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# Biologically-Driven Epistasis as a New Way of Approaching Genetic Analyses of Addiction

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Heritability estimates for neuropsychiatric conditions such as cocaine use disorder are high, but single-SNP association methods have been unable to detect consistent, repeatable genomic changes that can explain the residual heritability. Analyses with very large cohorts have revealed that at least a portion of the phenotypic traits are due to the cumulative small effect sizes arising from thousands of common variants. Two other important sources of heritability are genomic structural variants (such as copy number variation, insertions and deletions) and epistasis or interaction among variants (i.e., a mutation may only be biologically meaningful in the context of a linked, co-evolved haplotype). Standard methods to address epistasis, especially where it is to be interpreted biologically, require testing every pairwise SNP association across the genome, which is computationally intense. Standard methodologies have heavy statistical burdens to overcome to account for the multiple comparisons. We address these two major limitations by using the custom correlation coefficient (CCC) metric in the program BlocBuster, and by subsetting genome-wide SNPs based on their biology, dramatically reducing the number of comparisons. In a large ancestrally diverse polysubstance use cohort, using eQTLs and SNPs enriched for mQTLs, we built inherited gene expression and epigenetic networks that we then tested for association with a trait. We identified expression networks that regulate genes in the dopamine pathway including CYP2D6 and UNC13C, as well as epigenetic networks in the DRD2 gene associated with cocaine use. This approach provides a means to identify previously unknown genetic contributions to important traits.

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