Maternal and Infant Genetic Contributions to Spontaneous Very Preterm Birth in a State-Based Biobank

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Background and Objectives: Preterm birth (<37 weeks gestation) accounts for 12% of births in the United States and is the leading cause of infant mortality, with the majority of this mortality concentrated among very preterm infants (<32 weeks gestation). There are striking disparities in the rate and consequences of very preterm birth across racial and ethnic groups. Indeed, Non-Hispanic Blacks have more than twice the rate of very preterm births (3.8%) as either Non-Hispanic Whites (1.5%) or Mexican Hispanics (1.6%). In spite of the obvious impact on public health, the identification of markers to effectively predict spontaneous very preterm birth remains an ongoing challenge. The purpose of this investigation is to examine the association between polymorphisms in candidate inflammatory, endocrine and vascular system genes, environmental factors and spontaneous very preterm birth among mother-infant pairs of three racial / ethnic groups in a retrospective population-based nested case-control study.

Methods: The study population will include Non-Hispanic Black, Non-Hispanic White and Mexican Hispanic mother-infant pairs from a cohort of term (>37 weeks gestation) and very preterm (<32 weeks gestation) births in southern California. Candidate genes will be selected with a particular focus on the inflammatory, endocrine and thrombosis pathways due to their importance in the process of normal parturition. A tagSNPs approach based on the r^2 linkage disequilibrium statistic will be used to select approximately 1500 genetic polymorphisms to examine genetic variation across 90 confirmatory and exploratory candidate genes. Maternal and infant DNA will be extracted and genotyped from stored leftover maternal blood cell pellets specimens and newborn blood spots, respectively. Demographic and medical data will be collected from a variety of linked sources including medical records, vital records, census data and prenatal and newborn screening records. For final analysis, results will be stratified by race / ethnicity, and each group is projected to consist of 200 pairs of spontaneous very preterm infants and their mothers compared to 200 or more pairs of full term infants and their mothers.

Results: This investigation will determine whether there is an association and the nature and strength of the association between the risk of spontaneous very preterm birth and maternal and/or infant carriage of polymorphisms in candidate inflammatory, endocrine and vascular pathway genes. It will also assess potential maternal and/or infant gene-gene interactions (maternal-maternal, infant-infant, maternal-infant) and potential maternal and/or infant gene-environment interactions that contribute to the association with spontaneous very preterm birth.

Discussion/Conclusions: This investigation has a number of unique strengths. First, access to large population-based cohort of banked specimens will make sufficient sample size available to focus on the highest risk and potentially more homogenous group of spontaneous very preterm births (accounting for less than 2% of births). Second, analyzing mother-infant pairs will allow a comparative assessment of the contribution of both maternal and fetal genotypes in a single study. Third, analysis of three ethnic/racial groups in a population based setting free from biased referral patterns will inform our understanding of preterm etiology. Finally, examining up to 1500 polymorphisms in more than 90 candidate genes will allow simultaneous analysis of three overlapping biological pathways as they may contribute to the complex outcome of spontaneous very preterm birth.