Genome-wide studies uncover a potential burden of uncommon variants and polygenic basis of multiple-substance use disorders in an American Indian population

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Background: The higher rates of alcohol and substance use disorders (AUD & SUDs) exhibited by American Indians (AI) might be correlated to their possibly elevated multi-substance use disorders (MSUD). We herein evaluate whether there exists a genetic basis for MSUD in an AI population.

Methods: We assessed 876 AI community samples using Semi-Structured Assessment for the Genetics of Alcoholism. The clinical characteristics of lifetime DSM-5 moderate-or-severe AUD alone (n=146) and MSUD (alcohol and ≥1 other SUD) (n=284) were evaluated and compared to 347 participants without lifetime SUD. 742 participants had low-coverage whole genome sequencing. MSUD (including alcohol, marijuana, cocaine, opioid, stimulant) was indexed by dependence quantity weighted symptom counts for each individual. We conducted mixed linear model-based whole-genome association and gene-based rare-variant analyses, assessed the multidrug SNP-heritability, and estimated heritability enrichments of immune-related and unrelated genome partitions.

Results: 57% participants with a SUD had MSUD with 94% with alcohol, followed by stimulants (cocaine and/or amphetamine) and/or cannabis. Numerous variants were identified as significantly associated with multidrug-symptom-counts. Uncommon variants (MAF=0.01-0.05) predominated strongly. The most significant was rs200530573 (p=3.5e-19), downstream of gene *NDUFA12*, of NADH dehydrogenase complex, followed by variants on *GALNT15* and *ANK1*. While most significant variants were on introns or downstream/upstream of genes, a missense variant rs77920906 was identified (p=3.5e-8) on Calcineurin inhibitor gene *CABIN1*. The respiratory-chain was the most enriched functional group within significant variants. Including variants of suggestive significance rendered serotonin-receptor-signaling-pathway the most enriched. Rare variants in *ESF1* (p=6.6e-7) were associated with multidrug-symptom-counts, followed by cyclin gene *CCNE1* (p=5.7e-6), and calcium-binding gene *S100P* (p=8.4e-6). The SNP-heritability of multidrug-symptom-counts was 36.4%(p=4e-4). Portions of the genome harboring immune-related genes seemed to exhibit ~fivefold heritability-enrichment.

Conclusions: MSUD is prevalent in this sample. Our findings illuminate its genetic underpinnings. A burden of uncommon variants is likely underlying MSUD in this AI population.

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