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Gene-Environment Interaction and Risk of Schizophrenia

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Abstract: Schizophrenia is a chronic mental disease that affects less than 1% of the population in the United States. In the introduction, the article provides a general overview of schizophrenia disorder, incorporating potential causal factors of schizophrenia in biological and environmental areas. It also demonstrated the individual and social impacts with present symptoms. Later in the mainbody sections, the article presents the general effects of gene-environment interaction on the risk of schizophrenia and the moderating role of environmental factors in schizophrenia by looking at the influences of childhood adversity in siblings with and without schizhophrenia, the role of family history and epigenetics, the effect of socioeconomic status (SES), and the relationship between stress and neurotransmitter activity in schizophrenia. On of the limitations of previous studies is that they were mainly conducted in adults who were diagnosed with schizophrenia already. Future studies should identify at-risk children and families to conduct longitudianl studies on this topic. This review can provide some guidance to the desgin of prevention and intervention programs at schools and communities for at-risk families.

Keywords: schizophrenia, psychosis, gene-environment interactions, epigenetics.

1. Introduction

According to DSM-5, schizophrenia is a psychological disease defined by significant disturbances in emotion, thought, behavior, and perception, with continuous signs of the non-drug causing disruption persisting for at least 6 months [1]. The present symptoms usually include at least 2 of the following: disorganized speech and behavior, perception, hallucinations, perception, and negative symptoms. Furthermore, one or more important areas of functioning must be much lower than before the onset, ruling out depressive or bipolar illness and schizoaffective disorder with psychotic symptoms. For the essential history of schizophrenia term development, a well-known German psychiatrist named Emil Kraeplin came up with “dementia praecox” as a biological disorder caused by toxic processes or anatomical that differs from the term “manic depression” [1]. This finding ties the pathophysiology and appearance of psychiatric diseases together.

1.1. Impact of Schizophrenia

To understand the impact of schizophrenia, firstly, people should investigate the disorder’s symptoms. As introduced earlier, present symptoms of schizophrenia incorporate positive signs of disorganized speech and behavior, hallucinations, delusions, and negative symptoms. Positive symptoms tend to be the easiest to recognize. Positive symptoms are excessive or distortion of

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normal behavior, thoughts, and emotions, which are something individuals do or think. Negative symptoms, on the other side, are the things that an individual does not do, such as a reduction in or absence of normal incentive and interest-related activities and functions, as well as verbal or emotional expression. Based on DSM-5, the negative symptom domain has 5 crucial parts: alogia, asociality, avolition, blunted affect, and anhedonia. Negative symptoms are a crucial aspect of schizophrenia. They contribute to a major percentage of the disorder's long-term impairment and poor functional outcome [2].

Undoubtedly there are considerable personal, social, and interpersonal levels of impact on the individual who has the disorder depending on the severity. Based on several tests and experiments done by Liddle, he found that the symptoms led to executive function deficiencies, impaired performance on vigilance, verbal memory, and working memory tests, which are substantial indicators of impaired community outcomes and difficulty in learning new skills [3]. More importantly, the suicidal rate and attempts in patients with schizophrenia disorder are significantly high. For people with schizophrenia, between 4 and 13 percent committed suicide, and between 25 and 50 percent made suicidal attempts [4]. Past researchers also concluded that substance abuse, hopelessness, previous suicide attempts, melancholy, and male gender have all been recognized as suicide risk factors in people with schizophrenia. Furthermore, the patients have averagely a poorer standard of living in the interpersonal relationship and social aspects. Poorer standard of living was associated with psychotic symptoms, psychiatric admissions, depression, anxiety, alcohol abuse, no reliable friends or daily contact with family, few leisure activities, and being unemployed. Thornicroft claimed that it is also notable that schizophrenia caused occupational impairment, which is far more significant than typical controls due to some chronic and severe physical comorbid disorders, such as diabetes [5]. Schizophrenia not only lays a severe strain on the patient but also on their families. The lengthy recovery time places a significant load on both schizophrenia patients and their family members. Schizophrenia patients' family members often go through a sequence of traumatic experience during the first schizophrenia episode. Positive qualities of caregivers arise at a central position within this circle, according to Shiraishi and Reilly, because family members can recognize values, such as learning knowledge and skills, family solidarity, affection, admiration, personal growth, appreciation, compassion, self-confidence, and affirmation [6].

1.2. Etiology of Schizophrenia

Both environmental and genetic factors play an important role in the development of schizophrenia. Previous studies revealed that brain structure patterns could be linked to higher disorder vulnerability in genetically transmitted illnesses like schizophrenia, and sites where non-genetic stimuli may initiate disease can be identified and mapped [7, 8]. Researchers from the past decades show that schizophrenia is remarkably genetic based. According to previous family studies, schizophrenia was found to be substantially more common in families with schizophrenia family members than in the general population [9]. Based on Hans and other researchers' findings, even after considering non-proband parent's mental illness, those with a parent with schizophrenia had a greater rate of schizophrenia (17.1%) than others (5.3%) [10]. Another critical aspect of understanding the genetic risk factor of schizophrenia is shown by twin studies. Differences between identical (MZ) twins are assigned to the environment, while differences between dizygotic (DZ) twins are related to both environmental and genetic variables. Given that MZ and DZ twins share the same environment, better concordance rates in MZ twins over DZ twins are most likely attributable to genetic similarity. Schizophrenia concordance rates for MZ twins were reported to be around 40 to 50 percent, and they were significantly lower in DZ twins [11]. Last but not least, when it comes to genetic etiology, it's important to remember that schizophrenia is a complicated

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genetic condition involving numerous genes, each of which has only a minor impact on the phenotype [11]. Therefore, instead of looking for "a" gene responsible for schizophrenia causation, researchers should aim to look for a group of genes affecting the development of schizophrenia.

Substance abuse is a crucial environmental factor associated with the risk of schizophrenia. Cannabinoids, which is the most relevant substance with schizophrenia and studied the most, can produce acute and transient effects. However, whether cannabis can precipitate schizophrenia in those with genetic liability remained controversial for decades [12]. A more recent study reveals that psychosis-prone people are more likely to develop psychosis after being exposed to cannabis (both acute and long-term) [13]. A psychometric test or a family history of psychotic disease can both be used to determine psychosis-proneness. Individuals with a high psychosis-proneness measurement have an increased probability of having psychotic symptoms. Since psychosis is a core characteristic of schizophrenia consisting of delusions, formal thought disorder, and hallucinations, a conclusion can be drawn that cannabis use is relevant with the development of schizophrenia disorder in a certain way [14]. As stated above, schizophrenia is a genetic-based disorder with an unneglectable environmental effect. Understanding the causation will help researchers develop a more efficient way of preventing and treating the development of schizophrenia. However, past studies are mainly focused on one side of the potential cause of schizophrenia, in which the connection and interaction of genes and environment remained unclear.

With the concerns stated, this article aims to discuss the general effects of gene-environment interaction on the risk of schizophrenia and the moderating impact of environmental factors in schizophrenia. This review integrated studies regarding childhood adversity impact on risk for siblings, the role of family history and epigenetics, the effect of socioeconomic status (SES), and the effect of stress. This paper can provide some guidance to the design of prevention and intervention programs for at-risk children and families at schools and communities.

2. General Effects of Gene-Environment Interaction on Risk of Schizophrenia

2.1. Different Impacts of Childhood Adversity on Risk of Schizophrenia for Siblings

Understanding the effect of childhood adversity on the risk of schizophrenia is a critical aspect of looking into gene-environment interaction. Before delving into the effects of childhood adversity on the likelihood of schizophrenia in siblings, it is vital to understand that childhood adversity (CA) is linked to a variety of mental diseases. Furthermore, employing schizophrenia case-control data molecular genetic analysis and reporting as a polygenic risk score (PRS-SZ), the estimation of a model that predicts trait values from genetic variation directly assesses schizophrenia genetic risk for investigation. The risks of PRS and CA aren't limited to psychotic disorders. A previous study looked at how much the impact of CA and PRS-SZ on psychosis outcomes was influenced by the affective dysregulation presence, which was defined as substantial depressive symptoms [15].

With a sibling sample, NEMESIS-2 was done to investigate the course, consequences, incidence, and prevalence of brain disease in the Dutch general population. NEMESIS-2 presents evidence that PRS and CA moderated the association between psychosis and affective dysregulation phenotype [15]. In NEMESIS-2, the influence of PRS-SZ on psychosis was found to be highly dependent on the existence of affective dysregulation. The findings further imply that the relationship between PRS-SZ, CA and psychosis outcomes is conditional on the presence of affective dysregulation, suggesting that an affective pathway probability can modulate these risks [15]. These findings could explain the cross-diagnostic character of the risk linked to CA and PRS-SZ and the robust links psychosis between and affective dysregulation throughout the range of psychotic disorder and the presentation of psychotic experiences at the subthreshold. Affective dysregulation and CA had major effects on all three psychosis outcomes, whereas PRS did not. Furthermore, CA mediation by

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affective dysregulation was observed in both delusions and hallucinations, whereas PRS was only shown in delusions.

Pre-stated data reveal a distinction in the extend of mediation by affective dysregulation between non-genetic and genetic etiological variables, resulting in hallucinations and delusions diverging. However, the role of the sibling's sample in this experiment still needs to be explored; But based on what is presented above, people can directly see that, to some extent, CA is responsible for a decent amount of impact on the risk of schizophrenia, at least with sibling's sample. According to cognitive models of psychosis, decision-making dysfunctions are implicated in the construction and preservation of positive psychotic experience. Individuals who engage in this process, known as jumping to conclusions (JTC), draw inferences based on inadequate information and assess ambiguous inputs, which can lead to delusional experiences [16]. Another study result revealed that more specific sibling factors could influence the likelihood of schizophrenia, which is linked to JTC bias. The link between JTC and psychotic states appears to be predominantly psychotic, as relationships among people with non-psychotic brain disorders with JTC bias are modest and very variable. Furthermore, the link between JTC and delusional ideation seems to be specific in delusion, and people with a mental illness who have a higher scores of delusional ideations have more JTC bias than those who do not. JTC bias was positively associated with sibling status and patient status, according to multinomial logistic regression analysis, and the association between sibling status and JTC bias was larger in those with higher scores of delusional thoughts [16].

To summarize, JTC bias was more common in patients with psychotic illnesses and their non-ill siblings than in controls. Furthermore, evidence of delusional thought was required for the association to exist, with JTC being most firmly connected to sibling status if there was also evidence of delusional thought; in other words, the link between psychosis liability and JTC is exclusive to delusions. Based on the analysis of the two experiments mentioned above, the conclusion can be drawn that different impacts of childhood adversity on the risk of schizophrenia for siblings are critical to understand the general impacts of gene-environment interplay on the schizophrenia risk.

2.2. The Roles of Family History and Epigenetics in Schizophrenia

To study the overall effect of interaction of gene-environment on the schizophrenia risk, the roles of family history in schizophrenia should also be paid attention to. Firstly, as mentioned briefly above, psychosis is a type of severe brain disorder characterized by delusions, disordered conduct, and hallucinations. Schizophrenia and other varieties of psychosis create significant health-care costs, the loss of human potential, and misery due to a combination of poor therapeutic response and early onset. Many environmental exposures have been linked to psychosis in epidemiological studies, although the impact of these exposures varies depending on the individual [17].

Psychotic disorder in a specific individual is caused by heredity and environment, according to previous research findings utilizing various family samples. Furthermore, while certain environmental factors increase the likelihood of psychosis, these unfavorable settings do not affect everyone in the same manner; in other words, psychosis is not random [17]. The non-random association between genotype and exposure is referred to as gene-environment correlation (rGE). When looking into potential causes of psychosis, it is critical to consider the role of rGE. Abuse of psychostimulants, for example, is often linked to acute psychosis; Nevertheless, people who take stimulants recreationally and have a family history of disorders are more likely to develop chronic psychotic symptoms. [17]. More importantly, interaction of gene-environment (GxE) appears to have a essential role in the psychosis development, according to two past studies. First, twin studies have yielded substantially higher estimates of schizophrenia heritability than molecular genetic research involving unrelated individuals. Second, despite epidemiological evidence suggesting

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family shared risk factors are among the most important environmental psychosis contributors, twin studies suggest that the shared environment has little or no impact on psychosis.

Moving to the role of epigenetics in schizophrenia, recent discoveries in schizophrenia mechanisms of epigenetic that govern GxE and genetics have laid the groundwork for a comprehensive model of schizophrenia risk that considers both environmental and genetic factors. Based on recent studies of the schizophrenia risk architecture with the epigenetics risk, researchers conclude that processes of epigenetic may be especially essential for understanding multifaceted disease like schizophrenia since they are reliably heritable despite having a poor and erratic relationship with individual genetic variants [18]. In the absence of a history of psychotic traits or schizotypal in the family, prenatal variables have no effect on the risk of schizophrenia. Nonetheless, the records indicate the risk is significantly higher in those offspring. Postnatal variables, like prenatal exposures, are rarely adequate to produce schizophrenia on their own, yet rather function in conjunction with a prior family history or on top of pre-existing vulnerabilities in the central nervous system linked to schizophrenia [18]. Finally, research demonstrates that both rare traits with large effects and common traits with moderate effects contribute to the schizophrenia genetic risk, with no evidence of clinical manifestation differences. As previously stated, no single gene can fully explain risk of schizophrenia, which is probably influenced by supplemental genetic and/or epigenetic factors [18]. Understanding the facts leads to the conclusion that the roles of family history and epigenetics in schizophrenia are critical to comprehending the general effects of gene-environment interaction on schizophrenia risk.

3. The Moderating Role of Environmental Factors in Schizophrenia

3.1. The Effects of Socioeconomic Status

Moving to the moderating role of environmental factors in schizophrenia, socioeconomic status could significantly impact it. To begin, it is important to emphasize that schizophrenia is due to a combination of hereditary and environmental variables, as twin studies first demonstrated. Previous studies looked at the effects of a variety of factors on socioeconomic indicators in patients with schizophrenia, both individually and in combination. They investigated environmental risk exposure prior to disease onset in particular [19]. As a result of the findings, the study concludes that when many environmental factors (low SES) are combined, they represent a substantial risk factor for early schizophrenia onset. The study finds that patients with a perinatal problems history and individuals who started taking marijuana before the onset of illness were admitted to the hospital at higher rates [19]. Psychotrauma, such as sexual and physical abuse and the loss of a close emotional bond, as well as cannabis use and migration, was linked to fewer years of education. Cannabis usage, a preventable environmental risk factor, is also strongly linked to a younger prodrome age [19]. The findings reveal that cumulative environmental factor has a significant impact on the age at which schizophrenia or its prodrome appears in the same group of schizophrenia patients. Thus, the conclusion can be drawn that SES, one of the most critical environmental factors, can impact the risk of schizophrenia. Another longitudinal research in the UK also supported the socioeconomic hypothesis, which targets explicitly socioenvironmental factors.

Psychosis has long been linked to socioenvironmental factors such as urbanization and neighborhood poor. The researchers questioned whether these links were causal. Genetic confounding may emerge as a result of persons with a high genetic risk of psychiatric issues moving downhill into poor surroundings [20]. The study discovered that increased indicators of genetic risk was linked to riskier rearing circumstances. It also suggests that there was additional evidence for gene-environment interactions grew stronger with time [20]. After covariate correction for genetic risk, however, relationships between socio-environmental hazards and psychotic experiences

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largely remained significant. Genetics, according to researchers, is unlikely to muddle connections thoroughly. There were connections between socio-environmental risk variables and teenage psychotic experiences that went beyond the five indices of genetic risk. Finally, the study found a link between socio-environmental risk variables and psychotic experiences in addition to the five genetic risk indices [20]. Though residual confounding is unavoidable, the data suggest that socio-environmental circumstances during childhood play an essential role in early manifestations of psychosis, which ultimately will affect the risk of schizophrenia.

3.2. The Relationship between Stress and the Activity of a Neurotransmitter in Schizophrenia

The association between stress and the activity of a neurotransmitter in schizophrenia is another important part of knowing the function of environmental factors in schizophrenia. The dopamine hypothesis is the pathobiological schizophrenia theory that has been around the longest. Furthermore, dorsolateral prefrontal cortex (DLPFC) dopaminergic hypofunction has been proposed as a source of cognitive symptoms and negative, and schizophrenia patients have been found to have reduced DLPFC dopamine release [21]. Stressors, on the other hand, are now well recognized as raising the risk of schizophrenia. Psychotic symptoms are triggered by acute stress, and poor stress tolerance is linked to prodromal symptoms. Putting together, Acute stresses cause cortical dopamine release, which dampens striatal dopamine release, according to animal research.

In both those at psychosis risk and those with schizophrenia, more dopaminergic release in response to acute social anxiety has been seen. Individuals who were exposed to early adversity also had higher dopamine synthesis and release capacities [21]. In comparison to healthy controls, first degree relatives of those with schizophrenia had a lower total cortical dopaminergic response to stress. This was linked to higher psychotic-like stress reactions and subjective stress. The expression and functioning of the association of dopamine release and stress are also affected by genetic polymorphisms and environmental factors. As shown in a volunteer research, heterozygotes with a dopamine single nucleotide polymorphism demonstrated more stress-induced striatal dopamine release than homozygotes [21]. Based on clearing the association between stress and dopamine activity, we can see that environmental factors play a role significantly to the schizophrenia risk, interacting with prenatal factors.

4. Conclusions

In sum, biological and environmental factors are both associated with the risk of schizophrenia. Moreover, schizophrenia not only has a severe impact on the individual's well-being and social functioning but also can impact their families. In addition, to avoid the negative outcome, appropriate drug treatment combined with social support should be provided to the patient based on their conditions. Furthermore, previous research show that childhood adversity, at-risk family history and epigenetics, the effect of SES, and the impact of stress can all influence the risk of schizophrenia. Previous studies also demonstrated the moderating role of environmental factors in schizophrenia to some extent by analyzing all of those factors. Despite the fact that previous studies have revealed crucial information about gene-environment interaction in schizophrenia, many elements still need to be addressed. One limitation of the previous studies is that past researchers only used interview to investigate past experiences in childhood for targeted siblings, and this recalling approach might be biased. Future study should identify high-risk families and conduct longitudinal studies from childhood. This review can provide some guidance to the design of prevention programs for at-risk children and families at schools and communities.

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