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Association of Polygenic Risk Scores with the Need for Pharmacologic Treatment of Neonatal Abstinence Syndrome: Results from a Genome Wide Association Study

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Neonatal Abstinence Syndrome (NAS) is a constellation of signs of withdrawal in the neonate secondary to prolonged in-utero exposure to maternal opioids. Despite clinical need, accurate prediction of NAS severity remains elusive. This study aimed to identify genetic variants associated with NAS severity through a Genome Wide Association Study (GWAS) and to estimate a Polygenic Risk Score (PRS) for NAS severity. Subjects were drawn from a prospective case-control study that included 476 in-utero opioid-exposed term neonates of European and African descent. A cross-ancestry GWAS identified one intergenic locus on chromosome 7 near *SNX13* associated with need for pharmacotherapy at genome-wide significance (rs73313986, $p=4.22E-08$). Look up of 7 previously reported candidate variants in this much larger GWAS found nominal significance for one (rs2614095, $p=0.042$). PRS models estimating genetic predisposition for pharmacotherapy were generated via a nested cross-validation approach using 382 neonates of European ancestry. PRS models derived from a subset of the European ancestry neonates reliably discriminated need for pharmacotherapy using cis variant effect sizes within validation sets of European and African American ancestry neonates ($p<3E-06$, AUROC >0.75), but were less effective when applying variant effect sizes across datasets ($p>0.02$, AUROC ≈ 0.60) and in calibration analyses. This study demonstrated the potential to identify genetic risks for NAS and enable development of PRS with clinical utility for predicting NAS severity. However, larger GWAS with additional ancestries are needed to confirm the observed *SNX13* association and enhance the accuracy of PRS in NAS risk prediction models to make them clinically useful.