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Rethinking the connection between bipolar disorder and epilepsy from genetic perspectives

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Epilepsy and bipolar disorder (BD) exhibit considerable biochemical and genetic overlap. Our study unveiled a significant genetic correlation ($r_g = 0.154$, $P = 9.24 \times 10^{-6}$) between BD-I and epilepsy, indicating a meaningful causal effect of epilepsy on BD-I ($P = 0.0079$, bxy = 0.1721, SE = 0.0648). Additionally, we identified 1.3k shared genetic variants and 6 significant loci, demonstrating substantial polygenic overlap. Notably, the rs9639379 variant within the SP4 gene exhibited strong associations with both BD-I and epilepsy, implicating SP4 in the etiology of both disorders.

Epilepsy and bipolar disorder (BD) or mania are postulated to share a common biological underpinning. Altered intracellular calcium ion concentration ([Ca^{2+}]) is a consistent biochemical finding in BD and epilepsy (1, 2). Certain antiepileptic drugs act as mood stabilizers by inhibiting calcium currents and are effective in treating patients with epilepsy as well as patients with BD. These findings imply a potential link between mood polarity (particularly mania) and seizures. As both epilepsy and BD have well-described genetic substrates, in this analysis we ascertained shared genetic underpinnings and causal effects and unveiled six independent genomic loci significantly linked to BD and epilepsy.

Utilizing genome-wide association study (GWAS) data from European populations, comprising 26,352 epilepsy cases and 774,517 controls (3), as well as 25,060 BD type I (BD-I) cases and 307,499 controls (4), we observed a significant positive genetic correlation ($r_g = 0.154$, $P = 9.24 \times 10^{-6}$) between BD-I and epilepsy. Furthermore, we indicated a meaningful causal effect of epilepsy on BD-I ($P = 0.0079$, $b_{xy} = 0.1721$, SE = 0.0648).

Our MiXeR analysis identified approximately 7.8K variants influencing BD-I and 3.0K impacting epilepsy, with 1.3K variants implicated in both conditions (Figure 1A). We unveiled six independent genomic loci ($r^2 < 0.2$) significantly linked to BD-I and epilepsy using Conjunctional False Discovery Rate (conjFDR) analysis (conjFDR < 0.05, Figure 1B), among which four loci exhibited consistent allelic effect direction between BD-I and epilepsy, while the remaining two loci showed opposite direction. Moreover, we found that five of the six risk loci showed expression quantitative trait loci associations in cortex tissues or specific cell types ($P < 1.00 \times 10^{-5}$, Supplemental Table S1).

We focused on rs9639379 in the SP4 gene, finding strong associations with both risk of BD-I (odds ratio (OR) = 1.0638, $P = 1.41 \times 10^{-6}$) and epilepsy (OR = 1.0437, $P = 2.31 \times 10^{-5}$) (conjFDR = 1.24×10^{-2}, Figure 1C). The stability of SP4 protein was modulated by neuronal activity, with lithium demonstrating the ability to stabilize SP4 levels, thereby suggesting

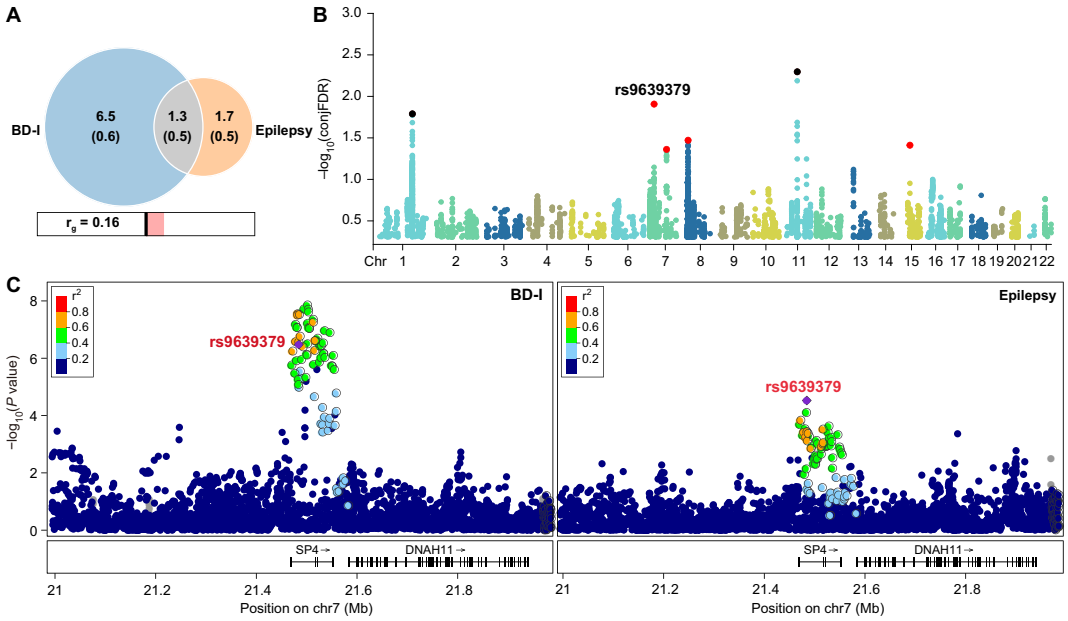

Figure 1. (A) Venn plot shows the number of specific and shared causal variants between BD-I and epilepsy. The genetic correlation of r_g was estimated by Linkage Disequilibrium Score Regression (LDSC). (B) Manhattan plot of conjFDR result. Lead Single Nucleotide Polymorphisms (SNPs) in each independent risk loci with the same direction of allelic effects between BD-I and epilepsy are marked in red, and lead SNPs in each independent risk loci with opposite direction of allelic effects between BD-I and epilepsy are marked in black. (C) LocusZoom plots show the genetic associations with BD-I and epilepsy in the SP4 locus. Physical maps blow the plots depict known genes within the region, and the Linkage Disequilibrium (LD) is defined based on the SNP rs9639379.

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therapeutic benefits in mood disorder management (5). While the direct association between SP4 and epilepsy remains unclear, the involvement of SP4 in the transcriptional regulation of neuronal energy metabolism suggested a plausible link to epileptic seizures (6).

This study provides a novel rethinking of the connection between epilepsy and BD, which is in line with the fact that mood stabilizers are effective in the treatment of both illnesses. Although the relationship between shared risk genes and mood stabilizers is still unclear, their potential involvement in drug-mediated neurobiological mechanisms is worth further investigation. Limitations include the focus on European populations, which may constrain the generalizability of the findings, and the reliance on public GWAS data without sex-specific information restricting us from conducting a gender-based analysis.

Author Contributions

ML oversaw the project, conceived and designed the study and JHH performed the primary analysis and drafted the first version of the manuscript. All authors revised the manuscript critically and approved the final version.

Conflicts of Interest

None declared.

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