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BIO158

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Final Project

Genome-wide Approach to the Complexities of Schizophrenia:

A Meta-Analysis of the Genetic and

Epigenetic Changes of Schizophrenia

Schizophrenia is a mental disorder characterized by abnormal thinking, social engagement, and interpretation of reality (World Health Organization). This disease is a crippling disorder that has spurred much research over the past decades with the aims of finding a specific cure. The polygenetic nature of the disease and potential environmental factors that affect it as well make elucidating a distinct pathophysiology very elusive (Schizophrenia Working Group of the Psychiatric Genomics Consortium). However, the advancement of next generation sequencing and the combined efforts of research centers, universities, medical institutions have made the use of genome-wide mapping an efficient strategy in elucidating patterns and associations regarding schizophrenia (Dempster, Yongsheng). Through a meta-analysis of multiple genome-wide association studies regarding the genetic and epigenetic associations of schizophrenia, the complexities of this elusive disease and the possibilities of a distinct etiology will become more comprehensive.

The symptoms of schizophrenia are most commonly broken up into two categories: positive and negative. Positive symptoms are characteristics that are not typically found in the majority of people's normal functioning. A common positive

symptom of schizophrenia is having delusional thoughts (Carson). These are usually false beliefs that are not based in our reality. Individuals with delusional thoughts often have an unstable sense of their own self (Sims). Schizophrenic individuals may also experience hallucinations (Sims). These can be attributed to any of the senses; however, schizophrenics most commonly experience auditory hallucinations, usually in the form of hearing voices (Sims). These auditory hallucinations tend to have structure to them and resemble actual figures. Another frequent positive symptom in schizophrenic individual is making loose associations (Hirsch). This is where a person's thoughts or speech illogically progresses to ideas or phrases that are very loosely associated in meaning. Somewhat less frequent of a symptom is a tendency to have random outbursts of violence (Hirsch). When a person does exhibit this trait, the violence is usually not directed at other people, but instead at their own self. This leads to a higher than average rate of suicide in people with schizophrenia (Harkavy). Most available antipsychotic drugs aimed at treating schizophrenia, such as clozapine, olanzapine, risperidone, and amisulpride, are able to decently remedy these symptoms, however, the negative symptoms prove to be more evasive (Kneisl).

Negative symptoms are characteristics that normal healthy people have, but that have either been reduced or nonexistent in a person with schizophrenia (Sims). An example of these is a lack of social cognition. This leads to a reduced desire to form relationships, difficulties understanding emotional facial expressions, and withdrawal from society (Carson). Schizophrenics tend to have diminished emotions themselves as well as lowered motivation and difficulties feeling pleasure. Another very common inability experienced is the difficulty in understanding abstract things, such as proverbs

(Barry). These symptoms tend to be the most debilitating in society and, unfortunately, do not respond well to medications.

The demographics of schizophrenia are fairly similar worldwide. Around 0.3 to 0.7% of people around the world suffer from schizophrenia, which is around 24 million people worldwide (Os, World Health Organization). There is no difference in the rates of schizophrenia between people of different socioeconomic statuses, however, people of lower economic standing tend to be diagnosed much later after their onset, are more likely to go untreated, or cannot efficiently treat their illness due to inadequate healthcare systems (Os). There also is no significant difference in incidence between males and females; however, there is a difference in their ages of onset. Both genders' peak ages of onset occur in early adulthood, however, schizophrenia tends to appear earlier in men, with a peak at 21 years old, and slightly later in women, with a peak at 25 years old (Os).

Schizophrenia has been shown to have a high level of heritability, with estimates as far as 80% (Sullivan). However, schizophrenia is a polygentic disease, meaning it is caused by more than one gene, and finding a specific pathophysiology has proven to be quite difficult. Research has now been directed at trying to determine what common genic variations attribute to schizophrenia. Current estimates state that common polygenetic variations are accountable for one-third of the total genetic variation in schizophrenia (Sklar). The method of using genome-wide association studies (GWAS) has been very helpful in elucidating the intricacies of complex diseases that have multifaceted components to their condition. GWAS use DNA microarrays to identify single nucleotide polymorphisms in databases of millions of varying genomes. The studies are used to find associations in genetic variations that could be used to identify,

avert, and counteract these complex conditions. One of the biggest hurdles in applying a GWAS on schizophrenia, however, is finding enough suitable patients for the study (Schizophrenia Working Group of the Psychiatric Genomics Consortium). In order to go about this, consortiums, comprised of many universities medical institutions, and research centers from around the world, pool together many databases of DNA microarrays in order to extract a comprehensive analysis.

Around two-dozen large GWAS have been performed in order to identify schizophrenia-associated loci and just over 100 distinct loci with significant associations have been found (International Schizophrenia Consortium, Ripke, Ikeda, Hamshere, O'Donovan, Rietschel, Schizophrenia Psychiatric Genome-Wide Association Study Consortium, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Irish Schizophrenia Genomics Consortium, Shi, Shi, Stefansson, Steinberg, Yue, Lancz, Psychiatric GWAS Consortium). A p-value of 5x10^-8 or less was used to define a significantly associated loci. In order to properly characterize the disease and with the need of space in mind, only specific loci and their associated genes will be elaborated upon based on the current understanding of schizophrenia's characteristics.

A schizophrenic-associated loci was found at 11q23.2, which corresponds to the DRD2 gene. This gene encodes for the D2 subtype of the dopamine receptor. This protein is the receptor for its endogenous ligand, dopamine, and is pivotal in dopaminergic neurotransmission. Dopamine is a neurotransmitter that is responsible for reward-motivated behavior, motor control, memory, and cognition. Many atypical antipsychotic drugs aimed at treating schizophrenia, such as amisulpride, olanzapine, risperidone, and clozapine, work as D2 receptor antagonists, thus decreasing dopaminergic

neurotransmission and blocking off mesolimbic and prefrontal cortex limbic pathways. This in turn can help remedy the positive symptoms of schizophrenia as well as some negative cognitive symptoms. (Schizophrenia Working Group of the Psychiatric Genomics Consortium)

Schizophrenic-associated loci were also found at 7q21.12, 16p13.2, 5q33.2, 17p13.3, 4q33, and 16q21 and correspond to the genes GRM3, GRIN2A, GRIA1, SRR, CLCN3, and SLC38A7 respectively. These genes are all associated with the neurotransmission of glutamate, which is an excitatory neurotransmitter in the nervous system. Glutamate is responsible for synaptic plasticity, which plays a role in memory, learning, and long-term potentiation. Glutamate also plays a role in cross talk between synapses, the regulation of growth cones, and synaptogenesis. Glutamate has four types of receptors – NMDA receptors, kainate receptors, AMPA receptors, and mGluR. GRIA1 encodes for a subunit of an AMPA receptor, GRM3 encodes for a subunit of a mGluR, and GRIN2A encodes for a NMDA receptor. While SRR, CLCN3, and SLC38A7 deal with the activation of NMDA, ion channels for glutaminergic synapses, and the reuptake of glutamate respectively. (Schizophrenia Working Group of the Psychiatric Genomics Consortium)

The functioning of plasticity and synapses may also play a role in the etiology of schizophrenia. A multitude of loci (16p11.2, Xp21.33-32, 11q25, 3p26.3, 5q14.3, 7q33, Xp22.12, 15q14, 6q14.2) all correspond to genes that regulate the structure of synapses, formation of synapses and presynapses, development of interneurons, network formation, neurogenesis, and neurite and dendritic growth, among many other processes. Other loci seem to similar genes that help regulate neurodevelopment such as FXR1, SATB2,

PODXL, BCL11B, TLE1, TLE3, and FAM5B. Previous research has already shown functional differences in brain structure and activity in individuals with schizophrenia compared with those who don't. (Schizophrenia Working Group of the Psychiatric Genomics Consortium)

Lastly, there was an abundance of loci (22q13.1, 6q12-13, 20q13.13, 5p21, 15q25.1) that correspond to genes such as CACNA1I, RIMS1, KCB1, HCN1, and CHRNA3 that relate to neuronal ion channels. In particular, there is a high relationship to calcium (L and T type) ion channels, but there are also genes that encode for potassium. Voltage-gated calcium ion channels have roles in exciting neurons and initiating synaptic transmission (Catterall, Schizophrenia Working Group of the Psychiatric Genomics Consortium).

After categorizing a multitude of schizophrenia-associated loci, the characteristics of the disease become a little more comprehensive. The GWAS loci may imply a convergence of abnormalities dealing with the neurotransmission of dopamine and glutamate, the function and structure of synapses and plasticity, and calcium ion channels.

All of the loci mentioned point to abnormalities within the brain, however, that is also because that is where most of the current research being performed on schizophrenia is being focused on. In one of the largest GWAS on schizophrenia to date, with 36,989 cases and 113,075 controls, the Schizophrenia Working Group of the Psychiatric Genomics Consortium mapped their 108 significantly found schizophrenia-associated loci to epigenetic markers that correspond to cell and tissue type specific active enhancers from 56 cell line and tissue samples. Their data confirmed that the schizophrenia-

associated loci were significantly abundant at enhancers in the brain and not so in other places such as the liver, kidney, and bone. However, they also found that the loci were significantly enriched in tissues related to immune functions. Specifically, enhancers active in tissue lines associated with B-lymphocyte antigens such as CD19 and CD20. Both of these proteins are expressed on B-cells and are responsible for gaining immunity and activating B-cell immune response (Gaughran). There have been previous finding that point to the dysregulation of the immune system being involved in the pathology of schizophrenia, but these associations help us reaffirm this interest and guide us to other areas of exploration in regards to schizophrenic etiology (Gaughran). (Schizophrenia Working Group of the Psychiatric Genomics Consortium)

Another area in particular is the potential role that epigenetic changes affect the pathology of schizophrenia. An epigenetic change is a heritable modification in the expression of a gene that is not induced by a change in the DNA sequence. Epigenetic changes regularly occur naturally throughout time, however, they can also be brought about by outside effects such as the environment, disease, and age. The two main mechanisms behind epigenetic changes are DNA methylation, histone modification, and non-coding RNA-associated modification. As we have already begun to learn, schizophrenia is a very complex polygenetic disease and it does not simply follow Mendelian inheritance, suggesting that common genetic variations cannot fully explain this multifaceted disease. Research into the epigenetic changes possibly involved in the etiology of schizophrenia has begun to increase in the last few years.

One of the most commonly hypothesized mechanisms for epigenetic changes associated with schizophrenia is DNA methylation. This process is where

methyltransferase (DNMT) enzymes covalently add a methyl group to the DNA nucleotides, cytosine or adenine. This methylation is usually found in CpG sites – locations in the DNA sequence where a cytosine nucleotide is placed right next to a guanine nucleotide. The exception to this is CpG islands; these are clusters of CpG sites that are usually located near promoters of a gene. When a CpG island is methylated, the methyl group sticks into the major groove of DNA near the promoter and sterically inhibits DNA transcription, thereby reducing gene expression. This change in expression can be a permanent as cells divide and specify, which can cause genomic imprinting. DNA methylation is important in neurobiological and cognitive functions such as memory, learning and neural development. (Dempster)

The first form of a genome-wide epigenomic approach to major psychosis was taken in 2008 by performing a microarray-based epigenomic scan using CpG island microarrays. They found epigenetic dysregulation by way of DNA methylation near multiple genes involved in neuronal development, GABA neurotransmission, glutamitergic neurotransmission, and several other genes previously linked to major psychosis. (Mill)

Since then, many genome-wide epigenomic studies have been aimed at schizophrenia. Many of the results have linked very well with the findings previously reported in the multiple GWAS on common genetic variations. A study examining the 5'-regulatory region of the DRD2 gene in two pairs of monozygotic twins (one concordant and one discordant for schizophrenia) found that the there was nonuniform methylation patterns in the pair of discordant monozygotic twins, and that the afflicted twin in the discordant pair was epigenetic more similar to the concordant pair of twin. This suggests

that epigenetic variation may be a factor in regards to susceptibility to schizophrenia. (Petronis)

Lastly, in 2014 a genome wide mapping study was performed to examine the genomic distribution of abnormal DNA methylation in six subjects with schizophrenia and three subjects with bipolar disorder and compare them to a normal positive control. The study found specific DNA methylation patterns around transcriptional start sites in "CpG island shores" (locations that are a couple of kilobases away from CpG islands) and in promoters without CpG islands. The study also found hundreds of original schizophrenia- and bipolar-associated genes that are involved in processes such as signaling pathways, long-term potentiation and metabolism. (Yongsheng)

Specifically taking a look at the data involving the aberrant DNA methylation in schizophrenia, the study sorted through individual variations and found "ultra DMRS," which are regions that are hyper- or hypo-methylated in over 50% of the samples. A total of 5,338 hyper-methylated DMRs and 13,630 hypo-methylated DMRs were found in the DNA of schizophrenic subjects. These methylation regions were in many "CpG shores" that were associated with genes previously associated with schizophrenia. In fact, 23.8% of the genes identified in the study were genes previously associated with schizophrenia. These genes include important hotspot genes such as DNMT1, CACNA1S, PRAME, SMAD3, ARHGAP26, and CREB. These results help suggest that the epigenetic mechanism of DNA methylation may play an important role in the pathology of schizophrenia as well as show that it may be possible to use specific methylation patterns as biomarkers for characterizing schizophrenia. (Yongsheng)

As we can see through a meta-analysis of multiple GWAS aimed at elucidating specific common genetic variations and epigenetic patterns, the nature of schizophrenia is a very polygenetic disease that is influenced by a plethora of factors that are situated in casual and rare genetic variations associated with dopaminergic and glutamatergic neurotransmission, neuronal ion channels, and the functioning of synapses and plasticity as well as epigenetic changes brought about by the mechanism of DNA methylation, particularly near “CpG shores”. Although a distinct pathophysiology has not been elucidated, the advancement of genomic sequencing strategies has built a more comprehensive characterization of the disease and the possibility of specific patterns useful as biomarkers may slowly make this multifaceted disease easier to treat and detect.

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