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Expression-based polygenic score derived from corticolimbic *DCC* gene co-expression networks as a biomarker of SUD risk

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By the time humans reach adolescence, most neuroanatomical foundations are set in place. An exception is the establishment of dopamine (DA) connectivity in the prefrontal cortex (PFC), which reaches full maturation in adulthood. Altered PFC DA connectivity/function is linked to cognitive control deficits observed in substance use disorder (SUD). Given the central role of the guidance cue *DCC* signaling pathway in the delayed PFC DA development, we investigated whether a polygenic score reflecting variation in the expression of the *DCC* gene networks in target regions of mesocorticolimbic DA neurons (i.e., nucleus accumbens, NAcc, and PFC) is associated with addiction-like traits in adults. We compiled SNPs from the co-expressed genes into an ePRS score using the SNP-gene expression related betas described in GTEx and investigated its ability to predict addiction-related traits in adults. In the SUD-focused SAGE study, we observed a main effect of the score, such that high ePRS predicts a higher number of addiction comorbidities (n=2,719) and an earlier diagnosis of SUD. For the population based UKBioBank (n=127,949), the high ePRS score is a strong predictor of self-harm behavior (p<0.01), but the main effect of the score does not quite reach significance to predict SUD (p=0.08), probably due to the smaller prevalence of SUD and older age of the UKB participants in comparison to SAGE. These results suggest that the ePRS for the corticolimbic *DCC* co-expression networks is linked to an overall increased risk for developing SUD, and can serve as a potential biomarker of vulnerability to SUD and related psychiatric conditions.