Scientific Research Publishing

Journal of Biosciences and Medicines, 2023, 11, 191-199
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Advancing Neuropsychiatric Care through Genetic and Molecular Insights

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How to cite this paper: Shi, E. (2023) Advancing Neuropsychiatric Care through Genetic and Molecular Insights. *Journal of Biosciences and Medicines*, **11**, 191-199.
https://doi.org/10.4236/jbm.2023.1110018

Received: September 13, 2023
Accepted: October 24, 2023
Published: October 27, 2023

Abstract

Neuropsychiatric diseases, including ADHD, schizophrenia, and bipolar disorder, are increasingly prevalent but poorly understood at the molecular level. The complexities of diagnosing and treating these disorders emphasize the need for objective, quantitative data to improve diagnostic accuracy and treatment efficacy. This study aims to explore the genetic underpinnings of neuropsychiatric diseases, contrasting them with well-characterized diseases like breast cancer, and discuss the role of specific genetic mutations and their implications for personalized treatment. The paper delves into the genetic and molecular insights of neuropsychiatric diseases, examining the role of specific genetic mutations and the potential for gene editing technologies like CRISPR. It contrasts the genetic underpinnings of neuropsychiatric diseases with well-characterized diseases like breast cancer, highlighting the potential for a shift towards molecular and genetic-based diagnostics and treatments. The study argues that a shift towards molecular and genetic-based diagnostics and treatments could revolutionize our approach to neuropsychiatric diseases, much like how biomarker tests have transformed breast cancer treatment. It concludes by advocating for a more personalized approach to healthcare, tailored to an individual's unique genetic makeup, as the future of neuropsychiatric disease diagnosis and treatment.

Keywords

Neuropsychiatric Diseases, ADHD, Huntington's Disease, Molecular Biology, Genetics

1. Introduction

Neuropsychiatric diseases, encompassing a wide range of disorders such as ADHD (attention deficit hyperactivity disorder), schizophrenia, and bipolar disorder, are

a growing concern in the world. Recent data underscore the urgency of this issue. The incidence of ADHD alone has seen a significant rise: national population surveys reflect an increase in the prevalence of ADHD diagnoses from 6.1% to 10.2% in the 20-year period from 1997 to 2016 [1]. This trend is not confined to ADHD, but is reflective of a broader surge in neuropsychiatric conditions. While increased awareness among reporting entities may account in part for the rise in prevalence in part, the difference is nonetheless significant. However, despite their prevalence, the genetics and molecular causes of many neuropsychiatric diseases are still poorly understood. As the diagnosis of neuropsychiatric diseases is currently based more on symptoms than biochemical markers, they are difficult to characterize. Two people may express similar symptoms and be diagnosed with the same neuropsychiatric disease. Still, they may have completely different underlying causes, and understanding these causes is critical to optimizing successful patient treatment and outcomes.

The Molecular Characterization of Breast Cancer vs. Neuropsychiatric Diseases

In contrast, many physical diseases such as breast cancer are fairly well characterized on the molecular level. Breast cancer—*i.e.* tumors with uncontrolled cellular division forming in the breast—can be caused by a number of different underlying causes and mutations, resulting in different types of masses, including luminal A, luminal B, triple-negative, and HER2-enriched breast cancers. At the molecular level, breast cancer can be characterized by specific genetic changes. For instance, mutations in the BRCA1 and BRCA2 genes are known to significantly increase the risk of developing breast cancer [2]. However, by using specific biomarker tests and knowing the type of breast cancer, doctors are able to tailor treatment with significant specificity.

As a result, treatment for breast cancer has become significantly more effective in recent decades. The same could apply to neuropsychiatric diseases with greater understanding on a molecular level.

Currently, most diagnostic procedures for neuropsychiatric diseases are observational and performance-based, with little or no molecular aspect. Without hard metrics, neuropsychiatric diagnostics cannot be exact as many symptoms overlap between neuropsychiatric diseases. A quantitative, laboratory-based approach would provide doctors with important information about a specific disease and differentiate between its variants. Doctors will be able to make more informed decisions regarding diagnosis and, ideally, better treatment options.

2. The Importance of Quantitative Data and Research

Significant advances in understanding and subsequent development of effective treatments for neuropsychiatric diseases could be achieved by prioritizing objective measurements and molecular/biological data over subjective evaluations.

Molecular and biological markers, as part of these objective measurements,

offer an unbiased and concrete perspective in improving the accuracy of our diagnostic methods. Subjective or qualitative diagnostic tests are prone to bias and errors due to their dependence on personal interpretations by patients and medical evaluators alike. An individual experiencing fatigue or lack of concentration, for instance, might skew the results of a symptom-based assessment.

Furthermore, utilizing objective measurements and molecular/biological data in research can lead to a more profound understanding of the root causes of neuropsychiatric diseases. This understanding is an essential first step toward discovering more targeted and effective treatments.

3. What We Currently Know about Neuropsychiatric Disorders?

The genetics of neuropsychiatric disorders can be quite complicated. Monogenic diseases are caused by mutations in a single gene. However, a single gene is often responsible for multiple disease manifestations. This can be because of three reasons which are distinct locations of mutations, the extent of functional change, and qualitatively different effects. There is also a case where the same mutation causes different diseases. Some examples of monogenic diseases include sickle cell anemia, cystic fibrosis, and Huntington's disease [3].

One mechanism of specificity is the location of the mutation. Mutations in different functional domains of the same gene can lead to different diseases. For example, mutations in the BRCA1 gene can cause either breast or ovarian cancer, depending on the location of the mutation.

Another mechanism of specificity is the extent of functional change. Mutations that affect the function of the protein produced by a gene can have different degrees of severity and absence or presence of specific symptoms, resulting in different diseases. For example, among the four clinically discernible ciliopathies, all have similar features caused by TMEM67 mutations. What makes nephronophthisis with liver fibrosis (NPHP11) different from the other three ciliopathies is that it has mild to no neurological involvement. This ciliopathy mostly affects the kidney and liver instead [4].

In some cases, the same exact mutation can cause different diseases. A mutation can cause different diseases based on zygosity, genetic background, and environmental factors.

While the genetics of many neuropsychiatric disorders are still poorly understood, several of these conditions have known genetic origins. For example, Huntington's disease is caused by excessive CAG repeats in the HTT gene, and ADHD has several genes that appear related to the disorder and genetic syndromes that have comorbidity with ADHD.

3.1. A Deeper Look into CAG Repeat-Expansion Diseases

CAG repeats encode polyglutamine (polyQ) tracts in genes, which can cause the resulting proteins to aggregate. In addition to Huntington's disease, CAG repeats

are also responsible for dentatorubral-pallidoluysian atrophy (DRPLA), spinal and bulbar muscular atrophy (SBMA), and spinocerebellar ataxias (SCAs) Types 1, 2, 3 (also known as Machado-Joseph disease), 6, 7, and 17 [5].

In the case of Huntington's disease (HD), the CAG repeat is in a protein called huntingtin. The role of huntingtin in the body's tissues is as yet unclear, but it is particularly concentrated in the brain and thus is likely to help protect neuron structure, facilitate neural communication, or some similar function. Huntington's disease is a fatal inherited neuropsychiatric disease that targets a range of nerve cells, gradually impairing cognitive, behavioral, and motor functions. The CAG repeat expansion causes the protein to form misshapen structures that collect in brain cells, leading to diminishing neuron function. The first symptoms of HD—typically difficulties in motor control and emotional control—usually appear in mid-life and worsen over time. In late-stage HD, patients are often bedridden and have difficulty speaking or swallowing. Thinking patterns also degrade, leading to loss of judgment, personality changes, and other effects. The mutation is dominant, so children of HD have a 50% chance of developing the disease.

The formation of clusters called neuronal intranuclear inclusions (NIIs) has become a pathological hallmark common to all CAG repeat diseases; however, the exact function of NIIs is not known. It has been thought that NIIs were toxic structures responsible for the death of neuronal cells, but other research has raised the possibility that NII formation may be a cellular response to reduce the toxic effect of mutant cells [6].

Another type of neurodegenerative CAG repeat disease called spinocerebellar ataxias is characterized by the degeneration of the spinal cord and cerebellum [7].

- SCA Type 1 is caused by an expansion of CAG repeats on chromosome 6p23. NII formation is also observed in many brain areas.
- In SCA Type 2, the CAG repeats are on chromosome 12p24.1. However, NII formation is not prominent.
- SCA Type 3, also known as Machado-Joseph disease (MJD), is caused by CAG repeats on chromosome 14q32.1. NII formation is found in the affected brain areas and detectable in unaffected regions.

3.2. Certain Genes Show a Correlation with ADHD

In contrast to CAG repeat diseases, the genetics and inheritance of neuropsychiatric diseases like ADHD are complex and not well understood at the present time. The research into ADHD's underlying genetic factors suggests an intricate interplay of various genes, contributing to the multifaceted nature of this neurodevelopmental disorder.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder with symptoms of inattentiveness, impulsiveness, and hyperactivity. Patients with ADHD show high comorbidity with autism, obesity, bipolar disorder,

depression, anxiety, and substance use disorder. This phenomenon could signify common underlying risk gene variants among these diseases [8] [9].

The heritability of ADHD is 77% - 88% in twin studies and 22% in SNP-based heritability. These statistics suggest that genetic factors account for a mere 22% of heritability, indicating our limited understanding of ADHD inheritance [10].

One explanation for this gap in heritability is that the sample size was too small to accurately predict genetic associations. Another explanation for this gap could be copy number variations (CNVs), sections of DNA that occur in multiple copies or deletions of certain chromosomal sections. Small CNVs are not effectively detected by Genome-Wide Association Studies (GWAS), which may contribute to the issue. CNVs are quite common in ADHD patients and make up a large portion of genetic variability in ADHD.

A study of ADHD-affected children showed strong genetic associations of the genes GFOD1 and CHD13, which suggests that mutations or deletions in these genes can cause ADHD or ADHD-associated symptoms [11].

The gene GFOD1 is expressed in the frontal cortex; however, the exact function of the gene is not yet known [12]. The CDH13 gene encodes for a calcium-dependent cell-cell adhesion protein that influences neuronal development and synaptic plasticity. In a knockout mouse model of CDH13, mice showed hyperlocomotion and learning deficits. Other research shows that CHD13 is associated with autism, schizophrenia, bipolar disorder, and depression, which makes CDH13 a good candidate gene for ADHD [13].

Another ADHD candidate gene is ADGRL3, which codes for a brain-specific G protein-coupled receptor with cell adhesion function. In a knockdown zebrafish model of ADGRL3, the zebrafish showed reduced dopaminergic neurons in the ventral diencephalon and a hyperactive/impulsive phenotype [14]. In ADGRL3-knockout mice, an increase in reward motivation, activity level, and dysregulation of the dopamine transporter suggests that this is a good ADHD candidate gene [15]. Dopamine is a critical neurotransmitter with a range of roles, including motor control and reward centers in the brain.

The implications of these discoveries could be groundbreaking for the diagnosis and treatment of ADHD. By enabling genetic testing for these associated genes, medical professionals could potentially indicate the presence of ADHD more accurately in patients. Further, knowing the specific gene causing the disorder would allow treatment to be more targeted, focusing on repairing the gene or invoking compensatory mechanisms. The development of CRISPR technology offers the potential for direct gene editing to correct or compensate for the underlying genetic abnormalities associated with ADHD. By precisely modifying faulty genes, CRISPR technology could potentially address the root cause of ADHD rather than merely managing its symptoms. However, gene-repair methods would most likely need to be done at a very young age and could also have many ethical concerns.

Another option would be pharmacogenetics. Pharmacogenetics might help to

customize treatment strategies based on the patient's genetic profile. For instance, if a patient has a mutation in the GFOD1, CHD13, or ADGRL3 genes that is linked to ADHD, physicians might be able to prescribe specific drugs that can address these specific mutations or their effects on the brain.

For example, if the ADGRL3 gene mutation is causing dysregulation of the dopamine transporter, resulting in lower levels of dopamine in the brain (a trait associated with ADHD), then a drug that increases dopamine levels might be prescribed. This could potentially be more effective than a one-size-fits-all approach to prescribing medication.

Genetic syndromes are also often associated with ADHD during childhood. The characteristics and prevalence of ADHD vary among these conditions (Figure 1).

- Fragile X syndrome (FXS), for instance, is associated with ADHD in about 59% of affected boys [13]. The FMR1 gene, which produces the RNA-binding protein known as fragile X mental retardation protein, is the root cause of FXS. It has been suggested that the primary mechanisms underlying FXS involve diminished signaling of the inhibitory neurotransmitter GABA and heightened glutamatergic excitation.
- Neurofibromin 1 (NF1), another genetic disorder, leads to the formation of tumors in the eyes, skin, and central nervous system, and is linked with ADHD symptoms in approximately one-third of children affected by it.
- Tuberous sclerosis complex (TSC), a disorder causing brain malformations, tumors, skin lesions, benign tumors in organs, epileptic seizures, and cognitive

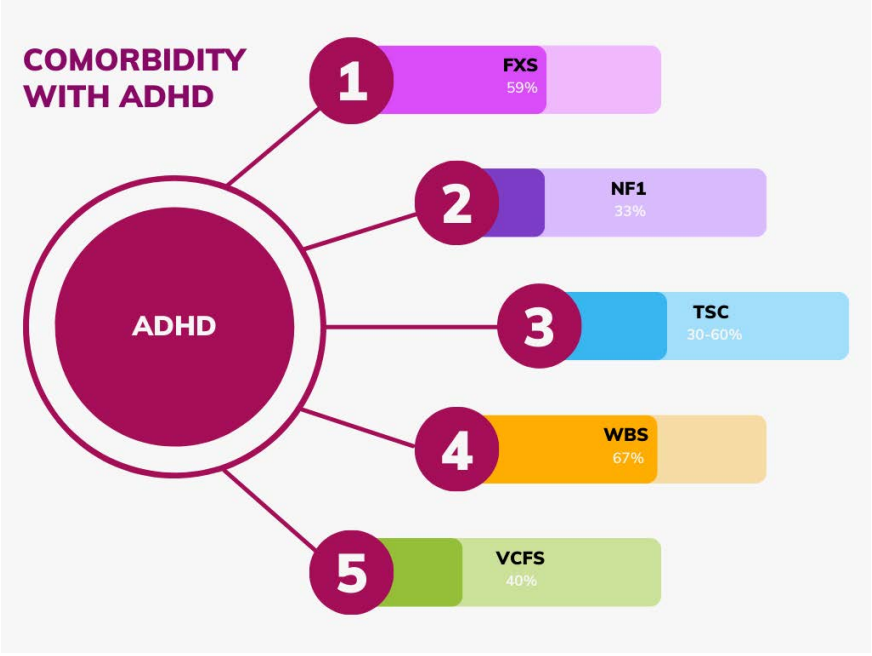

Figure 1. The diagram shows the comorbidity rate of ADHD with the following genetic syndromes: Fragile X syndrome (FXS), Neurofibromin 1 (NF1), Tuberous sclerosis complex (TSC), Williams-Beuren syndrome (WBS), Velo-cardio-facial/DiGeorge syndrome (VCFS).

impairment, is also frequently tied to ADHD, with 30% to 60% of patients experiencing ADHD symptoms [13].

- Turner syndrome and Klinefelter syndrome: These syndromes are sexual aneuploidies which refer to an abnormality in the number of sex chromosomes, and have been associated with ADHD. Around 63% of Klinefelter syndrome patients have ADHD [13].
- Williams-Beuren syndrome (WBS), a condition involving a microdeletion on chromosome 7, is linked with a broad array of symptoms, from distinctive "elf-like" facial features to cardiovascular abnormalities. About two-thirds of individuals with WBS exhibit ADHD symptoms.
- Velo-cardio-facial/DiGeorge syndrome (VCFS) causes cardiovascular abnormalities and a variety of psychiatric disorders. 40% of patients suffer from ADHD [13].

4. What Does This Mean for Treatment?

As shown, distinct illnesses can often give similar symptoms to ADHD. Despite sharing symptoms with ADHD, these different neuropsychiatric disorders require markedly varied treatment approaches, which suggest fundamental differences on the genetic and molecular level. Currently, however, diagnostics for ADHD is essentially a collection of symptoms grouped together. The challenge arises when the current testing methods for ADHD focus solely on symptomatic manifestations instead of the underlying causality. This approach overlooks the need to address the underlying causative factors of these symptoms, which can lead to misdiagnosis and inadequate treatment due to the confluence of symptoms from disparate disorders.

These factors suggest that a more comprehensive and precise approach to diagnosing neuropsychiatric disorders such as ADHD would incorporate molecular measurements. This method could entail techniques such as genetic testing, neuroimaging, or biomarker identification that could help explain the distinct molecular characteristics or deviations associated with ADHD. Additionally, subclassification based on quantitative testing could prove beneficial. This could involve the use of standardized rating scales, cognitive tests, or behavioral assessments that allow for a more refined, quantifiable understanding of the patient's condition.

For example, molecular tests to diagnose Turner syndrome and Klinefelter syndrome are fairly simple and unambiguous, analyzing an individual's chromosomal composition through karyotyping or chromosomal microarray analysis.

The treatment for patients with Turner syndrome and Klinefelter syndrome may include hormone-replacement therapy to address hormonal imbalances, growth hormone therapy to promote proper development, psychological support, and counseling to address emotional and behavioral challenges, and educational interventions to assist with learning difficulties.

This approach applied to ADHD patients would give doctors a much better

understanding of underlying causalities for ADHD in each person. This means they could create a treatment plan that works better for that specific person.

5. Conclusions

The epidemiology of neuropsychiatric diseases such as ADHD suggests a critical need to delve deeper into their genetic and molecular origins. Such insights can equip doctors and patients with more precise and effective diagnostic tools and treatments. Genetics and molecular biology have a crucial role in this journey. By uncovering the underlying genetic and molecular causes of these diseases, we can develop better diagnostic tests, tailored to the specific genetics of each patient.

Understanding that neuropsychiatric diseases can have varied underlying causes, despite displaying similar symptoms, indicates a requirement for more personalized medicine. Patients need treatments and drugs that are designed to fit the unique genetic or molecular abnormalities causing their disease. Just as breast cancer treatments have advanced through the use of specific biomarker tests, neuropsychiatric disease treatments can be revolutionized through a similar approach.

Additionally, given the wide array of genetic factors contributing to diseases like ADHD, implementing a personalized approach to treatment becomes even more paramount. A focus on understanding and addressing the specific molecular changes or genetic mutations responsible for each individual's disorder is highly likely to improve outcomes.

Thus, the heart of personalized healthcare: for successful diagnosis and treatment of patients, researchers and medical practitioners in the field need to know their unique genetic makeup. This approach opens the possibility of combating the root cause of illness rather than simply managing symptoms. As such, the fields of genetics and molecular biology are crucial in bringing advancements in health care for neuropsychiatric diseases. Investing effort and resources in researching and creating tailored medical treatments is vital to fully meet the needs of those suffering from neuropsychiatric conditions.

Acknowledgements

I would like to express my gratitude to Professor Timp for his guidance and mentorship throughout the course of this research. This research paper received no external funding or financial support.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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