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Association of *OPRM1* and *COMT* Single-Nucleotide Polymorphisms With Hospital Length of Stay and Treatment of Neonatal Abstinence Syndrome FREE

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ABSTRACT

Importance Neonatal abstinence syndrome (NAS) caused by in utero opioid exposure is a growing problem; genetic factors influencing the incidence and severity have not been previously examined. Single-nucleotide polymorphisms (SNPs) in the μ-opioid receptor (*OPRM1*), multidrug resistance (*ABCB1*), and catechol-o-methyltransferase (*COMT*) genes are associated with risk for opioid addiction in adults.

Objective To determine whether SNPs in the *OPRM1*, *ABCB1*, and *COMT* genes are associated with length of hospital stay and the need for treatment of NAS.

Design, Setting, and Participants Prospective multicenter cohort study conducted at 5 tertiary care centers and community hospitals in Massachusetts and Maine between July 2011 and July 2012. DNA samples were genotyped for SNPs, and then NAS outcomes were correlated with genotype. Eighty-six of 140 eligible mother-infant dyads were enrolled. Infants were eligible if they were 36 weeks' gestational age or older and exposed to methadone or buprenorphine in utero .

Main Outcomes and Measures Primary outcome measure was length of hospital stay, with between-group differences expressed as β and calculated with linear regression models. Secondary outcome measures included need for any medical treatment for NAS and treatment with 2 or more medications.

Results Infants with the *OPRM1* 118A>G AG/GG genotype had shortened length of stay (β = −8.5 days; 95% CI, −14.9 to −2.1 days; P = .009) and were less likely to receive any treatment than AA infants (48% vs 72%; adjusted odds ratio, 0.76; 95% CI, 0.63-0.96; P = .006). The *COMT* 158A>G AG/GG genotype was associated with shortened length of stay (β = −10.8 days; 95% CI, −18.2 to −3.4 days; P = .005) and less treatment with 2 or more medications (18% vs 56%; adjusted odds ratio, 0.68; 95% CI, 0.55-0.86; P = .001) than the AA genotype. Associations with the *ABCB1* SNPs were not significant.

Conclusions and Relevance Among infants with NAS, variants in the *OPRM1* and *COMT* genes were associated with a shorter length of hospital stay and less need for treatment. These preliminary findings may provide insight into the mechanisms underlying NAS.

In the past decade, there has been a significant increase in opioid use during pregnancy, estimated to affect 5.6 per 1000 births.[1,2] Neonatal abstinence syndrome (NAS) is a disorder composed of a constellation of signs and

Table 3. Potential Covariates of Neonatal Abstinence Syndrome Severity

Variable	Length of Stay, Mean (95% CI), d	*P* Value	Infants Treated, No. (%)	*P* Value
Methadone (n = 55)	24.2 (19.7-28.7)	.15[a]	38 (69)	.30[b]
Buprenorphine (n = 31)	18.9 (13.2-24.6)		18 (58)	
Methadone maternal dose, mg[c]	*r* = 0.15	.29[d]	Treated: 99.9 (77.4-122.4) vs untreated: 109.0 (84.9-133.1)	.57[a]
Buprenorphine maternal dose, mg[c]	*r* = 0.08	.69[d]	Treated: 15.7 (10.6-20.8) vs untreated: 15.8 (11.5-20.1)	.96[a]
Benzodiazepines				
No (n = 74)	21.1 (17.6-24.6)	.27[a]	47 (63)	.69[b]
Yes (n = 10)	30.1 (13.0-47.2)		7 (70)	
Smoking				
No (n = 19)	18.4 (11.3-25.5)	.22[a]	11 (58)	.45[b]
Yes (n = 67)	23.4 (19.3-27.5)		45 (67)	
Breastfeeding				
No (n = 48)	27.4 (22.5-32.3)	<.001[a]	37 (77)	.009[b]
Yes (n = 38)	15.8 (11.5-20.1)		19 (50)	
Gestational age, wk				
<38 (n = 16)	25.5 (16.0-35.0)	.43[a]	11 (69)	.74[b]
≥38 (n = 70)	21.6 (17.8-25.4)		45 (64)	

Variables related to NAS severity are shown in Table 3. Breastfeeding demonstrated a consistent association with all outcome measures, with breastfed infants demonstrating decreased LOS (15.8 vs 27.4 days; $P < .001$) and receipt of any medical treatment for NAS (50% vs 77%; $P = .009$). Infants born to mothers who smoked cigarettes had a higher likelihood of receiving 2 or more medications (31% vs 0%; $\chi^2 = 7.88$; $P = .005$). However, cigarette smoking was not found to be significantly related to other NAS severity outcome measures (Table 3). Maternal methadone or buprenorphine dose at delivery did not correlate with any NAS outcome measure.

Table 3. Potential Covariates of Neonatal Abstinence Syndrome Severity