

Machine learning reveals genetic modifiers of the immune microenvironment of cancer

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Heritability in the immune tumor microenvironment (iTME) has been widely observed yet remains largely uncharacterized. Here, we developed a machine learning approach to map iTME modifiers within loci from genome-wide association studies (GWASs) for breast cancer (BrCa) incidence. A random forest model was trained on a positive set of immune-oncology (I-O) targets, and then used to assign I-O target probability scores to 1,362 candidate genes in linkage disequilibrium with 155 BrCa GWAS loci. Cluster analysis of the most probable candidates revealed two subfamilies of genes related to effector functions and adaptive immune responses, suggesting that iTME modifiers impact multiple aspects of anticancer immunity. Two of the top ranking BrCa candidates, *LSP1* and *TLR1*, were orthogonally validated as iTME modifiers using BrCa patient biopsies and comparative mapping studies, respectively. Collectively, these data demonstrate a robust and flexible framework for functionally fine-mapping GWAS risk loci to identify translatable therapeutic targets.