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Epigenetics and Genetics of Schizophrenia

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ABSTRACT

Millions of people around the world suffer from schizophrenia and the resulting delusions, social withdrawal and other symptoms. All of these symptoms have treatments available such as anti-psychotics and therapy. However, these treatments are merely symptomatic and do not address the root of the disorder. The treatments can dull the impact of the symptoms of schizophrenia but cannot treat the disorder itself, therefore more effective treatments must be offered. Schizophrenia is an extremely heritable disorder, so genetics, as well as epigenetics, plays a crucial role in the prevalence and severity of the disorder. Studying the epigenetics and genetics of schizophrenia can help to gain a more thorough understanding of the disorder to help develop and test treatments that aren't just symptomatic. There have been various studies searching for parts of the genome that could play a role in an individual's likelihood to develop schizophrenia and gene therapy could be used to edit these parts of the genome. Epigenetics refers to the alteration in how one's body reads the genome using histone modification. Although there is minimal research in the area and as a result, there are also no treatments currently being researched or tested, epigenetic treatments have the potential to become a revolutionary treatment for schizophrenia. However, considering the lack of knowledge and research surrounding epigenetics, currently, genetic treatment has more likelihood of being a useful treatment in the near future. Nonetheless, increased research about epigenetics and genetics can help create more treatments to help those suffering from this disorder.

Introduction

Schizophrenia affects nearly 20 million people worldwide. It is a debilitating chronic psychological disorder that impacts the way a person feels, thinks, behaves and interacts with others. (*Diagnostic and statistical manual of mental disorders: DSM-5*) Schizophrenia can have a lasting impact on a person's relationships, learning, and career, thereby having a significant impact on their daily life. It is also estimated to be the seventh most expensive medical illness to society in terms of decrease in productivity and costs of care. (Ibi & González-Maeso, 2015) The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) states that schizophrenia is defined as abnormalities in either delusions, hallucinations, disorganized thinking/speech, disorganized or abnormal motor behaviour, and negative symptoms. The first four are positive symptoms. The two main negative symptoms that distinguish schizophrenia from other psychotic disorders are diminished emotional expression and avolition, which is a decrease in motivated, self-initiated purposeful activities. Other negative symptoms include lack of ability to focus, withdrawal from social life, and cognitive deficits like abnormalities in perception, memory issues and problems with language processing and motor function. (*Diagnostic and statistical manual of mental disorders: DSM-5*) While no single gene is thought to cause the mental disorder, genetics plays a large role in a person's predisposition to it. The probability of developing schizophrenia in the general population is only 1. However, the probability of developing it for someone with one parent with the mental disorder is 17% and for someone whose parents both have the mental disorder is 46%. (Ananloo, 2018)

Mutations and alterations of various genes can make people exceedingly more susceptible to getting schizophrenia. The treatments for schizophrenia that are currently being used in practice attempt to treat the symptoms of the mental disorder and reduce their impact on the affected person's life. In addition, the available

symptomatic treatment is just partially successful. This is not enough. Therefore, studying the genetics behind schizophrenia helps us understand this extremely nuanced psychological disorder on a much higher level as well as allows us to produce more innovative and technologically advanced treatments that do a better job of treating the mental disorder. Genetic and epigenetic treatments can find and treat the root of the problem, thereby ensuring a much better quality of life for people with schizophrenia. Genetic treatment focuses specifically on modifying the gene itself. This could be by removing a part of the genetic code, adding to it or both. Epigenetic treatment focuses on modifying the expression of the genetic code. Rather than altering the gene itself, it changes how an individual's body reads the DNA sequence. This can be done through histone modification. The most well-understood types of histone modification are DNA methylation, DNA acetylation, and DNA phosphorylation. Both of these treatment methods focus on correcting and treating the root of the problem and ensure that the problem caused by that genetic mutation or alteration is corrected permanently and that the patient feels better and can live their life to the fullest.

Overview of Schizophrenia

Schizophrenia is an incredibly complex mental illness that can make it hard to distinguish fantasy from reality, express and manage emotions, make decisions and more. This mental disorder has an immense impact on a person's life and overall well-being. People with schizophrenia can experience hallucinations, hear imaginary voices, have altered sleep patterns, have delusions, experience paranoia and more. Current treatments for schizophrenia include talk therapy, antipsychotics and more. However, these treatments treat the symptoms of the psychological disorder which is not good enough. Even with these treatments, people with schizophrenia suffer. As a matter of fact, the suicide rate for individuals with schizophrenia is significantly higher than that of the general population with approximately 10% of people with schizophrenia ultimately having committed suicide (Hor & Taylor, 2010) and the estimated reported suicide attempt rate ranges from 18% to 55%. (Sher & Kahn, 2019) As can be seen, current treatments available for schizophrenic patients are not doing remotely enough to help these individuals. They are still suffering, and it is evident that these treatments are not effective enough. When asked by an interviewer, "Do you believe you possess the ability to be happy?" Daniel, a person with schizophrenia replied by saying, "No [...] I don't think I can experience joy". (Special Books by Special Kids, 2019) All of this just goes to show how little the currently used schizophrenia treatments are really doing for schizophrenic patients. We need to offer these individuals newer, better, and more advanced treatments that have the potential to make an actual difference in their quality of life. We need to be targeting the root of the problem rather than its symptoms, and this can be achieved by using both genetic and epigenetic treatments.

Genetics and Schizophrenia

The role of genetics in schizophrenia is important to understand in order to explore genetic and epigenetic treatments for this mental disorder. The heritability of schizophrenia has been estimated to be from 81% to 85%. Considering how high the heritability of the mental disorder is, genetic treatments have the potential to prove extremely effective.

Candidate gene association studies have been a huge approach in regard to discovering the causative genetic factors of complex disorders Before Genome-wide association studies, candidate gene association studies were a major approach in the genetics of schizophrenia. These studies are relatively cheap and can be performed quickly. The SZGene database listed 1727 candidate gene papers of which 1008 genes and 8788 polymorphisms were investigated. According to published genetic association studies of schizophrenia, it has been reported that across 118 meta-analyses, 16 genes, consisting of APOE, COMT, DAO, DRD1, DRD2, DRD4,

DTNBP1, GABRB2, GRIN2B, HP, IL1B, MTHFR, PLXNA2, SLC6A4, TP53, and TPH1 showed significant effects. (Ananloo, 2018)

Genome-wide association studies is an approach that rapidly scans genetic variants across various peoples' genomes to find variations that are associated with a particular trait or disease. By utilizing this approach, researchers are able to use the information to create and develop improved hypotheses to treat, detect and prevent the disease. These types of studies are extremely useful for finding genetic variations that contribute to mental disorders like schizophrenia. This type of study searches the genome for a genome-wide group of genetic variants in varying people to see if any variant is associated with a normal trait or a disease. It is a hypothesis-free strategy that usually looks through the genome for CNVs, or SNPs that occur more frequently in people with a certain disease than in people without the disease. Throughout the last few years, large-scale genome-wide association studies of schizophrenia have found numerous risk variants that have a significant association with the mental disorder. However, these variants were only able to explain a small proportion of the heritability of schizophrenia and their effect sizes were relatively small. This suggests that increasing the sample size in analysis can help to detect more risk variants. (Ananloo, 2018)

The analysis of a European ancestry sample GWAS and then through a replication study, found notable associations for seven loci, including 1p21.3, 2q32.3, 6p21.32-p22.1, 8p23.2, 8q21.3, 10q24.32-q24.33, and 18q21.2 with schizophrenia. The most impactful finding was with a miRNA-137 SNP. In a meta-analysis of 18 genome-wide association studies and a replication study, *TCF4*, *NOTCH4*, *POM121L2*, *AS3MT*, *CNNM2*, and *NT5C2* genes were found to have a significant association with schizophrenia. (Ananloo, 2018)

Genetic Treatment of Schizophrenia

Considering the notable role that genetics plays in schizophrenia, genetic treatments and gene therapy can be good options for treating the root of the disorder. The genetic treatments can cut out and edit the exact gene that causes someone to be more susceptible to this psychological disorder to eliminate the likelihood of them developing schizophrenia later in life. Genetic treatments are currently not available for clinical use to treat schizophrenia; however, it is being studied and tested so that one day it can help treat people with this disorder. One very popular example of genetic treatment is using CRISPR Cas9 for genomic editing. We can use technology like CRISPR to find, target, alter and correct these genes, as they are shown to be the root of the problem. CRISPR stands for clustered regularly interspaced short palindromic repeats. These are classes of repeated DNA sequences that act jointly with CRISPR-associated (Cas) genes. A single guide RNA (sgRNA) recruits the Cas9 nuclease to specific genomic locations through standard Watson-Crick base pairing. The creation of site-specific double-strand breaks (DSBs) by the CRISPR/Cas9 complex then triggers genome editing. (Savić & Schwank, 2015) Although genome editing can offer effective treatment for schizophrenia, there are some risks and cons to the treatment. Firstly, this treatment is prone to errors such which can potentially make the mistake in one's genome worse. It could potentially edit the wrong part of the DNA or insert an incorrect new replacement strand. In addition, it would take a lot of time and resources for researchers to find the accurate part of the genome to edit and/or replace. Moreover, using CRISPR to treat any disease is extremely expensive and unfortunately, that means that the treatment is not accessible for many people. Although the treatment is innovative and effective, most people suffering from schizophrenia are likely unable to obtain this form of treatment.

On the plus side, taking into account that genetics mainly plays a role in how susceptible an individual is to develop schizophrenia later in life, using these treatments can not only treat the mental disorder itself but can treat people with genetic susceptibility of developing schizophrenia before the disorder develops to prevent the person from ever getting schizophrenia in the first place.

Epigenetics of Schizophrenia

Epigenetics is a process that alters how your body reads a genetic sequence rather than altering the genetic sequence itself. This is done through histone modification. The main types of histone modification that are also the most well understood are DNA methylation, DNA acetylation and DNA phosphorylation. These processes are used to activate and deactivate various parts of your DNA to create alterations in the resulting phenotype. The main structural unit of chromatin is the nucleosome, which is made up of of a standard length of DNA that is wrapped around a histone octamer made up of four pairs of basic histone proteins; H2A, H2B, H3 and H4. The formation and organization of chromatin depends on covalent modifications known as epigenetic factors including DNA methylation and histone modifications that occur mainly on their N-tails. The methylation of CpG dinucleotides inside proximal gene promoters in vertebrates is often linked to transcriptional repression. (Ibi & González-Maeso, 2015) (Fig 1)

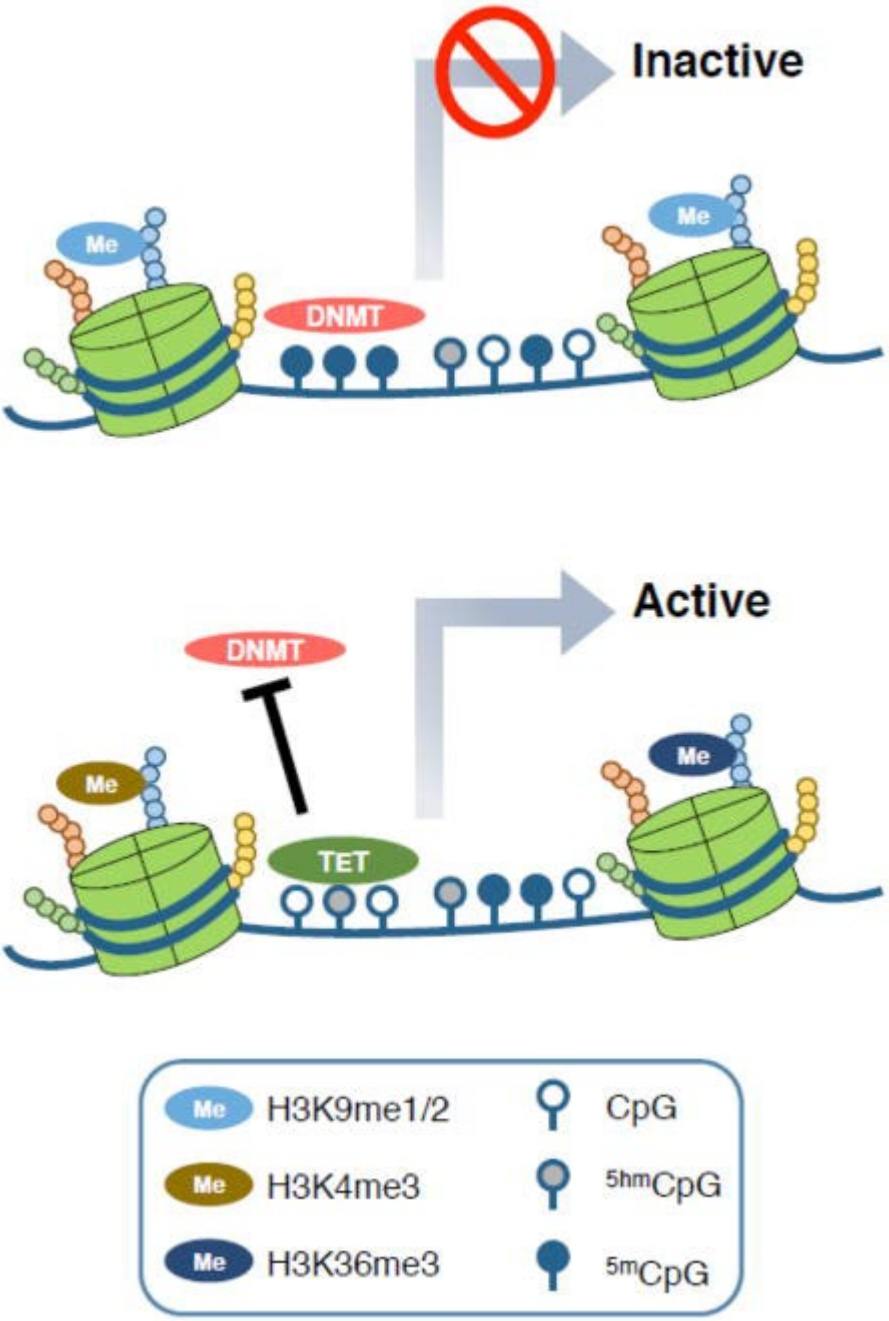

Figure 1. Link Between DNA Methylation and Gene Expression. (Ibi & González-Maeso, 2015)

A few of the histone modifications are associated with transcriptional activation, for example, acetylation, whereas other types, like methylation, correlate with gene activation and repression depending on the specific position of the histone tail residue. (Ibi & González-Maeso, 2015)

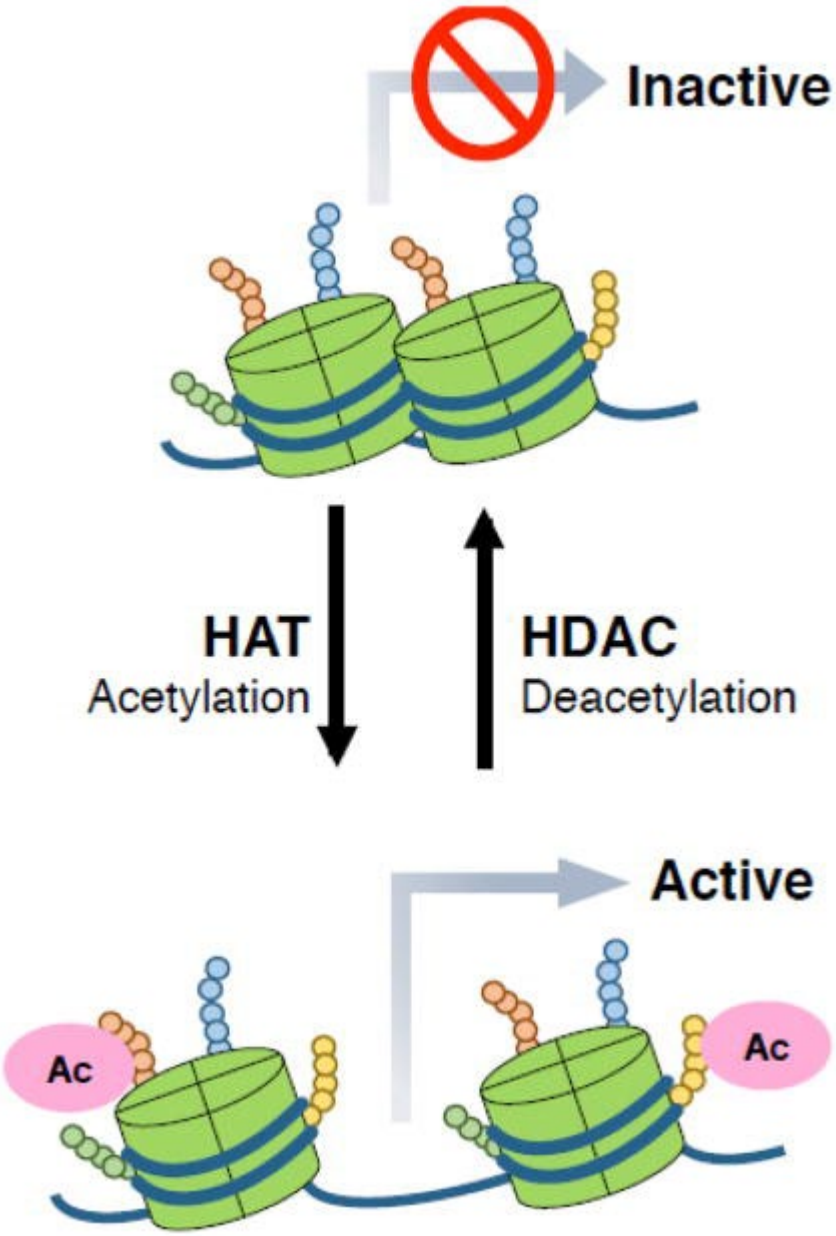

Figure 2. Model of DNA acetylation and deacetylation(Ibi & González-Maeso, 2015)

This alteration in how your body reads the genotype results in an altered phenotype. If the correct portions of an individual's genetic sequence are activated and/or repressed, the disorder could be "removed" or corrected so that the patient would no longer suffer from schizophrenia. Most work about epigenetically characterizing the schizophrenia epigenome has involved measuring direct DNA methylation through bisulphite sequencing and other similar methods. For example, a study that used blood samples identified many differentially methylated loci. In addition, differential DNA methylation studies have mapped to major neurotransmitter pathways. To demonstrate, in schizophrenia, components of the y-aminobutyric acid-ergic pathway, as well as promoters of the glutamic acid decarboxylase (GAD1) and reelin genes are hypermethylated. On the other hand, a component of the dopaminergic pathway, the promoter of the catechol-O-methyltransferase gene, was found to be hypomethylated in the post-mortem schizophrenia brain. The serotonin pathway has also been indicated with hypermethylation of the promoter of the serotonin receptor type-1 (HTR1A) gene having been reported

for blood samples of schizophrenia patients relative to controls. Adding on, the effect of antipsychotics on DNA methylation has now been widely reported. (Föcking et al., 2019)

Epigenetic Treatment of Schizophrenia

Unfortunately, there are no epigenetic treatments currently in use or any that have been researched. This can be attributed to the highly specialized technologies required to study epigenetics thoroughly and to research for a treatment and how difficult it is to obtain adequate samples to use for the research.

Genetic Treatment of Schizophrenia vs. Epigenetic Treatment of Schizophrenia

Obviously, genetics and epigenetics both play large roles in the study, research and treatment of schizophrenia. Genetic treatment has the potential to be a ground-breaking treatment for individuals with schizophrenia. Even though it is still in the research and testing stage, most animal trials are showing great success. Epigenetic treatments could also have the potential to help a lot of people. That being said how do genetic and epigenetic treatments compare? Which could be the better option, and what are the pros and cons of each? On one hand, genetic treatments are more likely to be clinically available treatments for schizophrenia sometime in the near future. Very few, if any epigenetic treatments for schizophrenia are even being tested or studied, so, odds are they will likely not be available as a treatment for quite some time. Genetic treatment also tends to be very expensive however, the estimated cost of epigenetic modification is not clear as epigenetics and histone modification are relatively new topics of research and there is not a lot of information about them. Genetic therapy can also be quite risky which is definitely something that should be considered when judging the efficacy of the treatment. Just like for expenses it is also unknown exactly how risky and prone to error epigenetic treatment can be. Overall, both have their fair share of pros and cons. That being said, too much is unknown about epigenetics and epigenetic treatment to determine its efficacy and therefore genetic treatment would currently be the better option. Further research could come up proving that epigenetic treatment is more efficient and effective, however currently genetic treatment is the more plausible option.

Genetic Treatment vs. Epigenetic Treatment

Genetic Treatment	Epigenetic Treatment	Current Treatment
More likely to be available to the public in the near future.	It likely won't be publicly available for quite some time.	Currently available to public
Expensive.	The cost is unknown. Potentially expensive	Is cheaper than genetic treatment, but can still be inaccessible
Has some risks involved.	Risks are unknown.	Little to no risks

Targets root of disorder (Genetic)	Targets root of disorder (Genetic)	Treats the symptoms of the disorder
Long-term benefits	Long-term benefits	Short term relief

Conclusion

Schizophrenia affects so many people around the world. All of whom suffer from psychotic and other symptoms that have a huge impact on how they live their life. The current symptomatic treatment isn't doing enough for them. Unfortunately, no genetic treatments are available currently, though some are being studied and almost no epigenetic treatments are being researched. Nonetheless, both play a large role in schizophrenia, its prevalence, and how it impacts individuals and both genetics and epigenetic have a large chance of ultimately becoming an innovative and more effective treatment for the disorder. Although, considering the lack of information and research on the two treatments they also have the potential to prove as poor treatments for schizophrenia. In addition, any cons or risks of either treatment can ultimately be solved. Of course, since neither of these is offered to patients currently, those suffering from schizophrenia will have to make do with symptomatic treatment, but further studies on histone modification and its applications as well as more trials of gene therapy's use for treating schizophrenia can help make these treatments available sooner to help everyone suffering from this disorder.

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