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Dose-Response Analysis to Advance Gene and Pathway Identification for Risk Estimation of Substance Use Disorder

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The heritability of substance use disorder (SUD) makes it critical to understand the underlying etiology through genes and pathways to advance SUD prevention. The genome-wide association studies, a common approach to identify single nucleotide polymorphisms (SNPs) that are potentially associated with SUD, may provide inconsistent results due to their unstable performance given limited sample size. The main objective of this study is to develop a modeling methodology to enhance the accuracy of SUD-associated genes and pathways identification by utilizing substance-dose and SUD-response relationship to quantitatively characterize gene-SUD association. The central hypothesis is that genetic variants involved in the formation of SUD can be "activated" when substance use reaches a critical level indicating that the genetic risk of SUDs is dose dependent. The rationale arises from a biologically plausible assumption that SUD risk and cumulative dose are positively associated. The analysis procedures sequentially include screening out invalid SNPs, converting the genotype to dose-response data with confounding variables adjusted odds ratio and substance-dependence status, and calculating benchmark dose (BMD) to identify dose-sensitive genes and associated pathways. The proposed method was applied to the SAGE dataset to demonstrate its feasibility. The top 15 SNPs-related genes identified are directly related to smoking and SUD-induced diseases, e.g., gene `MDH1' (rs9309355) is related to smoking status. Eleven pathways are directly related to the drug response, after exposure to cigarettes. Overall, employing the BMD method by employing the dose-response information for SNP identification is more sensitive to detecting the trend, which may potentially advance the prevention strategies.