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Novel pathway transcriptomics method greatly increases detection of molecular pathways associated with substance use disorder

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Genetic signal detection in genome-wide association studies (GWAS) is improved by pooling information from multiple single nucleotide polymorphism (SNP). Because many genes influence trait via gene expression, it is of interest to combine information from Quantitative Trait Loci (eQTLs) in a gene or genes in the same pathway. Transcriptomics methods use eQTLs to infer the association between trait and predicted expression of gene under study.

However, due to the $O(n2)$ computational burden for computing linkage disequilibrium (LD) between numerous (n) SNPs these methods are not yet applicable to large sets of pathways. To overcome this obstacle, we propose a novel $O(n)$ transcriptomics method (JEPEGMIX2-P), which 1) computes LD for gene statistics and 2) uses LD and GWAS summary statistics to rapidly test for the association between trait and expression of genes in pathways. It first computes chromosome arm pathway χ2 tests as Mahalanobis statistics of Z-scores for genes in the pathway and chromosome arm. Subsequently, JEPEGMIX2-P χ2 pathway statistics and degrees of freedom are simply the sum of their chromosome arm counterparts.

To underline its potential for greatly increasing the power to uncover genetic signals over existing (non-transcriptomics) pathway methods, we applied JEPEGMIX2-P to the latest metanalyses of substance use disorders. The findings underline possible directions for drug development.