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Whole-Exome Sequencing Study of Opioid Dependence Offers Novel Insights into the Contributions of Exome Variants

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Opioid dependence (OD) is epidemic in the United States and it is associated with a variety of adverse health effects. Its estimated heritability is ~50%, and recent genome-wide association studies have identified more than a dozen common risk variants. However, there are no published studies of rare OD risk variants. In this study, we analyzed whole-exome sequencing data from the Yale-Penn cohort, comprising 2,100 participants of European ancestry (EUR; 1,321 OD cases) and 1,790 of African ancestry (AFR; 864 cases). A novel low-frequency variant (rs746301110) in the RUVBL2 gene was identified in EUR ($p=6.59\times10\text{-}10$). Suggestive associations ($p<1\times10\text{-}5$) were observed in TMCO3 in EUR, in NEIL2 and CFAP44 in AFR, and in FAM210B in the cross-ancestry meta-analysis. Gene-based collapsing tests identified SLC22A10, TMCO3, FAM90A1, DHX58, CHRND, GLDN, PLAT, H1-4, COL3A1, GPHB5 and QPCTL as top genes ($p<1\times10\text{-}4$) with most associations attributable to rare variants and driven by the burden of predicted loss-of-function and missense variants. This study begins to fill the gap in our understanding of the genetic architecture of OD, providing insights into the contribution of rare coding variants and potential targets for future functional studies and drug development.