

# Quantifying the impact of genetically regulated expression on complex traits and diseases

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**Abstract:** By leveraging existing GWAS and eQTL resources, transcriptome-wide association studies (TWAS) have achieved many successes in identifying trait-associations of genetically-regulated expression (GREX) levels. TWAS analysis relies on the shared GREX variation across GWAS and the reference eQTL data, which depends on the cellular conditions of the eQTL data. Considering the increasing availability of eQTL data from different conditions and the often unknown trait-relevant cell/tissue-types, we propose a method and tool, IGREX, for precisely quantifying the proportion of phenotypic variation attributed to the GREX component. IGREX takes as input a reference eQTL panel and individual-level or summary-level GWAS data. Using eQTL data of 48 tissue types from the GTEx project as a reference panel, we evaluated the tissue-specific IGREX impact on a wide spectrum of phenotypes. We observed strong GREX effects on immune-related protein biomarkers. By incorporating trans-eQTLs and analyzing genetically-regulated alternative splicing events, we evaluated new potential directions for TWAS analysis.