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Transdiagnostic and cross-ancestry genetic liability in major psychiatric disorders: insights from multi-omics and clinical implications

Qianfa Yuan

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INTRODUCTION

Bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SCZ) are among the leading causes of global disability, collectively affecting over one billion people worldwide. Although traditionally classified as distinct diagnostic entities, these disorders exhibit substantial clinical comorbidity, familial aggregation, and genetic overlap[1,2]. Understanding the shared genetic architecture underlying these major psychiatric conditions has become a central question in precision psychiatry. In this context, the study by Feng *et al.* published in *Molecular Psychiatry* (2026) represents a landmark advance. By integrating European (EUR) and East Asian (EAS) Genome-Wide Association Study (GWAS) data and employing genomic structural equation modeling (gSEM), the authors systematically delineate the cross-diagnostic, cross-ancestry shared genetic liability of BD, MDD, and SCZ, providing critical new insights into their common biological mechanisms[1].

SHARED GENETIC ARCHITECTURE ACROSS DIAGNOSES

One of the most important conceptual contributions of this work is the demonstration of the power of multivariate modeling in capturing transdiagnostic genetic liability[3]. Feng *et al.* constructed a latent "common liability" factor that explained 66.5% of the total genetic variance across the three disorders[1]. The analysis revealed the strongest polygenic overlap between BD and SCZ (Dice coefficient 0.84), followed by BD and MDD, challenging traditional categorical diagnostic boundaries and supporting a dimensional view of psychiatric risk[2,3].

CROSS-ANCESTRY FINE-MAPPING AND STRUCTURAL INSIGHTS

A second highlight is the rigorous cross-ancestry design[4]. Through meta-analysis and MESuSiE fine-mapping of EUR and EAS data, the authors identified 32 single-nucleotide polymorphisms (SNPs) with high shared posterior inclusion probability (PIP_shared > 0.5), most notably the intronic variant rs7596038 in *VRK2*. This signal reached genome-wide significance in both ancestries with a consistent direction of

Fujian Psychiatric Center, Fujian Clinical Research Center for Mental Disorders, Xiamen XianYue Hospital, Xian Yue Hospital Affiliated with Xiamen Medical College, Xiamen 361000, Fujian, China.

Correspondence to: Dr. Qianfa Yuan, Fujian Psychiatric Center, Fujian Clinical Research Center for Mental Disorders, Xiamen XianYue Hospital, Xian Yue Hospital Affiliated with Xiamen Medical College, Xiamen 361000, Fujian, China. E-mail: yqf1123@hotmail.com

effect, supporting a robust shared cross-ancestry genetic signal; however, fine-mapping alone does not establish a conserved causal mechanism[1,4].

MECHANISTIC INTERPRETATION FROM GENES TO CELLS

The authors went beyond statistical associations to uncover biological meaning. Using six complementary gene-prioritization approaches, they nominated 90 high-confidence candidate genes significantly enriched in neurodevelopmental and synaptic pathways[5,6]. Single-nucleus RNA sequencing from human orbitofrontal cortex localized risk primarily to excitatory neurons and astrocytes, with 83 of the 90 genes showing disease-associated differential expression[1,7]. CellChat analysis further identified prominent NCAM1-FGFR1 and NEGR1-NEGR1 intercellular signaling axes, highlighting candidate pathways potentially involved in neurite outgrowth, synaptic plasticity, and glia-neuron communication[1].

Complementing the genomic findings of Feng *et al.*[1], brain-based epigenomic studies provide relevant, although not directly overlapping, molecular evidence. In the human frontal cortex, schizophrenia-associated DNA methylation differences were enriched in genes related to development and neurodifferentiation and showed modest enrichment at schizophrenia risk loci[8]. Assay for Transposase-Accessible Chromatin (ATAC)-seq profiling of the postmortem prefrontal cortex further demonstrated that open chromatin regions were enriched for schizophrenia SNP heritability, although case-control differences in chromatin accessibility were limited[9]. More recently, single-nucleus multi-omic profiling of the human orbitofrontal cortex across SCZ, BD, and MDD identified cell-type-specific changes in gene expression and chromatin accessibility associated with clinical diagnosis and polygenic risk[10]. Together with the transcriptomic and CellChat analyses reported by Feng *et al.*[1], these studies provide complementary, but not locus-specific or causal, evidence linking psychiatric genetic liability to transcriptional and epigenomic variation in relevant brain cell types and to candidate intercellular signaling mechanisms.

CAUSAL EFFECTS ON BRAIN STRUCTURE AND CLINICAL TRANSLATION

Mendelian randomization analyses provided causal evidence linking shared genetic liability to structural brain alterations, particularly increased volume in emotion- and cognition-related regions and compromised white-matter integrity[11]. Polygenic risk scores derived from the shared liability loci (PRS_gSEM) outperformed disorder-specific PRSs for BD and SCZ prediction in independent EUR cohorts and retained significant utility in EAS samples[12]. Gene-environment interaction analyses additionally showed that childhood physical violence can amplify genetic risk, offering population-level support for the classic diathesis-stress model[1,13].

LIMITATIONS AND FUTURE DIRECTIONS

The authors noted that the smaller EAS discovery sample reduced statistical power and that the one-factor gSEM model may not capture additional latent dimensions across a broader range of psychiatric disorders[1]. Although the EAS sample size remains smaller than the EUR cohort, which may limit power for ancestry-specific analyses, this study lays an important foundation for globally applicable precision psychiatry[4]. Additional limitations include the reliance on a one-factor gSEM model, which, while powerful, may not fully capture potential multi-dimensional genetic architectures when a broader range of psychiatric traits is considered[3]. Future studies with larger non-European samples, multi-dimensional modeling, and integration of longitudinal multi-omics data will be essential.

CONCLUSION

Feng *et al.*'s study marks a significant shift in psychiatric genetics from "single-disorder, single-ancestry,

purely statistical associations" toward "cross-diagnostic, cross-ancestry, multi-omics integration, and mechanistic interpretation[1,3]". It demonstrates that, despite distinct clinical diagnoses, BD, MDD, and SCZ partially converge on shared biological processes involving neurodevelopment, synaptic function, excitatory neuronal activity, and glia-neuron communication[1,7]. In the era of precision psychiatry, expanding non-European ancestry samples, conducting longitudinal multi-omics follow-up, and integrating environmental exposures will be critical future directions. Only through larger, more diverse, longitudinal, and functionally validated studies can psychiatric genetic discoveries be reliably translated into risk stratification, mechanistic research, and precise interventions[12,13].

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

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Consent for publication

Not applicable.

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