A Not-So Beautiful Mind: A Review of the Genetics of Schizophrenia

by Lydia Pack

Abstract: Schizophrenia is often called "the cancer of the brain" because of the lifelong, horrendous implications of the disease. Though research has been conducted on schizophrenia for a century or more, it has just recently been realized how large a role genetics may play in the development of the disease. This review will discuss why research on schizophrenic genes has been difficult, what genes have been found, how the current treatments are being revolutionized, and how to progress in this field. The difficulty in research is due in part to the complex genetics behind the disease as well as possible environmental factors. The two genes to be discussed in depth, Neuregulin 1 and SNAP-25, are notable for their complexity. Neuregulin 1 has multiple types of isoforms and genetic variants that could lead to schizophrenia and make it difficult to determine where the mutations might be. The SNAP-25 gene serves multiple purposes in various body and brain regions as an aid to release neurotransmitters, so it can be difficult to say which part of the body affected by the gene could lead to a schizophrenia diagnosis. The future of schizophrenia research could possibly involve glutamate because of its demonstrated abnormal correlation with schizophrenia. Moreover, it's important that future research focus not only on treating symptoms, but also the patient as a whole.

Introduction

Schizophrenia affects approximately one percent of the population around the world and is often incredibly debilitating (Jia et al., 2010). Schizophrenia is over-represented in homeless populations, likely because the extreme symptoms of the disease can cause people to lose their jobs and homes (Fond et al., 2018). Schizophrenic populations are largely underdiagnosed, undertreated, and often have a multitude of physical and mental illnesses in addition to the disease. Since schizophrenia is so incapacitating, it makes sense that it is considered one of the top twenty causes of disability in the world (Leucht et al., 2013).

Schizophrenia is a complex disease that is typically categorized into two different types: positive or negative. The positive type of schizophrenia is characterized by symptoms of hallucinations, delusions, and disorganized thinking, while the negative type is associated with a loss of cognitive and social functions (Kay et al., 1987). With recent medical advances, negative symptoms are typically more difficult to address, as the positive symptoms can be treated with antipsychotic medication (Kirkpatrick et al., 2006). In a study that followed schizophrenic patients for seven years, the patients with the least amount of negative symptoms were most successful in recovering normal functions (Milev et al., 2005).

There is no cure for schizophrenia, which is why it remains a pertinent issue. There are a number of treatment options available, and controversy remains over what treatments are most effective. Often, the symptoms of schizophrenia are treated instead of the condition itself (Harvey et al., 2004). Even if medication can be effective, most are expensive, have debilitating side effects, and can lead to serious effects if discontinued (Leucht et al., 2013). Also, improving the symptoms of schizophrenia through antipsychotic medication or other types of medication does not always, or completely, help an individual. Social functioning, the ability to live independently, and employment are all challenges that schizophrenics face beyond the symptoms of their illness (Harvey et al., 2004).

Schizophrenic research is ongoing; however, from the research already conducted, it seems that schizophrenia is based on both environmental and genetic factors, but especially genetic. The heritability estimates of schizophrenic genes are approximately

eighty percent, meaning heritability has been shown to have a much greater effect than the environment (Jia et al., 2010). Research suggests that a family history of schizophrenia can be a significant risk factor, but there are also many cases of specific gene changes that are risk factors for schizophrenia (Yunjung et al., 2011).

This paper will address the effect of genetics on schizophrenia. The first objective will discuss why research on schizophrenia has been difficult due to the number of possible causal genes and the complexity of those genes. The second and third objectives will analyze specific genes that may be linked to schizophrenia: the Neuregulin 1 gene and SNAP-25 gene respectively. The fourth objective will look at the current treatments, like antipsychotic medication, and discuss future research needs in genetics to improve schizophrenia treatments. Schizophrenia research has come a long way; however, there must be continued research in order to better treat not just the symptoms, but the causes.

Objective 1: Difficulties in Research

While there has been extensive research on schizophrenia, there have been multiple roadblocks that have prevented progress. The biggest problem has been the lack of knowledge about the underlying structure and complexity of the genes affected (Yunjung et al., 2011). The human genome was only mapped out less than twenty years ago, and since then, there has been much to learn about how certain parts of genes can cause such detrimental effects.

There have been multiple types of studies to determine possible causes of schizophrenia, one of which is karyotyping, a detection of chromosome abnormalities through the number and visual appearance of chromosomes in a cell's nucleus. Karyotyping showed that a deletion of area 22q11.2 on a chromosome was a rare but potent risk factor for schizophrenia. Similarly, specific copy number variations (CNVs)—sections of the genome that are repeated—showed this deletion as well as changes on areas 15q13.3, 16p11.2, 1q21.1, and NRXN1 on the chromosome (Yunjung et al., 2011). Through a genomic search for loci that differ between schizophrenic patients and non-schizophrenics, evidence suggested that schizophrenia was polygenic, meaning that genes with too small of a phenotypic effect to be observed acted together to create a noticeable variation (Yunjung et al., 2011). This genomic search also showed that there were no common variations of loci to produce a strong enough effect. The variety of information from this study shows how difficult the genomics of schizophrenia are to discern because the possible genetic risk factors are often rare or polygenic. Empirical data representing a spectrum of risk for specific alleles related to schizophrenia are shown in Figure 1, which shows that schizophrenic inheritance is based on both rare, Mendelian-like genes and polygenes.

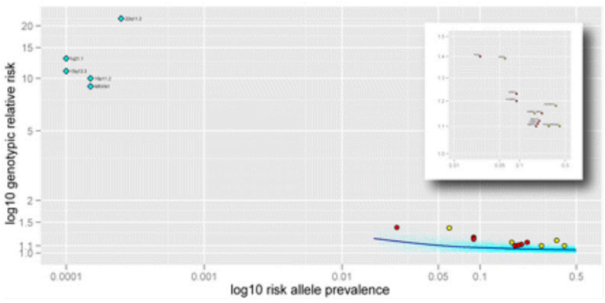

Figure 1. The rare copy number variations (CNVs) are in the upper left corner, and the more common variants of genes (right and yellow dots) and polygenes (blue best fit line) are in the lower right corner. The x-axis is the prevalence of the possible risk allele, and the y-axis represents the relative risk genotypically. Adapted from Yunjung et al. (2011).

As aforementioned, the heritability of schizophrenia is around eighty percent, which means there is still a small portion of causality due to environmental factors. However, these environmental factors are notorious for being more difficult to identify than the biological aspects because of the wide range of possible factors, including drug abuse, trauma during mother's pregnancy, nutritional factors, prenatal and postnatal development, and any other possible trauma, physical or emotional (Petronis, 2004). Since the environmental factors of schizophrenia and other mental illnesses are so elusive, the genomic side has dominated the field of research. However, the genomic side is as equally complex as the environmental factors; it dominates the research side because the genetics can be tested experimentally more easily than testing traumas (Petronis, 2004). Despite the difficulties in researching this complex disease, there has been some progress made, as certain genes may play a role in the development of the disease.

Objective 2: The Neuregulin 1 Gene

The Neuregulin 1 gene is known as a schizophrenia susceptibility gene and is also incredibly complex. The neuregulin genes are a family of four genes that play a key part in developmental processes, neuroplasticity, and oncogenesis (a process in which healthy cells become cancer cells). The Neuregulin 1 gene, located at chromosome 8p13, [0] has been associated with key functions in the heart, breast, and nervous system. (Harrison et al., 2003). The gene's structure consists of 1.4 megabases and has more than twenty exons as seen in Figure 2. Neuregulin 1 has six isoforms for one gene (Harrison et al., 2003). The differences in promoters can result in differences in expression patterns between different isoforms. If either exon E68 or E59 are in the gene, there will be variants. Exon E68 causes an inclusion of EGFα variants, while exon E59 leads to EGFβ variants, and the β variants are much more potent than the α equivalents (Steinthorsdottir et al., 2004).

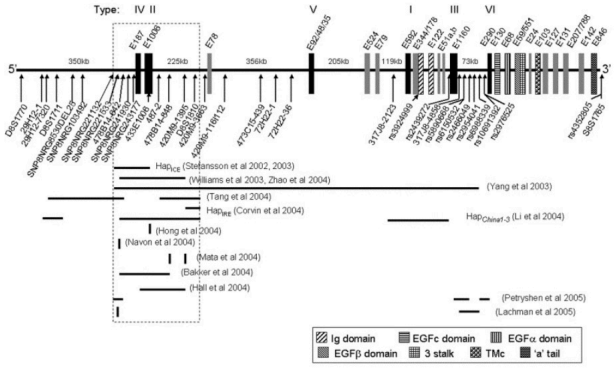

Figure 2. The exons are represented by vertical bars, and the specific 5' exons that determine the types of Neuregulin 1 are in black. The patterned exons are the ones that perform key functions, and the others are gray. Non-coding exons were omitted from the figure. The lines below the gene are risk haplotypes (groups of alleles), with the length of the line representing the extent of the risk. The dashed box shows where the most positive associations have been found between schizophrenia and the haplotypes/exons. Adapted from Steinthorsdottir et al. (2004).

The Neuregulin 1 protein has been noted for binding to receptor tyrosine kinases called ErbB, and it has also been noted that any irregularities in the pathway of the gene and this receptor has been found in schizophrenic patients (Jagannath et al., 2018). A study was conducted in mice with mutations in Neuregulin 1 and ErbB, and the mice with the mutations showed "schizophrenic-like" symptoms and were hyperactive (Mei et al., 2008). It has also been shown that Neuregulin 1 gene polymorphisms can predict schizophrenia patients at-risk of psychosis (Jagannath et al., 2018). Both of these studies have supported that the Neuregulin 1 gene is part of the cause of schizophrenia; however, it would be difficult to repair this gene because there are so many exons and loci on the gene that could be responsible for the schizophrenic symptoms. Research suggests that most of the genetic variants on Neuregulin 1 were either on introns, part of synonymous exon substitution, or in a non-coding region near the 5' or 3' end (Mei et al., 2008). These differences are said to cause a change at the level of transcription or splicing, and aid in showing the complexity of this gene as to how it could cause schizophrenia.

It is significant to have research on a gene that is likely responsible for causing susceptibility to schizophrenia. With the information of what genes are responsible for creating the incorrect proteins, research can continue to determine how this can be prevented, or how treatments could overcome the effects of the mutations.

Objective 3: The SNAP-25 Gene

Another gene that studies have found may play a role in causing schizophrenia is the SNAP-25 gene. This gene is part of a complex that allows presynaptic vesicle trafficking, which also means the gene helps to release neurotransmitters (Müller et al., 2005). In a study of mutant mice without the SNAP-25 gene revealed that this gene is essential for synaptic transmission, but not for neurotransmitter release without a stimulant (Corradini et al., 2009). Along with this role, SNAP-25 also interacts with different voltage-gated calcium channels. It interacts with these channels through a region called synaptic protein interaction and controls neuronal calcium responsiveness to depolarization through inhibition of the calcium channels (Corradini et al., 2009). The SNAP-25 gene is also therefore a synaptic protein that aids in synaptic vesicle fusion and moderating calcium dynamics in response to depolarization, as can be seen in Figure 3.

In schizophrenic patients, there have been quantitative differences in the expression of SNAP-25 in the brain and cerebrospinal fluid (Müller et al., 2005). Decreased levels of the gene's expression were found in the hippocampus and frontal lobe within

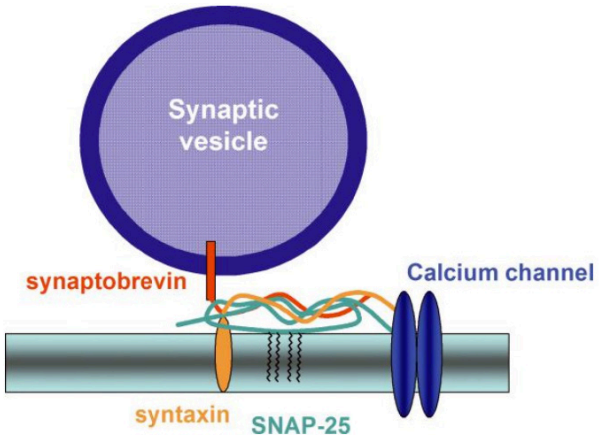

Figure 3. Illustration of SNAP-25's capabilities in assisting the calcium channel through depolarization. Adapted from Corradini et al. (2009).

schizophrenic patients versus healthy controls. Researchers suggested that this decrease coincided with the hyperactivity of other parts of the brain that are typically associated with schizophrenia (Corradini et al., 2009).

A study conducted on mice with a point mutation called blind drunk or Bdr, which is associated with the SNAP-25 gene, showed the influence of this gene and the environment, specifically prenatal stress, on schizophrenia. The study's results showed that sensorimotor deficits that were noted with only the point mutation were increased in the presence of prenatal stress (Oliver et al., 2009). The results also showed that only when the mice had both the point mutation and prenatal stress did social interaction abnormalities arise within the offspring (Oliver et al., 2009). These social interaction abnormalities are similar to the social interaction abnormalities that can be seen with the negative type of schizophrenia; therefore, this study supports that environmental prenatal stress and the point mutation can lead to schizophrenic symptoms. This study not only continues to show the possible effect that the SNAP-25 gene has on increasing the risk of schizophrenia, but also how the genetics and the environment could possibly intertwine. While the heritability of schizophrenia is high, the environment can also contribute either individually or together with genetic susceptibility, which raises a whole other set of circumstances and obstacles to understanding this disease.

Objective 4: Treatments and Future Research

While there is still much to be researched regarding the genetics of schizophrenia, there are treatments now to help address the symptoms of the disease. Most of the treatments available for the symptoms are antipsychotic medications or cognitive behavioral therapy. As stated before in the introduction, a majority of the antipsychotic medications are too expensive (especially considering the large number of schizophrenics who are unemployed and homeless), have various side effects, and can lead to detrimental effects when the medication is discontinued (Leucht et al., 2013). The antipsychotics typically reduce dopamine receptor function which can help to defray some symptoms, but also have dangerous side effects, such as diabetes and an increase in blood lipids (Moghaddam, 2004).

More recent research has tried to find other ways of treating schizophrenics beyond the antipsychotics. One study revealed the role of glutamate in schizophrenia because multiple parts of the body (frontal cortical systems, limbic system, basal ganglia, and thalamus) and multiple connections (corticocortical, corticolimbic, and corticothalamic) that are affected in people with schizophrenia are glutamatergic (Moghaddam, 2004). In addition, there have been reports since the mid-twentieth century about an abnormal amount of glutamate and an abnormal amount of postmortem glutamate receptor binding in schizophrenic patients (Moghaddam, 2004). Gated ion channels known as NMDA receptors and two ligands—glutamate and glycine—are responsible for regulating the release of glutamate, glycine, and D-serine through presynaptic mechanisms (Moghaddam, 2004). These NMDA receptors have been shown to possibly cause schizophrenic symptoms if there is any small change to the receptor, and factors that could cause these changes can be seen in Figure 4. Also shown in the figure are the pharmacological sites on the NMDA receptor that could be used to treat schizophrenia, such as glycine and D-serine binding sites, the glycine transporter (Gly T), and the metabotropic glutamate (mGlu) receptors (Moghaddam, 2004).

Another study showed similar discoveries about glutamate and using the findings about glutamate for future treatments. This study analyzed seven different genes that were said to be linked with

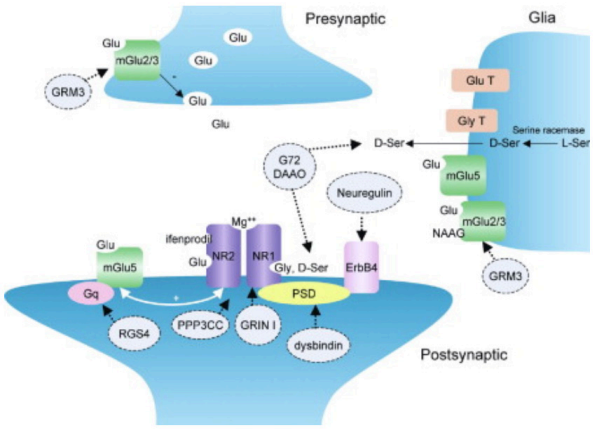

Figure 4. The diagram illustrates the complicated process of creating certain proteins from the genetic code. The genes listed within the dotted gray bubbles are known schizophrenia susceptibility genes. Other notable parts of the illustration are the possible sites of intervention for treatments. Adapted from Moghaddam (2004).

schizophrenia and found the common theme of glutamatergic synapses among all of them (Harrison et al., 2003). Figure 5 shows a hypothetical scenario in which the seven genes have a shared effect on the synapses, which supports the importance of glutamate. By looking into these potential genetic sites for intervention, there is hope for more than just treating the symptoms, but actually being able to treat, or possibly cure, the root cause of schizophrenia.

There are decades, perhaps even centuries, of research done on schizophrenia, but there is only

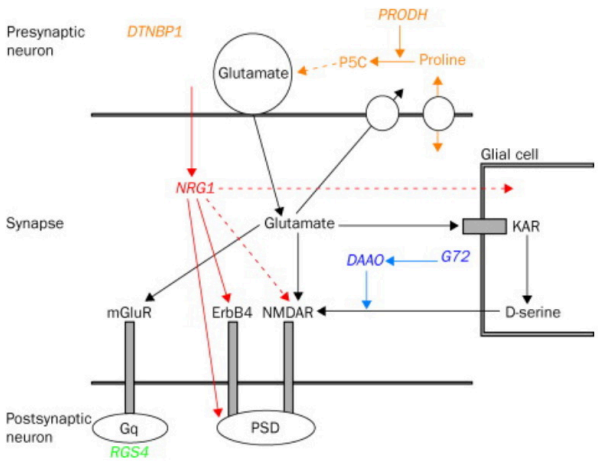

Figure 5. Illustration of the genes' shared effect with glutamate. The solid arrows represent direct interactions, and the dotted arrows indicate indirect interactions. Adapted from Harrison et al. (2003).

a small amount understood about the disease. The genes discussed earlier, the Neuregulin 1 and SNAP-25, are not the only genes to have been linked to schizophrenia over the years. Other gene linkages to have been reported include dysbindin (a protein of a dystrophin-associated complex), Catechol-o-methyltransferase (one of enzyme that degrades catecholamines), the DISC1 (encoding a brain protein), RGS4 (Regulator of G-protein Signaling 4), GRM3 (metabotropic glutamate receptor), and the gene G72, which encodes a protein in the brain thought to modulate NMDA glutamate receptor function as discussed before (Kirov et al., 2006). Research suggests that all of these genes have some link to the development of schizophrenia. Although there is knowledge about these genes, and where they are, and what they are doing wrong, there is very little knowledge about how to treat them or change them (if ethically these treatments were approved).

However, even if there were a cure to treat the genetic abnormalities that play a large part in causing schizophrenia, many schizophrenic patients may need help relearning societal expectations. In a study of schizophrenic patients who had undergone antipsychotic treatment, half of the sample had never been married and ninety-five percent of the sample had impaired social relationships (Harvey et al., 2004). Within the same study, the quality of life among schizophrenic patients was found to be low even after they had received treatment. Many of the patients said that their symptoms of schizophrenia were not the reason for their lower quality of life, and many cited medication side effects were the main culprit (Harvey et al., 2004). The future of schizophrenia research will likely involve addressing the other issues patients face beyond their generalized symptoms.

Conclusion

From 1955 to 2005, the percentage of Americans disabled by mental illness increased fivefold to almost six million Americans disabled (Whitaker, 1970). Schizophrenia is part of this mental illness epidemic, as it affects almost one percent of the worldwide population (Jia et al., 2010).

The difficulty in understanding schizophrenia is largely due to its complexity. Environmental factors have at least a small impact on causing these symptoms, and these factors can take the form

of prenatal chemicals to living emotional trauma (Petronis, 2004). The larger complexity though comes from genetic factors, but these are not just simple Mendelian-like genes. For instance, the Neuregulin 1 gene can have variant introns, synonymous exon substitution, or variants in non-coding regions (Mei et al., 2008). Without having just one variant, it can be difficult to determine which specific variant is causing the abnormality. Another reason for the difficulty is that genes like the SNAP-25 gene (where it can be seen that there is a correlation between schizophrenia and the gene) play a role in so many vital parts of the body that it can be difficult to understand how exactly SNAP-25 is affecting a certain part (Corradini et al., 2009).

However, the understanding of genes has allowed for some progress in the pharmacology of treating symptoms of schizophrenia. The recent research in how glutamate could play a role in the actual genetics aspect of schizophrenia could make a difference in one day finding a cure. Future endeavors in research for schizophrenia will hopefully either provide a solid cure for the root cause in an individual, or more likely, will help to treat the individual in a holistic way.

References

Corradini, I., Verderio, C., Sala, M., Wilson, M. C., & Matteoli, M. (2009). SNAP-25 in neuropsychiatric disorders. *Annals of the New York Academy of Sciences, 1152,* 93-99. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2706123/.

Fond, G., Tinland, A., Boucekine, M., Girard, V., Loubière, S., & Boyer, L. (2018). The need to improve detection and treatment of physical pain of homeless people with schizophrenia and bipolar disorders. Results from the French Housing First Study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 88,* 175-180. https://www-sciencedirect-com.ezproxy.uky.edu/science/article/pii/S027858461830366X.

Harrison, P., & Law, A. (2006). Neuregulin 1 and schizophrenia: Genetics, gene expression, and neurobiology. *Biological Psychiatry, 60*(2), 132-140. https://www.sciencedirect.com/science/article/pii/S0006322305013892.

Harrison, P., & Owen, M. (2003). Genes for schizophrenia? Recent findings and their pathophysiological implications. *The Lancet, 361*(9355), 417-419. https://www.sciencedirect.com/science/article/pii/S0140673603123793.

Harvey, P., Green, M., Keefe, R., & Velligan, D. (2004). Cognitive functioning in schizophrenia: A consensus statement on its role in the definition and evaluation of effective treatments for the illness. *The Journal of Clinical Psychiatry, 65*(3), 361-372. https://www.psychiatrist.com/JCP/article/Pages/2004/v65n03/v65n0312.aspx.

Jagannath, V., Gerstenberg, M., & Walitza, S. (2018). Neuregulin 1 (NRG1) gene expression predicts functional outcomes in individuals at clinical high-risk for psychosis. *Psychiatry Research, 266,* 143-146. https://www-sciencedirect-com.ezproxy.uky.edu/science/article/pii/S0165178117322758.

Jia, P., Sun, J., Guo, A., & Zhao, Z. (2010). SZGR: A comprehensive schizophrenia gene resource. *Molecular Psychiatry, 15,* 453-462. https://www.nature.com/articles/mp200993.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*(2), 261-276. https://www.ncbi.nlm.nih.gov/pubmed/3616518.

Kirkpatrick, B., Fenton, W. S., Carpenter, W. T., & Marder, S. R. (2006). The NIMH-MATRICS consensus statement on negative symptoms. *Schizophrenia Bulletin, 32*(2), 214-219. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2632223/.

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., . . . Davis, J. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. *The Lancet,*

382 (9896), 951-962. https://www.sciencedirect.com/science/article/pii/S0140673613607333.

Mei, L., & Xiong, W. (2008). Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. *Nature Reviews Neuroscience, 9,* 437-452. https://www.nature.com/articles/nrn2392.

Milev, P., Ho, B. C., Arndt, S., & Andreasen, N. C. (2005). Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: A longitudinal first-episode study with 7-year follow-up. *Schizophrenia Bulletin, 162*(3), 495-506. https://www.ncbi.nlm.nih.gov/pubmed/15741466.

Moghaddam, B. (2004). Bringing Order to the Glutamate Chaos in Schizophrenia. *Neuron, 40*(5), 881-884. https://www.sciencedirect.com/science/article/pii/S0896627303007578.

Müller, D., Klepman, T., & De Luca, V. (2005). The SNAP-25 gene may be associated with clinical response and weight gain in antipsychotic treatment of schizophrenia. *Neuroscience Letters, 379*(2), 81-89. https://www.sciencedirect.com/science/article/pii/S0304394004015629.

O'Donovan, M. C., & Owen, M. J. (2005). Finding schizophrenia genes. *The Journal of Clinical Investigation, 115*(6), 1440-1448. https://www.jci.org/articles/view/24759.

Oliver, P. L., & Davies, K. K. (2009). Interaction between environmental and genetic factors modulates schizophrenic endophenotypes in the Snap-25 mouse mutant blind-drunk. *Human Molecular Genetics, 18(*23), 4576-4589. https://academic.oup.com/hmg/article/18/23/4576/665946.

Petronis, A. (2004). The origin of schizophrenia: Genetic thesis, epigenetic antithesis, and resolving synthesis. *Biological Psychiatry, 55*(10), 965-970. https://www.sciencedirect.com/science/article/pii/S0006322304001465.

Steinthorsdottir, V., Stefansson, H., & Ghosh, S. (2004). Multiple novel transcription initiation sites for NRG1. *Gene, 342*(1), 97-105. https://www.sciencedirect.com/science/article/pii/S037811190400472X.

Whitaker, R. (1970). Anatomy of an epidemic: Psychiatric drugs and the astonishing rise of mental illness in America. *Ethical Human Services and Sciences, 7*(1), 23-35. https://www.ingentaconnect.com/content/springer/ehss/2005/00000007/00000001/art00003.

Yunjung, K., Zerwas, S., Trace, S., & Sullivan, P. (2011). Schizophrenia genetics: Where next? *Schizophrenia Bulletin, 37*(3), 456-463. https://academic.oup.com/schizophreniabulletin/article/37/3/456/1895795.