Predictability enrichment outperforms heritability enrichment for linking genomic annotations to biological insights for complex traits

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Identifying relevant cell types for complex traits remains challenging. While previous approaches use SNP-based heritability enrichment, we introduce a complementary metric—SNP predictability enrichment—that measures per-SNP contribution to trait prediction. We analysed 12 complex traits from UK Biobank using single-cell transcriptomic annotations from mouse and human datasets. By estimating cell-type-specific polygenic scores (ctPGS) via SBayesRC, we found that biologically relevant cell types showed an average two-fold gain in prediction R^2. Our predictability enrichment metric yielded approximately 1.5 times higher enrichment values for critical cell types compared to heritability enrichment. Through controlled simulations, we validated that our metric accurately captures genetic architecture while providing appropriate uncertainty measures through a jackknife-based approach. The enrichment metric can also be estimated using GWAS summary statistics alone, enabling broad application. Our findings include significant cell-type specificity across multiple traits, with notable enrichment of immune cells for autoimmune diseases and metabolic cells for related disorders. This approach provides a robust and computationally efficient tool for prioritizing disease-relevant cell types in complex trait genetics.