Multi-omics analysis identifies EFR3B as a driver of chemoresistance in breast cancer through epithelial–endothelial cell communication

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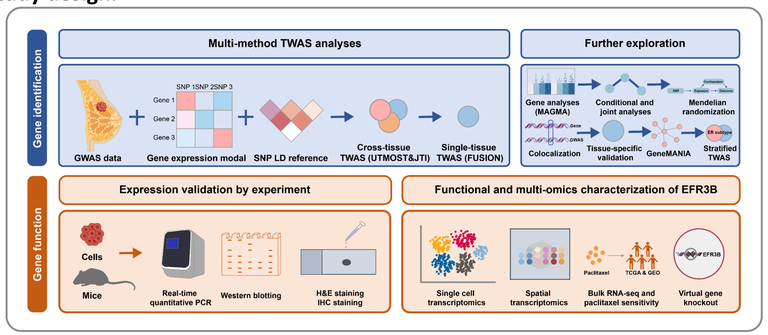
Background

- Breast cancer is one of the most common malignancies in women.
- Although previous genome-wide association studies (GWAS) have identified multiple susceptibility loci, they account for only a small portion of the heritable risk.
- Transcriptome-wide association studies (TWAS), which integrate GWAS and expression quantitative trait loci (eQTL) data, offer a more effective strategy for uncovering functional genes involved in complex traits.
- This study aims to systematically identify breast cancer susceptibility genes through multiple TWAS frameworks and to elucidate their biological roles using multi-omics integration.

Methods

- We performed cross-tissue TWAS for breast cancer using both Unified Test for Molecular Signature (UTMOST) and joint tissue imputation (JTI) frameworks. Next, single-tissue associations were evaluated via Functional Summary-based Imputation (FUSION) and validated using Multi-marker Analysis of Genomic Annotation (MAGMA).
- We further prioritized key genes through Mendelian Randomization (MR) and colocalization analyses, followed by experimental validation.
- Single-cell and spatial transcriptomic data were employed to delineate gene expression patterns, intercellular communication, and spatial heterogeneity.
- Additionally, drug resistance profiles were constructed using TCGA transcriptomic data and verified across multiple pharmacogenomics databases.

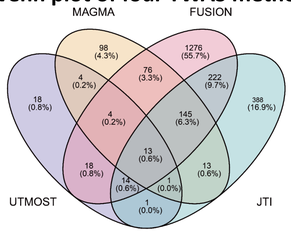
Figure 1. Study design.



Results

- Cross-tissue TWAS analysis identified 29 candidate susceptibility genes for overall breast cancer. The FUSION method detected 1,768 genes with FDR < 0.05 in at least one tissue, while MAGMA analysis revealed 354 breast cancer–associated genes.
- By integrating results from four analytical approaches, we prioritized 13 high-confidence susceptibility genes, including EFR3B, CASP8, and XBP1.

Figure 2. Venn plot of four TWAS methods.



- MR and colocalization analyses confirmed EFR3B and CASP8 as causal genes with shared genetic architecture in breast cancer.
- EFR3B, a susceptibility gene for both ER-positive and ER-negative breast cancer, was experimentally validated to be overexpressed in breast cancer cell lines and tumor tissues using Western blot, real-time PCR, and immunohistochemistry.

Figure 3. The result of colocalization analysis.

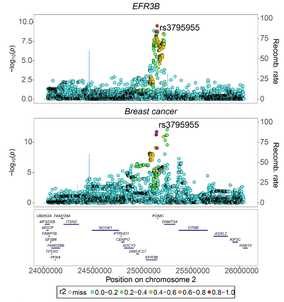
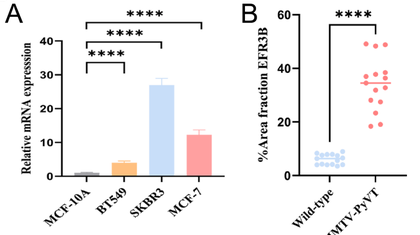
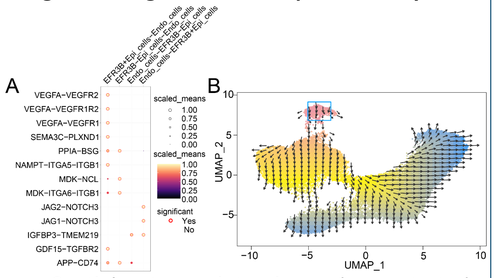


Figure 4. The differential expression of EFR3B.



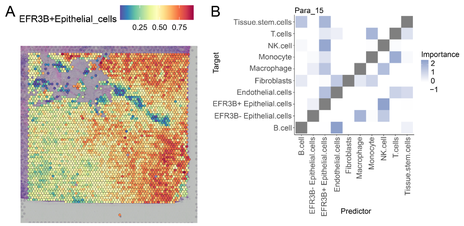
- Single-cell transcriptomic analysis revealed that EFR3B was predominantly expressed in specific epithelial and endothelial cells
- Analysis of VEGFA ligand-receptor signaling indicated enhanced intercellular communication between EFR3B-positive epithelial and endothelial cells.

Figure 5. Single-cell transcriptomic analysis.



- Spatial transcriptomics demonstrated heterogeneous expression of EFR3B in tumor tissues. EFR3B-positive epithelial cells were spatially co-localized with vascular endothelial cells.

Figure 6. Spatial transcriptomics analysis.



- Finally, drug sensitivity analysis revealed that high EFR3B expression was significantly associated with resistance to paclitaxel.

Conclusion

This study identified 13 breast cancer susceptibility genes through integrative TWAS approaches, providing new insights into the genetic architecture of the disease. EFR3B emerged as a key risk gene involved in tumor microenvironment modulation and chemotherapy resistance, representing a potential therapeutic target for personalized treatment strategies in breast cancer.

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