Review on Genetic Causes of Schizophrenia

Zhixiao Feng
Georges Vanier Secondary School, Toronto, Ontario, Canada
jane.feng616@gmail.com

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Abstract: This essay examines two theories of the genetic causes of schizophrenia. In the first section, I summarize the brief history of this field of schizophrenia, and state that there are two major theories of schizophrenia. In the second section, I explain the reasoning of Dopamine Theory and why some scientists still argue this theory. In the third section, I clarify other theory called The Theory of Chromosomal Mutation. To be more specific, my analysis focuses on the 22q11 Deletion Syndrome, and I also summarize an experiment on this theory. In the final section, I conclude two potential directions on this field of study.

1. Introduction

Schizophrenia may result in hallucinations, delusions, memory loss and extreme disordered thinking and behavior. Schizophrenia affects 0.5-1% of the population. As we know both genetic and environmental factors contribute to the pathogenesis of schizophrenia. In terms of genetics, its inheritance does not follow the Mendelian rules and is extremely complicated. In the field that analyzes the causes of schizophrenia, scientists purposed many different theories, which can be either environmental or genetic. Despite decades of research, the pathogenesis of schizophrenia remains one of the significant challenges in psychiatry and neuroscience. This literature review explores two major theories of the genetic causes of schizophrenia from different perspectives. This review will also discuss some research details, conclusions, and limitations of these two theories.

2. History of the Field

The study of Pulver et al. (1994) is a foundational source in understanding the genetic basis of schizophrenia since it represents the first influential finding of the research interest in the field. Before, there were many kinds of research done in pre-molecular genetics, such as developmental twin studies. Since 1990, scientists had moved the focus to molecular genetics, but they could not identify a specific gene with much evidence until Pulver et al. (1994) first identified chromosome 22q, which is the stem of more studies on the 22q1 region of chromosome later. In 1999, Bassett and Chow cited the study of Pulver et al. (1994) and discussed 22q11 deletion syndrome, a genetic syndrome associated with microdeletions on chromosome 22 and often includes speech and learning difficulties. The meta-analyses (Badner and Gershon, 2002) suggest that many chromosomal regions may contain schizophrenia susceptibility loci, which reconfirms an earlier study in 1995 that Wang et al. discovered chromosome 6p could also be one of the possibilities of the regions that are associated with schizophrenia.

One study (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) used some available schizophrenia GWAS samples to successfully identify 128 schizophrenia associations by doing a single gene analysis. For example, dopamine receptor D2 is associated with neurotransmission and some parts of the immune system. The idea of dopamine theory is originated from Van Rossum in 1967, and these results provide a fundamental support for the studies on possible

links between schizophrenia and dopamine.

Furthermore, associations of schizophrenia have been found explicitly across the Major Histocompatibility Complex (MHC) locus on chromosome 6, stating that it might be the most influential association of the hypothesized regions (Shi et al., 2009). Recently, a study found that the association between schizophrenia and the MHC locus comes from the alleles of C4, which were found to affect the expression of C4A and C4B in the brain and are associated with schizophrenia (Sekar et al., 2016).

3. The Dopamine Theory of Disorder of the Synapse

The dopamine theory is one of the most convincing theories of schizophrenia. The classic dopamine hypothesis points out that schizophrenia is due to a hyperdopaminergic state, and the higher potency of antipsychotic drugs (antagonists) means the better ability to block dopamine receptors (Owen, 2005). In recent years, it has been found that amphetamine can promote the release of dopamine into the synaptic space and make normal people produce a kind of clinical manifestations of schizophrenia (Ashok et al., 2017). Moreover, antipsychotics can prevent the onset of type I schizophrenia and have been found to be potent blockers of the DA receptors, particularly the D2 receptors. This suggests that the onset of psychosis is specifically associated with the activation of the DA receptor (Seeman & Kapur, 2000).

However, there are still some voices that disagree with this hypothesis. One of the supporting evidence of the dopamine hypothesis was that stimulants would cause dopamine increases, while the increase of dopamine caused schizophrenia. However, Joanna states that the mechanism for stimulant-induced schizophrenia has not been clarified, and stimulants are known to affect many neurotransmitters other than dopamine. Therefore, dopamine might not cause schizophrenia, instead, it is likely to be affected by other neurotransmitters. Furthermore, some of the factors that are thought to lead to increased dopamine do not necessarily lead to increased dopamine. For example, amphetamine has been shown to increase dopamine production in the striatum, but some studies have shown it doesn't. In addition, confounding effects could be present in dopamine release factors such as sports, arousal and stress, which could cause diseases other than schizophrenia. However, scientists rareky study these. There are some studies have studied the dopamine level of post-mortem brain tissue to verify the dopamine hypothesis, which is inconclusive since the dopamine level of dead brain is not accurate (Moncrieff, 2009).

4. The Theory of Chromosomal Mutation

Another major theory of the genetic causes of schizophrenia is about chromosomal mutations. One of the possible locations of the mutation is on chromosome 22, which is called 22q11 Deletion Syndrome (22qDS). It is an under-recognized genetic syndrome caused by microdeletions on chromosome 22. Preliminary evidence suggests that only a small number of patients with schizophrenia (approximately 2%) may have 22qDS, and the prevalence may be higher in the subgroup with developmental delay (Bassett & Chow, 1999). Bassett did an experiment with other scientists in 2003. Standard measurements of signs, symptoms, and disease course were performed on 16 adults with 22qDS schizophrenia who were not mental retarded and 46 adults with schizophrenia without 22qDS schizophrenia in a sample of community families. The results indicated that there were no significant differences in life cycle and overall function between the two groups of schizophrenic patients. There was no significant difference in the severity of anxiety and depression symptoms between the two groups. In conclusion, the clinical phenotype of schizophrenia cannot distinguish individuals that have 22qDS subtype from those who do not have 22qDS subtype. However, these results act as a neurodevelopmental model of schizophrenia and provide support for further studies of 22qDS

schizophrenia, and also help 22qDS individuals to help identify some precursors of schizophrenia (Bassett et al., 2003).

5. Conclusions and Implications

In the last decade, scientists have produced novel findings about the genetic causes of schizophrenia, and Human Genome Project made a great contribution in genetic areas of schizophrenia.

There are two potential directions for future research: one is related to neoroscience. Synapse disorders may lead to schizophrenia, which can be treated by modifying neuroreceptors. For instance, hyperdopamine is treated with dopamine antagonist drugs such as chlorpromazine. Another main direction is to research the different regions of different chromosomes. Possible related locations can be chromosome 5, chromosome 6 and 22q11 chromosome. These implications reflect scholars' different focuses of the research, but what they have in common is that all researchers in this field contribute to understand the genetic causes of Schizophrenia as well as how it can be treated more efficiently.

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