

Polygenic Risk Scores for Bipolar Disorder: Progress and Perspectives

Huanxi Liu^{1,2}, Ligang Wang², Hui Yu², Jun Chen^{3,*}, Ping Sun^{2,*}

¹Qingdao Medical College, Qingdao University, Qingdao, 266071, People's Republic of China; ²Qingdao Mental Health Center, Qingdao, 266034, People's Republic of China; ³Clinical Research Center, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jun Chen, Clinical Research Center, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China, Email doctorcj2010@gmail.com; Ping Sun, Mental Health Center, Qingdao, 266034, People's Republic of China, Tel +86 13589394393, Email qdsunping99@sina.com

Abstract: Bipolar disorder (BD) is a common and highly heritable psychiatric disorder, the study of BD genetic characteristics can help with early prevention and individualized treatment. At the same time, BD is a highly heterogeneous polygenic genetic disorder with significant genetic overlap with other psychiatric disorders. In recent years, polygenic risk scores (PRS) derived from genome-wide association studies (GWAS) data have been widely used in genetic studies of various complex diseases and can be used to explore the genetic susceptibility of diseases. This review discusses phenotypic associations and genetic correlations with other conditions of BD based on PRS, and provides ideas for genetic studies and prevention of BD.

Keywords: bipolar disorder, polygenic risk scores, risk forecast

Introduction

Bipolar disorder (BD) is a relapsing chronic disorder characterized by fluctuations in state of mind and energy fluctuations affecting more than 1% of the world's population. And it is associated with an increased risk of self-harm, suicide and premature death in young people, which has the highest heritability of all mental and behavioral disorders.^{1,2} Genome-wide association studies (GWAS) studies have shown that most common diseases are associated with polygenic mutations, which means that there are thousands of DNA variants contributing to disease risk. Polygenic risk scores (PRS) is a comprehensive assessment of the risk for a particular disease by amalgamating information from thousands of single nucleotide polymorphisms (SNPs) within large-scale genomic data.³ It calculates a risk score for each individual based on these genetic variants, allowing the identification of high-risk individuals and exploration of the association between genetic risk and disease development. Previous studies have identified thousands of risk genes affecting schizophrenia (SCZ) and BD, providing the basis for PRS studies in SCZ and BD.⁴ Since then, researchers have conducted extensive studies on PRS in SCZ and BD, mainly focusing on phenotypes, genetic correlations with other diseases, and the application prospects of PRS.

This paper aims to explore the latest developments in the use of PRS in BD research. We will review relevant literature, introduce the principles and applications of PRS, and delve into its specific use in BD research. Furthermore, we will discuss the clinical and research challenges associated with PRS and its potential applications in future research. By delving deeper into the role of PRS in bipolar disorder research, we hope to gain a better understanding of the genetic basis of this disorder, offering new directions for precision medicine and individualized treatment. The ongoing progress in this field provides insights into the genetic and biological factors at play in BD, presenting new opportunities for improving diagnosis, treatment, and care for affected individuals.

PRS and Its Predictive Accuracy

The classical PRS method combines the effect sizes of multiple SNPs from large GWAS studies into a single aggregated score, which can be used to predict an individual's disease risk. This approach greatly improves the small effect size of individual SNPs in GWAS results, and can be applied to target samples with relatively small sample sizes. From the current study, the predictive accuracy of PRS in psychiatric disorders is insufficient for clinical applications. Still, the ability of PRS to predict disease status helps us to understand the genetic structure of psychiatric traits.

Although PRS cannot individually predict disease risk, it has been successfully used to show significant associations within and between traits. For instance, GWAS of SCZ has been used to predict risk in target samples with various phenotypes such as BD.⁵ One of the characteristics of psychiatric disorders is the association of GWAS markers with different diseases caused by a polygenic basis. This type of cross-prediction cannot be achieved in other clinical conditions, such as cardiovascular diseases. PRS analysis is characterized by using foundational data of SNPs obtained from GWAS, along with a target number of genotype or phenotype samples.⁶ After constructing the PRS for all participants in the target sample, it can be used in logistic regression analysis to predict traits that have potential genetic overlap with the studied trait. The predictive accuracy of PRS mainly depends on the shared genetic variance of the analyzed trait, the number of SNPs used, and the sample size of the discovery sample, which can be measured using the R^2 statistic in regression analysis. The size of the target sample only affects the reliability of R^2 . If the trait's shared genetic variance and the discovery sample's sample size of the discovery sample are sufficiently large, several thousand participants in the target sample are typically needed to achieve a significant R^2 .⁷ The study by Dudbridge suggests that the power of PRS association testing is optimized by using equal-sized reference and target sample sizes. In contrast, individual-level prediction accuracy is optimized by maximizing the reference sample size.⁸ In summary, PRS currently performs better for association testing than for predicting complex diseases, but as sample sizes continue to increase, the prediction will become more feasible.

The Phenotype of BD Based on PRS

The Advancements in the Application of PRS in BD

Diagnostic Prediction and Staging of BD

Identifying high-risk individuals with increased genetic susceptibility to BD can provide new insights into the etiology of BD and aid in the early diagnosis of BD patients. BD patients, Birmaher et al evaluated the specific associations of bipolar disorder polygenic risk scores (BD-PRS) with familial transmission and effectiveness in pediatric BD, and explored the genetic contributions of BD transmission from parents to offspring. The results revealed that the BD-PRS of parents and offspring were independently associated with the risk of BD in offspring. However, due to the relatively small magnitude of the association with BD-PRS, it is currently insufficient to be used alone to determine BD risk.⁹ PRS has also made further progress in identifying disease subtypes. In the classification of psychiatric disorders, BD is divided into three types based on the prominence, severity, and timing of psychotic symptoms, mania, and depression: bipolar I disorder (BD-I), bipolar II disorder (BD-II), and schizoaffective bipolar type (SAB). Currently, the diagnosis and classification of BD subtypes mainly rely on clinical presentations. However, in recent years, researchers have attempted to incorporate genetic risk factors into the diagnosis and classification of BD subtypes. Charney et al compared the relative contribution of rare copy number variations (CNVs) and common SCZ risk alleles to the risk of psychosis, showing that compared to BD-I without psychosis, SAB had increased CNV burden and SCZ-PRS, and the presence of psychotic symptoms in BD-I was associated with increased SCZ-PRS.¹⁰ Aminoff et al also confirmed that BD-PRS was significantly higher in patients with psychotic BD compared to those with non-psychotic BD.¹¹ Subsequently, studies by Markota and Guzman-Parra further supported this finding. They found that BD-I with manic psychosis had significantly higher SCZ-PRS compared to other types of BD patients and the control group. These patients also exhibited lower MDD-PRS, suggesting that this subtype of patients is genetically more similar to SCZ than any other BD subtype.^{12,13}

With the advancement of research on PRS, new explorations have emerged in the diagnosis and differential diagnosis of other mental disorders. Calafato et al found a significant increase in BD and SCZ PRSs in individuals with a broad range of psychiatric disorders, and their relatives also showed a milder increase in PRS.¹⁴ Biere's research confirmed that

increased BD-PRS are significant predictive factors for major depressive disorder and attention-deficit hyperactivity disorder (ADHD).¹⁵ These studies support the existence of shared risks between other mental disorders and BD, and increasing our understanding of the underlying genetic characteristics of these phenotypes can aid in early disease identification and risk stratification. David et al indicated that BD and SCZ PRSs provide a moderate level of independent differentiation between BD and MDD cases, suggesting that PRS for psychiatric disorders can somewhat differentiate between the two diseases.¹⁶ In the future, utilizing PRS for differential diagnosis between diseases may be an important application direction.

Treatment Efficacy Study and Efficacy Prediction of BD

Lithium is a commonly used medication for the treatment of BD. There is significant variability in the response of BD patients to lithium, PRS can reveal pharmacogenomic effects and may help predict drug responses. The studies by Coombes and Schuber suggested that higher ADHD-PRS and MDD-PRS are associated with a poorer response to lithium treatment. Additionally, higher SCZ-PRS was associated with poorer lithium treatment response whereas BD-PRS had no association with treatment outcome.^{17,18} Due to the high genetic overlap between BD and other psychiatric disorders, combining genetic risk factors for ADHD, MDD, and SCZ with clinical risk factors may provide insights into the clinical care of BD patients. Cearns et al employed PRS for stratifying BD patients based on their genetic profile, and then they trained a machine learning model using clinical predictive factors. This approach resulted in significant improvements in predicting lithium response compared to single-genomic studies. In the future, combining with other PRS and biological markers may help inform which patients are more likely to respond favorably to lithium treatment.¹⁹

In addition to the well-known lithium, chlorpromazine (CLZ) is a commonly used mood stabilizer in clinical practice. In order to identify predictive factors for CLZ metabolism, dosage, and treatment response, Mayén-Lobo et al integrated PRS analysis based on methylation spectra to explore the genomic and epigenomic characteristics of 44 treatment-resistant psychiatric patients receiving CLZ therapy. They discovered an enrichment of the GABAergic synaptic pathway in BD-PRS that was associated with CLZ metabolism ratio, and this interaction provided support for the role of CLZ as a mood stabilizer.²⁰

Electroconvulsive therapy (ECT) has shown efficacy in cases of acute severe manic episodes, severe suicidal attempts in depression, or patients who are unresponsive to lithium treatment. Sigström et al examined whether the increased PRS for MDD, BD, and SCZ were associated with improvement in severe depression following ECT. The results showed that higher BD-PRS was associated with greater clinical improvement after ECT, whereas MDD-PRS showed the opposite effect, and SCZ-PRS was unrelated to improvement.²¹

Suicide Risk in BD Based on PRS

Patients with BD have a higher risk of suicide attempts (30–50%) and mortality (15–20%), about twice that of MDD. Their mortality rate is only lower than that of SCZ, so it is crucial to differentiate patients at high risk of suicide to better predict and prevent suicidal behavior and to identify suicidal risk factors in BD.²² As reliable biomarkers of suicide attempts (SA) are lacking, Overs et al investigated the relationships between potential genetic and neuroimaging biomarkers of SA, found that SA-in-BD PRS and risky behavior PRS were negatively correlated with the volume of anterior cingulate structures on the lateral and caudal sides of the brain, respectively, whereas both SA-in-MDD PRS and SA-in-BD PRS were positively correlated with measured cuneate volume.²³ This study demonstrates the correlation between PRS for suicide-related phenotypes and brain structural variations associated with SA. Future explorations of PRS, combined with a range of biological, phenotypic, environmental, and clinical data in high-risk populations, may provide valuable information for predictive models of suicidal behavior.

Research addressing suicide risk has progressed in ethnically diverse populations. A study conducted on a large European sample identified clinical risk factors for suicide death and SA in patients with BD, guiding the testing of potential multigenic risk factors. PRS assessments revealed risk factors for suicide death in BD patients, including post-traumatic stress disorder (PTSD), female ADHD, and male insomnia, supporting the increased risk of suicide death in European BD patients associated with trauma-related dysregulation.²⁴ Lee et al applied the SA-PRS calculated from GWAS results of European BD samples to Korean patients and explored the genetic structure of SA in Korean BD

patients. They found that SA-PRS was associated with lifetime SA in Korean BD participants. Additionally, PRS for obsessive-compulsive disorder (OCD) may have an influence on recurrent SA.²⁵ This suggests that future genomics studies will require larger, more diverse samples with finer phenotypic characterization to determine the genetic architecture of SA. These studies provide examples of the generalizability of PRS in different populations. In future research, in addition to increasing the sample size of GWAS studies in specific populations, existing large-scale GWAS results can also be applied to other populations to explore the genetic overlap and differences in phenotypes across different ethnicities.

The Relationship Between PRS and Brain Structural Function and Cognitive Impairment in BD

Neuroimaging studies in patients with BD often involve investigating the limbic system network. Functional imaging studies in BD have reported excessive activity in the limbic regions, which aligns with the theory of enhanced emotional reactivity in this disorder. Whalley et al's research suggested that increased BD-PRS is associated with increased activation in limbic regions, including the anterior cingulate cortex and amygdala.²⁶ Similarly, Tesli et al conducted a cross-sectional study using a whole-brain exploratory approach to investigate the potential impact of BD-PRS on brain activation in individuals with BD compared to the control group. They found that BD-PRS was positively correlated with increased activation in the right ventrolateral prefrontal cortex during negative facial emotion processing.²⁷ Based on the above two studies, Dima et al investigated the impact of BD-PRS on brain magnetic resonance imaging (MRI) data during facial emotion and working memory processing tasks in individuals with BD, unaffected relatives, and healthy controls. Consistent with previous findings, BD patients exhibited higher BD-PRS scores.²⁸

Jiang et al's study found that BD-PRS is associated with abnormal resting-state functional connectivity (rsFC) patterns in the adolescent brain. Higher BD-PRS is linked to decreased rsFC in the salience network and increased rsFC in the frontoparietal network with frontal and parietal regions.²⁹ In another study by Jiang, the association between adolescent BD-PRS and gray matter structure as well as white matter integrity was explored. The results showed that BD-PRS is negatively correlated with gray matter structure and fractional anisotropy (FA) in regions associated with BD in adolescents.³⁰ These research findings support the feasibility of BD-PRS as a neuroimaging marker for BD. Future longitudinal studies are needed to examine whether BD-PRS can predict neurodevelopmental changes between BD and healthy controls (HC), as well as its interaction with the course of illness and long-term medication use.

In previous research, the relationship between cognitive abilities and BD may be non-linear. Both individuals with lower cognitive abilities and those with higher cognitive abilities have shown an increased risk for developing BD.³¹ Mistry et al investigated that increased BD-PRS was associated with poorer performance in executive function, working memory, and processing speed, indicating a relationship between BD-PRS elevation and lower cognitive abilities in childhood.³² Takeuchi et al conducted a study using a large sample size and voxel-based whole-brain analysis to explore the relationship between BD-PRS, creativity measured by the divergent thinking (CMDT), and gray matter volume (rGMV) and regional gray matter volume (rWMV). The results showed that a higher BD-PRS was associated with a higher total CMDT fluency score, lower total mood disturbance, and a greater rWMV in the left middle frontal gyrus.³³ These studies suggest that elucidating the cognitive domains most affected by BD-PRS can contribute to understanding the etiology of BD and improving its predictive capability.

Genetic Correlations Between BD and Other Disorders

Genetic Correlation of BD-PRS with Other Psychiatric Disorders

SCZ

Due to the substantial overlap in genetic risk loci between BD and SCZ, there is a high relative risk (RR) among relatives of patients. However, studies have shown that diagnostic and molecular distinctions between BD and SCZ still exist. Ruderfer et al developed a PRS that is significantly different between BD and SCZ and found a significant correlation between BD-PRS and manic symptoms in SCZ patients.³⁴ Building upon this, another study found that BD patients with psychotic features had higher SCZ-PRS compared to BD patients without psychotic features, moreover, BD patients with

earlier onset had higher SCZ-PRS, and patients with higher BD and SCZ PRSs had more frequent hospitalizations.³⁵ The results suggested that combining diseases with similar genetic risk profiles improves the ability to detect shared risk loci, while also indicating that direct comparisons between BD and SCZ are likely to identify loci with significant differential effects. A study from Japan investigated the application of PRS derived from European populations in Japanese patients. The PRSs obtained from European SCZ and BD patients were higher in Japanese SCZ patients than in healthy controls (HCs). Furthermore, PRSs differentiating SCZ patients from European BD patients were higher in Japanese SCZ patients than in HCs. This suggests that PRS derived from European populations may potentially predict the risk of SCZ and BD in other ethnic populations.³⁶

In addition to genetic overlap, BD and SCZ also exhibit considerable phenotypic overlap, and a large number of studies on BD have included SCZ-PRS in their analyses to investigate whether phenotypic associations are associated with SNPs that share risk effects with SCZ. Most studies have found a negative correlation between SCZ and cognitive functioning, while there is no significant correlation between cognitive functioning and BD. However, a recent study has found extensive genetic overlap between SCZ, BD, and intelligence, suggesting that a large part of the underlying genetic structure of SCZ and BD also has an impact on cognition.³⁷ On this basis, I. Valli et al divided the participants into three groups based on their cognitive performance: intact, intermediate, and impaired, to investigate the association between brain structure and cognitive function. The results revealed that the total brain surface area was lower in the intermediate and impaired groups compared to the intact group, while the impaired cluster group had poorer psychosocial functioning and poorer PRS of cognitive function compared to the offspring of the other two groups and healthy controls.³⁸ Another study also related the cognitive subtypes of SCZ and BD to brain structure, Quidé et al examined the effect of the interaction of SCZ-PRS with two cognitive subtype groups of the schizophrenia spectrum and BD on brain gray matter volume (GMV) and found that higher SCZ-PRS was associated with reduced precentral gyrus volume in both cognitive impairment subgroups.³⁹ This suggests that our future studies should further explore the common genetic risk for intermediate phenotypes of SCZ, schizoaffective disorder and BD. As the sample size of psychiatric disease genetics increases, the PRS predictive power will become stronger, and other research directions in psychiatric genetics can be expanded on this basis, to provide stronger evidence for psychiatric disease mapping studies.

MDD

MDD, BD and SCZ show considerable phenotypic and genetic overlap. In a genetic association study including 4429 participants, Richards et al found that increased mania scores in BD were associated with higher SCZ-PRS, BD-PRS, and lower MDD-PRS, whereas increased depression scores in BD were associated with higher MDD-PRS and lower BD-PRS.⁴⁰ Similarly, another study of episode polarity in patients with BD had the same results as above, with the BD-PRS positively correlated with manic episodes, the MDD-PRS positively correlated with depressive symptoms and mixed symptom episodes and negatively correlated with manic episodes, while the SCZ-PRS was positively correlated with manic episodes only when psychotic symptoms were present.⁴¹ These findings suggest that BD-PRS and MDD-PRS are associated with episode polarity and psychotic symptoms in BD patients. In the future, further exploration of the impact of PRS for different disorders on BD polarity can be conducted, which would contribute to understanding the shared genetic basis of BD with other disorders and investigating their comorbidity.

BD or psychotic disorder patients often have experienced depression before their initial diagnosis of BD or psychotic disorder. Musliner et al assessed the extent to which genetic susceptibility measured by PRS is associated with the progression to BD or SCZ in individuals initially diagnosed with unipolar depression. The results showed that BD-PRS was significantly associated with the progression to BD only, while SCZ-PRS was significantly associated with the progression to psychotic disorders only, with no interaction observed between the PRS variables.⁴² Furthermore, the findings suggest that family history is a more powerful predictor of progression than PRS, and future studies combining family history, PRS, and other clinical predictors may yield greater predictive power.

In addition to genetic association studies focusing on individual disorders, there have been advances in the study of PRS in the symptom dimension across diseases. David et al used disease-specific PRS as predictive factors and symptom dimensions as outcomes to investigate the relationship between symptom dimensions and common genetic variations associated with MDD, BD, and SCZ. PRS for BD and SCZ positively associated with “Positive formal thought disorder”,

the SCZ-PRS was positively associated with “Paranoid-hallucinatory syndrome”, while the BD-PRS was negatively associated with “Depression”. No significant associations were observed for the MDD PRS.⁴³ The results of this study provide a basis for predicting similar symptoms across different diseases, but due to the multi-genetic contributions to cross-diagnostic psychiatric symptom dimensions and the small effect sizes, further research is needed in larger, fully phenotyped psychiatric cohorts.

Other Mental Disorders

In addition to the progress related to common psychiatric disorders mentioned above, BD-related PRS has been explored with other psychiatric disorders, such as sleep disorders, ADHD, anxiety, and substance abuse. Lewis et al evaluated whether PRS for sleep traits are associated with BD subtypes I and II. The results showed that insomnia PRS was associated with an increased risk of BD - II, but not BD - I. PRS for sleep duration was associated with BD - I, but not BD - II. With this analysis, BD subtypes differ in genetic susceptibility to insomnia and hypersomnia, giving further evidence for the genetic validity of the distinction between BD - I and BD - II.⁴⁴ This distinction will be critical for future participant selection to study the role of sleep disorders in BD.

The estimated comorbidity rate between BD and ADHD in adults ranges from 9% to 35%, and the comorbidity of BD and ADHD is associated with a significantly increased risk of substance abuse and anxiety disorders, which have a negative impact on the course of BD. Nunez et al examined the clinical and genetic correlates of BD and childhood onset ADHD (c-ADHD). They showed that all subgroups of BD patients had greater genetic risk for BD and ADHD compared to non-BD controls. At the same time, the higher ADHD-PRS in the BD + cADHD group may reflect a greater influence of genetic factors on the early manifestation of ADHD symptoms.⁴⁵ Müller et al explored the association of PRS with genome-wide DNA methylation (GMe) alterations in adults with ADHD and its comorbidity with BD, finding that higher ADHD-PRS was associated with lower levels of GMe in ADHD samples, and no association between ADHD - PRS and GMe in BD samples, but finding higher BD-PRS and higher GMe levels.⁴⁶ If it can be further established that both PRS and methylation patterns are associated with the occurrence of psychiatric disorders, then these two variables may become potential biomarkers for them, which clinicians can use to better guide prevention or treatment programs.

Anxiety and BD are highly comorbid, but the basis for this comorbidity has not been determined. Lopes et al tested whether BD comorbid anxiety reflects common genetic risk factors and found that anxious-PRS was associated with BD comorbid anxiety disorders and suicide attempts, but BD-PRS was not associated with any of these variables.⁴⁷ The findings point to a dual burden of BD comorbid anxiety disorder reflecting BD and anxiety-related genes, which may increase suicide risk. Recognizing and addressing this dual burden and improving the corresponding clinical care may help improve the prognosis of patients with BD and anxiety disorders.

Polimanti et al calculated PRS in 10,732 US Army soldiers to examine whether trauma exposure moderates the genetic association of substance use disorders with psychiatric disorders. BD-PRS was found to be positively associated with alcohol abuse in trauma-exposed military personnel, and it was negatively associated with alcohol abuse in trauma-non-exposed military personnel, with results suggesting a genetic overlap between BD and alcohol abuse, but whether exposure to a traumatic event changed the direction of the genetic association.⁴⁸ This study provides genetic insight into the complex mechanisms linking substance abuse, mental illness, and trauma exposure and provides ideas for future research on the correlation between trauma exposure and mental disorders.

Genetic Correlation of BD-PRS with Diseases in Other Disciplines

As mentioned earlier, individuals with BD have a higher mortality rate compared to other disorders. In addition to the significantly elevated suicide rate, their increased mortality is also strongly associated with other systemic diseases, among which are mainly attributed to comorbid cardiovascular and metabolic diseases, including coronary artery disease, stroke and type 2 diabetes, as well as risk factors such as high blood lipid levels and body mass index.⁴⁹ In recent years, with the development of GWAS research, there has been a great progress in the study of genetic etiology between different disciplines of diseases. So et al systematically investigated the common genetic etiology between BD and cardiometabolic traits.⁵⁰ They found that the reduced risk of BD was associated with a high PRS for cardiometabolic traits. On this basis, to identify common genetic etiologies in populations of European ancestry, Fürtjes et al calculated

PRS and genetic correlations between BD and cardiometabolic traits. The results were positive correlations between BD and triglycerides, waist-to-hip ratio, waist-to-hip ratio corrected for BMI, coronary heart disease, and type 2 diabetes after PRS, with waist-to-hip ratio PRS contributing the most to the explained variance of BD.⁵¹

Historically, comorbidity of psychiatric disorders with other illnesses in patients has been attributed to the side effects of medication or reduced health maintenance capacity. However, recent research suggests that shared genetic risk loci or common biological pathways may underlie the widespread pleiotropy between psychiatric and non-psychiatric disorders. Kember et al conducted a study in a specific pedigree to investigate all possible pathogenic variants of known Mendelian disease loci and performed genomic profile analysis using, from which common genetic etiological evidence was found between BD risk and PRS for lipid traits such as clinical autoimmune thyroid disease, diabetes mellitus and triglyceride levels.⁵² And the study provides evidence for broad genetic pleiotropy that could drive epidemiological findings of comorbidity between disease and other complex traits.

Discussion

One of the main challenges currently faced by the application of PRS is that their accuracy in predicting individual risk is significantly higher in European populations compared to other populations. This is primarily due to the fact that the majority of the existing GWAS studies have been conducted on European cohorts. According to population genetics theory, the accuracy of genetic risk prediction diminishes as the genetic differences between the original GWAS samples and the target population increase. Although some studies have explored the application of PRS derived from European samples in other racial/ethnic populations and demonstrated some feasibility, the decrease in accuracy cannot be ignored.^{24,36} Due to genetic differences across populations, PRS developed from European samples may not fully capture the genetic risk in other racial/ethnic populations. This implies that when applying PRS to other populations, further research is needed to address the challenges posed by genetic differences and ensure accuracy and reliability. With the increasing availability of multi-ethnic GWAS studies, we can expect improvements in the predictive ability of PRS in non-European populations in the future.

Currently, PRS only captures data on common genetic contributions and does not account for rare SNPs or copy number variations that may have larger contributions in certain psychiatric disorders such as SCZ.⁵³ Research has indicated that low-frequency and rare variants might explain a significant portion of the genetic heritability in SCZ and other psychiatric disorders. Therefore, the limited scope of PRS in capturing rare genetic variants remains a challenge in fully understanding the genetic architecture of these disorders. Future studies that incorporate rare variant analysis and more comprehensive genomic approaches may provide further insights into the genetic contributions of rare variants in psychiatric diseases.

In addition, genetic factors are not the sole risk factors in polygenic diseases, and the interaction between genes and the environment (G×E) is an essential aspect of genetic research on BD. Early-life stress and adverse life events are among the most prominent environmental risk factors. Anand et al found that the interaction between early-life trauma and genotype may have a significant impact on the occurrence and presentation of bipolar BD. Their research indicated that the age of onset for BD is significantly lowered with an increased frequency of traumatic events.⁵⁴ Et al studied the impact of BD-PRS and family environment on the incidence rate of offspring of BD patients. The results showed that BD-PRS of offspring with well-functioning family environment was positively correlated with the risk of BD, while offspring with high-conflict family environment had a higher risk of BD when BD-PRS was low. This result may be in line with the multi factor disease risk threshold model and support future research and intervention measures to improve family dynamics.⁵⁵ Geoffroy et al, in their study, combined the (G×E) with neuroimaging and found that environmental factors such as obstetric complications and cannabis use have clear effects on neuroimaging brain changes in SCZ, while the impact on BD remains uncertain, and larger samples are needed in the future to explore whether the (G×E) interaction has a significant role in BD.⁵⁶ In coming, a larger sample is needed to explore whether the (G×E) interaction has a significant role in BD.

At present, PRS has demonstrated high clinical value in studies of coronary artery disease (CAD), diabetes, breast cancer, and prostate cancer. The common goal is to use PRS to predict the risk of disease and identify high-risk groups, and to improve treatment targeting and screening modalities, which is consistent with the application of BD-PRS in this

paper. CAD-PRS can provide more accurate risk estimates and identify individuals who are most likely to benefit from statin therapy,⁵⁷ prostate cancer PRS can reduce overdiagnosis caused by prostate-specific antigen (PSA) screening.⁵ The successful application of PRS in these diseases demonstrates the feasibility of PRS in disease prediction. With the development of GWAS studies and PRS, PRS will provide reliable information for more accurate prediction of BD occurrence and treatment response in the future.

Conclusion

BD-PRS has played a significant role in genetic research on bipolar disorder. By integrating large-scale genomic data and disease phenotype information, researchers have been able to develop more precise and predictive BD-PRS models. These models aid in identifying the individual risk of developing BD, revealing genetic differences among different subtypes, and improving our understanding of the genetic foundations of BD, with the potential to advance the discovery of new disease mechanisms. With the help of BD-PRS, healthcare professionals can better tailor personalized treatment plans for BD patients based on their genetic risk factors. While BD-PRS provides valuable information regarding the genetic risk of bipolar disorder, it is not a perfect predictive tool and should be combined with clinical assessment to comprehensively evaluate a patient's risk. With the continuous advancement of technology and data, we can expect BD-PRS to continue playing a pivotal role in future research, thereby improving our understanding and treatment of this complex disorder.

Disclosure

The authors report no conflicts of interest in this work.

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