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Role of Genetic and Environment in the Development of Disorder: Schizophrenia

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Abstract:

Human population have one of most common, devastating and least understood neuropsychiatric illness that is schizophrenia. This disorder is generated by the action of genetic and environmental effects. Genome-wide association studies (GWAS) shows the result that more than 100 loci has been identified which have high risk of schizophrenia. Monozygotic twins have a high risk of this disorder as compare to the dizygotic disorder. Different models has been developed to find the relation between genetic and schizophrenia. In the same way, Environmental is also a factor that give their impact in the generation of schizophrenia. In environmental factors, parental, perinatal, season birth and so on may be the cause of schizophrenia. But it is found that individually genes or individually environment is not responsible for the development of disorder. The gene as well as environment both are necessary to produce the disorder. This paper represents the role of genetic and environment in the development of schizophrenia disorder.

Keywords: *Schizophrenia, Genetics, Perinatal, Monozygotic*

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Introduction

A debilitating disorder that occurs approximately 0.5 to 1% within any given population. Complex genetic, environmental and psychological etiologies come under the pathophysiology of schizophrenia. A multi-factorial disease 'Schizophrenia' is characterized by a genetic factor (high heritability) and environmental risk factors including social stress and cannabis use. It is caused by the mutual action of multiple genes that have small effect size and various environmental factors due to which mental disorder developed. It is considered as 'Two-Hit Hypothesis' of schizophrenia that assumes that both genetic and environmental risk factors aggressively cause the development of the disorder. Genetic interacts with the environment when the expression of one's genetic tendency depends on the environment in which he/she is living or the effects of environment on a trait are differed according to the genome of an individual.

Nowadays, mental disorders are recognized as a disease that affects human populations around the world. In most common and important disorders, genetic factors play an important role. The most severe psychiatric disorders of adults are functional psychoses that are divided into two main diagnostic categories: schizophrenia and bipolar disorder. Schizophrenia is a disorder that occurs equally in male and female at risk 1%. Schizophrenia is characterized by psychotic features like delusions and hallucinations.

Genetic epidemiology of Schizophrenia

A group of pathologies from which schizophrenia belongs is known as complex genetic disorders. It means many genes are involved in each disorder with each gene that has a small effect on the phenotype. The mechanisms of genetic in the production of schizophrenia have been explained by many theories. One hypothesis in which schizophrenia has a homogeneous pathogenic genotype with pleiotropic effects. Example of pleiotropy is Marfan's syndrome that is a connective tissue disorder with 12 recognizable abnormalities. 88% of patients are affected by the most common of this disorder and only 12% of patients have the least common disorder. A variety of symptoms may be present in an individual with schizophrenia. The great numbers of evidence show that most of the cases of schizophrenia are caused by a common gene. Particularly, single gene models are not able to define the familial patterns of illness accurately. Families or twins; multi-factorial polygenic models can explain such data in the better way.

Genetic Transmission Model for Schizophrenia

It is well known that the madness and many other human afflictions and characteristics move from generation to generation. Some authors/ researchers described that schizophrenia is inherited characteristic due to the familial aggregation of the disease or its milder variants. The schizophrenic monogenic model was very attractive because of the various reasons such as simplicity, a hope of discovering a corresponding, simple pathophysiological mechanism and fit into theoretical options like recessive, dominant and with varying penetrance. But it is not followed now these days because it does not fit into the empirical data and the idea of one specific gene or few specific genes required for etiological not sufficient for the emergence of schizophrenia. For example in 1962, Meehl used monogenic necessary gene in which polygenic factors were used to modify the action. Holzman in 1989 gave latent trait model in which dominant gene as a latent trait, a postulated neural deficit with potentially pleiotropic manifestations such as schizophrenia, schizotypy or eye-movement disorder. Then, Risch and Bardon in 1984 discussed a mixed model in which specific gene in the combination with a few oligogenes and the genetic substrate is formed with the polygenic multifactorial background. All these models have been applied to fit that have a varying degree of success to the available epidemiological data of schizophrenia.

Multi-factorial Polygenic Models

Schizophrenia results as the risk of illness is increased between the relatives of affected individuals due to genes rather than environments. The risk of schizophrenia is high in children and siblings compared to the parents. The studies of research show the result that monozygotic concordances criteria are at high risk (41-65%) compared to dizygotic concordances (0-28%). Genetic epidemiology clears that the mode of transmission is complicated. There are many factors which are still unknown that include disease risk is conferred by each locus, number of susceptibility loci, the extent of genetic heterogeneity and degree of interaction among loci. Improved twin and adoption studies became very important for the determination of familial clustering and concordance rates for schizophrenia in the 1960s. The etiology of illness has a strong genetic component that contributes to undermine the psychoanalytical hypothesis of schizophrenic causation which claims that schizophrenogenic rearing is a sufficient cause for the development of schizophrenia. The twin studies have the basic intuition which are these as follows:

- Monozygotic twins (Share 100% genes) and dizygotic twins (Share 50% genes) also share the environment in which they are growing.
- Genetic similarity results in the form of high concordance rates in monozygotic (MZ) and Dizygotic (DZ) twins.

Many studies have been done on twin theory in monozygotic twin have a high risk of schizophrenia compared to a dizygotic twin. A meta-analysis of twin studies is done that estimates the liability of genetic to schizophrenia at 81% while environmental influences that are shared by twin have only 11%. According to studies, unaffected monozygotic twins also carry a silent susceptibility genes for schizophrenia. While, in children of discordant dizygotic twins, affected dizygotic twins have a higher risk rather than children of an unaffected dizygotic twin.

In adoption studies, it is documented that adopted-away children of mothers adopt schizophrenia spectrum disorders more frequently than their control adoptees. A cross-fostering study stated that the children of healthy parents adopted by a family where one parent has schizophrenia disorder do not have an effect on the children. The children of schizophrenic mothers have the same risk of developing disorder whether they are adopted by another parent that does not have any history of illness.

Molecular genetic

In molecular genetic research, the Human Genome Project has been instrumented for schizophrenia. It was an international research project in which the sequence of the human genome that has 3 billion base pairs was determined and mapped the genes. In the early 1980s, according to the researchers DNA availability would disclose the biological causes of disorder joined with the twin and adoption studies.

The 'linkage analysis' was the first DNA based method that had the aim to discover the genome regions in a sample of affected extended or nuclear families and sibling pairs without the specific allelic variant. The degree of co-segregation of genetic markers and predefined phenotypic traits like schizophrenia spectrum diagnosis is examined by which linkage between the illness and genomic loci was estimated. This linkage analysis is based on the genetic marker observation which is located physically on the same chromosome tend to inherited together as they remain linked at the time of meiosis. Numerous linkage studies regarding the schizophrenia disorder were conducted but positive findings showed difficulty to replicate in subsequent studies. In short term, a meta-analysis was considered as many chromosomal regions can have schizophrenia susceptibility loci. It is a well-known fact that loci do not confer any risk by own but may encourage the variance in this. These results make clear that linkage design power was very weak for addressing the genomic loci with small effects; the sample size that was required to detect the linkage was practically impossible. Hence, there is a requirement of other DNA-based methods to point out the genes that are involved in the etiology of schizophrenia.

Another phenomenon in molecular genetic research for schizophrenia is 'candidate gene' approach that uses a case-control design and explored if susceptibility genes connected with the disorder. In compare to linkage analysis, candidate gene approach are able to detect genes with small effect alleles provided that the sample size is appropriate. Due to their position and functionality, candidate genes have been selected. More than 1000 candidate genes have been verified, although the identification of some genes with small effect alleles, the candidate gene studies results were disappointed. There are some candidate genes such as DISC1, DTNBP1, NRG1, and COMT. These candidate genes' pathogenetic involvement in schizophrenic disorder remains questioned. Significant discoveries were absent because of many reasons difficulties in replicating positive findings, inadequate statistical power and limited knowledge of genes as the involvement in the field of the pathophysiology of schizophrenia.

Environmental Factors in Schizophrenia

The ancient and powerful belief that place and time do not affect the incidence of schizophrenia has been failed by the productive period for the study of the epidemiology of schizophrenia. The results of epidemiology indicate the specific circumstances in which schizophrenia risk is increased. These circumstances are various obstetric complications, urban birth and residence, famines, migrant status and seasonal effects. Other than these, advanced paternal age, cerebral hypoxia and other severe pregnancy and perinatal complications are also environmental risk factors. Overall, the landscape of environmental risks is fruitful and grow rapidly that point out to many risk factors act early at the time of development. Those individual effects that are biologically catastrophic such as famines caused by environmental risks are small. Between environmental risk factors and schizophrenic, specific pathophysiological connections remain largely tentative. Finally, the risk for schizophrenia is increased by the additional environmental factors. The understanding of gene-environment interactions is very important for disclosing the biology of schizophrenia.

Preconceptual risk factors for Schizophrenia

"Preconception" is one of the environmental risk factors that involve demographic or other parental features are recognizable prior to conception. The prime example of a preconception risk factor is advanced paternal age. The mutation rate for base substitutions is much higher in men than in women because of a large number of cell divisions at the time of spermatogenesis. This mutation rate is increased with paternal age. A de nova mutations explanation is offered for schizophrenia. Another reason for the risk of schizophrenia is a prolonged delay between pregnancies. An indicator of reproductive health and fitness may be calculated using a standard measure of reproduction function in both sex and can relate to the biological processes involves in the reproductive and genetic damage. In the addition, time to pregnancy is defined as the reported length of time is taken to conceive an intended pregnancy may be the cause of schizophrenic risk in offspring. If the times of conception is more than 12 months, the risk of schizophrenia is increased. Schizophrenia may be caused by the parental reproductive health. The environmental dynamics like exposure to chemicals and smoking are accumulated in the body and affect the health and fertility. It is still not known that smoking and exposure to chemicals contribute to the development of schizophrenia directly or not. But these conditions give their effects on genetic material.

Prenatal Risk Factors for Schizophrenia

Maternal Infection

The development of schizophrenia is caused by the maternal exposure to infection during gestation. Research in the field of the infection that occurs in the mother during pregnancy affects the prenatal in the form of mental disorders. When viral pathogens exposed through the maternal placenta cause the disruption in normal fetal brain development resulting in abnormal neurodevelopment. In order to achieve greater insight into the risk factors of environment, schizophrenia investigators have sought to apply this phenomenon to the specific early manifestation of disease in the studies of epidemiological, ecological and translation. The investigators have identified several maternally acquired infections which are the causes of schizophrenia. These infected viruses are herpes simplex virus type-2, genital and reproductive infections, polio, influenza, rubella and respiratory infections and protozoan parasite Toxoplasma gondii.

Perinatal Risk factors for schizophrenia

A serious risk for schizophrenia is developed by the brain trauma linked with obstetric complications. By the study of monozygotic twins for the schizophrenia, a significant correlation between an individual with increased lateral and third-ventricle size and history of obstetrical complications and prolonged delivery time was found by the researcher. They also detected a significant relationship between decreased left and right hippocampi size and a history of obstetrical complications.

The risk of schizophrenia is higher in the obstetrical complications compare to others. It has been studied that obstetric complications show the symptoms of schizophrenia at a younger age. Another study shows that there is no significant difference between early-onset or very early-onset schizophrenia and a history of obstetrical complications. One obstetric complication is Hypoxia or reduction of oxygen that relates with a diagnosis of schizophrenia later in life. During birth, hypoxia associated with greater structural abnormalities that affect both grey matter mass and cerebral spinal fluid levels in the brain of people with schizophrenia. This relationship is greater 2-3 times in the case of born pre-term and small in gestational age. While another study stated that long-term exposure to intrauterine hypoxia is significant rather than the short-term hypoxia during birth. During childbirth, a lack of oxygen is related to the diagnosis of schizophrenia.

Cannabis

The psychotic symptoms are the symptoms of schizophrenia. These psychotic symptoms are increased with the use of cannabis. A person who is suffering from psychotic symptoms takes more cannabis to compare to the general population. According to the report of a meta-analysis, the risk of developing psychotic symptoms or psychotic disorders increase the use of cannabis. Some neuroimaging studies stated that in both gray and white matter linked with heavy cannabis, structural is changed that is used in both healthy subjects and FEP patients. While psychosis is developed early in cannabis users that can be explained by the differences in use patterns and age at that time it was used. In THE Dunedin birth cohort study, the person who starts to take cannabis at the age of 15 years or earlier has a great risk of schizophrenia at the age of 26 years than those who started at 18 years of age.

Review of Literature

Sobell, Mikesell, and McMurray (2002) in the development of schizophrenia, genetic contribution is a clear evidence. In spite of this, tested hypothesis and current methods have been failed in the identification of specific genetic factors due to which disorders occur. It is assumed that by the study in the field of

neuroanatomy, functional neuroanatomy, neuropathology, neurochemistry, molecular neuroscience, neuropsychology, neurodevelopment, and molecular epidemiology, new clues can be developed about the pathophysiology and gene systems. With neurodevelopmental and neurodegenerative processes, Heterogeneity of genetic and etiologic factors is the expectation. Currently known, or yet to be identified as suspect candidate genes play a vital role in the development and progression of the disease, also in the medication response to therapy.

Leask (2004) in their study they concluded that awareness should be generated from a clinical perspective regarding the exposure. They found in their patient that genetic predisposition has a history in the development of schizophrenia or signs of illness prodrome. There is a need for more work before list any environmental influences can be confidently rejected or considered as casual that contribute to illness.

Graae (2007) studied the social factor effects in the development of schizophrenia by taking the population of migrants in Europe. In this research, they concluded that the social factors exert their influence by which mechanism is unknown. They suggested that in the future investigation of social causation, the temporal relation between exposure to social defeat and social adversity, and the development of psychotic symptoms should be clarified.

Stilo, Forti, and Murray (2011) discussed the causal risk factors for schizophrenia. The gene-environment interactions highlight the development of schizophrenia. According to them, neither individual gene nor individually environment is responsible for the schizophrenia. The disorder is caused by the effect of both. A variety of approaches from medication and psychological interventions to this disorder are used in an attempt to prevent the onset of full-blown psychosis.

Sariaslan, Larsson, and Fazel (2016) proposed that the patients who are diagnosed with the psychotic disorder have a high risk of committing violent offenses because of the influence of genetic. In case of bi-polar, genetic influences increase the risk of violent crime by fifth times while genetic influence does not contribute to schizophrenia for increasing such risk. Future research should effort in integrating violence-related phenotypes into psychiatric genetic studies. And the identification of environmental predictors of violence in the patient groups.

Henriksen, Nordgaard, and Jansson (2017) studied pre-molecular and molecular genetic in which they concluded that a strong risk factor is formed by genetics for schizophrenia. The relationship between schizophrenia and more than 100 susceptibility loci (copy number variations (CNVs), and single nucleotide variants (SNVs)) indicated as a number of scores. It is also important to note that the thousands of common alleles give a small effect form a polygenic component of schizophrenia risk. In brief, the knowledge about the interaction of schizophrenia and genotype-environment is still unknown to a large extent.

Conclusion

'Schizophrenia' is a disorder that occurs rarely in population. But due to the generation of this disorder, a person may commit crime and harm to itself. This paper discussed the two factors which are responsible for the development of schizophrenia. Many studies have been conducted on this topic to find the main cause of it. Many researchers mentioned that genetic factor play a vital role in the development. As well as, environmental factors are also responsible for this disorder. Beside many studies results about genetic and environmental factors impact on the development, the main mechanism of the development is not understood. So, there is a need for more study to know the main mechanism of it by which the development of risk of schizophrenia can be reduced.

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