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Genetic basis of schizophrenia: Basic hypothesis pathways and gene functions

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ABSTRACT

Schizophrenia is a neurodegenerative disease in which cognitive and behavioral disorders coexist. Based on magnetic resonance imaging (MRI) studies, there are problems in neuron connections and the prefrontal lobe is almost completely disrupted. It is highly inherited. Genome scans have shown that variations in the major histocompatibility complex (MHC) genes may be a risk factor for schizophrenia. Detection of the differences in allele frequency is also important in the etiology studies of the disease. Schizophrenia is a very complex disease due to dysfunction of almost entire neurocognitive related systems. With the discovery of antipsychotic drugs, many hypotheses have been put forward on the etiology of the disease. One of them is dopamine hypothesis of schizophrenia and the other is glutamate hypothesis of schizophrenia. Antipsychotic drugs alleviate psychosis symptoms by interacting with protein receptors or ion channels involved in dopamine glutamate and gamma aminobutyric acid (GABA) pathways. In this review, we discuss dopamine and glutamate hypotheses based on the etiology of schizophrenia and the genes that have the most evidence for their relationship with the disease.

Keywords: COMT, DISC1, Dopamine, DRD2, GLIN2A, glutamate, NRG1, schizophrenia gene.

Schizophrenia is a complex disease that negatively affects individuals' lives and their function in the society. As there is no known biochemical abnormality, the diagnosis is made according to symptoms observed during clinical examination.[1] The lifetime risk of the disease is approximately 1% in the general population.[2] This indicates that, in the society as a whole, there are a considerable number of schizophrenia patients. It has been demonstrated by twin and family studies that 60 to 80% of schizophrenia is inherited.[3] In studies conducted on parents and children of schizophrenia patients, the incidence of schizophrenia in children of parents with schizophrenia and schizophrenia-like disorders was found to be much higher compared to the general population.[2,4] It has attracted such a great interest that genetic factors have such a large impact on the disease. With the latest researches, more than 600 genes that might be associated with schizophrenia have been identified.[5] Due to the absence of biochemical abnormalities, a gene product as a protein or enzyme defect, cannot be associated with the disease.

Studies are conducted on genes that play a role in a wide pathway such as a neurotransmitter metabolism, and their contribution to the etiology of the disease is investigated. Defects in genes that play a role in these pathways contribute to the formation of disease character at different rates.[6] Disease-related gene and gene regions can be predicted by conducting studies on clinically suspicious genes or by genome-wide scans.[7]

Genome-Wide Association Study (GWAS)

Single nucleotide variations (SNVs) are mutations that underlie genetic diversity and are inherited through the generations. They can cause alterations in the structure of the gene product or change the amount of expression. These can provide the continuity of the species

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in the evolutionary process and can also form the basis of various diseases.[8]

The GWAS is a method applied to compare SNV differences between sample and control groups genome-wide. In this method, which can be also applied in complex psychiatric disorders such as schizophrenia, when the SNV differences between the sample two groups are statistically compared, the significantly different SNV regions are determined as suspicious genes that form the genetic basis of the disease.[9] More consistent results can be achieved by expanding the sample and control group. The Psychiatric Genomics Consortium 2 (PGC2) was arranged to summarize the GWAS studies conducted for this purpose with a single study. In particular, 128 loci containing genes associated with abnormal glutamatergic synaptic and calcium channel function have been identified as suspected SNV.[7] However, it would not be proper to say that these are alleles or genes that cause schizophrenia. Since there is naturally a difference in allele frequencies between ethnic groups such as Europe, East Asia and Africa where the study was conducted. The fact that the sample selection is made from different ethnic groups, which it is not homogeneous, causes inconsistency in the result of GWAS.[10]

DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

Dopamine plays a role in the regulation of motor, cognition and emotional behavior and have specific tasks in regulating motivation and goal-achieving motives. These effects are regulated by neuronal release when necessary. Dopaminergic system dysfunction causes psychiatric diseases such as schizophrenia, Parkinson's disease, and depression.[11,12] Almost all of the dopaminergic neurons are located in the mesencephalon, substantia nigra pars compact. It connects to the dorsal striatum, nucleus accumbens, and prefrontal cortex by the nigrostriatal, mesolimbic, and mesocortical pathways, respectively.

It plays a role in cognitive functions in the relevant cerebrum regions.[13] Brain imaging studies for schizophrenia reveal a reduction in the entire cortical surface area and thickness. The regions with the greatest reduction are shown as frontal and temporal lobes.[14] The cerebral atrophy that occurs in these regions is thought to be related to the disruption in the dopaminergic pathway. Since, phospholipase C-calcium pathway is induced in neurons exposed to dopamine for a long time, and cortical apoptosis occurs by stimulation of calcium cytochrome C release and activation of caspase pathways. Therefore, atrophy occurs.[15]

In addition, the discovery of antipsychotic drugs that affect dopaminergic function has increased the consistency of the dopamine hypothesis of schizophrenia on the etiology of schizophrenia.[16] Antipsychotic drugs that are still widely used in the treatment of schizophrenia are usually dopamine postsynaptic receptor antagonists.[17] For example, aripiprazole and amisulpride are agents that provide postsynaptic dopamine D2 receptor blockage. They enable the elimination of positive symptoms related to increased dopamine sensitivity. Depending on the dopamine level, they might also exhibit partial agonist behavior or exhibit presynaptic receptor antagonism. Therefore, they might increase psychosis as an adverse effect.[18,19]

Catechol-O-methyltransferase (COMT)

The COMT gene encodes an enzyme involved in the catabolism of catecholamines such as dopamine, epinephrine, catechol estrogen. There are two forms of this enzyme, a soluble form (S-COMT) and a membrane-bound form (MB-COMT).[20] In experiments with COMT knockout mice, in the absence of dopamine transport, dopamine levels increase in the whole cerebrum, mostly in the prefrontal cortex.[21] Catechol-O-methyltransferase can be included in the suspect gene group as it is associated with increased dopamine activity. In addition, COMT is among the suspected genes in PGC2.[7]

Alterations occur in the enzyme structure with SNVs. With G> A (rs4680) SNV, a relatively low enzyme activity occurs when methionine is replaced by valine at the 158th amino acid position in the wild type.[22] Valine is a more apolar amino acid compared to methionine. Proteins with more hydrophobic amino acids in their outer layer are more stable. With the G> A transmutation, enzymes with a lower half-life of methionine allele are produced. Dopamine activity increases as a result of reduced catecholamine catabolism. Therefore, SNV mutations increase the effectiveness of dopamine,

which contributes to schizophrenia symptoms by decreasing enzyme activity.[23] According to the dopamine hypothesis, increased dopamine would trigger increased psychosis.[24,25]

However, although it seems unreasonable considering the above inferences, there are also experimental studies in which the COMT-Val allele instead of the COMT-Met allele is associated with the disease. Patients with the COMT-Met allele have been reported to have better neurocognitive activity.[26] It has also been demonstrated that the dopamine level has a changing activity in the prefrontal cortex. This relationship can be compared to the inverted "U" shape. Dopamine concentration should be within a certain level range. It causes dysfunction in both as insufficient and as excess.[27,28]

Dopamine Receptor D2 (DRD2)

Dopamine receptor genes divide into two classes as, D1 (D1 and D5) and D2 (D2,3,4).[29,30] Although these two enzyme classes have mutual domains, they show different pharmacological characteristics. D1 class dopamine receptors are generally located in postsynaptic neurons. With the G-protein activity, adenyl cyclase and then the secondary messenger cAMP (cyclic adenosine monophosphate) are released and the cellular response is provided. D2 class receptors provide adenyl cyclase inhibition. Unlike those in the D1 class, they are located in postsynaptic and presynaptic dopaminergic neurons.[31,32] In addition, there are differences between these gene groups as intron exon structures. D1 class receptors do not have introns. However, D2 class has intron and exon regions. Different forms of these receptors can be formed by alternative splicing in the cell.[33]

D2S and D2L are variants of the dopamine D2 receptor. Dopaminergic neurons auto-control dopamine secretion depending on the intracellular calcium signal concentration. These two forms work together in the dopaminergic neuron autoinhibition mechanism and control dopamine secretion.[34] The D2S form is located in the presynaptic neuron and the D2L variant is mostly located in the postsynaptic neuron. Presynaptic D2 receptors cause auto inhibition of dopamine release according to extracellular dopamine concentration. Postsynaptic D2 receptors show activity according to the presence of D2 agonist in auto control. Presynaptic dopamine D2 receptors are more responsive to receptor agonists. These differences affect dopamine metabolism and thus the behavior of the individual.

The concentrations of the D2S and D2L variants mentioned earlier contribute to the biphasic effect of D2 receptor agonists (such as aripiprazole and cannabidiol) used in the therapeutic treatment of psychiatric disorders.[35-37] Almost all of the clinically successful drugs used in the treatment of schizophrenia and bipolar disorders provide dopamine D2 receptor blockage. Therefore, this is the key reason of DRD2 has a place in the etiology of schizophrenia.[38,39] One of the SNVs presented in PGC2 is rs2514218. This SNV is located 47 kbp upstream of the DRD2 gene initiation site on chromosome 11. The rs2514218 polymorphism represents the C> T nucleotide transmutation. The risk allele C is wild type.[7] With postmortem analysis, it was not determined that rs2514218 contributed to the increase in allelic expression in the striatum.[40] However, a study was conducted to determine the relationship of this allele to anhedonia and its effect on prefrontal cortex volumes in a group of Russian samples.[41] The sample group was formed by selecting healthy individuals (without schizophrenia). Although the contribution of the allele to gene expression was not determined, it was determined that there was an anhedonia relationship and a thinned prefrontal cortex structure in the samples containing the risk allele. In conclusion, the risk allele contributes to the pathogenesis of schizophrenia, but there is not enough resource to determine of its role in the genome.

GLUTAMATE HYPOTHESIS OF SCHIZOPHRENIA

Dopamine activity increased by methamphetamine can produce positive symptoms of schizophrenia.[41] The dopamine hypothesis is associated with positive symptoms in schizophrenia.[42] However, it is insufficient to explain the negative symptoms. Almost all antipsychotic drugs have been reported to interact with dopamine receptors.[17] Except in exceptional cases, all other dopamine receptor antagonist drugs such as clozapine are known to reduce positive symptoms but not affect negative

symptoms.[43] Atrophy resulting from long-term dopamine exposure might be associated with negative symptoms, but not with the severity of symptoms.[15,44,45]

Glutamate is the most abundant neurotransmitter in brain tissue. It is found in 5 to 15 mmoL/kg concentration.[46] Glutamate uptake into cells in brain tissue is excessive and has a stimulating effect.[47,48] It provides cell signaling and activation of secondary messengers by binding to ionotropic channels in the postsynaptic cell.[49] The most well-known of these ionotropic channel receptors are N-methyl-D-aspartate (NMDA) receptors.[50] Glutamate acts as an agonist by binding to the NMDA receptor and provide calcium passage into the cell.[51] It has a multi-subunit structure and is not specific to glutamate.

However, there are subunits to which neurotransmitters specifically bind. While the GluN1 subunit is specific to glycine, GluN2 is the region where glutamate binds and activates the channel.[50] Phencyclidine (PCP) and MK-801 are NMDA receptor antagonists.[52] These substances terminate the agonist effect of glutamate and cause schizophrenia psychosis. Schizophrenic psychosis is seen in individuals with the use of PCP.[53] These substances are also used to form animal models of schizophrenia.[54] Thus, it has been suggested that schizophrenia is caused by a decrease in NMDA receptor activity, therefore, glutamate deficiency is the factor that causes psychosis in a person with schizophrenia. This hypothesis is called the glutamate hypothesis of schizophrenia.[55]

Glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A)

The NMDA is an ionotropic receptor densely located in the cerebral cortex and hippocampus. GluN1 is formed by the combination of different subunits, the obligatory subunit, in the form of tetramer in different compositions.[49] The GRIN2A is the gene encoding GluN2A, one of the subunits of NMDA, which is a glutamate receptor. The rs9922678 variant of GRIN2A, PGC2, is one of the SNVs associated with schizophrenia. G> A refers to the nucleotide transmutation occurring in the intron region of the gene.[7] However, models for the association of this risk variant with the disease have not been investigated. The contribution of the risk allele to the disease etiology remains unclear.

One of the variations associated with schizophrenia is the change in promoter activity. The NRG1A gene has T-G repeating sequences in the promoter region. In the control group comparisons, these repetitions were higher in schizophrenia patients compared to the control group and were associated with their role in disease etiology. Elongation in repeat regions causes alteration in promoter activity and leads to decreased gene expression.[56] According to the glutamate hypothesis, this mutation would cause a disruption in glutamate signal due to the decreased glutamate binding site.[55] It has been reported that this variation causes an increase in the incidence of alcohol dependence and schizophrenia.[57]

Neuregulin-1 (NRG1)

Neuregulin-1 (NRG1) is a protein involved in cell-cell interactions. It is encoded from the NRG1 gene. It plays a role in the formation of tissue systems and differentiation of organs.[58] The gene product is the ligand of the ErbB receptor that plays a role in a neurodevelopmental pathway. ErbB is a tyrosine kinase receptor. Neuregulin-1 binds to these subunits, resulting in many cellular responses as neuronal migration, cell differentiation, cell proliferation.[59] Schizophrenia linkage studies have shown that the region of chromosome 8p21-22 is the schizophrenia risk zone in the Irish sample group.[60] This region is the NRG1 gene region. It is a large reading zone covering 1 million 100 thousand base pairs. Different subtypes are formed by alternative mRNA segments. They are examined in six groups classified as Type I-VI. Epidermal growth factor (EGF) is the E130 exon and is an essential domain. It is included in all six groups.[61] There is an immunoglobulin-like region in Type 1,2,3,4 NRG1. In addition, this area is associated with epidermal growth factor. In addition, type-3 serves as a transmembrane signaling molecule unlike others.[62,63]

The mouse model was used to determine the relationship of the NRG1 gene disruption to schizophrenia. The NRG1 gene is an essential gene for life. Therefore, mutant mice were used to study the function of a single allele in the NRG1 gene. It was aimed to determine whether schizophrenia-like behaviors would occur during

the developmental period. Neuregulin-1 single allele knockout mice have been reported to have symptoms of aberration and hyperactivity disorder in the startle reflex test. It has also been reported that this mutation causes a change in glutamate activity by lowering NMDAR levels.[64,65] There are other studies on the effect of NRG1 variants of the gene on schizophrenia. The first is the study in which NRG1 gene exons were sequenced and compared to look for SNV differences in Iceland. The link between SNVs and disease has been found.[66] However, this is just a link study between a small group. Later, studies conducted with different ethnic group sample groups provided more evidence for gene-disease relationship. Similar studies were conducted in England and Scotland, but no major differences were observed between significance levels (p=0003 and p<0.04, respectively).[67,68]

Mutations are the main causes of differences within species. They can also occur in the external parts of the genes that turn into proteins. They may not contribute to the structure of the gene product, but may cause a change in the amount of expression. rs6994992 is a polymorphism located in the promoter region of the NRG1 gene.

Variations have been found to be functional by promoter and regional mutagenesis assays.[58] Dorsolateral prefrontal cortex and hippocampus have also been associated with an increase in NRG1-type IV. The rs6994992 A> T transformation occurs as the risk allele.[69] Neuroimaging studies have also been conducted in connection with this risk allele. Low neuronal connectivity and abnormal brain morphology have been observed.[69,70] Due to the low hippocampal and cortical volume, there is a decrease in sensory function and cognitive activity with negative symptoms of schizophrenia. Having more data related to the subject would enable more accurate inferences. However, studies have supported the link between the NRG1 rs6994992 A> T allele and the disease.[71]

DISC1 (DISC1 Scaffold protein)

In a pedigree analysis conducted in Edinburgh, an autosomal inherited abnormality was discovered in a Scottish family. It has been determined that a gene region is disrupted by a balanced translocation between chromosomes 1 and 11 and two genes are disrupted by the breakage on chromosome 1 and one of them encodes a protein. These genes are DISC1 and DISC2.[72] DISC1 encodes a protein located in the cytoskeleton and involved in synaptic plasticity.[73] Impairment caused by translocation can also be associated with autism spectrum disorder other than schizophrenia.[74]

The DISC1 protein consists of 850 amino acid units. It can be divided into two main regions. The N-terminal region (first 350 amino acids) is the head and the remaining part is the tail. While the head part contains mostly evolutionary unprotected motifs, the tail part contains relatively more conserved regions. That is, the tail region differs less between species.[75] DISC1 is a protein that can form multimers. It provides this with amino acids 403-504 remaining in the tail region. It forms octamers first followed by dimers.[76] It can form a multimeric structure with many interactive proteins. Glycogen synthase kinase 3 (GSK3), Phosphodiesterase 4 (PDE4), phosphodiesterase 4B (PDE4B), Growth factor receptor-dependent protein 2 (GFRB2) are some of the DISC1 interactors.[77-80] DISC1 usually tends to bind to 1 interactor. In the case of binding to excessive interactors, it can form aggregates by performing overexpression.[81] The insoluble form DISC1 is responsible for physiopathology. There are also studies showing that DISC1 aggregation is achieved through dopamine control.[82]

As in all neuropsychiatric diseases, neurodegeneration is present in schizophrenia.[83] DISC1 is localized in postsynaptic neuron dendrites. DISC1 mutations have been associated with neuroplasticity. PDE4B is a protein that can interact with the N and C-terminals of DISC1. The cAMP secondary messenger is activated by the interaction of DISC1-PDE4B. GluA1, the AMPA receptor subunit, is phosphorylated. As a result of this interaction, there is a change in neuronal activity by suppressing protein kinase A activity.[84] This pathway cannot be activated in L100P mice with a mutation in the PDE4B binding region. These mice exhibit increased schizophrenia attitude. Decreased PSD95 and pCREB protein expression was also detected in the occipital lobe. These findings suggest that DISC1 plays a role in neuronal plasticity.[73]

In conclusion, schizophrenia has been proven to be substantially inheritable by twin

studies and ancestry analysis. However, due to the absence of a biochemical marker that cannot be associated with the etiology of the disease, making it difficult to determine the genes of schizophrenia. With the discovery of antipsychotic drugs, hypotheses on disease etiology have been suggested. The dopamine hypothesis is one of them. With the observation that dopamine receptor antagonist reduces the positive symptoms of schizophrenia, it has been thought that there is a problem in genes involved in the dopaminergic pathway. Studies have shown that dopamine D2 receptor has been associated with schizophrenia, but it has been observed that the variation in this gene is not responsible for all disease symptoms. In this case, schizophrenia emerges as a complex disease in which a gene affects more than one phenotype (pleiotropy) and co-expressions with other genes are involved in the process. However, despite these special functions of genes, there are also common points. These are the neurotransmitter pathways involved in synaptic transmission. The basic principle of action of antipsychotic drugs is to change the activities of the receptors on these pathways. In this way, schizophrenia diseases based on different genetic bases can be treated with the same psychiatric drugs. Suspicious genes can also be detected by comparing the genomes of the sick group and normal groups. This is a very good method to get a general view. However, the fact that not every gene contributes to the etiology of the disease at the same rate causes these tests might not be fully satisfactory.

In addition, the allele frequency of an allele with a very high contribution to disease development might be too low, or genetic heterogeneity may prevent this effect from being observed. Therefore, a meaningful result cannot be obtained in the comparison made. Reproducible studies in which the effects of gene variations are determined would provide us to make inferences from data instead of predicting about the disease. More studies are needed to analyze gene and phenotype relationships.

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