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Fine Mapping Causal Variants of Smoking and Drinking Addiction Related Traits

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Genetic studies for smoking and alcohol use have implicated common genetic variants in multiple loci. Advancements in exome arrays and genotype imputation now allow for the analysis of rare nonsynonymous and loss of function variants. These coding variants potentially have clearer functional consequences that may contribute to smoking and alcohol use traits. These specialized exome arrays also provide greater resolution for fine mapping studies of associated loci. Here we conducted fine-mapping with the integration of functional genomic annotations on the GWAS results of nicotine and alcohol use. Functional fine mapping was performed on four phenotypes: cigarettes per day, pack years, smoking initiation, and alcoholic drinks per week. The summary statistics for the study of these traits were obtained from an analysis of ~250,000 rare variants from 17 independent studies genotyped with exome arrays and augmented with imputed data from the UK Biobank with total sample size >350,000. From the GWAS, 174 genome-wide significant loci were identified across the four phenotypes. The functional fine mapping procedure identified 95% credible variant sets with double base-pair resolution at 35 of these loci, and winnowed the number of putative causal variants to <10 for 63 loci. In conclusion, our results represented the first effort to dissect the causal variants for smoking and drinking phenotypes for modern biobank datasets. The use of fine mapping with functional annotation integration and exome arrays deciphers the putative causal variants in GWAS significant loci that contribute to the biological etiology behind substance use.