Genetic Research and its *Revolutionary?* Contributions to Schizophrenia Prevention

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Introduction

For over a century, physicians, neurologists, psychiatrists, biologists, and eventually geneticists have been working hard to answer the question: what causes schizophrenia and its related disorders? In earlier days of research, much of the focus was placed on the treatment of such conditions, and scientists have made great advancements in this area. For example, in the early 19th century, it was typical to see patients with schizophrenia exhibit catatonia, which is a symptom characterized by a decrease in reactivity to environmental stimuli. These patients were stuck within these states for days or weeks. Now, catatonia is treated with benzodiazepines, and patients can return to non-catatonic functioning over a much shorter period of time. Sienart et al., 2014). This pharmacological discovery has improved the lives of schizophrenia patients dramatically and has shifted the typical symptomology observed in this disorder. Yet, the question remains: what causes this disorder, and can we use that knowledge to prevent its development in the first place? Investigations into the etiology (or causes) of schizophrenia have proven to be less fruitful than their treatment-based counterparts. The knowledge that schizophrenia is at least partially genetic motivated a surge of investigations into the human genome. This research began with studies using molecular genetics, a method proven to be incredibly effective in discoveries into etiology of other genetic diseases. With the completion of the Human Genome Project (HGP), genome-wide investigations came to the forefront. It was initially projected that the data collected from the HGP would revolutionize the screening, diagnosis, and treatment of mental illnesses. However, 20 years after this prediction was made, the etiology of these conditions remains unclear, as the nature of these illnesses has been found to be difficult to discern through genetic studies.

Schizophrenia Spectrum Disorder (also known as schizophrenia) is characterized by symptoms of three types: positive, negative, and disorganized symptoms, with a poor prognosis and heavy cost toward the individual, their family, and society. Positive symptoms are referred to as such because their symptoms add characteristics that are not already present in normal functioning, such as hallucinations or delusions. Negative symptoms are the opposite, “taking away” from normative functioning, such as avolition (lack of motivation) and diminished emotional expression. Disorganized symptoms refer to a lack of order and form in terms of thinking or activity, such as disorganized speech and motor behavior (American Psychological Association, 2022). Schizophrenia exists on a spectrum of disorders and is believed to be at least partially caused by genetics. The risk of developing schizophrenia is linked to the degree of relation to a family member with schizophrenia. As seen in Figure 1, a first degree relative to a patient with schizophrenia would have a 3.0% hospitalization rate for psychosis, and a second degree relative would have a 2.2% hospitalization rate, both

compared to the general population hospitalization rate of 0.9% (Karlsson, 1971). This disorder can be debilitating, often requiring full-time hospitalization and lifetime treatment. Many patients never return to normal functioning, even between episodes. There is also a higher risk of suicide and early death associated with this disorder (Jobe & Harrow, 2005). The severity of such a disease, combined with its proven genetic component, has driven large-scale research into the etiology of schizophrenia at the order of the genes, producing a myriad of results.

Relationship	Population born 1881–1910		Population born 1911–1940	
	N	Hosp rate	N	Hosp. rate
First degree relatives	*1547*	*5.7*	*492*	*3.0*
Fathers	159	2.5	- -	- -
Mothers	165	7.9		
Brothers	571	5.3	198	3.5
Sisters	511	6.1	179	2.8
Sons	73	5.5	57	1.8
Daughters	68	8.8	58	3.4
Second degree relatives	*726*	*3.5*	*511*	*2.2*
Uncles	242	2.1	-	- -
Aunts	207	4.8	-	
Nephews	139	1.4	269	1.9
Nieces	138	5.8	242	2.5
Third degree relatives	*879*	*2.2*	*1206*	*0.6*
Male 1st cousins	441	1.4	608	0.5
Female 1st cousins	438	3.0	598	0.7
General population	*6700*	*1.4*	*14447*	*0.9*
Males	3456	1.1	7330	0.8
Females	3244	1.8	7117	0.9

Table 1. Rates of hospitalization with functional psychosis in relatives of psychotic index cases in Iceland.

Research Method #1: Molecular Genetics

Biologists have been using the varying tools at their disposal over time to investigate the etiology of genetic diseases, with one of these methods being molecular genetics. This research revealed key insights into the fields of biology, neurology, and genetics, though it was not as comparatively impactful in psychiatry. Molecular genetics, a field of research that studies genes on a molecular level, focuses on variations in DNA. Studies using this framework have shed light on the genetic mutations behind a number of neurological disorders, such as Huntington's disease (HD), Fragile X Syndrome (FXS), and Amyotrophic Lateral Sclerosis (ALS) (Cowan et al., 2002). These discoveries allowed for improved screening and early identification of these conditions. However, studies using molecular genetics to find the causes of mental illnesses gave mixed results of small effect sizes. This difference can be explained through the nature of these conditions, particularly within the inheritance patterns of the disorder whose causes were found.

Many Americans are made aware of Mendelian patterns of inheritance, though they may not know it by that name, while taking high school biology, through lessons about yellow and green peas and Punnett squares. Classic Mendelian patterns of inheritance involve patterns of segregation such as dominant, recessive, and X-linked (Chial, 2008). One can follow along using genetic information to make reasonable predictions about the phenotype, such as hair or eye color, of an organism by simply examining their pedigree. The diseases with causes found through molecular genetics followed Mendelian patterns of inheritance, such as Huntington's disease, whose pattern of inheritance can be observed in Figure 2. By comparing the genes of people who both do and do not have a familial disorder, target genes can be identified. Additionally, disorders such as HD and ALS are caused by a single defective gene that can be isolated and identified relatively easily. On the contrary, mental illnesses do not follow Mendelian patterns of inheritance. They are likely polygenic (caused by multiple genes) and multifactorial (caused by genetic and environmental factors, as well as interactions between genes and environment). By using these methods of searching and comparing target areas of the genome, there were genes identified as possibly being involved in mental illnesses, but the results weren't as clear-cut as finding one gene that causes a certain disorder.

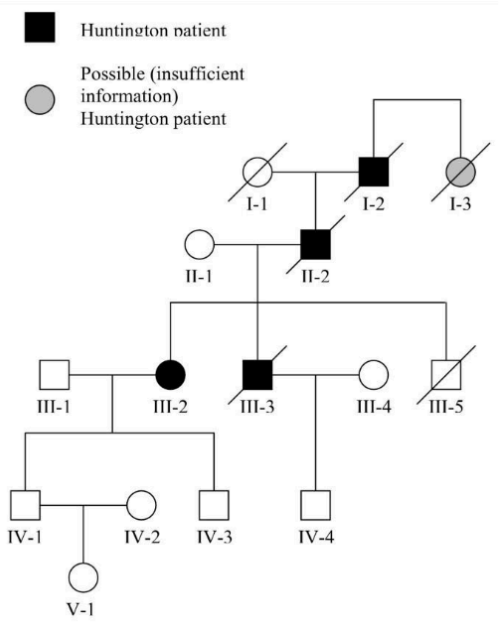

Figure 1. Correa & Guimaraes (2006). Pedigree showcasing the inheritance of Huntington's Disease (HD).

While investigating the human genome to find associations between certain genes and specific psychiatric disorders, a number of loci were identified. Linkage analysis was often used in these studies prior to the completion of the Human Genome Project, which uses genetic markers to find areas on the genome that are close to genes thought to cause certain conditions (Pulst, 1999). Some well-known findings from analyses looking into schizophrenia identified chromosomal regions associated with the serotonin 5HT2A receptor gene (13q14.1-32), as well as chromosomal regions related to synapse-related genes (22q11-12) (Cowan et al., 2002). These findings garnered interest, considering the importance of synapses in neuronal function and serotonin's role in mood regulation and homeostatic roles (Mohammad-Zadeh & Bryant, 2008). With the advent of new

techniques and technology, it was believed that we would be able to find clearer answers in these areas and their connection to schizophrenia.

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Research Method #2: Data Analysis from The Human Genome Project

The Human Genome Project (HGP) was a moon-shot project, with the goal of sequencing the entire human genome, and its completion created a new wave of data and discoveries into the field of genetic biology. Launching in 1990 and concluding in 2003, the HGP cost $3 billion (Gannett, 2023). The ability to map the entire human genome created a vast bank of data that could be utilized when researching, for example, cancer and its treatment (Rood & Regev, 2021). It was predicted that the discoveries resulting from the HGP data would allow for gene-based treatments for critical disease such as diabetes and hypertension, as well as change the game for the treatment of mental illnesses. Some scientists went so far as to say that the impact the HGP would have on the field of medicine would be comparable to the discovery of antibiotics (Torrey, 2024). Genome wide association studies (GWAS) were conducted using the new data, and nearly 300 single nucleotide polymorphism (SNP) genetic loci were linked to an increased risk of the development of schizophrenia. Such findings seemed to signal that major breakthroughs were on the way.

Unfortunately, much of the evidence uncovered through GWAS did not hold up under scrutiny. Through comparisons between studies, about half of the genomic loci associated with schizophrenia was discovered to also be associated with other disorders believed to be partially genetic, such as bipolar disorder and autism (Torrey, 2024). Therefore, an argument can be made that these loci are associated with psychiatric disorders as a whole, rather than schizophrenia specifically. Additionally, many of the SNPs identified were found to have a very small effect size, and while they could be linked to schizophrenia, they could not be linked to a cause of schizophrenia. This bears resemblance to how a reduction in size of the frontal lobe is associated with depression, but it is not known if this reduction causes depression, or is caused by depression (Joseph et al., 2025). Despite these discouraging findings, there may be one with promise.

A change in the region of the genome known as the Major Histocompatibility Complex presents strong evidence of an association with schizophrenia, potentially revealing a link between the disorder and the immune system. The Major Histocompatibility Complex (MHC), located on chromosome 6, is associated with the regulation of immune functions, as well as many infectious diseases and autoimmune disorders (Abualros et al., 2021). A GWAS revealed an association between a small alteration in this area and the development of schizophrenia (Caseras et al., 2024). While this finding may initially seem confusing, it does connect some previous findings and hypotheses about schizophrenia. The presence of some infectious diseases during pregnancy, such as influenza, though new evidence reveals that more research is needed in this area (Fung et al., 2022), and Toxoplasma gondii (Yang et al., 2024), are known to slightly increase the risk of the child developing schizophrenia. The MHC's association to autoimmune disorders could also shed light onto the hypothesis that differences in the functions of microglia (the "brain's immune system") could explain some of the symptoms of schizophrenia, as it is hypothesized that essential synapses could be erroneously tagged for consumption by microglia as a part of the brain's synaptic pruning process used to clear unused and unneeded synapses (Li et al., 2023). This incorrect deletion of synapses could explain the cognitive and disorganized issues often associated with schizophrenia, as vital neuronal pathways could be disrupted. Unfortunately, this finding only had a polygenic risk score, which gives an estimate of an individual's genetic risk for developing a specific trait, to explain less than 10% of the variation in liability for the disease (Andreassen et al., 2023). While these findings are promising, they are far from the revolution that was predicted.

Future Directions

Despite the lack of definitive findings through genetic studies, there may still be something to be gleaned from this data. The results of the HGP still have hopes of finding significant results, as researchers hope to use newly introduced machine learning functions to aid in their search. They are also making efforts to factor in potential epigenetic changes caused by environmental factors and gene x environment interactions, or perhaps the solution lies in something that hasn't been considered yet.

It is possible that the flaw in this system is the question itself. It is widely accepted that there is no single or primary cause of many mental disorders, and it is possible that these disorders are the result of multiple different pathways. To explain this, we may look toward an example in the medical world: obesity, and its association with Leptin and Leptin genes. Leptin is a hormone that signals satiety, telling the body when it should stop eating. Leptin receptor deficiency is a rare genetic disorder which causes a mutation in the Leptin gene that results in an inability for the body to produce Leptin. Without a satiety signal, the body's ability to regulate eating is compromised, and the subject becomes

obese. However, when this subject is treated with Leptin supplements, their food intake regulation ability is restored, and they return to a normal weight. In this case, this mutation causes obesity. But not all cases can be explained this way. Leptin treatment only works on obese patients who have this mutation, and if they do not, the treatment produces little effect (Milan et al., 2021). Obesity has multiple causes, and treatment must be derived based on the specific cause. Could a similar approach be applied to schizophrenia, where different treatments could be used for different causes? Could we pinpoint these different causes?

One of the most important traits needed in research is curiosity. While many may be discouraged by the lack of major breakthroughs in the genetic research of schizophrenia and other psychiatric disorders, others may see this as eye-opening, and an invitation to think nontraditionally about these findings. While it was originally believed that genetic research such as molecular genetics, linkage analysis, genome wide association studies, and more would be the key to understanding the etiology of schizophrenia, this was found to be inaccurate, but that doesn't mean that all hope is lost. All that is needed is a new question to be asked.

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About the Author

Brianna Mae is a Junior at the University of Illinois majoring in Clinical/Community Psychology. She became involved in Brain Matters to gain more experience researching and writing about the current research in Neuroscience. When she is not writing for Brain Matters, she is also involved in Dr. Kwapil's Project on Life Experiences Lab, and is the Treasurer for the Psychology Research and Community Club (PRACC). Brianna Mae is hoping to pursue a PhD in Clinical Neuropsychology and conduct research about the neurological basis behind different clinical disorders.