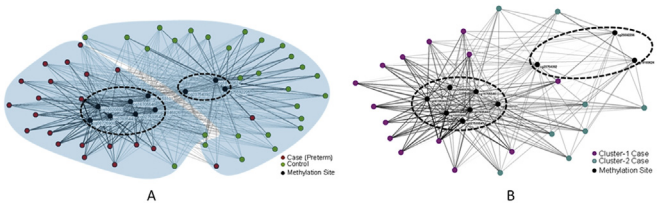
are cell cycle promoters, suggests that senescence is an unlikely pathology in PTB in the absence of preterm premature rupture of membranes. Furthermore, a case-only analysis (Fig. 1B) revealed that a subset of the cases have hypomethylated CpG sites in BMI1, CDKN2C, and IRF8, suggesting heterogeneity in PTB pathophysiology.

CONCLUSION: Bipartite network analysis helped to reveal heterogeneity in PTB and to infer the pathways involved in subphenotypes. These results should help improve the future modeling of PTB risk.



(A) Bipartite network of 50 cases/controls, and top-10 significant methylation sites, with superimposed clusters shaded in blue. (B) Bipartite network of only 22 preterm cases, and top-10 significant methylation sites with superimposed clusters, revealing 2 subphenotypes.

15 Genetic predisposition to adverse neurodevelopmental outcome after early preterm birth: a validation analysis

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OBJECTIVE: Validate genetic risk loci associated with adverse neurodevelopment after early preterm birth.

STUDY DESIGN: We previously conducted a large candidate gene association study in a cohort of 1013 extremely low birth weight infants (<1000 gms). The case-control analysis utilized samples in the NICHD Neonatal Research Network's DNA Bank and evaluated 1634 SNPs in 145 genes in hypothesized causal pathways, with emphasis on inflammation, angiogenesis, and brain development. Cases were children who died by age 1 or who were diagnosed with CP or neurodevelopmental delay (Bayley II MDI or PDI <70) by 18-22 months. Controls were survivors with normal neurodevelopment. The outcomes of CP, combined CP or death, mental delay (MDI<70), and motor delay (PDI<70) were evaluated. Twenty-five SNPs with P<0.01 for one or more outcomes in the previous analysis were selected for validation in this analysis. Validation samples were derived from an RCT of magnesium sulfate before anticipated early preterm birth (<32 weeks) for prevention of cerebral palsy (CP). Case/control definitions were equivalent to the primary cohort, with the exception that neurodevelopmental outcomes were evaluated at 24 months. As in the primary analysis, four outcomes were evaluated. Cases and controls were matched for race and infant sex; covariates included gestational age at birth, small for gestational age, maternal education level, treatment group, and antenatal corticosteroids. Significance in the validation cohort was defined as P<0.05.

RESULTS: The validation cohort included 364 infants, 170 cases and 192 controls. Three genetic loci from the primary analysis were significantly associated with the outcomes CP, CP/death and mental delay after early preterm birth in the validation analysis (Table).

CONCLUSION: Genetic loci involved in inflammation and brain development are associated with CP, CP/death, and mental delay after early preterm birth in primary and validation genetic analyses.

OUTCOME	GENE	FUNCTION	SNP (rs)	OR (95% CI)
CP	ARHGAP29	Craniofacial development	1931566	3.7 (1.1-11.9)
CP/Death	SERPINE1	Inhibits fibrinolysis	2227667	0.4 (0.2-1.0)
MDI<70	GRIN2B	NMDA glutamate receptor	11611183	3.4 (1.3-9.4)

16 MMP-8 correlates with an increase in anxiety and depression during early pregnancy and the postpartum period

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OBJECTIVE: Anxiety, depression, and systemic inflammation have been independently associated with preterm birth. It is unknown whether and when during pregnancy an increase in inflammatory cytokines may correlate with anxiety and/or depression. Our aim is to quantify this latter relationship.

STUDY DESIGN: This was a planned secondary analysis of a prospective, longitudinal multi-center trial in which pregnant women with singleton gestations underwent serum sampling and both anxiety and depression screening during each trimester. Cytokines (IL-1a, IL-1b, IL-6, IL-8, IL-10, TNFa), MMP-8, and CRP were measured using a multiplex beadlyte assay on a Luminex IS-100. Anxiety and depression were screened for using DASS-21 scale and Edinburgh Depression scale, respectively. Analyses were performed using multiple linear regression and ANOVA.

RESULTS: 400 women underwent evaluation in the first trimester, 321 in the second and 290 in the third. MMP-8 was significantly positively correlated with maternal anxiety scores during the first (p=.003) and third (p=.04) trimesters and during the postpartum period (p=.006). MMP-8 and anxiety scores were also significantly related at the same time points with race. Similar significant associations were seen between MMP-8 and depression scores during the first trimester (p=.0019) and postpartum (p=.0005). MMP-8 remained a significant independent predictor of anxiety and depression when race (Caucasian/not), obesity (yes/no) and smoking (yes/no) were included in multiple linear regression models. No significant associations were found among IL-1a, IL-1b, IL-6, IL-8, IL-10, TNFa and anxiety scores or depression scores at any time point sampled.

CONCLUSION: MMP-8 levels significantly positively correlate with anxiety and depression scores during the first trimester and postpartum period and are related to maternal race. These findings may suggest a common pathway for an inflammatory state.

17 Dynamic acetylation of histone 3 lysine 9 (H3K9) regulates corticotropin releasing hormone (CRH) in the human placenta

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OBJECTIVE: Human placental CRH is part of a clock that governs the length of pregnancy. CRH is upregulated by glucocorticoid (GC) in the placenta, but is down regulated by GC in other human tissues. We hypothesized that epigenetic regulation is responsible for this difference in CRH regulation in the placenta.

STUDY DESIGN: Human midtrimester (MT) and term placentas were collected and cytotrophoblasts were cultured. Histone lysine acetylation was determined by electrophoresis and Western blot.