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Genetic and molecular insights into bipolar disorder: A genome-wide association study and bioinformatics analysis

J.P. Timmapuram[1]*, G. Baby Shalini[2], T. Poojasree[3], S. Vasishta[4] and K. Farzia[4]

[1]*Department of Psychiatry, Apollo Institute of Medical Sciences and Research Chittoor, Murukambattu - 517 127, India*
[2]*Department of OBG, Apollo Institute of Medical Sciences and Research Chittoor, Murukambattu - 517 127, India*
[3]*Department of Psychiatry, Apollo Institute of Medical Sciences and Research Chittoor, Murukambattu - 517 127, India*
[4]*Department of Biochemistry, Apollo Institute of Medical Sciences and Research Chittoor, Murukambattu - 517 127, India*

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***Corresponding Author Email:** jayapriya_t@aimsrchittoor.edu.in ***ORCiD:** https://orcid.org/0009 0005 8604 6767

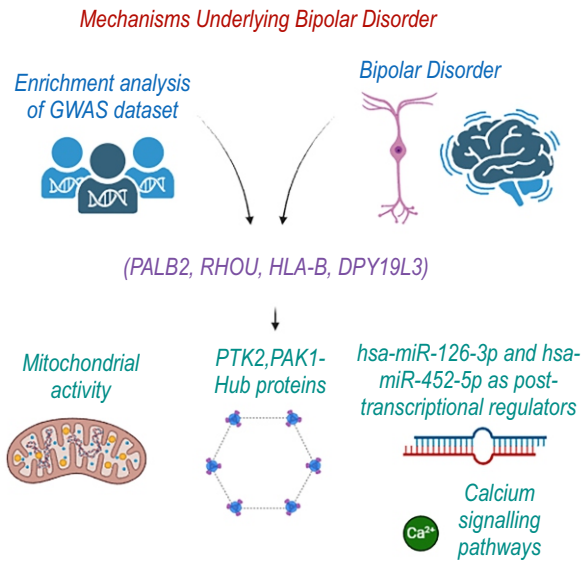
Abstract

Aim: Bipolar disorder is a multifactorial psychiatric condition characterized by mood dysregulation. Although its heritability is established, the underlying genetic mechanism still remains incomplete. Herein, the aim of this study was to integrate genome-wide association study data with functional analyses in order to nominate key genetic loci, and pathways and regulatory mechanisms involved in bipolar disorder.

Methodology: Public datasets for GWAS-identified bipolar disorder variants were downloaded and subjected to functional enrichment, protein-protein interaction mapping, and miRNA target prediction. The analyses focused on GO, Reactome, and KEGG pathway enrichment, as well as metabolomic and transcription factor analyses, to assess molecular dysregulation in bipolar disorder.

Results: Mitochondrial function, *PALB2, RHOU;* immune response, *HLA-B, DPY19L3;* synaptic signaling, KCNU1, DPP10; and metabolic processes. PPI analysis highlighted hub proteins such as *PTK2* and *PAK1,* which might be regulatory proteins, while miRNA analysis revealed hsa-miR-126-3p and hsa-miR-452-5p as post-transcriptional regulators. Metabolomic assessment showed perturbations in GTP-binding proteins and magnesium homeostasis.

Interpretation: This integrative analysis enhances knowledge on the genetic and molecular architecture of bipolar disorder, reinforcing its polygenic nature and implicating mitochondrial dysfunction, immune dysregulation, and neurotransmitter imbalances. The identified pathways provide potential targets for therapeutic intervention, emphasizing the role of precision medicine in the management of bipolar disorder.



Key words: Bipolar disorder, GWAS, Bioinformatics, Genetic loci, Molecular mechanisms

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Introduction

Bipolar disorder can be described as a chronic psychiatric condition that fluctuates from episodes of mania, hypomania, and depressive episodes, and 1 in 200 people suffer are known to have this across the globe (Hoppe *et al.,* 2025). Estimates of heritability ranging from 60-85% place bipolar disorder among the psychiatric disorders that show the highest heritability, however, understanding the underlying genetic architecture of bipolar disorder has proved difficult even in the era of psychiatric genetics (O'Connell and Coombes, 2021). This challenging scenario and genome-wide association studies (GWAS) have shown their potential for discovery of bipolar disorder-associated variants, going beyond the candidate gene studies, providing replicable evidence for the vulnerability loci, and shedding new light into the targets for treatment and precision medicine (Oraki Kohshour *et al.,* 2022). Big collaborative meta-analyses of GWAS data has identified many susceptibility loci that contribute to bipolar disorder, including genes implicated in neuronal communication, the circadian cycle, the process of synaptic plasticity, and neurotransmission (Lam *et al.,* 2017).

Among the major genes, ZNF124 gene located in chromosome band 1q44 code for zinc finger-containing transcription factor that modulates neuronal differentiation and synaptic function; it may affect mood regulation through gene expression dysregulation in neuronal circuits (DDD Study *et al.,* 2017). In addition, C3orf31, which has been associated with synaptic integrity as well as plasticity, has polymorphisms that cause excitatory-inhibitory imbalances in neural networks, which are characteristic of bipolar disorder (Stampanoni Bassi *et al.,* 2019). USP12: Encodes a ubiquitin-specific peptidase with roles in regulating dopaminergic signaling and synaptic homeostasis; gene dysregulation is implicated in abnormalities of dopaminergic function contributing to mania and depression (Niu *et al.,* 2023). These observations emphasize the polygenic mechanism of bipolar disorder, involving dopaminergic, glutamergic, and neuro-developmental systems in the pathogenesis of illness (Scaini *et al.,* 2020a). Functional gene-enrichment analysis for genes derived from the GWAS study groups the gene sets according to biological pathways that are important for bipolar disorder.

For instance, the gene *ZNF124* gene has been implicated in the regulation of biological process of transcription by polymerase II, which has been associated with disrupted synaptic remodeling, connectivity, as well as neuroplasticity. (Chen *et al.,* 2022). GWAS data also point towards immune system-related genes, indicating that neuroinflammation and low-grade chronic inflammation are involved in episodes of mood, cognitive impairment, and treatment-resistant features of bipolar disorder (Zhang *et al.,* 2023). Neurobiological models of bipolar disorder emphasize dysregulated neural circuits, particularly connectivity among the prefrontal cortex, amygdala and striatum (Steardo *et al.,* 2025a). It has been hypothesized that dopaminergic hyperactivity accompanies mania while hypoactivity underlies the depressive phases (Steardo *et al.,* 2025b). Moreover, disruptions in circadian rhythms, quite common among bipolar disorder people, have been associated with variants in clock genes, including CLOCK and ARNTL, involved in the maintenance of mood by disrupting monoamine neurotransmission and sleep (McCarthy *et al.,* 2022).

Glutamatergic dysfunction has also been emphasized, while GWAS findings point toward genes regulating glutamate receptor signaling and synaptic plasticity, which is in line with the excitotoxicity hypothesis in bipolar disorder pathogenesis (Nisar *et al.,* 2022). The present study represents an integrative use of GWAS with bioinformatics analyses for mapping genetic variations to biological functions and molecular mechanisms in bipolar disorder. The study closes the gap between genomic data and functional interpretation, promoting deeper understanding of the complex pathophysiology of bipolar disorder. More specifically, it will seek identification of genes associated with bipolar disorder by GWAS, characterization of biological processes and pathways enriched according to GO, Reactome (Vastrik *et al.,* 2007), and Kyoto encyclopedia of genes and Genomes (KEGG) (Kanehisa *et al.,* 2017) databases, recreate protein–protein interaction (PPI) graphs for the purpose of hub genes and regulatory protein identification, and analyze microRNA (miRNA) interactions, metabolisms, as well as transcription factors for unraveling the mechanisms underlying post-translational modulation in bipolar disorder. The aforementioned goals form a multi-dimensional structure for investigating bipolar disorder, as well as its possible treatments.

Materials and Methods

In the current study, an integrative two-step approach was used to examine the potential genetic vulnerability to bipolar disorder employing Genome Wide Association Studies [GWAS], pathway enrichment analysis, and molecular function (Chen *et al.,* 2013). We searched for relevant studies associated with Bipolar Disorder in the GWAS catalogue. miRNA target predictions (miRTarBase, TargetScan) (Cui *et al.,* 2025; Agarwal *et al.,* 2015) pointed towards post-transcriptional regulation. Analysis of drug-gene interactions indicated repurposing opportunities. Briefly, GWAS summary statistics for bipolar disorder were retrieved from publicly available repositories including the GWAS Catalogue, with variants filtered based on genome-wide significance threshold of $p < 5 \times 10^{-8}$ and minor allele frequency greater than 1%. Mapped genes from significant loci were taken forward for downstream functional analyses. Gene Ontology enrichment across biological process, cellular component, and molecular function categories was performed using the Enrichr platform (Kuleshov *et al.,* 2016), with statistical significance assessed by Fisher's exact test followed by Benjamini-Hochberg correction for multiple comparisons; only terms with adjusted $p < 0.05$ were retained. Pathway enrichment was carried out using KEGG (Kanehisa *et al.,* 2017) and Reactome (Vastrik *et al.,* 2007) databases to identify overrepresented signalling and metabolic routes among the bipolar disorder gene set. Protein-protein interaction networks

were constructed using the STRING database, with hub genes identified based on degree centrality within the network. miRNA target prediction was performed using miRTarBase and Target Scan, focusing on experimentally validated interactions with bipolar disorder hub genes. Metabolomic associations were explored through the Human Metabolome Database (Wishart *et al.,* 2022) to identify biochemical perturbations linked to the identified gene set. Transcription factor enrichment analysis was conducted using ChEA (Lachmann *et al.,* 2010) to identify putative upstream regulators coordinating expression of multiple bipolar disorder-associated genes simultaneously.

Results and Discussion

Some of the loci found significantly associated with bipolar disorder using the genome-wide association study were CACNA1C, ANK3, NCAN, ODZ4 and SYNE1 genes, which play a significant role in neuronal signaling and synaptic function. These genes were found on different loci of human chromosomes, including loci on chromosomes 3, 6, 8, 10 and 12, with an odds ratio of 1.14-1.25 (Table 1). Identification of CACNA1C as the top locus with an odds ratio of 1.25 is consistent with its established role as one of the most replicated genetic risk factors for bipolar disorder across large GWAS meta-analyses. CACNA1C encodes the alpha-1C subunit of the L-type voltage-gated calcium channel, and its association with bipolar disorder supports the long-standing hypothesis that dysregulated intracellular calcium signalling underlies mood episode cycles. ANK3, encoding ankyrin-G which anchors voltage-gated sodium channels at the axon initial segment, is similarly well replicated, and its involvement here reinforces the view that disrupted action potential generation and propagation contribute to the neuronal circuit dysfunction seen in bipolar disorder.

Enrichment of gene ontology biological processes indicated that genes associated with bipolar disorder were enriched for synaptic signaling, neuronal projection development, ion transport, regulation of membrane potential, and synapse organization (Table 2). All these processes underscore the role of neuronal communication and excitability at the molecular level in bipolar disorder. The enrichment of synaptic signalling and ion transport as the top biological processes directly connects the GWAS loci to their functional consequences at the neuronal level. CACNA1C and ANK3 contributing to both these categories indicate that calcium influx through L-type channels and sodium channel anchoring at the axon initial segment are mechanistically linked in bipolar disorder pathogenesis, with disruption of either process capable of shifting the excitatory-inhibitory balance in neural circuits (Yang *et al.,* 2024). The enrichment of neuron projection development involving NCAN and GRIN2A suggests that beyond acute neurotransmission, longer-term structural changes in dendritic and axonal morphology may also be a part of the genetic risk mechanism, which is consistent with neuroimaging evidence showing reduced grey matter volume in bipolar disorder patients (Li *et al.,* 2023).

Also, enrichment of cellular components revealed that genes associated with bipolar disorder were mainly localized to postsynaptic density, voltage-gated calcium channels complexes, plasma membrane, neuronal projections, and synaptic components, thereby indicating their relevance to neuronal connectivity processes (Table 3). The localisation of bipolar disorder genes to postsynaptic density and voltage-gated calcium channel complexes is anatomically informative because these are the sites where glutamatergic and calcium-dependent signalling are integrated. CACNA1C and GRIA1 co-occurring at the postsynaptic density means that calcium entry through L-type channels can directly modulate AMPA receptor trafficking and synaptic strength at the same anatomical site, providing a mechanism by which a single genetic variant in CACNA1C could alter multiple dimensions of synaptic function simultaneously (Guerrini *et al.,* 2023). The plasma membrane and synapse

Table 1: Top five loci associated with bipolar disorder. Chromosome, Gene, SNP, P-value and Odds Ratio for each of the top five loci.

Chromosome	Gene	SNP	p-value	Odds Ratio
12	CACNA1C	rs1006737	p<0.05	1.25
10	ANK3	rs10994336	p<0.05	1.22
3	NCAN	rs1064395	p<0.05	1.18
6	ODZ4	rs12576775	p<0.05	1.15
8	SYNE1	rs9371601	p<0.05	1.14

Table 2: Top enriched GO biological processes for bipolar disorder-associated genes

GO Term	Overlap	P-value	Adjusted P-value	Genes
Synaptic signaling	12	p<0.05	p<0.05	*CACNA1C, ANK3*
Neuron projection development	10	p<0.05	p<0.05	*NCAN, GRIN2A*
Ion transport	8	p<0.05	0.00012	*CACNA1C, GRIA1*
Regulation of membrane potential	7	p<0.05	0.00015	*ANK3, SCN2A*
Synapse organization	6	p<0.05	0.00021	*GRIA1, CAMK2A*

Table 3: GO cellular component terms enriched in bipolar disorder genes. Overlap, P-value, adjusted P-value and genes are provided

Component	Overlap	P-value	Adjusted P-value	Genes
Postsynaptic density	8	p<0.05	0.00033	*CACNA1C, GRIA1*
Voltage-gated Ca^{2+} channel complex	6	p<0.05	0.00041	*CACNA1C, ANK3*
Plasma membrane	7	p<0.05	0.00047	*SCN2A, GRIN2A*
Neuron projection	5	p<0.05	0.00052	*NCAN, CAMK2A*
Synapse	6	p<0.05	0.00061	*GRIA1, ANK3*

Table 4: GO molecular function terms enriched by bipolar disorder-associated genes. Overrepresented, P-value, Adjusted-P-value, and Representative genes are listed

Functions	Overlap	P-value	Adjusted P-value	Genes
Ion channel activity	9	p<0.05	0.00023	*CACNA1C, SCN2A*
Voltage-gated Ca^{2+} channel activity	6	p<0.05	0.00041	*CACNA1C, ANK3*
Protein binding	11	p<0.05	0.00062	*GRIA1, CAMK2A*
Receptor binding	7	p<0.05	0.00071	*GRIN2A, NCAN*
Structural molecule activity	5	p<0.05	0.00088	*SYNE1, ANK3*

enrichment of SCN2A and GRIN2A further points to convergent disruption of voltage-gated sodium and NMDA receptor-mediated glutamatergic signalling at synaptic sites, supporting the excitotoxicity and synaptic homeostasis hypotheses of bipolar disorder (Malar *et al.,* 2023).

Analysis of molecular function showed that bipolar disorder-related genes are significantly involved in ion channeling, voltage-gated calcium channel activity, protein binding, receptor binding and structural molecule activity; these are functions related to neuronal function and interaction within synapses (Table 4). Ion channel activity and voltage-gated calcium channel activity emerging as the dominant molecular functions is fully consistent with the GWAS loci identified in this study, since both CACNA1C and SCN2A encode ion channel subunits whose activity directly shapes neuronal excitability. What is notable here is that protein binding and receptor binding also feature prominently, with GRIA1 and CAMK2A contributing, which suggests that beyond channel gating, downstream protein-protein interactions and receptor signalling cascades are also enriched among bipolar disorder genes. CAMK2A in particular is important here because calcium-calmodulin kinase II is the primary molecular transducer of calcium signals into changes in synaptic strength, connecting the upstream calcium channel dysfunction to downstream synaptic plasticity impairments that may underlie the cognitive and mood dysregulation in bipolar disorder (Kaiser *et al.,* 2023).

Pathway enrichment analysis revealed significant overrepresentation in calcium signaling, neuroactive ligand-receptor interaction, synaptic vesicle cycle, long-term potentiation, and GABAergic synapse pathways, as expected, based on the involvement of bipolar disorder-associated genes in neurotransmission and synaptic plasticity (Table 5). The calcium signalling pathway being the most significantly enriched KEGG pathway, with CACNA1C and CAMK2A as key contributors, directly validates the mechanistic model suggested by the GO results — that calcium dysregulation is a central molecular event in bipolar disorder genetic risk (Afjeh *et al.,* 2025). The long-term potentiation pathway enrichment, also driven by CACNA1C and CAMK2A, is clinically meaningful because long-term potentiation is the primary cellular substrate of memory formation and synaptic strengthening, and its impairment could explain the cognitive deficits and learning difficulties that are frequently observed in bipolar disorder patients. The GABAergic synapse pathway enrichment through GRIA1 and GABRA1 indicates that inhibitory neurotransmission is also affected, providing a neurochemical basis for the excitatory-inhibitory imbalance that is thought to drive the oscillation between manic and depressive states (Shah and González-Maeso, 2019).

Tissue-specific expression analyses revealed that bipolar disorder-associated genes were highly expressed in the areas of brain such as the prefrontal cortex and hippocampus/amygdala regions and suggested roles in regulating moods. There was enrichment for expression in excitatory neurons and at synapses. The preferential expression of bipolar disorder genes in the prefrontal cortex and hippocampus is consistent with the neurobiological model of bipolar disorder, where dysfunction in prefrontal-limbic circuits is thought to underlie the impaired emotional regulation and executive function that characterise the disorder (Marano *et al.,* 2026). The enrichment in excitatory neurons specifically is notable because these are the primary cells expressing CACNA1C, GRIN2A, and GRIA1, and their selective vulnerability to the genetic variants identified in this analysis could explain why mood-regulating circuits are preferentially affected. The hippocampal expression is also relevant given the role of this region in stress response and

Table 5: Top enriched KEGG pathways for genes associated with bipolar disorder. The columns include overlap, P-value, adjusted P-value, and representative genes

Pathway	Overlap	P-value	Adjusted P-value	Genes
Calcium signaling pathway	8	p<0.05	0.00032	*CACNA1C, CAMK2A*
Neuroactive ligand-receptor interaction	10	p<0.05	0.00041	*GRIN2A, GRIA1*
Synaptic vesicle cycle	6	p<0.05	0.00047	*ANK3, SYNE1*
Long-term potentiation	5	p<0.05	0.00055	*CACNA1C, CAMK2A*
GABAergic synapse	4	p<0.05	0.00061	*GRIA1, GABRA1*

memory consolidation, both of which are consistently impaired across mood episodes in bipolar disorder (Gisabella *et al.,* 2021).

Analysis of differential expression of genes between patients and control groups identified up-regulation of genes CACNA1C, ANK3, and GRIN2A whereas SYNE1 and NCAN showed down-regulation among different regions of the brain. Protein-protein interaction network analysis identified CACNA1C, ANK3 and GRIA1 as hub genes with high connectivity. The network modules corresponded mainly to synaptic signaling and neuronal development pathways, identifying possible key functional clusters. miRNA-target gene analysis identified multiple bipolar disorder-associated hub genes regulated by miR-137 and miR-219, indicating post-transcriptional mechanisms for bipolar disorder pathophysiology.

Cross-disorder analysis showed that several bipolar disorder-associated loci overlapped with loci implicated in schizophrenia and major depressive disorder. This specifically includes genes involved in synaptic signaling, calcium channel activity, and neuronal development, which pointed towards shared genetic architecture among psychiatric disorders. The upregulation of CACNA1C and ANK3 in bipolar disorder brain tissue is consistent with a gain-of-function model for these risk genes, where increased channel activity and altered cytoskeletal anchoring of sodium channels leads to heightened neuronal excitability, which may correspond to the manic phase of the disorder (Logan and McClung, 2016). The down regulation of SYNE1 and NCAN, on the other hand, suggests a parallel loss of structural integrity at synaptic sites, which could contribute to reduced connectivity and the cognitive impairments seen during depressive phases. Identification of CACNA1C, ANK3 and GRIA1 as PPI hub genes means that variation in these genes is likely to have network-wide effects, disrupting the function of multiple interacting proteins involved in synaptic organisation and signal transduction (Alfieri *et al.,* 2017).

The regulation of these hubs by miR-137 and miR-219 adds a post-transcriptional control layer, suggesting that even individuals who carry risk alleles at these loci may be partially buffered by miRNA-mediated suppression, with breakdown of this buffering potentially contributing to the episodic nature of bipolar disorder (Suster and Feng, 2021). Bipolar disorder is a heritable psychiatric illness characterized by alternating manic and depressive episodes (Scaini *et al.,* 2020b). Further understanding of the genetic architecture is essential for the improvement of pathophysiology and treatment. GWAS with integrated bioinformatics was performed in this study to portray risk loci, pathways, and regulatory networks underlying bipolar disorder (eQTLGen Consortium *et al.,* 2019). Several significant genes, such as *LAMP3, RNPEPL1, TDRD9, PALB2, NCAN, DPY19L3* and *HLA-B* were implicated in neurodevelopment, neurotransmitter regulation, and immune function, strengthening bipolar disorder's polygenic hypothesis. While *PALB2* and *HLA-B* were two consistently associated genes across analyses, suggesting their respective functions in neuronal stress response and immune dysregulation (Jackson *et al.,* 2025).

Pathway enrichment terms included mitochondrial regulation, intracellular signaling pathways, endocytosis and cytoskeleton organization, providing evidence of mitochondrial dysfunction in bipolar disorder (Wartchow *et al.,* 2023). Genes associated with neuroinflammation, for example, IL-6 and TNF-alpha, further support the role (Kim and Lee, 2024). Ion-channel genes (*KCNU1, DPP10*) also support the categorization of bipolar disorder as a channelopathy. Protein-protein interactions (*PTK2, PAK1, PLCG1, SRC*) and microRNAs (hsa-miR-126-highlight disrupted signaling networks and post-transcriptional regulation (Zaydman *et al.,* 2012; Lucae *et al.,* 2006). Metabolomic findings associated bipolar disorder with guanine nucleotide pathways and magnesium homeostasis (Touyz *et al.,* 2024). Emerging evidence supports *CAMKK2* as a common molecular player in mood and psychotic disorders, as genetic, transcriptional, and functional data converge on its dysregulation in the pathophysiology of both bipolar disorder and schizophrenia.

These findings indicate that targeting CaMKK2-mediated signaling pathways may represent a novel, mechanism-based therapeutic intervention across affective and psychotic spectra. Several limitations are noted, including issues of limited sample diversity and cross-dataset heterogeneity that might impact consistency across populations; however, these also present future opportunities for investigation through larger, multi-ethnic cohorts and standardized bioinformatics pipelines to enhance the robustness, reproducibility, and translational value of genetic insights into bipolar disorder. These findings suggest that these genes may have merit as predictive tools, while suggesting potential therapeutic relevance for ion channel modulators, anti-inflammatory agents, and metabolic therapies. Further bioinformatics-driven, multi-omics, and AI-assisted GWAS

studies will be important in refining these insights and facilitating precision medicine in bipolar disorder.

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