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Genetic factors in the occurrence of schizophrenia and the effects of physical activity on schizophrenia symptoms

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ABSTRACT

Schizophrenia is a severe mental disorder that affects approximately 1% of the general population. Genetic factors play a complex role in its development. The inheritance pattern is complex, non-Mendelian, and usually results from a combination of genetic factors. In addition to environmental factors, whose exact impact remains unknown, this work summarizes the genetic variants influencing the occurrence of schizophrenia. Analysis of schizophrenia inheritance focuses on evaluating genetic transmission through genome-wide association studies, studies on copy-number variants, and next-generation sequencing. Additionally, this study examines the impact of physical exercise on schizophrenia symptoms. The following research highlights the crucial role of genes in the inheritance of schizophrenia. Furthermore, it demonstrates the initial effectiveness of physical activity in schizophrenia treatment.

Keywords: Schizophrenia, GWAS, complex disorders, physical exercise, polygenic, genetics

1. INTRODUCTION

Schizophrenia is a complex and variable disorder characterized by impairments in cognitive, social, and affective functions. Examples of symptoms include delusions, auditory hallucinations, thought disorders, unusual speech and behavior, and social problems (Giegling et al., 2017). According to a study conducted at Chestnut Lodge, suicide is the most common cause of death among people with schizophrenia, in which 40% of patients reported suicidal thoughts, 23% attempted suicide, and 6.4% died by suicide (Giegling et al., 2017; Agerbo et al., 2015).

Schizophrenia spectrum disorders are often observed in families with a reported history of the illness. In 2000, the first studies confirming the hereditary nature of schizophrenia were conducted by (Cardno and Gottesman, 2000). Although the lifetime risk of developing schizophrenia varies across countries, an individual's risk increases nonlinearly with the degree of genetic relatedness to someone affected by the disorder; for third-degree relatives, it is approximately 2% and increases to about 9% for first-degree relatives, or, in the case of children of two affected parents, about 27%. For monozygotic twins, the risk of developing the disorder is about 50%.

It is essential to note that adopted children whose biological parent has schizophrenia have a 6–10 times higher risk of developing the illness than the general population (Giegling et al., 2017; Cardno and Gottesman, 2000). In summary, schizophrenia heritability is estimated to range from 64% to 81%. Numerous genetic variations contribute to the disorder's complex inheritance pattern. Advancements in research methods have contributed to a better understanding of the inheritance of schizophrenia.

2. METHODOLOGY

The study involved explored databases such as Google Scholar and PubMed, using keywords like genetics, schizophrenia, inheritance, and physical exercise. Our search consisted of selecting articles based on their titles, and then, after analysis of the abstracts, we selected the most appropriate ones. Various scientific sources on both Polish and global schizophrenia inheritance realities were analyzed, with a focus on evaluating inheritance based on genome-wide association studies, research on copy-number variants, or next-generation sequencing.

3. RESULTS AND DISCUSSION

Linkage studies

One of the most significant achievements of humanity is the discovery of the human genome. The Genome Project is a global study plan to determine the order of three billion base pairs in the human genome and map all its genes. The Human Genome Project has also helped with gene work on schizophrenia (Andreasen, 1984). The first way to use DNA was linkage analysis to discover genomic regions in samples of families affected by the disease. Evidence of linkage between the disease and genomic loci was obtained (Todorov and Rao, 1997).

Linkage analysis is conducted based on the observation that genetic markers located close to each other on the same chromosome are usually inherited together and remain linked during meiosis. Numerous linkage studies on mental illness have been conducted, but it has been shown that good results are hard to repeat in later tests (Risch and Merikangas, 1996). The first studies hinted at the role of risk genes on chromosome 5 [5q11.2 to 5q13.3], but this discovery was not widely confirmed.

One of the most extensive meta-analyses was conducted in 2009 by Kennedy et al., (1988), including 32 independent whole-genome linkage scans and a total of 3255 pedigrees and 7413 genotyped cases that had schizophrenia or similar issues. The results showed proof of connection on 5q (142–168 Mb) and 2q (103–134 Mb). A second look at families of European background provided a hint of a link on chromosome 8p (16–33 Mb) (Ng et al., 2009). Up to now, these linkage studies have not definitively identified any risk genes, although some new meta-analyses showed a bit of overlap on 5p14.1 and 10q26.12 (Vieland et al., 2014).

Candidate gene

Unlike linkage analysis, the candidate gene approach allows for detecting genes with alleles of small effect, provided that the sample size is adequate. Candidate genes are typically selected based on their position or functionality (e.g., genes encoding proteins associated with dopamine or serotonin neurotransmission). Overall, the results of candidate gene studies have been disappointing.

Many frequently mentioned candidate genes include DISC1, DTNBP1, NRG1, and COMT, but their possible role in schizophrenia remains debated (Giegling et al., 2017; Levinson et al., 2000). The lack of significant findings may have several causes, such as difficulties in replicating positive results, insufficient statistical power, and limited knowledge about genes involved in the pathophysiology of schizophrenia (Sanders et al., 2008; Sun et al., 2009).

GWAS

A genome-wide association study (GWAS) is a study that looks for variants in the genome associated with the risk of a disease or a given trait. A thorough examination of the genome and searching for correlations between genomic variants and a given disease are the

main assumptions of GWAS (Giegling et al., 2017; Kennedy et al., 1988). In 2009, a significant attempt was made by (Hreinn et al., 2009). Strong association signals were detected in 5,013 cases and 15,559 controls from four additional European sample sets, leading to the identification of three new potential schizophrenia loci: NRGRN (encoding neurogranin), TCF4 (encoding transcription factor 4), and the central histocompatibility complex region (Image 1).

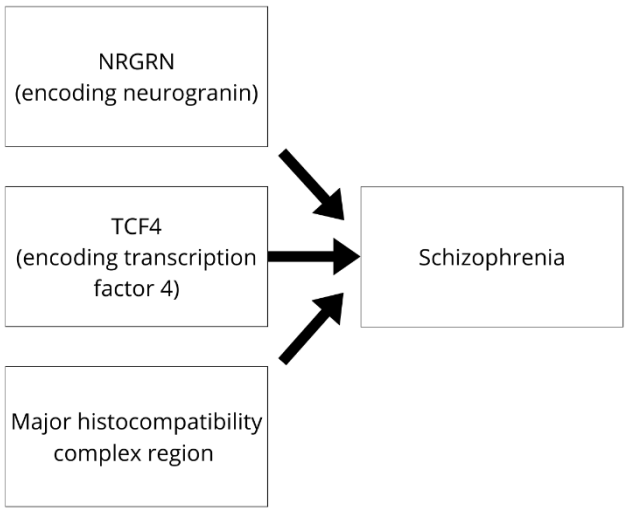

Image 1 Three potential schizophrenia loci

The most recent and largest GWAS on schizophrenia was published in 2014 by the schizophrenia PGC team, including a multi-stage GWA study of 36,989 cases and 113,075 controls (Giegling et al., 2017). A total of 128 associations in 108 independent loci were identified, with the most strongly associated locus being an extended region on chromosome 6, which contains numerous genes, including the MHC region (P¼3.4810–31) (Ripke et al., 2013).

New associations for 83 loci were identified, but these were linked to regions rather than to a specific gene. Associations were more pronounced in genes exhibiting epigenetic markers indicative of expression in the brain. Notably, several loci with known candidate genes (e.g., DRD2) and genes linked to glutamate signaling (GRM3, GRIN2A, SRR, GRIA1) reached genome-wide significance, highlighting their therapeutic relevance and supporting existing hypotheses about the illness (Image 2).

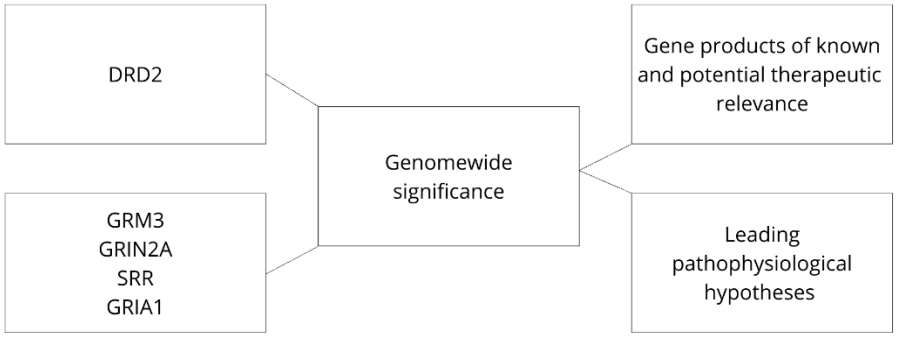

Image 2 The impact of genetic factors on schizophrenia

The PGC study was also provided with evidence that associations were enriched in genes expressed in tissues related to immunity. However, a more sophisticated re-analysis of the data failed to support this, confirming only the enrichment of brain-expressed genes (Finucane et al., 2015). The most consistent result throughout the GWAS of schizophrenia is the association with the extended MHC region, observed in several independent samples of moderate to large sizes (Grayton et al., 2012). Allelic variation at the Complement

component C4A locus, situated in the MHC region, accounts for part of the heritability of schizophrenia. (Image 3) (Giegling et al., 2017).

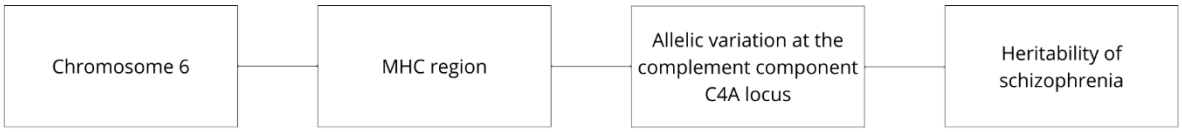

Image 3 The association between extended MHC region and schizophrenia

Effects of Physical Activity on Schizophrenia Symptoms

Individuals with schizophrenia experience a premature mortality gap of between 10 and 20 years from the general population (Walker et al., 2015). There is evidence in the literature that people with schizophrenia have high levels of metabolic syndrome Mitchell et al., (2013), type 2 diabetes, and cardiovascular disease, which cause premature mortality in over 70% (Lawrence et al., 2013) (Image 4). Physical activity (PA), even without weight loss, improves cardio-metabolic results and has a positive effect on mental symptoms in people who have schizophrenia (Image 5). PA intervention, i.e. performing 150 minutes of moderate-intensity PA per week, is a factor that is not present in most people with schizophrenia. Unfortunately, there is insufficient evidence about what type of physical activity and intensity is the most effective.

Physical activity reduces cardiovascular risk and may also alleviate symptoms. Understanding the level of physical activity and predictive factors in people with schizophrenia is of great clinical importance. Physical activity has a positive effect on both positive and negative symptoms, as well as on general psychopathological symptoms, which are reflected in cognitive abilities. These connections are at a similar level in people who have schizophrenia and among people with other psychotic disorders. Guidelines should be established for PA interventions that apply to the treatment of people with schizophrenia and other psychotic disorders (Mitchell et al., 2013; Lawrence et al., 2013).

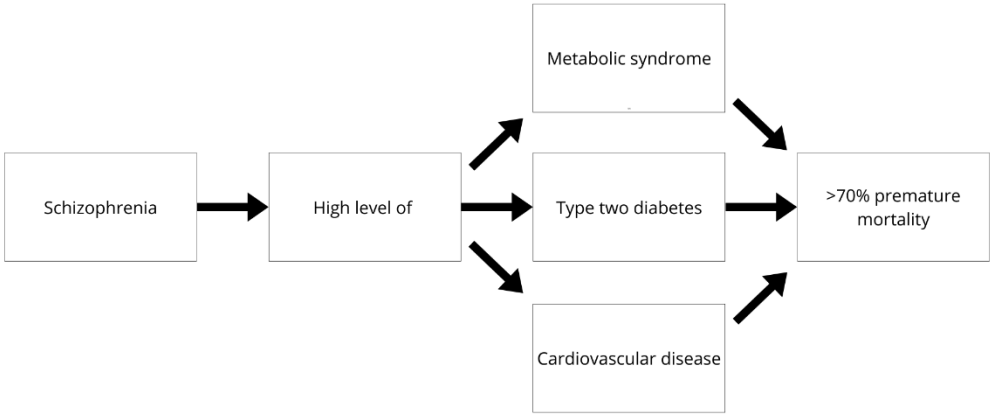

Image 4 Premature mortality in people with schizophrenia

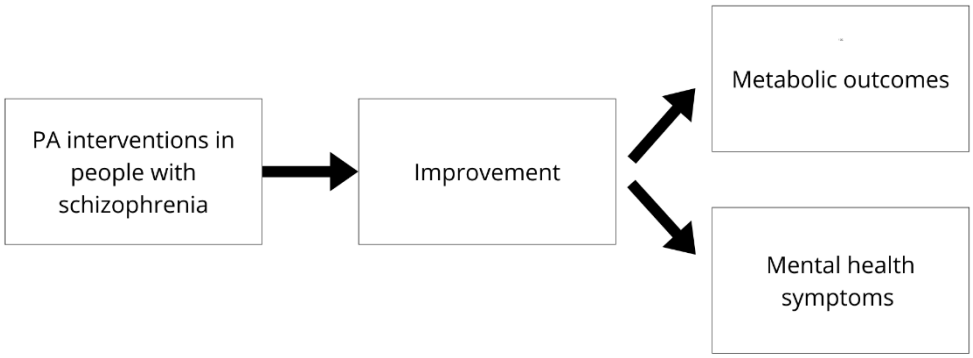

Image 5 Physical activity in people with schizophrenia

4. CONCLUSIONS

Premolecular and molecular genetic studies indicate a significant contribution of genetics to the occurrence of schizophrenia in the population. Replication of numerous findings from genome-wide association studies (GWAS) has consolidated our knowledge, and several have achieved genome-wide meta-analytic significance. Furthermore, strong correlations between schizophrenia and over 100 susceptibility loci have been demonstrated, and copy number variations (CNVs) and single nucleotide variations (SNVs) have been discovered, which is considered promising for further research. Moreover, thousands of common alleles have been shown to have little effect individually but collectively contribute significantly to the risk of schizophrenia.

Thanks to this research, it will be possible to introduce innovative therapeutic techniques. However, statistical associations between common (SNP) or rare (CNV, SNV) genetic variants and schizophrenia are apparent but do not always explain the cause. Many of the identified associations are related not only to schizophrenia but also to other mental disorders. Although many studies indicate a correlation between specific genotypes and the development of schizophrenia, it is essential to consider the complex interactions between genotype and environment that influence the onset of mental illnesses.

Care should be taken when interpreting the extent of genetic influence on the etiology of schizophrenia. The initiation of physical activity and the minimization of risk factors are closely linked to the reduction of premature mortality and the occurrence of metabolic syndrome. PA interventions have a positive impact on the circulatory system and psychological symptoms in people who have schizophrenia. Lifestyle modification by introducing physical activity should be part of the therapy for people with psychotic disorders.

Authors contribution

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Writing - review and editing: Urszula Muroń
Visualization: Filip Lachowski
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All authors have read and agreed with the final, published version of the manuscript.

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Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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