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Dopaminergic Epistasis: Substance Use Disorders *vs.* Parkinson's Disease

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BACKGROUND: It is established that SUDs and Parkinson's Disease (PD) among many other neuropsychiatric disorders are dopamine(DA)-related brain disorders with strong heritability. However, it is unclear whether DA-associated genetic risks share commonality across these disorders.

AIM: Determine whether these neuropsychiatric disorders have common risks in DA-associated genes, including DA synthesis (2 genes), metabolism (2 genes), receptors (DRs, 5 genes), monoamine transporters (5 genes), an uptake modulator (alpha-synuclein: SNCA), and transcription factors (7 genes).

MATERIALS & METHODS: This study utilizes the dbGaP GWAS from 6,500+ subjects for each disease, and analyzes case-control-based epistasis among these 22 DAergic genes.

RESULTS: Extensive and significant epistasis signals were uncovered between gene variants and SUDs or, to less extent, PD. For SUDs, the strongest significant interaction was *SNCA* with the developmentally expressed vesicular monoamine transporter 1 gene *SLC18A1* and our recently discovered TFs. The largest number of significant interactions was between the DA transporter gene *SLC6A3* and 21 of the 22 genes including two DR genes, *DRD3* and *DRD5*. For PD, DRD3 interacted with the tyrosine hydroxylase gene *TH* and the dopa-decarboxylase gene *DDC*; *SLC6A3* interacted with 6 of the 22 target genes. Interestingly, the interaction between *DRD3* and the NET gene (*SLC6A2*) was implicated in both diseases.

CONCLUSIONS: DA pathways are significantly implicated in the genetic etiology of both SUDs and PD but much more in the former. Epistatic effects may represent a major portion of missing heritability observed in current main effect-oriented GWAS analyses.