D6, and polymorphisms in the CYP2D6 and DRD2 genes influence its metabolism and pharmacological properties [25] (**Table 2**).

4.23. Thioridazine

Thioridazine is a phenothiazine which blocks postsynaptic mesolimbic dopaminergic receptors and α-adrenergic receptors, also acting as an inverse agonist of 5-HT$_6$ and 5-HT$_7$ receptors, and as an antagonist of 5-HT$_{2c}$ receptors. This typical antipsychotic is a major substrate of CYP1A2, CYP2D6, CYP2J2, and CYP3A4, a minor substrate of CYP2C19, a weak inhibitor of CYP1A2, CYP2C9, CYP2E1, and DRD1, a moderate inhibitor of CYP2D6, and a strong blocker of ADRA1s, ADRA2s, and ADRBs. Caution and personalized dose adjustment should be made in patients with the following genotypes: ADRA1A (Arg347Cys), CYP2D6 (CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*10, CYP2D6*17), and KCNE2 (Gln9Glu, Met54Thr, Thr8Ala). Other genes that may be involved in thioridazine metabolism and pharmacological effects include ABCB1, CHRM2, CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2E1, CYP2J2, CYP3A4, DRD2, FABP1, HRH1, KCNE1, KCNH2, KCNQ1, and KCNJ11 [25] (**Table 2**).

4.24. Thiothixene

Thiothixene is a thioxanthene which inhibits dopamine receptors, blocks α-adrenergic receptors, and is an antagonist of 5-HT$_{2a}$ receptors. This typical antipsychotic is a major substrate of CYP1A2 and a weak inhibitor of CYP2D6. Caution and personalized dose adjustment should be made in patients with the following genotypes: ADRA1A (Arg347Cys), CYP1A2 (C734A, G-2964A), KCNE2 (Gln9Glu, Met54Thr, Thr8Ala), KCNQ1 (Arg583Cys), KCNH6 (Arg784Trp), and SCN5A (Gly615Glu, Leu618Phe, Phe1250Leu, Leu1825Pro). Other genes potentially involved in thiothixene metabolism and pharmacological effects are CYP2D6, DRD2, and KCNE1 [25] (**Table 2**).

4.25. Trifluoperazine

Trifluoperazine is a phenothiazine which blocks postsynaptic mesolimbic dopaminergic receptors and α-adrenergic receptors. This typical antipsychotic is a major substrate of CYP1A2 and UGT1A4. Caution and personalized dose adjustment should be made in patients with the following genotypes: ADRA1A (Arg347Cys), and CYP1A2 (C734A, G-2964A). Some other genes (ABCB1, DRD2, IL12B, UGT1A4) may affect trifluoperazine pharmacokinetics and pharmacodynamics [25] (**Table 2**).

4.26. Ziprasidone

Ziprasidone is a benzylisothiazolylpiperazine with high affinity for D$_2$, D$_3$, 5-HT$_{2A}$, 5-HT$_{1A}$, 5-HT$_{2C}$, 5-HT$_{1D}$ and α_1-adrenergic receptors; moderate affinity for histamine H$_1$ receptors; antagonist of D$_2$, 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_{1D}$ receptors; full agonist of 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors; partial agonist of 5-HT$_{1A}$ receptors; and inverse agonist of 5-HT$_{2c}$ and 5-HT$_7$ receptors. This atypical antipsychotic is a major substrate of CYP3A4, a minor substrate of CYP1A2, a substrate of AOXs and HTR1A, and an inhibitor of CYP2D6, CYP3A4, HTR2A, and DRD2. Caution and personalized dose adjustment should be made in in patients with the following genotypes: CYP3A4 (CYP3A4*1, CYP3A4*1B, CYP3A4*2, CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*6, CYP3A4*8, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*15, CYP3A4*17, CYP3A4*18, CYP3A4*19), HTR2A (His452Tyr, His368Tyr, Ile197Val, Ile113Val, Ala447Val, Ala363Val, Thr25Asn), KCNH2 (Tyr652Ala, Phe656Ala), and RGS4 (rs951439, rs2661319, rs2842030). Other genes involved in ziprasidone pharmacokinetics and pharmacodynamics include AOX1, CYP1A2, CYP2D6, DRD2, DRD4, HTR1A, HTR2A, HRH1, and KCNH2 [25] (**Table 2**).

4.27. Zuclopenthixol

Zuclopenthixol is a thioxanthene which blocks postsynaptic mesolimbic dopaminergic receptors. This typical antipsychotic is a major substrate of CYP2D6; consequently, caution and personalized dose adjustment should be made in patients with the following CYP2D6 variants: CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*10, CYP2D6*17, CYP2D6*1xN. Other genes to take into account in the pharmacokinetics and pharmacodynamics of zuclopenthixol are ADRA1A, DRD1, DRD2, KCNE2, and SCN5A [25] (**Table 2**).

5. FUTURE DIRECTIONS

Historically, the vast majority of pharmacogenetic studies of CNS disorders have been addressed to evaluate the impact of cytochrome P450 enzymes on drug metabolism, and conventional targets for psychotropic drugs were dopamine, serotonin, noradrenaline, GABA, ion channels, acetylcholine and their respective biosynthetic and catalyzing enzymes, receptors and transporters; however, in the past few years many different genes have been associated with both pathogenesis and pharmacogenomics of neuropsychiatric disorders [1,2,5,6,17]. Some of these genes and their products constitute potential targets for future treatments. New developments in genomics, including whole genome genotyping approaches and comprehensive information on genomic

variation across populations, coupled with large-scale clinical trials in which DNA collection is routine, now provide the impetus for a next generation of pharmacogenetic studies and identification of novel candidate drugs.

Priority areas for pharmacogenetic research are predicting serious adverse reactions (ADRs) and establishing variation in efficacy [348]. Both requirements are necessary in CNS disorders to cope with efficacy and safety issues associated with both current psychotropic drugs and new drugs. Since drug response is a complex trait, genome-wide approaches may provide new insights into drug metabolism and drug response. Of paramount importance is the identification of polymorphisms affecting gene regulation and mRNA processing in genes encoding cytochrome P450s and other drug-metabolizing enzymes, drug transporters, and drug targets and receptors, with broad implication in pharmacogenetics since functional polymorphisms which alter gene expression and mRNA processing appear to play a critical role in shaping human phenotypic variability [349]. It is also most relevant, from a practical point of view, to understand the pharmacogenomics of drug transporters, especially ABCB1 (P-glycoprotein/MDR1) variants, due to the pleiotropic activity of this gene on a large number of drugs [350]. It is necessary to have a better documentation related to the pharmacogenetic roles of the enormous number (>170) of human solute carrier transporters which transport a variety of substrates, including amino acids, lipids, inorganic ions, peptides, saccharides, metals, drugs, toxic xenobiotics, chemical compounds, and proteins [351]. RNAi pharmacogenomics will also bring new insights into the nature and therapeutic value of gene silencing in CNS disorders [352-356].

The optimization of CNS therapeutics, in general, and the pharmacological treatment of SCZ and psychotic disorders, in particular, requires the establishment of new postulates regarding 1) the costs of medicines; 2) the assessment of protocols for multifactorial treatment in chronic disorders; 3) the implementation of novel therapeutics addressing causative factors; and 4) the seting-up of pharmacogenomic strategies for drug development and drugs on the market [2,6,14].

By knowing the pharmacogenomic profiles of patients who require treatments with psychotropic drugs of current use, it might be possible to obtain some of the following benefits: 1) to identify candidate patients with the ideal genomic profile to receive a particular drug; 2) to adapt the dose in over 60% - 90% of the cases according to the condition of EM, IM, PM or UM (diminishing the occurrence of direct side-effects in 30% - 50% of the cases); 3) to reduce drug interactions by 30% - 50% (avoiding the administration of inhibitors or inducers able to modify the normal enzymatic activity on a particular substrate); 4) to enhance efficacy and pharmacodynamic specificity; and 5) to eliminate unnecessary costs (>30% of pharmaceutical costs) derived from the consequences of an inappropriate drug selection and the overmedication administered to mitigate ADRs.

6. ACKNOWLEDGEMENTS

REFERENCES

[1] Cacabelos, R., Fernández-Novoa, L., Lombardi, V., Carril, J.C., Corzo, L., Carrera, I., Tellado, I., Martínez, R., McKay, A. and Takeda, M. (2011) Genomics of schizophrenia and psychotic disorders. *The EuroEspes Journal*: Gen-T, **3**, 6-86. http://www.gen-t.es/

[2] Cacabelos, R., Martínez-Bouza, R., Carril, J.C., Fernández-Novoa, L., Lombardi, V., Carrera, I., Corzo, L. and McKay, A. (2012) Genomics and pharmacogenomics of brain disorders. *Current Pharmaceutical Biotechnology*, **13**, 674-725. doi:10.2174/138920112799857576

[3] Andlin-Sobocki, P., Jönsson, B., Wittchen, H.-U. and Olesen, J. (2005) Costs of disorders of the brain in Europe. *European Journal of Neurology*, **12**, 1-27.

[4] Cacabelos, R. (2008) Pharmacogenomics in Alzheimer disease. *Methods in Molecular Biology*, **448**, 213-357. doi:10.1007/978-1-59745-205-2_10

[5] Cacabelos, R. (2009) Pharmacogenomic biomarkers in neuropsychiatry: The path to personalized medicine in mental disorders. In: Ritsner, M.S., Ed., *The Handbook of Neuropsychiatric Biomarkers*, *Endophenotypes and Genes*, Springer, Berlin, 3-63. doi:10.1007/978-90-481-2298-1_1

[6] Cacabelos, R., Martínez, R., Fernández-Novoa, L., Carril, J.C., Lombardi, V., Carrera, I., Corzo, L., Tellado, I., Leszek, J., McKay, A. and Takeda, M. (2012) Genomics of dementia: APOE- and CYP2D6-Related pharmacogenetics. *International Journal of Alzheimer disease*, **2012**, 37. doi:10.1155/2012/518901

[7] Malhotra, A.K., Lencz, T., Correll, C.U. and Kane, J.M. (2007) Genomics and the future of pharmacotherapy in psychiatry. *International Review of Psychiatry*, **19**, 523-530. doi:10.1080/09540260701563460

[8] Zhou, S.F., Di, Y.M., Chan, E., Du, Y.M., Chow, V.D., Xue, C.C., Lai, X., Wang, J.C., Li, C.G., Tian, M. and Duan, W. (2008) Clinical pharmacogenetics and potential application in personalized medicine. *Current Drug Metabolism*, **9**, 738-784. doi:10.2174/138920008786049302

[9] Cacabelos, R. (2008) Pharmacogenomics and therapeutic prospects in dementia. *European Archives of Psychiatry and Clinical Neuroscience*, **258**, 28-47. doi:10.1007/s00406-007-1006-x

[10] Cacabelos, R. (2007) Pharmacogenetic basis for the-

rapeutic optimization in Alzheimer disease. *Molecular Diagnosis & Therapy*, **11**, 385-405. doi:10.1007/BF03256262

[11] Cacabelos, R. (2007) Molecular pathology and pharmacogenomics in Alzheimer disease: Polygenic-related effects of multifactorial treatments on cognition, anxiety, and depression. *Methods & Findings in Experimental & Clinical Pharmacology*, **29**, 1-91.

[12] Cacabelos, R. (2005) Pharmacogenomics and therapeutic prospects in Alzheimer disease. *Expert Opinion on Pharmacotherapy*, **6**, 1967-1987. doi:10.1517/14656566.6.12.1967

[13] Cacabelos, R. (2009) Pharmacogenomics and therapeutic strategies for dementia. *Expert Review of Molecular Diagnostics*, **9**, 567-611. doi:10.1586/erm.09.42

[14] Cacabelos, R., Fernández-Novoa, L., Martínez-Bouza, R., McKay, A., Carril, J.C., Lombardi, V., Corzo, L., Carrera, I., Tellado, I., Nebril, L., Alcaraz, M., Rodríguez, S., Casas, A., Couceiro, V. and Alvarez, A. (2010) Future trends in the pharmacogenomics of brain disorders and dementia: Influence of APOE and CYP2D6 variants. *Pharmaceuticals*, **3**, 3040-3100. doi:10.3390/ph3103040

[15] Claes, S., Tang, Y.L., Gillespie, C.F. and Cubells, J.F. (2012) Human genetics of schizophrenia. *Handbook of Clinical Neurology*, **106**, 37-52. doi:10.1016/B978-0-444-52002-9.00003-6

[16] Boshes, R.A., Manschreck, T.C. and Konigsberg, W. (2012) Genetics of the schizophrenias: A model accounting for their persistence and myriad phenotypes. *Harvard Review of Psychiatry*, **20**, 119-129. doi:10.3109/10673229.2012.694321

[17] Cacabelos, R. and Martínez-Bouza, R. (2010) Genomics and pharmacogenomics of schizophrenia. *CNS Neuroscience & Therapeutics*, **17**, 541-565. doi:10.111_j.1755-5949.2010.00187

[18] Howes, O.D. and Kapur, S. (2009) The dopamine hypothesis of schizophrenia: Version III—the final common pathway. *Schizophrenia Bulletin*, **35**, 549-562. doi:10.1093/schbul/sbp006

[19] Bennett, M. (2009) Positive and negative symptoms in schizophrenia: The NMDA receptor hypofunction hypothesis, neuregulin/ErbB4 and synapse regression. *Australian & New Zealand Journal of Psychiatry*, **43**, 711-721. doi:10.1080/00048670903001943

[20] Fatemi, S.H. and Folsom, T.D. (2009) The neuro-developmental hypothesis of schizophrenia, revisited. *Schizophrenia Bulletin*, **35**, 528-548. doi:10.1093/schbul/sbn187

[21] Dean, B. (2009) Is schizophrenia the price of human central nervous system complexity? *Australian & New Zealand Journal of Psychiatry*, **43**, 13-24. doi:10.1080/00048670802534416

[22] Teo, C., Zai, C., Borlido, C., Tomasetti, C., Strauss, J., Shinkai, T., Le Foll, B., Wong, A., Kennedy, J.L. and De Luca, V. (2012) Analysis of treatment-resistant schizophrenia and 384 markers from candidate genes. *Pharmacogenet Genomics*, **22**, 807-811. doi:10.1097/FPC.0b013e3283586c04

[23] Ingelman-Sundberg, M., Sim, S.C., Gomez, A. and Rodríguez-Antona, C. (2007) Influence of cytochrome P450 polymorphisms on drug therapies: Pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacology & Therapeutics*, **116**, 496-526. doi:10.1016/j.pharmthera.2007.09.004

[24] National Center for Biotechnology Information (2012) Online Mendelian Inheritance in Man. http://www.ncbi.nlm.nih.gov/omim

[25] Cacabelos, R. (2012) World guide for drug use and pharmacogenomics. EuroEspes Publishing, Corunna. http://www.wgpgx.com/

[26] Xie, H.G., Kim, R.B., Wood, A.J. and Stein, C.M. (2001) Molecular basis of ethnic differences in drug disposition and response. *Annual Reviews*, *Pharmacology and Toxicology*, **41**, 815-850. doi:10.1146/annurev.pharmtox.41.1.815

[27] Isaza, C.A., Henao, J., López, A.M. and Cacabelos, R. (2000) Isolation, sequence and genotyping of the drug metabolizer CYP2D6 gene in the Colombian population. *Methods & Findings in Experimental & Clinical Pharmacology*, **22**, 695-705. doi:10.1358/mf.2000.22.9.802286

[28] Mizutani, T. (2003) PM frequencies of major CYPs in Asians and Caucasians. *Drug Metabolism Reviews*, **35**, 99-106. doi:10.1081/DMR-120023681

[29] Ozawa, S., Soyama, A., Saeki, M., Fukushima-Uesaka, H., Itoda, M., Koyano, S., Sai, K., Ohno, Y., Saito, Y. and Sawada, J. (2004) Ethnic differences in genetic polymorphisms of CYP2D6, CYP2C19, CYP3As and MDR1/ABCB1. *Drug Metabolism and Pharmacokinetics*, **19**, 83-95. doi:10.2133/dmpk.19.83

[30] Weinshilboum, R.M. and Wang, L. (2006) Pharmacogenetics and pharmacogenomics: Development, science, and translation. *Annual Reviews*, *Genomics and Human Genetics*, **7**, 223-245. doi:10.1146/annurev.genom.6.080604.162315

[31] Marquez, B. and van Bambeke, F. (2011) ABC multidrug transporters: Target for modulation of drug pharmacokinetics and drug-drug interactions. *Current Drug Targets*, **12**, 600-620. doi:10.2174/138945011795378504

[32] Haufroid, V. (2011) Genetic polymorphisms of ATP-binding cassette transporters ABCB1 and ABCC2 and their impact on drug disposition. *Current Drug Targets*, **12**, 631-646. doi:10.2174/138945011795378487

[33] Hosoya, K. and Tachikawa, M. (2011) Roles of organic anion/cation transporters at the blood-brain and blood-cerebrospinal fluid barriers involving uremic toxins. *Clinical and Experimental Nephrology*, **15**, 478-485. doi:10.1007/s10157-011-0460-y

[34] Carl, S.M., Lindley, D.J., Couraud, P.O., Weksler, B.B., Romero, I., Mowery, S.A. and Knipp, G.T. (2010) ANC and SLC transporter expression and pot substrate characterization across the human CMEC/D3 blood-brain barrier cell line. *Molecular Pharmaceutics*, **7**, 1057-1068. doi:10.1021/mp900178j

[35] Cacabelos, R., Fernández-Novoa, L., Lombardi, V., Kubota, Y. and Takeda, M. (2005) Molecular genetics of

Alzheimer disease and aging. *Methods & Findings in Experimental & Clinical Pharmacology*, **27**, 1-573.

[36] Chen, L.S., Rice, T.K., Thompson, P.A., Barch, D.M. and Csernansky, J.G. (2009) Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia. *Schizophrenia Research*, **111**, 159-166. doi:10.1016/j.schres.2009.03.030

[37] Lichtenstein, P., Yip, B.H., Björk, C., Pawitan, Y., Cannon, T.D., Sullivan, P.F. and Hultman, C.M. (2009) Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: A population-based study. *The Lancet*, **373**, 234-239. doi:10.1016/S0140-6736(09)60072-6

[38] Wiener, H.W., Klei, L., Irvin, M.D., Perry, R.T., Aliyu, M.H., Allen, T.B., Bradford, L.D., Calkins, M.E., Devlin, B., Edwards, N., Gur, R.E., Gur, R.C., Kwentus, J., Lyons, P.D., McEvoy, J.P., Nasrallah, H.A., Nimgaonkar,V.L., O'Jile, J., Santos, A.B., Savage, R.M. and Go, R.C. (2009) Linkage analysis of schizophrenia in African-American families. *Schizophrenia Research*, **109**, 70-79. doi:10.1016/j.schres.2009.02.007

[39] Holmans, P.A., Riley, B., Pulver, A.E., Owen, M.J., Wildenauer, D.B., Gejman, P.V., Mowry, B.J., Laurent, C., Kendler, K.S., Nestadt, G., Williams, N.M., Schwab, S.G., Sanders, A.R., Nertney, D., Mallet, J., Wormley, B., Lasseter, V.K., O'Donovan, M.C., Duan, J., Albus, M., Alexander. M., Godard, S., Ribble, R., Liang, K.Y., Norton, N., Maier, W., Papadimitriou, G., Walsh, D., Jay, M., O'Neill, A., Lerer, F.B., Dikeos, D., Crowe, R.R., Silverman, J.M. and Levinson, D.F. (2009) Genomewide linkage scan of schizophrenia in a large multicenter pedigree sample using single nucleotide polymorphisms. *Molecular Psychiatry*, **14**, 786-795. doi:10.1038/mp.2009.11

[40] Escamilla, M., Hare, E., Dassori, A.M., Peralta, J.M., Ontiveros, A., Nicolini, H., Raventós, H., Medina, R., Mendoza, R., Jerez, A., Muñoz, R. and Almasy, L. (2009) A schizophrenia gene locus on chromosome 17q21 in a new set of families of Mexican and central American ancestry: Evidence from the NIMH genetics of schizophrenia in Latino populations study. *The American Journal of Psychiatry*, **166**, 442-449. doi:10.1176/appi.ajp.2008.08040612

[41] Mefford, H.C. and Eichler, E.E. (2009) Duplication hotspots, rare genomic disorders, and common disease. *Current Opinion in Genetics & Development*, **19**, 196-204. doi:10.1016/j.gde.2009.04.003

[42] Sun, J., Han, L. and Zhao, Z. (2010) Gene- and evidence-based candidate gene selection for schizophrenia and gene feature analysis. *Artificial Intelligence in Medicine*, **48**, 99-106. doi:10.1016/j.artmed.2009.07.009

[43] Le Strat, Y., Ramoz, N. and Gorwood, P. (2009) The role of genes involved in neuroplasticity and neurogenesis in the observation of a gene-environment interaction (GxE) in schizophrenia. *Current Molecular Medicine*, **9**, 506-518. doi:10.2174/156652409788167104

[44] Jönsson, E.G., Saetre, P., Vares, M., Andreou, D., Larsson, K., Timm, S., Rasmussen, H.B., Djurovic, S., Melle, I., Andreassen, O.A., Agartz, I., Werge, T., Hall, H. and Terenius, L. (2009) DTNBP1, NRG1, DAOA, DAO and GRM3 polymorphisms and schizophrenia: An association study. *Neuropsychobiology*, **59**, 142-150.

[45] Psychiatric GWAS Consortium Coordinating Committee, Cichon, S., Craddock, N., Daly, M., Faraone, S.V., Gejman, P.V., Kelsoe, J., Lehner, T., Levinson, D.F., Moran, A., Sklar, P. and Sullivan, P.F. (2009) Genomewide association studies: History, rationale, and prospects for psychiatric disorders. *The American Journal of Psychiatry*, **166**, 540-556. doi:10.1176/appi.ajp.2008.08091354

[46] Psychiatric GWAS Consortium Steering Committee, (2009) A framework for interpreting genome-wide association studies of psychiatric disorders. *Molecular Psychiatry*, **14**, 10-17. doi:10.1038/mp.2008.126

[47] Hamshere, M.L., Walters, J.T., Smith, R., Richards, A.L., Green, E., Grozeva, D., Jones, I., Forty, L., Jones, L., Gordon-Smith, K., Riley, B., O'Neill, T., Kendler, K.S., Sklar, P., Purcell, S., Kranz, J., The schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC), Wellcome Trust Case Control Consortium+ (WTCCC+), Wellcome Trust Case Control Consortium 2 (WTCCC2), Morris, D., Gill, M., Holmans, P., Craddock, N., Corvin, A., Wwen, M.J. and O'Donovan, M.C. (2012) Genome-wide significant associations in schizophrenia to ITIH3/4, CACNA1C and SDCCAG8, and extensive replication of associations reported by the Schizophrenia PGC. *Molecular Psychiatry*. doi:10.1038/mp.2012.67

[48] Bergen, S.E., O'Dushlaine, C.T., Ripke, S., Lee, P.H., Ruderfer, D.M., Akterin, S., Moran, J.L., Chambert, K.D., Handsaker, R.E., Backlund, L., Osby, U., McCarroll, S., Landen, M., Scolnick, E.M., Magnusson, P.K., Lichtenstein, P., Hultman, C.M., Purcell, S.M., Sklar, P. and Sullivan, P.F. (2012) Genome-wide association study in a Swedish population yields support for greater CNV and MHC involvement in schizophrenia compared with bipolar disorder. *Molecular Psychiatry*, **17**, 880-886. doi:10.1038/mp.2012.73

[49] O'Donovan, M.C., Craddock, N.J. and Owen, M.J. (2009) Genetics of psychosis; insights from views across the genome. *Human Genetics*, **126**, 3-12. doi:10.1007/s00439-009-0703-0

[50] Ng, M.Y., Levinson, D.F., Faraone, S.V., Suarez, B.K., DeLisi, L.E., Arinami, T., Riley, B., Paunio, T., Pulver, A.E., Irmansyah, Holmans, P.A., Escamilla, M., Wildenauer, D.B., Williams, N.M., Laurent, C., Mowry, B.J., Brzustowicz, L.M., Maziade, M., Sklar, P., Garver, D.L., Abecasis, G.R., Lerer, B., Fallin, M.D., Gurling, H.M., Gejman, P.V., Lindholm, E., Moises, H.W., Byerley, W., Wijsman, E.M., Forabosco, P., Tsuang, M.T., Hwu, H.G., Okazaki, Y., Kendler, K.S., Wormley, B., Fanous, A., Walsh, D., O'Neill, F.A., Peltonen, L., Nestadt, G., Lasseter, V.K., Liang, K.Y., Papadimitriou, G.M., Dikeos, D.G., Schwab, S.G., Owen, M.J., O'Donovan, M.C., Norton, N., Hare, E., Raventos, H., Nicolini, H., Albus, M., Maier, W., Nimgaonkar, V.L., Terenius, L., Mallet, J., Jay, M., Godard, S., Nertney, D., Alexander, M., Crowe, R.R., Silverman, J.M., Bassett, A.S., Roy, M.A., Mérette, C., Pato, C.N., Pato, M.T., Roos, J.L., Kohn, Y., Amann-Zalcenstein, D., Kalsi, G., McQuillin, A., Curtis, D., Brynjolfson, J., Sigmundsson, T., Petursson, H., Sanders, A.R., Duan, J., Jazin, E., Myles-Worsley, M.,

Karayiorgou, M. and Lewis, C.M. (2009) Meta-analysis of 32 genome-wide linkage studies of schizophrenia. *Molecular Psychiatry*, **14**, 774-785. doi:10.1038/mp.2008.135

[51] Moskvina, V., Craddock, N., Holmans, P., Nikolov, I., Pahwa, J.S., Green, E., Wellcome Trust Case Control Consortium, Owen, M.J. and O'Donovan, M.C. (2009) Gene-wide analyses of genome-wide association data sets: Evidence for multiple common risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk. *Molecular Psychiatry*, **14**, 252-260. doi:10.1038/mp.2008.133

[52] Knight, H.M., Pickard, B.S., Maclean, A., Malloy, M.P., Soares, D.C., McRae, A.F., Condie, A., White, A., Hawkins, W., McGhee, K., van Beck, M., MacIntyre, D.J., Starr, J.M., Deary, I.J., Visscher, P.M., Porteous, D.J., Cannon, R.E., St Clair, D., Muir, W.J. and Blackwood, D.H. (2009) A cytogenetic abnormality and rare coding variants identify ABCA13 as a candidate gene in schizophrenia, bipolar disorder, and depression. *The American Journal of Human Genetics*, **85**, 833-846. doi:10.1016/j.ajhg.2009.11.003

[53] Ingason, A., Giegling, I., Cichon, S., Hansen, T., Rasmussen, H.B., Nielsen, J., Jürgens, G., Muglia, P., Hartmann, A.M., Strengman, E., Vasilescu, C., Mühleisen, T.W., Djurovic, S., Melle, I., Lerer, B., M?ller, H.J., Francks, C., Pietiläinen, O.P., Lonnqvist, J., Suvisaari, J., Tuulio-Henriksson, A., Walshe, M., Vassos, E., Di Forti, M., Murray, R., Bonetto, C., Tosato, S.; GROUP Investigators, Cantor, R.M., Rietschel, M., Craddock, N., Owen, M.J., Peltonen, L., Andreassen, O.A., Nöthen, M.M., St Clair, D., Ophoff, R.A., O'Donovan, M.C., Collier, D.A., Werge, T. and Rujescu, D. (2010) A large replication study and meta-analysis in European samples provides further support for association of AHI1 markers with schizophrenia. *Human Molecular Genetics*, **19**, 1379-1386. doi:10.1093/hmg/ddq009

[54] Ikeda, M., Tomita, Y., Mouri, A., Koga, M., Okochi, T., Yoshimura, R., Yamanouchi, Y., Kinoshita, Y., Hashimoto, R., Williams, H.J., Takeda, M., Nakamura, J., Nabeshima, T., Owen, M.J., O'Donovan, M.C., Honda, H., Arinami, T., Ozaki, N. and Iwata, N. (2010) Identification of novel candidate genes for treatment response to risperidone and susceptibility for schizophrenia: Integrated analysis among pharmacogenomics, mouse expression, and genetic case-control association approaches. *Biological Psychiatry*, **67**, 263-269. doi:10.1016/j.biopsych.2009.08.030

[55] Rivero, O., Reif, A., Sanjuán, J., Moltó, M.D., Kittel-Schneider, S., Nájera, S., Töpner, T. and Lesch, K.P. (2010) Impact of the AHI1 gene on the vulnerability to schizophrenia: A case-control association study. *PLoS One*, **5**, e12254. doi:10.1371/journal.pone.0012254

[56] Zhang, F., Xu, Y., Liu, P., Fan, H., Huang, X., Sun, G., Song, Y. and Sham, P.C. (2008) Association analyses of the interaction between the ADSS and ATM genes with schizophrenia in a Chinese population. *BMC Medical Genetics*, **9**, 119. doi:10.1186/1471-2350-9-119

[57] Yamaguchi, W., Shinkai, T., Inoue, Y., Utsunomiya, K., Sakata, S., Fukunaka, Y., Yamada, K., Chen, H.I., Hwang, R., Ohmori, O. and Nakamura, J. (2009) Association analysis between the C-1291G polymorphism in the promoter region of the adrenergic alpha2A receptor gene and polydipsia in schizophrenia. *Progress in Neuro-Psychopharmacology Biological Psychiatry*, **33**, 499-502. doi:10.1016/j.pnpbp.2009.01.012

[58] Wan, C., Shi, Y., Zhao, X., Tang, W., Zhang, M., Ji, B., Zhu, H., Xu, Y., Li, H., Feng, G. and He, L. (2009) Positive association between ALDH1A2 and schizophrenia in the Chinese population. *Progress in Neuro-Psychopharmacology Biological Psychiatry*, **33**, 1491-1495. doi:10.1016/j.pnpbp.2009.08.008

[59] Noori-Daloii, M.R., Kheirollahi, M., Mahbod, P., Mohammadi, F., Astaneh, A.N., Zarindast, M.R., Azimi, C. and Mohammadi, M.R. (2010) Alpha- and beta-synucleins mRNA expression in lymphocytes of schizophrenia patients. *Genetic Testing and Molecular Biomarkers*, **14**, 725-729. doi:10.1089/gtmb.2010.0050

[60] Kucukali, C.I., Aydin, M., Ozkok, E., Bilge, E., Zengin, A., Cakir, U. and Kara, I. (2010) Angiotensin-converting enzyme polymorphism in schizophrenia, bipolar disorders, and their first-degree relatives. *Psychiatric Genetics*, **20**, 14-19. doi:10.1097/YPG.0b013e3283351194

[61] Hashimoto, R., Ohi, K., Okada, T., Yasuda, Y., Yamamori, H., Hori, H., Hikita, T., Taya, S., Saitoh, O., Kosuga, A., Tatsumi, M., Kamijima, K., Kaibuchi, K., Takeda, M. and Kunugi, H. (2009) Association analysis between schizophrenia and the AP-3 complex genes. *Neuroscience Research*, **65**, 113-115. doi:10.1016/j.neures.2009.05.008

[62] Vik-Mo, A.O., Fernø, J., Skrede, S. and Steen, V.M. (2009) Psychotropic drugs up-regulate the expression of cholesterol transport proteins including ApoE in cultured human CNS- and liver cells. *BMC Pharmacology*, **9**, 10. doi:10.1186/1471-2210-9-10

[63] Chen, X., Sun, C., Chen, Q., O'Neill, F.A., Walsh, D., Fanous, A.H., Chowdari, K.V., Nimgaonkar, V.L., Scott, A., Schwab, S.G., Wildenauer, D.B., Che, R., Tang, W., Shi, Y., He, L., Luo, X.J., Su, B., Edwards, T.L., Zhao, Z. and Kendler, K.S. (2009) Apoptotic engulfment pathway and schizophrenia. *PLoS One*, **4**, e6875. doi:10.1371/journal.pone.0006875

[64] Levin, R., Heresco-Levy, U., Bachner-Melman, R., Israel, S., Shalev, I. and Ebstein, R.P. (2009) Association between arginine vasopressin 1a receptor (AVPR1a) promoter region polymorphisms and prepulse inhibition. *Psychoneuroendocrinology*, **34**, 901-908. doi:10.1016/j.psyneuen.2008.12.014

[65] Israel, S., Lerer, E., Shalev, I., Uzefovsky, F., Reibold, M., Bachner-Melman, R., Granot, R., Bornstein, G., Knafo, A., Yirmiya, N. and Ebstein, R.P. (2008) Molecular genetic studies of the arginine vasopressin 1a receptor (AVPR1a) and the oxytocin receptor (OXTR) in human behaviour: From autism to altruism with some notes in between. *Progress in Brain Research*, **170**, 435-449. doi:10.1016/S0079-6123(08)00434-2

[66] Hammock, E.A. and Young, L.J. (2006) Oxytocin, vasopressin and pair bonding: Implications for autism. *Philosophical Transactions of the Royal Society B Biological Sciences*, **361**, 2187-2198. doi:10.1098/rstb.2006.1939

[67] Liou, Y.J., Wang, Y.C., Chen, J.Y., Chen, M.L., Chen, T.T., Bai, Y.M., Lin, C.C., Liao, D.L. and Lai, I.C. (2008) The coding-synonymous polymorphism rs1045280 (Ser-280Ser) in beta-arrestin 2 (ARRB2) gene is associated with tardive dyskinesia in Chinese patients with schizophrenia. European Journal of Neurology, **15**, 1406-1408. doi:10.1111/j.1468-1331.2008.02316.x

[68] Ohi, K., Hashimoto, R., Yasuda, Y., Yamamori, H., Hori, H., Saitoh, O., Tatsumi, M., Takeda, M., Iwata, N., Ozaki, N., Kamijima, K. and Kunugi, H. (2009) No association between the Bcl2-interacting killer (BIK) gene and schizophrenia. Neuroscience Letters, **463**, 60-63. doi:10.1016/j.neulet.2009.07.063

[69] Cheli, V.T., Daniels, R.W., Godoy, R., Hoyle, D.J., Kandachar, V., Starcevic, M., Martinez-Agosto, J.A., Poole, S., DiAntonio, A., Lloyd, V.K., Chang, H.C., Krantz, D.E. and Dell'Angelica, E.C. (2009) Genetic modifiers of abnormal organelle biogenesis in a Drosophila model of BLOC-1 deficiency. Human Molecular Genetics, **19**, 861-878. doi:10.1093/hmg/ddp555

[70] Kawashima, K., Ikeda, M., Kishi, T., Kitajima, T., Yamanouchi, Y., Kinoshita, Y., Okochi, T., Aleksic, B., Tomita, M., Okada, T., Kunugi, H., Inada, T., Ozaki, N. and Iwata, N. (2009) BDNF is not associated with schizophrenia: Data from a Japanese population study and meta-analysis. Schizophrenia Research, **112**, 72-79. doi:10.1016/j.schres.2009.03.040

[71] Chang, H.A., Lu, R.B., Shy, M.J., Chang, C.C., Lee, M.S. and Huang, S.Y. (2009) Brain-derived neurotrophic factor Val66Met polymorphism: Association with psychopathological symptoms of schizophrenia? The Journal of Neuropsychiatry & Clinical Neurosciences, **21**, 30-37. doi:10.1176/appi.neuropsych.21.1.30

[72] Lencz, T., Lipsky, R.H., DeRosse, P., Burdick, K.E., Kane, J.M. and Malhotra, A.K. (2009) Molecular differentiation of schizoaffective disorder from schizophrenia using BDNF haplotypes. The British Journal of Psychiatry, **194**, 313-318. doi:10.1192/bjp.bp.108.050401

[73] Wong, J., Webster, M.J., Cassano, H. and Weickert, C.S. (2009) Changes in alternative brain-derived neurotrophic factor transcript expression in the developing human prefrontal cortex. European Journal of Neuroscience, **29**, 1311-1322. doi:10.1111/j.1460-9568.2009.06669.x

[74] Dunham, J.S., Deakin, J.F., Miyajima, F., Payton, A. and Toro, C.T. (2009) Expression of hippocampal brain-derived neurotrophic factor and its receptors in Stanley consortium brains. Journal of Psychiatric Research, **43**, 1175-1184. doi:10.1016/j.jpsychires.2009.03.008

[75] Park, S.W., Lee, J.G., Kong, B.G., Lee, S.J., Lee, C.H., Kim, J.I. and Kim, Y.H. (2009) Genetic association of BDNF Val66Met and GSK-3beta-50T/C polymorphisms with tardive dyskinesia. Psychiatry and Clinical Neurosciences, **63**, 433-439. doi:10.1111/j.1440-1819.2009.01976.x

[76] Nyegaard, M., Severinsen, J.E., Als, T.D., Hedemand, A., Straarup, S., Nordentoft, M., McQuillin, A., Bass, N., Lawrence, J., Thirumalai, S., Pereira, A.C., Kandaswamy, R., Lydall, G.J., Sklar, P., Scolnick, E., Purcell, S., Curtis, D., Gurling, H.M., Mortensen, P.B., Mors, O. and Børglum, A.D. (2010) Support of association between BRD1

and both schizophrenia and bipolar affective disorder. American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics, **153B**, 582-591.

[77] Green, E.K., Grozeva, D., Jones, I., Jones, L., Kirov, G., Caesar, S., Gordon-Smith, K., Fraser, C., Forty, L., Russell, E., Hamshere, M.L., Moskvina, V., Nikolov, I., Farmer, A., McGuffin, P., Wellcome Trust Case Control Consortium, Holmans, P.A., Owen, M.J., O'Donovan, M.C. and Craddock, N. (2010) The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia. Molecular Psychiatry, **15**, 1016-1022. doi:10.1038/mp.2009.49

[78] McMahon, F.J., Akula, N., Schulze, T.G., Muglia, P., Tozzi, F., Detera-Wadleigh, S.D., Steele, C.J., Breuer, R., Strohmaier, J., Wendland, J.R., Mattheisen, M., Mühleisen, T.W., Maier, W., Nöthen, M.M., Cichon, S., Farmer, A., Vincent, J.B., Holsboer, F., Preisig, M., Rietschel, M. and Bipolar Disorder and Genome Study (BiGS) Consortium (2010) Meta-analysis of genome-wide association data identifies a risk locus for major mood disorders on 3p21.1. Nature Genetics, **42**, 128-131. doi:10.1038/ng.523

[79] Bigos, K.L., Mattay, V.S., Callicott, J.H., Straub, R.E., Vakkalanka, R., Kolachana, B., Hyde, T.M., Lipska, B.K., Kleinman, J.E. and Weinberger, D.R. (2010) Genetic variation in CACNA1C affects brain circuitries related to mental illness. Archives of General Psychiatry, **67**, 939-945. doi:10.1001/archgenpsychiatry.2010.96

[80] Farokhashtiani, T., Mirabzadeh, A., Olad Nabi, M., Magham, Z.G, Khorshid, H.R., Najmabadi, H. and Ohadi, M. (2010) Reversion of the human calreticulin gene promoter to the ancestral type as a result of a novel psychosis-associated mutation. Progress in Neuro-Psychopharmacology and Biological Psychiatry, **35**, 541-544. doi:10.1016/j.pnpbp.2010.12.012

[81] Ishiguro, H., Horiuchi, Y., Ishikawa, M., Koga, M., Imai, K., Suzuki, Y., Morikawa, M., Inada, T., Watanabe, Y., Takahashi, M., Someya, T., Ujike, H., Iwata, N., Ozaki, N., Onaivi, E.S., Kunugi, H., Sasaki, T., Itokawa, M., Arai, M., Niizato, K., Iritani, S., Naka, I., Ohashi, J., Kakita, A., Takahashi, H., Nawa, H. and Arinami, T. (2010) Brain cannabinoid CB$_2$ receptor in schizophrenia. Biological Psychiatry, **67**, 974-982. doi:10.1016/j.biopsych.2009.09.024

[82] Lendeckel, U., Kähne, T., Ten Have, S., Bukowska, A., Wolke, C., Bogerts, B., Keilhoff, G. and Bernstein, H.G. (2009) Cathepsin K generates enkephalin from beta-endorphin: A new mechanism with possible relevance for schizophrenia. Neurochemistry International, **54**, 410-417. doi:10.1016/j.neuint.2009.01.011

[83] Minato, T., Tochigi, M., Kato, N. and Sasaki, T. (2007) Association study between the cholecystokinin A receptor gene and schizophrenia in the Japanese population. Psychiatric Genetics, **17**, 117-119. doi:10.1097/YPG.0b013e328011c02e

[84] Sinkus, M.L., Lee, M.J., Gault, J., Logel, J., Short, M., Freedman, R., Christian, S.L., Lyon, J. and Leonard, S. (2009) A 2-base pair deletion polymorphism in the partial duplication of the alpha7 nicotinic acetylcholine gene (CHRFAM7A) on chromosome 15q14 is associated with

schizophrenia. *Brain Research*, **1291**, 1-11. doi:10.1016/j.brainres.2009.07.041

[85] Stephens, S.H., Logel, J., Barton, A., Franks, A., Schultz, J., Short, M., Dickenson, J., James, B., Fingerlin, T.E., Wagner, B., Hodgkinson, C., Graw, S., Ross, R.G., Freedman, R. and Leonard, S. (2009) Association of the 5'-upstream regulatory region of the alpha7 nicotinic acetylcholine receptor subunit gene (CHRNA7) with schizophrenia. *Schizophrenia Research*, **109**, 102-112. doi:10.1016/j.schres.2008.12.017

[86] Kishi, T., Kitajima, T., Ikeda, M., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., Okochi, T., Okumura, T., Tsunoka, T., Inada, T., Ozaki, N. and Iwata, N. (2009) Association study of clock gene (CLOCK) and schizophrenia and mood disorders in the Japanese population. *European Archives of Psychiatry and Clinical Neuroscience*, **259**, 293-297. doi:10.1007/s00406-009-0869-4

[87] Zhou, Y., Wang, J., Wang, K., Li, S., Song, X., Ye, Y., Wang, L. and Ying, B. (2010) Association analysis between the rs11136000 single nucleotide polymorphism in clusterin gene, rs3851179 single nucleotide polymorphism in clathrin assembly lymphoid myeloid protein gene and the patients with schizophrenia in the Chinese population. *DNA and Cell Biology*, **29**, 745-751. doi:10.1089/dna.2010.1075

[88] Chen, X., Lee, G., Maher, B.S., Fanous, A.H., Chen, J., Zhao, Z., Guo, A., van den Oord, E., Sullivan, P.F., Shi, J., Levinson, D.F., Gejman, P.V., Sanders, A., Duan, J., Owen, M.J., Craddock, N.J., O'Donovan, M.C., Blackman, J., Lewis, D., Kirov, G.K., Qin, W., Schwab, S., Wildenauer, D., Chowdari, K., Nimgaonkar, V., Straub, R.E., Weinberger, D.R., O'Neill, F.A., Walsh, D., Bronstein, M., Darvasi, A., Lencz, T., Malhotra, A.K., Rujescu, D., Giegling, I., Werge, T., Hansen, T., Ingason, A., N?ethen, M.M., Rietschel, M., Cichon, S., Djurovic, S., Andreassen, O.A., Cantor, R.M., Ophoff, R., Corvin, A., Morris, D.W., Gill, M., Pato, C.N., Pato, M.T., Macedo, A., Gurling, H.M., McQuillin, A., Pimm, J., Hultman, C., Lichtenstein, P., Sklar, P., Purcell, S.M., Scolnick, E., St Clair, D., Blackwood, D.H., Kendler, K.S. and GROUP investigators and International Schizophrenia Consortium (2010) GWA study data mining and independent replication identify cardiomyopathy-associated 5 (CMYA5) as a risk gene for schizophrenia. *Molecular Psychiatry*, **16**, 1117-1129. doi:10.1038/mp.2010.96

[89] Che, R., Tang, W., Zhang, J., Wei, Z., Zhang, Z., Huang, K., Zhao, X., Gao, J., Zhou, G., Huang, P., He, L. and Shi, Y. (2009) No relationship between 2',3'-cyclic nucleotide 3'-phosphodiesterase and schizophrenia in the Chinese Han population: An expression study and meta-analysis. *BMC Medical Genetics*, **10**, 31. doi:10.1186/1471-2350-10-31

[90] Zweier, C., de Jong, E.K., Zweier, M., Orrico, A., Ousager, L.B., Collins, A.L., Bijlsma, E.K., Oortveld, M.A., Ekici, A.B., Reis, A., Schenck, A. and Rauch, A. (2009) CNTNAP2 and NRXN1 are mutated in autosomal-recessive pitt-hopkins-like mental retardation and determine the level of a common synaptic protein in drosophila. *The American Journal of Human Genetics*, **85**, 655-666. doi:10.1016/j.ajhg.2009.10.004

[91] Begemann, M., Grube, S., Papiol, S., Malzahn, D., Krampe, H., Ribbe, K., Friedrichs, H., Radyushkin, K.A., El-Kordi, A., Benseler, F., Hannke, K., Sperling, S., Schwerdtfeger, D., Thanhäuser, I., Gerchen, M.F., Ghorbani, M., Gutwinski, S., Hilmes, C., Leppert, R., Ronnenberg, A., Sowislo, J., Stawicki, S., Stödtke, M., Szuszies, C., Reim, K., Riggert, J., Eckstein, F., Falkai, P., Bickeböller, H., Nave, K.A., Brose, N. and Ehrenreich, H. (2010) Modification of cognitive performance in schizophrenia by complexin 2 gene polymorphisms. *Archives of General Psychiatry*, **67**, 879-888. doi:10.1001/archgenpsychiatry.2010.107

[92] Rutherford, K. and Daggett, V. (2009) A hotspot of inactivation: The A22S and V108M polymorphisms individually destabilize the active site structure of catechol O-methyltransferase. *Biochemistry*, **48**, 6450-6460. doi:10.1021/bi900174v

[93] Williams, H.J., Owen, M.J. and O'Donovan, M.C. (2007) Is COMT a susceptibility gene for schizophrenia? *Schizophrenia Bulletin*, **33**, 635-641. doi:10.1093/schbul/sbm019

[94] Fan, J.B., Zhang, C.S., Gu, N.F., Li, X.W., Sun, W.W., Wang, H.Y., Feng, G.Y., St Clair, D. and He, L. (2005) Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: A large-scale association study plus meta-analysis. *Biological Psychiatry*, **57**, 139-144. doi:10.1016/j.biopsych.2004.10.018

[95] Zhang, F., Liu, C., Chen, Y., Wang, L., Lu, T., Yan, H., Ruan, Y., Yue, W. and Zhang, D. (2012) No association of catechol-O-methyltransferase polymorphisms with schizophrenia in the Han Chinese population. *Genetic Testing and Molecular Biomarkers*, **16**, 1138-1141. doi:10.1089/gtmb.2012.0061

[96] Okochi, T., Ikeda, M., Kishi, T., Kawashima, K., Kinoshita, Y., Kitajima, T., Yamanouchi, Y., Tomita, M., Inada, T., Ozaki, N. and Iwata, N. (2009) Meta-analysis of association between genetic variants in COMT and schizophrenia: An update. *Schizophrenia Research*, **110**, 140-148. doi:10.1016/j.schres.2009.02.019

[97] Weinberger, D.R. (2005) Genetic mechanisms of psychosis: *In vivo* and post-mortem genomics. *Clinical Therapeutics*, **27**, S8-S15. doi:10.1016/j.clinthera.2005.07.016

[98] Srivastava, V., Deshpande, S.N. and Thelma, B.K. (2009) Dopaminergic pathway gene polymorphisms and genetic susceptibility to schizophrenia among north Indians. *Neuropsychobiology*, **61**, 64-70. doi:10.1159/000265131

[99] Park, B.L., Shin, H.D., Cheong, H.S., Park, C.S., Sohn, J.W., Kim, B.J., Seo, H.K., Kim, J.W., Kim, K.H., Shin, T.M., Choi, I.G., Kim, S.G. and Woo, S.I. (2009) Association analysis of COMT polymorphisms with schizophrenia and smooth pursuit eye movement abnormality. *Journal of Human Genetics*, **54**, 709-712. doi:10.1038/jhg.2009.102

[100] Gu, Y., Yun, L., Tian, Y. and Hu, Z. (2009) Association between COMT gene and Chinese male schizophrenic patients with violent behavior. *Medical Science Monitor*, **15**, CR484-9.

[101] Neuhaus, A.H., Opgen-Rhein, C., Urbanek, C., Hahn, E.,

Ta, T.M., Seidelsohn, M., Strathmann, S., Kley, F., Wieseke, N., Sander, T. and Dettling, M. (2009) COMT Val 158 Met polymorphism is associated with cognitive flexibility in a signal discrimination task in schizophrenia. *Pharmacopsychiatry*, **42**, 141-144. doi:10.1055/s-0028-1112132

[102] Takizawa, R., Tochigi, M., Kawakubo, Y., Marumo, K., Sasaki, T., Fukuda, M. and Kasai, K. (2009) Association between catechol-O-methyltrasferase Val108/158Met genotype and prefrontal hemodynamic response in schizophrenia. *PLoS One*, **4**, e5495. doi:10.1371/journal.pone.0005495

[103] Chien, Y.L., Liu, C.M., Fann, C.S., Liu, Y.L. and Hwu, H.G. (2009) Association of the 3' region of COMT with schizophrenia in Taiwan. *Journal of the Formosan Medical Association*, **108**, 301-309. doi:10.1016/S0929-6646(09)60070-X

[104] Liao, S.Y., Lin, S.H., Liu, C.M., Hsieh, M.H., Hwang, T.J., Liu, S.K., Guo, S.C., Hwu, H.G. and Chen, W.J. (2009) Genetic variants in COMT and neurocognitive impairment in families of patients with schizophrenia. *Genes*, *Brain and Behavior*, **8**, 228-237. doi:10.1111/j.1601-183X.2008.00467.x

[105] Wang, Y., Hu, Y., Fang, Y., *et al.* (2009) Evidence of epistasis between the catechol-O-methyltransferase and aldehyde dehydrogenase 3B$_1$ genes in paranoid schizophrenia. *Biological Psychiatry*, **65**, 1048-1054. doi:10.1016/j.biopsych.2008.11.027

[106] Chen, P., Huang, K., Zhou, G., Zeng, Z., Wang, T., Li, B., Wang, Y., He, L., Feng, G. and Shi, Y. (2011) Common SNPs in CSF2RB are associated with major depression and schizophrenia in the Chinese Han population. *World Journal of Biological Psychiatry*, **12**, 233-238. doi:10.3109/15622975.2010.544328

[107] Liu, J., Li, J., Li, T., Wang, T., Li, Y., Zeng, Z., Li, Z., Chen, P., Hu, Z., Zheng, L., Ji, J., Lin, H., Feng, G. and Shi, Y. (2011) CTLA-4 confers a risk of recurrent schizophrenia, major depressive disorder and bipolar disorder in the Chinese Han population. *Brain*, *Behavior*, *and Immunity*, **25**, 429-433. doi:10.1016/j.bbi.2010.10.024

[108] Du, J., Xu, Y., Duan, S., Zhang, A., Xuan, J., Wang, L., Yu, L., Wang, H., Li, X., Feng, G., He, L. and Xing, Q. (2009) A case-control association study between the CYP3A4 and CYP3A5 genes and schizophrenia in the Chinese Han population. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **33**, 1200-1204. doi:10.1016/j.pnpbp.2009.06.023

[109] Ohi, K., Hashimoto, R., Yasuda, Y., Yoshida, T., Takahashi, H., Iike, N., Fukumoto, M., Takamura, H., Iwase, M., Kamino, K., Ishii, R., Kazui, H., Sekiyama, R., Kitamura, Y., Azechi, M., Ikezawa, K., Kurimoto, R., Kamagata, E., Tanimukai, H., Tagami, S., Morihara, T., Ogasawara, M., Okochi, M., Tokunaga, H., Numata, S., Ikeda, M., Ohnuma, T., Ueno, S., Fukunaga, T., Tanaka, T., Kudo, T., Arai, H., Ohmori, T., Iwata, N., Ozaki, N. and Takeda, M. (2009) Association study of the G72 gene with schizophrenia in a Japanese population: A multicenter study. *Schizophrenia Research*, **109**, 80-85. doi:10.1016/j.schres.2009.01.019

[110] Detera-Wadleigh, S.D. and McMahon, F.J. (2006) G72/G30 in schizophrenia and bipolar disorder: Review and meta-analysis. *Biological Psychiatry*, **60**, 106-114. doi:10.1016/j.biopsych.2006.01.019

[111] Gomez, L., Wigg, K., Feng, Y., Kiss, E., Kapornai, K., Tamás, Z., Mayer, L., Baji, I., Daróczi, G., Benák, I., Kothencné, V.O., Dombovári, E., Kaczvinszk, E., Besnyo, M., Gádoros, J., King, N., Székely, J., Kovacs, M., Vetró, A., Kennedy, J.L. and Barr, C.L. (2009) G72/G30 (DAOA) and juvenile-onset mood disorders. *American Journal of Medical Genetics Part B*: *Neuropsychiatric Genetics*, **150**, 1007-1012. doi:10.1002/ajmg.b.30904

[112] Benzel, I., Kew, J.N., Viknaraja, R., Kelly, F., de Belleroche, J., Hirsch, S., Sanderson, T.H. and Maycox, P.R. (2008) Investigation of G72 (DAOA) expression in the human brain. *BMC Psychiatry*, **8**, 94. doi:10.1186/1471-244X-8-94

[113] Chubb, J.E., Bradshaw, N.J., Soares, D.C., Porteous, D.J. and Millar, J.K. (2008) The DISC locus in psychiatric illness. *Molecular Psychiatry*, **13**, 36-64. doi:10.1038/sj.mp.4002106

[114] Nakata, K., Lipska, B.K., Hyde, T.M., Ye, T., Newburn, E.N., Morita, Y., Vakkalanka, R., Barenboim, M., Sei, Y., Weinberger, D.R. and Kleinman, J.E. (2009) DISC1 splice variants are upregulated in schizophrenia and associated with risk polymorphisms. *Proceedings of the National Academy of Sciences of USA*, **106**, 15873-15878. doi:10.1073/pnas.0903413106

[115] Crepel, A., Breckpot, J., Fryns, J.P., De la Marche, W., Steyaert, J., Devriendt, K. and Peeters, H. (2010) DISC1 duplication in two brothers with autism and mild mental retardation. *Clinical Genetics*, **77**, 389-394. doi:10.1111/j.1399-0004.2009.01318.x

[116] Enomoto, A., Asai, N., Namba, T., Wang, Y., Kato, T., Tanaka, M., Tatsumi, H., Taya, S., Tsuboi, D., Kuroda, K., Kaneko, N., Sawamoto, K., Miyamoto, R., Jijiwa, M., Murakumo, Y., Sokabe, M., Seki, T., Kaibuchi, K. and Takahashi, M. (2009) Roles of disrupted-in-schizophrenia 1-interacting protein girdin in postnatal development of the dentate gyrus. *Neuron*, **63**, 774-787. doi:10.1016/j.neuron.2009.08.015

[117] Kim, J.Y., Duan, X., Liu, C.Y., Jang, M.H., Guo, J.U., Pow-anpongkul, N., Kang, E., Song, H. and Ming, G.L. (2009) DISC1 regulates new neuron development in the adult brain via modulation of AKT-mTOR signaling through KIAA1212. *Neuron*, **63**, 761-773. doi:10.1016/j.neuron.2009.08.008

[118] Matsuzaki, S. and Tohyama, M. (2007) Molecular mechanism of schizophrenia with reference to disrupted-in-schizophrenia 1 (DISC1). *Neurochemistry International*, **51**, 165-172. doi:10.1016/j.neuint.2007.06.018

[119] Millar, J.K., Mackie, S., Clapcote, S.J., Murdoch, H., Pickard, B.S., Christie, S., Muir, W.J., Blackwood, D.H., Roder, J.C., Houslay, M.D. and Porteous, D.J. (2007) Disrupted in schizophrenia 1 and phosphodiesterase 4B: Towards an understanding of psychiatric illness. *The Journal of Physiology*, **584**, 401-405. doi:10.1113/jphysiol.2007.140210

[120] Bradshaw, N.J., Ogawa, F., Antolin-Fontes, B., Chubb,

J.E., Carlyle, B.C., Christie, S., Claessens, A., Porteous, D.J. and Millar, J.K. (2008) DISC1, PDE4B, and NDE1 at the centrosome and synapse. *Biochemical and Biophysical Research Communications*, **377**, 1091-1096. doi:10.1016/j.bbrc.2008.10.120

[121] Tomppo, L., Hennah, W., Lahermo, P., Loukola, A., Tuulio-Henriksson, A., Suvisaari, J., Partonen, T., Ekelund, J., Lännqvist, J. and Peltonen, L. (2009) Association between genes of disrupted in schizophrenia 1 (DISC1) interactors and schizophrenia supports the role of the DISC1 pathway in the etiology of major mental illnesses. *Biological Psychiatry*, **65**, 1055-1062. doi:10.1016/j.biopsych.2009.01.014

[122] Drerup, C.M., Wiora, H.M., Topczewski, J. and Morris, J.A. (2009) Disc1 regulates foxd3 and sox10 expression, affecting neural crest migration and differentiation. *Development*, **136**, 2623-2632. doi:10.1242/dev.030577

[123] Takahashi, T., Suzuki, M., Tsunoda, M., Maeno, N., Kawasaki, Y., Zhou, S.Y., Hagino, H., Niu, L., Tsuneki, H., Kobayashi, S., Sasaoka, T., Seto, H., Kurachi, M. and Ozaki, N. (2009) The disrupted-in-schizophrenia-1 Ser-704Cys polymorphism and brain morphology in schizophrenia. *Psychiatry Research*, **172**, 128-135. doi:10.1016/j.pscychresns.2009.01.005

[124] Schumacher, J., Laje, G., Abou Jamra, R., Becker, T., Mühleisen, T.W., Vasilescu, C., Mattheisen, M., Herms, S., Hoffmann, P., Hillmer, A.M., Georgi, A., Herold, C., Schulze, T.G., Propping, P., Rietschel, M., McMahon, F.J., Nöthen, M.M. and Cichon, S. (2009) The DISC locus and schizophrenia: evidence from an association study in a central European sample and from a meta-analysis across different European populations. *Human Molecular Genetics*, **18**, 2719-2727. doi:10.1093/hmg/ddp204

[125] Zhang, C., Fang, Y., Xie, B., Cheng, W., Du, Y., Wang, D. and Yu, S. (2009) DNA methyltransferase 3B gene increases risk of early onset schizophrenia. *Neuroscience Letters*, **462**, 308-311. doi:10.1016/j.neulet.2009.06.085

[126] Zhubi, A., Veldic, M., Puri, N.V., Kadriu, B., Caruncho, H., Loza, I., Sershen, H., Lajtha, A., Smith, R.C., Guidotti, A., Davis, J.M. and Costa, E. (2009) An upregulation of DNA-methyltransferase 1 and 3a expressed in telencephalic GABAergic neurons of schizophrenia patients is also detected in peripheral blood lymphocytes. *Schizophrenia Research*, **111**, 115-122. doi:10.1016/j.schres.2009.03.020

[127] Reuter, M., Weber, B., Fiebach, C.J., Elger, C., Montag, C. (2009) The biological basis of anger: Associations with the gene coding for DARPP-32 (PPP1R1B) and with amygdala volume. *Behavioural Brain Research*, **202**, 179-183. doi:10.1016/j.bbr.2009.03.032

[128] Prata, D.P., Mechelli, A., Fu, C.H., Picchioni, M., Toulopoulou, T., Bramon, E., Walshe, M., Murray, R.M., Collier, D.A. and McGuire, P. (2009) Epistasis between the DAT 3' UTR VNTR and the COMT Val158Met SNP on cortical function in healthy subjects and patients with schizophrenia. *Proceedings of the National Academy of Sciences of the USA*, **106**, 13600-13605. doi:10.1073/pnas.0903007106

[129] Prata, D.P., Mechelli, A., Picchioni, M.M., Fu, C.H.,

Toulopoulou, T., Bramon, E., Walshe, M., Murray, R.M., Collier, D.A. and McGuire, P. (2009) Altered effect of dopamine transporter 3'UTR VNTR genotype on prefrontal and striatal function in schizophrenia. *Archives of General Psychiatry*, **66**, 1162-1172. doi:10.1001/archgenpsychiatry.2009.147

[130] Gupta, M., Chauhan, C., Bhatnagar, P., Gupta, S., Grover, S., Singh, P.K., Purushottam, M., Mukherjee, O., Jain, S., Brahmachari, S.K. and Kukreti, R. (2009) Genetic susceptibility to schizophrenia: role of dopaminergic pathway gene polymorphisms. *Pharmacogenomics*, **10**, 277-291. doi:10.2217/14622416.10.2.277

[131] Hattori, E., Nakajima, M., Yamada, K., Iwayama, Y., Toyota, T., Saitou, N. and Yoshikawa, T. (2009) Variable number of tandem repeat polymorphisms of DRD4: Re-evaluation of selection hypothesis and analysis of association with schizophrenia. *European Journal of Human Genetics*, **17**, 793-801. doi:10.1038/ejhg.2008.247

[132] Zai, C.C., Tiwari, A.K., De Luca, V., Müller, D.J., Bulgin, N., Hwang, R., Zai, G.C., King, N., Voineskos, A.N., Meltzer, H.Y., Lieberman, J.A., Potkin, S.G., Remington, G. and Kennedy, J.L. (2009) Genetic study of BDNF, DRD3, and their interaction in tardive dyskinesia. *European Neuropsychopharmacology*, **19**, 317-328. doi:10.1016/j.euroneuro.2009.01.001

[133] Zai, C.C., Tiwari, A.K., Basile, V., De Luca, V., Müller, D.J., King, N., Voineskos, A.N., Remington, G., Meltzer, H.Y., Lieberman, J.A., Potkin, S.G. and Kennedy, J.L. (2009) Association study of tardive dyskinesia and five DRD4 polymorphisms in schizophrenia patients. *Journal of Pharmacogenomics*, **9**, 168-174. doi:10.1038/tpj.2009.2

[134] Maher, B.S., Reimers, M.A., Riley, B.P. and Kendler, K.S. (2009) Allelic heterogeneity in genetic association meta-analysis: An application to DTNBP1 and schizophrenia. *Human Heredity*, **69**, 71-79. doi:10.1159/000264445

[135] Dwyer, S., Carroll, L., Mantripragada, K.K., Owen, M.J., O'Donovan, M.C. and Williams, N.M. (2010) Mutation screening of the DTNBP1 exonic sequence in 669 schizophrenics and 710 controls using high-resolution melting analysis. *American Journal of Medical Genetics Part B*: *Neuropsychiatric Genetics*, **153B**, 766-774. doi:10.1002/ajmg.b.31045

[136] Ryder, P.V. and Faundez, V. (2009) Schizophrenia: The "BLOC" may be in the endosomes. *Science Signaling*, **2**, e66. doi:10.1126/scisignal.293pe66

[137] Taneichi-Kuroda, S., Taya, S., Hikita, T., Fujino, Y. and Kaibuchi, K. (2009) Direct interaction of Dysbindin with the AP-3 complex via its mu subunit. *Neurochemistry International*, **54**, 431-438. doi:10.1016/j.neuint.2009.01.014

[138] Hikita, T., Taya, S., Fujino, Y., Taneichi-Kuroda, S., Ohta, K., Tsuboi, D., Shinoda, T., Kuroda, K., Funahashi, Y., Uraguchi-Asaki, J., Hashimoto, R. and Kaibuchi, K. (2009) Proteomic analysis reveals novel binding partners of dysbindin, a schizophrenia-related protein. *Journal of Neurochemistry*, **110**, 1567-1574. doi:10.1111/j.1471-4159.2009.06257.x

[139] Donohoe, G., Frodl, T., Morris, D., Spoletini, I., Cannon, D.M., Cherubini, A., Caltagirone, C., Bossù, P., McDonald, C., Gill, M., Corvin, A.P. and Spalletta, G. (2010) Reduced occipital and prefrontal brain volumes in dysbindin-associated schizophrenia. *Neuropsychopharmacology*, **35**, 368-373. doi:10.1038/npp.2009.140

[140] Pae, C.U., Mandelli, L., De Ronchi, D., Kim, J.J., Jun, T.Y., Patkar, A.A. and Serretti, A. (2009) Dysbindin gene (DTNBP1) and schizophrenia in Korean population. *European Archives of Psychiatry and Clinical Neuroscience*, **259**, 137-142. doi:10.1007/s00406-008-0830-y

[141] Gaysina, D., Cohen-Woods, S., Chow, P.C., Martucci, L., Schosser, A., Ball, H.A., Tozzi, F., Perry, J., Muglia, P., Craig, I.W., McGuffin, P. and Farmer, A. (2009) Association of the dystrobrevin binding protein 1 gene (DTNBP1) in a bipolar case-control study (BACCS). *American Journal of Medical Genetics Part B*: *Neuropsychiatric Genetics*, **150**, 836-844. doi:10.1002/ajmg.b.30906

[142] Tan, W., Dean, M. and Law, A.J. (2010) Molecular cloning and characterization of the human ErbB4 gene: Identification of novel splice isoforms in the developing and adult brain. *PLoS One*, **5**, e12924. doi:10.1371/journal.pone.0012924

[143] Wong, J. and Weickert, C.S. (2009) Transcriptional interaction of an estrogen receptor splice variant and ErbB4 suggests convergence in gene susceptibility pathways in schizophrenia. *The Journal of Biological Chemisty*, **284**, 18824-18832. doi:10.1074/jbc.M109.013243

[144] Li, D., Feng, G. and He, L. (2009) Case-control study of association between the functional candidate gene ERBB3 and schizophrenia in Caucasian population. *World Journal of Biological Psychiatry*, **10**, 595-598. doi:10.1080/15622970903304442

[145] McNamara, R.K., Jandacek, R., Rider, T., Tso, P., Hahn, C.G., Richtand, N.M. and Stanford, K.E. (2007) Abnormalities in the fatty acid composition of the post-mortem orbitofrontal cortex of schizophrenic patients: Gender differences and partial normalization with antipsychotic medications. *Schizophrenia Research*, **91**, 37-50. doi:10.1016/j.schres.2006.11.027

[146] Liu, Y., Jandacek, R., Rider, T., Tso, P. and McNamara, R.K. (2009) Elevated delta-6 desaturase (FADS2) expression in the post-mortem prefrontal cortex of schizophrenic patients: Relationship with fatty acid composition. *Schizophrenia Research*, **109**, 113-120. doi:10.1016/j.schres.2008.12.027

[147] Perez-Iglesias, R., Mata, I., Amado, J.A., Berja, A., Garcia-Unzueta, M.T., Martínez, G.O., Arranz, M.J., Vazquez-Barquero, J.L. and Crespo-Facorro, B. (2010) Effect of FTO, SH2B1, LEP, and LEPR polymorphisms on weight gain associated with antipsychotic treatment. *Journal of Clinical Psychopharmacology*, **30**, 661-666. doi:10.1097/JCP.0b013e3181fae248

[148] Zhong, N., Zhang, R., Qiu, C., Yan, H., Valenzuela, R.K., Zhang, H., Kang, W., Lu, S., Guo, T. and Ma, J. (2011) A novel replicated association between FXYD6 gene and schizophrenia. *Biochemical and Biophysical Research Communications*, **405**, 118-121.

doi:10.1016/j.bbrc.2011.01.005

[149] Hattori, K., Fukuzako, H., Hashiguchi, T., Hamada, S., Murata, Y., Isosaka, T., Yuasa, S. and Yagi, T. (2009) Decreased expression of Fyn protein and disbalanced alternative splicing patterns in platelets from patients with schizophrenia. *Psychiatry Research*, **168**, 119-128. doi:10.1016/j.psychres.2008.04.014

[150] Szczepankiewicz, A., Rybakowski, J.K., Skibinska, M., Dmitrzak-Weglarz, M., Leszczynska-Rodziewicz, A., Wilkosc, M. and Hauser, J. (2009) FYN kinase gene: Another glutamatergic gene associated with bipolar disorder? *Neuropsychobiology*, **59**, 178-183. doi:10.1159/000219305

[151] Mellios, N., Huang, H.S., Baker, S.P., Galdzicka, M., Ginns, E. and Akbarian, S. (2009) Molecular determinants of dysregulated GABAergic gene expression in the prefrontal cortex of subjects with schizophrenia. *Biological Psychiatry*, **65**, 1006-1014. doi:10.1016/j.biopsych.2008.11.019

[152] Hirunsatit, R., George, E.D., Lipska, B.K., Elwafi, H.M., Sander, L., Yrigollen, C.M., Gelernter, J., Grigorenko, E.L., Lappalainen, J., Mane, S., Nairn, A.C., Kleinman, J.E. and Simen, A.A. (2009) Twenty-one-base-pair insertion polymorphism creates an enhancer element and potentiates SLC6A1 GABA transporter promoter activity. *Pharmacogenetics Genomics*, **19**, 53-65. doi:10.1097/FPC.0b013e328318b21a

[153] Butticaz, C., Werge, T., Beckmann, J.S., Cuénod, M., Do, K.Q. and Rivolta, C. (2009) Mutation screening of the glutamate cysteine ligase modifier (GCLM) gene in patients with schizophrenia. *Psychiatric Genetics*, **19**, 201-208. doi:10.1097/YPG.0b013e32832cef21

[154] Segnitz, N., Schmitt, A., Gebicke-Härter, P.J. and Zink, M. (2009) Differential expression of glutamate transporter genes after chronic oral treatment with aripiprazole in rats. *Neurochemistry International*, **55**, 619-628. doi:10.1016/j.neuint.2009.06.003

[155] Arai, S., Shibata, H., Sakai, M., Ninomiya, H., Iwata, N., Ozaki, N. and Fukumaki, Y. (2009) Association analysis of the glutamic acid decarboxylase 2 and the glutamine synthetase genes (GAD2, GLUL) with schizophrenia. *Psychiatric Genetics*, **19**, 6-13.

[156] Kilic, G., Ismail, K.C., Orhan, N., Ozkok, E., Zengin, A., Aydin, M. and Kara, I. (2009) Are GRIK3 (T928G) gene variants in schizophrenia patients different from those in their first-degree relatives? *Psychiatry Research*, **175**, 43-46.

[157] Gaisler-Salomon, I., Miller, G.M., Chuhma, N., Lee, S., Zhang, H., Ghoddoussi, F., Lewandowski, N., Fairhurst, S., Wang, Y., Conjard-Duplany, A., Masson, J., Balsam, P., Hen, R., Arancio, O., Galloway, M.P., Moore, H.M., Small, S.A. and Rayport, S. (2009) Glutaminase-deficient mice display hippocampal hypoactivity, insensitivity to pro-psychotic drugs and potentiated latent inhibition: Relevance to schizophrenia. *Neuropsychopharmacology*, **34**, 2305-2322. doi:10.1038/npp.2009.58

[158] Treutlein, J., Mühleisen, T.W., Frank, J., Mattheisen, M., Herms, S., Ludwig, K.U., Treutlein, T., Schmael, C., Strohmaier, J., Bösshenz, K.V., Breuer, R., Paul, T., Witt, S.H., Schulze, T.G., Schlösser, R.G., Nenadic, I., Sauer,

OPEN ACCESS

H., Becker, T., Maier, W., Cichon, S., Nöthen, M.M. and Rietschel, M. (2009) Dissection of phenotype reveals possible association between schizophrenia and glutamate receptor delta 1 (GRID1) gene promoter. *Schizophrenia Research*, **111**, 123-130. doi:10.1016/j.schres.2009.03.011

[159] Ghose, S., Chin, R., Gallegos, A., Roberts, R., Coyle, J. and Tamminga, C. (2009) Localization of NAAG-related gene expression deficits to the anterior hippocampus in schizophrenia. *Schizophrenia Research*, **111**, 131-137. doi:10.1016/j.schres.2009.03.038

[160] Shibata, H., Tani, A., Chikuhara, T., Kikuta, R., Sakai, M., Ninomiya, H., Tashiro, N., Iwata, N., Ozaki, N. and Fukumaki, Y. (2009) Association study of polymorphisms in the group III metabotropic glutamate receptor genes, GRM4 and GRM7, with schizophrenia. *Psychiatry Research*, **167**, 88-96. doi:10.1016/j.psychres.2007.12.002

[161] Ohnuma, T., Shibata, N., Maeshima, H., Baba, H., Hatano, T., Hanzawa, R. and Arai, H. (2009) Association analysis of glycine- and serine-related genes in a Japanese population of patients with schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **33**, 511-518. doi:10.1016/j.pnpbp.2009.02.004

[162] Belforte, J.E., Zsiros, V., Sklar, E.R., Jiang, Z., Yu, G., Li, Y., Quinlan, E.M. and Nakazawa, K. (2009) Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. *Nature Neuroscience*, **13**, 76-83. doi:10.1038/nn.2447

[163] Li, B., Devidze, N., Barengolts, D., Prostak, N., Sphicas, E., Apicella, A.J., Malinow, R. and Emamian, E.S. (2009) NMDA receptor phosphorylation at a site affected in schizophrenia controls synaptic and behavioral plasticity. *The Journal of Neuroscience*, **29**, 11965-11972. doi:10.1523/JNEUROSCI.2109-09.2009

[164] Kang, S.G., Lee, H.J., Choi, J.E., An, H., Rhee, M. and Kim, L. (2009) Association study between glutathione S-transferase GST-M1, GST-T1, and GST-P1 polymorphisms and tardive dyskinesia. *Human Psychopharmacology*, **24**, 55-60. doi:10.1002/hup.988

[165] Eom, T.Y. and Jope, R.S. (2009) Blocked inhibitory serine-phosphorylation of glycogen synthase kinase-3alpha/beta impairs in vivo neural precursor cell proliferation. *Biological Psychiatry*, **66**, 494-502. doi:10.1016/j.biopsych.2009.04.015

[166] Dewachter, I., Ris, L., Jaworski, T., Seymour, C.M., Kremer, A., Borghgraef, P., De Vijver, H., Godaux, E. and Van Leuven, F. (2009) GSK3beta, a centre-staged kinase in neuropsychiatric disorders, modulates long term memory by inhibitory phosphorylation at serine-9. *Neurobiology of Disease*, **35**, 193-200. doi:10.1016/j.nbd.2009.04.003

[167] Baruch, K., Silberberg, G., Aviv, A., Shamir, E., Bening-Abu-Shach, U., Baruch, Y., Darvasi, A. and Navon, R. (2009) Association between golli-MBP and schizophrenia in the Jewish Ashkenazi population: Are regulatory regions involved? *The International Journal of Neuropsychopharmacology*, **12**, 885-894. doi:10.1017/S1461145708009887

[168] Kalkman, H.O. (2009) Altered growth factor signaling pathways as the basis of aberrant stem cell maturation in schizophrenia. *Pharmacology & Therapeutics*, **121**, 115-122. doi:10.1016/j.pharmthera.2008.11.002

[169] Klejbor, I., Kucinski, A., Wersinger, S.R., Corso, T., Spodnik, J.H., Dziewiatkowski, J., Moryś, J., Hesse, R.A., Rice, K.C., Miletich, R., Stachowiak, E.K. and Stachowiak, M.K. (2009) Serotonergic hyperinnervation and effective serotonin blockade in an FGF receptor developmental model of psychosis. *Schizophrenia Research*, **113**, 308-321. doi:10.1016/j.schres.2009.06.006

[170] Pae, C.U., Drago, A., Kim, J.J., Mandelli, L., De Ronchi, D. and Serretti, A. (2009) The impact of heat shock protein 70 gene variations on clinical presentation and outcome in schizophrenic inpatients. *Neuropsychobiology*, **59**, 135-141. doi:10.1159/000218075

[171] Gilks, W.P., Allott, E.H., Donohoe, G., Cummings, E., International Schizophrenia Consortium, Gill, M., Corvin, A.P. and Morris, D.W. (2009) Replicated genetic evidence supports a role for HOMER2 in schizophrenia. *Neuroscience Letters*, **468**, 229-233. doi:10.1016/j.neulet.2009.11.003

[172] Paul-Samojedny, M., Owczarek, A., Suchanek, R., Kowalczyk, M., Fila-Danilow, A., Borkowska, P., Kucia, K. and Kowalski, J. (2011) Association study of interferon gamma (IFN-*γ*) +874T/A gene polymorphism in patients with paranoid schizophrenia. *Journal of Moleuar Neuroscience*, **43**, 309-315. doi:10.1007/s12031-010-9442-x

[173] Frezza, D., Giambra, V., Mattioli, C., Piccoli, K., Massoud, R., Siracusano, A., Di Giannantonio, M., Birshtein, B.K. and Rubino, I.A. (2009) Allelic frequencies of 3' Ig heavy chain locus enhancer HS1,2-A associated with Ig levels in patients with schizophrenia. *International Journal of Immunopathology and Pharmacology*, **22**, 115-123.

[174] Bonvicini, C., Gennarelli, M., Scassellati, C., Bignotti, S., Gardella, R., Barlati, S., Valsecchi, P. and Sacchetti, E. (2010) Polymorphic CA repeat in IGF-I gene: Lack of association with schizophrenia. *Psychiatric Genetics*, **20**, 44-45. doi:10.1097/YPG.0b013e3283351167

[175] Bernstein, H.G., Ernst, T., Lendeckel, U., Bukowska, A., Ansorge, S., Stauch, R., Have, S.T., Steiner, J., Dobrowolny, H. and Bogerts, B. (2009) Reduced neuronal expression of insulin-degrading enzyme in the dorsolateral prefrontal cortex of patients with haloperidol-treated, chronic schizophrenia. *Journal of Psychiatric Research*, **43**, 1095-1105. doi:10.1016/j.jpsychires.2009.03.006

[176] Sun, S., Wei, J., Li, H., Jin, S., Li, P., Ju, G., Liu, Y. and Zhang, X.Y. (2009) A family-based study of the IL3RA gene on susceptibility to schizophrenia in a Chinese Han population. *Brain Research*, **1268**, 13-16. doi:10.1016/j.brainres.2009.02.071

[177] Ozbey, U., Tug, E. and Namli, M. (2009) Interleukin-10 gene promoter polymorphism in patients with schizophrenia in a region of East Turkey. *World Journal of Biological Psychiatry*, **10**, 461-468. doi:10.1080/15622970802626580

[178] Liu, Y., Chen, G. and Norton, N. (2009) Whole genome association study in a homogenous population in Shandong peninsula of China reveals JARID2 as a susceptibil-

ity gene for schizophrenia. *Journal of Biomedicine and Biotechnology*, **2009**, 536918. doi:10.1155/2009/536918

[179] Huffaker, S.J., Chen, J., Nicodemus, K.K., Sambataro, F., Yang, F., Mattay, V., Lipska, B.K., Hyde, T.M., Song, J., Rujescu, D., Giegling, I., Mayilyan, K., Proust, M.J., Soghoyan, A., Caforio, G., Callicott, J.H., Bertolino, A., Meyer-Lindenberg A., Chang, J., Ji, Y., Egan, M.F., Goldberg, T.E., Kleinman, J.E., Lu, B. and Weinberger, D.R. (2009) A primate-specific, brain isoform of KCNH2 affects cortical physiology, cognition, neuronal repolarization and risk of schizophrenia. *Nature Medicine*, 15, 509-18. doi:10.1038/nm.1962

[180] Shen, Q., Zhang, J., Wang, Y., Liu, B., Li, X., Zhao, Q., Chen, S., Ji, J., Yang, F., Wan, C., Gao, L., Xu, Y., Feng, G., He, L. and He, G. (2011) No association between the KCNH1, KCNJ10 and KCNN3 genes and schizophrenia in the Han Chinese population. *Neuroscience Letters*, **487**, 61-65. doi:10.1016/j.neulet.2010.09.074

[181] Miller, C.L., Murakami, P., Ruczinski, I., Ross, R.G., Sinkus, M., Sullivan, B. and Leonard, S. (2009) Two complex genotypes relevant to the kynurenine pathway and melanotropin function show association with schizophrenia and bipolar disorders. *Schizophrenia Research*, **113**, 259-267. doi:10.1016/j.schres.2009.05.014

[182] Koide, T., Banno, M., Aleksic, B., Yamashita, S., Kikuchi, T., Kohmura, K., Adachi, Y., Kawano, N., Kushima, I., Nakamura, Y., Okada, T., Ikeda, M., Ohi, K., Yasuda, Y., Hashimoto, R., Inada, T., Ujike, H., Iidaka, T., Suzuki, M., Takeda, M., Iwata, N. and Ozaki, N. (2012) Common variants in MAGI2 gene are associated with increased risk for cognitive impairment in schizophrenic patients. *PLoS One*, **7**, e36836. doi:10.1371/journal.pone.0036836

[183] International Schizophrenia Consortium. (2008) Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature*, **455**, 237-241. doi:10.1038/nature07239

[184] Stefansson, H., Ophoff, R.A., Steinberg, S., Andreassen, O.A., Cichon, S., Rujescu, D., Werge, T., Pietiläinen, O.P., Mors, O., Mortensen, P.B., Sigurdsson, E., Gustafsson, O., Nyegaard, M., Tuulio-Henriksson, A., Ingason, A., Hansen, T., Suvisaari, J., Lonnqvist, J., Paunio, T., Børglum, A.D., Hartmann, A., Fink-Jensen, A., Nordentoft, M., Hougaard, D., Norgaard-Pedersen, B., Böttcher, Y., Olesen, J., Breuer, R., Möller, H.J., Giegling, I., Rasmussen, H.B., Timm, S., Mattheisen, M., Bitter, I., Réthelyi, J.M., Magnusdottir, B.B., Sigmundsson, T., Olason, P., Masson, G., Gulcher, J.R., Haraldsson, M., Fossdal, R., Thorgeirsson, T.E., Thorsteinsdottir, U., Ruggeri, M., Tosato, S., Franke, B., Strengman, E., Kiemeney, L.A.; Genetic Risk and Outcome in Psychosis (GROUP), Melle, I., Djurovic, S., Abramova, L., Kaleda, V., Sanjuan, J., de Frutos R., Bramon, E., Vassos, E., Fraser, G., Ettinger, U., Picchioni, M., Walker, N., Toulopoulou, T., Need, A.C., Ge, D., Yoon, J.L., Shianna, K.V., Freimer, N.B., Cantor, R.M., Murray, R., Kong, A., Golimbet, V., Carracedo, A., Arango, C., Costas, J., Jönsson, E.G., Terenius, L., Agartz, I., Petursson, H., N?then, M.M., Rietschel, M., Matthews, P.M., Muglia, P., Peltonen, L., St Clair D., Goldstein, D.B., Stefansson, K. and Collier, D. A. (2009) Common variants conferring risk of schizophrenia. *Nature*, **460**, 744-747.

http://www.ncbi.nlm.nih.gov/pubmed/19571808

[185] Lee, B.D., Walss-Bass, C., Thompson, P.M., Dassori, A., Montero, P.A., Medina, R., Contreras, S., Armas, R., Ramirez, M., Pereira, M., Salazar, R., Leach, R.J, Quezada, P., Raventos, H. and Escamilla, M.A. (2007) Malic enzyme 2 and susceptibility to psychosis and mania. *Psychiatry Researchearch*, **150**, 1-11. doi:10.1016/j.psychres.2006.06.001

[186] Kucukali, C.I., Aydin, M., Ozkok, E., Bilge, E., Orhan, N., Zengin, A. and Kara, I. (2009) Do schizophrenia and bipolar disorders share a common disease susceptibility variant at the MMP3 gene? *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **33**, 557-561. doi:10.1016/j.pnpbp.2009.02.012

[187] Rybakowski, J.K., Skibinska, M., Leszczynska-Rodziewicz, A., Kaczmarek, L. and Hauser, J. (2009) Matrix metalloproteinase-9 gene and bipolar mood disorder. *NeuroMolecular Medicineicine*, **11**, 128-132. doi:10.1007/s12017-009-8072-3

[188] Djurovic, S., Le Hellard, S., Kähler, A.K., Jönsson, E.G., Agartz, I., Steen, V.M., Hall, H., Wang, A.G., Rasmussen, H.B., Melle, I., Werge, T. and Andreassen, O.A. (2009) Association of MCTP2 gene variants with schizophrenia in three independent samples of Scandinavian origin (SCOPE). *Psychiatry Researchearch*, **168**, 256-258. doi:10.1016/j.psychres.2008.08.007

[189] Feng, L.G., Song, Z.W., Xin, F, and Hu, J. (2009) Association of plasma homocysteine and methylenetetrahydrofolate reductase C677T gene variant with schizophrenia: A Chinese Han population-based case-control study. *Psychiatry Research*, **168**, 205-208. doi:10.1016/j.psychres.2008.05.009

[190] Zhang, C., Xie, B., Du, Y., Cheng, W., Fang, Y. and Yu, S. (2010) Further evidence that methylenetetrahydrofolate reductase A1298C polymorphism is a risk factor for schizophrenia. *Journal of Neural Transmission*, **117**, 1115-1117. doi:10.1007/s00702-010-0442-3

[191] Kähler, A.K., Djurovic, S., Kulle, B., Jönsson, E.G., Agartz, I., Hall, H., Opjordsmoen, S., Jakobsen, K.D., Hansen, T., Melle, I., Werge, T., Steen, V.M. and Andreassen, O.A. (2008) Association analysis of schizophrenia on 18 genes involved in neuronal migration: MDGA1 as a new susceptibility gene. *American Journal of Medical Genetics*, *Part B*, *Neuropsychiatric Genetics*, **147B**, 1089-1100. http://www.ncbi.nlm.nih.gov/pubmed/18384059

[192] Li, J., Liu, J., Feng, G., Li, T., Zhao, Q., Li, Y., Hu, Z., Zheng, L., Zeng, Z., He, L., Wang, T. and Shi, Y. (2011) The MDGA1 gene confers risk to schizophrenia and bipolar disorders. *Schizophrenia Research*, **125**, 194-200. doi:10.1016/j.schres.2010.11.002

[193] Sorce, S., Schiavone, S., Tucci, P., Colaianna, M., Jaquet, V., Cuomo, V., Dubois-Dauphin, M., Trabace, L. and Krause, K.H. (2010) The NADPH oxidase NOX2 controls glutamate release: A novel mechanism involved in psychosis-like ketamine responses. *The Journal of Neuroscience*, **30**, 11317-11325. doi:10.1523/JNEUROSCI.1491-10.2010

[194] Gibbons, A.S., Thomas, E.A. and Dean, B. (2009) Regional and duration of illness differences in the alteration

of NCAM-180 mRNA expression within the cortex of subjects with schizophrenia. *Schizophrenia Research*, **112**, 65-71. doi:10.1016/j.schres.2009.04.002

[195] Cox, E.T., Brennaman, L.H., Gable, K.L., Hamer, R.M., Glantz, L.A., Lamantia, A.S., Lieberman, J.A., Gilmore, J.H., Maness, P.F. and Jarskog, L.F. (2009) Developmental regulation of neural cell adhesion molecule in human prefrontal cortex. *Neuroscience*, **162**, 96-105. doi:10.1016/j.neuroscience.2009.04.037

[196] Alaerts, M., Ceulemans, S., Forero, D., Moens, L.N., De Zutter, S., Heyrman, L., Lenaerts, A.S., Norrback, K.F., De Rijk, P., Nilsson, L.G., Goossens, D., Adolfsson, R. and Del-Favero, J. (2009) Support for NRG1 as a susceptibility factor for schizophrenia in a northern Swedish isolated population. *Achives of General Psychiatry*, **66**, 828-37. doi:10.1001/archgenpsychiatry.2009.82

[197] Li, D., Collier, D.A. and He, L. (2006) Meta-analysis shows strong positive association of the neuregulin 1 (NRG1) gene with schizophrenia. *Human Molecular Genetics*, **15**, 1995-2002. doi:10.1093/hmg/ddl122

[198] Pedrosa, E., Nolan, K.A., Stefanescu, R., Herskovits, P., Novak, T., Zukov, I., Stopkova, P. and Lachman, H.M. (2009) Analysis of a promoter polymorphism in the SMDF neuregulin 1 isoform in Schizophrenia. *Neuropsychobiology*, **59**, 205-212. doi:10.1159/000223732

[199] Prata, D.P., Breen, G., Osborne, S., Munro, J., St Clair, D. and Collier, D.A. (2009) An association study of the neuregulin 1 gene, bipolar affective disorder and psychosis. *Psychiatric Genetics*, **19**, 113-116. doi:10.1097/YPG.0b013e32832a4f69

[200] Wang, F., Jiang, T., Sun, Z., Teng, S.L., Luo, X., Zhu, Z., Zang, Y., Zhang, H., Yue, W., Qu, M., Lu, T., Hong, N., Huang, H., Blumberg, H.P. and Zhang, D. (2009) Neuregulin 1 genetic variation and anterior cingulum integrity in patients with schizophrenia and healthy controls. *Journal of Psychiatry and Neuroscience*, **34**, 181-186. http://www.ncbi.nlm.nih.gov/pubmed/19448847

[201] Gong, Y.G., Wu, C.N., Xing, Q.H., Zhao, X.Z., Zhu, J. and He, L. (2009) A two-method meta-analysis of Neuregulin 1 (NRG1) association and heterogeneity in schizophrenia. *Schizophrenia Reseaech*, **111**, 109-114. doi:10.1016/j.schres.2009.03.017

[202] Zhang, H.X., Li, W.Q., Zhang, Y., Zhao, J.P., Lv, L.X. and Yang, G. (2009) Association analysis of neuregulin 1 gene polymorphism with schizophrenia in Chinese Han population. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*, **26**, 16-20. http://www.ncbi.nlm.nih.gov/pubmed/19199244

[203] Deakin, I.H., Law, A.J., Oliver, P.L., Schwab, M.H., Nave, K.A., Harrison, P.J. and Bannerman, D.M. (2009) Behavioural characterization of neuregulin 1 type I overexpressing transgenic mice. *Neuro Report*, **20**, 1523-1528. doi:10.1097/WNR.0b013e328330f6e7

[204] Vullhorst, D., Neddens, J., Karavanova, I., Tricoire, L., Petralia, R.S., McBain, C.J. and Buonanno, A. (2009) Selective expression of ErbB4 in interneurons, but not pyramidal cells, of the rodent hippocampus. *The Journal of Neuroscience*, **29**, 12255-12264. doi:10.1523/JNEUROSCI.2454-09.2009

[205] Mata, I., Perez-Iglesias, R., Roiz-Santiañez, R., Tordesillas-Gutierrez, D., Gonzalez-Mandly, A., Vazquez-Barquero, J.L. and Crespo-Facorro, B. (2009) A neuregulin 1 variant is associated with increased lateral ventricle volume in patients with first-episode schizophrenia. *Biological Psychiatry*, **65**, 535-40. doi:10.1016/j.biopsych.2008.10.020

[206] Chen, P.L., Avramopoulos, D., Lasseter, V.K., McGrath, J.A., Fallin, M.D., Liang, K.Y., Nestadt, G., Feng, N., Steel, G., Cutting, A.S., Wolyniec, P., Pulver, A.E. and Valle, D. (2009) Fine mapping on chromosome 10q22-q23 implicates Neuregulin 3 in schizophrenia. *The American Journal of Human Genetics*, 84, 21-34. doi:10.1016/j.ajhg.2008.12.005

[207] Zhang, R., Du, X.Y., Yu, J., Xu, N., Zheng, Y.W., Zhao, Y.L., Zhang, H. and Ma, J. (2012) No genetic evidence for Neuregulin 3 conferring risk of schizophrenia in the Chinese population. *Psychiatry Research* (in press). doi:10.1016/j.psychres.2012.08.017

[208] Stefansson, H., Rujescu, D., Cichon, S., Pietil?inen, O.P., Ingason, A., Steinberg, S., Fossdal, R., Sigurdsson, E., Sigmundsson, T., Buizer-Voskamp, J.E., Hansen, T., Jakobsen, K.D., Muglia, P., Francks, C., Matthews, P.M., Gylfason, A., Halldorsson, B.V., Gudbjartsson, D., Thorgeirsson, T.E., Sigurdsson, A., Jonasdottir, A., Jonasdottir, A., Bjornsson, A., Mattiasdottir, S., Blondal, T., Haraldsson, M., Magnusdottir, B.B., Giegling, I., Möller, H.J., Hartmann, A., Shianna, K.V., Ge, D., Need, A.C., Crombie, C., Fraser, G., Walker, N., Lonnqvist, J., Suvisaari, J., Tuulio-Henriksson, A., Paunio, T., Toulopoulou, T., Bramon, E., Di Forti, M., Murray, R., Ruggeri, M., Vassos, E., Tosato, S., Walshe, M., Li, T., Vasilescu, C., Mühleisen, T.W., Wang, A.G., Ullum, H., Djurovic, S., Melle, I., Olesen, J., Kiemeney, L.A., Franke, B.; GROUP, Sabatti, C., Freimer, N.B., Gulcher, J.R., Thorsteinsdottir, U., Kong, A., Andreassen, O.A., Ophoff, R.A., Georgi, A., Rietschel, M., Werge, T., Petursson, H., Goldstein, D.B., Nöthen, M.M., Peltonen, L., Collier, D.A., St Clair, D. and Stefansson, K. (2008) Large recurrent microdeletions associated with schizophrenia. *Nature*, **455**, 232-236. doi:10.1038/nature07229

[209] Ruano, D., Aulchenko, Y.S., Macedo, A., Soares, M.J., Valente, J., Azevedo, M.H., Hutz, M.H., Gama, C.S., Lobato, M.I., Belmonte-de-Abreu, P., Goodman, A.B., Pato, C., Heutink, P. and Palha, J.A. (2008) Association of the gene encoding neurogranin with schizophrenia in males. *Journal of Psychiatric Research*, **42**, 125-133. doi:10.1016/j.jpsychires.2006.10.008

[210] Inoue, Y., Shinkai, T., Utsunomiya, K., Sakata, S., Fukunaka, Y., Yamaguchi, W., Yamada, K., Chen, H.I., Hwang, R., Ohmori, O. and Nakamura, J. (2009) No association between a functional polymorphism in the promoter region of the neuropeptide Y gene (–485C > T) and schizophrenia. *Neuroscience Letters*, **452**, 72-74. doi:10.1016/j.neulet.2009.01.005

[211] Otnaess, M.K., Djurovic, S., Rimol, L.M., Kulle, B., Kähler, A.K., Jönsson, E.G., Agartz, I., Sundet, K., Hall, H., Timm, S., Hansen, T., Callicott, J.H., Melle, I., Werge, T. and Andreassen, O.A. (2009) Evidence for a possible association of neurotrophin receptor (NTRK-3) gene polymorphisms with hippocampal function and schizophrenia. *Neurobiology of Disease*, **34**, 518-524.

doi:10.1016/j.nbd.2009.03.011

[212] Donohoe, G., Walters, J., Morris, D.W., Quinn, E.M., Judge, R., Norton, N., Giegling, I., Hartmann, A.M., Möller, H.J., Muglia, P., Williams, H., Moskvina, V., Peel, R., O'Donoghue, T., Owen, M.J., O'Donovan, M.C., Gill, M., Rujescu, D. and Corvin, A. (2009) Influence of NOS1 on verbal intelligence and working memory in both patients with schizophrenia and healthy control subjects. *Achives of General Psychiatry*, **66**, 1045-1054. doi:10.1001/archgenpsychiatry.2009.139

[213] Okumura, T., Okochi, T., Kishi, T., Ikeda, M., Kitajima, T., Yamanouchi, Y., Kinoshita, Y., Kawashima, K., Tsunoka, T., Ujike, H., Inada, T., Ozaki, N. and Iwata, N. (2009) No association between polymorphisms of neuronal oxide synthase 1 gene (NOS1) and schizophrenia in a Japanese population. *NeuroMolecular Medicine*, **11**, 123-127. doi:10.1007/s12017-009-8068-z

[214] Riley, B., Thiselton, D., Maher, B.S., Bigdeli, T., Wormley, B., McMichael, G.O., Fanous, A.H., Vladimirov, V., O'Neill, F.A, Walsh, D. and Kendler, K.S. (2010) Replication of association between schizophrenia and ZNF804A in the Irish case-control study of Schizophrenia sample. *Molecular Psychiatry*, **15**, 29-37. doi:10.1038/mp.2009.109

[215] Wratten, N.S., Memoli, H., Huang, Y., Dulencin, A.M., Matteson, P.G., Cornacchia, M.A., Azaro, M.A., Messenger, J., Hayter, J.E., Bassett, A.S., Buyske, S., Millonig, J.H., Vieland, V.J. and Brzustowicz, L.M. (2009) Identification of a schizophrenia-associated functional noncoding variant in NOS1AP. *The American Journal of Psychiatry*, **166**, 434-441. doi:10.1176/appi.ajp.2008.08081266

[216] Kremeyer, B., García, J., Kymäläinen, H., Wratten, N., Restrepo, G., Palacio, C., Miranda, A.L., López, C., Restrepo, M., Bedoya, G., Brzustowicz, L.M., Ospina-Duque, J., Arbeláez, M.P. and Ruiz-Linares, A. (2009) Evidence for a role of the NOS1AP (CAPON) gene in schizophrenia and its clinical dimensions: An association study in a South American population isolate. *Human Heredity*, **67**, 163-173. doi:10.1159/000181154

[217] Arion, D. and Lewis, D.A. (2011) Altered expression of regulators of the cortical chloride transporters NKCC1 and KCC2 in schizophrenia. *Archives of General Psychiatry*, **68**, 21-31. doi:10.1001/archgenpsychiatry.2010.114

[218] Sinibaldi, L., De Luca, A., Bellacchio, E., Conti, E., Pasini, A., Paloscia, C., Spalletta, G., Caltagirone, C., Pizzuti, A. and Dallapiccola, B. (2004) Mutations of the Nogo-66 receptor (RTN4R) gene in schizophrenia. *Human Mutation*, **24**, 534-535. doi:10.1002/humu.9292

[219] Meng, J., Shi, Y., Zhao, X., Guo, S., Wang, H., Zheng, Y., Tang, R., Feng, G., Gu, N., Liu, H., Zhu, S. and He, L. (2007) No association between the genetic polymorphisms in the RTN4R gene and schizophrenia in the Chinese population. *Journal of Neural Transmission*, **114**, 249-254. doi:10.1007/s00702-006-0538-y

[220] Hsu, R., Woodroffe, A., Lai, W.S., Cook, M.N., Mukai, J., Dunning, J.P., Swanson, D.J., Roos, J.L., Abecasis, G.R., Karayiorgou, M. and Gogos, J.A. (2007) Nogo Receptor 1 (RTN4R) as a candidate gene for schizophrenia: Analysis using human and mouse genetic approaches. *PLoS One*, **2**, e1234. doi:10.1371/journal.pone.0001234

[221] Budel, S., Padukkavidana, T., Liu, B.P., Feng, Z., Hu, F., Johnson, S., Lauren, J., Park, J.H., McGee, A.W., Liao, J., Stillman, A., Kim, J.E., Yang, B.Z., Sodi, S., Gelernter, J., Zhao, H., Hisama, F., Arnsten, A.F. and Strittmatter, S.M. (2008) Genetic variants of Nogo-66 receptor with possible association to schizophrenia block myelin inhibition of axon growth. *The Journal of Neuroscience*, **28**, 13161-13172. doi:10.1523/JNEUROSCI.3828-08.2008

[222] McDonald, P.P., O'Reilly, R. and Singh, S.M. (2011) Methylation analysis of the NOTCH4-25 C/T polymorphism in schizophrenia. *Psychiatric Genetics*, **21**, 5-13. doi:10.1097/YPG.0b013e32834133bc

[223] Schaaf, C.P., Boone, P.M., Sampath, S., Williams, C., Bader, P.I., Mueller, J.M., Shchelochkov, O.A., Brown, C.W., Crawford, H.P., Phalen, J.A., Tartaglia, N.R., Evans, P., Campbell, W.M., Chun-Hui Tsai, A., Parsley, L., Grayson, S.W., Scheuerle, A., Luzzi, C.D., Thomas, S.K., Eng, P.A., Kang, S.H., Patel, A., Stankiewicz, P. and Cheung, S.W. (2012) Phenotypic spectrum and genotype-phenotype correlations of NRXN1 exon deletions. *European Journal of Human Genetics*, **12**, 1240-1247. doi:10.1038/ejhg.2012.95

[224] Georgieva, L., Moskvina, V., Peirce, T., Norton, N., Bray, N.J., Jones, L., Holmans, P., Macgregor, S., Zammit, S., Wilkinson, J., Williams, H., Nikolov, I., Williams, N., Ivanov, D., Davis, K.L., Haroutunian, V., Buxbaum, J.D., Craddock, N., Kirov, G., Owen, M.J. and O'Donovan, M.C. (2006) Convergent evidence that oligodendrocyte lineage transcription factor 2 (OLIG2) and interacting genes influence susceptibility to schizophrenia. *Proceedings of the National Academy of Sciences*, **103**, 12469-12474. doi:10.1073/pnas.0603029103

[225] Sims, R., Hollingworth, P., Moskvina, V., Dowzell, K., O'Donovan, M.C., Powell, J., Lovestone, S., Brayne, C., Rubinsztein, D., Owen, M.J., Williams, J. and Abraham, R. (2009) Evidence that variation in the oligodendrocyte lineage transcription factor 2 (OLIG2) gene is associated with psychosis in Alzheimer disease. *Neuroscience Letters*, **461**, 54-59. doi:10.1016/j.neulet.2009.05.051

[226] Barley, K., Dracheva, S. and Byne, W. (2009) Subcortical oligodendrocyte- and astrocyte-associated gene expression in subjects with schizophrenia, major depression and bipolar disorders. *Schizophrenia Research*, **112**, 54-64. doi:10.1016/j.schres.2009.04.019

[227] Tesli, M., Athanasiu, L., Mattingsdal, M., Kähler, A.K., Gustafsson, O., Andreassen, B.K., Werge, T., Hansen, T., Mors, O., Mellerup, E., Koefoed, P., Jönsson, E.G., Agartz, I., Melle, I., Morken, G., Djurovic, S. and Andreassen, O.A. (2010) Association analysis of PALB2 and BRCA2 in bipolar disorders and schizophrenia in a Scandinavian case-control sample. *American Journal of Medical Genetics Part B*: *Neuropsychiatric Genetics*, **153B**, 1276-1282. doi:10.1002/ajmg.b.31098

[228] Numata, S., Iga, J., Nakataki, M., Tayoshi, S., Tanahashi, T., Itakura, M., Ueno, S. and Ohmori, T. (2009) Positive association of the pericentrin (PCNT) gene with major depressive disorder in the Japanese population. *Journal of*

Psychiatry and Neuroscience: JPN, **34**, 195-198.
http://www.ncbi.nlm.nih.gov/pubmed/19448849

[229] Mathur, A., Law, M.H., Hamzehloei, T., Megson, I.L., Shaw, D.J. and Wei, J. (2009) No association between the PPARG gene and schizophrenia in a British population. *Prostaglandins*, *Leukotrienes and Essential Fatty Acids*, **81**, 273-277. doi:10.1016/j.plefa.2009.06.001

[230] Houlihan, L.M., Christoforou, A., Arbuckle, M.I., Torrance, H.S., Anderson, S.M., Muir, W.J., Porteous, D.J., Blackwood, D.H. and Evans, K.L. (2009) A case-control association study and family-based expression analysis of the bipolar disorders candidate gene PI4K2B. *Journal of Psychiatric Research*, **43**, 1272-1277. doi:10.1016/j.jpsychires.2009.05.004

[231] Zhang, J., Chen, J., Xu, Q. and Shen, Y. (2009) Does the presenilin 2 gene predispose to schizophrenia? *Schizophrenia Research*, **109**, 121-129. doi:10.1016/j.schres.2009.01.013

[232] Roussos, P., Giakoumaki, S.G. and Bitsios, P. (2009) A risk PRODH haplotype affects sensorimotor gating, memory, schizotypy, and anxiety in healthy male subjects. *Biological Psychiatry*, **65**, 1063-1070. doi:10.1016/j.biopsych.2009.01.003

[233] Aberg, K., Saetre, P., Lindholm, E., Ekholm, B., Pettersson, U., Adolfsson, R. and Jazin, E. (2006) Human QKI, a new candidate gene for schizophrenia involved in myelination. *American Journal of Medical Genetics Part B*: *Neuropsychiatric Genetics*, **141**, 84-90. doi:10.1002/ajmg.b.30243

[234] Jiang, L., Saetre, P., Jazin, E. and Carlström, E.L. (2009) Haloperidol changes mRNA expression of a QKI splice variant in human astrocytoma cells. *BMC Pharmacol*, **9**. doi:10.1186/1471-2210-9-6

[235] Cheong, H.S., Park, B.L., Kim, E.M., Park, C.S., Sohn, J.W., Kim, B.J., Kim, J.W., Kim, K.H., Shin, T.M., Choi, I.G., Han, S.W., Hwang, J., Koh, I., Shin, H.D. and Woo, S.I. (2011) Association of RANBP1 haplotype with smooth pursuit eye movement abnormality. *American Journal of Medical Genetics Part B*: *Neuropsychiatric Genetics*, **156**, 67-71. doi:10.1002/ajmg.b.31139

[236] Goes, F.S., Willour, V.L., Zandi, P.P., Belmonte, P.L., MacKinnon, D.F., Mondimore, F.M., Schweizer, B., National Institute of Mental Health Genetics Initiative Bipolar disorders Consortium, DePaulo, J.R. Jr, Gershon, E.S., McMahon, F.J. and Potash, J.B. (2010) Sex-specific association of the reelin gene with bipolar disorders. *American Journal of Medical Genetics Part B*: *Neuropsychiatric Genetics*, **153B**, 549-553. http://www.ncbi.nlm.nih.gov/pubmed/19691043

[237] Wedenoja, J., Tuulio-Henriksson, A., Suvisaari, J., Loukola, A., Paunio, T., Partonen, T., Varilo, T., Lönnqvist, J. and Peltonen, L. (2010) Replication of association between working memory and reelin, a potential modifier gene in schizophrenia. *Biological Psychiatry*, **67**, 983-991. doi:10.1016/j.biopsych.2009.09.026

[238] Lintas, C. and Persico, A.M. (2010) Neocortical RELN promoter methylation increases significantly after puberty. *Neuroreport*, **21**, 114-118. doi:10.1097/WNR.0b013e328334b343

[239] Campo, C.G., Sinagra, M., Verrier, D., Manzoni, O.J. and Chavis, P. (2009) Reelin secreted by GABAergic neurons regulates glutamate receptor homeostasis. *PLoS One*, **4**, e5505. doi:10.1371/journal.pone.0005505

[240] Ammassari-Teule, M., Sgobio, C., Biamonte, F., Marrone, C., Mercuri, N.B. and Keller, F. (2009) Reelin haploinsufficiency reduces the density of PV+ neurons in circumscribed regions of the striatum and selectively alters striatal-based behaviors. *Psychopharmacology*, **204**, 511-521. doi:10.1007/s00213-009-1483-x

[241] Tueting, P., Doueiri, M.S., Guidotti, A., Davis, J.M. and Costa, E. (2006) Reelin down-regulation in mice and psychosis endophenotypes. *Neuroscience & Biobehavioral Reviews*, **30**, 1065-1077. doi:10.1016/j.neubiorev.2006.04.001

[242] Noh, J.S., Sharma, R.P., Veldic, M., Salvacion, A.A., Jia, X., Chen, Y., Costa, E., Guidotti, A. and Grayson, D.R. (2005) DNA methyltransferase 1 regulates reelin mRNA expression in mouse primary cortical cultures. *Proceedings of the National Academy of Sciences*, **102**, 1749-1754. doi:10.1073/pnas.0409648102

[243] Kanazawa, T., Glatt, S.J., Faraone, S.V., Hwu, H.G., Yoneda, H. and Tsuang, M.T. (2009) Family-based association study of SELENBP1 in schizophrenia. *Schizophrenia Reseaech*, 113, 268-272. doi:10.1016/j.schres.2009.06.011

[244] Labrie, V., Fukumura, R., Rastogi, A., Fick, L.J., Wang, W., Boutros, P.C., Kennedy, J.L., Semeralul, M.O., Lee, F.H., Baker, G.B., Belsham, D.D., Barger, S.W., Gondo, Y., Wong, A.H. and Roder, J.C. (2009) Serine racemase is associated with schizophrenia susceptibility in humans and in a mouse model. *Human Molecular Genetics*, **18**, 3227-3243. doi:10.1093/hmg/ddp261

[245] Kishi, T., Fukuo, Y., Okochi, T., Kawashima, K., Kitajima, T., Inada, T., Ozaki, N., Musso, G.M., Kane, J.M., Correll, C.U. and Iwata, N. (2012) Serotonin 6 receptor gene and schizophrenia: Case-control study and meta-analysis. *Human Psychopharmacology*, **27**, 63-69. doi:10.1002/hup.1266

[246] Vijayan, N.N., Iwayama, Y., Koshy, L.V., Natarajan, C., Nair, C., Allencherry, P.M., Yoshikawa, T. and Banerjee, M. (2009) Evidence of association of serotonin transporter gene polymorphisms with schizophrenia in a South Indian population. *Journal of Human Genetics*, **54**, 538-542. doi:10.1038/jhg.2009.76

[247] Lin, C., Tang, W., Hu, J., Gao, L., Huang, K., Xu, Y., He, G., Liang, P., Feng, G., He, L. and Shi, Y. (2009) Haplotype analysis confirms association of the serotonin transporter (5-HTT) gene with schizophrenia in the Han Chinese population. *Neuroscience Letters*, **453**, 210-213. doi:10.1016/j.neulet.2009.02.023

[248] Goldberg, T.E., Kotov, R., Lee, A.T., Gregersen, P.K., Lencz, T., Bromet, E. and Malhotra, A.K. (2009) The serotonin transporter gene and disease modification in psychosis: Evidence for systematic differences in allelic directionality at the 5-HTTLPR locus. *Schizophrenia Research*, **111**, 103-108. doi:10.1016/j.schres.2009.03.021

[249] Kim, Y.R., Jahng, J.W. and Min, S.K. (2009) Association between the serotonin transporter gene (5-HTTLPR) and

anger-related traits in Korean schizophrenic patients. *Neuropsychobiology*, **59**, 165-171. doi:10.1159/000218079

[250] Bachmann-Gagescu, R., Mefford, H.C., Cowan, C., Glew, G.M., Hing, A.V., Wallace, S., Bader, P.I., Hamati, A., Reitnauer, P.J., Smith, R., Stockton, D.W., Muhle, H., Helbig, I., Eichler, E.E., Ballif, B.C., Rosenfeld, J. and Tsuchiya, K.D. (2010) Recurrent 200-kb deletions of 16p11.2 that include the SH2B1 gene are associated with developmental delay and obesity. *Genetics in Medicine*, **12**, 641-647. doi:10.1097/GIM.0b013e3181ef4286

[251] Maekawa, M., Ohnishi, T., Hashimoto, K., Watanabe, A., Iwayama, Y., Ohba, H., Hattori, E., Yamada, K. and Yoshikawa, T. (2010) Analysis of strain-dependent prepulse inhibition points to a role for Shmt1 (SHMT1) in mice and in schizophrenia. *Journal of Neurochemistry*, **115**, 1374-1385. doi:10.1111/j.1471-4159.2010.07039.x

[252] McAuley, E.Z., Scimone, A., Tiwari, Y., Agahi, G., Mowry, B.J., Holliday, E.G., Donald, J.A., Weickert, C.S., Mitchell, P.B., Schofield, P.R. and Fullerton, J.M. (2012) Identification of sialyltransferase 8B as a generalized susceptibility gene for psychotic and mood disorders on chromosome 15q25-26. *PLoS One*, **7**, e38172. doi:10.1371/journal.pone.0038172

[253] Takizawa, R., Hashimoto, K., Tochigi, M., Kawakubo, Y., Marumo, K., Sasaki, T., Fukuda, M. and Kasai, K. (2009) Association between sigma-1 receptor gene polymorphism and prefrontal hemodynamic response induced by cognitive activation in schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **33**, 491-498. doi:10.1016/j.pnpbp.2009.01.014

[254] Cordeiro, Q., Siqueira-Roberto, J. and Vallada, H. (2010) Association between the SLC6A3 A1343G polymorphism and schizophrenia. *Arquivos de Neuropsiquiatria*, **68**, 716-719. doi:10.1590/S0004-282X2010000500008

[255] Koga, M., Ishiguro, H., Yazaki, S., Horiuchi, Y., Arai, M., Niizato, K., Iritani, S., Itokawa, M., Inada, T., Iwata, N., Ozaki, N., Ujike, H., Kunugi, H., Sasaki, T., Takahashi, M., Watanabe, Y., Someya, T., Kakita, A., Takahashi, H., Nawa, H., Muchardt, C., Yaniv, M. and Arinami, T. (2009) Involvement of SMARCA2/BRM in the SWI/SNF chromatin-remodeling complex in schizophrenia. *Human Molecular Genetics*, **18**, 2483-2494. doi:10.1093/hmg/ddp166

[256] Yuan, A., Yi, Z., Sun, J., Du, Y., Yu, T., Zhang, C., Liu, Y., Zhou, Y., Liu, D., Li, H., Xu, Y., Cheng, Z., Li, W. and Yu, S. (2012) Effect of SOX10 gene polymorphism on early onset schizophrenia in Chinese Han population. *Neuroscience Letters*, **521**, 93-97. doi:10.1016/j.neulet.2012.05.040

[257] Zhou, X., Tang, W., Greenwood, T.A., Guo, S., He, L., Geyer, M.A. and Kelsoe, J.R. (2009) Transcription factor SP4 is a susceptibility gene for bipolar disorders. *PLoS One*, **4**, e5196. doi:10.1371/journal.pone.0005196

[258] Bermudo-Soriano, C.R., Vaquero-Lorenzo, C., Diaz-Hernandez, M., Perez-Rodriguez, M.M., Fernandez-Piqueras, J., Saiz-Ruiz, J. and Baca-Garcia E. (2009) SAT-1-1415T/C polymorphism and susceptibility to schizophrenia. *Progress in Neuro-Psychopharmacol Biological Psychiatry*, **33**, 345-348. doi:10.1016/j.pnpbp.2008.12.015

[259] Lewis, A.G. and Minchin, R.F. (2009) Lack of exonic sulfotransferase 4A1 mutations in controls and schizophrenia cases. *Psychiatric Genetics*, **19**, 53-55. doi:10.1097/YPG.0b013e3283118776

[260] Chen, Q., Che, R., Wang, X., O'Neill, F.A., Walsh, D., Tang, W., Shi, Y., He, L., Kendler, K.S. and Chen, X. (2009) Association and expression study of synapsin III and schizophrenia. *Neuroscience Letters*, **465**, 248-251. doi:10.1016/j.neulet.2009.09.032

[261] Murphy, B.C., O'Reilly, R.L. and Singh, S.M. (2008) DNA methylation and mRNA expression of SYN III, a candidate gene for schizophrenia. *BMC Medical Genetics*, **9**, 115. doi:10.1186/1471-2350-9-115

[262] Iatropoulos, P., Gardella, R., Valsecchi, P., Magri, C., Ratti, C., Podavini, D., Rossi, G., Gennarelli, M., Sacchetti, E. and Barlati, S. (2009) Association study and mutational screening of SYNGR1 as a candidate susceptibility gene for schizophrenia. *Psychiatric Genetics*, **19**, 237-243. doi:10.1097/YPG.0b013e32832cebf7

[263] Wang, Y., Yu, L., Zhao, T., Xu, J., Liu, Z., Liu, Y., Feng, G., He, L. and Li, S. (2009) No association between bipolar disorders and syngr1 or synapsin II polymorphisms in the Han Chinese population. *Psychiatry Research*, **169**, 167-168. doi:10.1016/j.psychres.2008.12.005

[264] Corradini, I., Verderio, C., Sala, M., Wilson, M.C. and Matteoli, M. (2009) SNAP-25 in neuropsychiatric disorders. *Annals of the New York Academy of Sciences*, **1152**, 93-99. doi:10.1111/j.1749-6632.2008.03995.x

[265] McKee, A.G., Loscher, J.S., O'Sullivan, N.C., Chadderton, N., Palfi, A., Batti, L., Sheridan, G.K., O'Shea, S., Moran, M., McCabe, O., Fernández, A.B., Pangalos, M.N., O'Connor, J.J., Regan, C.M., O'Connor, W.T., Humphries, P., Farrar, G.J. and Murphy, K.J. (2009) AAV-mediated chronic over-expression of SNAP-25 in adult rat dorsal hippocampus impairs memory-associated synaptic plasticity. *Journal of Neurochemistry*, **112**, 991-1004. doi:10.1111/j.1471-4159.2009.06516.x

[266] Fellerhoff, B. and Wank, R. (2009) Transporter associated with antigen processing and the chaperone tapasin: Are non-classical HLA genes keys to the pathogenesis of schizophrenia? *Medical Hypotheses*, **72**, 535-538. doi:10.1016/j.mehy.2008.12.036

[267] Ohi, K., Hashimoto, R., Yasuda, Y., Kiribayashi, M., Iike, N., Yoshida, T., Azechi, M., Ikezawa, K., Takahashi, H., Morihara, T., Ishii, R., Tagami, S., Iwase, M., Okochi, M., Kamino, K., Kazui, H., Tanaka, T., Kudo, T. and Takeda, M. (2009) TATA box-binding protein gene is associated with risk for schizophrenia, age at onset and prefrontal function. *Genes, Brain and Behavior*, **8**, 473-480. doi:10.1111/j.1601-183X.2009.00497.x

[268] Geser, F., Robinson, J.L., Malunda, J.A., Xie, S.X., Clark, C.M., Kwong, L.K., Moberg, P.J., Moore, E.M., Van Deerlin, V.M., Lee, V.M., Arnold, S.E. and Trojanowski, J.Q. (2010) Pathological 43-kDa transactivation response DNA-binding protein in older adults with and without severe mental illness. *Archives of Neurology*, **67**, 1238-1250. doi:10.1001/archneurol.2010.254

[269] Wirgenes, K.V., Sønderby, I.E., Haukvik, U.K., Mat-

tingsdal, M., Tesli, M., Athanasiu, L., Sundet, K., Røssberg, J.I., Dale, A.M., Brown, A.A., Agartz, I., Melle, I., Djurovic, S. and Andreassen, O.A. (2012) TCF4 sequence variants and mRNA levels are associated with neurodevelopmental characteristics in psychotic disorders. *Translational Psychiatry*, **2**, e112. doi:10.1038/tp.2012.39

[270] Locke, M., Tinsley, C.L., Benson, M.A. and Blake, D.J. (2009) TRIM32 is an E3 ubiquitin ligase for dysbindin. *Human Molecular Genetics*, **18**, 2344-2358. doi:10.1093/hmg/ddp167

[271] Grover, D., Verma, R., Goes, F.S., Mahon, P.L., Gershon, E.S., McMahon, F.J., Potash, J.B., NIMH Genetics Initiative Bipolar disorders Collaborative, Bipolar disorders Phenome Group, Gershon, E.S., McMahon, F.J. and Potash, J.B. (2009) Family-based association of YWHAH in psychotic bipolar disorders. *American Journal of Medical Genetics Part B*: Neuropsychiatric Genetics, **150**, 977-983. doi:10.1002/ajmg.b.30927

[272] Amato, R., Pinelli, M., Monticelli, A., Miele, G. and Cocozza, S. (2010) Schizophrenia and vitamin D-related genes could have been subject to latitude-driven adaptation. *BMC Evolutionary Biology*, **10**, 351. doi:10.1186/1471-2148-10-351

[273] Derakhshandeh, S., Saadat, I., Farrashbandi, H. and Saadat, M. (2009) Association between genetic polymorphism of XRCC1 Arg194Trp and risk of schizophrenia. *Psychiatry Research*, **169**, 186. doi:10.1016/j.psychres.2009.03.022

[274] Wang, Y., Wang, L., Li, X., Liu, B., Zhao, Q., Chen, P., Wang, T., Li, T., Ji, J., Yang, F., Wang, Q., Wang, J., Xiao, Y., Xu, Y., Feng, G., Peng, Z., He, L. and He, G. (2010) Polymorphisms of XRCC4 are involved in reduced colorectal cancer risk in Chinese schizophrenia patients. *BMC Cancer*, **10**, 523. doi:10.1186/1471-2407-10-523

[275] Liu, J., Zhou, G., Ji, W., Li, J., Li, T., Wang, T., Li, Y., Zeng, Z., Hu, Z., Zheng, L., Ji, J., Wang, Y., Wei, Z., Feng, G., He, L. and Shi, Y. (2010) No association of the YWHAE gene with schizophrenia, major depressive disorder or bipolar disorders in the Han Chinese population. *Behavior Genetics*, **41**, 557-564. doi:10.1007/s10519-010-9426-1

[276] Esslinger, C., Walter, H., Kirsch, P., Erk, S., Schnell, K., Arnold, C., Haddad, L., Mier, D., Opitz von Boberfeld, C., Raab, K., Witt, S.H., Rietschel, M., Cichon, S. and Meyer-Lindenberg, A. (2009) Neural mechanisms of a genome-wide supported psychosis variant. *Science*, **324**, 605. doi:10.1126/science.1167768

[277] Donohoe, G., Rose, E., Frodl, T., Morris, D., Spoletini, I., Adriano, F., Bernardini, S., Caltagirone, C., Bossù, P., Gill, M., Corvin, A.P. and Spalletta, G. (2011) ZNF804A risk allele is associated with relatively intact gray matter volume in patients with schizophrenia. *Neuroimage*, **54**, 2132-2137. doi:10.1016/j.neuroimage.2010.09.089

[278] Dwyer, S., Williams, H., Holmans, P., Moskvina, V., Craddock, N., Owen, M.J. and O'Donovan, M.C. (2010) No evidence that rare coding variants in ZNF804A confer risk of schizophrenia. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, **153B**, 1411-1416.

doi:10.1002/ajmg.b.31117

[279] Donohoe, G., Morris, D.W. and Corvin, A. (2010) The psychosis susceptibility gene ZNF804A: Associations, functions, and phenotypes. *Schizophrenia Bulletin*, **36**, 904-909. doi:10.1093/schbul/sbq080

[280] Kim, A.H., Parker, E.K., Williamson, V., McMichael, G.O., Fanous, A.H. and Vladimirov, V.I. (2012) Experimental validation of candidate schizophrenia gene ZNF-804A as target for hsa-miR-137. *Schizophrenia Research*. **141**, 60-64. doi:10.1016/j.schres.2012.06.038

[281] Yurov, Y.B., Iourov, I.Y., Vorsanova, S.G., Liehr, T., Kolotii, A.D., Kutsev, S.I., Pellestor, F., Beresheva, A.K., Demidova, I.A., Kravets, V.S., Monakhov, V.V. and Soloviev, I.V. (2007) Aneuploidy and confined chromosomal mosaicism in the developing human brain. *PLoS One*, **2**, e558. doi:10.1371/journal.pone.0000558

[282] Iourov, I.Y., Vorsanova, S.G., Liehr, T. and Yurov, Y.B. (2009) Aneuploidy in the normal, Alzheimer disease and ataxia-telangiectasia brain: Differential expression and pathological meaning. *Neurobiology of Disease*, **34**, 212-220. doi:10.1016/j.nbd.2009.01.003

[283] Yurov, Y.B., Iourov, I.Y., Vorsanova, S.G., Demidova, I.A., Kravetz, V.S., Beresheva, A.K., Kolotii, A.D., Monakchov, V.V., Uranova, N.A., Vostrikov, V.M., Soloviev, I.V. and Liehr, T. (2008) The schizophrenia brain exhibits low-level aneuploidy involving chromosome 1. *Schizophrenia Research*, **98**, 139-147. doi:10.1016/j.schres.2007.07.035

[284] Fromer, M., Moran, J.L., Chambert, K., Banks, E., Bergen, S.E., Ruderfer, D.M., Handsaker, R.E., McCarroll, S.A., O'Donovan, M.C., Owen, M.J., Kirov, G., Sullivan, P.F., Hultman, C.M., Sklar, P. and Purcell, S.M. (2012) Discovery and statistical genotyping of copy-number variation from whole-exome sequencing depth. *The American Journal of Human Genetics*, **91**, 597-607. doi:10.1016/j.ajhg.2012.08.005

[285] Ikeda, M., Aleksic, B., Kirov, G., Kinoshita, Y., Yamanouchi, Y., Kitajima, T., Kawashima, K., Okochi, T., Kishi, T., Zaharieva, I., Owen, M.J., O'Donovan, M.C., Ozaki, N. and Iwata, N. (2010) Copy number variation in schizophrenia in the Japanese population. *Biological Psychiatry*, **67**, 283-286. doi:10.1016/j.biopsych.2009.08.034

[286] Tabarés-Seisdedos, R. and Rubenstein, J.L. (2009) Chromosome 8p as a potential hub for developmental neuropsychiatric disorders: Implications for schizophrenia, autism and cancer. *Molecular Psychiatry*, **14**, 563-589. doi:10.1038/mp.2009.2

[287] Need, A.C., Attix, D.K., McEvoy, J.M., Cirulli, E.T., Linney, K.L., Hunt, P., Ge, D., Heinzen, E.L., Maia, J.M., Shianna, K.V., Weale, M.E., Cherkas, L.F., Clement, G., Spector, T.D., Gibson, G. and Goldstein, D.B. (2009) A genome-wide investigation of SNPs and CNVs in schizophrenia. *PLoS Genetics*, **5**, e1000373. doi:10.1371/journal.pgen.1000373

[288] Kirov, G., Grozeva, D., Norton, N., Ivanov, D., Mantripragada, K.K., Holmans, P., International Schizophrenia Consortium; Wellcome Trust Case Control Consortium, Craddock, N., Owen, M.J. and O'Donovan, M.C. (2009)

Support for the involvement of large copy number variants in the pathogenesis of schizophrenia. *Human Molecular Genetics*, **18**, 1497-1503.
doi:10.1093/hmg/ddp043

[289] Maziade, M., Chagnon, Y.C., Roy, M.A., Bureau, A., Fournier, A. and Mérette, C. (2009) Chromosome 13q13-q14 locus overlaps mood and psychotic disorders: The relevance for redefining phenotype. *European Journal of Human Genetics*, 17, 1034-1042.
doi:10.1038/ejhg.2008.268

[290] de Kovel, C.G., Trucks, H., Helbig, I., Mefford, H.C., Baker, C., Leu, C., Kluck, C., Muhle, H., von Spiczak, S., Ostertag, P., Obermeier, T., Kleefuss-Lie, A.A., Hallmann, K., Steffens, M., Gaus, V., Klein, K.M., Hamer, H.M., Rosenow, F., Brilstra, E.H., Trenité, D.K.-N., Swinkels, M.E., Weber, Y.G., Unterberger, I., Zimprich, F., Urak, L., Feucht, M., Fuchs, K., Møller, R.S., Hjalgrim, H., De Jonghe, P., Suls, A., Rückert, I.M., Wichmann, H.E., Franke, A., Schreiber, S., Nürnberg, P., Elger, C.E., Lerche, H., Stephani, U., Koeleman, B.P., Lindhout, D., Eichler, E.E. and Sander, T. (2010) Recurrent microdeletions at 15q11.2 and 16p13.11 predispose to idiopathic generalized epilepsies. *Brain*, **133**, 23-32.
doi:10.1093/brain/awp262

[291] Dibbens, L.M., Mullen, S., Helbig, I., Mefford, H.C., Bayly, M.A., Bellows, S., Leu, C., Trucks, H., Obermeier, T., Wittig, M., Franke, A., Caglayan, H., Yapici, Z., EPICURE Consortium, Sander, T., Eichler, E.E., Scheffer, I.E., Mulley, J.C. and Berkovic, S.F. (2009) Familial and sporadic 15q13.3 microdeletions in idiopathic generalized epilepsy: Precedent for disorders with complex inheritance. *Human Molecular Genetics*, **18**, 3626-3631.
doi:10.1093/hmg/ddp311

[292] Ben-Shachar, S., Lanpher, B., German, J.R., Qasaymeh, M., Potocki, L., Nagamani, S.C., Franco, L.M., Malphrus, A., Bottenfield, G.W., Spence, J.E., Amato, S., Rousseau, J.A., Moghaddam, B., Skinner, C., Skinner, S.A., Bernes, S., Armstrong, N., Shinawi, M., Stankiewicz, P., Patel, A., Cheung, S.W., Lupski, J.R., Beaudet, A.L. and Sahoo, T. (2009) Microdeletion 15q13.3: A locus with incomplete penetrance for autism, mental retardation, and psychiatric disorders. *Journal of Medical Genetics*, **46**, 382-388.
doi:10.1136/jmg.2008.064378

[293] Leonard, S. and Freedman, R. (2006) Genetics of chromosome 15q13-q14 in schizophrenia. *Biological Psychiatry*, **60**, 115-122.
doi:10.1016/j.biopsych.2006.03.054

[294] Pagnamenta, A.T., Wing, K., Sadighi Akha, E., Knight, S.J., Bölte, S., Schmötzer, G., Duketis, E., Poustka, F., Klauck, S.M., Poustka, A., Ragoussis, J., Bailey, A.J., Monaco, A.P. and International Molecular Genetic Study of Autism Consortium. (2009) A 15q13.3 microdeletion segregating with autism. *European Journal of Human Genetics*, **17**, 687-692. doi:10.1038/ejhg.2008.228

[295] Ingason, A., Rujescu, D., Cichon, S., Sigurdsson, E., Sigmundsson, T., Pietiläinen, O.P., Buizer-Voskamp, J.E., Strengman, E., Francks, C., Muglia, P., Gylfason, A., Gustafsson, O., Olason, P.I., Steinberg, S., Hansen, T., Jakobsen, K.D., Rasmussen, H.B., Giegling, I., Möller, H.J., Hartmann, A., Crombie, C., Fraser, G., Walker, N., Lonnqvist, J., Suvisaari, J., Tuulio-Henriksson, A., Bramon, E., Kiemeney, L.A., Franke, B., Murray, R., Vassos, E., Toulopoulou, T., Mühleisen, T.W., Tosato, S., Ruggeri, M., Djurovic, S., Andreassen, O.A., Zhang, Z., Werge, T., Ophoff, R.A., Group Investigators, Rietschel, M., Nöthen, M.M., Petursson, H., Stefansson, H., Peltonen, L., Collier, D., Stefansson, K. and St Clair, D.M. (2011) Copy number variations of chromosome 16p13.1 region associated with schizophrenia. *Molecular Psychiatry*, **16**, 17-25. doi:10.1038/mp.2009.101

[296] Jolin, E.M., Weller, R.A. and Weller, E.B. (2009) Psychosis in children with velocardiofacial syndrome (22q11.2 deletion syndrome). *Current Psychiatry Reports*, **11**, 99-105. doi:10.1007/s11920-009-0016-y

[297] Shashi, V., Kwapil, T.R., Kaczorowski, J., Berry, M.N., Santos, C.S., Howard, T.D., Goradia, D., Prasad, K., Vaibhav, D., Rajarethinam, R., Spence, E. and Keshavan, M.S. (2010) Evidence of gray matter reduction and dysfunction in chromosome 22q11.2 deletion syndrome. *Psychiatry Research*, **181**, 1-8.
doi:10.1016/j.pscychresns.2009.07.003

[298] Guilmatre, A., Dubourg, C., Mosca, A.L., Legallic, S., Goldenberg, A., Drouin-Garraud, V., Layet, V., Rosier, A., Briault, S., Bonnet-Brilhault, F., Laumonnier, F., Odent, S., Le Vacon, G., Joly-Helas, G., David, V., Bendavid, C., Pinoit, J.M., Henry, C., Impallomeni, C., Germano, E., Tortorella, G., Di Rosa, G., Barthelemy, C., Andres, C., Faivre, L., Frébourg, T., Saugier Veber, P. and Campion, D. (2009) Recurrent rearrangements in synaptic and neurodevelopmental genes and shared biologic pathways in schizophrenia, autism, and mental retardation. *Archives of General Psychiatry*, **66**, 947-956.
doi:10.1001/archgenpsychiatry.2009.80

[299] Meechan, D.W., Tucker, E.S., Maynard, T.M. and LaMantia, A.S. (2009) Diminished dosage of 22q11 genes disrupts neurogenesis and cortical development in a mouse model of 22q11 deletion/DiGeorge syndrome. *Proceedings of the National Academy of Sciences*, **106**, 16434-16445.
doi:10.1073/pnas.0905696106

[300] Prasad, S.E., Howley, S. and Murphy, K.C. (2008) Candidate genes and the behavioral phenotype in 22q11.2 deletion syndrome. *Developmental Disabilities Research Reviews*, **14**, 26-34. doi:10.1002/ddrr.5

[301] Vincent, J.B., Paterson, A.D., Strong, E., Petronis, A. and Kennedy, J.L. (2000) The unstable trinucleotide repeat story of major psychosis. *American Journal of Medical Genetics*, **97**, 77-97.
doi:10.1002/(SICI)1096-8628(200021)97:1<77::AID-AJMG11>3.0.CO;2-3

[302] Bruce, H.A., Sachs, N., Rudnicki, D.D., Lin, S.G., Willour, V.L., Cowell, J.K., Conroy, J., McQuaid, D.E., Rossi, M., Gaile, D.P., Nowak, N.J., Holmes, S.E., Sklar, P., Ross, C.A., Delisi, L.E. and Margolis, R.L. (2009) Long tandem repeats as a form of genomic copy number variation: Structure and length polymorphism of a chromosome 5p repeat in control and schizophrenia populations. *Psychiatric Genetics*, **19**, 64-71.
doi:10.1097/YPG.0b013e3283207ff6

[303] Hamshere, M.L., Schulze, T.G., Schumacher, J., Corvin, A., Owen, M.J., Jamra, R.A., Propping, P., Maier, W.,

Orozco y Diaz, G., Mayoral, F., Rivas, F., Jones, I., Jones, L., Kirov, G., Gill, M., Holmans, P.A., Nöthen, M.M., Cichon, S., Rietschel, M. and Craddock, N. (2009) Mood-incongruent psychosis in bipolar disorders: Conditional linkage analysis shows genome-wide suggestive linkage at 1q32.3, 7p13 and 20q13.31. *Bipolar disorders*, **11**, 610-620. [doi:10.1111/j.1399-5618.2009.00736.x](doi:10.1111/j.1399-5618.2009.00736.x)

[304] Shaffer, L.G., Theisen, A., Bejjani, B.A., Ballif, B.C., Aylsworth, A.S., Lim, C., McDonald, M., Ellison, J.W., Kostiner, D., Saitta, S. and Shaikh, T. (2007) The discovery of microdeletion syndromes in the post-genomic era: Review of the methodology and characterization of a new 1q41q42 microdeletion syndrome. *Genetics in Medicine*, **9**, 607-616. [doi:10.1097/GIM.0b013e3181484b49](doi:10.1097/GIM.0b013e3181484b49)

[305] Slavotinek, A.M. (2008) Novel microdeletion syndromes detected by chromosome microarrays. *Human Genetics*, **124**, 1-17. [doi:10.1007/s00439-008-0513-9](doi:10.1007/s00439-008-0513-9)

[306] Glessner, J.T., Wang, K., Cai, G., Korvatska, O., Kim, C.E., Wood, S., Zhang, H., Estes, A., Brune, C.W., Bradfield, J.P., Imielinski, M., Frackelton, E.C., Reichert, J., Crawford, E.L., Munson, J., Sleiman, P.M., Chiavacci, R., Annaiah, K., Thomas, K., Hou, C., Glaberson, W., Flory, J., Otieno, F., Garris, M., Soorya, L., Klei, L., Piven, J., Meyer, K.J., Anagnostou, E., Sakurai, T., Game, R.M., Rudd, D.S., Zurawiecki, D., McDougle, C.J., Davis, L.K., Miller, J., Posey, D.J., Michaels, S., Kolevzon, A., Silverman, J.M., Bernier, R., Levy, S.E., Schultz, R.T., Dawson, G., Owley, T., McMahon, W.M., Wassink, T.H., Sweeney, J.A., Nurnberger, J.I., Coon, H., Sutcliffe, J.S., Minshew, N.J., Grant, S.F., Bucan, M., Cook, E.H., Buxbaum, J.D., Devlin, B., Schellenberg, G.D. and Hakonarson, H. (2009) Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. *Nature*, **459**, 569-573. doi:10.1038/nature07953

[307] Bucan, M., Abrahams, B.S., Wang, K., Glessner, J.T., Herman, E.I., Sonnenblick, L.I., Alvarez Retuerto, A.I., Imielinski, M., Hadley, D., Bradfield, J.P., Kim, C., Gidaya, N.B., Lindquist, I., Hutman, T., Sigman, M., Kustanovich, V., Lajonchere, C.M., Singleton, A., Kim, J., Wassink, T.H., McMahon, W.M., Owley, T., Sweeney, J.A., Coon, H., Nurnberger, J.I., Li, M., Cantor, R.M., Minshew, N.J., Sutcliffe, J.S., Cook, E.H., Dawson, G., Buxbaum, J.D., Grant, S.F., Schellenberg, G.D., Geschwind, D.H. and Hakonarson, H. (2009) Genome-wide analyses of exonic copy number variants in a family-based study point to novel autism susceptibility genes. *PLoS Genetics*, **5**, e1000536. doi:10.1371/journal.pgen.1000536

[308] Kumar, R.A. and Christian, S.L. (2009) Genetics of autism spectrum disorders. *Current Neurology and Neuroscience Reports*, **9**, 188-197. [doi:10.1007/s11910-009-0029-2](doi:10.1007/s11910-009-0029-2)

[309] Yan, J., Zhang, F., Brundage, E., Scheuerle, A., Lanpher, B., Erickson, R.P., Powis, Z., Robinson, H.B., Trapane, P.L., Stachiw-Hietpas, D., Keppler-Noreuil, K.M., Lalani, S.R., Sahoo, T., Chinault, A.C., Patel, A., Cheung, S.W. and Lupski, J.R. (2009) Genomic duplication resulting in increased copy number of genes encoding the sister chromatid cohesion complex conveys clinical consequences distinct from Cornelia de Lange. *Journal of Medical Genetics*, **46**, 626-634. [doi:10.1136/jmg.2008.062471](doi:10.1136/jmg.2008.062471)

[310] Kong, A., Frigge, M.L., Masson, G., Besenbacher, S., Sulem, P., Magnusson, G., Gudjonsson, S.A., Sigurdsson, A., Jonasdottir, A., Jonasdottir, A., Wong, W.S., Sigurdsson, G., Walters, G.B., Steinberg, S., Helgason, H., Thorleifsson, G., Gudbjartsson, D.F., Helgason, A., Magnusson, O.T., Thorsteinsdottir, U. and Stefansson, K. (2012) Rate of de novo mutations and the importance of father's age to disease risk. *Nature*, **488**, 471-475. doi:10.1038/nature11396

[311] Sun, G., Yan, J., Noltner, K., Feng, J., Li, H., Sarkis, D.A., Sommer, S.S. and Rossi, J.J. (2009) SNPs in human miRNA genes affect biogenesis and function. *RNA*, **15**, 1640-1651. [doi:10.1261/rna.1560209](doi:10.1261/rna.1560209)

[312] Feng, J., Sun, G., Yan, J., Noltner, K., Li, W., Buzin, C.H., Longmate, J., Heston, L.L., Rossi, J. and Sommer, S.S. (2009) Evidence for X-chromosomal schizophrenia associated with microRNA alterations. *PLoS One*, **4**, e6121. doi:10.1371/journal.pone.0006121

[313] Burmistrova, O.A., Goltsov, A.Y., Abramova, L.I., Kaleda, V.G., Orlova, V.A. and Rogaev, E.I. (2007) MicroRNA in schizophrenia: Genetic and expression analysis of miR-130b (22q11). *Biochemistry* (*Moscow*), **72**, 578-582. [doi:10.1134/S0006297907050161](doi:10.1134/S0006297907050161)

[314] Gregory, R.I., Chendrimada, T.P. and Shiekhattar, R. (2006) MicroRNA biogenesis: Isolation and characterization of the microprocessor complex. *Methods in Molecular Biology*, **342**, 33-47. http://www.ncbi.nlm.nih.gov/pubmed/16957365

[315] Zhu, Y., Kalbfleisch, T., Brennan, M.D. and Li, Y. (2009) MicroRNA gene is hosted in an intron of a schizophrenia-susceptibility gene. *Schizophrenia Research*, **109**, 86-89. doi:10.1016/j.schres.2009.01.022

[316] Cummings, E., Donohoe, G., Hargreaves, A., Moore, S., Fahey, C., Dinan, T.G., McDonald, C., O'Callaghan, E., O'Neill, F.A., Waddington, J.L., Murphy, K.C., Morris, D.W., Gill, M. and Corvin, A. (2012) Mood congruent psychotic symptoms and specific cognitive deficits in carriers of the novel schizophrenia risk variant at MIR-137. *Neuroscience Letters* (in press). doi:10.1016/j.neulet.2012.08.065

[317] Pinsonneault, J.K., Papp, A.C. and Sadée, W. (2006) Allelic mRNA expression of X-linked monoamine oxidase a (MAOA) in human brain: Dissection of epigenetic and genetic factors. *Human Molecular Genetics*, **15**, 2636-2649. [doi:10.1093/hmg/ddl192](doi:10.1093/hmg/ddl192)

[318] Crews, D. (2008) Epigenetics and its implications for behavioural neuroendocrinology. *Neuroendocrinology*, **29**, 344-357. doi:10.1016/j.yfrne.2008.01.003

[319] Feng, J. and Fan, G. (2009) The role of DNA methylation in the central nervous system and neuropsychiatric disorders. *International Review of Neurobiology*, **89**, 67-84. [doi:10.1016/S0074-7742(09)89004-1](doi:10.1016/S0074-7742(09)89004-1)

[320] Reichenberg, A., Mill, J. and MacCabe, J.H. (2009) Epigenetics, genomic mutations and cognitive function. *Cognitive Neuropsychiatry*, **14**, 377-390. [doi:10.1080/13546800902978417](doi:10.1080/13546800902978417)

[321] MacDonald, J.L. and Roskams, A.J. (2009) Epigenetic regulation of nervous system development by DNA methylation and histone deacetylation. *Progress in Neurobiology*, **88**, 170-183. doi:10.1016/j.pneurobio.2009.04.002

[322] Urdinguio, R.G., Sanchez-Mut, J.V. and Esteller, M. (2009) Epigenetic mechanisms in neurological diseases: Genes, syndromes, and therapies. *The Lancet Neurology*, **8**, 1056-1072. doi:10.1016/S1474-4422(09)70262-5

[323] Bronner, C., Chataigneau, T., Schini-Kerth, V.B. and Landry, Y. (2007) The "Epigenetic Code Replication Machinery", ECREM: A promising drugable target of the epigenetic cell memory. *Current Medicinal Chemistry*, **14**, 2629-2641. doi:10.2174/092986707782023244

[324] Chavez-Blanco, A., Perez-Plasencia, C., Perez-Cardenas, E., Carrasco-Legleu, C., Rangel-Lopez, E., Segura-Pacheco, B., Taja-Chayeb, L., Trejo-Becerril, C., Gonzalez-Fierro, A., Candelaria, M., Cabrera, G. and Duenas-Gonzalez, A. (2006) Antineoplastic effects of the DNA methylation inhibitor hydralazine and the histone deacetylase inhibitor valproic acid in cancer cell lines. *Cancer Cell International*, **6**, 2. doi:10.1186/1475-2867-6-2

[325] Abdolmaleky, H.M., Smith, C.L., Zhou, J.R. and Thiagalingam, S. (2008) Epigenetic alterations of the dopaminergic system in major psychiatric disorders. *Methods in Molecular Biology*, **448**, 187-212. doi:10.1007/978-1-59745-205-2_9

[326] Kazantsev, A.G. and Thompson, L.M. (2008) Therapeutic application of histone deacetylase inhibitors for central nervous system disorders. *Nature Reviews Drug Discovery*, **7**, 854-868. doi:10.1038/nrd2681

[327] Dong, E., Nelson, M., Grayson, D.R., Costa, E. and Guidotti, A. (2008) Clozapine and sulpiride but not haloperidol or olanzapine activate brain DNA demethylation. *Proceedings of the National Academy of Sciences*, **105**, 13614-13619. doi:10.1073/pnas.0805493105

[328] Guidotti, A., Dong, E., Kundakovic, M., Satta, R., Grayson, D.R. and Costa, E. (2009) Characterization of the action of antipsychotic subtypes on valproate-induced chromatin remodeling. *Trends in Pharmacological Sciences*, **30**, 55-60. doi:10.1016/j.tips.2008.10.010

[329] Costa, E., Chen, Y., Dong, E., Grayson, D.R., Kundakovic, M., Maloku, E., Ruzicka, W., Satta, R., Veldic, M., Zhubi, A. and Guidotti, A. (2009) GABAergic promoter hypermethylation as a model to study the neurochemistry of schizophrenia vulnerability. *Expert Review of Neurotherapeutics*, **9**, 87-98. doi:10.1586/14737175.9.1.87

[330] Dong, E., Agis-Balboa, R.C., Simonini, M.V., Grayson, D.R., Costa, E. and Guidotti, A. (2005) Reelin and glutamic acid decarboxylase67 promoter remodeling in an epigenetic methionine-induced mouse model of schizophrenia. *Proceedings of the National Academy of Sciences of USA*, **102**, 12578-12583. doi:10.1073/pnas.0505394102

[331] Grayson, D.R., Chen, Y., Dong, E., Kundakovic, M. and Guidotti, A. (2009) From trans-methylation to cytosine methylation: Evolution of the methylation hypothesis of schizophrenia. *Epigenetics*, **4**, 144-149. doi:10.4161/epi.4.3.8534

[332] Gavin, D.P., Kartan, S., Chase, K., Jayaraman, S. and Sharma, R.P. (2009) Histone deacetylase inhibitors and candidate gene expression: An *in vivo* and *in vitro* approach to studying chromatin remodeling in a clinical population. *Journal of Psychiatric Research*, **43**, 870-876.

doi:10.1016/j.jpsychires.2008.12.006

[333] Li, J., Harris, R.A., Cheung, S.W., Coarfa, C., Jeong, M., Goodell, M.A., White, L.D., Patel, A., Kang, S.H., Shaw, C., Chinault, A.C., Gambin, T., Gambin, A., Lupski, J.R. and Milosavljevic, A. (2012) Genomic hypomethylation in the human germline associates with selective structural mutability in the human genome. *PLoS Genetics*. **8**, e1002692. doi:10.1371/journal.pgen.1002692

[334] Rezin, G.T., Amboni, G., Zugno, A.I., Quevedo, J. and Streck, E.L. (2009) Mitochondrial dysfunction and psychiatric disorders. *Neurochemical Research*, **34**, 1021-1029. doi:10.1007/s11064-008-9865-8

[335] Shao, L., Martin, M.V., Watson, S.J., Schatzberg, A., Akil, H., Myers, R.M., Jones, E.G., Bunney, W.E. and Vawter, M.P. (2008) Mitochondrial involvement in psychiatric disorders. *Annals of Medicine*, **40**, 281-295. doi:10.1080/07853890801923753

[336] Rollins, B., Martin, M.V., Sequeira, P.A., Moon, E.A., Morgan, L.Z., Watson, S.J., Schatzberg, A., Akil, H., Myers, R.M., Jones, E.G., Wallace, D.C., Bunney WE and Vawter MP, (2009) Mitochondrial variants in schizophrenia, bipolar disorders, and major depressive disorder. *PLoS One*, **4**, e4913. doi:10.1371/journal.pone.0004913

[337] Munakata, K., Iwamoto, K., Bundo, M. and Kato, T. (2005) Mitochondrial DNA 3243A > G mutation and increased expression of LARS2 gene in the brains of patients with bipolar disorders and schizophrenia. *Biological Psychiatry*, **57**, 525-532. doi:10.1016/j.biopsych.2004.11.041

[338] Washizuka S, Iwamoto K, Kakiuchi C, Bundo M and Kato T. (2009) Expression of mitochondrial complex I subunit gene NDUFV2 in the lymphoblastoid cells derived from patients with bipolar disorders and schizophrenia. *Neuroscience Reseasrch*, **63**, 199-204. doi:10.1016/j.neures.2008.12.004

[339] Park, Y.U., Jeong, J., Lee, H., Mun, J.Y., Kim, J.H., Lee, J.S., Nguyen, M.D., Han, S.S., Suh, P.G. and Park, S.K. (2010) Disrupted-in-schizophrenia 1 (DISC1) plays essential roles in mitochondria in collaboration with Mitofilin. *Proceedings of the National Academy of Sciences*, **107**, 17785-17790. doi:10.1073/pnas.1004361107

[340] Bilder, R.M., Sabb, F.W., Parker, D.S., Kalar, D., Chu, W.W., Fox, J., Freimer, N.B. and Poldrack, R.A. (2009) Cognitive ontologies for neuropsychiatric phenomics research. *Cognitive Neuropsychiatry*, **14**, 419-450. doi:10.1080/13546800902787180

[341] Meda, S.A., Jagannathan, K., Gelernter, J., Calhoun, V.D., Liu, J., Stevens, M.C. and Pearlson, G.D. (2010) A pilot multivariate parallel ICA study to investigate differential linkage between neural networks and genetic profiles in schizophrenia. *Neuroimage*, **53**, 1007-1015. doi:10.1016/j.neuroimage.2009.11.052

[342] Bergen, S.E., Fanous, A.H., Walsh, D., O'Neill, F.A. and Kendler, K.S. (2009) Polymorphisms in SLC6A4, PAH, GABRB3, and MAOB and modification of psychotic disorder features. *Schizophrenia Research*, **109**, 94-97. doi:10.1016/j.schres.2009.02.009

[343] Chu TT, Liu Y and Kemether E. (2009) Thalamic tran-

scriptome screening in three psychiatric states. *Journal of Human Genetics*, **54**, 665-675. doi:10.1038/jhg.2009.93

[344] Dean, B., Boer, S., Gibbons, A., Money, T. and Scarr. E. (2009) Recent advances in post-mortem pathology and neurochemistry in schizophrenia. *Current Opinion in Psychiatry*, **22**, 154-160. doi:10.1097/YCO.0b013e328323d52e

[345] Martins-de-Souza, D., Gattaz, W.F., Schmitt, A., Novello, J.C., Marangoni, S., Turck, C.W. and Dias-Neto, E. (2009) Proteome analysis of schizophrenia patients Wernicke's area reveals an energy metabolism dysregulation. *BMC Psychiatry*, **9**, 17. doi:10.1186/1471-244X-9-17

[346] Kuzman, M.R., Medved, V., Terzic, J. and Krainc, D. (2009) Genome-wide expression analysis of peripheral blood identifies candidate biomarkers for schizophrenia. *Journal of Psychiatric Research*, **43**, 1073-1077. doi:10.1016/j.jpsychires.2009.03.005

[347] Quinones, M.P. and Kaddurah-Daouk, R. (2009) Metabolomics tools for identifying biomarkers for neuropsychiatric diseases. *Neurobiology of Disease*, **35**, 165-76. doi:10.1016/j.nbd.2009.02.019

[348] Need, A.C., Motulsky, A.G. and Goldstein, D.B. (2005) Priorities and standards in pharmacogenetic research. *Nature Genetics*, **37**, 671-681. doi:10.1038/ng1593

[349] Johnson, A.D., Wang, S. and Sadee, W. (2005) Polymorphisms affecting gene regulation and mRNA processing: Broad implications for pharmacogenetics. *Pharmacology & Therapeutics*, **106**, 19-38. doi:10.1016/j.pharmthera.2004.11.001

[350] Ishikawa, T., Onishi, Y., Hirano, H., Oosumi, K., Nagakura, M. and Tarui, S. (2004) Pharmacogenomics of drug transporters: A new approach to functional analysis of the genetic polymorphisms of ABCB1 (P-glycoprotein/MDR1). *Biological & Pharmaceutical Bulletin*, **27**, 939-948. doi:10.1248/bpb.27.939

[351] Nishimura, M. and Naito, S. (2008) Tissue-specific mRNA expression profiles of human solute carrier transporter superfamilies. *Drug Metabolism and Pharmacokinetics*, **23**, 22-44. doi:10.2133/dmpk.23.22

[352] Agrawal, N., Dasaradhi, P.V., Mohmmed, A., Malhotra, P., Bhatnagar, R.K. and Mukherjee, S.K. (2003) RNA interference: biology, mechanism, and applications. *Microbiology and Molecular Biology Reviews*, **67**, 657-685. doi:10.1128/MMBR.67.4.657-685.2003

[353] Leung, R.K. and Whittaker, P.A. (2005) RNA interference: From gene silencing to gene-specific therapeutics. *Pharmacology & Therapeutics*, **107**, 222-239. doi:10.1016/j.pharmthera.2005.03.004

[354] Gonzalez-Alegre, P. (2007) Therapeutic RNA interference for neurodegenerative diseases: From promise to progress. *Pharmacology & Therapeutics*, **114**, 34-55. doi:10.1016/j.pharmthera.2007.01.003

[355] Ying, S.Y. and Lin, S.L. (2009) Intron-mediated RNA interference and microRNA biogenesis. *Methods in Molecular Biology*, **487**, 387-413. doi:10.1007/978-1-60327-547-7_19

[356] Boudreau, R.L., Spengler, R.M., and Davidson, B.L. (2011) Rational design of therapeutic siRNAs: minimizing off-targeting potential to improve the safety of RNAi therapy for Huntington's disease. *Molecular Therapy*, **19**, 2169-2177. doi:10.1038/mt.2011.185