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Mini Review

Applications of Polygenic Risk Scores in Psychiatric Genetics

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Abstract

Polygenic risk score (PRS) is a powerful tool for studying the genetic architecture of complex diseases, including psychiatric disorders. This review highlights the use of PRS in psychiatric genetics, including its application in identifying high-risk individuals, estimating heritability, assessing shared etiology between phenotypes, and personalizing treatment plans. It also explains the methodology for calculating PRS, the challenges associated with their use in clinical settings, and future research directions. The main limitation of PRS is that the current models only account for a small fraction of the heritability of psychiatric disorders. Despite this limitation, PRS represents a valuable tool that has already yielded important insights into the genetic architecture of psychiatric disorders.

Keywords: *Polygenic Risk Score; Psychiatric Genetics; Risk Assessment; Shared Etiology; Pleiotropy*

Introduction

Psychiatric disorders have a complex genetic architecture, with heritability estimates ranging from 40 - 80% [1]. Despite the progress made through genome-wide association studies (GWAS) in identifying common genetic variants linked to different psychiatric disorders, the precise role of genetic and environmental factors in their development and progression remains incompletely understood. However, the advent of polygenic risk scores (PRS) has revolutionized the study of multifactorial diseases, including psychiatric disorders. By aggregating the effects of numerous common genetic variants into a single score, PRS provides a quantitative measure of an individual's inherited risk for a specific disorder, making it a powerful tool for identifying high-risk individuals and facilitating early intervention and treatment [2-4]. Moreover, PRS can help explore the underlying biology of psychiatric disorders and identify potential drug targets [5]. This review article will focus on the application of PRS in psychiatric genetics, exploring its current use in identifying high-risk individuals and understanding the underlying biology of these conditions, as well as the challenges associated with its use in clinical settings and future research directions.

Methodology

For this review article, a systematic literature search was conducted using the PubMed database to identify papers published between 2010 and 2023. The search was conducted using relevant keywords such as, but not limited to, "PRS", "polygenic risk score", "psychiatry", "genetics", "mental illness" and "heritability". The quality of the papers was assessed, and only those that met the inclusion criteria were included in the article.

Calculation of PRS

There are two ways to determine the PRS [2,6]: the traditional and alternative methods. The traditional approach adds up the risk alleles an individual carries, with the weights determined by the effect sizes estimated by a GWAS on the trait. The score is based on the number of risk alleles an individual has for each included variant, with each risk allele's genotype dosage multiplied by its respective weight and summed across all variants in the score. The alternative method uses genome-wide genotypes, weighted by effect size estimates from GWAS summary data. The PRS combines the genetic effects of a group of SNPs that may not be individually significant but can contribute to phenotypic variance cumulatively. This approach quantitatively measures an individual's inherited risk based on the collective impact of numerous common polymorphisms.

Applications of PRS

PRS has various applications in psychiatric genetics. PRS can first establish shared etiology among major psychiatric disorders such as schizophrenia, bipolar disorder, major depressive disorder, and autism spectrum disorder by identifying risk loci with shared effects [7-12]. Furthermore, PRS has clinical utility in genetic counseling by forecasting the probability of developing psychiatric disorders. PRS can help identify high-risk groups and enable more thorough screening and preventative therapies [2,4,13,14]. Comparing the outcomes of individuals with low and high PRS values is also possible [2]. PRS can also be an effective predictor for various medical and psychiatric conditions, such as breast cancer, schizophrenia, and cardiovascular disease [15].

In addition, PRS can evaluate the interaction between genes and the environment and gene-to-gene interactions, and be useful in conducting Mendelian randomization studies to infer causal relationships [2,4,6,16]. Lastly, PRS can aid in estimating heritability, examining pleiotropy, patient stratification and sub-phenotyping, and personalization of treatment plans of complex mental health conditions [2,4].

Limitations and Future Directions

PRS holds great promise in predicting the risk of psychiatric disorders. However, there are several limitations and challenges that must be addressed. One major challenge is the lack of diversity in the reference datasets used to construct PRS. These models are typically based on specific ethnic groups, such as Europeans, and may not be relevant to other ethnicities. Additionally, the majority of current PRS models account for only a small portion of the heritability of psychiatric disorders [16], leaving a considerable amount of the genetic structure unexplained. PRS only captures the effects of common genetic variants and does not account for rare variants or non-genetic factors that may contribute to the development of psychiatric disorders. Moreover, the ability of PRS to predict risk is still limited, and there is a significant overlap between the PRS of individuals with and without psychiatric disorders. Consequently, PRS should not be used as a diagnostic tool, but as one aspect of a more comprehensive clinical evaluation. Future research should focus on developing more comprehensive and accurate PRS models, as well as integrating PRS with other genomic and clinical data to improve risk prediction and inform personalized treatment strategies. Despite these limitations, PRSs represent a valuable tool that has already yielded important insights into the genetic architecture of psychiatric disorders.

Conclusion

In conclusion, PRS has emerged as powerful tools for studying the genetic architecture of psychiatric disorders, enabling the identification of novel risk loci, individual-level risk prediction, and improved treatment decisions. The potential applications of PRS include

estimating heritability, assessing shared etiology between phenotypes, providing individual genetic predictions of phenotypes, and identifying individuals at high risk for a given disease for enhanced screening or preventive therapies. Although there are still limitations and challenges to be addressed, PRS has the potential to revolutionize the field of psychiatric genetics and improve our ability to prevent and treat these devastating disorders.

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