Shared Genetic Architecture between Breast Cancer and Psychiatric Disorders: Insights from Large-Scale Genome-wide Cross-trait Analysis

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Abstract

Using summary statistics from genome-wide association studies (GWAS), this analysis assessed significant genetic correlations and overlaps between Breast cancer (BC) and psychiatric disorders. Additionally, this analysis identified pleiotropic genetic structure (e.g., MTRFA, FGFR2) and potential mechanisms linking psychiatric disorders to BC.

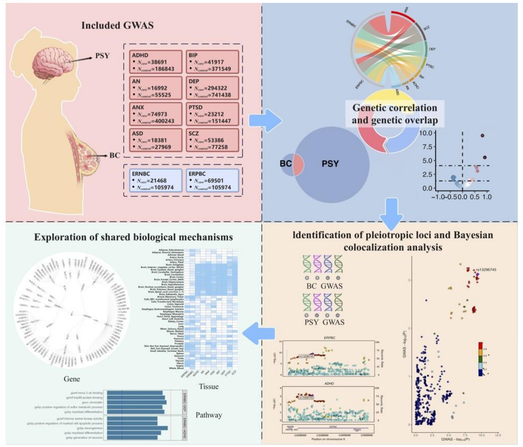


Figure 1. An overview of this study's data sources, analytical flow and methodology. BC, breast cancer; PSY, psychiatric disorders.

Introduction

BC is a heterogeneous malignancy including a series of subtypes such as estrogen receptor-positive breast cancer （ERPBC）and estrogen receptor-negative breast cancer （ERNBC). Risk factors like psychiatric disorders (e.g.attention deficit hyperactivity disorder (ADHD), anorexia nervosa (AN), anxiety disorders (ANX), autism spectrum disorder (ASD), bipolar disorder (BIP), depression (DEP), post-traumatic stress disorder (PTSD) and schizophrenia (SCZ)) strongly influence BC progression. However, the genetic structure and underlying molecular mechanisms remain unclear.

Methods and Materials

GWAS statistics for psychiatric disorders and BC are all from European samples. Genetic correlations were quantified via LDSC and LAVA. MiXeR further assessed genetic overlaps, while LCV and LHC-MR explored causal relationships.

As PLACO identified pleiotropic SNPs, risk loci were indentified and annotated by FUMA. Bayesian colocalization identified shared causal SNPs. Gene-level analyses used MAGMA, E-MAGMA, and H-MAGMA to indentify the pleiotropic gene. Significant pathways were indentified via gene set analysis. Additionally, pQTL-based SMR elucidated protein-disease causality.

Results

LDSC analysis showed that four trait pairs showed significant genetic correlations. MiXeR validated genetic overlap, with ERNBC-ANX showing the strongest (Dice=0.123) overlap. LAVA identified 24 loci showing significant local correlations and indicated that there are local genetic correlations with different directions in the same trait pair (**Figure 2**). Causal analyses revealed ANX and PTSD increased ERNBC risk, while ERPBC elevated PTSD risk .

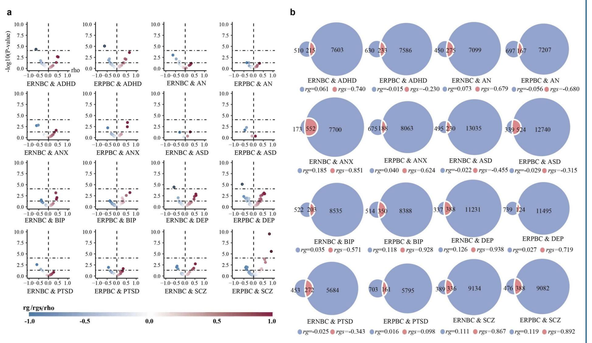


Figure 2. Local genetic correlation and genetic overlap. **a.** Volcano plots of LAVA local genetic correlation coefficients. **b.** MiXeR results showed in Venn diagrams.

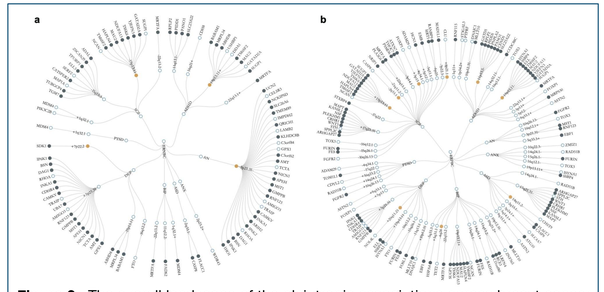


Figure 3. The overall landscape of the pleiotropic associations across breast cancer and eight psychiatric disorders

PLACO identified 7,274 pleiotropic SNPs (p<5E-08), mapping to 156 loci (including key 19p13.11). Addditionally,MAGMA/E-MAGMA identified 142 pleiotropic genes (e.g., MRTFA、FGF2) **(Figure 3)**.

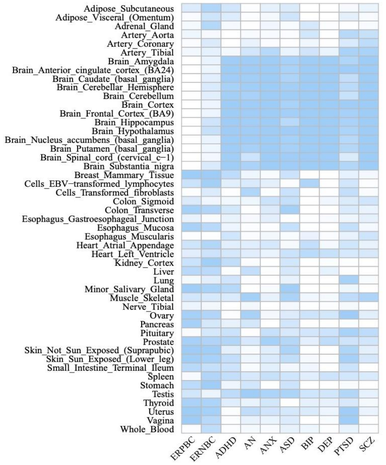


Figure 4. Tissue enrichment analyses. Tissue type-specific enrichment of SNP heritability for BC and PSY in 49 tissues from GTEx v8 estimated using LDSC-SEG.

LDSC-SEG found enrichment of these traits in a series of tissues**(Figure 4)**. Pathways enriched in RNA metabolism were identified in further analysis, highlighting estrogen's role **(Figure 5)**. SMR linked 41 proteins to disease risk, with no associations for PTSD

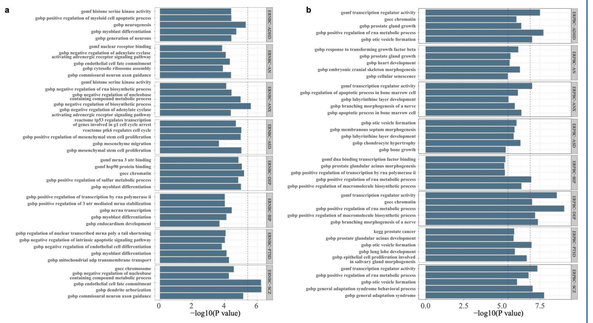


Figure 5. Bar plot showing enrichment of shared pathway between trait pairs in MAGMA gene-set analyses. The red line represents the P threshold at 1E-05. **a** analysis between ERNBC and PSY. **b** analysis between ERPBC and PSY.

Discussion

This is the largest genetic study exploring shared genetic links between psychiatric disorders and BC. Based the results of PLACO,this analysis identified 156 pleiotropic loci using FUMA platform, including 19p13.11. And pleiotropic genes like MRTFA and FGFR2 were identified in this loci.

MRTFA influences tumor metastasis processes by upregulating myosin-regulated light chain 9[1]. It plays a crucial role in the pathogenesis of SCZ by interacting with the expression products of GSK3B and BDNF[2]. Additionally, the FGFR2 regulates BC risk by binding to FGF2 or enhancing estrogen sensitivity[3,4]. Furthermore, one study indicates that FGFR2 may elevate SCZ risk through interactions with the dopamine system[5].

Conclusions

This study elaborated the complex associations between psychiatric disorders and BC. The identification of pleiotropic genes, druggable targets, and potential pathways revealed the underlying mechanisms.

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