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Molecular Signatures of Bipolar Disorder: A Review of Genetic and Epigenetic Evidence

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ABSTRACT

Bipolar Disorder (BD) is a chronic psychiatric condition characterised by episodic shifts between depressive and manic states. BD has a highly polygenic architecture, which contributes to its substantial heritability and clinical variability. The disorder also shares genetic susceptibility with schizophrenia and major depressive disorder (MDD). Besides inherited risk, epigenetic processes—such as DNA methylation, histone modifications, and noncoding RNAs—mediate gene–environment interactions, influencing disease onset and progression. This review assesses the potential of genetic and epigenetic markers to guide subtype-specific treatment in BD, discusses present limitations, and proposes practical recommendations for future research to support clinical implementation.

Keywords: bipolar disorder, genetic markers, epigenetics, psychiatric genomics, biomarkers

1. INTRODUCTION

BD affects ~1–2% of the global population and carries a considerable public health burden; in 2019, mental disorders accounted for about 5% of global disability-adjusted life years (DALYs) (Merikangas et al., 2011; GBD 2019 Collaborators, 2022). Despite its significant impact, BD remains poorly understood due to its complex underlying biology, which limits progress in diagnosis, treatment, and outcomes.

Genetic research has shed new light on the etiology of BD. Twin studies have estimated heritability at 60-80% (McGuffin et al., 2003; Kieseppä et al., 2004; Edvardsen et al., 2008). Genome-wide association studies (GWAS) have identified numerous risk loci, each associated only moderately with overall risk (Stahl et al., 2019; Mullins et al., 2021). These findings support a polygenic architecture of BD in which numerous variants contribute to risk and interact with environmental exposures.

Recently, attention has focused on epigenetic mechanisms as potential mediators of gene–environment interactions relevant to disease onset and course (Mill et al., 2013; Nestler, 2016). Advances in high-throughput sequencing, neuroimaging, and computational methods—including machine learning—have identified additional biomarkers and biological pathways in BD (Nunes et al., 2020;

Ching et al., 2022; Meda et al., 2014). Collectively, multi-omics and transdiagnostic approaches are shifting the psychiatric field toward diagnostic frameworks grounded in biological signatures rather than symptom clusters alone.

This review brings together recent findings on possible genetic and epigenetic markers for bipolar disorder. Evidence from extensive genomic studies, EWAS, and biomarker research helps build a framework that explains individual differences and the biological processes involved.

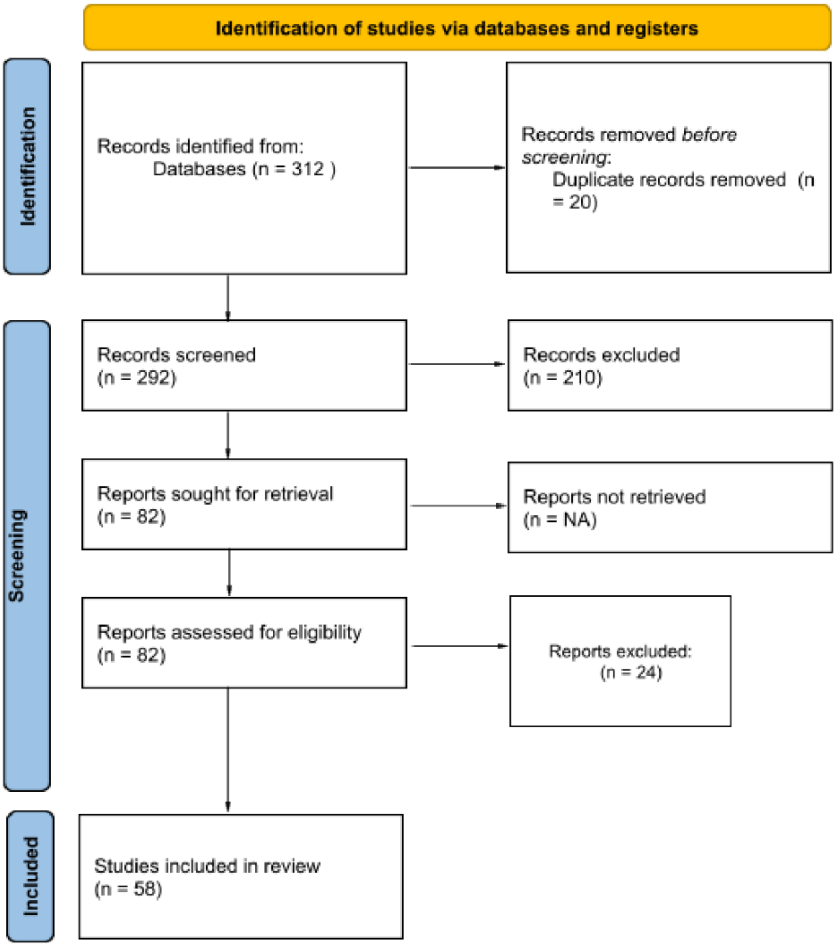

Figure 1 PRISMA flow diagram

2. REVIEW METHODS

We conducted a structured narrative literature search to identify studies on genetic and epigenetic markers of bipolar disorder (BD), focusing on recent, high-quality evidence published in English from December 2001 to January 2025. We searched PubMed, Scopus, Web of Science, and Google Scholar using the following keywords: bipolar disorder, genetic markers, genome-wide association studies, epigenetics, DNA methylation, histone modification, gene expression, translational psychiatry, biomarkers, and psychiatric genomics. We included peer-reviewed original research, meta-analyses, and systematic reviews that evaluated genetic or epigenetic factors, investigated biological pathways relevant to BD, and focused on adults with a formal DSM-IV, DSM-5, or ICD-10 diagnosis. We excluded case reports, editorials, conference abstracts, or studies lacking BD-specific analyses. This process yielded 312 records. After removing duplicates and screening titles and abstracts, we reviewed 82 full-text articles that met our criteria. Ultimately, 58 studies were selected based on their relevance, strong methodology, and detailed analysis of biomarkers or pathways. From these, we extracted data on study design, sample characteristics, methods, identified markers, and their possible impact on diagnosis or treatment (Figure 1).

3. RESULTS AND DISCUSSION

Genetic Markers

Twin studies estimate the heritability of BD at roughly 60-80% (McGuffin et al., 2003; Kieseppä et al., 2004; Edvardsen et al., 2008). Over the past decade, GWAS and sequencing have identified numerous risk loci, supporting a highly polygenic architecture. In 2025, a large multi-ancestry GWAS meta-analysis with fine-mapping reported 298 BD risk loci and proposed 36 candidate effector genes at these loci. The analysis also identified differences in genetic architecture between BD-I and BD-II (O'Connell et al., 2025).

Although rare copy-number variants (CNVs) increase the risk for several neuropsychiatric disorders, their role in BD appears to be more nuanced (Rees and Kirov, 2021). Extensive case-control studies generally do not show a global excess of rare CNVs in a typical adult-onset BD (Charney et al., 2019; Green et al., 2016). In contrast, family/early-onset studies report an elevated rate of de novo CNVs in early-onset cases of BD (Malhotra et al., 2011; Priebe et al., 2012; Georgieva et al., 2014; Green et al., 2016). Pathogenic CNVs strongly associated with schizophrenia show weaker and less consistent associations with BD (Green et al., 2016).

Common-variant genome-wide association studies (GWAS) reproducibly implicate genes encoding voltage-gated calcium-channel subunits—particularly CACNA1C and CACNB2 (Ferreira et al., 2008; Cross-Disorder Working Group of the PGC, 2013). Mentioned genes influence neuronal excitability and synaptic function by regulating activity-dependent Ca^{2+} influx. These findings are consistent with the disruption of these mechanisms in BD (Ferreira et al., 2008; Cross-Disorder Working Group of the PGC, 2013).

Finally, cross-disorder genomic analyses indicate that BD shares substantial common-variant liability with schizophrenia and a moderate overlap with MDD (Cross-Disorder Working Group of the PGC, 2013; Anttila et al., 2018; Lee et al., 2019). Taken together, these findings may support a mood-psychosis spectrum, with MDD, BD, schizoaffective disorder, and schizophrenia arrayed along a shared liability continuum rather than entirely distinct, symptom-based categories.

Epigenetic Markers

The most consistent epigenetic biomarker signals in BD derive from studies of DNA methylation, histone acetylation, and noncoding RNA. Several markers appear mood state- and treatment-responsive rather than strictly diagnostic (Pisanu, 2023; Martinez and Peplow, 2024).

Researchers identified differentially methylated positions/regions (DMPs/DMRs) in BD through blood-based EWAS. Although these changes at specific genetic sites are usually small and vary between individuals, analysis of multiple studies shows nonrandom clustering of DMPs/DMRs. Notably, these methylation patterns tend to cluster within genes associated with synaptic and inflammatory functions (Hesam-Shariati et al., 2022; Kaminsky et al., 2012). EWAS comparing BD patients with and without a history of suicide attempt have identified methylation signatures specific to suicide-attempt history rather than to BD itself (Mirza et al., 2024; Jeremian et al., 2017).

Epigenetic clocks are machine-learning models that estimate biological age based on DNA methylation at selected CpG sites (Table 1). First-generation clocks primarily track chronological age, whereas newer models predict morbidity, mortality risk, and the pace of aging. Patients with BD show clinical features of premature aging, which may partly contribute to the higher prevalence of age-related medical conditions (Fries et al., 2020). In a 2017 case-control study of peripheral-blood DNA (22 BD I patients, 16 unaffected siblings, and 20 healthy controls), older patients with BD I showed significantly accelerated epigenetic aging relative to controls; by contrast, younger participants showed no difference (Fries, 2017). Some observational studies have noted partial deceleration in epigenetic aging, specifically among patients treated with lithium (Okazaki et al., 2020; Zafrilla-López et al., 2024).

Postmortem brain studies have identified BD-related differences in histone modifications. The most reproducible signals involve H3K27ac (enhancer-associated), whereas findings for H3K4me3 (active promoter) are less consistent across cohorts (Girdhar et al., 2022; Girdhar et al., 2018; Cruceanu et al., 2012). Changes in these marks generally parallel transcriptional activity of nearby genes (Bannister and Kouzarides, 2011). Clinically, this is relevant because valproate, a mood stabilizer used in BD, inhibits histone deacetylases (HDACs), increases histone acetylation, and modulates gene expression (Göttlicher et al., 2001; Gurvich et al., 2004). However, direct evidence for altered HDAC activity in the prefrontal cortex of patients with BD is limited (Tseng et al., 2020; Ludwig et al., 2016).

Several studies have reported alterations in peripheral microRNAs (miRNAs) among patients diagnosed with BD, specifically noting the upregulation or downregulation of specific miRNAs compared to controls (Clausen et al., 2022; Martinez et al., 2024; Coradduzza et al., 2022). These findings, while repeatedly observed, are difficult to reproduce due to small sample sizes, batch effects, and preanalytical variables such as hemolysis (Smith et al., 2022; Chan et al., 2023). Comparative research indicates that miRNA expression varies depending on affective episode, with distinct profiles observed during mania, depression, and periods of stability

(Camkurt et al., 2020; Clausen et al., 2022; Martinez et al., 2024). Medications used in the treatment of BD, such as lithium or valproate, can modulate circulating or peripheral miRNAs, further complicating interpretation (Rong et al., 2011; Coradduzza et al., 2022). In contrast, meta-analyses report stronger and more consistent circulating-miRNA signals in MDD and schizophrenia than in BD (Liu et al., 2017; Li et al., 2023; Liu et al., 2024).

Table 1. Epigenetic Markers in Bipolar Disorder: Signals, Context, and Clinical Relevance

Marker	Main signals	Modulation	Tissue sample	Clinical potential
DMPs/DMRs	Clustering in synaptic and inflammatory genes.	Suicide attempt history.	Peripheral blood.	Subphenotype stratification.
Epigenetic clocks	Age acceleration in older BD patients.	Lithium treatment.	Peripheral blood, brain tissue (post-mortem).	Reflective of disease burden.
Histone acetylation marks	Correlate with the transcription rate of nearby genes.	Valproate treatment.	Prefrontal cortex tissue (post-mortem).	Gene expression modulated by medication.
miRNA	Mood state-dependent shifts.	Lithium and valproate treatment.	Peripheral blood.	Monitoring episode transitions and treatment response.

Limitations and Future Directions

Recent research has improved our understanding of the genetic and epigenetic factors in bipolar disorder, but methodological issues continue to limit the application of these findings to clinical practice. BD's phenotypic heterogeneity is a significant obstacle. Bipolar I, bipolar II, and cyclothymia differ in their molecular profiles, but genomic studies often analyze them jointly, obscuring subtype-specific signals (Vieta et al., 2018).

Tissue specificity further limits epigenetic research. Most psychiatric studies rely on peripheral blood samples, whereas the most relevant alterations likely occur in brain tissue (Mill et al., 2013). Postmortem brain studies try to overcome this issue, but face problems like limited sample availability, tissue degradation, and confounding factors such as medication use and illness duration. As a result, there is an ongoing debate about the validity and utility of peripheral epigenetic markers in psychiatric research (Provencal et al., 2015).

Stress, substance use, diet, and medications influence gene expression and may confound causal interpretations. If these exposures are not measured and controlled, results may be misattributed to biological mechanisms (Klengel and Binder, 2015). Longitudinal studies of individuals over time are rare, and causal mechanisms are not yet clearly distinguished from mood state-dependent or treatment-related effects (Tsankova et al., 2007).

4. CONCLUSION

Reviewed evidence indicates that BD has a highly polygenic architecture and shares substantial heritable risk with schizophrenia, with a more moderate overlap with MDD. Genetic analyses further distinguish BD-I from BD-II and separate early-onset from adult-onset illness, suggesting partially distinct genetic architectures across subtypes.

Nonrandom clustering of DMPs/DMRs within genes involved in synaptic signaling and inflammatory pathways suggests that dysregulation of neural communication and immune function may be essential mechanisms in the pathogenesis of BD. Methylation signatures specific to suicide-attempt history further support subphenotype-specific biology within BD. Epigenetic age acceleration in BD is seen mainly in older patients. This pattern suggests cumulative illness and exposure effects, indicating that epigenetic clocks primarily reflect disease burden rather than inherent liability. Circulating miRNAs serve as mood state-dependent markers for tracking episode transitions and treatment response, rather than as BD-specific diagnostic tests.

Translating these findings into clinically useful tools requires the establishment of large, multi-ancestry longitudinal cohorts. The development of standardized protocols, integration of single-cell and spatial brain multi-omics, and implementation of rigorous

variant-to-gene mapping are also essential. Following these steps, researchers should conduct causal and functional validation. This process will facilitate the development of integrated genetic and epigenetic models for risk stratification, treatment selection, and longitudinal monitoring.

List of abbreviations
BD - bipolar disorder
MDD - Major Depressive Disorder
DALY - Disability Adjusted Life Years
GWAS - Genome Wide Association Study
CNV - Copy Number Variant
EWAS - Epigenome Wide Association Study
DMP - Differentially Methylated Positions
DMR - Differentially Methylated Regions
miRNA – microRNA

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Conflict of interest
The authors declare that there is no conflict of interest.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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