

Machine learning reveals genetic modifiers of the immune microenvironment of cancer

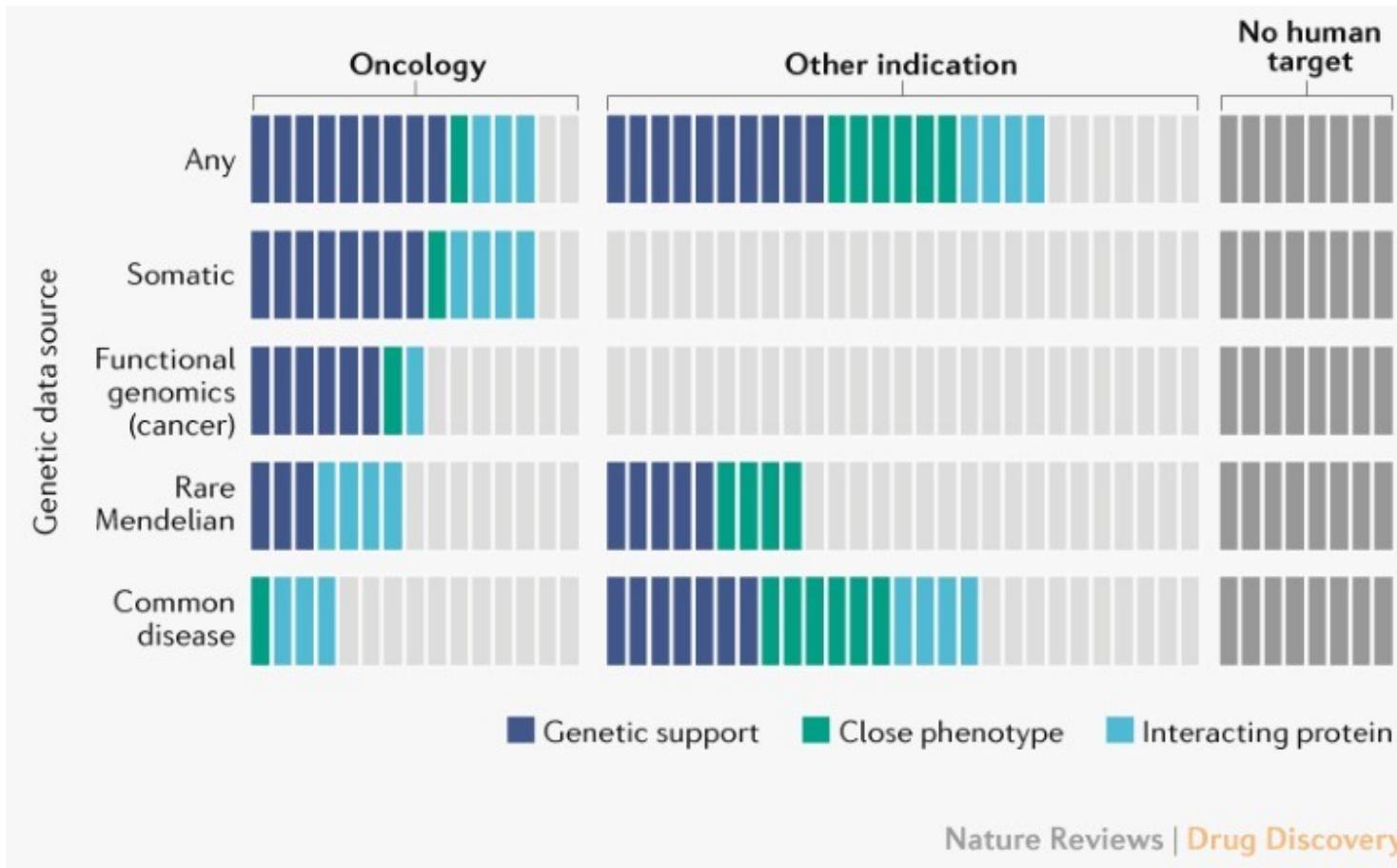
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Disclosures

- All animal studies and histological analysis of human breast cancer specimens presented in this study were conducted at the Medical College of Wisconsin (MCW), at which time I was a full-time faculty member.
- All procedures performed on animals were in accordance with regulations and established guidelines and were reviewed and approved by an Institutional Animal Care and Use Committee or through an ethical review process at the Medical College of Wisconsin.
- I was a full-time employee of AbbVie when all other study-related work was completed. The design, study conduct and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review and approval of the publication.
- I am currently a full-time employee of Pfizer and an Adjunct Faculty Member of the Medical College of Wisconsin.

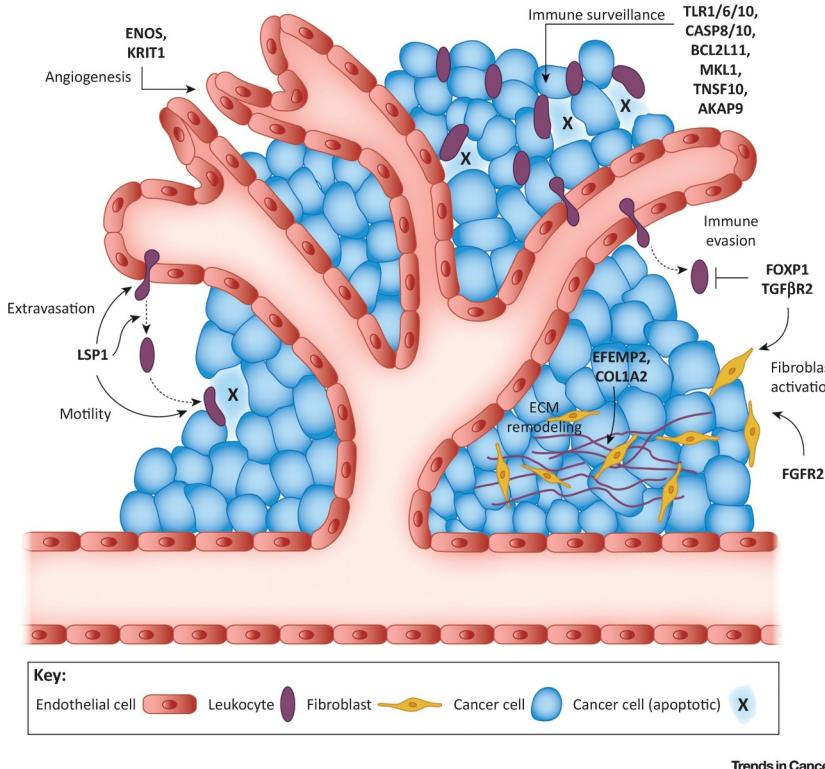
Leveraging genetic evidence for drug discovery



Human genetics evidence supports two-thirds of the 2021 FDA-approved drugs (nature.com)

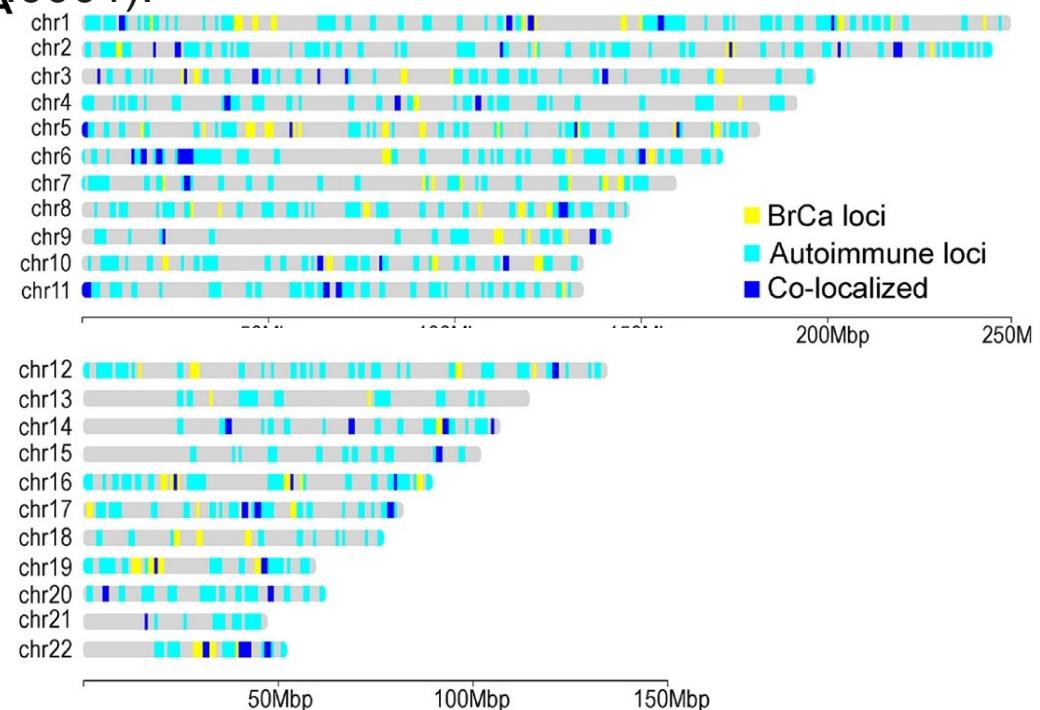
Immune modulators are frequently associated with breast cancer risk

Schematic of immune modulators associated with breast cancer risk



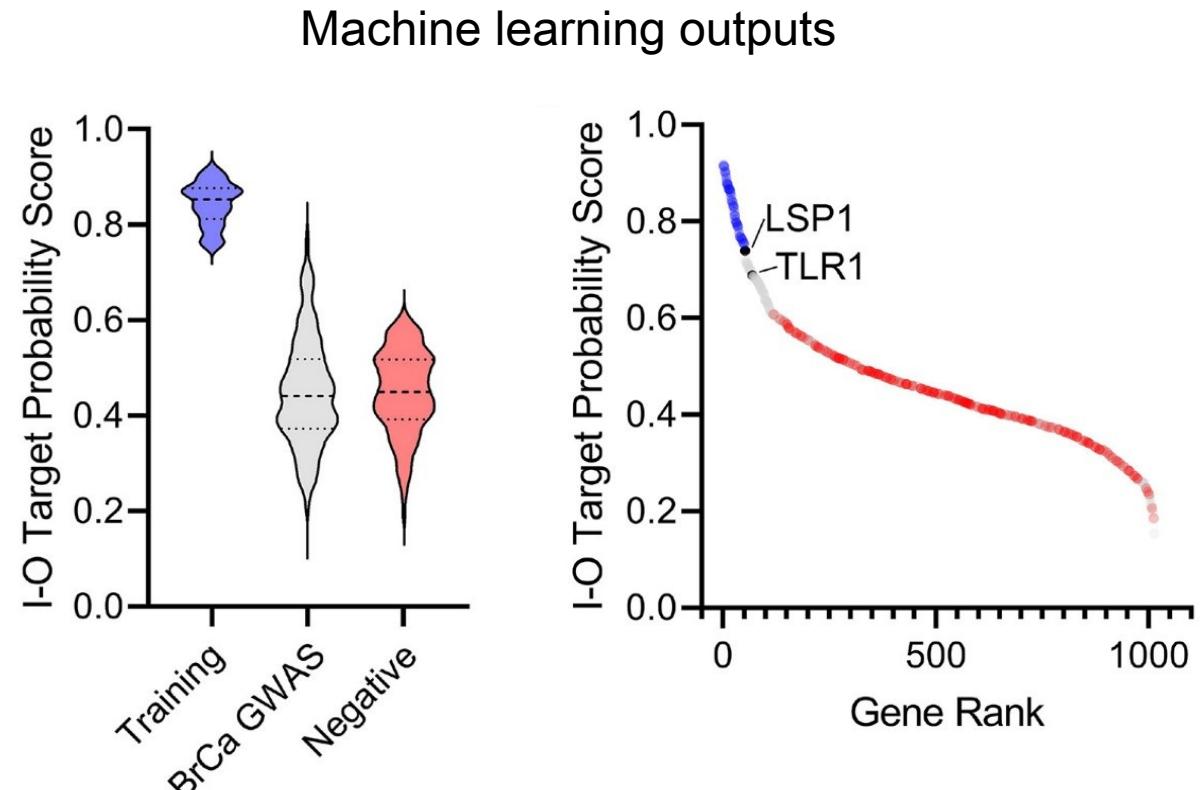
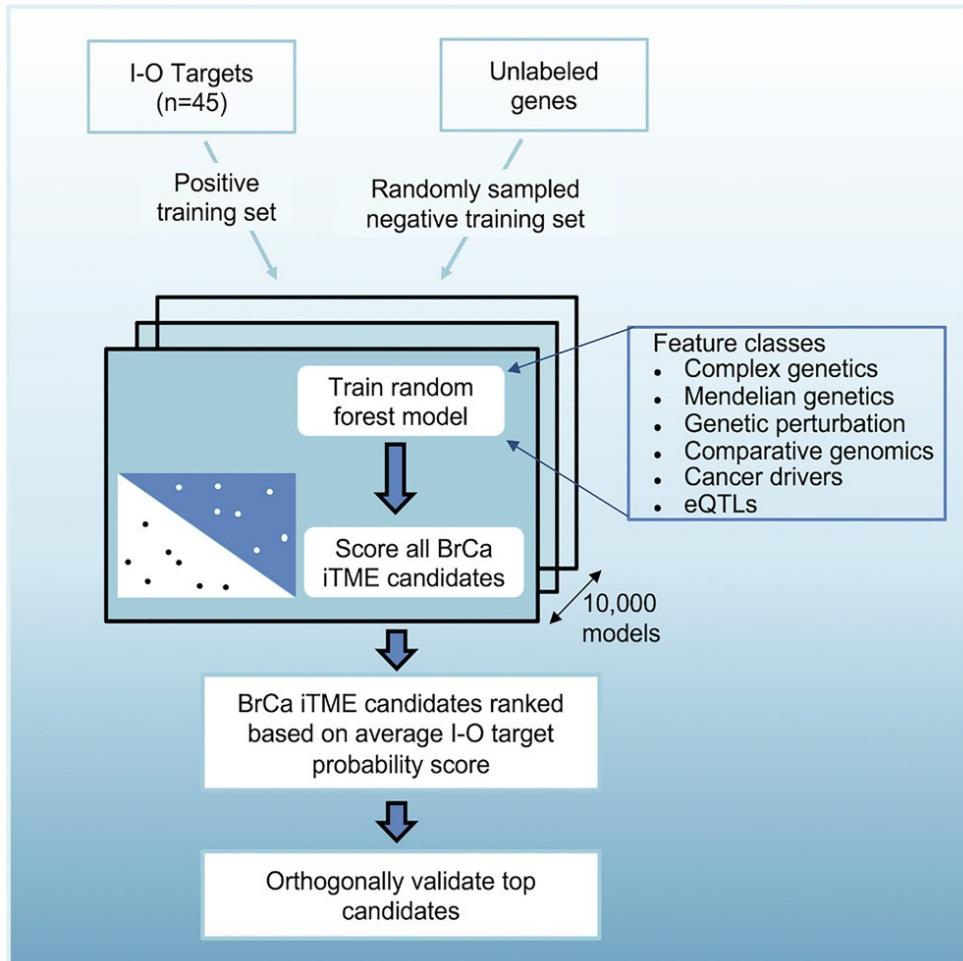
[Genetic Modifiers of the Breast Tumor Microenvironment: Trends in Cancer \(cell.com\)](#)

Alignment of GWAS risk loci for breast cancer and autoimmunity revealed significant colocalization (48% of loci, $p < 0.0001$).



[Machine learning reveals genetic modifiers of the immune microenvironment of cancer - ScienceDirect](#)

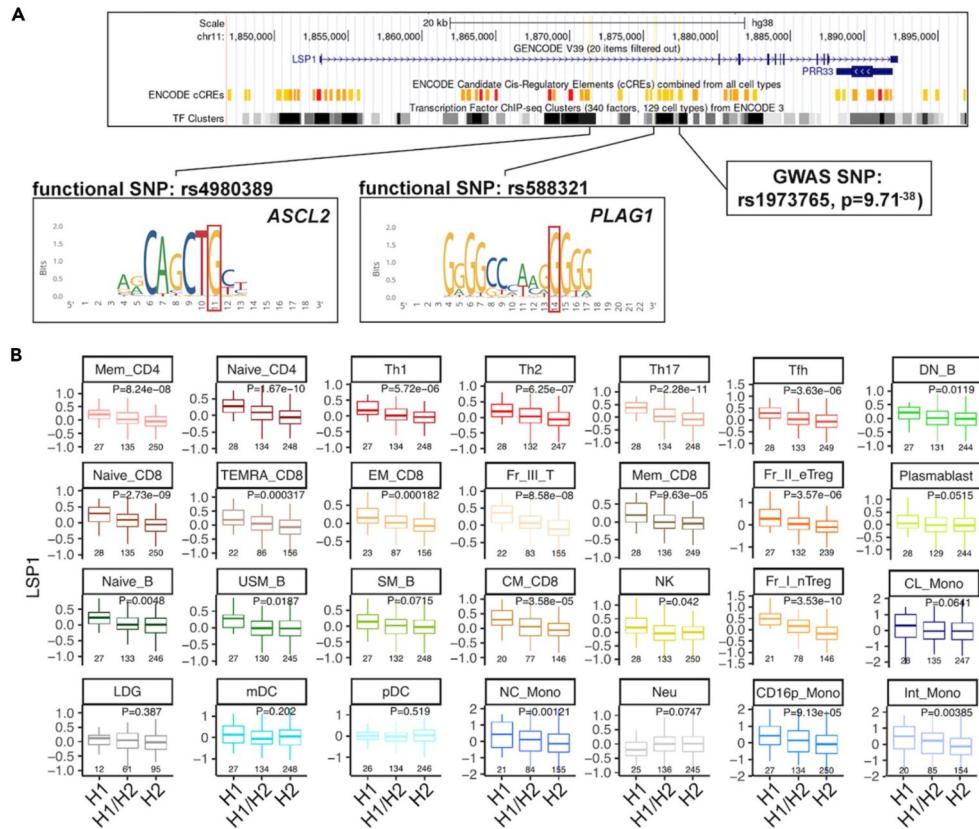
Using machine learning to annotate breast cancer risk modifiers that are immunomodulatory



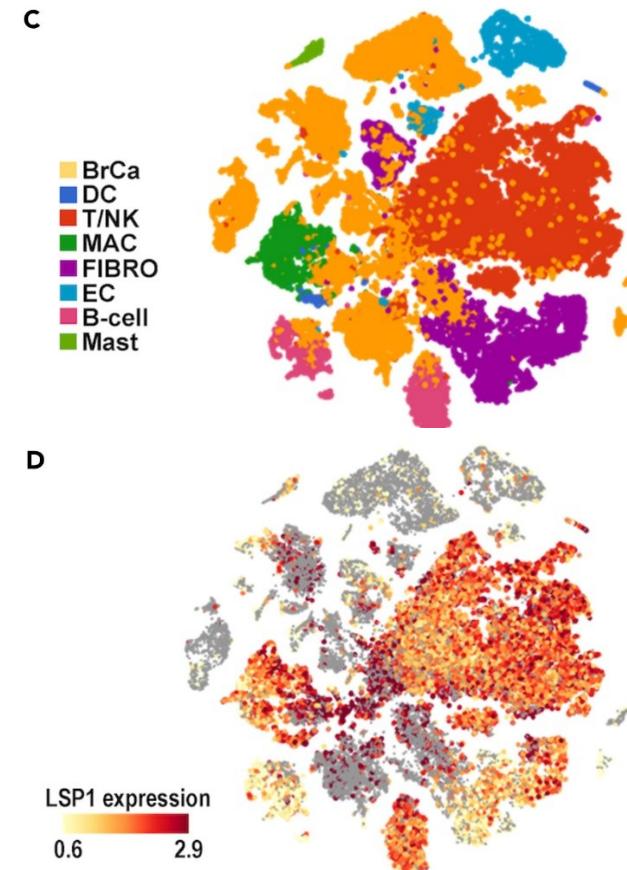
Machine learning reveals genetic modifiers of the immune microenvironment of cancer - ScienceDirect

LSP1 expression is modified by breast cancer risk locus and is restricted to immune cells

Fine-mapping of the *LSP1* locus reveals causal variants

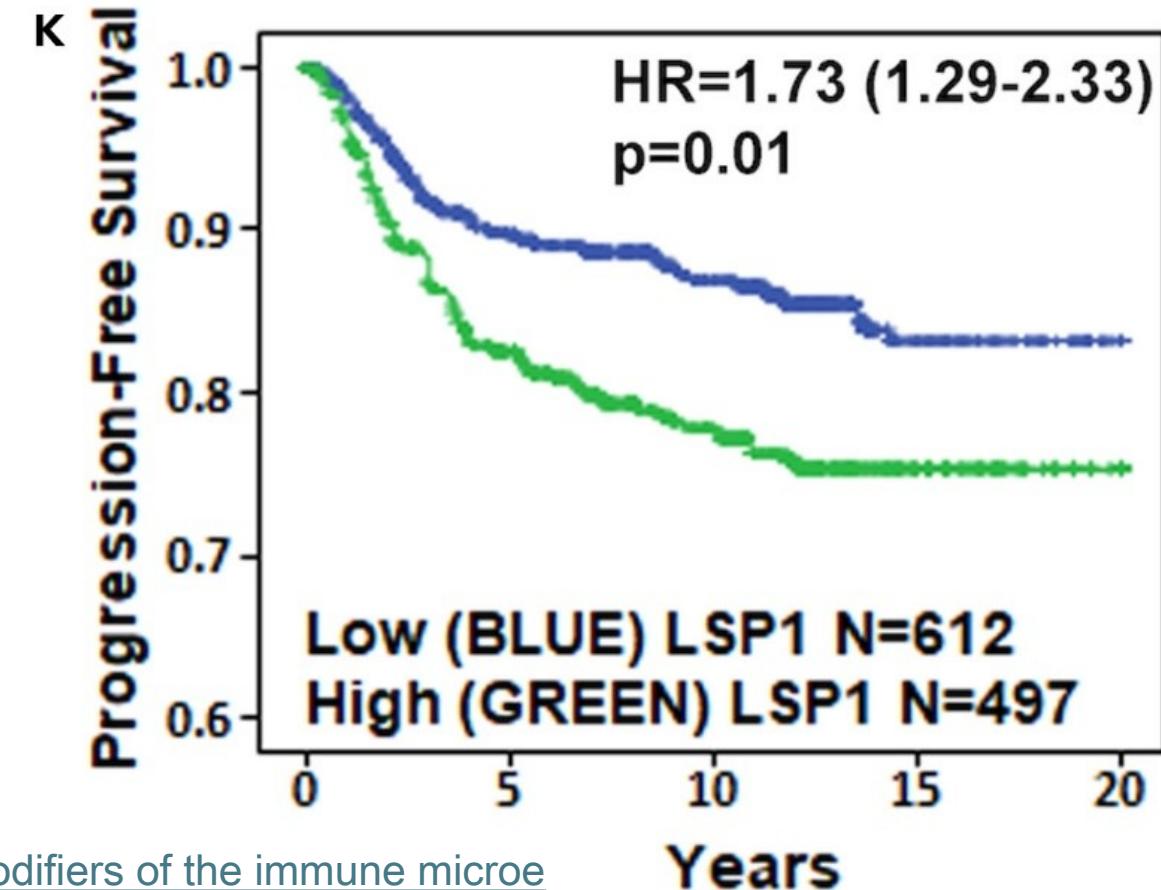
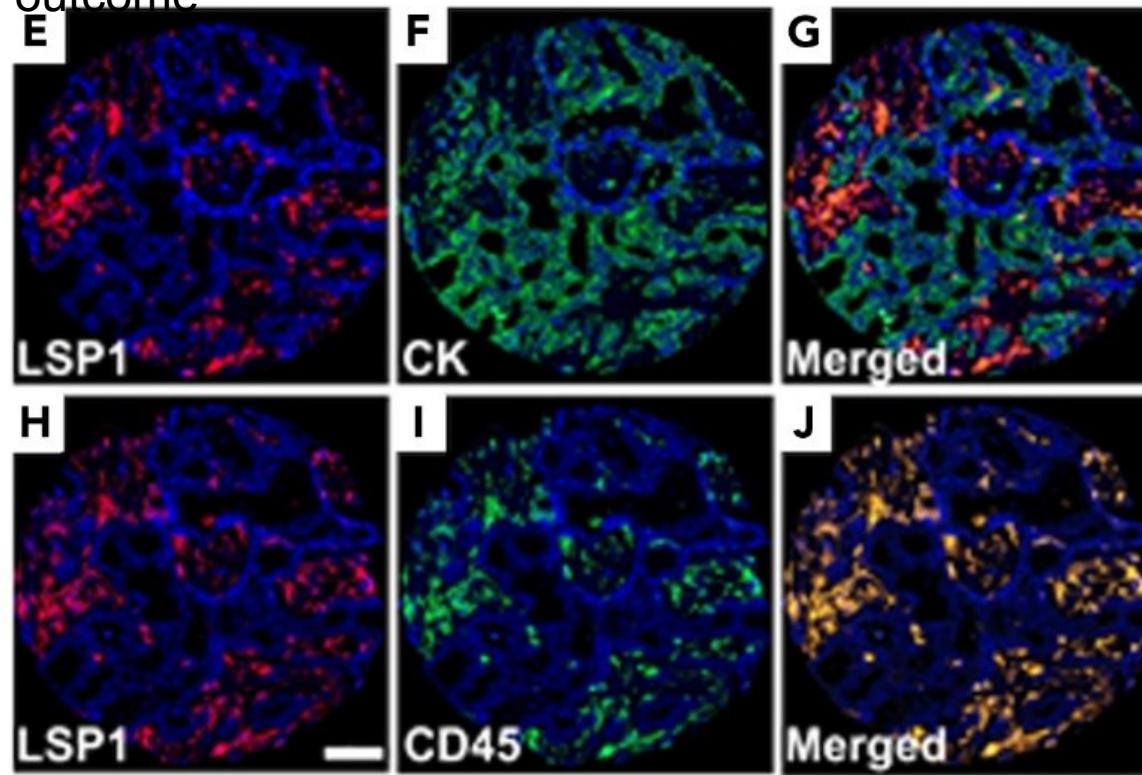


scRNAseq from human breast cancer biopsies localizes *LSP1* to immune cells



LSP1 is an I-O target associated with breast cancer risk and outcome

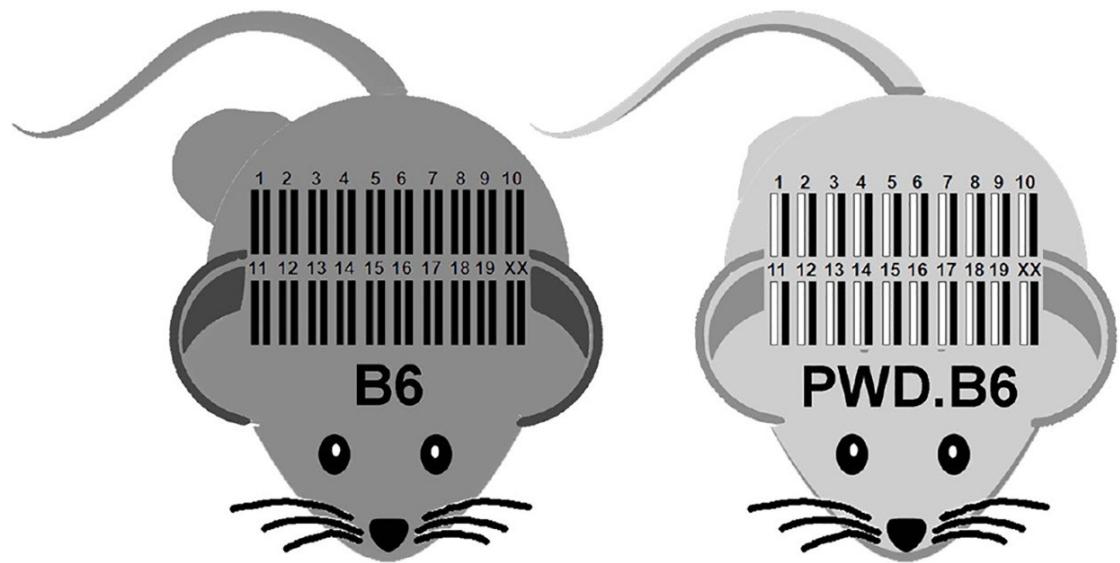
LSP1 protein expression is colocalized to tumor infiltrating immune cells and inversely associated with outcome



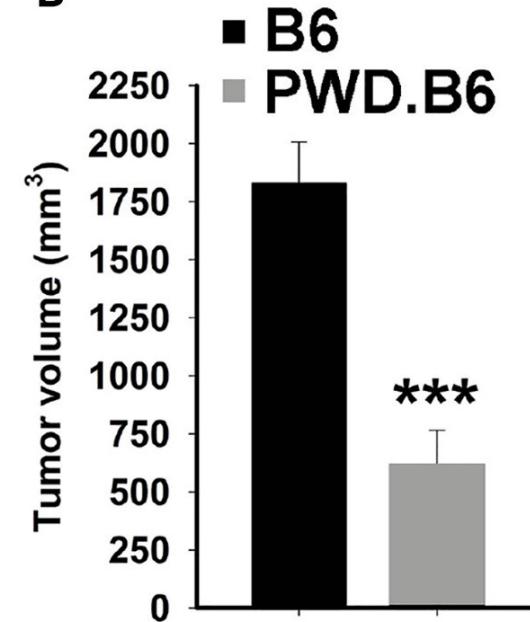
Using comparative mapping in the mouse TME to refine the list of potential I-O targets

50% allelic representation of the PWD.PhJ genome is enough to suppress E0771 mammary tumors

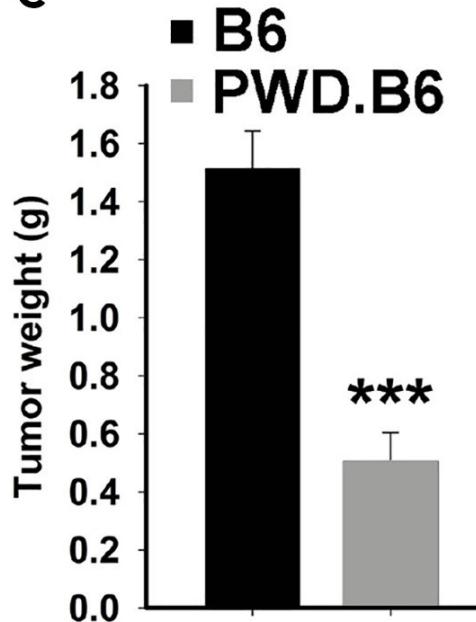
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B

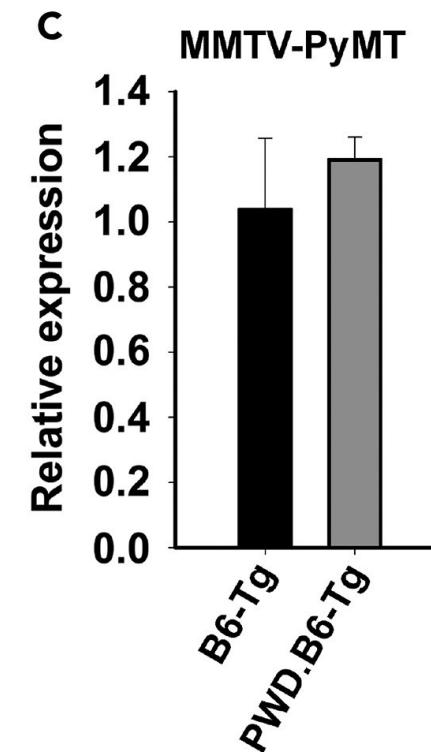
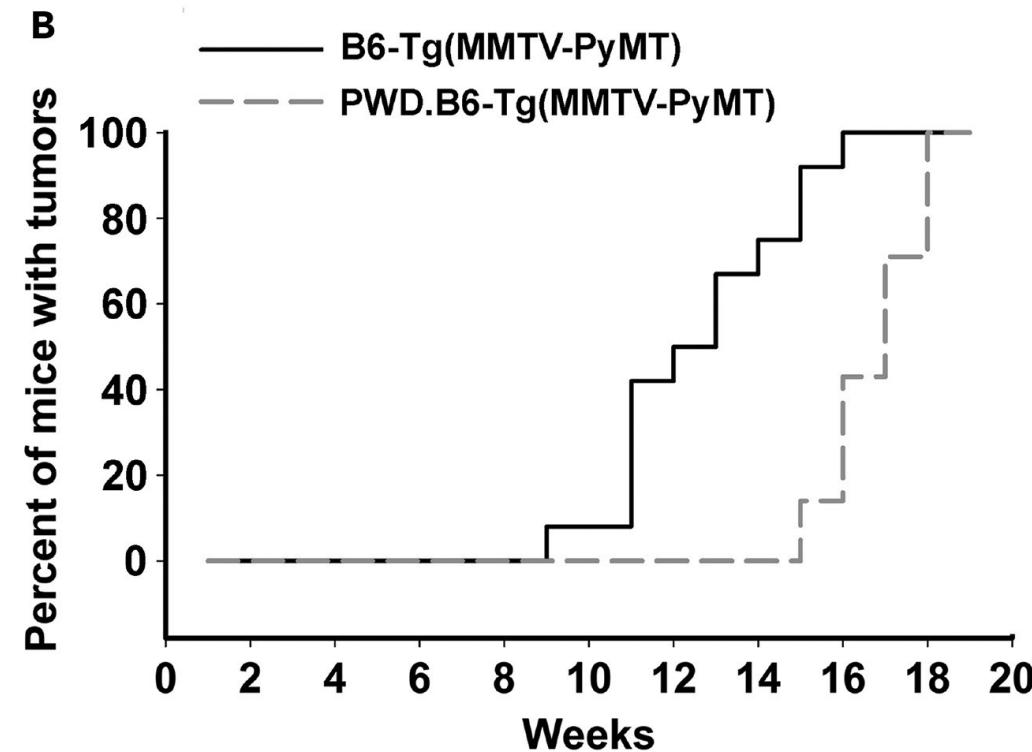


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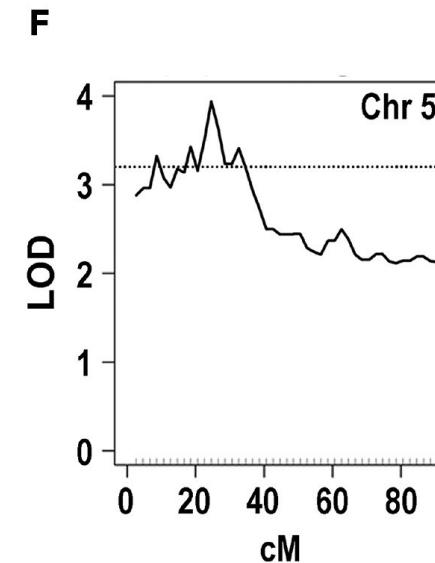
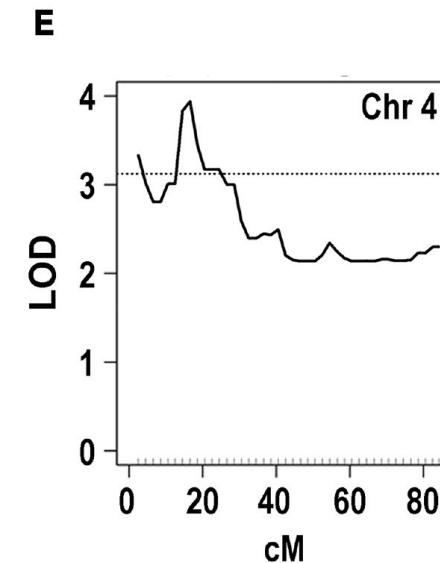
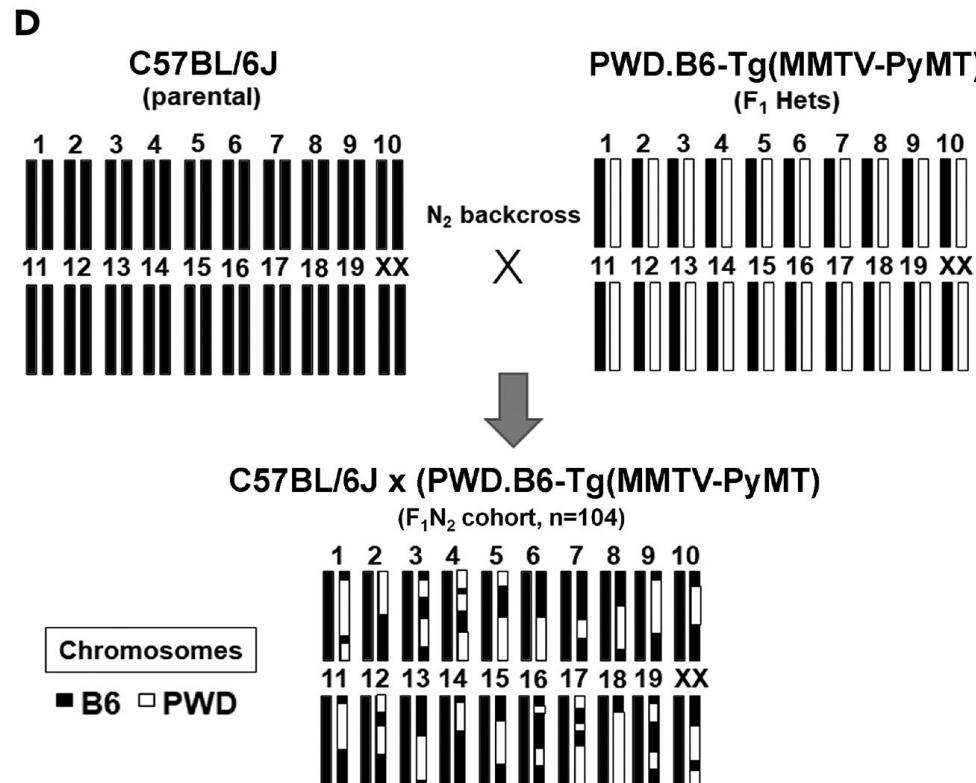
Using comparative mapping in the mouse TME to refine the list of potential I-O targets

50% allelic representation of the PWD.PhJ genome is enough to suppress spontaneous mammary tumors



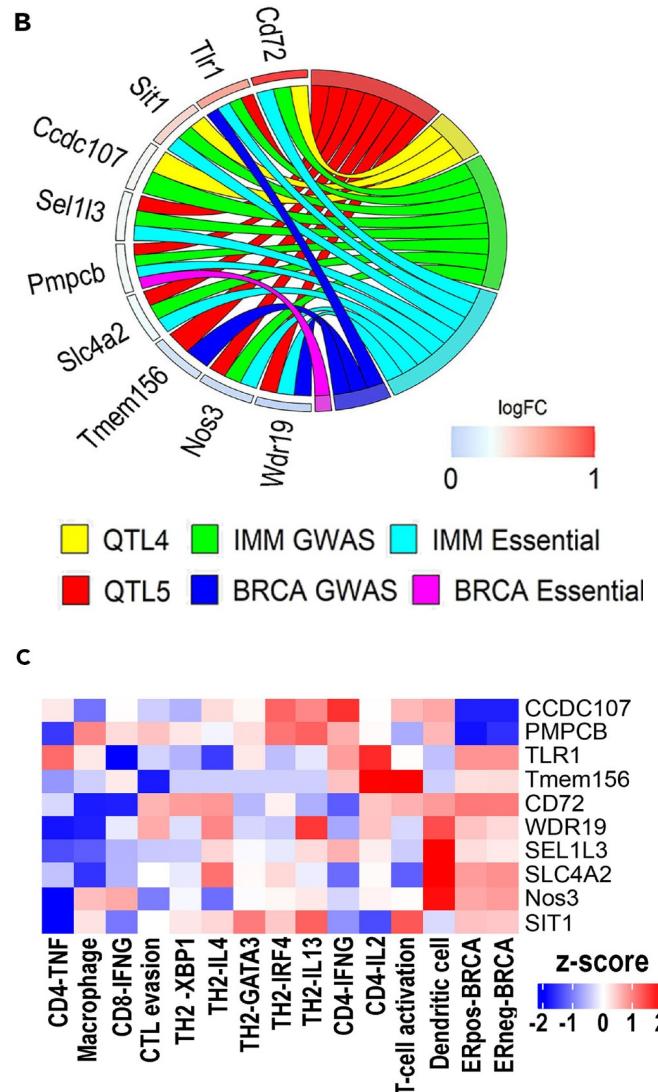
Using comparative mapping in the mouse TME to refine the list of potential I-O targets

Comparative mapping using linkage analysis reveals two potential QTLs

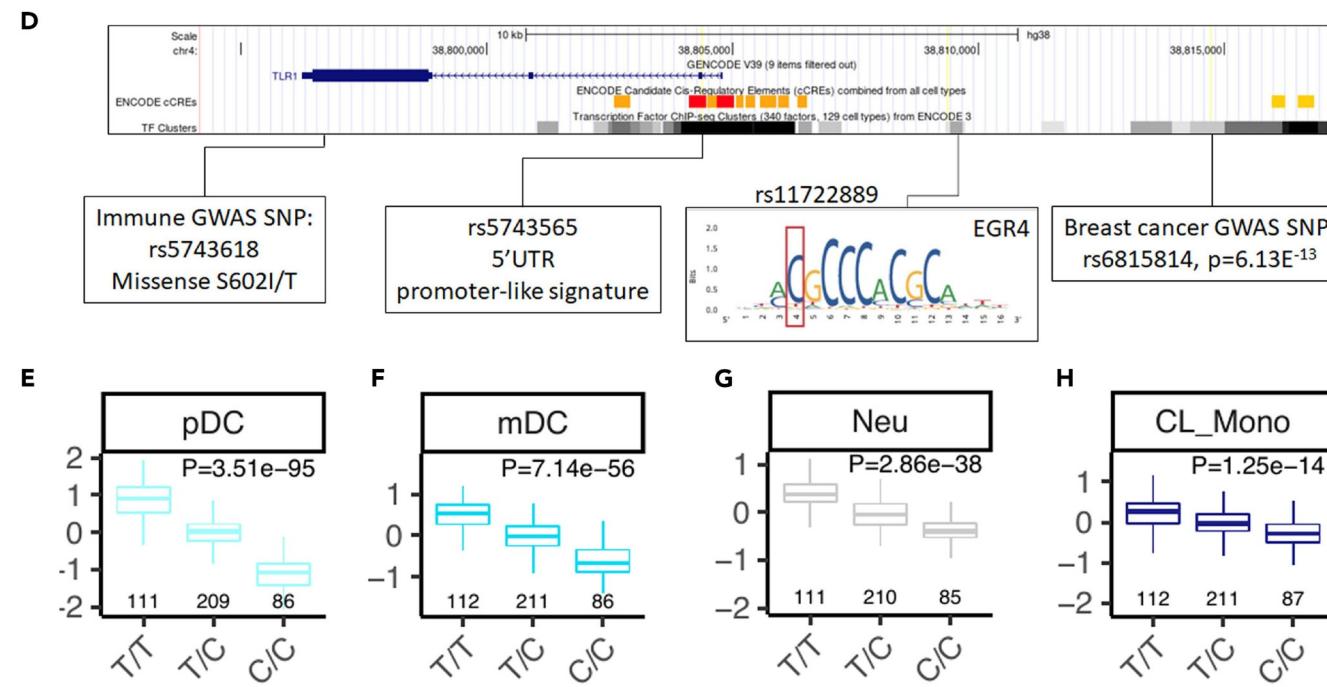


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Using comparative mapping in the mouse TME to refine the list of potential I-O targets



Comparative fine-mapping reveals multiple TME modifiers, including *TLR1* that is also associated with human breast cancer risk



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Summary & Highlights

- Machine learning enables functional fine-mapping of breast cancer risk loci
- Prioritized breast cancer I-O targets, including *LSP1* and *TLR1*
- Orthogonal validation in patient tumor biopsies and mouse comparative models
- Flexible framework integrates genotypic, phenotypic, and functional data

Acknowledgements

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