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Schizophrenia: an Elusive Disease Caused by Chromosomal Abnormalities

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Although it is understood that Schizophrenia is somehow caused by genetics, scientists are unsure where the information is coded. To unlock the location of the genetic information, SNP and CNV analyses are performed. Those studies and their purposes are explained in the following review. Their goal is to find patterns on chromosomes that alter chromosomal function. SNPs were previously thought to show where the mutations occur and the means by which they persist. Researchers are now looking to CNVs for answers. These studies could contribute to the discovery of the link between chromosome deletions, duplications, or any other mutation leading to the development of Schizophrenia. If there is widespread knowledge of the precise causes of Schizophrenia and on which chromosomes the mutations are located, researchers may be able to outline a revolutionary way to reverse the mutation and improve the quality of many lives.

Introduction

Schizophrenia is a widely known disease that affects approximately 1% of the population. It is unknown why this mental disorder occurs. An individual with perfectly healthy parents can be diagnosed leaving the family baffled. A person in their early twenties can begin to display symptoms after living their entire lives previously unaffected. This elusive disease offers little insight, as it is caused by unseen factors that may go unnoticed for years. While the symptoms are relatively easy to diagnose, Schizophrenia is incredibly difficult to study. Regardless, it is known that Schizophrenia is acquired hereditarily. Much of the public considers the disease to be a split personality disorder in which a person is unable to commit to a single personality. People think those affected spend their life in constant turmoil, battling among personalities. That line of thought is inaccurate. In reality, the majority of Schizophrenic diagnoses comprise personality deficiencies such as anxiety, manic depression, clinical depression, and others. Behavior is a major issue with Schizophrenic patients. They experience delusions, paranoia, hallucinations, and unusual reactiveness to emotions. Often, the affected person cannot function well in social situations with family members, friends, or colleagues. Since many Schizophrenics are unable to cope with societal norms, they are often prevented from being successful in the work place due to their unusual behavior.

The symptoms may be obvious, but what causes Schizophrenia? There has been research concluding that genetic mutations occur. In the world of cell and molecular biology, the term "genetic mutations" is extremely vague. Three studies including *Segment-Wise Genome-Wide Association Analysis Identifies a Candidate Region Associated with Schizophrenia in Three Independent Samples* by Thomas E. Gladwin, et al, *Genome-Wide Analysis Shows Increased Frequency of Copy Number Variation Deletions in Dutch Schizophrenia Patients* by Buizer-Voskamp, Jacobine E., et al, and *Recurrent CNVs Disrupt Three Candidate Genes in Schizophrenia Patients* by Terry Vrijenhoek, et al, discuss the frontier of studying the genetic factors that pave the way for Schizophrenia.

Recent Progress

A person's likelihood of having Schizophrenia depends totally on genetics. If a member of a person's nuclear family has the disorder, they are much more likely to be diagnosed. To look further into the genetics of the disorder, researchers must analyze single genes. In

Segment-Wise Genome-Wide Association Analysis Identifies a Candidate Region Associated with Schizophrenia in Three Independent Samples by Thomas E. Gladwin, et al. the authors disclose that the variation occurs on Single Nucleotide Polymorphisms, or SNPs, which are variations on an allele. Because it is extremely difficult and expensive to study SNPs, the researchers set out to discover whether or not the variation affects an entire gene segment. It is much less difficult to look at the gene as a whole. Ideally, they thought the genes with the Schizophrenic mutation would be clustered in small groups rather than randomly distributed across the entire genome.

In their experiment, they focused on genes ranging from 2 Mbp-32 Mbp in a "segment wise method" used to determine whether or not consecutive genes contained information for genetic mutations. The outdated method for conducting the genome wide search is looking at 500,000 SNPs at once, instead of only looking at a few hundred. When looking at a few hundred SNPs at a time, it is much easier to observe mutations, and the risk of error decreases tremendously. Looking at a few hundred SNPs is a happy medium between looking at a very few and the entire genome.

The authors failed to accept the null hypothesis. The null hypothesis used stated there was no correlation between looking at a few SNPs at a time for genetic variants and finding the mutation that inevitably causes Schizophrenia. Genetic information relating to Schizophrenia was located on Chromosome 5 in contiguous genes, or those genes that neighbor the aforementioned gene. They discovered that there are groups of genes containing Schizophrenia-related SNPs, which means it was safe to fail to accept the null hypothesis. However, after their triumph, they could not decipher which SNPs were directly related to the mutations causing Schizophrenia. The researchers suggested that the SNPs responsible for directly causing Schizophrenia are on a higher level in the genome, possibly including the part of the gene in which expression functions reside. The researchers speculate that co-expression of genes could explain the closeness of the genes coding for Schizophrenia. Regardless of the reasons for the close proximity of the Schizophrenia information in the genome, they discovered that clusters of these genes occur.

In addition to the first study, further research was conducted. The second study was called *Recurrent CNVs Disrupt Three Candidate Genes in Schizophrenia Patient.* This study carries the findings of the previous report one step further. The previous work only brought SNPs into account when discussing the mutation locations. Rather than only looking to SNPs for answers and coming up short, the researchers in this study assessed the role played by CNVs, or copy-number variations. CNVs are even less noticeable than SNPs. CNVs are cytogenetic mutations that are hardly noticeable and are responsible for deletions or duplications of 1 kb-3 Mb in the genome. CNVs are the causation for disorders including autism, mental retardation, and Schizophrenia. In this study, the authors used Copy Number Analyzer for Affymetrix GeneChip (CNAG) v2.0 software to screen the genome for CNVs that cause Schizophrenia. Fifty-four patients with a severe form of Schizophrenia called "deficit Schizophrenia" were asked to participate in this research. The researches scanned the 54 patients' genomes as well as the genomes of a control group containing individuals unaffected by Schizophrenia. They closely observed the patients' genes and discovered that the four most prominently affected by Schizophrenia include MYT1L, CTNND2, NRXN1, and ASTN2. Each of these four genes plays substantial roles in neural migration, functioning, and adhesion.

In order to begin a search for the reversal of the genetic mutations responsible for Schizophrenia, it is necessary to study these specific genes. Studies performed by other researchers have resulted in similar conclusions. This most recent study was astounding due to the fact that the scientific world was previously unaware the gene NRXN1 was affected by mutations leading to the mental disorder. It was encouraging to discover previously unknown data. This study takes the research one step further in discovering more about the cause of Schizophrenia. They also resolved 13 more CNVs that were previously undiscovered. Although the four deletions and three duplications only occurred in 7% of those tested, the discovery is essential in acquiring more knowledge as to the cause of Schizophrenia. However, there is still little known about how frequently the CNVs occur or exactly where they are located on the gene.

A third study helps contribute to the understanding of the role CNVs play in unfortunate mutations that cause Schizophrenia. The work is entitled *Genome-Wide Analysis Shows Increased Frequency of Copy Number Variation Deletions in Dutch Schizophrenia Patients* and discusses in further detail the role of CNVs, simultaneously supporting the findings of the second work discussed. The researchers tested the genomes of 834 Dutch schizophrenia patients and 672 Dutch control subjects for CNVs to determine a correlation between CNVs and pathogenicity. After scanning the genome for mutations using QuantiSNP and PennCNV software, they identified three deletions at chromosome 1q211, 15q13.3, and 15q11.2. Deletions were much more common than duplications, but duplications existed nonetheless.

Discussion

The general consensus of all three studies is the etiology, or the origination, of Schizophrenia is exceptionally complex. Treatment paths are highly debated. Psychiatrists argue the importance of mind versus body

conditioning. One side makes an argument that the body must be treated rather than the mind. They wish to use drugs and electroshock therapy are more necessary to submerse the disorder they believe is affecting the body as much as the mind. The other side makes an argument that emphasis should be placed on psychotherapy to treat the mind and encourage socially acceptable behavior. It is likely that a combination of both is highly important to allow for patients to be functioning members of society. However, in order to adequately treat suffering patients, dissecting the source of the mutation holds significance. If the exact path to Schizophrenia is discovered, perhaps the exact reversal of those steps can be performed to treat the mutated genes and prevent symptoms from the beginning, or alter genes in a person who already displays symptoms. Another argument surrounding research involves the great nature versus nurture debate. Internal factors include genetic predisposition. Some external factors may decide the fate of people who are genetically susceptible to the disorder. Environmental factors include but are not limited to substance abuse, childhood abuse, unhealthy or stressful living conditions, negligence in adolescence, and general environmental dysfunction. If a person's body is under constant stress and is perpetually fatigued due to harsh physical circumstances, their bodies could deteriorate more quickly. They could inevitably be more susceptible to expression of genetic mutations leading to disorders like Schizophrenia.

The findings of all three papers support the concept that the loci that are susceptible to Schizophrenia are clumped closely together. It seems that schizophrenia-susceptible loci are not equally distributed across the human genome, but clustered together in specific regions. It has also been found that SNPs and CNVs are mechanisms by which mutations occur.

Further research should absolutely be performed to determine the precise cause of Schizophrenia. If anyone was able to discover the exact performance of the mutations, they could prevent mutations therefore allowing for the vertical transfer of healthy genes and preventing the transfer of mutated genes. If the mutations were reversed inside a living person's genome, there would be no Schizophrenia-causing mutations to pass on to offspring. The mutations would be reversed and humans would evolve without suffering from this mental disorder. The importance of the three studies lies with the possibility of someday finding a cure. Unfortunately, it is unknown exactly why or how Schizophrenia occurs. As technology is progressed, scientists will be able to more clearly observe the points on the genome at which the mutations that cause Schizophrenia occur. Once they find the culprits, they can continue research to find how the mutations affect means necessary to reverse the disorder.

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