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Review

Neuregulin 1 and Its Roles in Schizophrenia: A Systematic Review

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ABSTRACT

Schizophrenia is a complex disease with a multifactorial inheritance model, characterized by self-esteem and thought disorder. Neuregulin 1 (NRG1) gene is among the schizophrenia genetic factors. This gene plays a role in the erythroblastic leukemia viral oncogene homolog (ErbB) signaling pathway and many biological processes. Symptoms of schizophrenia are observed with the impairment of NRG1's function in the ErbB4 signaling pathway. As a result of its overexpression, it is known that there is an important relationship between the dysfunction of N-methyl D-aspartate receptors and schizophrenia. It is also supported by epistasis studies, gene expression studies, studies investigating the relationship between mental state and psychosis, and genotype-phenotype correlation studies. In this review, the connections of the NRG1 gene and schizophrenia were discussed.

Keywords: ErbB, neuregulin1 (NRG1), neurodevelopment, schizophrenia

Schizophrenia is a neurodegenerative psychiatric disorder in which thought and sense of self are impaired and reality is indistinguishable. Delusions have clinical symptoms such as loss of abstract thought, withdrawal from society/withdrawal (social communication disorder), perception disturbances, mood swings, disorientation, impulse deprivation, arousal, and catatonic excitation, sleep disturbance and wasting genetic factors, structural changes in the brain, neurochemical and neurophysiological changes and endocrine factors are factors that play a role in the etiology of schizophrenia with a prevalence of 81%, genetic factors play a significant role in the inheritance of schizophrenia.[1-3]

In determining the genes that cause susceptibility in schizophrenia, candidate genes are determined with the help of bioinformatics methods using genetic linkage and association studies. Neuregulin 1 (NRG1), Catechol-O-methyltransferase (COMT), dystrobrevin-binding protein 1 (DTNBP1), D-amino acid oxidase activator (DAOA), disrupted-in-schizophrenia-1 protein (DISC1), Epsin 4 (EPN4) genes are among the genes that cause susceptibility to schizophrenia.[4-7]

Disruption of the regulation abilities of epigenetic mechanisms can cause schizophrenia by affecting neurodevelopment. Neurodegenerative disorder such as schizophrenia occurs as a result of mutations in NRG1, Ankyrin 3 (ANK3), Neuritin (NRN), and transcription factor 4 (TCF4) genes that play a role in neurodevelopment.[8]

The NRG1 gene is a subfamily of epidermal growth factor (EGF)-like molecules that are located in the p arm of the eighth chromosome, have six types of isoforms, and have a role in many processes including embryogenesis. This gene has many molecular functions; It takes part in embryogenesis, organogenesis, neuronal development, differentiation, and regulation of nervous system cells. It is also an important gene linked to neurodegenerative disorders such as schizophrenia and Alzheimer's disease.[9,10]

Studies investigating the relationship between the NRG1 gene and schizophrenia and its relationship with epistasis, mental state, and psychosis show that it is effective on schizophrenia in the light of the

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information obtained as a result of gene expression studies and genotype-phenotype correlations.[11-27]

NEUREGULIN 1

Neuregulins are a subfamily of epidermal growth factor (EGF)-like molecules that have important roles in embryogenesis. They are involved in cardiac development, differentiation of Schwann cells and oligodendrocytes (neural cell differentiation and regulation), some stages of neuronal development, and the formation of neuromuscular synapses. Heregulin (HRG) is in the neuregulin family, a differentiation factor; inducing the synthesis of acetylcholine receptors; glial growth factor; It is a sensory and motor-neuron origin factor. Family members are formed by the alternative splicing pathway or through transcription initiation regions specific to certain cell types. They enable the activation of receptor tyrosine kinases by binding to the erythroblastic leukemia viral oncogene homolog 2 (ErbB2/HER2), erythroblastic leukemia viral oncogene homolog 3 (ErbB3/HER3), and erythroblastic leukemia viral oncogene homolog 4 (ErbB4/HER4) families.[10]

Neuregulin has six isoforms: type I, type II, type III, type IV, type V and type VI. These isoforms are classified according to their amino-terminal sequences. The amino-terminal sequence in type III isoforms includes a cysteine-rich domain (CRD) that has the transmembrane domain (TMn). All isoforms have an EGF-like domain. While types I, II, IV, and V link to the EGF domain after binding to a domain like an immunoglobulin (Ig), independent of the presence of the spacer region (S); types III and VI bind directly to the EGF domain. Variants are created by splicing in the linker and C-terminal regions. The C-terminal transmembrane domain (TMc) is located between the linker and the C-terminal regions.[28]

Most NRG1 isoforms are synthesized as pro-NRG1 (membrane-bound NRG1 isoforms) with the EGF domain found outside the cell. Pro-NRG1's are named as pro-NRG1 type I-VI according to the sequence they contain. In the type III isoform, unlike other isoforms, the N and C-terminal regions are located inside the cell. Pro-NRG1s undergoes proteolytic cleavage by type I transmembrane proteases such as tumor necrosis factor-alpha (TNF-α) converting enzyme (TACE, ADAM17), beta-site amyloid precursor protein cleaving enzyme (BACE, memapsin-2), and meltrin-beta (ADAM19).[29-33] Due to this separation, mature NRG1s are synthesized, but this event does not occur in the type III NRG1 isoform. In some isoforms, they are synthesized and released directly into the extracellular space without the need for a transmembrane protein.[34] The neuronal activity provides pro-NRG1 expression and regulation of this process.[28]

The expression levels of NRG1 isoforms differ specifically for the brain and various tissues. Different expression levels due to this specificity also result in abnormal expression of some isoforms in schizophrenia patients.[28,35,36]

The NRG1 acts by stimulating ErbB proteins.[37] ErbB1 is an epidermal growth factor receptor (EGFR) and although it cannot bind NRG1, it can form a heterodimer with ErbB4 protein. ErbB2 is a protein that acts as a co-receptor by forming heterodimers with ErbBs attached to the ligand.[38] When the ErbB3 protein binds to NRG1, its homodimers become catalytically inactive, so the kinase cannot function.[39] ErbB4 is only a protein specific to NRG1 that can interact with the ligand.[38]

Any defect in NRG1/ErbB signaling causes schizophrenia. In particular, ErbB4 loss decreases interneurons density in the postnatal cortex. A variable number of GABAergic neurons is formed as the density of interneurons decreases and their differentiation deteriorates. With the change in their expression in NRG1 and its isoforms, the regulation of migration of GABAergic interneurons is lost. This situation is related to the neurodevelopmental pathology of GABAergic interneurons observed in schizophrenia.[40-42]

Neuregulin regulates the function of N-methyl-D-aspartate (NMDA) receptors in the brain.[43] Postsynaptic density protein-95 (PSD-95) is a protein associated with plasticity. PSD-95 binds with ErbB4 and NMDA receptors at synapses and increases NRG1 signaling by facilitating ErbB4 dimerization.[44,45] NRG1 increases the translocation of the C-terminal fragment (CTF) to the nucleus through synaptic activity. The transcription of PSD-95 increases by binding to the CTF transcription factor Eos.[46] NRG1 overexpression reduces NMDA receptor-mediated synaptic signaling.[47] This suggests a link with the dysfunction of NMDA receptors that occurs in schizophrenia.[48] Specifically to NRG1 isoforms in the nervous system; In the developmental stages of the organism, glia, and neurons, and also in the interactions of these cells, they have roles that have short or long-term effects.[49-55] Most NRG1-affected processes are common to processes and pathways in schizophrenia.[56]

GENETIC FACTORS OF SCHIZOPHRENIA

Schizophrenia is a neurocognitive disorder characterized by delusions, hallucinations, uncoordinated behavior, and impairments in social skills (social communication disorder).[57-59] Family studies, twin studies, and adoption studies were carried out to clarify the genetic etiology of schizophrenia.[2,60] Incidence of schizophrenia in family studies with heritability rate; concordat rates in monozygotic and dizygotic twins in twin studies; in adoption studies, the effect of genetic and environmental factors were examined comparatively. As a result of these studies, the effect of heredity has been confirmed as a risk factor for it. In schizophrenia etiology, genetic factors are of great importance with an 81% heritability rate and environmental factors have an 11% rate.[2] Genetic studies have focused on the 5th, 6th, 8th, 13th, and 15th chromosomes, which are thought to be particularly related to it.[59] Its concordat rates were found to be more critically high in identical twins than double identical twins and siblings.[61]

The lifetime risk of developing schizophrenia was 0.85%-1% in the general population, while the risk of developing it in children of the family from which a parent inherited it was observed was 10%-15%. If it is inherited by both parents, it is concluded that this rate is increasing to 40%.[62]

In the twin studies, it was determined that the concordat (harmony) ratio between monozygotic (identical) twins was higher than the concordat rate between dizygotic (double egg) twins.[61]

Adoption studies have reported no significant difference between the rate of schizophrenia seen among children adopted from a schizophrenic family, in a family that was separated after birth or not schizophrenic.[62]

After family, twins, and adoption studies determined that schizophrenia was largely inheritable, studies continued to find genes or genes that cause it. Linkage and association studies are used at the molecular level to find genes that cause schizophrenia predisposition. The studies look at whether the disease is inherited through genetic markers in families with at least two individuals affected by schizophrenia. Chromosome regions with genetic markers are considered risk zones that may carry schizophrenia predisposition genes. These regions are examined by bioinformatics or molecular methods and then-candidate genes are determined. The relationship between genes and the disease is determined by the examination of the polymorphic points carried by the candidate genes and the data obtained as a result of the examination of the distribution of the disorder in the population.[63]

The genes determined as a result of the candidate gene studies associated with schizophrenia predisposition: 22q11-q12 (COMT), 8p22-p21 (NRG1), 6p22 (DTNBP1), 13q14-q32 (DAOA), 1q42 (DISC1), 1q22-q23 (C-terminal PDZ ligand of neuronal nitric oxide synthase - CAPON), 5q33 (EPN4).[4-7]

EPIGENETIC CHANGES

Epigenetics are inheritable changes in chromatin levels without any changes in DNA sequence.[64] It causes genes to change transcription by causing differences in promoter regions, so transcription can be suppressed or increased.[65] Studies showing that changes in epigenetic mechanisms are influencing the etiology of schizophrenia argue that there are mechanisms that control and regulate gene-environment interactions and their impact on the environment. If the effect of the environment cannot be regulated by epigenetic mechanisms, it is seen that symptoms of schizophrenia occur.[66]

Genes are classified according to the processes they affect in schizophrenia etiology. Those that act on neurodevelopment or neuroplasticity; ANK3, dedicator of cytokinesis 4 (DOCK4), ligand-of-Numb protein-X2 (LNX2), neurogranin (NRGN), TCF4, reelin (RELN), Autophagy and Beclin-1 regulator 1 (AMBRA1), NRG1, and proline dehydrogenase (PRODH); those that are effective in the immune system, toll-like receptor 4 (TLR-4), major histocompatibility complex, class II, DR beta 1 precursor (HLA-DRB1), prostaglandin-endoperoxide synthase-2 (PTGS2), interleukin-3 receptor subunit alpha (IL3RA), colony-stimulating factor 2 receptor subunit alpha (CSF2RA), sperm autoantigenic protein 17 (SPA17); neuroendocrine affects the system, NRGN and peptidylglycine alpha-amidating monooxygenase (PAM) and other processes are effective in ATP/GTP binding protein-like 1 (AGBL1), deleted in bladder cancer 1 (DBC1), Notch receptor 4 (NOTCH4), UDP-Glucuronosyltransferase family 1 member A1 (UGT1), polypyrimidine tract-binding protein 2 (PTBP2).[65]

The ANK3, NRGN, TCF4, and NRG1 genes were found to have an impact on neurodevelopment as a result of genome-wide association study (GWAS) studies.[8] ANK3 was observed to be low in research evaluating exercise memory functions of

schizophrenia patients with mutations in this gene by taking part in cognitive functions.[67] NRGN performs the synthesis of proteins involved in regulating postsynaptic calmodulin-Ca2+ balance[68] in neurons. It is expressed in high levels of the anterior cingulate cortex[69] and hippocampus pyramidal neurons in the neurons of the regions responsible for eccentric functions in the brain. In addition, it has important roles in long-term memory, episodic memory, visual and special memory functions, and hippocampal plasticity.[70] TCF4 was found to be effective in disrupting attention and extrusive functions by taking part in cognitive functions.[71] Toll-like receptors (TLR) are receptors in the immune system to which viruses and bacteria are attached. Inflammatory cytokines are synthesized as a result of antigen binding to TLR3 and TLR4. This inflammatory response leads to neurodegeneration, causing pathogenesis of schizophrenia and bipolar disorder.[72, 73]

GENETIC VARIATION OF THE NRG1 GENE AND ITS ASSOCIATION WITH SCHIZOPHRENIA

Neuregulin is one of the susceptibility genes for schizophrenia. Linkage and genome scans revealed that the p arm of the 8th chromosome, especially the 8p21.1-22 chromosomes, is a locus containing NRG1, one of the schizophrenia predisposition genes.[9]

Studies on the Relationship Between Mental State and Psychosis: A study was carried out that investigated the effects of the NRG1 variant associated with abnormal cortical function and its effect on psychotic symptoms. One of the single nucleotide polymorphism (SNP) of NRG1 is SNP8NRG243177. SNP8NRG243177 (rs 94942) risk is highly variable in itself with those in embedded applications. SNP8NRG243177 polymorphism is 100% associated with the development of T/T variant psychotic symptoms; C/C and C/T variants were found to be 50% related. In addition, individuals with T/T variants were found to have a lower IQ than other variants.[11] A clinical trial has been conducted examining the effect of the NRG1 variant on schizophrenia in individuals at high risk of psychosis. The previous study showed that the occurrence of psychosis was 100 percent supported in the presence of the SNP8NRG243177 variant in high-risk individuals. It was observed that individuals with the T/T genotype of this variant developed psychosis and had a low IQ as in the previous study.[12] Another comprehensive study has been created that investigates the relationship of the NRG1 variant with the transition to psychosis. This research supported the results of the two studies mentioned. rs6994992 T/T carriers as well as; rs4281084 A/A variant 46.2%; it was concluded that 44% of individuals with the rs12155594 T variant developed psychosis.[13]

Studies on NRG1's Interactions with Genes (NRG1 and Epistasis): Due to the findings of a study investigating the effect of NRG1/ErbB4 on schizophrenia; the interaction of NRG1 and ErbB4 was found to increase the susceptibility to schizophrenia.[14]

A study was carried out investigating the genes neuropathology of schizophrenia. As a result of the study, it was observed that the Val158Met polymorphism in the COMT gene increased the risk of schizophrenia and in addition, the COMT and NRG1 genes were matched on common loci. From this point of view, it's understood that the interaction of NRG1-COMT -Va158Met increases susceptibility to schizophrenia.[15] As a result of a study examining the interaction between NRG1/ErbB4 and AKT serine/threonine kinase 1 (AKT1) may be effective in schizophrenia.[16]

Neuroglycan C (NGC) is another gene that predisposes to schizophrenia. Through data from a study investigating the epistasis of the NGC gene, it was concluded that the interaction of NGC-NRG1-ErbB4 may be effective in schizophrenia.[17]

Gene Expression Studies: A study was conducted examining messenger RNA (mRNA) levels of NRG1 in the dorsolateral prefrontal cortex (DLPFC) in schizophrenia patients. Patients had a low increase in type I NRG1 expression level; expressions of type II and type III NRG1 isoforms were observed to decrease. Results from the data revealed that changes in the levels of NRG1 transcripts in the DLPFC region were linked to schizophrenia.[18] A study was conducted to investigate the relationship between SNP variants of NRG1 and schizophrenia. While the mRNA level of NRG1 type I isoforms increases in the hippocampal tissue of schizophrenia patients; there was no difference in mRNA levels of type II, III, and IV isoforms. SNP8NRG221132 was found to have an increase in type I NRG1 expression (DLPFC region) in schizophrenia patients with G/G (G homozygote) alleles; compared to patients with G/A and G/G alleles, control individuals with A allele carriers had higher type I NRG1 expression. SNP8NRG243177 was observed that individuals with T allele homozygotes had greater expression of type IV NRG1 than individuals with C/C and C/T alleles.[19] As a result of a study investigating the expression of NRG1 type III

isoform in the hippocampal tissue of schizophrenia patients, it was observed that the expression levels of those carrying the T/T allele increased compared to A/A and A/T alleles.[20]

In elderly schizophrenia patients, a study was conducted that specifically examined the expressions of NRG1 isoforms to certain tissues in the brain. Expression of type III isoforms in the ninth Brodmann region of the prefrontal cortex was more observed in control and schizophrenia patients. However, the expression level of type III and type I isoforms of the healthy group was higher compared to schizophrenia patients; the expression level of type II isoform was found to be higher in schizophrenia patients. 10th in the Brodmann region, the expression of type III isoforms is greater in both groups; expression levels of type III and type II isoforms are higher in schizophrenia patients compared to controls; the expression level of type I was found to be higher in the control group. Type I isoform in the hippocampus has high expression in both groups; expression of type III and type II isoforms was higher in schizophrenia patients; it was observed that type I isoform was more expressive level in the control group. In general, NRG1 expression is expressed more in the hippocampal tissue and the healthy group in the 10th Brodmann region; In the ninth Brodmann region, it was found that there was no difference between the expression levels of both groups.[21]

A study was carried out that examined the expressions of NRG1 type I-IV isoforms of the human brain in the fetal developmental stage in the prefrontal cortex. NRG1 type I isoform at the 15th week of pregnancy; type II isoform in 20 weeks; type III isoform is expressed the most at 39 weeks and type IV isoform at 19 weeks. NRG1 type I isoform continues to be expressed steadily in the period after birth; it was concluded that type II isoform is gradually decreasing and type III isoform is expressed steadily.[22] Due to data from a study examining the changing expression of NRG1 with age; NRG1 was found to decrease in early adulthood and then increase or persist steadily. In ErbB3, expression continues in the same case as NRG1 and the conclusion from these findings showed that ErbB3 expression decreased in the frontal cortex of schizophrenia patients.[23]

Neuregulin 1 plays a role in the regulation of the expression of alpha7 nicotinic acetylcholine receptors (α7 nAChR). A study has been conducted examining the relationship of α7 nAChR expression levels to schizophrenia. The expression level of α7 nAChR in smokers in DLPFC was higher in controls than in schizophrenic patients; In non-smoking schizophrenia patients, this level of expression was found to be higher than in the controls. When the expression levels of smokers and non-smokers in the hippocampus region were examined, it was found that they were more in the control group. In DLPFC, it was observed that the G/G and G/A variants of SNP8NRG221132 were high in α7 nAChR expression level control groups. It was found that schizophrenia patients with G/A (p=0.01) variant had a higher α7 nAChR expression level than individuals with G/G variant. RS6994992 compared to α7 nAChR expression levels in individuals with C/C and T allele variants, schizophrenia patients with variant C/C (p=0.008) had more expression than controls; Control groups with T allele (p=0.02) carriers were found to be more expressed than schizophrenia patients.[24]

GENOTYPIC AND PHENOTYPIC CORRELATIONS

A study investigated the relationship between missing schizophrenia patients and non-deficient schizophrenia patients and NRG1. SNP8NRG221533 polymorphism was seen in non-deficient schizophrenia patients, which showed that stop NRG1 was associated with non-deficient schizophrenia.[25]

It was supported by the discovery of a common locus through all genome link studies, where schizophrenia predisposition genes are also linked to psychosis-bipolar disorder. NRG1 is linked to bipolar and psychotic disorder as well as schizophrenia.[26]

The NRG1 gene was found to be associated with cognitive perception, interpersonal dysfunctions, and disorganization in adolescent individuals with the A/A variant of rs3924999 polymorphism, as well as affecting schizophrenic personality and perceptual aberrations.[27]

In conclusion, schizophrenia is not specific to any age group but is a complex disorder that is inherited by multiple factors characterized by changing the perception of the individual's perception of reality, the appearance of thought and affection disorders, the appearance of delusions, and the loss of normal functions perceptively. Dysfunctions in the NRG1/ErbB signal pathway, ErbB4 loss cause schizophrenia. As a result of excessive expression of NRG1, NMDA synaptic signaling decreases, which is explained by the dysfunction of NMDA receptors observed in schizophrenia. The processes in which NRG1 isoforms play a role in the nervous system and their effects on them are common to the processes

and pathways that occur in schizophrenia. As a result of studies investigating the relationship of NRG1 with mental state and psychosis, it was confirmed that NRG1 causes the transition to psychosis in individuals with T/T variants, and it is also associated with low IQ. The findings from NRG1's gene expression studies revealed that different types of isoforms are expressed specifically for different tissues, and these expression levels are linked to schizophrenia. As a result of studies examining NRG1 and its epistasis, it has been observed that the interaction of NRG1 with certain genes may increase the risk of schizophrenia, but it has not been confirmed and more studies need to be carried out in this field. This review supports that the NRG1 gene is one of the susceptibility genes for schizophrenia.

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