Preterm birth (PTB) studies in the NCS: NCS Project 2-38 and 2-44

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Introduction: Preterm birth (PTB) is a major contributor internationally to mortality and morbidity and has a clear genetic component. The prospective approach of enrollment in the NCS enables studies of environmental contributors and epigenetic alterations that can be studied in concert with genetics to elucidate the fetal and/or maternal determinants of PTB. Genetic studies can use either candidate or genome wide approaches.

Methods: We have conducted preliminary candidate gene and genome wide association studies of PTB using samples collected in Iowa and Denmark. We are exploring a three-generation sample collection approach ideally suited for expansion in the NCS by collecting data and samples from PTB cases, both parents, and the maternal grandparents. Genotyping has been performed either by TaqMan assays for candidate genes or Illumina chips for genome wide association tailored for detecting common variants, but the potential exists in the future for using whole exome/genome sequencing for detecting rare as well as common variants.

Results: We have studied over 200 candidate genes for maternal and fetal effects and 20 genes on a panel of 500 trios consisting of the mother of a preterm infant and her parents. This effort had identified the progesterone and oxytocin receptors as strong candidates for PTB. In genome wide association studies of 1000 mother/baby cases and 1000 mother/baby controls no SNPs have reached genome wide levels of significance.

Conclusions: Based upon the limited pre-pilot data set, the NCS collection should provide material that is robust for genome wide association studies and greatly increased power over the current more limited data set. The NCS samples will also be available for exome and whole genome sequencing approaches that can identify not only the common variants found by association approaches but rare variants that are not found despite greater individual impact but limited population impact. All genetic data can then use environmental and epigenetic covariates to further identify risk and move to improved diagnosis and prevention.