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Review

Association of NOS1AP Variants in Schizophrenia

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ABSTRACT

Schizophrenia is a mental disorder that affects about 0.5-1% of the general population. The word schizophrenia originated in the Greek language and it comes from the combination of the words "schizo," which means divided (schizein, σχίζειν) and the words "frenos," (phren, φρεν). There are several genes linked to schizophrenia. One of them is the nitric oxide synthase 1 adapter protein (NOS1AP) gene. It shows that excessive expression of long isoform (NOS1AP-L), short isoform (NOS1AP-S) and a novel short isoform (NOS1AP-S') of NOS1AP alters the actin cytoskeleton and synaptic function. These three isoforms were found to be linked to actin-myosin and N-methyl-D-aspartate receptors. The alteration caused by the mutation in this gene and signal pathways has an influence on schizophrenia. In this review, the link between schizophrenia and NOS1AP was investigated.

Keywords: Actin, CAPON, exon, NMDA, NOS1AP, schizophrenia, single nucleotide polymorphism (SNP)

Schizophrenia is a mental disorder that affects around 0.5-1% of the general population.[1] The word schizophrenia originated in the Greek language and it comes from the combination of the words "schizo," which means divided (schizein, σχίζειν) and the words "frenos," (phrēn, phren-φρήν, φρεν-). It means that one believes in two different realities at the same time and not in two personalities.[2] Since the cause of this disorder was not known as pathology in the first studies, it was first known by Kraepelin and Bleuler as "dementia praecox" and "premature dementia".[3] Schizophrenia is a severe mental disorder associated with neurodevelopmental. The behavior of individuals with this disorder has been proven by studies of both mental and material responses.[4] Recent studies show that the population with schizophrenia is approximately 80%.[5] The schizophrenia frequency rate in the general population is about 10% in the first-degree relatives of the person with schizophrenia, meaning the risk for the patient's first-degree relatives is 10-20 times that for the general population. This rate drops as kinship moves away.[6] Among the causes of schizophrenia are genetic and environmental factors that largely contribute to schizophrenia.[7] It is a chronic, debilitating neuropsychiatric disorder with multiple risk factors involving multiple complex genetic effects.[8] This condition has three types of symptom scales: positive, negative, and cognitive symptoms.

Positive symptoms: These can be defined as "psychotic behaviors that show the difference with healthy people" and are most easily defined in this disorder. Symptoms include delusions, hallucinations, and abnormal motor behavior of varying degrees of severity.

Negative symptoms: It is a condition that is seen in healthy individuals. These symptoms include loss of motivation (amotivation), inability to enjoy things that used to be enjoyable (anhedonia), and asociality.

Cognitive symptoms: Moderate in a variety of areas, including attention deficit hyperactivity disorder, working memory, learning, and memory.[9]

In controlled neuropathology in individuals with this disorder, the appearance of structural changes in the brain (white matter, gray matter, size) led to the idea that schizophrenia could be a true psychosomatic

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disorder. The onset of the horizontal is sudden and insidious. The estimated timing of emergence: late adolescence or 40-50 years in the middle. In cases noticed late, episodic memory (memory of daily events) worsens, making prognosis (diagnosis) difficult.[10]

The onset of schizophrenia in utero (uterus) is one reason for its development.[11] Obstetric complications such as bleeding during pregnancy, gestational (pregnancy) diabetes, emergency cesarean section, asphyxia (lack of pulse), and low weight have been associated with schizophrenia later in life.[12] Fetal disorders, a key stage in fetal neurodevelopment during the trimester, have been investigated by researchers. Infections and extreme stress levels during this period doubled children's risk of developing schizophrenia.[13]

According to the International Classification of Diseases (ICD)-10 there are clinical subtypes of schizophrenia: Paranoid, hebephrenic, catatonic, undifferentiated, post-schizophrenic depression, residual, simple schizophrenia, and other schizophrenia.[14,15]

Paranoid schizophrenia: It is a common form of schizophrenia. The positive symptoms of the disorder predominate. Individuals hear voices with pronounced hallucinations. There are obvious delusions. Speech and emotions may not be affected.[16]

Hebephrenic schizophrenia: Irresponsible and unpredictable behaviors, distinctly messy thoughts, problems with speech, being nerdy, self-joking, and giggling are among the symptoms. This symptom is usually diagnosed during adolescence or in adults.[17]

Catatonic Schizophrenia: Observed rarer than other symptoms. Not wanting to talk, unusual movements, or being too still.[18]

Many of the symptoms seen in other subtypes occur in these patients, and the symptoms are of similar dominance.[19,20]

Abnormalities in neurotransmission have formed the basis of theories on the pathophysiology of schizophrenia. Research has revealed that excess or deficiency of neurotransmitters, including dopamine, serotonin, and glutamate, cause schizophrenia.[21] Another reason; includes mutations that occur in aspartate, glycine, and gamma-aminobutyric acid (GABA).[22]

Accurate communication between neurons depends on the proper modeling of dendrites and the correct distribution and structure of spines. Schizophrenia is a neuropsychiatric disorder characterized by changes in the intensity of dendritic branching.

NOS1AP AND SCHIZOPHRENIA

Nitric oxide synthase 1 adapter protein (NOS1AP), is one of the risk genes for schizophrenia. This gene encodes proteins regulated in the dorsolateral prefrontal cortex (DLPFC) NOS1.[23] AP protein 1st in the chromosome (1q23.3).[24] The NOS1AP protein was first identified as the neuronal nitric oxide synthase (nNOS) binding factor in the rat. It was originally used as the carboxy-terminal PDZ ligand of neuronal nitric oxide synthase (CAPON) protein.[25] In line with research, it turns out that NOS1AP has three variant isoforms. These variants are NOS1AP-L (long isoform), NOS1AP-S (short isoform), and NOS1AP-S' (a novel short isoform).[26]

NOS1AP-L is a protein from the exon and contains 501 amino acids. The event thus described includes the 1 to 10 e exon region of NOS1AP-L, the NOS1AP-S' 15kDA region, and the carboxyl-terminal PDZ-binding domain. NOS1AP-S is characterized by a; 5' exon and transcriptional start site. This isoform contains two functional areas, the N-terminal phosphotyrosine-binding (PTB) area and the C-terminal PDZ-binding area. When the last two exons are copied; NOS1AP-S consists of 211 amino acids and also contains the PDZ-binding motif in the carboxyl-terminal.[27]

NOS1AP has a C-terminal PDZ-connecting area, which is responsible for the interaction of nNOS.[28] The area responsible for connecting to DexRas1, synapsin, and scribble is the PTB area of NOS1AP-L.[29] In a recent study; with the help of an area (amino acids 181-307) located in the middle of NOS1AP-L, it was revealed that interacts with carboxypeptidase E (CPE) and NOS1AP regulates dendrite morphology with this interaction. Overexpression of NOS1AP-L has been found to significantly reduce dendrite numbers. NOS1AP-S has been revealed to increase overexpression dendrite numbers.[30]

There are many genes that act on schizophrenia. One of them is NOS1AP. It is estimated that there are between 50 and 100 single nucleotide polymorphisms (SNPs) to fully evaluate NOS1AP for association with schizophrenia.[31] There are different factors that this gene creates for schizophrenia. One of them is the differentiation of the actin cytoskeleton by reshaping is a common problem shared among

various risk factors for schizophrenia both NOS1AP-L and NOS1AP-S combine with F-actin.[32] With this interaction, it connects both isoforms to the actin cytoskeleton. There are different factors that this gene creates for schizophrenia. One of them is the differentiation of the actin cytoskeleton by reshaping is a common problem shared among various risk factors for schizophrenia.[33] Both NOS1AP-L and NOS1AP-S combine with F-actin. With this interaction, it connects both isoforms to the actin cytoskeleton. When NOS1AP-L and NOS1AP-S were overproduced, it became apparent that the actin cytoskeleton had been stopped from reshaping. NOS1AP-L and NOS1AP-S have different mechanisms of action. NOS1AP-S has been proven to increase the activation of GTPase Rac1 and the PTB field of NOS1AP-L is responsible for this activation.[34] The Rho family of GTPase consists of intracellular regulators of spinal development, such as Rac1, affecting the actin cytoskeleton.

Research has shown that a NOS1AP-L mutant state lacking a PTB field can rearrange the actin cytoskeleton but does not prevent it from moving out of the membrane as observed by excessive expression of NOS1AP-L.[35] NOS1AP, neuronal nitric oxide synthase is known to interact with the PDZ field (nNOS or NOS-I encoded by the NOS1 gene) as well as an ExF motif and a PDZ-motif.[36] The link between the NOS1AP and the PDZ field suggests a heterodivalent interaction. In neurons, nNOS is linked to the postsynaptic density (PSD) of glutamatergic synapses through interaction with the PDZ2 field of PSD-93 or PSD-95.[37] This interaction brings nNOS closer to N-methyl-D-aspartate (NMDA) receptors, providing NMDA receptor-dependent Ca^{+2}.[38]

Neuronal change to activate NOS1AP also leads to regressive effects.[39] It is strongly argued that NOS1AP is an important effector component for glutamatergic signal pathways, and in doing so psychiatric disorders facilitate phenotypic diagnosis.[40] Phenotypically one of the most effective diagnostic stages is the study of brain structure disorder with brain imaging studies.[41] Despite the increase in NOS1AP the important role of neuronal nitric oxide signaling in the hippocampus, the potential involvement of mRNA, hippocampal NOS1AP in patients suffering from schizophrenia, and its link between the nNOS/PSD-95/NMDA receptor complex and different endophenotypes of severe mental disorders, are yet to be investigated in detail.[42] Research has shown that NOS1AP, which is necessary for NMDA/nNOS/NOS1AP, is overexpressed in order to further clarify the neural and behavioral effects affected by NOS1AP due to impaired NOS1AP/nNOS signaling, thereby solving psychiatric phenotypes.[43-44] Wild-type mice were also incorporated into the literature in the study, in which they influenced the interaction in the hippocampus and the resulting changes in gene expression, neuronal morphology, and behavior.[45] In a 2009 study, 24 Canadian families of European descent were selected for the study because they were clinically diagnosed with schizophrenia or schizoaffective disorder.[46] Postmortem samples from the dorsolateral prefrontal cortex were collected to find out if there was a link between markers in NOS1AP and schizophrenia. In this study, 60 SNP regions of NOS1AP were studied by transferring each allelic variant of the SNP with a vector containing the NOS1AP promoter and a luciferase gene.[47] Allele regions whose expression underwent change were further strengthened by evaluating them with electrophoresis methods for binding proteins. Some region mutations of NOS1AP investigated for schizophrenia are respectively: In exon 6 rs3751284 (C>T), exon 9 rs348624 (C>C), exon 10 rs164146 (G>C)/rs164147 (C>A), intron 2 rs10918776 (G) >C), intron 3 rs10800405 (C>G), intron 5 rs347306 (C>T) and rs347307 (T>C), intron 6 rs3751285 (A>G), intron 8 rs905721 (C>T), intron 9 are regions with rs1964052 (T>T). As the studies progress, there is an increase in the regions that are looked at and examined.[48]

In a recent study, 24 regions were scanned for SNPs. SNPs are scattered in intron and exon regions. These SNP areas; rs1572495, rs1538018, rs945713, rs1415263, rs3924139, rs4145621, rs2661818, rs3751284, rs348624, rs12090585, rs11579080, rs6664602, rs4592244, rs4657179, rs4656362, rs6680461, rs4657181, rs10800405, rs1504430, rs17468951, rs12122048, rs905720 , rs1123005, rs11806859. They showed that the expression of schizophrenia increased significantly.[49,50] The association of different SNPs within the NOS1AP with schizophrenia was proven in a Chinese and South American population sample to be associated with schizophrenia, further strengthening the link between NOS1AP and schizophrenia.[51-52]

A study collected samples from the cerebellum found in the brain of healthy and sick individuals who died to learn about NOS1AP's connection to schizophrenia. To assess the expression levels of these two NOS1AP isoforms in human brain tissue, samples were taken at the Brodmann area (BA) 46, BA11, medial temporal lobe (MTL), and occipital lobe (OL).[53]

According to results from the Human Brain and Spinal Fluid Resource Center (HBSFRC), actin

normalization and glutamate receptors with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) marker were analyzed using Western blot. Logarithms of normalized values for the brain taken from the same area for the schizophrenia sufferer and normal individual, standard t-test ($p<0.05$ (nominal)). In BA46 of schizophrenia patients reported, L (long) p=0,0067, S (short isoform) p=0.0082, and S (short) p=0.0041. These data are consistent with previous studies implying a dominant schizophrenia etiology in this region. NOS1AP is also shown to have a role in glutamate receptors and schizophrenia.[54]

NOS1AP long and short isoforms were not only confined to the brain but were also detected in the testicle, prostate, small intestine, blood leukocyte, heart, placenta, lung, kidney, and pancreas.[55-57]

In conclusion, one of the most dominant theories is that schizophrenia is a neurodevelopmental disorder. Up to 60 SNP mutations have been identified for schizophrenia in the NOS1AP gene by this time. These mutations are expected to increase and research is ongoing. The cause of these mutations has been proven to be linked to altered schizophrenia in the actin cytoskeleton-dependent glutamatergic and NMDA neurochemical structures. This gene, along with schizophrenia, has been reported as a result of research that causes disorders such as depression, autism, heart conditions, and Alzheimer's. It is thought the NOS1AP could reduce schizophrenic effects, a new step into future studies, where it could regulate neurodevelopmental processes.

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