

## **Title: Replication Study of the Association of Genetic Variants in COMT and PNOC with Neonatal Abstinence Syndrome Outcomes**

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**Background:** There is significant variability in severity of neonatal abstinence syndrome (NAS) due to *in-utero* opioid exposure. Preliminary studies have suggested that genetic variations in opioid receptor and stress response genes contribute to these differences. These genetic associations require replication to validate findings.

**Objective:** To determine if previously identified single nucleotide polymorphisms (SNPs) are associated with differences in NAS severity in an independent cohort of opioid-exposed mother-infant dyads. Outcome measures included length of hospital stay (LOS) and need for pharmacologic treatment.

**Design/Methods:** Full-term opioid-exposed newborns and their mothers (n=113 pairs) from 2 institutions were studied. A DNA sample was obtained and then genotyped for 7 SNPs in the *OPRM1*, *OPRD1*, *PNOC*, and *COMT* genes utilizing a custom designed microarray. SNPs were chosen based on previous genetic associations identified in NAS infants. Infants were monitored for NAS and treated with replacement opioids according to institutional protocol. The association of each SNP with NAS outcome measures was evaluated using multivariate regression models adjusting for significant co-variables of breastfeeding and maternal opioid agonist. An additive genetic model was used, and a significance threshold of  $\alpha = 0.007$  was applied to correct for the number of independent tests.

**Results:** Sixty-eight (60.2%) infants were methadone and 45 (39.8%) buprenorphine exposed. Eighty-seven percent were White Non-Hispanic, as in previous studies. The mean LOS for all infants was 18.9 days (95% CI 17.0, 20.8). Ninety-four (83.2%) infants required pharmacologic treatment and 29 (25.7%) required 2 medications. We replicated our prior findings for 3 of the 7 SNPs tested. The minor A allele in rs2614095 in the *PNOC* gene in the infants was associated with decreased infant pharmacotherapy (OR=0.47, CI 0.23, 0.99, p=0.04). The minor allele of 2 SNPs in the *COMT* gene in the mothers were associated with improved NAS outcomes: The A allele in rs740603 was associated with shorter LOS by 3.2 days (CI 0.4, 6.0, p=0.03) and the rs4680 G allele with decreased odds of requiring 2 medications (OR=0.47, CI 0.20, 0.90, p=0.04). The SNP associations met point-wise but not experiment-wise statistical significance.

**Conclusions:** Consistent with previous findings, this study suggests that SNPs in the *PNOC* and *COMT* genes are associated with improved NAS outcomes. Examining genetic contributors to NAS outcomes may allow for future tailoring of treatment regimens according to genetic risk profile.