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Genome-wide association study and polygenic risk score analysis for bipolar disorder in the Korean population

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ABSTRACT

This study aimed to identify common genetic variants associated with bipolar disorder (BD) in the Korean population and to evaluate the predictive performance of polygenic risk scores (PRSs) derived from other population data. A cohort of 1538 individuals diagnosed with bipolar I or II disorder (DSM-IV) and 2271 healthy controls were recruited from seven academic institutions and their affiliated hospitals in South Korea through the Korean Psychiatric Genome-Wide Association Study (GWAS) Project. After imputation, 7655,788 single-nucleotide polymorphisms (SNPs) were analyzed for the association with BD. For the PRS analysis, we utilized the latest GWAS summary statistics from the Psychiatric Genomics Consortium for BD and schizophrenia. We identified one genome-wide significant locus, rs75776799, an intronic SNP in the solute carrier family 25 member 12 gene ($P = 2.45 \times 10^{-9}$; odds ratio = 2.65; 95% confidence interval = 1.92–3.64; effect allele frequency = 0.0398), which has been previously implicated in autism spectrum disorder. Summary data-based Mendelian Randomization (SMR) analysis using East Asian mQTL data identified several CpG probes mapping to *DLX2-AS1* and *ITGA6* showing a suggestive association with BD. The PRS analysis revealed the highest explained variances of BD in the Korean sample when using multi-ancestry BD GWAS data. This study identified a genome-wide significant locus in this cohort for BD, which suggests a potential role of mitochondrial function in its pathogenesis, expanding our understanding of the genetic architecture of BD.

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1. Introduction

Bipolar disorder (BD) is a chronic psychiatric disorder with fluctuations in mood state and energy affecting more than 1% of the global population (Grande et al., 2016). Given that BD is a complex genetic disorder (Grande et al., 2016), large-scale genome-wide association studies (GWASs) are among the most successful strategies for identifying genetic variants associated with BD (O'Connell and Coombes, 2021). Multiple GWASs have provided evidence for the genetic etiology of BD (Baum et al., 2008; Mullins et al., 2021; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Stahl et al., 2019). The largest-scale GWAS analyzed data from 158,036 cases with BD and 2.8 million controls from various ancestries, identifying 298 genome-wide significant loci (O'Connell et al., 2025). However, a substantial portion of the heritability of BD remains elusive.

Additionally, as risk alleles are identified from GWAS results, the polygenic risk score (PRS), the sum of risk alleles for distinct phenotypes weighted by their effect size estimates, has been calculated (Choi et al., 2020). PRS analysis is useful for predicting individualized disease risk and illness course (Khera et al., 2018) and is widely used for BD (Birmaher et al., 2022; Lee et al., 2024; Song et al., 2024).

Although East Asians represent approximately 22% of the global population (Pan and Xu, 2020), data from European ancestries account for a large portion of large-scale GWASs. Recent studies have shown that PRS analysis has lower cross-population prediction accuracy due to ancestral-specific linkage disequilibrium (LD) structures and differences in allele frequencies (Duncan et al., 2019). Therefore, optimizing PRS performance in underrepresented populations is essential to improve its applicability across ancestries.

Even within East Asian populations, ethnic groups such as the Han Chinese, Japanese, and Koreans have distinct genetic profiles and appear to be differentiated at the genomic level (Wang et al., 2018). Several GWASs have been conducted in East Asian populations, including a recent GWAS in Han Chinese populations (Zhang et al., 2025). However, Korean populations remain underrepresented in current genomic datasets. Thus, identifying common genetic variants significantly associated with BD in the Korean population is important for understanding its genomic features.

This study aimed to identify common genetic variants of BD in the Korean population using a GWAS conducted on patients with BD and healthy controls recruited from multiple centers in South Korea. Thereafter, we performed a PRS analysis using large-scale multi-ancestry GWAS data to evaluate the performance of PRS across ancestries. This study is the first multi-center GWAS on Korean patients with BD.

2. Materials and methods

2.1. Study participants

Participants were recruited through a nationwide GWAS collaboration called the Korean Psychiatric GWAS Project (KPGP) between seven academic institutes located in South Korea. Patients and controls were recruited from studies conducted at each institute, and those who agreed to the usage of their DNA and clinical data in future general research provided informed consent at the time of their recruitment (Table S1). Patients were diagnosed with BD based on the DSM-IV criteria. Healthy controls were recruited from community volunteers, hospital staff, and college students. All control participants were screened through psychiatric interviews to confirm the absence of any lifetime psychiatric disorders. The KPGP used blood samples, clinical and demographic data, and generated genomic data for GWAS. The GWASs conducted through the KPGP were approved by the institutional review board of each institute and the Broad Institute, which provided a grant for the project.

From the KPGP samples, 1538 patients diagnosed with bipolar I or II disorder (584 male, 954 female; mean age 34.2 years) and 2271 healthy controls (954 male, 1317 female; mean age 27.2 years) were included in the analysis (Table S2, S3). The distribution of cases and controls across recruitment sites and chip versions is provided in Table S2. Detailed subtype distribution among BD diagnoses was not consistently available across all cohorts and was therefore not analyzed separately. This study followed the Strengthening the Reporting of Genetic Association Studies reporting guidelines.

2.2. Genotyping and quality control

Korea Biobank Array v1.0 and v1.1, commonly known as the Korean Chip (K-CHIP), were used for genomic DNA extraction and single-nucleotide polymorphism (SNP) genotyping. Korea Biobank Array protocol (Moon et al., 2019) was used for the QC for each chip version. Variants with a variant call rate < 0.98, Hardy–Weinberg equilibrium $P < 10^{-6}$, minor allele frequency < 0.01, or duplicate SNPs were excluded. Samples with a call rate < 0.98, excessive heterozygosity, or sex discrepancy were also removed. Genetic relatedness was assessed using kinship-based inference for GWAS (Manichaikul et al., 2010) and samples with kinship coefficients corresponding to second-degree relatedness or closer (kinship coefficient > 0.0884) were excluded. Excessive heterozygosity was evaluated using PLINK, and samples exceeding ± 5 standard deviations from the mean heterozygosity rate were considered outliers. Principal component analysis (PCA) was performed after linkage disequilibrium pruning using a sliding window approach (window size = 50 SNPs, step size = 5 SNPs, r^2 threshold = 0.5). Visual inspection of the PCA plot indicated no substantial population outliers within the cohort (Figure S1). To further control for residual population stratification, the top five PCs were included as covariates in the association analyses.

After the sample and variant QC for each chip version, 3806 individuals were retained (after excluding 3 samples), with 526,581 and 597,571 SNPs remaining in K-CHIP v1.0 and v1.1, respectively. To ensure consistency between array versions, only SNPs shared between the two K-CHIP versions were retained for downstream analyses. The number of SNPs shared between the two K-CHIP versions was 475,187, corresponding to 90.2% and 80.0% of the SNPs in v1.0 and v1.1, respectively.

After merging the datasets based on shared SNPs, principal component analysis was performed to evaluate potential batch effects between array versions. No distinct clustering by chip version was observed, indicating minimal batch effects (Figure S1).

Phasing and imputation were performed with Eagle v2.4 and Minimac 4 using the Korean Imputation Service Phase 1 reference panel with the set of shared SNPs (Hwang et al., 2022). Variants with an imputation quality of $R^2 < 0.95$ or minor allele frequency (MAF) < 0.005 were removed. A relatively stringent imputation quality threshold was applied to ensure high confidence in imputed variants, while a lower MAF threshold was used to include potentially informative low-frequency variants in the Korean sample. Logistic mixed model analysis was conducted to assess potential group-specific biases related to the imputation process, and 43 variants showing significant association with imputation groups were removed (Bonferroni-corrected $P < 0.05$). Finally, 7655,788 SNPs were used for data analysis. The principal components of genetic ancestry were calculated using PLINK version 1.9 (Purcell et al., 2007) and used as covariates in the GWAS analysis.

2.3. GWAS

Adjustments for sex, age, and the first five principal components of genetic ancestry were performed for logistic regression analysis. The Manhattan plot was generated using R, and the regional association plot was generated using LocusZoom (http://locuszoom.sph.umich.edu). Post hoc power was calculated at the genome-wide significance level, which was set at 5×10^{-8}, using R (version 4.5.2). The effective sample

size was calculated as 4/(1/case N + 1/control N), yielding a value of 3668. The suggestive significance level was set at 1×10^{-5}. SNP locus data and gene annotations were obtained from public genomic databases. To evaluate the robustness of the association results and potential batch effects, we conducted additional stratified analyses by recruitment site and sensitivity analyses by genotyping chip version for the lead SNP using Firth logistic regression. Standard logistic regression was used for the analysis of K-CHIP v1.1 because Firth regression did not converge. Furthermore, to definitively rule out confounding by array versions, a formal adjustment analysis was performed for the lead SNP by incorporating genotyping array version as an additional covariate in the logistic regression model.

To identify potential causal relationships between the gene and phenotype, we performed summary data–based Mendelian randomization (SMR) analysis using the target SNP. We used brain-specific eQTL summary statistics from the BrainMeta v2 dataset (Qi et al., 2022) and East Asian–specific mQTL summary statistics (Hatton et al., 2024). After the SMR analysis, we performed a heterogeneity in dependent instruments (HEIDI) test to evaluate the effect of pleiotropy. Probes were considered to pass the HEIDI test regarding *P*-value and the number of SNPs used in the HEIDI test ($P_{HEIDI} \geq 0.01$, number of $SNP_{HEIDI} \geq 3$).

To identify candidate genes in the absence of direct eQTLGen signal for the target variant, genes whose most 5' transcription start site (TSS) was located within ±750 kb distance from rs75776799 were extracted. The window size was selected based on commonly used cis-eQTL ranges (typically ±500 kb to 1 Mb) in previous studies, aiming to balance coverage of regulatory regions with reduction of spurious associations. For each gene, the top cis-eQTL was selected from the dataset based on the smallest p-value. When multiple SNPs share the same minimum p-value, SNP with the largest absolute Z-score, calculated as beta divided by standard error, was chosen. If beta and standard error were identical, the SNP located closest to the gene was selected.

For the East Asian mQTL-based SMR analysis, CpG probes located within ±750 kb of rs75776799 were extracted. For each probe, the top mQTL SNP was selected using the same criteria as in the eQTL analysis. To ensure that our findings were not overly dependent on the specific physical distance window, we additionally conducted a sensitivity analysis using a more stringent threshold of ±500 kb for both locus definition and probe selection.

Cross-ancestry genetic correlations between East Asian and European populations for BD and schizophrenia were estimated using Popcorn v1.1 (Brown et al., 2016) under the genetic-effect model with pre-computed cross-population LD scores from the 1000 Genomes Project.

2.4. PRS analysis

We utilized PRS-CS for single-ancestry GWAS-based PRS analyses, and PRS-CSx for multi-ancestry GWAS-based PRS analyses. PRS-CSx was developed to improve cross-population polygenic prediction by integrating GWAS summary statistics from multiple populations (Ruan et al., 2022). PRS-CSx uses a shared continuous shrinkage prior to couple SNP effects across populations to estimate a more accurate effect size (Ruan et al., 2022). Nagelkerke's R^2 was identified in each GWAS statistic to measure model performance. The most recent GWAS summary statistics from the Psychiatric Genomics Consortium (PGC) was used for the analysis. East Asian, European, and multi-ancestry data were obtained from the BD (O'Connell et al., 2025) and schizophrenia (Trubetskoy et al., 2022) data (Table S4). The schizophrenia GWAS data were included due to the well-established genetic overlap between BD and schizophrenia, as consistently demonstrated in previous large-scale studies. For the East Asian data, we excluded Korean GWAS data from the PGC summary statistics to avoid sample overlap.

3. Results

3.1. GWAS

By analyzing 7655,788 SNPs after imputation, we identified one genome-wide significant locus, rs75776799, showing an association with BD ($P = 2.45 \times 10^{-9}$; odds ratio = 2.65; 95% confidence interval = 1.92–3.64; effect allele frequency = 0.0398) (Table 1, Fig. 1a). A regional association plot for this locus shows that no additional SNPs in strong LD with rs75776799 were significantly associated with BD (Fig. 2). This variant was substantially more frequent in individuals with BD in the Korean population compared to other ancestral groups in the gnomAD database (BD case = 4.8%, BD control = 3.5%, East Asian = 2.6%, non-Finnish European = 0.028%, African = 0.0048%) (Fig. 1b).

No noticeable inflation was observed in the GWAS results, as indicated by the quantile-quantile plot (Figure S2). Specifically, the genomic inflation factor ($\lambda_{GC} = 1.053$) indicated minimal inflation of test statistics due to population stratification or cryptic relatedness. Furthermore, the post hoc power analysis indicated sufficient power at the genome-wide significance threshold ($P = 5 \times 10^{-8}$), with an estimated power of 69.61%.

We next examined whether this locus was significantly associated with BD in the PGC4 European GWAS. Due to its extreme rarity, the lead variant was not available in the summary statistics, and variants within ±50 kb of the locus did not show strong association. rs75776799 was not identified as a significant SNP in previous studies of BD (Gordovez and McMahon, 2020; O'Connell et al., 2025). We further examined the association of rs75776799 in the Taiwan Precision Medicine Initiative (TPMI) dataset. However, the variant did not show significant associations with psychiatric or neurological phenotypes in the TPMI cohort (all $P > 0.1$).

SNP-based heritability of BD was estimated using linkage disequilibrium score regression (LDSC), yielding an observed-scale h^2 of 0.51 (SE = 0.21). The LDSC intercept was 1.025 (SE = 0.009), indicating minimal confounding due to population stratification or cryptic relatedness. In addition, the liability-scale heritability was estimated to be 0.29 under an assumed population prevalence of 0.01.

Stratified analyses in three cohorts with both cases and controls (Samsung Medical Center, Seoul National University Hospital, and Eulji Medical Center) showed a consistent direction of effect (OR > 1) for rs75776799. Sensitivity analyses stratified by genotyping chip version also demonstrated consistent effect directions across both K-CHIP v1.0 and K-CHIP v1.1 **(**Table S5**)**. In the adjustment analysis controlling for the genotyping array as a covariate, the lead SNP maintained a robust association with a highly consistent effect size (OR = 1.62, 95% CI = 1.24 – 2.11, $P = 3.93 \times 10^{-4}$), confirming that the primary signal was not artifactually driven by batch effects **(**Table S5**)**.

For the SMR analysis using brain cis-eQTL data, a total of 27 genes were located within ±750 kb of rs75776799, of which 10 genes were available in both the BrainMeta cis-eQTL dataset and our GWAS summary statistics, including *CYBRD1*, *DCAF17*, *DYNC1I2*, *HAT1*, *ITGA6*, *METAP1D*, *METTL8*, *PDK1*, *SLC25A12*, and *Y_RNA*. From 10 top cis-eQTLs, two cis-eQTLs (rs13023417 for *METTL8*, rs6706526 for *CYBRD1*) with substantial allele frequency discrepancies were excluded from the analysis. In addition, *Y_RNA* was excluded because it lacked suitable gene-level cis-eQTL information. Consequently, SMR analyses were performed for the remaining seven genes. None of the genes showed a statistically significant association between gene expression and BD risk (all $P_{SMR} > 0.05$), and no evidence of a causal variant was observed **(**Table S6**)**.

For the East Asian mQTL-based SMR analysis, 301 CpG probes located within ±750 kb of rs75776799 were available in both the mQTL dataset and our GWAS data. Of the 301 probe-SNP pairs, one pair (cg16350446-rs71405425) showed a substantial difference in allele frequency between the mQTL and GWAS datasets, and was therefore removed from further analysis. No probes remained statistically

Table 1
Single-nucleotide polymorphism showing significant associations with bipolar disorder.

SNP	Chr	BP (GRCh37)	Gene	Effective allele	Non-effective allele	Effect allele frequency	OR	95% CI	*P*-value
rs75776799	2	172,721,341	*SLC25A12*	C	G	0.0398	2.65	1.92–3.64	2.45×10^{-9}

Abbreviations: BP, Base-pair position (GRCh37); Chr, Chromosome; CI, Confidence interval; OR, Odds ratio; SNP, Single-nucleotide polymorphism.

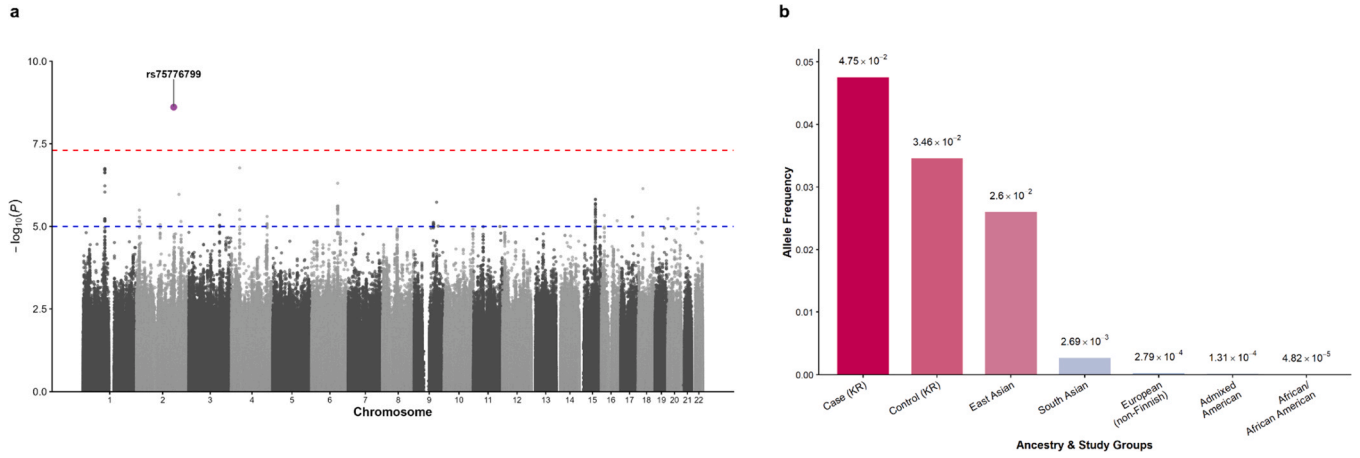

Fig. 1. Genome-wide association study results of bipolar disorder in the Korean population. a. Manhattan plot of the genome-wide association study for bipolar disorder in the Korean population. The red line indicates the genome-wide significance threshold (5×10^{-8}), and the blue line represents the suggestive significance threshold (1×10^{-5}). The lead variant (rs75776799) reaching genome-wide significance is highlighted in purple. b. Effect allele frequency (AF) of the lead variant (rs75776799) in the current study and across major ancestry groups in the gnomAD v4 database. The variant is notably enriched in individuals with bipolar disorder in the Korean (KR) population, with higher frequency in East Asians compared to other global populations.

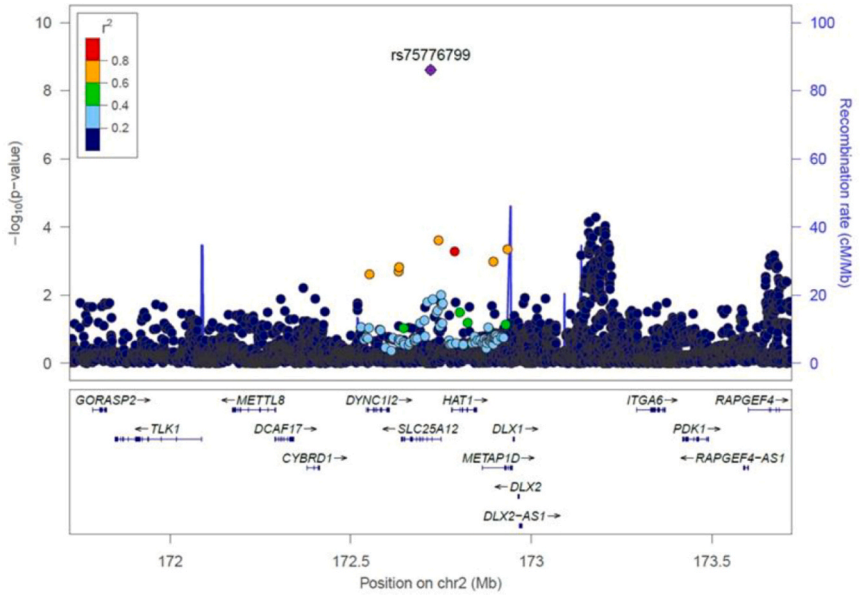

Fig. 2. Regional plot of the significant association result for the region of ±1 Mb from the lead variant (rs75776799). Each dot represents a variant plotted as -$\log_{10}$(P) on the y-axis against the corresponding variant position (Mb) on the x-axis. The dots are in different colors according to linkage disequilibrium with the lead variant (a purple solid rhombus).

significant after corrections for multiple testing regarding the false discovery rate (FDR) and Bonferroni methods (Table S7). However, seven CpG probes showed evidence of association ($P_{SMR} < 0.05$), mapping primarily to the distal-less homeobox 2 antisense RNA 1 (*DLX2-AS1*) gene and the integrin subunit alpha 6 (*ITGA6*) gene (Table S8).

Considering that CpG probes are often correlated, we conducted an additional gene-level analysis by treating each gene as the unit of independent testing and applying multiple-testing correction across genes (Table S9). Seven CpG probes mapping to the *DLX2-AS1* and *ITGA6* genes demonstrated significant p-values ($P_{SMR} < 0.05$) and survived FDR correction at the gene level. (Table S10). Furthermore, in the sensitivity analysis applying the more stringent ±500 kb window, the top CpG probes, including cg03724229 mapping to *DLX2-AS1*, retained their statistical significance, supporting the robustness of our SMR findings across different distance thresholds (Tables S11, S12, and S13).

Cross-ancestry genetic correlation analyses showed a high genetic correlation between East Asian and European populations for BD ($r_g = 0.95$), and a substantial genetic correlation for schizophrenia ($r_g = 0.79$)

(Table S14).

3.2. PRS analysis

The PRSs derived from large-scale GWAS summary statistics for BD and schizophrenia in different ancestry groups showed significant associations with BD in Korean samples (all $P < 1 \times 10^{-7}$; Table S15). We compared the value of the area under the receiver operating characteristic curve and the variances explained by PRSs according to the base GWAS data.

Nagelkerke's R^2 values for BD in the Korean samples were 0.011, 0.061, and 0.070 when using the PRS derived from BD GWASs of East Asian, European, and multi-ancestry populations, respectively. In the PRS derived from schizophrenia GWAS summary statistics, Nagelkerke's R^2 values for BD were 0.026, 0.039, and 0.089 for East Asian, European, and multi-ancestry populations, respectively (Fig. 3, Table S15).

4. Discussion

In the present study, we identified a genome-wide significant locus for BD at rs75776799, an intronic variant within the *SLC25A12* gene. SMR and HEIDI analyses did not identify statistically significant associations after multiple testing correction. However, nominal associations with the *DLX2-AS1* and *ITGA6* genes in mQTL data were identified, providing suggestive evidence for potential epigenetic mechanisms of these genes. Additionally, PRS analyses indicated an overlap between genetic architectures of BD and schizophrenia, with the superior predictive power (Nagelkerke's R^2) of multi-ancestry-derived PRSs, highlighting the impact of sample-size disparities on PRS performance and the cross-ancestry portability of genetic risk models.

Collectively, these findings suggest that the genetic architecture of BD in the Korean population is generally consistent with known trans-ancestry patterns, yet it simultaneously offers an opportunity to identify previously unreported candidate loci. This notion is supported by the latest meta-analysis (Zhang et al., 2025) incorporating substantial East Asian samples from PGC4 GWAS, which demonstrated a high genetic correlation between East Asian and European populations (r_g = 0.86). Nevertheless, despite this shared architecture, the East Asian GWAS identified 23 novel risk loci not detected in European ancestry analyses and achieved improved fine-mapping resolution. Of note, the GWAS variant identified in our analyses is approximately 100 times more frequent in East Asians than other ancestries, which may explain the high likelihood of identifying the association in East Asian studies.

Importantly, heterogeneity persists even within East Asian populations, raising concerns about further signal dilution when distinct sub-populations are aggregated. For example, Han Chinese studies have shown genome-wide significant associations in the MHC region (Zhang et al., 2025), while Japanese GWAS have reported genome-wide significant loci within gene clusters related to lipid metabolism (Ikeda et al., 2018). Conversely, several loci identified in the PGC4 East Asian GWAS were not replicated in Han Chinese samples, supporting the existence of population-specific risk variants. Neither the Han Chinese–specific nor Japanese-specific loci were identified in our Korean cohort.

These findings emphasize that ancestry- and ethnicity-specific GWAS are essential for maximizing genetic resolution, minimizing signal dilution, and uncovering biologically meaningful variation in BD. Expanding well-powered Korean and East Asian genomic studies will be critical for advancing a more comprehensive and globally representative understanding of BD genetics.

The genome-wide significant locus identified in our study, rs75776799, is located in *SLC25A12*, which encodes a calcium-binding carrier protein located in the mitochondria that provides energy to neurons in the central nervous system (Napolioni et al., 2011; Palmieri et al., 2001). Another SNP, rs6716901, in *SLC25A12* is known to be significantly associated with autism spectrum disorder (Durdiakova et al., 2014), suggesting possible roles for *SLC25A12* in brain metabolic abnormalities such as mitochondrial oxidative dysfunction and neuronal changes like hypomyelination in autism spectrum disorders (Pons et al., 2004; Sakurai et al., 2010). Higher prevalence of mitochondrial dysfunction, especially energy metabolism dysfunction and mitochondrial damage (Gigante et al., 2011; Zuccoli et al., 2017), has been reported in people with BD (Manji et al., 2012). Also, previous studies demonstrated associations between BD and mitochondrial DNA variants, such as *NDUFV1*, *NDUFS8*, and *NDUFS7*, which encode for the subunit of mitochondrial complex I (Andreazza et al., 2010), and *POLG1*, which encodes for the mitochondrial polymerase (Kasahara et al., 2017).

Functional annotation of rs75776799 showed limited evidence of direct regulatory function based on RegulomeDB (rank = 5, score = 0.135), and CADD (Phred score = 0.868). HaploReg annotation suggested the presence of enhancer histone marks in multiple tissues including the brain anterior caudate, and predicted alterations in several transcription factor binding motifs. However, these in silico predictions should be interpreted with caution, as they do not provide direct evidence of functional effects. In addition, rs75776799 was not identified as a significant eQTL in GTEx V10 across any tissue, consistent with the absence of significant cis-eQTL signals in the BrainMeta dataset, further supporting the limited functional evidence at this locus. Although the findings of the present study may suggest a possible link to

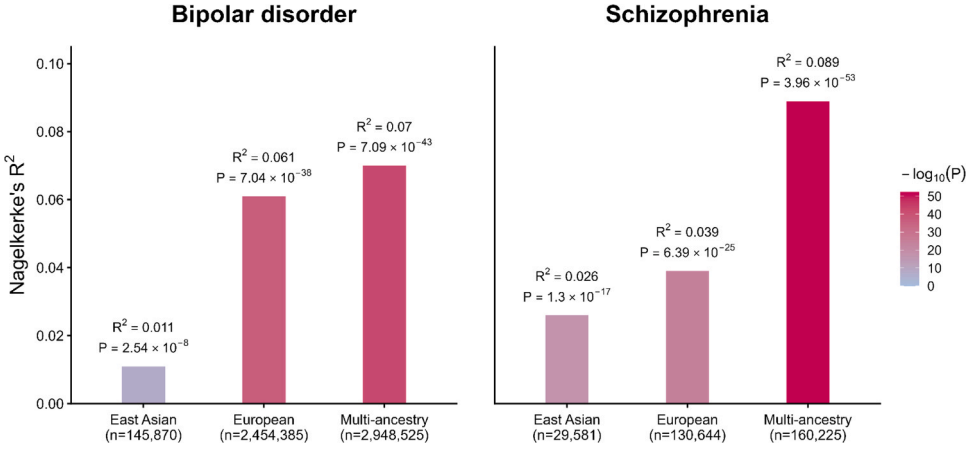

Fig. 3. Performance of polygenic risk scores (PRS) in a Korean population according to ancestries of the discovery GWAS of bipolar disorder or schizophrenia. Bar plot shows Nagelkerke's R^2 values of PRS constructed using GWAS summary statistics from East Asian, European, and multi-ancestry datasets. Color intensity represents the strength of association, expressed as -$\log_{10}(P)$. For East Asian GWAS, Korean samples were excluded prior to PRS construction to avoid sample overlap.

mitochondrial dysfunction in BD, this interpretation still requires further functional validation.

The SMR and HEIDI analyses using brain cis-eQTL and East Asian mQTL datasets did not identify strong evidence for a shared causal variant linking the rs75776799 locus to the gene expression or DNA methylation changes after multiple-testing correction. However, the mQTL-based SMR analysis revealed that CpG probes mapping to the *DLX2-AS1* and *ITGA6* genes were associated with BD risk. These probes passed the HEIDI test, indicating potential pleiotropic effects rather than linkage. Although these signals did not remain significant after probe-level multiple testing correction, the probes showed suggestive results after additional gene-level multiple testing correction. These findings suggest that the association signal at rs75776799 is unlikely to be driven by a single strong regulatory effect. Instead, clustered methylation signals may reflect subtle regulatory mechanisms that are not fully captured by bulk-tissue based QTL resources. Overall, the SMR results provide limited and indirect evidence for functional mechanisms underlying the association signal at this locus. The lack of significant eQTL may be attributable in part to the rarity of rs75776799 in European populations because these resources were mainly based on samples of European ancestry. Larger, ancestry-matched datasets and cell-type-specific data would be necessary to validate the observed signals.

The PRS analysis revealed the highest correlation between the risk of BD in Koreans and multi-ancestry BD GWAS with an R^2 of 7.0%. European and East Asian BD GWASs explained smaller proportions of variance with an R^2 of 6.1% and 1.1%, respectively. This pattern likely reflects differences in discovery GWAS sample size across datasets. Consistent with this, predictive performance increased broadly in proportion to discovery sample size across datasets, supporting a substantial contribution of sample size effects. However, the relatively modest reduction in performance of East Asian PRS despite smaller sample sizes suggests that ancestry matching between discovery and target samples may partially mitigate this effect. To further investigate this, we performed cross-ancestry genetic correlation analyses using Popcorn. The genetic correlation between East Asian and European populations was high for BD ($r_g = 0.95$), while schizophrenia also showed a substantial cross-ancestry genetic correlation ($r_g = 0.79$). These findings suggest that both disorders share considerable genetic architecture across populations, and that differences in PRS transferability may be influenced by multiple factors such as discovery sample size, linkage disequilibrium structure, and allele frequency differences across populations. Schizophrenia PRSs were also significantly associated with BD risk across all ancestry groups, consistent with previous PGC findings and further supporting the well-established genetic and symptomatological correlations between schizophrenia and BD (Lee et al., 2024).

This study has several limitations. First, although our effective sample size provided 78.7% power to detect variants with a minor allele frequency (MAF) of 0.2 and an odds ratio (OR) of 1.2 at the genome-wide significance level ($\alpha = 5 \times 10^{-8}$), the power was substantially lower for variants with smaller effect sizes (OR = 1.1), ranging from approximately 1.3–4.4% depending on allele frequency. This indicates that while our study was primarily powered to detect relatively common variants with moderate effect sizes, it may have limited the detection of additional risk loci with subtle genetic effects. In addition, although we performed functional follow-up analyses using brain-specific eQTL data and East Asian-specific mQTL datasets through SMR and HEIDI analyses, none of the signals remained significant after multiple-testing correction for eQTL-based analysis, and the findings therefore represent indirect or suggestive functional evidence. Although it is well known that the genetic control of DNA methylation is largely shared across European and East Asian populations (Hatton et al., 2024), since the GWAS data used in this study derived from Korean population, genetic differences such as LD structure and allele frequency and sample characteristics between the mQTL data and the GWAS data may still influence the interpretation of the result. Large-scale ancestry-matched eQTL datasets will be necessary to elucidate the relationship between gene expression and SNPs. Finally, detailed phenotypic information, including BD subtypes, was not available, which may have limited subtype-specific interpretations.

Despite these limitations, our study identified a candidate locus associated with the risk of BD and potential mediating genes in the Korean population, and also demonstrated the transferability of cross-ancestral and cross-diagnostic PRSs. Our findings may expand the current understanding of the genetic architecture of BD mostly derived from European studies, by providing insight into the shared and distinct genetic basis of BD across ancestries. Replication in larger independent samples and further functional studies are required to confirm our findings.

CRediT authorship contribution statement

Kyung Sue Hong: Writing – review & editing, Resources. **Hong-Hee Won:** Writing – review & editing, Supervision, Conceptualization. **Se Hyun Kim:** Writing – review & editing, Resources. **Ji Hyun Baek:** Writing – review & editing, Supervision, Conceptualization. **Byung Dae Lee:** Writing – review & editing, Resources. **Tae Hyon Ha:** Writing – review & editing, Resources. **Se Joo Kim:** Writing – review & editing, Resources. **Young-Chul Chung:** Writing – review & editing, Resources. **Sung-Wan Kim:** Writing – review & editing, Resources. **Min Jun Choi:** Writing – original draft, Formal analysis. **Eun-Young Cho:** Writing – review & editing, Resources. **Yujin Kim:** Writing – review & editing, Formal analysis, Data curation. **Dong Bin Lee:** Writing – review & editing, Resources. **Heon-Jeong Lee:** Writing – review & editing, Resources. **Hailiang Huang:** Writing – review & editing, Resources. **Eun-Jeong Joo:** Writing – review & editing, Resources. **Kyooseob Ha:** Writing – review & editing, Resources. **Yong Min Ahn:** Writing – review & editing, Resources. **Woojae Myung:** Writing – review & editing, Resources.

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Declaration of Competing Interest

The authors have nothing to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2026.105034.

Data availability

Original data is available from the corresponding author upon reasonable request.

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