Genetic and Environmental Factors in Schizophrenia

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 Mental disorders are among the most persisting challenges to public health both in the United States and around the world. Schizophrenia is a chronic mental condition that often has a profound, debilitating effect on the lives of affected individuals. Despite a relatively comprehensive understanding of the symptoms, changes in cognitive characteristics, and course of the disease little is still known regarding etiology of schizophrenia. Historically, various theories have been proposed to explain the origin of the disease. While environmental factors are also considered to play a role in schizophrenia scientists are currently focusing on research on genetic risk factors. The growing body of facts indicates that both genetics and environment can contribute to higher risks of schizophrenia.

 Schizophrenia is a chronic mental illness that usually manifests in young adults. Symptoms of schizophrenia are typically divided into three categories: positive, negative and cognitive. Positive symptoms are characterized by instances of psychotic behavior such as hallucinations, thought disorders, delusions, and movement disorders (Gejman, Sanders, & Duan, 2010). Negative symptoms include reduced speaking, muted emotional response and impaired feeling of pleasure or satisfaction in everyday life. Cognitive symptoms vary greatly among patients and include trouble to remain focused, difficulties with working memory, and poor executive functioning. Schizophrenia also shares symptoms with other mental disorders pointing at possible common genetic causes. The risk of developing schizophrenia is now considered mostly inherited.

 Present knowledge of molecular mechanics behind the disease is still limited because of the biological complexity of schizophrenia that has proven to be significantly higher than anticipated. (Gejman, Sanders, & Duan, 2010). Being a complex genetic disorder, schizophrenia is presumed to be a result of abnormalities in many genes with each gene coffering a minor effect on a general phenotype. Thus, the combined effect of several mutated genes can result in cognitive abnormality of different kinds, including schizophrenia.

 Interactions of an epistatic nature between affected genes and environmental risk factors are considered to be a highly plausible explanation of the origin of the condition. Epidemiological studies of schizophrenia have shown how various environmental circumstances lead to an increased risk of the disease (Gejman, Sanders, & Duan, 2010). Obstetric complications, in particular, have been shown to correlate with higher risks of schizophrenia (Byrne, Agerbo, Bennedsen, Eaton, & Mortensen, 2007). Seasonal effects that affect fetal development such as influenza or prenatal infections may induce early onset of the disease. Advanced parental age is also presumed to be a strong environmental factor that raises the possibility of gene mutations leading to schizophrenia development. Epidemiological findings provide enough data for molecule genetic experiments that may help in establishing a pathophysiological connection between environmental risk factors and schizophrenia (Gejman, Sanders, & Duan, 2010). Consequently, scientists are becoming more aware of the intricate connection between genes and environmental factors that influence their expression and possible mutations. A better understanding of gene-environmental interactions can potentially lead to a discovery of other environmental factors that trough epigenetics can lead to higher risks of schizophrenia development. However, a psychological hypothesis of schizophrenia was rejected as a result of twin and adoption studies which paved the way for the research on genetic risk factors.

 Studies of monozygotic twins allow for separation of genetic risk factors from environmental contributors. The rate of concordance of the disease for monozygotic twins have been estimated at a range of 40 to 50%, and heritability rate of 80% (Gejman, Sanders, & Duan, 2010). According to a number of studies, offspring of unaffected and affected twin will have a similar risk of developing schizophrenia and related disorders. The information suggests that heritable genetic risk factors for schizophrenia are carried by the unaffected twin without symptom manifestation. The difference in DNA methylation has been recently proposed as an explanation of discordance between monozygotic twins (Mill et al., 2008). Additionally, it may provide a mechanism for a range of environmental factors for schizophrenia.

 Adoption studies have further proved the dominant role of genetic risk factors for schizophrenia. Studies on high-risk adoptees from parents with schizophrenia or schizophrenia spectrum disorders have found higher risk for psychosis notwithstanding the time of onset in parents. The biological relationship was shown to indicate the prevalence of the disease (Gejman, Sanders, & Duan, 2010). Offspring of schizophrenia parents had similar risks whether they were raised by adoptive non-schizophrenic or affected the biological parent. Moreover, offspring of non-affected mother raised by adoptive parents with psychotic disorders did not have a higher risk of developing the condition. Despite the fact that schizophrenia is a highly heritable disease identifying susceptibility genes proved to be a daunting task before implementation of genome-wide association studies (GWAS). Thanks to the ongoing advancements in molecular biology, current understanding of the genetic mutations and changes can yield light on readability of mental conditions.

 GWAS have yielded significant genome-wide results relevant to schizophrenia. Recent meta-analysis GWAS data provided definitive evidence to support an involvement of Major Histocompatibility Complex (MHC) which is a group of genes coding for cell surface-bound proteins involved in recognition of foreign and hazardous substances and increased risk for schizophrenia (Mukherjee et al., 2014). In 2009 a study with a large sample of 8,008 patients indicated that the MHC region on chromosome 6 is associated with the disease (Mukherjee et al., 2014). One of the recent studies showed a correlation between excess of homozygosity in the MHC in people affected with schizophrenia. The strongest receive effects were localized on yet poorly examined genes, TRIM10, TRIM 40, and TRIM 15 (Gejman, Sanders, & Duan, 2010). Furthermore, an adjacent segment in the MHC complex has demonstrated an additive effect on the risks of schizophrenia. Further analysis of GWAS data uncovered evidence to support an association with NRGN gene coding for neurogranin protein that in humans is exclusively expressed in the brain where it participates in the signaling pathways of protein kinase and mediation of NMDA receptor that is important for memory and learning (Gejman, Sanders, & Duan, 2010). It has also been proposed that in schizophrenia patients NRNG is relevant to glutamate pathophysiology. Similarly to NRGN, transcription factor 4 (TCF4) is essential for proper brain development, more specifically neurogenesis (Gejman, Sanders, & Duan, 2010). Mutations in this gene known to cause neurodevelopment disorders.

 The occurrence of genomic deletions or duplications of a varied range that tend to have a pronounced phenotypical effect has also been linked to schizophrenia. Copy number variations (CNVs) study provided evidence that allows associating NRNX1 gene with the disease (Kirov et al., 2009). NRNXN1 encodes for a cognominal synaptic neuronal adhesion molecule that is essential for synapse function. Experiments on cell cultures have shown that dysfunction in these molecules leads to impairment in properties of synapses that in its turn result in neural network disruption. Deletions in NRNXN genes have been already linked to autism and mental retardation with recent findings strongly indicating a link to schizophrenia (Kerner, 2014). With improvements in array technology detection of CNVs become more precise leading to additional findings of deletions in NRXN1 (Kirov et al., 2009). Research on 2977 schizophrenia patients examined gene in question for CNVs. As a result, 61 deletion and 5 duplications were found with 12 deletions occurring in patients with schizophrenia (Gejman, Sanders, & Duan, 2010). Additional studies have provided conclusive evidence to support mutations in the NRXN1 gene as being associated with schizophrenia.

 Microdeletions in chromosome 22 that contains unto 600 genes are now linked to increased risk of schizophrenia (Chow & Bassett, 2016). Among many genetic forms of the disease deletion in the 22q11 region of chromosome 22 is the only clinical recognised, recurrent, and has efficient genetic testing available. Prevalence of 22q11 deletion syndrome (22qDS) is estimated to be 1 in 100 in patients with schizophrenia. However, researchers presume higher prevalence rates after considering demographics of sample groups (Chow & Bassett, 2016). Moreover, studies indicate that the lifetime risks of schizophrenia in individuals with 22qDS are 25 times higher than in the general population (Chow & Bassett, 2016).

 Conclusively, schizophrenia is a chronic mental illness with high heritability rates that is indicative of a serious genetic component. Both environmental and genetic risk factors have to be closely considered regarding etiology of schizophrenia. Mutations in a number of genes are now recognized to contribute to the disease making schizophrenia one of the most difficult disorders to study and understand. Genome-wide association studies have provided substantial evidence to link schizophrenia to deletions or duplications in genes that play a significant role in learning, memory and overall neural development.

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