Charting the shared genetic architecture between breast cancer and major depressive disorder based on genome-wide association study

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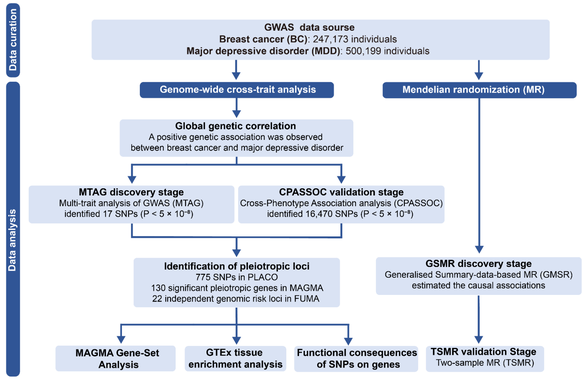
Background

- Though the phenotypic association between breast cancer (BC) and major depressive disorder (MDD) has been studied, the genetic architecture and causal relationship remain unclear.
- This study aims to chart the shared genetic structure and investigate causal relationships between BC and MDD.

Methods

- Utilizing genome-wide association studies of BC and MDD, we assessed the genetic correlation between BC and MDD through linkage disequilibrium score regression (LDSC).
- Then, we conducted genome-wide cross-trait analysis using multi-trait analysis of GWAS (MTAG), Cross-Phenotype Association analysis (CPASSOC), and pleiotropic analysis under composite null hypothesis (PLACO) analysis to identify pleiotropic loci.
- Based on the PLACO analysis, we further conducted Functional Mapping and Annotation of Genetic Associations (FUMA) and multimarker analysis of GenoMic annotation (MAGMA) analyses to identify potential shared risk loci and genes.
- Finally, we assessed the causal associations between BC and MDD using onducted Generalised Summary-data-based Mendelian Randomization (GSMR) and Two-sample Mendelian Randomization (TSMR).

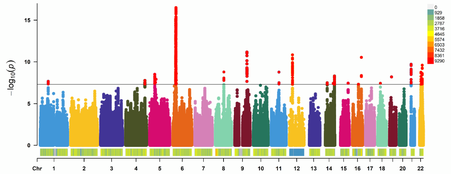
Figure 1. Study design.



Results

- The LDSC analysis indicated a positive genome-wide correlation between BC and MDD (rg = 0.0545, SE = 0.0151, P = 3 × 10^{-4}).
- The MTAG analysis identified 17 pleiotropic SNPs that meet genomic significance, while CPASSOC and PLACO analyses identified 16,470 and 775 SNPs.

Figure 2. Manhattan plot of pleiotropic SNPs identified by PLACO.



- After integrating these results, 17 SNPs identified as genome-wide significant by MTAG also maintained their significance in the CPASSOC and PLACO analysis.
- Based on the PLACO analysis, FUMA analysis revealed 22 independent genomic risk loci and MAGMA analysis identified 130 significant pleiotropic genes.

Figure 3. The results of FUMA and MAGMA analysis.

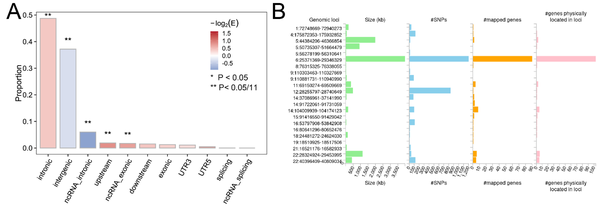
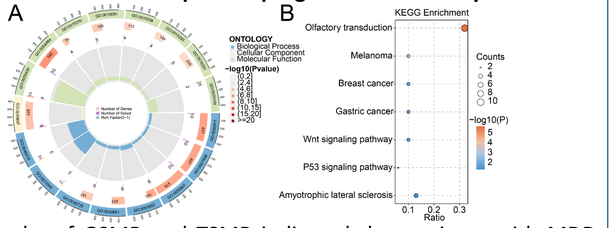
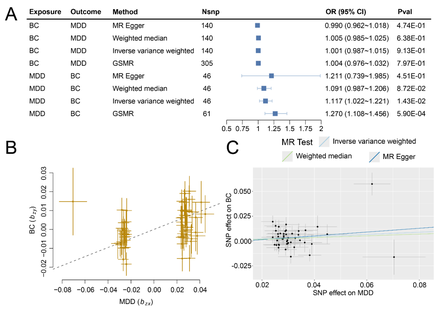


Figure 4. The Enrichment of pleiotropic genes identified by MAGMA.



- The results of GSMR and TSMR indicated that patients with MDD may increase their BC risk significantly (OR=1.27 ,95%CI: [1.11 - 1.46], P = 5.90 × 10^{-4}).
- The sensitivity analysis suggested that the results of TSMR were not affected by horizontal pleiotropy (P = 0.75).
- However, the reverse causality could not be detected (P > 0.05).

Figure 5. The causal associations between BC and MDD.



Conclusion

Our study charted the shared genetic architecture between BC and MDD and explored their potential causal relationship. The findings enhanced the understanding of the genetic pathways commonly involved in both BC and MDD, highlighting their complex interconnections. This research provided valuable insights for experimental studies aimed at developing new preventive measures and therapeutic interventions for BC and MDD.

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