Relations Between Polygenic Risk Scores of Internalizing and Externalizing Behaviors and Alcohol Use Disorder Symptoms

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July 29, 2021

Abstract
Many traits are polygenic, meaning they are influenced by many genomic regions. Polygenic risk scores (PRSs) summarize genetic risk for a given phenotype across the entire genome. Prior studies suggest that externalizing behaviors (i.e., oppositional behaviors and social norm violations) and internalizing behaviors (i.e., anxiety and mood related behaviors) uniquely predict alcohol use disorder (AUD) symptoms, raising the possibility that individual AUD symptoms may show differential genetic overlap with externalizing and internalizing behaviors. To examine this hypothesis, summary statistics from genome-wide association studies (GWASs) were utilized to generate PRSs for internalizing (i.e., neuroticism and worry) and externalizing (i.e., aggression and risk-taking) behaviors. These PRSs were used to predict each of the 11 DSM-5 AUD symptoms for participants in the UCSF Family Alcoholism study (n=2154). Regression analyses were conducted in R Studio using the *pedigreemm* package with a significance level of $p<0.05$. Specifically, the internalizing and externalizing PRSs were included as independent variables, and the individual AUD symptoms were included as dependent variables. Age and ancestry were included as covariates. The PRS for neuroticism positively predicted all AUD symptoms (p=0.00088-0.02037) except hazardous use (p=0.09041); the PRS for worry positively predicted inability to cut-down usage (p=0.02859) and role failure (p=0.04949). The PRS for aggression showed significant positive associations with all AUD symptoms (p=0.00022-0.01123) except withdrawal (p=0.06018) and role failure (p=0.06867), but the PRS for risk-taking did not significantly predict any symptoms (p's>0.05). Notably when PRSs for neuroticism and aggression were included in a model together, they largely explained non-overlapping variance in the AUD symptoms. These findings suggest that genetic risk for both internalizing and externalizing spectrum behaviors are broadly and uniquely related to AUD symptomatology, and do not show a clear pattern of differential relations with individual symptoms.