Review Article

An Overview of Genetic and Environmental Risk Factors Associated with Schizophrenia

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Abstract

Schizophrenia is a highly heritable and familial disorder. With current testing methods, the risk factors of schizophrenia with even the slightest association have been identified. More research is being conducted to strongly and evidentially associate these genes with schizophrenia. However, genetics is not the only factor increasing the risk of schizophrenia. The environment also plays an important role. The combination of environmental risk factors and genetic predisposition factors increases the chance of schizophrenia more than the environment or genetic factors separately. This review article provides an insight into the risk factors of schizophrenia mainly focusing on the genetic factors.

Keywords: Schizophrenia; Neuregulin-1; Neurogranin; Neurexin-1; Synapsin-2;

Introduction

Schizophrenia previously known as dementia praecox is a grave disorder of the brain which shows a variety of symptoms including cognitive impairment, hallucinations, and delusions. Schizophrenia has a prevalence of 1% of the world population and accounts for a considerable range of mortality and morbidity.[1] The age of onset for this disease can be anywhere from adolescence and adulthood. Schizophrenia is a condition that requires treatment and care throughout the life after its onset. Schizophrenia is caused by problems with the development of the brain that may be due to a genetic predisposition or environmental conditions including maternal malnourishment, prenatal infections, and stress.[2] In the late 20th century, Emil Kraepelin had found that schizophrenia was caused by disruption of the frontal lobes of the brain and this discovery of his steered the clinical approach of schizophrenia in the right direction.[3] Imaging studies of the schizophrenia patients revealed depletion of the white matter and pathological examination detected abnormalities in the myelin. Genetic studies, however, showed notable changes in the expression of genes associated with oligodendrocytes and astrocytes.[4] Some genes associated with schizophrenia discussed in this article include NRG1, NRGN, NRXN1, SYN2, and SYNGR1.[5]

Factors associated with schizophrenia

Genetic risk factors

Neuregulin-1

Neuregulin-1 (NRG1), a gene that is localized to the p arm of the 8th chromosome has been found to be in association with schizophrenia. NRG1 belongs to the neuregulin group of proteins, which remain to be a major aspect of the biological activities taking place in the Nervous System. NRG1 also consists of a structure similar to the EGF (Epidermal Growth Factor) that triggers tyrosine kinases that are associated with the membrane and in relation to the ErbB receptors. This EGF like motif is responsible for ErbB receptor binding, activation of the downstream signaling pathway, tyrosine phosphorylation, and dimerization. The neuregulin-1 gene codes for various alternative splicing variants that are categorized into three isoforms: NRG-1 Type I, NRG-1 Type II, and NRG-1 Type III. These isoforms of the neuregulin-1 gene have been found to play a major role in the nervous system development. This gene has also been found to regulate the plasticity and expression of the subtypes of nicotinic acetylcholine receptors (α5, α7, and β4), N-methyl-d-aspartate receptors, and β2 subunit of the γ-amino butyric acid receptor. Some of these receptors were found to be in association with the genetics of schizophrenia. A

study using the gene-targeting method analyzing the NRG1-ErbB signaling in mice exposed a behavioral phenotype concurrent to some animal models for schizophrenia. On the whole, there is genetic evidence that suggests the involvement of neuregulin-1 gene in the development of schizophrenia and the biological function of this gene also supports the genetic evidence (NRG1).[6]

Neurogranin

Neurogranin (NRGN) is located in the q-arm of chromosome 11 and is homologous to the neuron specific rat RC3/Neurogranin gene. This gene is 7.3kb long and has four exons of which a portion of the first and second exons code for a protein containing 78 amino acids while the third and fourth exons are untranslated sequences. The NRGN gene codes for a postsynaptic protein kinase, which is a substrate. This protein substrate binds to the calmodulin (CaM) when calcium is absent and plays an important role in the formation and plasticity of the dendritic spine and the synapse respectively. This gene possesses a major part in the Ca2+ - CaM signaling pathway. The oxidation of NRGN which is induced by the influx of calcium ions instigates CaM to cause postsynaptic activation of the CaM-dependant protein kinase II (CaMKII). CaMKII is however in relation to strengthened N-Methyl-D-asparate (NMDA) receptor signaling. Thus, inhibition or reduction in the activity of NRGN gene may lead to the hypo-functioning of the NMDA receptor signaling which is involved in the pathophysiology of schizophrenia. There is also abundant literature suggesting the association of the Neurogranin gene with schizophrenia.[7]

Neurexin 1

The Neurexin 1 (NRXN1) gene is located in the p-arm of chromosome 2 and stretches for 1.12Mb of the genome. This gene contains 23 exons and codes for a protein called the neurexin 1 belonging to the neurexin family of proteins. This protein is a synaptic neuronal adhesion molecule and through the interaction with pre-synaptic and postsynaptic proteins, it also plays a key role in the organization of synapse and synaptic transmissions. Neurexin 1 forms an inter-synaptic complex that is required for the establishment, maturation, and specification of the synapses. NRXN1 is distinctly expressed in the cerebral cortex of a developing brain and the expressions levels of this gene gets upregulated with increasing age. NRXN1 however, it presents with other proteins that are encoded by the isoforms of NRXN1 gene (NRXN1-α and NRXN1-β) which arise from different promoter regions.

The psychiatric problems caused because of mutation in the NRXN1 gene predominantly affect the promoter region of the NRXN1-α. It has been proven that deletions in the NRXN1 gene are a major risk factor for schizophrenia. The expression levels of the isoforms of this gene in the human brain were studied by Jenkins et al. in the year 2016. They observed high expression of both the isoforms of neurexin 1 gene in the fetal cortex, which peaked postnatally up to 3 years of age. However, the expression levels dropped drastically after this age and continued to drop until the levels reached a stable low level which remained constant for the rest of their lives. This study along with other studies monitoring the neurobiological effects of neurexin 1 gene supports the genetic evidence that NRXN1 gene is associated with schizophrenia.[8]

Synapsin 2

Synapsin 2 (SYN2) belongs to the synapsin group of genes which comprises of three genes that show association with the cytoplasm of the synaptic vesicles and are involved neurotransmission, neuronal development, and synaptogenesis. It also plays a significant role in localizing the nitric oxide synthase so that it is within the proximity of the nitric oxide targets present in the pre-synaptic neurons. Synapsin 2 is located in the p arm of chromosome 3. Two major functions of the SYN2 gene are associated with the etiology of schizophrenia: dysregulation of neurotransmitters and localizing the nitric oxide near its target. In case an exploit impending reaches the edge concerning a nerve, an incursion of calcium ions triggers vesicles to mingle with the plasma membrane which consequently leads to the discharge of neurotransmitters in the synaptic cleft. Disruption in this process leads to the dysregulation of the neurotransmitters.

The nitric oxide that is produced neutrally is reactive and is involved in the extension of neuronal processes and the release of neurotransmitters. Since nitric oxide cannot be stored in the vesicles, it is neuronally synthesized when the need arises, by the neuronal nitric oxide synthase (nNOS). However, to reduce the unwanted reaction of the nitric oxide molecules, adapter proteins such as nitric oxide synthase 1 coded by NOS1AP gene (or CAPON gene) are utilized to localize the nNOS. Synapsins occur together with CAPCON and the nNOS. Reduction in the levels of synapsin-2 showed improper localization of the nitric oxide which directly affected neurotransmission. Studies also showed decreased expression levels of synapsin-2 in the hippocampal region of the brain in schizophrenia patients. Hence both genetically and neurobiologically, the association of SYN2 with schizophrenia has been established.[9, 10]

Synaptogyrin 1

Synaptogyrin 1 (SYNGR1) gene is localized to the q arm of chromosome 22, a region that has been previously associated with schizophrenia. This gene spans for 36kb and has six exons producing 3

isoforms namely a, b and c. Among the three isoforms, the a isoform is the longest and shows increased expression in the brain in comparison to other tissues whereas b and c isoforms are relatively smaller and show expression in all the tissues including the brain. Synaptogyrin 1 is a transmembrane protein and shows association with the presynaptic vesicles found in the cytoplasm of the neuronal cells. The major functions of SYNGR1 include cortical connection establishment, synaptic plasticity, and release of the neurotransmitters and problems in these processes are found to cause schizophrenia. The expression levels of this gene in the prefrontal cortex of a schizophrenia patient also suggest its association with schizophrenia. SYNGR1 is a candidate gene because of its localization and very little research has been carried out to study its association with schizophrenia[11, 12] (Table 1).

Environmental factors

Although genetic factors play a great role in the development of schizophrenia, environmental factors also contribute to its development. Environmental factors can be psychological, social, biological, or physical influencing individuals at different stages of their life (fetal, childhood, adolescence, and adulthood). Some environmental factors associated with schizophrenia include complications during pregnancy, substance abuse, psychological trauma, infection, migration, and urbanization.

A study conducted by Martinez-Ortega and his colleagues (2011) has revealed that children born during the time period between late winter and early spring are more likely to develop schizophrenia. This is suspected to be due to an increase in influenza during that time period. Influenza infection can affect fetal brain development causing schizophrenia. Urbanization and immigration can also cause schizophrenia because of the noise pollution and stress associated with city life. Some pregnancy and birth complications associated with schizophrenia are stress during pregnancy in a mother carrying a genetically predisposed child, preeclampsia, vacuum extraction, fetal hypoxia, and nerve compression due to intense contractions. Continuous exposure to stress over a long period is also a risk factor.

Other common risk factors are childhood trauma, death in the family, abusive parenting, and trauma to the head.[13] In some cases, the environmental factors interact with a genetically predisposed individual to increase the risk of schizophrenia and one such interaction is the gene-cannabis interaction. The interaction between the genes and cannabis colloquially called marijuana has been studied to analyze the effect of dopaminergic genes. One such study by Caspi and his colleagues discovered that the chance of developing schizophrenia is increased in adolescents using cannabis who possess a COMT 158Val polymorphism. However, that was not the case with individuals carrying the COMT 158Met polymorphism.[14] Studying the environmental factors along with the genetic factors is also important. These environmental factors contribute a great deal in the diagnosis and management of this disorder (Fig 1).

Conclusion

Schizophrenia is a crippling disease that affects the livelihood of an affected individual and those around them. With great advances in science, studies can report the implications of genes and their interaction with the environment in the etiology of schizophrenia. GWAS and gene expression profiling studies have contributed a great deal in identifying the genes responsible for causing schizophrenia, and these results are supported by neurobiological studies. There are very few population oriented association studies linking these genes to schizophrenia. Identifying the susceptibility gene and environmental factors for schizophrenia is necessary in order to ensure early intervention and proper treatment of this disorder.

Gene Name	Gene Symbol	Chromosomal Location	Expression
Neuregulin-1	*NRG1*	8p12	Thyroid, Urinary bladder, Lung, Kidney, Liver, Brain, Colon, Appendix, Duodenum
Neurogranin	*NRGN*	11q24.2	Brain, Lung, Bone marrow, Spleen, Kidney
Neurexin-1	*NRXN1*	2p16.3	Brain, Colon, Heart, Adrenal, Esophagus, Gall bladder, Small intestine, Testis
Synapsin-2	*SYN2*	3p25.2	Brain, Fat, Adrenal, Placenta, Testis
Synaptogyrin-1	*SYNGR1*	22q13.1	Brain, Ovary, Skin, Adrenal, Bone marrow, Testis, Thyroid, Heart, Kidney, Prostate, Salivary glands

Table 1: Genes associated with schizophrenia

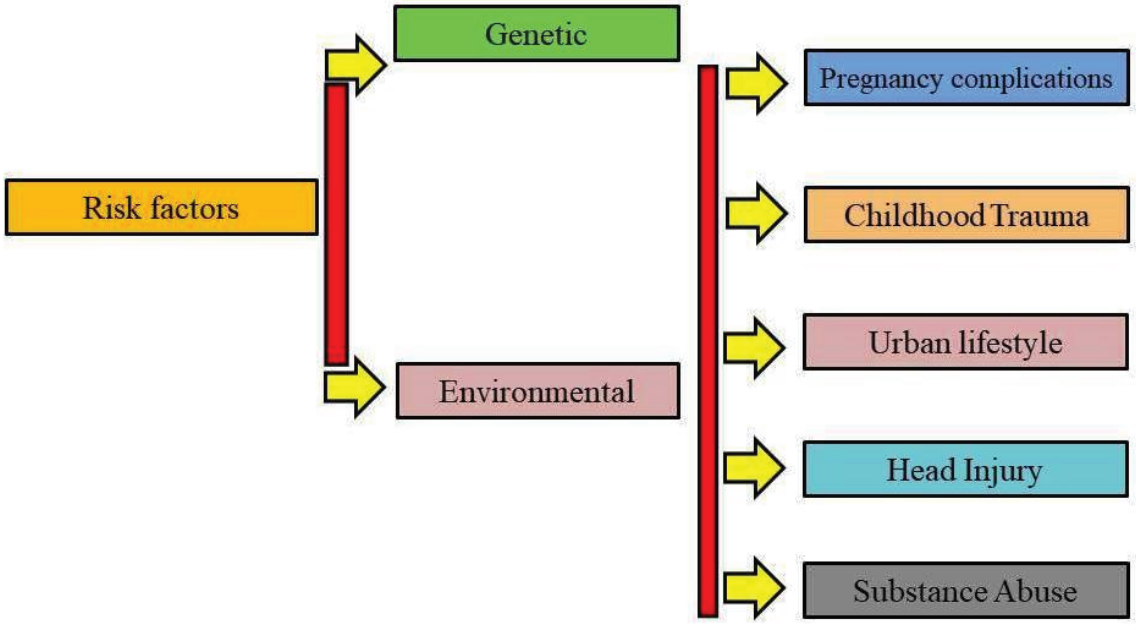

Figure 1: Risk factors associated with schizophrenia

Conflicts of interest

All the authors declare that they have no conflict of interest

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