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Autism: A Different Vision

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Abstract

Genomic analysis has emphasized the enormous genetic contribution to autism spectrum disorders, with over 80% of patients having changes demonstrable by high resolution chromosome (microarray) analysis or whole exome sequencing. An overview of these genetic changes demonstrates the expected role of synaptic transmission in autism and, together with clinical observations, emphasizes the importance of visual input on developing sensory systems and social responses. Neonatal recognition of autism predisposition through genetic analysis could allow sensory stimulation therapies during periods of neuroplasticity, an approach analogous to strabismus correction before the cortical dissociation of the deviant eye.

Keywords

Autism, Autism Spectrum Disorders, Genomics, Array-Comparative Genomic Hybridization, Microarray Analysis, Whole Exome Sequencing, Synaptic Transmission

1. Introduction

Recent advances in genetics and neuroscience, when focused by the appropriate clinical prism, reveal a glimpse of gold beneath the multicolored autism spectrum [1]. A profusion of low-frequency genetic changes [2] [3] [4] ends the dark of vaccine myths [5] and heralds a sunrise of early screening for autism susceptibility. The new challenge is to integrate highlighted genes with neurodevelopmental pathways, achieving early diagnosis and remodeling of neural architecture for the 1% of children who will become autistic [6]. This review updates autism genomics with an organizing hypothesis: Autism is an emergent disorder that reflects inborn errors of the sensory nervous system. We will catalogue genetic changes and their roles in neural patterning or synapse transmission (Table 1 and Table 2), examine environmental influences that could interact

with these genomic changes (Table 3), emphasize that timely stimulation therapies could remodel plastic neural pathways, and finish with an old medical dictum: Study the patient.

Table 1. Genetic alterations in patients with autism and without recognized genetic disorders.

	Genetic linkage (Lk)	Microarray analysis (CMA)	Gene-locus Association (A)	Gene sequence (M)	Gene expression (E)
	p [46]	p36- [49] p34.2- [50]	p33 *MTF*1 [55]		
1	q21.1 [47]	q21.1 ± *RBM*8*A* [51] [52]			
	q23q24.2 [48]	q23.3q24.2-(t) [53]			
		q41q42 ± [54]			
	p [56]	p15p16.3- *NRXN*1 [58] [59]		p16.3 *NRXN*1t [70]	
				p13 *RAB*11*FIP*5t [71]	
		q21q23 -/- *SCN*7*A* [60]			
2	q [57]	q23.1 ± *EPC*2 [61]	q24q33 *STK*39 [66]	q24.2 *SLC*4*A*10t [72]	
			q24 *SLC*25*A*12 [67]	q24.3 *SCN*1*A*m [73]	
	q32 [57]	q34q35- *MAP*2 [62]	q31q32 *ITGA*4 [68] *DLX*1/2 [69]	q31.1 *RAPGEF*4m [74]	q31 *GAD*1 [76]
		q35-*PAX*3 [63] q37 [64] [65]		q37.3 *CENTG*2m [75]	q34q35 *MAP*2 [62]
		p26.2- *OXTR* [77] p26 ± *CNTN*4 [78] p24- [79]		p26.2*OXTR*m [77]	p26.2 *OXTR* [83]
3		p14.2 ± *FHIT* [4]		p26p25 *CNTN*4t [81]	
		q24 -/-*SLC*9*A*9, *DIA*1 [60]		q21q22 *MBD*4m [82]	
	q25q27 [46]	q29- *PAK*2 *DLG*1 [80]			
4			p12 *GABRA*2 *GABRA*4 [84]		
		q28.3 -/- *PCDH*10 [84]		q21q25 *EIF*4*E*t [85]	
		p15.2- [79] p13- *NIPBL SLC*1*A*3 [87]	p15.2p14.1 *SEMA*5*A* [91] *CDH*9, *CDH*10 [92] *SLC*6*A*3 [93]		p13p15 *SEMA*5*A* [91] *SLC*1*A*3 [95]
5	q [86]	q14q21- *RASA*1, *MEF*2*C* [88]	q22.2 *APC* [86]		q12 *PDE*4*D* [96]
		q35.2/.3 ± *NSD*1 [89] [90]	q31 *PITX*1 [94]		q33 *AMPA*1 [95]
			q34q35.1 *GABRB*2 [84]		q34q35 *GABRA*1 [84]
		p23- [4] p21.3 -/- *RNF*8 [4]	p21.3p21.2 *GLO*1 [97]		
6	q21 [56]		q15 *GABRR*2 [84]		
			q16.3 *GRIK*2 [98]		q21q23.2 *GJA*1 [99]
		p22.1+/t *ACTB* [104] [105]	p15.3 *HOXA*1* [109]		
		p21.1- *MACC*1 [4]			
	q21.13 [60]	q11- [106] q11.23+ [62]	q22 *RELN* [110]	q11.2 *KIAA*0442t [116]	q22 *RELN* [121]
7	q22 [100]	q21q22.3- [107]	q31 *FOXP*2* [111] *MET* [112]	q31 *MET*m [117]	
	q22q32 [101]	q31-t [108]	q35q36 *CNTNAP*2 [113]	q31.3 *CADPS*2m [118]	
	q31.32 [100]		q36 *EN*2 [114]	q31.1q31.3 *ST*7t [119]	

Continued

	q31q34 [102]		q31/q31.2 *WNT2** [115]	q32 *SSBP1 T2R3*t [120]	
	q35q36 [103]				
8		p23.1- *MCPH1* [122] [123]	q21.13 *FABP5* (*FABP7*) [125]	q21 *MMP16*t [117]	
		q22.1q23- [124]		q23 *CSMD3*t [124]	
9	p13.1 [60]				
	q34.3 [60]				q34.3 *GRIN* [95]
		p12p11- *WAC* [126]			p11.23 *GAD2* [131]
10		q11.2- *CHAT SLC18A3* [127]		q11.1 *TRIP8 REEP3*t [129]	
		q22q23- [128]		q23.31 *PTEN*m [130]	
11	p12p13 [60]	p12p13- [4]	p13 *BDNF* [132]	p15.5 *SCT*m [133]	
12	q14.2 [134]	p13.33/.32- *CACNA1C* [135]	q14q15 *AVPR1A* [136]	p13.3 *CACNA1C*m [137]	
13	q12.2 [60]			q13.2 *NBEA*t [139]	
	q14.2q14.1 [138]	q14.2q14.1- [4]			
14		q11.2- *CHD8* [4] [140]			
	q11q13 [141]	q11.2 ± *CYFIP1*, *NIPA1* [142]	q11.2q12 *GABRB3** *GABRG3* [149]		
15		q11q13+ *UBE3A* [60] [143]			
		q13.2 ± *CHRNA7* [4] [144]	q11q13 *UBE3A* [150]	q13.1 *APBA2*m [151]	
		q22- *PTPN9* [145] q24- [146] q25.2 [147] q26qter- [148]			
	p13 [152]	p11.2 ± *SH2B* [3] [4] [153]	p11.2 *PRKCB1* [158]		p11.2 *PRKCB1* [158]
16		p13.1 ± *NDE1* [4] [154]	p13 *GRIN2A ABAT* [159]	p13.3 *A2BP1*t [160]	
		q23.2- *CMIP* [155] q24.2/.3- [156] [157]			
		p13.1- [162] p13.3+ [163]			
17	q11 [60]	p11.2 ± *NF1* [164] [165]	q11.1q12 *SLC6A4* [167]	q11.1q12 *SLC6A4*m [169]	
	q21 [161]	q12- [166]	q21.32 *ITGB3* [168]		
18		q12-t [170]			q11.2q12 *AQP4* [171]
19	p [172]	p13.13/.12- *AKAP8* [173]			
20		p13- [4]			
21	p13q11 [174]	q21 *NCAM2* [175] q21.1q21.3- [176]			
22		q11.2 ± [177]		q13.1 *ADSL*m [179]	
		q13.3- *SHANK3* [4] [178]		q13.33 *SHANK3*m [180]	
		p22.33- *NLGN4* [181]		p22.33 *NLGN4*m [188]	
		p22.2p22.3 ± *STS*, *NLGN4*, *VCX* cluster [182]		p21.3 *IL1RAPL1*mt [189]	
X		p22.12+ *RPS6KA3* [183]	p11.23 *MAOA* [187]	p21.3 *ARX*m [190]	
	q13 [1] [8]	p11.22- *PHF8 WNK3* [4] [184]		q13 *NLGN3*m [191]	

Continued

	q12q13.3+ [185]	q24q26 *UPF3B*m [192]
	q13q21+ [186]	q28 *FMR2*m [193]
	q28+ [194]	q28 *MECP2*m [194] [195]
Y		q11.2 *NLGN4Y*m [196]

Genetic loci are listed as p for chromosome short arm, q for long arm, numbers for bands, gene symbols as in Online Mendelian Inheritance in Man (http://www.omim.org/) referenced with OMIM numbers in the appended **Table A**; linkage includes traditional linkage studies focused on one locus and whole genome association linkage studies that analyze as many as 200 loci at once; microarray analysis loci defined by + for microduplication, - for microdeletion, -/- for homozygous microdeletion, -t for translocation and microdeletion; gene locus-association, allele association study with specific genes indicated (*when negative association studies also reported); gene sequence studies show m for mutation, t for a gene disrupted by translocation; gene expression involves measurement of RNA or protein species, often in brain.

Table 2. Summary of loci implicated in autism.

Locus	Implicated genes grouped by potential mechanism					Genetic approach				
	Pattern	Synapse-channels	Synapse-metabotropic	Synapse-adhesion	Immune	Unknown/other	Lk	CMA	A	M	E
Total							28	69	28	35	13
1q21							x	x			
1q23							x	x			
2p16p15				NRXN1							
2q23q24		*SCN7A*, *SCN1A*, *SLC25A12*, *SLC40A1*					x	x		x	
2q31q32	*DLX1* *DLX2*	*SLC40A1*	*RAPGEF4* *GAD1*		*ITGA4*		x	x	x	x	x
2q34q37	*PAX3*		*MAP2*			*CENTG2*		x		x	x
3p26				*CNTN3*		*OXTR*		x		x	x
3q24q29	*DLG1*	*NHE9*/*SLC9A9*	*PAK2*				x	x			
5p15p13				*SEMA5A*				x	x		x
5q31q35	*PITX1*		*AMPA* 1 *GABRB2* *GABRA1*				x		x		x
6p23p21						*GLO1* *RNF8*		x	x		
6q15q21			*GABRR2* *GRIK2*	*GJA1*			x		x		x
7q21q22	*NDE1*		*GRIN2A* *ABAT*			*A2BP1* *RELN*	x	x	x	x	x
7q31q36	*EN2* *MET* *WNT2*		*CADPS2*	*CNTNAP2*,		*FOXP2*	x	x	x	x	
8q21q23								x	x	x	
9q34			*GRIN1*				x				x
10q11			*REEP3*			*TRIP8*		x		x	
10q22q23								x		x	
11p15p12	*BDNF*					*SCT*	x	x	x	x	
12q14q15		*CACNA1C*				*AVPR1A*	x		x		
13q12q14				*NBEA*			x	x		x	
15q11q13			*GABRB3* *GABRA5* *GABRG3*	*CYFIP2*		*UBE3A* *APBA2*	x	x	x		

Continued

16p13p11			*PRKCB*1				x	x	x	x	x
17q11q12	*RAI*1	*SLC6A4*					x		x	x	
17q21					*ITGB*3		x		x		
18q12		*AQP*4						x			x
22q11q13				*SHANK*3		*ADSL*		x		x	
Xp22				*NLGN*4	*IL*1*IRAPL*1	*VCX*		x		x	
Xp11			*WNK*3 *MAOA*			*PHF*8		x	x		
Xq13				*NLGN*3			x			x	

Loci implicated by 2 genetic approaches are taken from **Table 1**, loci and gene symbols explained in the appended **Table A** with numbers assigned in Online Mendelian Inheritance in Man (http://www.omim.org/). Loci implicated by all 5 genetic approaches are highlighted in dark grey, those with 3 - 4 in light gray. Genetic approaches include Lk, whole genome linkage/association; CMA, aCGH-microarray analysis; A, association; M, mutation defined by DNA sequencing; E, expression studies (usually in brain).

Table 3. Potential environmental factors highlighted by autism-related genes.

Level of neural alteration	Autism-related genes	Potential environmental factors
	Sensory receptors	
Olfactory Retinal Cochlear Tongue, gut mucosa Pain, touch	Na, solute channels *SCN7A*, *SCN1A*, *SLC25A12*, *SLC40A1*, *SLC6A4* Na-H exchanger *NHE9*/*SLC9A9* Aquaporin *AQP4* Ca channels *CACNA1C*	**Sensory overload** Prenatal U/S, other radiation Urban noise, home media Gut allergens, toxins, bacteria **Sensory deprivation** Decreased sunlight
	Synapse connections	
Sensory receptors Presynaptic	Na, solute, Ca channels Cell adhesion *NXRN1*	**Nutritional deficiencies** Calcium, vitamin D deficiencies Essential lipids, fatty acids Decreased breast-feeding initiation and duration
Postsynaptic	Glutamate, GABA receptors *GABRR2 GRIK2* Cell adhesion-neuroligins *NLGN3*, *NLGN4*, *NLGN4Y*	
Formation of sensory maps, pathways (end-organ to thalamus, superior colliculus to cortical regions); central deficits (sensory cortex, amygdala)		
Pathway architecture Sensory integration		Light deprivation (as per myopia) Sensory overload, deprivation
Gut-brain connections	Integrins *ITGA4 ITGB3* Interleukin receptor *IL1IRAPL1*	Immune/inflammatory factors Rare vaccine reactions
Neuroendocrine	Thyroid receptor *TRIP*, Secretin *SCT*	Maternal hypothyroidism, diabetes
Parental/social interaction (infant touch, gaze stimulation)	Oxytocin receptor *OXTR*	Maternal depression/drug use Community, family deficiencies

Gene symbols are defined in appended **Table A**.

Autism is like other behavioral disorders in exhibiting multifactorial determination [7] [8], its altered gaze and genetic changes overlapping with schizophrenia [9] [10]. Foucault [11] recognized the dichotomy between a medicine of spi-

rit versus that of substance: "[The advent of pathology] … meant that the relation between visible and invisible—which is necessary to all concrete knowledge—changed its structure, revealing by gaze and language what had previously been below and beyond their domain."

There is a parallel between the flawed gaze and interaction of autistic children and the searching gaze of their students, striving to merge mute with savant in a language of mind and molecules.

2. The Rationale for Sensory Deficits

Frequent encounters with patients having autism and early visual deficits, supported by research demonstrating face perception changes [12] emphasize vision as a key problem in autism [13] [14] [15]. Certainly vision is pivotal for child development, perhaps foreshadowed by its catalysis of novelty during the Cambrian explosion [16], and recapitulated when a child's poor eye contact forecasts altered communication and social interaction. The optic nerve does contain 38% of cranial nerve fibers [17] but broader neurosensory disruption is suggested by the hypersensitivities of hearing or touch that often precede an autism diagnosis [18].

The many disorders with neurosensory deficits and autism include mixed hearing loss, strabismus, cataracts, or nystagmus in Down, Prader-Willi, Williams, and other chromosomal syndromes [7] [8] [19]. Sensory compensation may be evidenced by hyperacusis in Williams syndrome and by photophobia in Smith-Lemli-Opitz syndrome [20]. Vision impairment and autism are notable in aniridia, Leber amaurosis, Mobius syndrome, or thalidomide embryopathy [15] and, with some controversy about autism diagnosis, in the congenitally blind (10% - 15% autism prevalence) [21] [22] or deaf (7% autism prevalence with reciprocal frequencies of 7.9% - 18.5% mild/moderate and 3.5% profound hearing loss in autistic children) [23]. Congenitally blind children also have delayed maternal attachment, articulation problems, idiosyncratic language ("verbalisms"), stereotypy (repetitive movements or "blindisms"), and exploration of space with their hands (haptic perception) that mimic symptoms of autism [21].

Causative sensory deficits would clearly include processing and attention since numerous studies have pointed to altered sound recognition in autism that relates to the flat voice (altered prosody) [24] [25]. Various techniques demonstrate disturbed connectivity [26] including cortical disorganization with macrocephaly, small corpus callosum, and small cerebellum [27]. Altered sensorimotor connections could explain the fine motor incoordination of Asperger disorder, just as altered brain lateralization and lack of cortical dominance [28] can account for the cardinal language deficits that are accentuated by sensory deprivation [29]. The 27% incidence of autism in premature infants [30], increasing with lower birth weight and the presence of retrolental fibroplasia, emphasizes the importance of sensory pathway development and provides an opportunity to explore sensory measures for early diagnosis and therapy.

3. Neurosensory Measures Can Refine Autism Classification and Provide Earlier Diagnosis of Susceptibility

The classic autism triad described by Kanner in 1943 consisted of abnormal verbal/nonverbal communication, abnormal social interaction, and repetitive movements or routines, expanded a year later by Asperger to include social immaturity, eccentric behaviors, and restricted interests in children with normal cognitive function [31]. The DSM IV grouped several autism conditions with Rett syndrome in a pervasive developmental disorder (PDD) category, a mismatch improved by DSM V that also replaced Asperger disorder with the description of high-functioning autism [32] [33]. Insightful clinical delineation should separate patients with autism and global intellectual disability (ID) like those with Rett or fragile X syndromes [34] [35] from those with selective deficits (perhaps denoted as pure or primary autism). Defining essential autism pathways would allow explanation of its significant frequency in almost any disorder with ID, just as the focus on young people with heart attacks defined genetic hypercholesterolemia [36] and explained its occurrence in diabetes mellitus.

Autism diagnosis is currently based on subjective observation and parental questionnaires, with intentions to bring diagnosis from the standard age of 3 - 4 years to 18 months [31]. Novel neurophysiologic and neuro-imaging techniques [27] [37] could provide objective diagnosis much earlier, defining a new category of selective developmental disorders (SDD) based on subtle neurosensory deficits. Eye-tracking technologies reveal different gaze behaviors at age six months [38] illustrating a potential for early functional diagnosis heralded by genomic screening. This would be followed by remodeling of plastic neural pathways [37] [39] by stimulation therapies analogous to the eye patch for strabismus [40] or the cochlear implant for deafness [41]. A more definitive classification would include the timing of autistic symptoms, extent of ID, types of neurosensory deficits, and underlying disorders as presently known or newly defined.

4. The New Genomics of Autism

Evidence of polygenic-environmental interaction in autism has progressed from indirect family studies (60% - 90% concordance rates for monozygotic twins, 5% - 15% for sibs) [7] [8] to direct demonstration of altered genes or chromosome regions by molecular techniques. The presence of autistic symptoms in most chromosomal or genetic disorders that cause significant ID is now complemented by CGH-microarray analysis (CMA) [2] [3] [4] and candidate gene association/DNA sequencing studies [42] [43] that identify genetic variations in high-functioning autism. Copy number variants (CNVs) are detected by CMA in 5% - 10% of autistic children who had prior normal karyotypes, [2] [3] [4], revealing new candidate genes within aneuploid segments [44] that cause extremely variable phenotypes [45].

Table 1 presents a detailed list of chromosome regions and/or gene sequences highlighted in patients diagnosed with autism who do not have recognized conditions like Rett or fragile X syndromes [35]; gene symbols in Table 1 and Table 2 are explained in the appended Table A. Placing the autism diagnosis first, then the genetic finding avoids controversy about whether disorders like fragile X cause behaviors that merit a typical autism diagnosis [19]. Chromosome loci and genes are ordered by chromosome position (p for short arm, q for long arm, numbers reflecting bands) and partitioned in five columns based on the technology employed—first by genetic linkage that is now accelerated by whole genome association studies [43], second by microarray analysis/CMA [2] [3] [4], third by association with particular genes in the manner of the HLA B27 marker with ankylosing spondylitis [43], fourth and most convincing by showing mutations or translocations that disrupt particular genes [44], and fifth by showing altered gene expression [44]. As reviewed previously [2] and summarized in Table 2, Table 1 lists 69 genomic regions solidly implicated in autism by recurring microduplications or microdeletions detected by microarray analysis and another 35 documented by gene sequence mutation or disruption (translocation), supporting the polygenic inheritance implied by population studies. Less definitive are the loci implicated in autism by linkage (28 loci), association (28 loci), or expression studies (13 loci), the latter encompassing the sparsely explored domain of epigenetic influence [34].

The left column of Table 2 lists loci implicated by two or more genetic approaches, drawn from the detailed genetic changes listed in Table 1. Genes within the implicated regions listed in columns related to their potential influence on brain development and function, their symbols defined in appended Table A. Table 2 lists 30 loci implicated by at least two linkage, genomic, or expression techniques with 3 regions (2q31q32, 7q21q22, and 16p11p13) highlighted by all 5 genetic approaches and others (2q, 3p, 5q, 7q, 15q, 16p, 17q, and X) implicated by several. Genes within these susceptibility domains can be grouped by their potential regulation of early pattern, synaptogenesis, or other functions, discussed below from the perspective of neurosensory development.

Early pattern genes. Correlating with sensory importance [16] is the outside-in development of the nervous system, beginning with dorsal ectoderm that becomes midline neural plate with flanking neural folds and neural crest. Potential neural patterning genes include *PAX*3 (paired-box gene 3), *PITX*1 (paired-like homeodomain transcription factor-1), *EN*2 (engrailed-2), *WNT*2 (wingless-type MMTV integration site family, member 2), and the *MET* proto-oncogene among others in Table 2. *PAX*3 murine [197] and *WNT*3 avian [198] homologues are expressed in dorsal tube/neural crest, while cell adhesion mediated by cadherins [199] and the *FHIT* fragile site/tumor suppressor (that influences β-catenins within *WNT* pathways) [200] is involved in neural tube and neural crest patterning. Anterior signals amplify forebrain regions and dorsal sensory organs including special optic sulci and otic pits that appear even

before the anterior neuropore is closed at 25 days post-conception. Segmentation into fore- and hind-brain segments involves the sonic hedgehog *SHH* gene that is deleted in some cases of holoprosencephaly malformation [201] and signal molecules in the *HOXA*2, bone morphogenetic protein (*BMP*), and hedgehog families guide dorsoventral differentiation of the spinal cord, telencephalon, and hypothalamus [202]. The *SHH*, *BMP*, and *WNT* genes all have roles in patterning the cerebral cortex or pallium [201] [202].

Cephalic proliferation of the dorsal neural tube and the embryonic head fold bring dorsolateral optic and otic vesicles to their respective adult anterior and lateral positions. As the otic vesicles migrate ventrally, the branchial arches/pharyngeal grooves ascend anteriorly and reach toward olfactory and cochlear organs with mouth and ear canals. While the optic cups induce surface ectoderm to form the surface structures of vision (cornea, iris, lens), the olfactory nerves extend to cluster at the nasal cribiform plate near palate and tongue. The sensory organs of sight, smell, hearing, and taste all derive from neurectoderm and produce analogous neuron patterns, each with unique metabotropic receptors [37] that extend sensory maps from receptor to tract to processing center to sensory cortex [203] [204] [205] [206], each with unique connections that will be customized by experience-directed neural activity [37] [39] [203] [204] [205] [206].

Concordant molding of cerebral and optic pattern is illustrated by the single-eyed cyclops malformation that reflects underlying holoprosencephaly, an anomaly caused by mutations in the hedgehog pathway or by defective cholesterol synthesis in Smith-Lemli-Opitz syndrome with its frequent autism [20] [201]. The cholesterol moieties required for *SHH* action [201], like folic acid prevention of neural tube defects and the fetal brain anomalies with maternal diabetes, establish links between nutrients and brain development analogous to the enhancement of visual acuity and cognitive outcomes by essential fatty acids [207]. Cephalic enlargement relates to other genes listed in **Table 1**—*NDE*1 interacts with *DISC*1 (deleted in schizophrenia) to increased cortex gyral differentiation and size [208] while mice with *PTEN* mutations have macrocephaly [209]; humans with the latter mutations can manifest macrocephaly and autism [210].

5. Synapse and Connectivity Genes

The human brain contains over 100 trillion synapse units that are organized by morphogen, guidance, and cell adhesion molecules to produce highly specific neural connections and pathways [37] [204]. Neurons employ successive depolarization of Na/K chloride voltage-gated channels to jump synapses electrically or release neurotransmitters that trigger responses on the post-synaptic membrane [37]. Genes from **Table 1** and **Table 2** that could regulate sensory receptor activation and synapse transmission include those encoding channel proteins *SLC*40*A*1, *SCN7A*, *SCN*1*A*, *SLC*25*A*12, *SLC*40*A*1 *NHE*9/*SLC*9*A*9 (*SCN* for sodium channel, *SLC* for solute carrier family/transporter) plus *ACP*4 (aquaporin

4). Others encode the metabotropic receptors/regulators *GRIN*1, *GRIN*2*A* (glutamate receptors), the *GABRA*1, *GABRR*2, *GABRB*3, *GABRA*5, and *GABRG*3 gamma-aminobutyric acid receptors, and the calcium-dependent activator protein *CADPS*2. Several encode cell adhesion molecules including *NRXN*1 (neurexin 1), *CNTN*3 and *CNTNAP*2 (contactin or contactin-associated proteins), *GJA*1 (gap junction alpha-1/connexin 43), *SEMA*5*A* (semaphorin 5A), *SHANK*3 (SH3 and multiple ankyrin repeat domains 3), and the neuroligins *NLGN*4 and *NLGN*3.

Autism often involves altered connectivity [26] [35] but the challenge is to associate specific synaptic pathways with specific disorders and molecular deficits, e. g., the autism-associated neuroligin mutation that depletes its protein at neuronal surfaces [211]. Certain neurotransmitters like GABA are not only message but medium, playing structural roles in synapse maturation and stabilization. Down-regulation of the GABA-A alpha3 subunit decreases the number of GABAergic inhibitory synapses with mismatched synapse formation [212] while abnormal clustering of neuroligin-2 was observed when postsynaptic membranes were deprived of GABA-A receptors [213]. *In vivo* techniques [27] [37] should allow localization of altered receptors and synapse transmission in autistic patients.

6. Exploring Stimulation Therapies

As correlation of sensory pathways with particular synaptic molecules progresses, knowledge of experience-directed sculpting of these pathways is also expanding. Modulation of neuron clusters called barrels in the sensory cortex of rats can be achieved by ablation or stimulation of particular snout whiskers, and the plasticity of these barrel maps documented by *in vivo* photon or fluorescent imaging rather than postmortem histology [204]. The sculpting of sensory cortex maps in response to passive or training inputs is achieved by rapid long-term potentiation or depression of excitatory (NMDA/glutamate) and inhibitory (GABA) synaptic circuits as well as by slower rearrangement of synaptic connections [204] [205] [206]—processes involving genes that are well-represented in **Table 1**. A critical junction of change seems to be the post-synaptic dendritic spines, elements of excitatory sensory synapses that enlarge or contact in conjunction with synapse electrical activity [204]. The dependence of oriented cortex networks on sensory stimuli can be demonstrated by exposing kittens to one visual stimulus orientation or by connecting developing ferret retina to their auditory cortex; the kittens demonstrate a customized visual cortex and the ferrets an auditory cortex patterned by visual stimuli [204].

Modeling of the sensory cortex by perception of stimuli can also be demonstrated by fMRI studies of primates. Stimulation of the monkey frontal eye field produces general activity in the visual cortex, but production of topographically specific activity patterns required appropriate visual stimuli [214]. Objects also elicit different fMRI activities in the human hippocampus if they are perceived as different, providing a mechanism for visual "pattern separation" that simpli-

fies storage in memory [215]. Moreover, the ability of visual stimuli to elicit reproducible, topographically unique fMRI patterns in the human visual cortex required conscious recognition of the stimulus as a face or house; control images that exploited binocular fusion to obliterate image recognition elicited nonspecific fMRI activity in face-sensitive visual areas [216]. Completing the loop is a modification of visual perception by prior, experience-sculpted activity patterns—"predictive codes" that anticipate and facilitate recognition of familiar stimuli [217]. Such experiments preview neurodevelopmental cycles—input to perception to memory/experience to tailored perception—that would progressively mold the sensory processing maps used for language response and social interaction.

Developmental, experience-directed sculpting of sensory pathways is also demonstrated by perception of facial emotional expressions [218] and individuals with autism do show alterations in face and face emotion perception [12] [219] [220] with the expected changes in cortical connectivity [221] [222]. Changes in auditory processing and pitch discrimination [24] [25] have been demonstrated, along with impaired perception of linguistic and social auditory stimuli that may relate to song practice and, in birds, the FOXP2 gene [223]. Subtle auditory processing deficits could relate to noise sensitivities and musical savant tendencies in Williams syndrome and other disorders with frequent autism symptoms [223] [224] [225] [226].

Mirror neuron alterations have been claimed [224] or denied [225] in autism, but such changes, guided by the sensorimotor cortex [226], could certainly lead to altered voice inflection, language idiosyncracies, fine motor differences, and production of repetitive movements by sensorimotor disconnection. The smaller cerebellum [227] that stands out among cortex and amygdale volume differences in autism [27] may seem to contradict the hypothesis of sensory deficits unless coordinated development of sensory and motor pathways is recognized [228].

The preceding information shows how congenital deficits in detecting or processing sensory inputs would have cumulative effects, sometimes exacerbated by environmental factors, and emerge as the cardinal communication and social impairments of autism. A clear research pathway would combine genetic screening for autism susceptibility with neurosensory measures to document early sensory/perception deficits. Novel stimulation therapies to promote genesis of face or voice recognition pathways, not to be confused with discredited ocular therapies [229], would be employed before critical periods of neuroplasticity have expired. The occasional successes of sensory stimulation [18] or Applied Behavior Analysis/ABA [31] therapies may foreshadow more targeted strategies that make primary autism as treatable as strabismus [40] or deafness [41]; these approaches could substantially improve function in autistic children with global ID.

7. Genomic Guides to Environmental Factors

Autism-associated genes provide a rationale approach to environmental influ-

ence, approached through the framework of gene-environmental interactions and pharmacogenomics (**Table 3**). Sensory injury by overwhelming inputs could implicate increasing use of fetal ultrasound [230], higher radiation exposure [231] or urban noise. Reduced sensory inputs could implicate reduced exposure to outdoor light as suggested for myopia [232] and proven for vitamin D deficiency [233]. These factors highlight several calcium-dependent genes from **Table 1** (the *CACNA1C* calcium channel, the *CADPS2* calcium-dependent activator protein for secretion, and several neurotransmitter or adhesion-related genes). Deficits in gut sensation from smell/taste in the upper tract to mucosal receptors in the lower tract could explain early feeding and gastrointestinal problems that stoked fears of vaccine injuries in autism [5] [234] a "gut-brain" connection or immune pathogenesis [34] [235] involving nutrient deficiencies, food allergens, and toxins could be examined using candidate genes like *ITGB3* (integrin beta-3) or *IL1IRAPL1* (interleukin1 receptor accessory protein-like, calcium-related) from **Table 1**. However, recognition of the low frequency of any single causal factor should restrict trial of alternative therapies/elimination diets to those with the relevant genetic changes.

A complex area of environmental interaction concerns abnormal socialization as a core symptom of autism. Social deficits may relate to a lack of joint attention—the parallel processing of information about one's own and other people's visual attention—that begins developing at 4 - 6 months of infancy [236] [237]. Joint attention is the beginning of self-other perception, and it may be dependent on early social visual pursuit that can be measured by eye-tracking [27] [237] Although most would reject Bettleheim's emphasis on "refrigerator mothers" [234], coincidence of loci for schizophrenia and autism including the cadherin pathway [9] could underlie altered maternal-infant bonding and decreased infant stimulation. Altered face processing in parents of autistic children [238] and trends toward isolated family units and single parents could be additional factors that combine with genetic predisposition to increase autism prevalence.

8. Study the Patient

Now that whole genome techniques have defined chromosome regions and genes associated with autism as a broad phenotype, correlation of genetic changes with scrupulously defined patients is needed [239]. Trends toward proprietary genomic databases should be reversed so that benign CNVs and mutations can be distinguished from those related to autism, with or without global ID. The contribution of individual genes within aneuploid segments, easily identified through appropriate genome browsers [44], will likely require CSF RNA/protein expression studies [235]. These gaps in genomic knowledge emphasize that prenatal genetic screening should target autism as susceptibility rather than disease, coupled with novel therapies modeled by early enzyme supplementation in cystic fibrosis [240].

Clinical delineation, with a focus on essential autism as outlined here, is the

perhaps the greatest asset for future research. Autism registries should be viewed as dynamic resources where calibrated natural histories, morphologic changes, and behavioral symptoms are regrouped using the latest neurogenetic techniques. Particularly important is the single case, for patients are the elements of medicine and case presentations its essence, case reports [88] pure cultures compared to the mixed flora of group studies. Among the large registries may be some striking child who reveals a key scotoma of autism like the amnesiac H. M. [37] did for memory and the lobectomized Phineas Gage did for behavior [241]. As the geneticist Richard Goldschmidt stated [242]:

"Progress in biology is derived from cooperation of observation, experiment, and constructive thinking and none of these can *claim primary*. A good observation may lead to results which a meaningless experiment cannot achieve, and a good idea or analysis may accomplish with one strike what a thousand experiments cannot do. This truism, obvious as it is in the history of all sciences, is frequently forgotten in this era of overestimation of new techniques, which are tools of progress only when in the hands of constructive thinkers. We must therefore take whatever material is available in any field and try to use it to its full extent, subject to critical evaluation."

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Appendix

Table A. Key to gene symbols in **Tables 1-3**.

A2BP1, ataxin 2-binding protein 1 (605104); 16p13

ABAT, 4-(gamma)-aminobutyrate transferase (137150); 16p13.3

ACTB, actin-beta (102630), 7p22.1

ADSL, adenylosuccinate lyase (608222); 22q13.1

AKAP8, A-kinase anchor protein 6 (604692) 19p13.12

AMPA 1, GRIA1 glutamate receptor, ionotropic (138248); 5q33

ANKRD11, ankyrin repeat domain-containing protein 11 (611192); 16q24.3

APBA2, amyloid beta A4 precursor protein-binding, family A (602712); 15q13.1

APC, adenomatous polyposis coli (611731); 5q21q22

AQP4, aquaporin 4; (600308) 18q11.2q12.1

ARX, aristaless-related homeobox, X-linked (300382); Xp22.13

AVPR1A, arginine vasopressin receptor 1A (600821); 12q14q15

BDNF, brain-derived neurotropic factor (115505); 11p13

CACNA1C, calcium channel, voltage-dependent, L type, alpha-1C subunit (114205); 12p13.3

CADPS2, calcium-dependent activator protein for secretion 2 (609978); 7q31.3

CDH9, cadherin 9 (609974); 5p14 CDH10, cadherin 10 (604555);

CDH10, cadherin 10 (604555); 5p14p13

CENTG2, centaurin, gamma-2 (608651); 2q37.3

CHAT, choline acetyltransferase (118490); 10q11.23

CHRNA7, cholinergic receptor neuronal nicotinic alpha polypeptide 7 (118511); 15q14

CNTN3, contactin 3 (601325); 3p26

CNTN4, contactin 4 (607280); 3 p26p25

CNTNAP2, contactin-associated protein-like 2 (604569); 7q35q36

COMT, catechol-o-methyltransferase (116790); 22q11.2

CSMD3, cub and sushi multiple domains 3 (608399); 8q23.3

CYFIP1, cytoplastmic FMRP-interacting protein 1 (606322); 15q11

DIA1, CXORF36, deleted in autism 1; chromosome 3 open reading frame (612200); Xp11.3

DISC1, disrupted in schizophrenia 1 (605210); 1q42.2

DLG1, discs large, drosophila, homolog of (601104); 3q29

DLX1, distal-less homeobox 1 (600029); 2q32

DLX2, distal-less homeobox 2 (126255); 2q32

EIF4E, eucaryotic translation initiation factor 4E (133440); 4q21q25

EN2, engrailed 2 (131310); 7q36

EPC2, enhancer of polycomb, Drosophila, homolog of, 2 (611000); 2q23.1

FABP5; FABP7, fatty acid binding protein 5 (605168); 8q21.13; and 7 (602965); 6q22.31

FHIT, fragile histidine triad gene, fragile site (601153); 3p14.2

Continued

FMR2, fragile site, folic acid type, rare, FRAXE (300806); Xq28

FOXP2, forkhead box P2 (605317); 7q31

GABRA1 gamma-aminobutyric acid receptor, alpha-1 (137160); 5q34q35

GABRA2 gamma-aminobutyric acid receptor, alpha-2 (137140); 4p13p12

GABRA4 gamma-aminobutyric acid receptor, alpha-4 (137141); 4p13p12

GABRA5, gamma-aminobutyric acid receptor, alpha-5 (137142); 15q11.2q12

GABRB2 gamma-aminobutyric acid receptor, beta-2 (600232); 5q34q35

GABRB3, gamma-aminobutyric acid receptor, beta-3 (137192); 15q11.2q12

GABRG3, gamma-aminobutyric acid receptor, gamma 3 (600233); 15q11.2q12

GABRR2, gamma-aminobutyric acid receptor rho-2 (137162); 6q14q21

GAD1, glutamic acid decarboxylase-1 (605363); 2q31

GAD2 (glutamic acid decarboxylase-2 (138275); 10p11.23

GJA1, gap junction protein alpha-1, connexin 43-heart (121014); 6q21q23.2

GLO1, glyoxylase 1 (138750); 6p21.3p21.2

GRIK2, glutamate receptor, ionotropic kainate 2, gluR6 (138244); 6q21

GRIN1, glutamate receptor, ionotropic, N-methyl-D-aspartate subunit 1 (138249); 9q34.3

GRIN2A, glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2A (138252); 16p13

HOXA1, homeoboxA1 (142955); 7p15.3

IL1RAPL1, interleukin 1 receptor accessory protein-like calcium-related (300206); Xp21.3p21.2

ITGA4, integrin alpha-4 (192975); 2q31q33

ITGB3, integrin beta-3 (serotonin blood level trait-173470); 17q21.32

KIAA0442, Kazusa DNA Institute brain cDNA clone 0442 (607270); 7q11.2

MACC1, metastasis-associated gene in colon cancer 1 (612646); 7p21.1

MAOA, monoamine oxidase A (309850); Xp11.23

MAP2, microtubule-associated protein 2 (157130); 2q34q35

MBD3, methyl-CpG-binding domain protein 3(603573); 19p13.3 and 4 (603574); 3q21q22

MCPH1, microcephalin 1 (607117); 8p23

MECP2, methyl-CpG-binding protein 2 (30005); Xq28

MEF2C, MADS box transcription enhancer factor2, polypeptide C (600662): 5q14.3

MET, MET protooncogene (164860); 7q31

MMP16, matrix metalloproteinase 16 (602262); 8q21

MTF1, metal regulatory transcription factor-1 (600172); 1p33

NBEA, neurobeachin fragile site 13A (604889); 13q13.2

NCAM2, cell adhesion molecule, neural, 2 (602040); 21q21.1

NDE1, Nude, A. nidulans, homolog of 1 (609449); 16p13.1

NHE9/SLC9A9 sodium/hydrogen exchanger 9/solute carrier family 9 (608396); 3q24

NIPBL, nipped-B-like (608667); 5p13.2

Continued

NIPA1, non-imprinted gene in Prader-Willi/Angelman syndrome chromosome region 1 (608145); 15q11.1

NLGN3, NLGN4, NLGN4Y neuroligin 3 (300336); Xq13.1, 4(300427);Xp22.33, Y-linked (400028); Yq11.2

NRXN1, neurexin-1 (600565); 1p16.3

NSD1, nuclear receptor-binding set domain protein 1 (606681); 5q35.3

OXTR, oxytocin receptor (167055); 3p26.2

PAK2, p21-activated kinase2 (605022); 3q29

PAX3, paired box gene 3 (606597); 2q35

PCDH10, protocadherin 10 (608286); 4q28.3

PDE4D, phosphodiesterase 4D (600129); 5q12

PHF8, PHD finger protein 8 (300560); Xp11.2

PITX1, paired-like homeodomain transcription factor 1 (602149); 5q31

PRKCB1, protein kinase C beta-1 (176970); 16p11.2

PTEN, phosphatase and tensin homolog (601728); 10q23.31

PTPN9, protein-tyrosine phosphatase nonreceptor-type 9 (600768); (15q22q23)

RAB11FIP5; RAB11 family-interacting protein 5 (605536); 1p13

RAI1, retinoic acid induced gene (607642); 17p11.2

RAPGEF4, RAP, guanine nucleotide exchange factor (606058); 2q31.1

RASA1, RAS p21 protein activator 1 (139150); 5q14.3

RBM8A, RNAN-binding motif protein 8A (605313); 1q21.1

REEP3, receptor expression-enhancing protein 3; 10q21.3

RELN, Reelin, from mouse mutation "reeler" with poor coordination (600514); 7q22.1

RNF8, Ring finger protein 8 (611685); 6p21.3

RPS6KA3, ribosomal protein X6 kinase, 90-Kd, 3 (3000075); Xp22.12 and 7Z

SCN1A, SCN7A, sodium channel neuronal type I alpha subunit (182389); 2q24 and VII (182292); 2q21q23

SCT, secretin (182099); 11p15.5

SEMA5A, semaphoring 5A (609297); 5p15.2

SHANK3, SH3 and multiple ankyrin repeat domains 3 (606230); 22q13.3

SLC1A3, solute carrier family 1 (glial high affinity glutamate transporter, member 3-600111); 5p13

SLC4A10, solute carrier family 4 (sodium bicarbonate transporter-like) member 10 (605556); 2q24.2

SLC6A3/DAT1, SLC6A4, solute carrier family 6, member 3-dopamine transporter (126455); 5p15.3 and 4 (182138); 17q11.1q12

SLC9A9/(NHE9 sodium/hydrogen exchanger 9/solute carrier family 9 (608396); 3q24

SLC18A3, solute carrier family 18 (vesicular acetylcholine), member 3 (600336); 10q11.23

SLC25A12, solute carrier family 25 (mitochondrial carrier, ARALAR member (603667); 2q24

SLC40A1, solute carrier family 40 (iron-regulated transporter), member 1 (604653); 2q32

SSBP1, single-stranded DNA-binding protein 1 (600439); 7q34

ST7, RAY1, suppressor of tumorigenicity (600833); 7q31.1

STK, serine/threonine protein kinase 39 (607648); 2q24.3

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STS, Steroid sulfatase (300747); Xp22.32
T2R3, taste receptor type 2 member 3 (604868); 7q31.3q32
TRIP 8, JMJD1C, thyroid hormone receptor interactor 8, jumonji domain-containing protein 1 (604503); 10q11.1
UBE3A, ubiquitin-protein ligase E3A; 15q11q13
UPF3, yeast upf homolog-RNA decay protein (300298); Xq25q26
VCX, variably charged, X chromosome (300229); VCX2 (300532); VCX3A (300533); Xp22.3
WAC, WW domain-containing adaptor with coiled-coil region (615049); 10p12.1
WNK3, protein kinase, lysine-deficient; Xp11.2
WNT2, wingless-type MMTV integration site family, member 2 (147870); 7q31

Gene symbols are followed by their definition, number assigned in Online Mendelian Inheritance in Man (http://www.omim.org/), and their cytogenetic location (chromosome number, p for short, q for long arm, band number).