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Review

Schizophrenia Susceptibility Genes

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ABSTRACT

Schizophrenia is an inherited condition, and studies have revealed that environmental influences have a greater genetic effect. Histone modification is related to deoxyribonucleic acid methylation in epigenetics. One of the top potential genes for schizophrenia was thought to be WW domain binding protein 1-like. It also has a significant impact on the polymorphisms of the dopamine receptor (DR) D2 (DRD2) gene. Inconsistent findings have been found regarding the DRD2 gene's C957T and C939T polymorphisms and schizophrenia. The number of genetic variants found in patients with neurological disorders has significantly increased as a result of the quick advancement of sequencing technology. Patients with a variety of neuropsychiatric disorders have a startling number of variations in the glutamate ionotropic receptor N-methyl-D-aspartate (NMDA) type subunit (NMDAR or GRIN) genes that encode the NMDA glutamatergic receptor subunits. The effectiveness of the outcome was specifically assessed by contrasting the clinical and functional effects of genetic variants in (GRIN2A) and GRIN2B with previously published data. The brain contains a large number of DRs, which are important modulators of cognition, motor skills, motivation, and driving. Different receptor activities could be demonstrated in particular neural circuits as a result of the discovery of five genes encoding various DR subtypes. This review discusses genes associated with schizophrenia.

Keywords: DNA methylation, dopamine receptor, epigenetics, histone modification, polymorphism, schizophrenia

In schizophrenia, which is a persistent mental disorder, there are distortions in thought, perception, cognition, aspiration, and behavior.[1-7] A syndrome is a collection of a specific set of symptoms. Schizophrenia is a syndrome with multiple causes.[7] This disorder is defined as a collection of symptoms brought on by numerous different causes.

Each patient's schizophrenia-related symptoms are unique. Moreover, it can begin as abruptly as it does within this time frame, known as the pre-disease prodrome, where it may first manifest as slight symptoms. Pre-illness signs sometimes include self-indulgence, withdrawal from friends and hobbies, a deterioration in speech, and unusual pursuits. The most prevalent symptom of schizophrenia patients experiencing hallucinations or erratic speech during the disease's flare-up is that they don't believe the person is ill and lack insight. Delusions, theories, hallucinations, and other mental health issues are some more signs of schizophrenia.[8]

A condition with multiple causes would include schizophrenia. It has been demonstrated that several hereditary variables are connected to schizophrenia. In some families, schizophrenia is particularly prevalent. One of the reasons for schizophrenia is the environment, along with other elements including the mother's exposure to certain infectious diseases when she was pregnant. However, a number of theories have been put forth that link it to the structure and growth of the brain.[9]

Schizophrenia subgroups were eliminated from the present classification scheme. However, it is classified as follows under the previous method.[10]

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TYPES OF SCHIZOPHRENIA

Schizophrenia with paranoia

The kind of cognitive distortion that puts hallucinations front and center while keeping unfavorable symptoms like introversion more in the background and allowing for some degree of functional preservation.

Hebephrenic (disorganized) schizophrenia

Disorganized segments are hallucinations or presumptions when speech, behavior, and emotional organization are interrupted by meaningless facial expressions and laughter as well as daily activities and self-care abilities.

Catatonic schizophrenia

The type of severe motor activity reduction-extreme negativism, non-speech, and excessive motor activity-shows up in the motor system as repetition of the other person's words and actions, tightness of the muscles, and resistance to movement.

Undifferentiated schizophrenia

The properties of the three categories are displayed together in the type that counts above.

Residual schizophrenia

A form of schizophrenia is when the person has experienced an episode but no longer exhibits hallucinations, delusions, or mental confusion or behavior. According to a different classification scheme, schizophrenia might be classified as Type 1 or Type 2. More delusions and hallucinations, which we refer to as positive symptoms, are present in Type 1 patients. In Type 2, unfavorable symptoms, sometimes known as negative symptoms, such as introversion, speech reduction, and decline in self-care, seem to predominate. Typically, Type 1 schizophrenia responds better to treatment than Type 2, which has a worse prognosis.[10]

One of the most prevalent mental disorders, schizophrenia affects about 1% of the world's population.[11] Previous research has shown that both genetic and environmental variables might contribute to schizophrenia.[12] According to environmental variables, genetic factors are believed to be the main prerequisites for the emergence of schizophrenia with inheritance rates of up to 80–85% due to genetic and phenotypical heterogeneity, repeatability is rare despite the discovery of several susceptibility genes for schizophrenia.[13] In light of this, certain genes are more likely to be linked to clinical manifestations of the disease than to the overall diagnosis.[14]

EPIGENETICS

The term "epigenetics" refers to genetic traits that control gene expression chemically without changing the underlying deoxyribonucleic acid (DNA) sequence. Three main types of epigenetic modulation have been mentioned. Initially, postmortem brain tissue and peripheral blood samples from patients were examined to see whether DNA hypermethylation and hypomethylation were linked to schizophrenia. By detecting specific modifications of non-coding ribonucleic acids, in particular, microRNAs and long-chain non-coding RNAs, central and peripheral samples of schizophrenic patients have demonstrated considerable diagnostic values for the disorder. The relationship between histone modification and schizophrenia is largely uncertain.[15]

DNA methylation is the most investigated and best-characterized epigenetic mechanism. The process occurs mainly in CpG dinucleotides. Methylation of DNA molecules, under the catalysis of DNA methyltransferase, constitutes the transfer of methyl group from the S-adenyl methionine to the fifth carbon of the cytosine residue in DNA to form 5-methylcytosine.[16] A decrease in gene transcription activity or gene silencing is frequently linked to methylated DNA.[17,18] It is frequently connected to gene silence or a decline in the activity of genes.[19]

In the period just before and after the mother's birth, abnormal DNA methylation may be linked to neurodevelopmental behavior disorders like schizophrenia. Some schizophrenia-related genes, including disks large homolog 4 (DLG4), MIM 602887, dopamine receptor (DR) D2 (DRD2), MIM 126450, nitric oxide synthase 1 (NOS1), MIM 163731, neurexin-1 (NRXN1), MIM 600565, and sex-determining region Y-box 10 (SOX10), MIM 602229 have been proven to have age-related dynamically.[20]

The neurotrophic protein known as a brain-derived neurotrophic factor (BDNF) can promote the production of new synapses and accelerate neuronal development, both of which are necessary for the maintenance of memory and learning. When used to predict behavioral sensitivity brought on by early life exposure and environmental factors, BDNF DNA methylation in the blood can be utilized as a marker for BDNF DNA methylation and gene expression in the brain.[21]

EPIGENOME-WIDE ASSOCIATION STUDY

Differentially methylated positions (DMPs) have been linked to several pathways relevant to immune function, and epigenome-wide association study (EWAS) has found a number of DMPs that are connected to schizophrenia.[22] Twenty-three genes in schizophrenia, including Voltage-dependent L-type calcium channel subunit beta-2 (CACNB2) and parkin protein (PRKN), were shown to have varied levels of methylation in this EWAS in an earlier examination of the data.[23] Patients with first-episode schizophrenia in the Han Chinese population were shown to have the most significant DMPs associated with the genes C17orf53, THAP1, and potassium voltage-gated channel subfamily Q member 4 (KCNQ4).[24] The major histocompatibility complex (MHC), which has been proven to be closely associated with schizophrenia, overlapped the top-ranked differentially methylated regions, and those who have schizophrenia have higher polygenic risk scores than the controls The therapy of the disease may also be influenced by epigenetic alteration, which might therefore be used to anticipate how well a treatment will work. According to an EWAS meta-analysis, 1,048 distinct methylation sites were associated with schizophrenia, some of which were only found in patients with treatment-resistant schizophrenia.[22] DNA methylation in multiple places has been found after chloramine treatment in a lengthy investigation of leukocytes from schizophrenic patients who are resistant to treatment.[23]

DNA HYPERMETHYLATION/ HYPOMETHYLATION

Both hypermethylation and hypomethylation of DNA have been found, especially in schizophrenia patients. Particularly, DNA hypermethylation was initially discovered through the study of autopsy brain tissue and was connected to significant neurotransmission networks. For instance, prior autopsy investigations found hypermethylation at two CpG sites in the glutamic acid decarboxylase 1 (GAD1) gene and three CpG sites in the serotonin receptor 2A (HTR2A), which are linked to the risk of schizophrenia and the enzyme that controls the synthesis of gamma-aminobutyric acid.[25] DNA methylation has been linked to 5-hydroxytryptamine receptor 2A mRNA expression in addition to polymorphisms.[26] Analysis of the prefrontal cortex revealed hypermethylation of schizophrenia-related differentially methylated genes, including guanine nucleotide-binding protein subunit alpha-13 (GNA13), calpain small subunit 1 (CAPNS1), and GA binding protein transcription factor subunit beta 2 (GABPB2).[27] The organizer of HTR1A showed higher methylation in the blood of people with schizophrenia.[28] The current suicide trend in schizophrenia is linked to high levels of CpG methylation in solute carrier family 20 member 1 (SLC20A1).[29] When compared to controls, first-part schizophrenia had higher DNA methylation of leukocytes from human endogenous retrovirus K (HERV-K)-infected ambient blood.[30] Compared to the controls, paranoid schizophrenia patients introduced more The mitochondrial calcium (Ca^{2+}) uniporter complex (mCuC) and a lower percentage of cmC as long interspersed element-1 (LINE-1) partial methylation.[31] Additionally, DNA hypomethylation in schizophrenia individuals' peripheral blood and brain tissue has been documented. For instance, the frontal lobe of schizophrenia patients had hypomethylation of the catechol-O-methyltransferase (COMT) gene, which was derived from the dopaminergic pathway.[32]

Another study using peripheral blood mononuclear cells discovered that matrix metallopeptidase-9 (MMP9) expression was positively correlated with negative symptoms in schizophrenia and that open schizophrenic patients had reduced DNA methylation in MMP9 compared to non-explicit schizophrenic patients.[33] Other genes besides MMP9, including AluY A3 CpG, glutamate ionotropic receptor N-methyl-D-aspartate (NMDA) type subunit 2B (NMDAR or GRIN2B) in triggering receptor expressed on myeloid cells 2 (TREM2) intron, CpG2 and CpG3's supporter, CpG sites in the family with sequence similarity 63 member B (FAM63B), CpG sites in chromosome 16, intergenic zone, CpG sites in TBC1D22A, and COMT, also had hypomethylation as compared to controls. Additionally, compared to groups receiving conventional antipsychotics, COMT methylation was lower.[24,34-38]

HISTONE MODIFICATION

It has been established that these gene expressions are correlated with the acetylation of histone H3 at the promoters of the schizophrenia-related genes GAD78, translocase of outer mitochondrial membrane 70A homolog A (TOMM70A), HTR2C, and protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1E (PPM1E).[39] In schizophrenia, it has been demonstrated that an increase in methylation at arginine 17 of histone H3 (H3-methyl(methyl)argin 17) is connected with a decrease in the expression of numerous genes involved in metabolism.[40]

WBP1L GENE

The microRNA 137 (miR-137) targets WW domain binding protein 1-like (WBP1L; C10orf26), which has been proposed as a potential gene for schizophrenia. Through luciferase-based reporter assays, researchers have verified the site-specific regulation between miR-137 and transcription factor 4 (TCF4), calcium voltage-gated channel subunit alpha1 C (CACNA1C), CUB and Sushi multiple domains 1 (CSMD1), and WBP1L.[41] Since then, several studies have demonstrated that miR-137, TCF4, CSMD1, and CACNA1C are strongly linked with schizophrenia and cognitive function across ethnicities, indicating that miR-137 and its targets may be implicated in the etiology of schizophrenia. However, the connection between C10orf26 and schizophrenia has received relatively little attention.[42] Genome-wide association study data from a 507 Irish family sample that were specifically focused on the symptoms of schizophrenia and reported revealed considerable evidence of a robust correlation between WBP1L and the manic and depressive characteristics of schizophrenia patients. Therefore, it is logical to assume that WBP1L may be connected to the schizophrenia etiology and symptoms.[43]

There are currently no published reports of WBP1L with schizophrenia in the Han Chinese population, hence more replication of the candidate gene association studies in broad and diverse populations is required to corroborate the findings. Clarification of the link between clinical symptoms and potential genes may also help to fully comprehend the genotype-phenotype relationship in schizophrenia patients. Therefore, it is crucial to determine if the WBP1L gene is linked to schizophrenia symptoms in the Han Chinese population. The connection between WBP1L and the clinical symptoms of schizophrenia was investigated in the current study using a two-stage case-control association study from the Han Chinese population: miR-137 targets WBP1L, which is a potential gene for schizophrenia. To examine the relationships between WBP1L and schizophrenia and related symptom measures, 5,993 Han Chinese subjects-2,128 schizophrenia cases, and 3,865 controls were registered. For the replication effort, a separate sample of 1,052 schizophrenia patients and 2,124 controls were also collected. The WBP1L gene area had 32 labels that were chosen for single nucleotide polymorphism (SNP) genotyping and analysis. Using gene expression data from various human tissues, it has been determined how targeted SNPs' expression quantitative trait loci (eQTL) effects are expressed. Both rs4147157 and rs284854 were substantially related to schizophrenia, and these relationships were reproduced in the replication example (OR (odds ratio, a measure of association between an exposure and an outcome)=0.84 and p(probability of the data occurring under the null hypothesis) =1.51 10-5). A substantial correlation between the positive and negative syndrome scale scores in schizophrenia patients has been found using the statistical tests RS4147157, general ($\boldsymbol{\beta}$= -.66, p=.001), and total ($\boldsymbol{\beta}$= -.8 , p =0042) (a statistical test for the correctness of the hypothesis). For genes like ADP-ribosylation factor-like 3 (ARL3) and arsenite methyltransferase (AS3MT) that are located near WBP1L, both SNPs were significant eQTLs. SNPs 4147157 and rs284854 were consequently connected to schizophrenia in the Han Chinese population. In addition, the rs4147157 was substantially related to certain symptom features of schizophrenia.[44,45]

DRD2 GENE POLYMORPHISM

The dopamine D2 receptor gene's C957T and C939T polymorphisms have been linked to schizophrenia in a number of studies, but the findings are mixed. There was no association between schizophrenia and the C939T polymorphism in either the general or Asian population. This study suggests that the DRD2 gene polymorphism C957T, particularly in the Caucasus, may be a risk factor for schizophrenia.[46]

G-protein coupled receptors, DRs are divided into two main families: the dopamine D1 family, which includes the D1 and D5 receptors (DRD1 and DRD5); and the dopamine D2 family, which includes the D2, D3, and D4 receptors (DRD2, DRD3, and DRD4). Dopamine receptors are essential components of the dopaminergic system, which is thought to be disordered in schizophrenia's pathogenesis.[47,48] Animal models of psychosis demonstrate the relationship between a number of hereditary and non-genetic risk factors and the dopamine behavioral supersensitivity that is reflected in the levels of DRD2.[49]

The key activity area for the treatment of antipsychotic medicines is DRD2, which is expressed in the limbic system and is thought to be crucial in regulating the dopaminergic pathway in the brain.[50] A promising putative risk gene for schizophrenia is the DRD2 gene, which is found on chromosome 11q22–23.[51,52]

GRIN2A AND GRIN2B VARIANTS

The creation of a comprehensive database of variants in healthy individuals was made possible by the rapid advancements in sequencing technology, which resulted in an explosion of genetic variants in patients with neurological disorders. A startling number of GRIN gene variations were discovered in patients with schizophrenia. The GRIN2A variations are frequently linked to an epileptic phenotype in comparison to clinical phenotypes, whereas GRIN2B mutations are frequently seen in patients with neurodevelopmental problems. Functional investigation of GRIN2A and GRIN2B variants may shed light on the molecular processes underlying more precise subclassification of clinical symptoms.[53]

The majority of the variants with GRIN2A (46%) and GRIN2B (38%), followed by GRIN1 (14%), are those identified in the GRIN gene family.[54] The GRIN variations should be viewed as a bigger group of variants since mutations in the three genes can have similar effects of gain-of-function (GOF) or loss-of-function (LOF) on anti–NMDARs. It is crucial to remember that all of these genes can combine to make functioning receptors. Additionally, while GluN1 is present in all NMDARs, these variations are especially harmful to those that contain GluN2B and GluN2A. However, depending on regional and developmental expression patterns, there will be variations with GRIN2A in addition to the many roles that GRIN2B genes can play in their overall effects and circuit functions. Therefore, it is advantageous to liquidate variations with gene, GOF, and LOF despite the fact that they alter a number of NMDAR complexes expressed in the brain. Since GRIN2A and GRIN2B are the two most prevalent forms of GRIN, a thorough analysis of these two sub-units offers a chance to comprehend the structural, functional, and genetic roots of the problems these patients are suffering from.[55]

DOPAMINE RECEPTOR

The brain contains a lot of DRs, and these receptors are important modulators of driving, motivation, and motor skills. Differential receptor function was shown in several neurocircuits for various DR subtypes thanks to the definition of five genes encoding, which are pharmacologically categorized as D1- (D1 and D5) or D2-like (D2S, D2L, D3, and D4). Recent findings at the DR signaling site: glutamate-NMDA neurobiology in schizophrenia and the creation of novel treatments.[56]

Dopamine neurotransmission changes between adolescence and adulthood are linked to schizophrenia, which results in deficiencies in motivation, cognition, and sensory abilities.[57-59]

Developmental brain studies and the introduction of imaging tools have greatly increased our understanding of the role of DR in schizophrenia. Divergent temporal and coupling features of activation are correlated with DR expression among neuronal groups. While a number of β-arrestin-biased D2 receptor signals reveal obvious modifications in schizophrenia models, this distribution is respected in schizophrenia. When defining schizophrenia as a developmental disorder across circuits, certain developmental and connection elements of DR distribution are maintained across species.[59]

The majority of DR investigations are only connected to risk genes or schizophrenia. Although the molecular understanding of glutamate NMDA-dopamine interactions in schizophrenia has advanced, it is still insufficient, particularly with respect to negative symptoms and in areas of the brain like the ventral striatum. The distinction between cognitive and detrimental symptoms of schizophrenia would be even more blurred with improved circuit comprehension.[60]

In conclusion, chronic alterations in the composition and operation of brain circuits characterize mental disorders, which are multifactorial diseases with many complicated components. A highly heritable mental illness called schizophrenia affects a person's behavior, movements, perception of reality, and thoughts as well as his relationships with his family and peers. Epigenetics has been demonstrated to have a significant role, and there are many genes where schizophrenia has diverse impacts. Some genes have been examined for their schizophrenia. Schizophrenic individuals' peripheral responses have shown persistent abnormalities in brain tissues and in epigenetic markers, but additional research is needed to confirm these findings and understand the underlying mechanisms. Early diagnosis and isolation of these diseases are aided by a better knowledge of the role of epigenetic influences on the genesis and course of schizophrenia and other mental disorders.

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