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Project thesis, Faculty of Medicine

Potential clinical application of genome-wide association studies of schizophrenia

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February 2023

Abstract

Background and objective: Schizophrenia is associated with considerable functional impairment and high rates of treatment failure due to the variable effect of treatment, prominent side-effects, and delayed intervention. The disease has a substantial genetic component, with two large genome-wide associations studies (GWAS) recently making significant headway in our understanding of the genetic basis of schizophrenia. This project thesis aimed to study how and if findings from these two large GWASs of schizophrenia can be used in clinical settings.

Method: A systematic search was done in PubMed for English articles on the use of data from the PGC GWAS of schizophrenia (2014) in various clinical settings. The search was restricted to include articles from 2014 or later and resulted in 712 articles. Seven articles, including articles identified through manual search of the reference list of included articles, met the inclusion criteria. Ultimately, seven articles were included and analysed.

Results: Two articles were large schizophrenia GWAS that identified numerous genetic variants and loci associated with schizophrenia. Three articles researched the use of polygenic risk scores (PRS) to predict risk of schizophrenia and concluded that the effect size was too small for PRS to predict risk in clinical settings. Two articles discussed whether GWAS findings can be used to improve treatment and found that the findings could predict response to antipsychotics and help improve treatment.

Conclusion: There is potential for genetic risk scores to be used as predictors of schizophrenia risk and response to antipsychotic treatment. The measured effects of PRS are still insufficient for risk prediction in clinical settings but grant new opportunities for research. Due to various limitations of GWAS, more research must be conducted to fully understand the implications of GWAS findings for clinical practice.

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Glossary

Genes: A gene is a region of the genome that codes for specific proteins with various functions in the body. Genes contain information necessary to define physical and biological qualities.

Genome: The genome is the whole of DNA information found in a cell. The human genome contains 23 pairs of chromosomes.

Locus: the term "locus" refers to the physical location on a chromosome, like a street address. Loci is the plural of locus.

SNPs (Single Nucleotide Polymorphisms): A SNP is a genetic variation that affects only one base location in the DNA. It is a one-letter position where one genome sequence differs from another. SNPs are scattered throughout the entire genome.

PRS (Polygenic Risk Score): A person's PRS is calculated statistically based on the presence or absence of numerous genetic variations, without considering environmental or other factors. A PRS only uses genetic data to assess a person's risk of having or developing a certain trait.

Polygenic trait: A trait which is determined by more than two genes is referred to as a polygenic trait. Polygenic traits do not adhere to the rules of Mendelian inheritance because several genes are involved.

Genetic concordance rate: Concordance rate refers to the probability that two individuals with shared genes will develop the same trait or illness.

CNV (Copy Number Variation): CNV refers to an occurrence where the number of copies of a specific DNA sequence varies between different people's genomes. These variants can be short or include thousands of bases. CNVs can result from deletions, duplications, and other changes.

AUC (Area under the receiver operating curve): The AUC is a common metric used to evaluate predictive performance. It is a graphical plot created by plotting a true positive rate against a false positive rate at various thresholds.

PheWAS (Phenome-wide association study): A PheWAS is a study design that tests the association between SNPs or other genetic variants across many different phenotypes. It is a complementary approach to the GWAS methodology.

Introduction

Schizophrenia is a chronic, debilitating psychiatric disorder, once referred to as “the worst disease affecting mankind” (1, 2). It is a life-long disorder necessitating extensive care and a significant amount of mental health services. It is also among the most incapacitating of psychiatric disorders (3).

The onset of schizophrenia symptoms usually occur between the late teenage years and the mid-30s (4). Its onset is generally marked by social withdrawal and cognitive impairment that can precede the first psychotic episode by several years (1). The disorder is characterized by three heterogenous symptom categories, including psychotic (positive) symptoms, negative symptoms, and cognitive symptoms (3).

Among psychotic symptoms, loss of contact with consensus reality is a defining symptom, including persistent delusions (fixed false ideas), hallucinations (perceptual experiences not shared by others) and unusual behaviour. Schizophrenia can cause a variety of hallucinations, notably auditory, visual, olfactory, gustatory, or tactile, with auditory hallucinations being the most frequent (3). Characteristic delusions in schizophrenia include persecutory delusions, delusions of control (such as the belief that others are capable of interfering with one's thoughts), grandiose delusions (such as the belief that one is Jesus Christ), and somatic delusions (such as the belief that one's brain is rotting away). Psychotic symptoms are typically, but not always, episodic in their occurrence and severity over time (3).

In contrast, negative symptoms include a reduction in, or absence of typical behaviours related to motivation, interest, or expression (5). Commonly seen negative symptoms include dampened affect (e.g., motionless facial expression, monotone voice), anhedonia (lack of pleasure), avolition or apathy (lower ability to begin and carry out plans), and alogia (reduced amount or content of speech) (3). Negative symptoms have been described as one of the most frequent initial manifestations of schizophrenia. They often appear during the prodromal phase of the disorder and before the first acute psychotic episode but can manifest at any given moment during the course of illness (5).

Finally, cognitive symptoms are the newest classification in schizophrenia, and are characterized by impairments in attention and concentration, psychomotor speed, learning and memory, and executive processes (e.g., abstract reasoning, problem solving) (3, 6). Negative symptoms and cognitive impairment impact roughly 40% and 80% of people with

schizophrenia, respectively. Both are closely related to poor functional outcomes and compared to positive symptoms they contribute significantly to the overall illness burden (7).

As there is no objective test for schizophrenia, the diagnosis is based upon a checklist of criteria and requires a combination of certain symptoms, as described by internationally recognised diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Disorders (ICD) (1, 8). No single sign or symptom is pathognomonic of Schizophrenia (9). The DSM-5 diagnostic criteria for schizophrenia consists of six criteria, A to F, of which all must be met (10) . These include the presence of two or more of the following characteristic symptoms for at least one month: delusions, hallucinations, disorganized speech, highly disorganized or catatonic behaviour, and negative symptoms. And at least one of these symptoms must be delusions, hallucinations, or disorganized speech. In addition, it states that for a person to be diagnosed with schizophrenia, they must show impaired functioning in the areas of work, interpersonal relationships, or self-care. Furthermore, the symptoms of schizophrenia must persist for at least six months, including a one-month period consisting of the characteristic symptoms. Finally, the clinician must ensure that the symptoms are not caused by substance use or another medical issue (6, 10) .

Epidemiology

Schizophrenia is a disorder of relatively low prevalence affecting approximately 1% of the population worldwide (4), with an estimated age-standardized point prevalence of 0.28% (11). However, the rates vary depending on the diagnostic definition that is used (8). For example, using a narrow diagnostic definition —that includes patients with illness that has lasted at least six months, are under 45 years old, and have experienced negative symptoms— gives a lifetime prevalence and incidence of 0,30 to 0,66% and 10,2 to 22,0 per 100 000 person-years. In contrast, a broad definition of psychotic illness —one that encompasses diagnoses like delusional disorder, short-term psychotic disorder, and the comprehensive diagnostic category of psychotic disorder not otherwise specified— gives a lifetime prevalence of schizophrenia and associated conditions of 2.3% (8). Because schizophrenia is a life-long disorder, the lifetime prevalence, and the point prevalence are essentially the same (12). The disorder usually first manifests in adolescence and young adulthood, with prevalence peaking at about 40, and then declining in older age groups (11).

Despite its low prevalence, schizophrenia was classified as the 12th most debilitating disorder in 2016, contributing 13.4 million years of healthy life lost due to disability (YLDs) to global burden of disease. This excessive burden reflects the early onset, limited remission rates, and high disability associated with the disorder (11). The greatest burden of schizophrenia is in the 25–54-year age range, where people are more likely to be productive workers (11), as the overall employment rate of people with schizophrenia is approximately 21.5% (13). The substantial overall economic and social costs of schizophrenia place it amongst the world's top ten causes of disability-adjusted life years (3). The prognosis of patients with schizophrenia is usually unpredictable (6). Schizophrenia has a considerably high mortality rate, resulting in an average lifespan that's around 10-20 years shorter than of the overall population (14). The largest contributor of this excess mortality—nearly 50%—is caused by cardiovascular disease (15), 28% is attributed to suicide and 12% is due to accidents (16).
In contrast to earlier assumptions of equal rates of schizophrenia across the world, significant differences in prevalence and incidence have been reported throughout different nations and cultures (3, 17). The reported prevalence is higher in developed countries compared to less-developed countries (18). However, within communities, schizophrenia is reported to be more common in lower socioeconomic classes compared to higher socioeconomic classes (17).

The incidence of schizophrenia has been reported to be the same for both sexes when based on diagnostic categories that include more affective symptoms and brief presentations, each of which is associated with a better prognosis. Diagnostic categories that are skewed towards negative symptoms and prolonged illness, both of which are linked to poor outcomes, produce higher incidence rates for men than for women (8), implying that men experience more severe symptoms of schizophrenia than women. This argument is reinforced by the observation that men have an earlier disease onset, with women presenting on average 3 to 4 years later than men (19). In addition to having a later average age of onset than men, women also seem to have a more benign course of illness, with fewer hospitalizations and better social functioning (3).

Risk factors

Both genetic and environmental factors are involved in the aetiology of schizophrenia, with genetics accounting for about 80% of the risk associated with developing the disorder (3, 17).

Beyond genetic factors, which are discussed in more detail below, there are several environmental factors associated with an increased risk for developing schizophrenia(8). Urbanicity and migration are strongly associated with a higher risk of schizophrenia, with individuals born in urban areas having a higher risk of the disorder than those in rural areas and the risk being higher among immigrant ethnic groups than natives (17, 18). Poverty and lower social class have also been linked to higher rates of schizophrenia (3).

Pathophysiology and aetiology

Finding the pathophysiology that underlies schizophrenia has proven to be difficult. The most well-established hypotheses focus on dysregulation of the neurotransmitters dopamine, glutamate, serotonin, and GABA (6), which are believed to impact neuronal processes in the striatum, hippocampus, prefrontal cortex, and midbrain and consequently cause psychosis (1). According to a number of studies, excessive synaptic levels of dopamine and glutamate lead to enhanced postsynaptic activation, resulting in psychotic symptoms. The cause of these disturbances may be related to a shortage of GABA-inhibitory interneurons and underactive glutamate receptors (NMDARs), which disrupt the inhibitory-excitatory balance of neural pathways regulated by glutamate and dopamine (20).

The dopamine hypothesis of schizophrenia came to light when it was discovered that antipsychotic medications mediate their effects by blocking or partially inhibiting dopamine D2-receptors, suggesting that psychosis results from excess synaptic levels of dopamine, especially in the striatum (21). The glutamate hypothesis of schizophrenia is supported by studies showing that glutamate-receptor antagonists elicit schizophrenia-like symptoms in healthy individuals and worsen schizophrenia symptoms in patients with the illness (1). Furthermore, it has been suggested that processes that modulate the synthesis or metabolism of glutamate might also be responsible for the dysregulation and excess concentrations of glutamate at the synaptic level (20).

In addition, the neurodevelopmental model is one of the most widely accepted theories for the aetiology of schizophrenia. It argues that complex interactions between numerous genetic and environmental factors disrupt normal brain development, particularly synaptic formation and connectivity (1). The aetiology of schizophrenia has also been explained by the stress-vulnerability model, which suggests that an underlying psychobiological vulnerability established early in life causes schizophrenia (3).

Treatment

The objectives of schizophrenia treatment include targeting symptoms, preventing relapse, and enhancing adaptive functioning so that the patient can be reintegrated into the community. Pharmacotherapy is the cornerstone of schizophrenia management, but non-pharmacological therapies are also important as they fill in gaps in pharmacological strategies, and should be used as an addition to medication (6).

Antipsychotic medications are the main treatment of schizophrenia and have been used since the 1950s. They work by blocking dopamine D2-receptors, consequently supressing dopamine activity (8, 9). It has consistently been shown that antipsychotic action occurs when striatal D2- receptor occupation exceeds 65%; however, additional increases in the level of D2 -receptor inhibition do not result in improved antipsychotic effect. Instead, they result in side effects such as extrapyramidal side effects and hyperprolactinaemia (22).

First-generation antipsychotics were the first to be discovered and are effective in managing psychotic symptoms. However, these medications often lead to unbearable extrapyramidal side effects such as acute dystonia, akathisia, parkinsonism, and tardive dyskinesia (22). Due to the crippling side effects of the first-generation antipsychotics, second-generation antipsychotics were introduced in the 1990s. At moderate doses, these are less likely to elicit extrapyramidal side effects, but many are associated with a high risk of metabolic side effects like weight gain, increased triglycerides, and cholesterol (8, 22). Furthermore, second-generation antipsychotics are no better than the first-generation at alleviating negative and cognitive symptoms (22). A particularly important antipsychotic drug is clozapine. Which can be perceived as an independent “third class” of antipsychotics, as it is the only antipsychotic medication that has proven efficacy in treatment-resistant schizophrenia (TRS). However, the exact mechanism that makes clozapine so superior is still unknown (22).

In the event of an acute psychotic episode, prompt pharmacological treatment should be delivered. Following treatment for the acute episode of psychosis, maintenance therapy is indicated as it is essential to avoid relapse. The incidence of relapse is 18% to 32% among patients receiving maintenance therapy versus 60% to 80% among those not receiving this treatment. After the remission of the initial psychotic episode, drug therapy should be continued for at least a year (6).

Even though pharmacotherapy is the cornerstone of schizophrenia treatment, residual symptoms may persist. Therefore, non-pharmacological therapies are also important.

Pharmaceutical non-adherence is a serious concern, and one study reported that 74% of patients stopped taking their medicine within 18 months (23). Non-pharmacological treatments can make sure that patients remain adherent to their medication. This is extremely important because nonadherence increases risk of relapse (6). The relapse rate after discontinuing antipsychotic medication is estimated to be greater than 50%, and more than 50% of those re-hospitalized had stopped their medication. It has been shown that the correlation between bad outcome, increased symptoms, poor function, and nonadherence is causative, i.e., nonadherence causes poor outcome (24).

One type of non-pharmacological therapy that has shown promising results is community case management such as "Assertive community treatment" (ACT). Compared to conventional therapies, ACT reduces symptoms and rehospitalization, stabilizes housing in the community and improves the overall quality of life (3).
In Norway ACT was first established in 2013 as "Flexible Assertive Community Treatment" (FACT), and there are now 60 FACT-teams in the country. The implementation of ACT in Norway caused the rate of psychiatric admissions to remain unchanged, but the amount and duration of patients admitted dropped to around half of what it was two years before ACT. The total number of days spent in hospital were also reduced by 33% (25).

Despite the availability of almost 60 different antipsychotics, almost 30% of schizophrenia patients are considered to have TRS, as they show minimal or no response to two alternative antipsychotic treatments. Even though Clozapine is the only medication with a proven effect on TRS, 60% of TRS patients will not respond to clozapine and are subsequently diagnosed with clozapine resistant schizophrenia (CRS) (26, 27).
While current medications reduce positive symptoms of schizophrenia, they are inadequate against negative symptoms and cognitive impairment, despite their substantial contribution to lessening the overall burden of illness. Therefore, improving treatment of schizophrenia is a priority, and future pharmaceutical development must focus on the need for medicines that address negative symptoms and cognitive deficits (1, 22). Given schizophrenias high heritability, a better understanding of the genetics of schizophrenia may provide opportunities for improved treatment and outcomes.

Genetics of schizophrenia

Twin and family studies have clearly demonstrated that schizophrenia has a substantial genetic component, with a heritability of roughly 80-85% (28). Monozygotic twins were found to have more than a three-fold grater concordance for the disorder than dizygotic twins (17). Even though a genetic basis for schizophrenia has been well-established, it has been difficult to identify specific molecular genetic variants associated with the disorder. Therefore, the prevalent view of schizophrenia in terms of genetics is that it is a polygenic disorder, with a genetic architecture made up by many single nucleotide polymorphisms (SNPs), each with a small effect on disease vulnerability. This concept of schizophrenia serves as the basis for the current focus on genome-wide association studies (GWAS) combining multiple case-control studies across the world to maximise sample size (8, 17).

A genome-wide association study (GWAS) is a research method that tests millions of genetic variants across thousands of participants to detect variants that are statistically associated with a risk for a disease or a specific trait. As GWASs concentrate on statistical associations, they provide information about correlation and not causality (29). SNPs are the genetic variants that are most frequently analysed in GWAS. A GWAS usually presents sets of linked SNPs that all have a statistically significant correlation with the relevant trait (30). GWAS results have a variety of uses, such as understanding the genetic architecture of a trait, estimating its heritability, identifying genetic associations, estimating genetic risk, guiding pharmaceutical research, and determining possible causal links between risk factors and health outcomes (30).

Prior to 2014, multiple schizophrenia GWAS failed to identify a substantial number of markers reaching genome-wide significance. The 2014-GWAS of schizophrenia therefore represented a major breakthrough in our understanding of the genetic liability for schizophrenia. This study identified 128 genome-wide significant SNPs, spanning 108 independent loci, associated with schizophrenia. Not only was this study the first to identify a ground-breaking number of significant SNPs, but it was also the first to validate the GWAS approach in schizophrenia by discovering for the first time a genome-wide significant association with a polymorphism implicating the *DRD2-gene*. This was a crucial discovery because the *DRD2- gene* encodes the dopamine D2-receptor; the main target of all currently approved antipsychotic drugs (28).

Since 2014, there have been a plethora of studies leveraging the findings from the 2014-GWAS of schizophrenia applied to a variety of settings. In addition, an updated schizophrenia

GWAS incorporating over two times the number of participants was published in 2022. Given the high societal and individual burden associated with schizophrenia and the high rate of failed treatment, improvements in understanding and treatment are required. With clear evidence of a strong genetic component, findings from large scale molecular genetics studies have the potential to provide important insights which may result in improved outcomes for patients. Specifically, we aimed to first summarise the clinically applicable findings from the two largest schizophrenia GWAS. We then aimed to identify research articles which investigated whether or not large scale GWAS data could be used to inform clinical practice, either for diagnosis, treatment, or prognostication of schizophrenia patients.

Method

Search preparation

The topic question for this literature review was defined using the PICO-format, as it facilitates the search process by defining the key components that must be present in the article in order to provide an answer (31), thus helping to define appropriate search terms. Although the PICO-format consists of four components; Population/Patient, Intervention/Exposure/prognostic factor, Comparison and Outcome (31), only three components were applied to this topic question since the research question does not relate to a specific comparator.

Population/Patient (P)
The population of interest are adults (19+ years) diagnosed with schizophrenia.

Intervention/ Exposure/ Prognostic factor (I)
The application of GWAS based genetic findings in clinical practice.

Outcome (O)
Can the results of these studies have an impact on clinical care (treatment, diagnostics, prognosis)?

Search terms obtained using the PICO-format:

P	Schizophrenia Schizophrenic Schizophreniform Psychosis Psychotic disorder Schizoaffective
I	GWAS Genetics Genomic Genome-wide
O	Treatment Therapy Clinical Diagnose Diagnosis Prognosis Trajectory Stratification Prevention

Search strategy:

The search was carried out in the PubMed database, which has more than 34 million citations for biomedical literature from MEDLINE, life science journals, and online books (32).

Inclusion and exclusion criteria:

- Only articles available in English were included.
- Only research conducted on adults was included, as schizophrenia is typically diagnosed in the late teens and early adulthood even though it can -on rare occasions- occur in childhood, and is then referred to as early-onset schizophrenia (4).
- Given the recent advances and findings within GWAS of schizophrenia, only large schizophrenia GWAS and studies applying findings from these GWAS were included.
- The search was restricted to only include articles published in 2014 and later.
- Literature reviews were excluded.
- Candidate gene studies were excluded because findings from such studies have frequently failed to replicate and the "hypothesis free approach" of GWAS is now accepted as the preferred approach for complex human diseases (33).
- Twin-studies that do not directly include genetic data were excluded.
- Studies on pharmacogenetics were excluded.
- The search was restricted to articles available online.

A summary of the PubMed search phrases can be seen below:

- The search was initiated on 27.09.22 and completed on 06.11.22. Search words: "(*Schizophrenia OR Schizophrenic OR Schizophreniform OR psychosis OR «psychotic disorder» OR Schizoaffective) AND (GWAS OR genetics OR genomic OR genome-wide) AND (treatment OR therapy OR clinical OR diagnose OR diagnosis OR prognosis OR trajectory OR stratification OR prevention*)".

PubMed's filter option was utilized to narrow the search results to the types of articles that were most relevant based on the set inclusion and exclusion criteria. Added filters included, "*Case reports, Clinical study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative study, Controlled clinical Trial, Evaluation study, Guideline, Meta-analysis, Multicenter Study, Observational study, Practice guideline, Pragmatic Clinical Trial, Randomized Controlled Trial, English, Adult: 19+ years, Humans, from 2014-2022"*

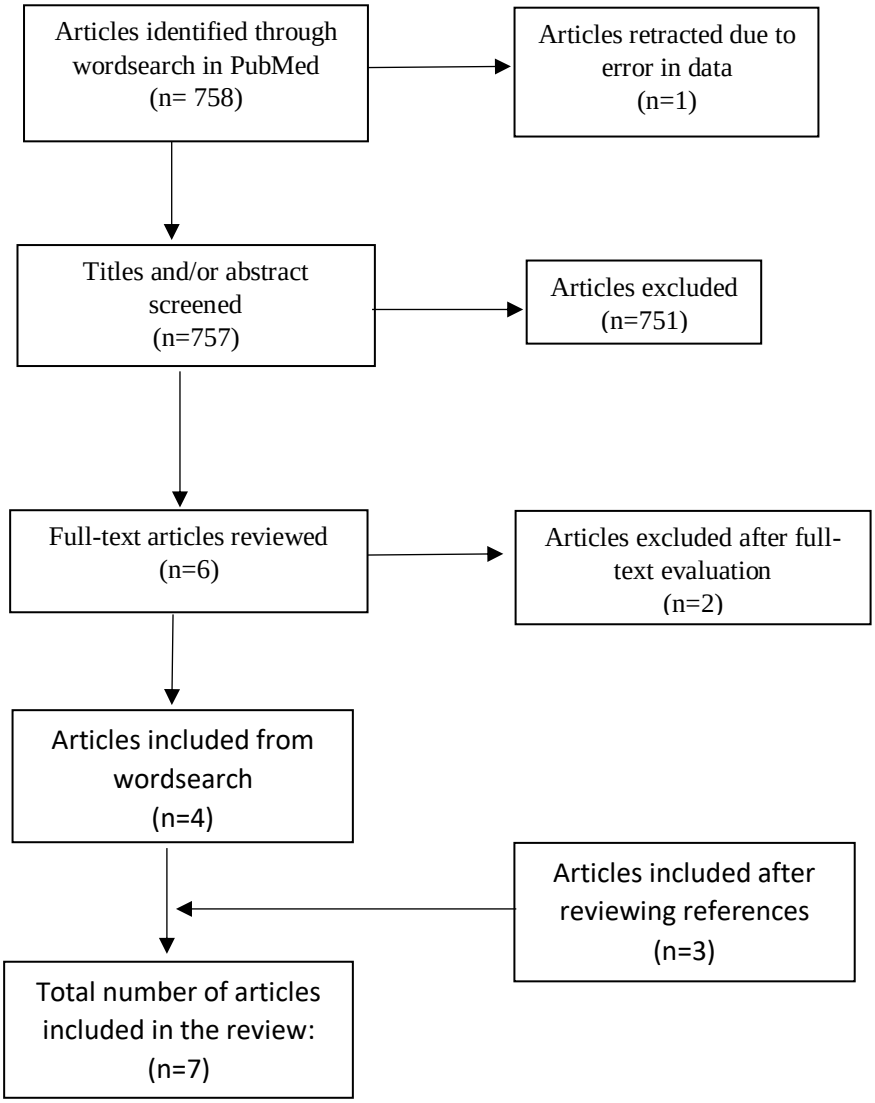
Database	**Search words**	**Filters activated**
PubMed	(*Schizophrenia OR Schizophrenic OR Schizophreniform OR psychosis OR «psychotic disorder» OR Schizoaffective*) AND	Case reports, Clinical study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative study,

	(GWAS OR genetics OR genomic OR genome-wide) AND *(treatment OR therapy OR clinical OR diagnose OR diagnosis OR prognosis OR trajectory OR stratification OR prevention*)	Controlled clinical Trial, Evaluation study, Guideline, Meta-analysis, Multicenter Study, Observational study, Practice guideline, Pragmatic Clinical Trial, Randomized Controlled Trial, English, Adult: 19+ years, Humans, from 2014-2022

Search results

The search in PubMed resulted in a total of 758 articles. We went through each articles title and abstract/summary before sorting them according to the specified inclusion- and exclusion criteria. Majority of the excluded studies focused primarily on illnesses other than schizophrenia, and those that did study the disorder did not address the genetics of it. Additionally, a large number of the excluded papers were candidate gene studies. Ultimately, the search left us focused on six articles. Two of them were excluded because although they discussed the genetics of schizophrenia, they did not study the clinical application of the findings. Thus, we had four articles relevant to the thesis question. Next, we looked through the reference lists of the articles already included and discovered three more that fit the inclusion criteria. Finally, we were left with seven articles to include in this thesis.

Flowchart:


Articles identified through wordsearch in PubMed (n= 758)
Articles retracted due to error in data (n=1)
Titles and/or abstract screened (n=757)
Articles excluded (n=751)
Full-text articles reviewed (n=6)
Articles excluded after full-text evaluation (n=2)
Articles included from wordsearch (n=4)
Articles included after reviewing references (n=3)
Total number of articles included in the review: (n=7)

Results

Overview of results

Author	Year	Title (Reference)	Design/ Sample size	Result
S. Ripke, B. M. Neale, A. Corvin, J. T. R. Walters, K.-H. Farh, P. A. Holmans, et al	2014	Biological insights from 108 schizophrenia-associated genetic loci. (34)	Genome-Wide Association Study. 36,989 cases and 113,075 controls.	Identified 128 independent associations of genome-wide significance spanning 108 loci. 83 loci were new discoveries. PRS value was too low to predict risk in clinical setting.
V. Trubetskoy, A. F. Pardiñas, T. Qi, G. Panagiotaropoulou, S. Awasthi, T. B. Bigdeli, et al.	2022	Mapping genomic loci implicates genes and synaptic biology in schizophrenia. (35)	Genome-Wide Association Study. 76,755 schizophrenia cases and 243,649 control individuals	Identified 287 loci with CNVs, and 120 genes underpin associations at some of the 287 loci. PRS was insufficient for predicting diagnose in general population.
Y. Lu, J. G. Pouget, O. A. Andreassen, S. Djurovic, T. Esko, C. M. Hultman, et al.	2018	Genetic risk scores and family history as predictors of schizophrenia in Nordic registers. (36)	Case-Control study. 5959 schizophrenia cases and 8717 controls	PRS was better at predicting risk of schizophrenia than family history, but combined they offer greater discrimination. Both measures, even when combined, did not meet the minimum AUC threshold for clinical utility.
A. B. Zheutlin, J. Dennis, R. Karlsson Linnér, A. Moscati, N. Restrepo, P. Straub, et al.	2019	Penetrance and Pleiotropy of Polygenic Risk Scores for Schizophrenia in 106,160 Patients Across Four Health Care Systems. (37)	Phenome-Wide Association Study. 106,160 individuals (56% female)	PRSs were strongly associated with schizophrenia. 1% absolute risk for the top PRS-decile. PRS effects were not big enough to predict risk in clinical setting.
D. O. Perkins, L. Olde Loohuis, J. Barbee, J. Ford, C. D. Jeffries, J. Addington, et al.	2020	Polygenic Risk Score Contribution to Psychosis Prediction in a Target Population of Persons at Clinical High Risk. (38)	Longitudinal Study. 764 psychosis high-risk participants and 279 unaffected participants.	Mean PRS was greatest for high-risk converters. PRS was more effective at predicting psychosis risk for Europeans than non-Europeans, but AUC was still under the threshold for clinical utility. Psychosis risk-calculator performed better when PRS was included.
D. M. Ruderfer, A. W. Charney, B. Readhead, B. A. Kidd, A. K. Kähler, P. J. Kenny, et al.	2016	Polygenic overlap between schizophrenia risk and antipsychotic response: a genomic medicine approach. (39)	Genomic Association Study.	Found that 35 of 167 gene sets of drug targets were enriched for schizophrenia-risk. Only antipsychotics had association for these genes. Findings suggest overlap between pathophysiology and antipsychotics mechanism of action. Results suggest the use of genomic data to improve effect of antipsychotics.
J. Li, A. Yoshikawa, M. D. Brennan, T. L. Ramsey and H. Y. Meltzer	2018	Genetic predictors of antipsychotic response to lurasidone identified in a genome wide association study and by schizophrenia risk genes. (40)	Study that coupled GWAS-data with results from two randomised controlled trials (RCT) of acutely psychotic schizophrenia patients. 478 patients in the 2011 clinical trial and 500 patients in the 2013 clinical trial.	Identified several gene variants strongly associated with response to lurasidone. None were of genome-wide significance, but many were linked to schizophrenia. Findings confirmed that variants with significant association to schizophrenia risk, contributed to predicting response to lurasidone.

Table 1: Overview of results

Summary of article results

Biological insights from 108 schizophrenia-associated genetic loci 2014 (34).

The authors theorized that sample size was one of the major factors limiting the GWAS approach in schizophrenia, and therefore conducted a large, multi-stage GWAS of schizophrenia with the aim to combine all available schizophrenia samples with published and unpublished GWAS genotypes into a single, systematic analysis. It comprised up to 36,989 cases and 113,075 controls. They collected genome-wide genotype data and created 49 ancestry-matched, non-overlapping case-control samples. 46 samples were of European ancestry, and three were of Asian ancestry. Each sample was then tested for associations. The study identified 128 independent associations exceeding genome-wide significance at 108 conservatively defined loci. Of the 108 identified loci, 83 had never previously been reported. 75% of the 108 loci were protein-coding genes. They discovered various associations relevant to major theories about the aetiology and treatment of schizophrenia, including the *DRD2*-gene (which codes for the dopamine receptor D2, the target of all approved antipsychotics (22)), genes implicated in glutamatergic neurotransmission and synaptic plasticity, and associations at genes encoding voltage-gated calcium channel subunits. They also discovered proof of overlap between genes within schizophrenia GWAS regions and genes affected in intellectual disability and autism spectrum disorder (ASD). Both, genes expressed in the brain as well as genes expressed in tissues with important immune functions were found to be significantly enriched for schizophrenia associations. It was also confirmed that polygenic risk score (PRS) derived from alleles showing modest associations with schizophrenia in a discovery GWAS can predict case-control status in independent samples.

The PRS generated in this study explained approximately 7% of variation on the liability scale to schizophrenia across all samples, about half of which (3,4%) was accounted for by genome-wide significant loci. The PRS had low sensitivity and specificity, with an area under the receiver operating curve (AUC) of 0.62 in one of the samples.

Mapping genomic loci implicates genes and synaptic biology in schizophrenia 2022 (35).

To better understand the role of common variants in schizophrenia, a large two-stage GWAS comprised of up to 76,755 cases and 243,649 controls, was conducted in 2022. First a primary GWAS was performed in 74,776 schizophrenia cases and 101,023 controls, followed by an extended GWAS including additional data for the most significant SNPs. They analysed

the results to prioritize variants, genes and biological mechanisms that might contribute to the pathophysiology of the disorder.

The study identified 287 genomic loci with common variant associations (CNV). Further analysis discovered 120 genes that may strengthen associations at some of these 287 loci. 106 of the 120 genes are protein-coding. Results showed an increasingly clear contrast between enrichments in brain and non-brain tissues. Associations were enriched in genes with high expression in excitatory glutamatergic neurons from the cerebral cortex and hippocampus, and in inhibitory cortical interneurons. Genes encoding receptors and ion channels, such as voltage-gated calcium channels, were also reported to be enriched for associations. Additionally, they found evidence suggesting that neuronal function, including synaptic organization, differentiation, and transmission are involved in disease pathophysiology.

It was confirmed that among the genes expressed in the brain, those relatively intolerant to loss-of-function mutations were especially enriched for schizophrenia associations. Of the 106 protein-coding genes identified, 15 genes had synaptic annotations; confirming that the pathophysiology of the disease is likely to entail both pre- and postsynaptic dysfunction. It also demonstrated that common variant schizophrenia associations were enriched at genes involved in neurodevelopmental disorders. In this study PRS-analysis explained 7.3% (0.073) of variance in liability, of which 2.4% (0.024) was explained by SNPs of genome-wide significance. The highest PRS-centile had an odds ratio for schizophrenia of 39 (95% CI: 29-53) when compared to the lowest PRS-centile. The PRS had a median AUC of 0.72 in the European cohorts.

Genetic risk scores and family history as predictors of schizophrenia in Nordic registers 2018 (36).

Aiming to evaluate whether the predictive power of family history could be minimized or eliminated by adding PRS, a direct measure of genetic liability, this study examined 5959 schizophrenia cases and 8717 controls from four Nordic nations. Information on case/control status and family history of schizophrenia was taken from national health registers. Cases included individuals with schizophrenia or schizoaffective disorder, while controls were subjected to different inclusion and exclusion criteria that varied by country. PRSs for schizophrenia were estimated based on results from the 2014-GWAS of schizophrenia. Results showed that a positive family history was present in 10-14% of cases and 1% of controls. A positive family history was linked to a roughly 10-fold increased risk of

developing schizophrenia. Negative family history increased the risk of schizophrenia 2.48 times and 5.9 times for individuals with moderate and high genetic risk, respectively, compared to those with low PRS. Compared to cases with a negative family history, cases with a positive family history had a considerably higher mean value of PRS. The average PRS-values reported were higher among cases than controls within each study site, and the case-control disparities were greatest for PRS for schizophrenia and bipolar disorder. Variance on the liability scale explained by PRS for schizophrenia was 5.3%. By increasing the schizophrenia PRS by one standard deviation, the risk for schizophrenia increased 83%. The study demonstrated that both family history and genetic risk profiles are powerful schizophrenia predictors, even when considered together. PRS combined with a thorough family history explained 9% of the variance in liability for schizophrenia. Combining both measures produced an AUC of 0.73.

Penetrance and Pleiotropy of Polygenic Risk Scores for Schizophrenia in 106,160 Patients Across Four Health Care Systems 2019 (37).

The aim of this study was to evaluate the usefulness of genetic profiling as a method for risk stratification in clinical settings as well as the impact high genetic risk for schizophrenia has on overall health. They calculated PRSs for schizophrenia and conducted a phenome-wide association study (PheWAS) to test the schizophrenia PRS for association with schizophrenia and 1,358 additional diseases.

The sample comprised 106,160 individuals (56% female) from four major U.S. healthcare systems with readily available electronic healthcare records (EHR) and genotype data. The PRS was calculated based on summary data from the 2014-GWAS of schizophrenia. This study was restricted to individuals of European-American ancestry only. Apart from data availability and ancestry restrictions, no additional criteria for inclusion or exclusion were set. Results showed that PRSs were strongly associated with schizophrenia, with an absolute risk of 1% for the top decile. Individuals in the top decile of PRS distribution had close to 4.6 times higher risk of developing schizophrenia than those is the lowest decile.

The study also revealed significant associations between schizophrenia PRSs and several other medical phenotypes, with psychiatric phenotypes such as bipolar disorder, anxiety disorder, depression, and substance use disorder exhibiting the strongest association. In contrast, obesity and morbid obesity were inversely correlated with schizophrenia PRS. The

observed PRS had an AUC that remained within 0.60-0.71 across all sites.

Polygenic Risk Score Contribution to Psychosis Prediction in a Target Population of Persons at Clinical High Risk 2020 (38).

The North American Prodrome Longitudinal Study, phase 2 (NAPLS-2), was an eight-site, two-year study to research mechanisms and predictors of psychosis conversion, including 764 psychosis high-risk and 279 healthy (unaffected) control participants. The purpose of this study was to examine how well PRS can predict psychosis in high-risk individuals and evaluate the effects of adding PRS to an already validated psychosis risk calculator. They calculated PRS based on results from the 2014-GWAS of schizophrenia and compared the PRS of high-risk participants who developed psychosis (converters) to the PRS of high-risk participants who didn't develop psychosis (non-converters) and unaffected participants. Furthermore, they added the PRS as an additional variable to an existing psychosis risk calculator to assess its impact.

The mean PRS values were greater in high-risk converters than in non-converters and unaffected participants, and higher in nonconverters than in unaffected individuals. PRS was higher in individuals with a positive family history of psychosis than in those with a negative family history. For Europeans, the PRS was significantly greater in converters than non-converters and unaffected individuals but was similar for unaffected individuals and non-converters. In non-Europeans the PRS was significantly greater in converters than in unaffected individuals and was similar for nonconverters and unaffected individuals. However, there was no significant difference between converters and nonconverters. When predicting two-year psychosis conversion risk in high-risk individuals, the PRS had more predictive power in Europeans than in non-Europeans, with a greater AUC for Europeans (0.65) than for non-Europeans (0.59).

The psychosis risk calculator performed better with PRS included than without PRS. For non-Europeans the AUC remained at 0.67 for the risk calculator both with and without the PRS. For Europeans the AUC increased from 0.70 to 0.71 when PRS was included in the risk calculator. The amount of risk prediction knowledge provided by the addition of the PRS to the psychosis risk calculator was approximately 15% for Europeans and 7% for non-Europeans. By eliminating family history as a variable in a risk calculator where PRS was included, the calculators' predictive accuracy remained unaffected for Europeans.

Polygenic overlap between schizophrenia risk and antipsychotic response: a genomic medicine approach 2016 (39).

To inform and enhance treatment of schizophrenia, this study aimed to connect schizophrenia risk loci with gene targets of a wide range of medications by trying to determine which medications target proteins encoded by genes assumed to have a role in schizophrenia. Schizophrenia risk loci were defined as loci that reached genome-wide significance in the 2014-GWAS of schizophrenia. Drug targets were grouped into 167 gene sets targeted by similar drugs and then analysed for enrichment of schizophrenia risk loci to find which medications were enriched for targeting these risk loci.

Results showed that of the 167 gene sets, 35 (21%) were enriched for genes within the schizophrenia risk loci, and out of all the drug-classes only antipsychotics had associations for these genes. Forty antipsychotics had at least one gene target enriched for schizophrenia risk. One of the targets included the *DRD2-gene.* Thus, they discovered that the drug class with the strongest genetic support for treating schizophrenia were antipsychotics, and that their effect is mediated by a polygenic mechanism.

*Genetic predictors of antipsychotic response to lurasidone identified in a genome wide association study and by schizophrenia risk genes 2018 (40)***.**

The authors sought to locate common variations in genes that might predict response to the atypical antipsychotic drug (AAPD) lurasidone, by coupling data from GWASs with changes in Positive and Negative Syndrome Scale (PANSS) scores from two clinical trials of acutely psychotic schizophrenia patients. Both trials were "six-week, randomized, double-blind, lurasidone, placebo-controlled, multicentre registration trials". PRS was calculated based on data from the 2014-GWAS of schizophrenia to assess whether the identified genetic variants associated with schizophrenia risk had a significant impact on predicting treatment response to lurasidone. Polygenic risk modelling was only conducted for Caucasian patients.

The study identified several genetic variants strongly associated with treatment response to lurasidone in schizophrenic patients with acute psychosis. The identified variants were related to synaptic adhesion and scaffolding genes, and genes related to synaptic plasticity. The top variants associated with predicting treatment response in the lurasidone group did not predict response in the placebo-treated group, indicating that these associations were unique to lurasidone. Although none of these variants achieved genome-wide significance, many of them have previously been linked to schizophrenia and other psychiatric disorders. It was

confirmed that the genetic variants with a genome-wide significant association with schizophrenia risk, substantially contributed to predicting response to treatment with lurasidone. Similarity among the findings in this study and the schizophrenia risk genes suggests that treatment response to lurasidone and other atypical antipsychotic medications may be driven by the pathology that underlies the disorder.

Discussion

This literature review aimed to first summarise the clinically applicable findings from the two largest schizophrenia GWAS. Additionally, it aimed to identify research articles which investigated whether or not largescale GWAS data could be used to inform clinical practice, either for diagnosis, treatment, or prognostication of schizophrenia patients. This review included seven articles that investigated various aspects of the genetics of schizophrenia and the use of PRS in predicting schizophrenia risk (36-38) and treatment response (39, 40). The results indicate that schizophrenia is a complex disorder with a significant genetic component, and that PRSs can potentially be used to predict the risk of schizophrenia and treatment response in certain populations. Although the potential is there, PRSs are not currently ready to be used in clinical practice.

Findings from the largest schizophrenia GWAS

The 2014-GWAS and 2022-GWAS of schizophrenia both aimed to investigate genetic factors that might contribute to the development of schizophrenia. The 2022-GWAS had a much bigger sample size and identified nearly twice as many loci and genetic variants associated with risk of schizophrenia (35). In addition, the 2014-GWAS focused on European ancestry participants, while the 2022-GWAS including participants from diverse ancestry backgrounds. Both demonstrated that associations are not randomly spread among all kinds of genes, suggesting that schizophrenia is largely a disorder of neuronal dysfunction but not limited to a specific area of the brain (34, 35). Both studies calculated PRSs and tested their ability to predict case-control status in separate samples. The PRS from the 2014-GWAS had an AUC of 0,62, while the PRS from the 2022-GWAS had an AUC of 0.72. Although the 2022-GWAS PRS had a larger AUC, it was still not sufficient to predict risk in the general population as the minimum AUC requirement for clinical use is 0.75. Nevertheless, both studies emphasized that PRS still holds value for further research as it opens new possibilities in clinical and epidemiological studies. Accordingly, several studies have later used the data from the 2014-GWAS of schizophrenia to calculate PRS-values and assess how the findings can be used in the clinic, including the five articles presented in this thesis.

Predicting risk of schizophrenia

While the prognosis of schizophrenic patients might be unpredictable (6), the disease is associated with significant disability and a considerably high mortality rate (11, 14).
Early detection is essential for better prognosis, but the lack of reliable biomarkers makes it difficult to detect early stages of the disease and diagnosis still relies on clinical observation

(41, 42). Given the polygenic architecture of the disease, there is growing interest in using quantitative markers of genetic risk, such as PRS, to predict schizophrenia risk (37).

Three articles analysed in this review demonstrated the potential of PRS as a predictor of schizophrenia risk (36-38). The studies found that PRS can predict the risk of schizophrenia to some degree, but accuracy varies depending on the population studied. All three studies used data from the 2014-GWAS of schizophrenia to calculate PRS (34). The study by Lu et al. found that PRS and family history both predicted schizophrenia risk in a Nordic sample, with PRS being a stronger predictor than family history alone. Family history only accounted for about half of the information provided by PRS. Although combining the two measures yielded a higher AUC than PRS alone, the AUC was still not sufficient for clinical use (36). Perkins et al. found that PRS alone was not a reliable predictor of psychosis risk in both Europeans and non-Europeans. However, when PRS was included in existing psychosis risk calculators, their predictive accuracy improved. Nonetheless, their accuracy remained too low for clinical use (38). The study also revealed that the risk calculators' performance was not impacted by the inclusion or exclusion of family history when PRS was included as a variable, suggesting that PRS is at least as effective, if not more so, at predicting the risk of schizophrenia compared to a thorough family history (38). This conclusion aligns with the findings from Lu et al.'s study, which demonstrated that PRS is a stronger predictor of schizophrenia risk than family history (36). Zheutelin et al. found that PRS in a sample of European-American ancestry had an AUC ranging from 0.60-0.71; values not high enough to predict risk of schizophrenia in a clinical setting (37). The PRS effects in this study might best reflect results that would be seen in real-world clinical setting, as it had a much bigger sample size and used passively collected clinical data instead of "clean" case-control samples like the other two studies (37).

While the predictive accuracy of PRS did not reach an AUC of 0.75 in any of these three studies, the reported AUC values between 0.59 - 0.73 were comparable to the AUC for PRS observed for schizophrenia (0.62) in the 2014-GWAS of schizophrenia and other complex diseases such as type-II diabetes (0.70), inflammatory bowel disease (0.60), and breast cancer (0.66), which have been considered to be reliable enough to be used in the clinic (37, 43). Even though PRS was found to be a strong predictor of schizophrenia, it never reached the minimum AUC requirement for clinical use. The authors concluded that combining PRS with other variables, such as family history, could improve discriminatory accuracy. However, results may not be generalizable to non-European populations as all studies were based on the 2014-GWAS of schizophrenia.

Predicting effect of treatment

Drugs whose targets are directly supported by genetic data are more likely to be clinically successful (39). Two of the articles reviewed in this thesis used data from the 2014-GWAS of schizophrenia to investigate the relationship between genetic risk for schizophrenia and response to antipsychotic medications (39, 40).

Ruderfer et al. found that many of the genetic variations associated with increased risk for schizophrenia were also associated with a better response to antipsychotic drugs.

The authors proposed that the genetic mechanism that contribute to the development of schizophrenia may also affect the response to treatment, leading to the possibility of personalising treatment based on a patients' genetic predisposition (39). The second study by Li et al. identified several genetic variations associated with a better response to the antipsychotic drug lurasidone. These variations were mostly located in genes related to neurotransmitter pathways, including the dopaminergic and serotonergic pathways, which are thought to play a role in the development of schizophrenia and the mechanism of action of antipsychotic drugs. The authors suggested that these genetic variations might impact the effectiveness of the drug by affecting neurotransmitter activity (40).

Both studies suggested that there is a genetic component to antipsychotic response in individuals with schizophrenia and discovered that many of the genetic variations associated with schizophrenia also influence the response to antipsychotic treatment.

Overall, they concluded that information from genetic studies of schizophrenia, such as PRS, could potentially be used to predict and improve response to antipsychotic treatment and advance personalised treatment of schizophrenia patients by tailoring the treatment based on their genetic risk profile. However, it is important to note that these studies only established associations and not causation, and it remains unclear if the identified genetic variants are directly involved in the observed variation in response to antipsychotic drugs. In addition, both studies had a small sample size, limiting the generalizability of their findings.

Ancestry

GWASs of schizophrenia have predominantly been conducted in samples of European ethnicity (28). Restricting a sample to participants of the same ancestry allows for better control of population stratification; an important issue in case-control studies as it is a possible source of false positive associations (44). However, excluding samples of other populations from studies will limit the generalizability of GWAS results to other populations and underestimate the genetic burden of disease in those populations and further perpetuate

existing health disparities (28, 45). For instance, a 2009 study found that PRS generated from a European population explained significantly less of the variance in an African American sample compared to two independent European samples (46). The 2022-GWAS of schizophrenia discovered that PRS had greater predictive power for almost all populations when based on risk alleles from a bigger combined ancestry GWAS rather than risk alleles from a matched ancestry GWAS (35). This means that because the 2014-GWAS of schizophrenia focused on European samples, its findings may not be generalizable to other populations.

Limitations

There are several limitations that can impact the accuracy and validity of the conclusions drawn from this literature review.

First, by limiting the search to exclude articles published before 2014 we may have missed out on important findings that could have been relevant to the thesis question, and by only focusing on the two largest schizophrenia GWAS and studies that used data from the 2014-GWAS, studies performed on non-European populations were dismissed. As a result, the findings are not representative for non-European populations. Yet, since schizophrenia GWASs before 2014 failed to identify a substantial number of markers reaching genome-wide significance, we are confident that we still managed to include the most relevant studies.

By applying the age filter "adult: 19+ years", instead of manually excluding irrelevant studies, we might have excluded potentially relevant findings related to implications of schizophrenia GWAS, simply because the studies focused on people under 19 years old. However, we feel confident that this choice did in fact include the most relevant studies.

Three of the articles included were identified through manual search which also suggest the search may have missed other relevant articles.

The small number of articles included in this review is also a limitation, as it makes it challenging to draw accurate and reliable conclusions.

The articles featured in this thesis did not draw from the results of the 2022-GWAS of schizophrenia, as the literature search was also conducted in 2022 and none of the articles retrieved made use of this study's findings. The 2022-GWAS is a combined-ancestry GWAS with a larger and more diverse sample than the 2014-GWAS of schizophrenia, which suggests that its outcomes may be more broadly applicable to non-European populations.

Due to these limitations, this review may portray the current state of knowledge on this

research topic in an incomplete or biased manner. If this study were to be repeated, we would consider performing the search with a second party to make the search process more rigorous.

Conclusion

The articles analysed in this thesis indicate that genetic information obtained from GWAS of schizophrenia holds potential for predicting the risk of developing the disease, predicting a patient's response to antipsychotic treatment, and finding the most appropriate treatment. However, the effect of PRS, alone or when combined with family history, was not sufficient for risk prediction in a clinical setting. Nonetheless, the accuracy of risk prediction improved when PRS was combined with other variables, such as family history, suggesting that PRS has extra predictive value and might even provide more information than family history. Additionally, the identification of polygenic overlap between schizophrenia risk and response to antipsychotic medication highlights the potential of genetic information to improve the effectiveness of treatments. Although the 2014-GWAS of schizophrenia provided important insight into the genetic basis of the disorder, its applicability to non-European populations may be limited due to its reliance on a sample of European populations. Thus, further research is needed to fully explore the clinical implications of schizophrenia and to improve clinical and patient outcomes.

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