Neuropsychiatric Disease and Treatment

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Associations of Rare Variants in the *AKAP11* Gene with Bipolar Disorder in Chinese Population

Yankai Zhang, Chunhui Qu, Tingting Wang, Xiangwen Wang, Shunkang Feng, Ping Sun

Department of Mood Disorders, Qingdao Mental Health Center, Qingdao, Shandong, People's Republic of China

Correspondence: Ping Sun, Department of Mood Disorders, Qingdao Mental Health Center, Qingdao, 266000, People's Republic of China, Tel +86 13589394393, Email qdsunping99@sina.com

Purpose: This pioneering study aimed to explore the associations between the A-kinase anchoring protein 11 (*AKAP11*) gene and bipolar disorder (BD) in a Chinese population. We sought to replicate findings from European populations regarding ultra-rare protein-truncating variants (PTVs) within exon 8 of *AKAP11* and identify any novel rare mutations linked to Chinese BD patients.

Methods: We conducted a case-control association study, including a cohort of 284 Chinese BD patients, with the control group comprising 10,588 individuals from the China Metabolic Analytics Project (ChinaMAP) database. Polymerase chain reaction (PCR) amplification and Sanger sequencing were performed to analyze exon 8 of the *AKAP11* gene. Statistical analysis involved chi-square tests on VassarStats to assess allele frequency differences between BD patients and the control group, along with power analysis using PASS (version 21.0.3).

Results: In 284 Chinese BD patients, within exon 8 of the *AKAP11* gene we did not find any ultra-rare PTVs previously identified in European BD patients. However, five additional rare variants were discovered, including three missense variants and two synonymous variants. Notably, rs2236364 showed concordant deleterious predictions across four computational tools, warranting prioritized investigation. Statistical analysis revealed no significant difference in allele frequencies between groups (P= 0.240), although a slightly higher proportion of rare variants was observed in cases versus controls. Additionally, three variants were not documented in the Bipolar Exomes Browser (BipEx) database, the frequencies of the other two were mildly lower in cases than controls, contrary to the trend observed in the Chinese population. The observed difference may be due to population genetic-environmental interaction.

Conclusion: In this pioneering Chinese population study of BD-*AKAP11*, we did not replicate the association of ultra-rare PTVs but identified five additional rare variants. Population-specific distribution patterns—exemplified by rs2236364 with computationally deleterious predictions—warrant validation in expanded cohorts to elucidate trans-ethnic risk mechanisms.

Keywords: bipolar disorder, *AKAP11*, East Asian People, rare mutation, case-control studies

Introduction

Bipolar disorder (BD) is a severe mental disorder characterized by the presence of manic or hypomanic episodes, as well as depressive episodes (typical features). Given its early onset, chronic course, and high suicide rate,[1] BD has emerged as a prominent public health concern and a significant global burden of disease.[2,3] As early as the mid-20th century, German physician Leonhard et al[4] pointed out the substantial familial aggregation of BD, shedding light on its hereditary implications. Although the exact pathogenesis of BD remains elusive, approximately 70% of the risk for BD is heritable,[5] thus highlighting the need to identify genetic variations associated with the disease.

In the quest to unravel the genetic underpinnings of BD, numerous scholars have undertaken an extensive exploration spanning several decades, including family,[6] twin,[7] adoption,[8] and molecular genetic studies,[9–13] which have led to the discovery of a number of genes associated with BD. Among these genes, a recent study[13] utilizing whole-exome sequencing (WES) highlighted the significance of A-kinase anchoring protein 11 (*AKAP11*). This study[13] discovered 16 ultra-rare protein-truncating variants (PTVs) within *AKAP11* in a large cohort of 13,933 BD patients, in stark contrast to their absence in 14,422 control subjects. Subsequently, a large-scale rare variant meta-analysis[14] confirmed loss-of-function variants in *AKAP11* as among the strongest BD genetic risks, with replication in the Bipolar Exome Consortium. Converging evidence supports

Received: 7 May 2025
Accepted: 13 August 2025
Published: 29 August 2025

AKAP11's pathogenetic role. Aryal et al[15] found that certain pathway alterations observed in the synaptic proteome of patients with schizophrenia and BD were similar to those in the synaptic proteome of *Akap11*-deficient mice, suggesting that defects or abnormalities in *Akap11* may be linked to synaptic dysfunction and the pathophysiological processes of BD. Additionally, the BrainEXP dataset[16] revealed a significant downregulation of *AKAP11* mRNA expression in the frontal cortex of BD patients compared to controls, further supporting the role of *AKAP11* in the pathogenesis of BD. *AKAP11*, a gene highly expressed in the brain, encodes for the AKAP-11 protein, also known as AKAP220. As a member of the scaffolding protein family, AKAP-11 binds to the regulatory subunit of PKA, facilitating precise targeting of PKA to specific substrates for phosphorylation and dephosphorylation. Notably, through its interaction with glycogen synthase kinase 3 beta (GSK3B), AKAP-11 mediates PKA-dependent inhibition of GSK3B. This interaction is particularly significant because GSK3B is hypothesized to be the target of lithium, which is the primary treatment for BD.[17] Rare variants in the *AKAP11* gene may disrupt the interaction between AKAP-11 and GSK3B, potentially affecting signaling pathways involved in mood regulation. Considering the large differences in the genetic background and population characteristics between Han Chinese and Europeans,[18] we need to further verify the relationship between BD and the *AKAP11* gene in other populations. Notably, we[19] have previously identified a nominal association between a common variant rs238330 within *AKAP11* and BD, which has been replicated in multiple independent samples. This finding not only enhances the credibility of *AKAP11* as a BD risk gene but also suggests that other variants within this gene, including both rare and common ones, may have important implications for the development of BD.

The primary aim of this study was to replicate the findings by Palmer et al[13] using polymerase chain reaction (PCR) amplification and Sanger sequencing, to determine whether rare PTVs in *AKAP11* gene are associated with BD in a Chinese population through a case-control association approach. It is noteworthy that among the 16 rare PTVs in the *AKAP11* gene observed in BD patients of European descent, 13 are located in exon 8. As such, our research will concentrate on evaluating exon 8 of the *AKAP11* gene. Accordingly, our secondary aim is to ascertain whether there are any further rare mutations in exon 8 of the *AKAP11* gene that could be associated with Chinese BD patients.

Methods

Subjects and Procedures

All subjects, who were of the Chinese population, provided written informed consent prior to the implementation of any study-related procedures. Patients with BD were diagnosed through the use of an extensive clinical interview and the Structured Clinical Interview for DSM-IV Axis I Disorders–Patient Version. A total of 284 individuals who met the criteria were enrolled in this study. The control group data, obtained from the China Metabolic Analytics Project (ChinaMAP, http://www.mbiobank.com/), encompassed deep whole-genome sequencing information from 10,588 individuals of Chinese ancestry.[20] While fine-scale genetic structure exists among Han Chinese subpopulations,[21] this structure has minimal impact on common variant association analyses. Our control cohort from ChinaMAP included samples from 27 provinces covering all major geographic regions,[20] ensuring representation of Han Chinese diversity.

DNA samples were extracted from the peripheral blood leukocytes of all subjects using the high salt method. The study protocol obtained approval from the ethics committee of Qingdao Mental Health Center (approval number: NO. 2023024).

AKAP11 Genomic Structure and PCR Amplification

The genome sequence of the human *AKAP11* gene, identified by the Ensembl ID ENSG00000023516, is available from the Ensembl database. Located on chromosome 13 at position q14.11, the *AKAP11* gene comprises a total of 13 exons. Leveraging the Primer-BLAST tool (https://www.ncbi.nlm.nih.gov/tools/primer-blast/index.cgi?LINK_LOC=BlastHome) within NCBI, we conducted primer design for the exon 8 region of the *AKAP11* gene. Subsequently, we employed the In-Silico PCR tool (https://genome.ucsc.edu/cgi-bin/hgPcr) based on UCSC to predict the target sequences and their genomic positions that can be amplified by the candidate primers, thus facilitating the selection of the optimal PCR amplification primer sequences. Primer sequences and the lengths of PCR products are listed in Table S1. In the PCR reaction, template DNA (20 ng) was amplified in a reaction volume of 20 μL containing 1 μL of 10 μM each of the

forward and reverse primers, ddH_2O and 10 μL of 2× Taq Plus Master Mix II (including all components necessary to perform DNA amplification). Touchdown PCR conditions consisted of an initial denaturation at 95°C for 5 minutes, followed by 20 cycles at 95°C for 30 seconds, 65°C for 30 seconds, 72°C for 1 minute and 5 seconds, then another 20 cycles at 95°C for 30 seconds, 55°C for 30 seconds, 72°C for 1 minute and 5 seconds, and a final extension step was performed at 72°C for 5 minutes.

DNA Sequencing and Analysis

The PCR products of 3 μL were separated by electrophoresis utilizing 1.2% agarose gels, thereafter, they were visualized by means of the Tanon 5200 Multi fully automated chemiluminescence imaging system (eg, Figure 1). PCR products that were valid and matched the target fragment size were sent to Sangon Biotech (Shanghai) Co., Ltd. for DNA Sanger sequencing using an ABI 3730XL gene sequencer with the sequencing primers listed in Table S2. Utilizing the SeqMan module of the Lasergene software (version 7.1.0.44), the obtained sequencing peak map files were aligned with the human genome reference sequence (GRCh38), as provided in the Ensembl database, to identify any possible mutation loci. Variant detection in cases was performed by Sanger sequencing,[22] while control data were derived from the ChinaMAP project using deep whole-genome sequencing.[20,23] Although the platforms differ, their accuracy in detecting point mutations and small indels is highly comparable.

Statistical Analysis

The chi-square test was employed to examine the difference in allele frequencies of the five single nucleotide variations located in exon 8 of the *AKAP11* gene between BD patients and the control group from the ChinaMAP database. The

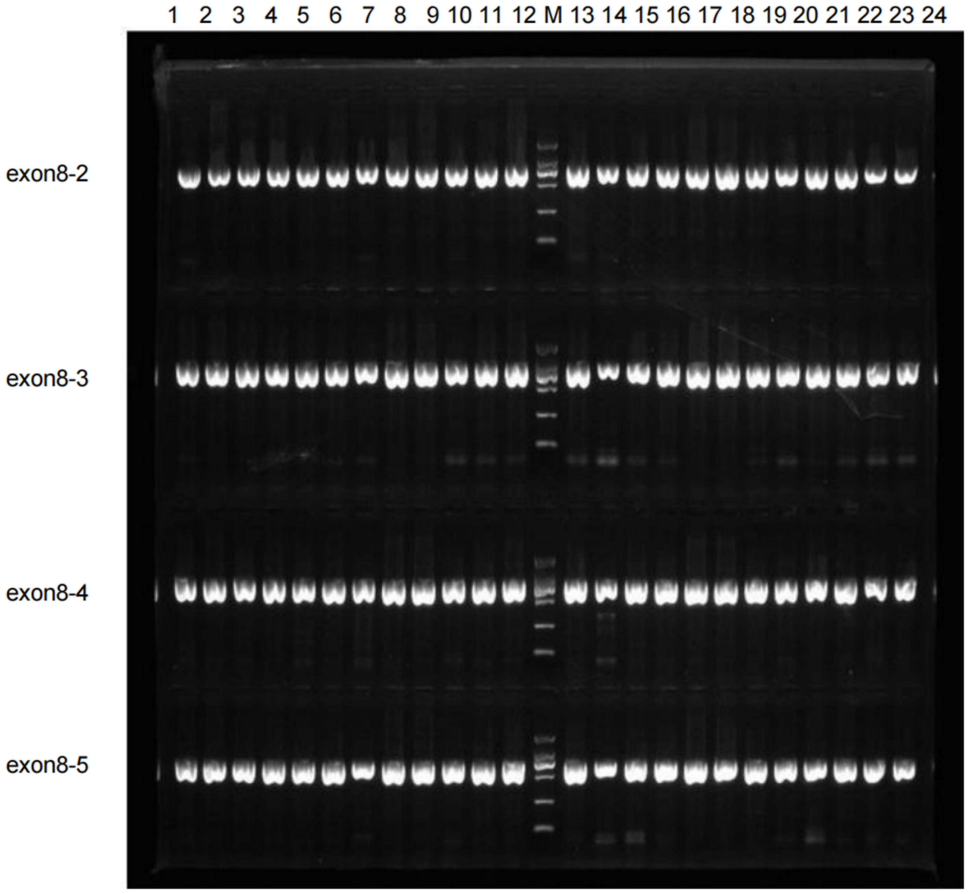

Figure 1 Electrophoretic profiles of *AKAP11* exon 8 PCR products in BD cases.M: D2000 marker; 1–24: Template DNA was obtained from various BD cases; exon8-n: PCR products corresponding to the column of amplicons in Table S1.

statistical analysis was conducted using the 2×2 contingency table function available at http://www.vassarstats.net/odds2x2.html, and $P<0.05$ was considered statistically significant. Post-hoc power analysis was implemented using the computer program PASS (version 21.0.3).

Results

Failure to Replicate European-Implicated Rare PTVs in *AKAP11* Exon 8 Among Chinese BD Patients

We initially determined the genotypes of exon 8 of the *AKAP11* gene in 284 Chinese BD patients, and then compared them with the variant IDs of rare PTVs identified in European BD patients, as reported by Palmer et al[13] on the Bipolar Exomes Browser (BipEx, https://bipex.broadinstitute.org/gene/ENSG00000023516). Our findings reveal that none of the rare PTVs identified in European populations within *AKAP11* exon 8 were observed in our study involving the 284 Chinese BD patients. Similarly, in the control group of this study, which consisted of the ChinaMAP database comprising 10,588 Chinese individuals, none of the PTVs were identified.

Identification of Five Additional Rare Variants in Exon 8 of the *AKAP11* Gene

After sequencing exon 8 of the *AKAP11* gene in the BD patients, we identified a total of five rare variants (alternative allele frequency < 0.05). Three of them were missense variants, and the remaining two were synonymous variants, all of which were single base substitutions documented in the single nucleotide polymorphism (SNP) database. Figure 2 depicts the locations of the five rare variants discovered in exon 8 of the *AKAP11* gene. Starting from the left, the first rare variant was a synonymous variant termed g.42300171T>C (ie, rs771987690), which does not alter the amino acid. It's worth noting that no variants have been identified at this specific locus in the ChinaMAP database, and similarly, the BipEx database did not report any findings at this locus. The second rare variant, identified as g.42300908C>G (rs2236364), is a missense variant that results in an amino acid alteration from serine to cysteine. This specific locus was also not reported in the BipEx database. The third variant, g.42301585A>G (ie, rs117141435), is a missense mutation that leads to the substitution of isoleucine with valine. Interestingly, this particular location was previously documented in the BipEx database; the allele frequency in the case group was 6.46×10^{-4} (18/27,866), while in the control group, it was 9.71×10^{-4} (28/28,844). The fourth mutation, named g.42301991G>T (ie, rs150773395), is another missense mutation that results in the substitution of glycine with valine, and this mutation was not found in the BipEx database. The fifth rare variant is a synonymous variant called g.42302154A>C (ie, rs41288311). It is present in the BipEx database, and its frequency was marginally lower in the case group compared to the control group, with values of 0.1440 (4014/27,866) and 0.1503 (4336/28,844), respectively. Table 1 presents the allele frequencies of these five rare variants in both Chinese and European control populations, as well as in BD patients for comparison.

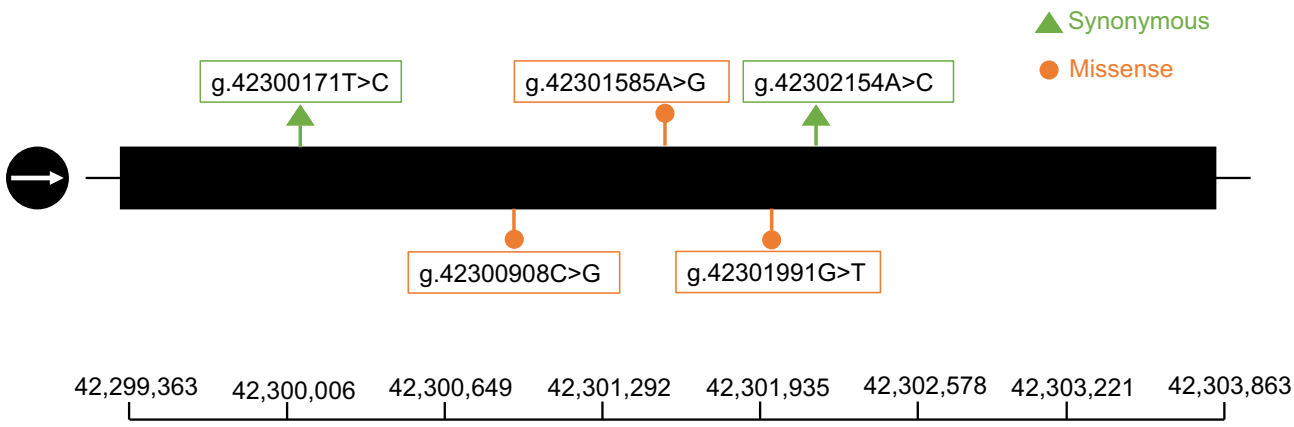

Figure 2 The locations of five rare variants within exon 8 of the *AKAP11* gene.

Table 1 Allele Frequencies of Rare Variants in Exon 8 of the *AKAP11* Gene in BD and Control Groups

Variant Name	HGVS p	Ref	Alt	AAF (Chinese Population)		AAF (European Population)	
				BD	Control	BD	Control
g.42300171T>C (rs771987690)	p.Asp475=	T	C	0.001805	–	–	–
g.42300908C>G (rs2236364)	p.Ser721Cys	C	G	0.01630	0.02182	–	–
g.42301585A>G (rs117141435)	p.Ile947Val	A	G	0.04754	0.04250	0.0006460	0.0009707
g.42301991G>T (rs150773395)	p.Gly1082Val	G	T	0.03369	0.02059	–	–
g.42302154A>C (rs41288311)	p.Thr1136=	A	C	0.001773	0.001369	0.1440	0.1503

Abbreviations: Ref, reference allele; Alt, alternative allele; AAF, alternative allele frequency.

Table 2 Association Analysis of Rare Variants in BD and Control Groups

Group	Total (count)	Ref (count)	Alt (count)	OR and.95 CI	Chi-Square	
					χ^2	*P*
BD	568	511	57	1.1813	1.38	0.2401
Control	21,176	19,349	1827	[0.8947–1.5597]		

Notes: $P < 0.05$ indicated statistical significance.
Abbreviations: Ref: reference allele; Alt: alternative allele; OR, Odds Ratio; CI, Confidence Intervals; χ^2, Chi-square statistics of Chi-square test.

Association Analysis of Rare Variants in BD and Control Groups

As shown in Table 1, the allele frequencies of five rare *AKAP11* variants in exon 8 did not differ significantly between BD cases and controls. Chi-square tests confirmed no significant association (Table 2: OR = 1.181, 95% CI = 0.895–1.560, $P = 0.240$). Although not statistically significant, a slightly higher proportion of these variants was observed in BD cases versus controls.

Power Analysis

The results of the post-hoc power analysis indicate that, with a total sample size of 21,744 (consisting of 568 cases and 21,176 controls), and an alpha level set at 0.05, the effect size for the chi-squared test is specified as 0.00798. Based on these parameters, the statistical power is calculated to be 0.2176.

Discussion

In this study, we aim to replicate the previously observed[13] association between rare PTVs within the *AKAP11* gene and BD using a sample of Chinese individuals. To the best of our knowledge, this represents the first investigation specifically conducted within the Chinese population regarding the relationship between BD and the *AKAP11* gene. However, it is worth noting that while our study includes 284 Chinese BD patients, the European WES study[13] examined a much larger cohort of 13,933 BD patients, identifying 16 ultra-rare PTVs within *AKAP11*, which contrast sharply with their absence in 14,422 control subjects. To construct the control group, we utilized the ChinaMAP database, a large cohort research project focusing on metabolic phenotyping data in Chinese populations. We included information on 10,588 individuals as a control group for BD. It is important to acknowledge, however, that due to data limitations, we are unable to fully ascertain whether these individuals included patients with BD, potentially compromising the purity of the control group. Despite these constraints, our study still provides valuable insights. The absence of these rare PTVs in our control sample, coupled with consistent findings in European controls, suggests that these variants may be

Table 3 Multi-Tool Predictive Evidence for Three Missense Variants

Variant	CADD _phred	GERP++ _RS	PolyPhen-2	SIFT
rs2236364	24.3	5.98	Probably Damaging	Deleterious
rs117141435	14.8	6.03	Benign	Tolerated
rs150773395	22.1	5.80	Benign	Tolerated

Abbreviations: CADD, Combined Annotation-Dependent Depletion; GERP, Genomic Evolutionary Rate Profiling; PolyPhen-2, Polymorphism Phenotyping v2; SIFT, Sorting Intolerant From Tolerant.

exceptionally rare or non-existent in both European and Chinese healthy populations. Nonetheless, given the limitations of our sample size, we must recognize that this may have restricted our ability to detect rare variants. Therefore, we can only conclude that rare PTVs are not found in the BD group in this study, without excluding the possibility of their presence in Chinese BD patients.

Furthermore, our study focused on rare variants in exon 8 of the *AKAP11* gene and identified five additional rare single-nucleotide variants, including three missense variants and two synonymous variants. To comprehensively assess their functional significance, we utilized four prediction tools: CADD (Combined Annotation-Dependent Depletion),[24] GERP (Genomic Evolutionary Rate Profiling),[25,26] PolyPhen-2 (Polymorphism Phenotyping v2),[27] and SIFT (Sorting Intolerant From Tolerant)[28] (Table 3). Among these variants, rs2236364 drew significant attention due to its substitution of serine with cysteine in the PKA-binding domain core (AA 715–725). The integrated predictions showed strong consistency, combined with its absence from the BipEx database and low frequency in Chinese populations, this variant may represent a population-specific putative gain-of-function variant. In contrast, rs117141435, though located in a highly conserved region, was predicted to be tolerated by structural tools and showed moderate impact. The discordance between conservation and functional predictions may stem from its surface-exposed location, necessitating three-dimensional structural modeling to verify potential effects on adjacent phosphorylation sites (AA 945–950). The third variant, rs150773395, exhibited unique predictive patterns: while CADD_phred=22.1 and GERP++_RS=5.80 suggested significant harm, PolyPhen-2 and SIFT both classified it as tolerated. This contradiction may reflect uncaptured impacts of C-terminal domain flexibility changes on protein interactions. Further validation via co-expression network analysis is warranted. Notably, this study focused on PTV detection without full exon sequencing, covering only ~2700 loci in exon 8, which may have overlooked variants in other critical regions. Additionally, functional validation (eg, protein stability assays) was not performed, highlighting the need for future multi-omics integration and cross-population studies to establish a comprehensive genotype-phenotype correlation framework.

Taken together, expanding the sample size of the study and selecting appropriate healthy controls, ideally with a ratio of approximately 1:1 to the BD patients (while also eliminating confounding factors such as demographic data), are imperative avenue for future research. By doing so, we can enhance the statistical power of the study, delve deeper into the genetic association of the *AKAP11* gene, and attain a more comprehensive understanding of the relationship between this gene and the genetic underpinnings of BD in the Chinese population. In addition, further expansion to the entire exon 8, or even the entire *AKAP11* gene, would aid in the discovery of additional, potentially more meaningful rare mutations. Subsequent studies could also provide insights into the functional implications of the identified variants. For instance, exploring how these variants affect the interaction of the AKAP-11 protein with GSK3B and related signaling pathways, potential convergence of *AKAP11*-dependent pathways with neuroinflammatory cascades,[29,30] to name a few.

Conclusion

In summary, we have been unable to replicate the ultra-rare PTVs in the *AKAP11* gene among Chinese BD patients. However, we have identified five other rare variants within exon 8 of *AKAP11*, among which rs2236364 represents a priority candidate based on: Concordant deleterious predictions across four computational tools; Localization in a conserved PKA-binding domain; have not been reported in the BipEx database. Although no significant enrichment of rare variants was observed in cases, the population-specific allele frequency patterns—particularly rs2236364's East Asian-specific occurrence—highlight potential trans-ethnic heterogeneity. As the inaugural systematic assessment of *AKAP11* in Chinese BD, this study establishes

essential groundwork for understanding population-divergent genetic architectures. Future directions include: Expanding sample sizes (ideally 1:1 case-control ratio) with rigorously screened controls; Integrating multi-omics approaches (eg, CRISPR validation, trans-ethnic meta-analysis); Investigating functional impacts on *AKAP11*-PKA complex activity and downstream pathways (eg, GSK3B interactions).

Abbreviations

The following abbreviations are used in this manuscript: *AKAP11*, A-kinase anchoring protein 11; BD, bipolar disorder; PTVs, protein-truncating variants; ChinaMAP, the China Metabolic Analytics Project; PCR, Polymerase chain reaction; BipEx, the Bipolar Exomes Browser; WES, whole-exome sequencing; SNP, the single nucleotide polymorphism; OR, Odds Ratio; CI, Confidence Intervals; Ref, reference allele; Alt, alternative allele; AAF, alternative allele frequency; PKA, protein kinase A; GSK3B, glycogen synthase kinase 3 beta; CADD, Combined Annotation-Dependent Depletion; GERP, Genomic Evolutionary Rate Profiling; PolyPhen-2, Polymorphism Phenotyping v2; SIFT, Sorting Intolerant From Tolerant.

Data Sharing Statement

The datasets generated and/or analysed during the current study are available in the dbSNP repository, SUB14032669, https://submit.ncbi.nlm.nih.gov/subs/variation_file/SUB14032669/overview.

Ethics Approval and Informed Consent

The study protocol obtained approval from the ethics committee of Qingdao Mental Health Center (approval number: NO. 2023024). Meanwhile, informed consent obtained from the study participants prior to study commencement. This study complies with the Declaration of Helsinki.

Acknowledgments

This paper has been uploaded to ResearchSquare) as a preprint: https://www.researchsquare.com/article/rs-3730655/v1.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The Medical and Health Scientific Research Guidance Programme of Qingdao Municipality (2022-WJZD168); Qingdao medical and health scientific research guidance project (2024-WJKY126); Qingdao Medical Research Guidance Plan (2024-WJKY132).

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Plans L, Barrot C, Nieto E, et al. Association between completed suicide and bipolar disorder: a systematic review of the literature. *J Affect Disord*. 2019;242:111–122. doi:10.1016/j.jad.2018.08.054
2. Ferrari AJ, Stockings E, Khoo JP, et al. The prevalence and burden of bipolar disorder: findings from the global burden of disease study 2013. *Bipolar Disord*. 2016;18(5):440–450. doi:10.1111/bdi.12423
3. Vos T, Abajobir AA, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet*. 2017;390(10100):1211–1259.
4. Leonhard K, Korff I, Schulz H. Temperament in families with monopolar and bipolar phasic psychoses. *Psychiatr Neurol*. 1962;143:416–434. doi:10.1159/000131146
5. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *Lancet*. 2020;396(10265):1841–1856. doi:10.1016/S0140-6736(20)31544-0

6. Song J, Bergen SE, Kuja-Halkola R, Larsson H, Landen M, Lichtenstein P. Bipolar disorder and its relation to major psychiatric disorders: a family-based study in the Swedish population. *Bipolar Disord*. 2015;17(2):184–193. doi:10.1111/bdi.12242
7. Kieseppä T, Partonen T, Haukka J, Kaprio J, Lönnqvist J. High concordance of bipolar I disorder in a nationwide sample of twins. *Am J Psychiatry*. 2004;161(10):1814–1821. doi:10.1176/ajp.161.10.1814
8. Mendlewicz J, Rainer JD. Adoption study supporting genetic transmission in manic--depressive illness. *Nature*. 1977;268(5618):327–329. doi:10.1038/268327a0
9. Stahl EA, Breen G, Forstner AJ, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet*. 2019;51(5):793–803. doi:10.1038/s41588-019-0397-8
10. Li HJ, Zhang C, Hui L, et al. Novel risk loci associated with genetic risk for bipolar disorder among han Chinese individuals: a genome-wide association study and meta-analysis. *JAMA Psychiatry*. 2021;78(3):320–330. doi:10.1001/jamapsychiatry.2020.3738
11. Mullins N, Forstner AJ, O'Connell KS, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet*. 2021;53(6):817–829. doi:10.1038/s41588-021-00857-4
12. Li M, Li T, Xiao X, Chen J, Hu Z, Fang Y. Phenotypes, mechanisms and therapeutics: insights from bipolar disorder GWAS findings. *Mol Psychiatry*. 2022;27(7):2927–2939. doi:10.1038/s41380-022-01523-9
13. Palmer DS, Howrigan DP, Chapman SB, et al. Exome sequencing in bipolar disorder identifies AKAP11 as a risk gene shared with schizophrenia. *Nat Genet*. 2022;54(5):541–547. doi:10.1038/s41588-022-01034-x
14. Thorgeirsson TE, Tragante V, Sveinbjornsson G, et al. Rare loss-of-function variants in HECTD2 and AKAP11 confer risk of bipolar disorder. *Nat Genet*. 2025;57(4):851–855. doi:10.1038/s41588-025-02141-1
15. Aryal S, Bonanno K, Song B, et al. Deep proteomics identifies shared molecular pathway alterations in synapses of patients with schizophrenia and bipolar disorder and mouse model. *Cell Rep*. 2023;42(5):112497. doi:10.1016/j.celrep.2023.112497
16. Jiao C, Yan P, Xia C, et al. BrainEXP: a database featuring with spatiotemporal expression variations and co-expression organizations in human brains. *Bioinformatics*. 2019;35(1):172–174. doi:10.1093/bioinformatics/bty576
17. Tanji C, Yamamoto H, Yorioka N, Kohno N, Kikuchi K, Kikuchi A. A-kinase anchoring protein AKAP220 binds to glycogen synthase kinase-3beta (GSK-3beta) and mediates protein kinase A-dependent inhibition of GSK-3beta. *J Biol Chem*. 2002;277(40):36955–36961. doi:10.1074/jbc.M206210200
18. Sirugo G, Williams SM, Tishkoff SA. The missing diversity in human genetic studies. *Cell*. 2019;177(4):1080. doi:10.1016/j.cell.2019.04.032
19. Sun P, Wang L, Yang Y, et al. Common variants associated with AKAP11 expression confer risk of bipolar disorder. *Asian J Psychiatr*. 2022;77:103271. doi:10.1016/j.ajp.2022.103271
20. Cao Y, Li L, Xu M, et al. The ChinaMAP analytics of deep whole genome sequences in 10,588 individuals. *Cell Res*. 2020;30(9):717–731.
21. Chen J, Zheng H, Bei JX, et al. Genetic structure of the Han Chinese population revealed by genome-wide SNP variation. *Am J Hum Genet*. 2009;85(6):775–785. doi:10.1016/j.ajhg.2009.10.016
22. Ewing B, Green P. Base-calling of automated sequencer traces using phred. II. Error probabilities. *Genome Res*. 1998;8(3):186–194. doi:10.1101/gr.8.3.186
23. Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*. 2016;536(7616):285–291. doi:10.1038/nature19057
24. Rentzsch P, Witten D, Cooper GM, Shendure J, Kircher M. CADD: predicting the deleteriousness of variants throughout the human genome. *Nucleic Acids Res*. 2019;47(D1):D886–d894. doi:10.1093/nar/gky1016
25. Davydov EV, Goode DL, Sirota M, Cooper GM, Sidow A, Batzoglou S. Identifying a high fraction of the human genome to be under selective constraint using GERP++. *PLoS Comput Biol*. 2010;6(12):e1001025. doi:10.1371/journal.pcbi.1001025
26. Cooper GM, Stone EA, Asimenos G, Green ED, Batzoglou S, Sidow A. Distribution and intensity of constraint in mammalian genomic sequence. *Genome Res*. 2005;15(7):901–913. doi:10.1101/gr.3577405
27. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. *Nat Methods*. 2010;7(4):248–249. doi:10.1038/nmeth0410-248
28. Ng PC, Henikoff S. SIFT: predicting amino acid changes that affect protein function. *Nucleic Acids Res*. 2003;31(13):3812–3814. doi:10.1093/nar/gkg509
29. Ş A K, Kızgın S, Oğuz EF, Neşelioğlu S, Ö E. Thiol-disulphide homeostasis, ischemia-modified albumin, complete blood count-derived inflammatory markers and C-reactive protein from acute mania to early remission in bipolar disorder. *J Affect Disord*. 2023;339:426–434. doi:10.1016/j.jad.2023.07.079
30. Ş A K, Kızgın S. Neutrophil/high-density lipoprotein cholesterol (HDL), monocyte/HDL and platelet/HDL ratios are increased in acute mania as markers of inflammation, even after controlling for confounding factors. *Curr Med Res Opin*. 2023;39(10):1383–1390. doi:10.1080/03007995.2023.2260302