A call for an international consortium on the genetics of preterm birth

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Despite enormous efforts, preterm birth (PTB) (<37 weeks’ gestational age) remains the leading cause of neonatal morbidity and mortality. In addition, there is increasing evidence that it has long-term sequelae, including behavioral and learning problems, developmental delays, and adult diseases, such as diabetes and cardiovascular disease. These complications of PTB are associated with an estimated annual costs of $26 billion in the United States.

The PTB rate continues to increase, with the most recent rise being in the United States of 12.5%. Other countries, both industrialized and developing, have shown similar increases in PTB rates. Some explanations for the rising PTB rates include increasing multiple births, advanced maternal age (≥35 years), and the use of assisted reproductive technologies, such as in vitro fertilization. However, these factors alone do not account for the largest proportion of this trend, and the majority of preterm deliveries are still unexplained.

Pregnancy and parturition involve complex molecular and physiologic pathways in both the mother and the fetus that are not well understood, but include stress, inflammation, hemorrhage, and pathologic uterine distension. These pathways can function independently, but usually act in concert in various combinations, adding to the complexity of the phenotype. Experimental approach to the myriad of possible pathways and their interactions physiologically is a truly daunting task. An alternative to this effort is an examination of static markers, such as genetic variants. These can help to define a priori the information that can be gleaned to only a small portion of the pathways involved, and not the system as a whole. Therefore, candidate gene studies are likely to miss genes outside of the known pathways. Epistasis, or gene-gene interaction, also has a potentially profound role in multiple disease processes and biologic pathways. A candidate gene approach could easily fail to detect this potential effect because of the narrow focus of investigation. Because of these evident problems, a whole genome approach is needed to identify the unexpected variants that can contribute to PTB.

In a whole-genome approach, a large set of sequence variants are used as markers to detect associations between a particular genomic region and a well-classified phenotype of interest. The variants themselves may or may not be functional or contributory to the phenotype, but instead they serve as a landmarks. Currently, it is feasible to genotype approximately 1 million genetic markers that enable finding an association with genetic markers within a susceptibility gene or regulatory element, or very close to it. The whole-genome association studies can be best appreciated as a first step of hypothesis testing for known candidates and also as hypothesis generating in novel pathways/gens.

The sample size required for a whole-genome study is quite large because of the large number of comparisons, unless the effect size of the genotype is extraordinary, an event that is unlikely, given the putative multifactorial model of the genetics of PTB. Although studies of PTB will still need sample sizes larger than any published in candidate gene studies on PTB (thousands of cases and thousands of controls), these strategies, once considered a Herculean task, are now feasible. One way to assure that the numbers of samples are large enough to achieve sufficient power is to develop consortia that combine

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resources from multiple teams. This approach has been successful for studies of autism, multiple sclerosis, and several other diseases (Wellcome Trust Case Control Consortium [WTCCC]). We propose to apply it to the study of PTB.

To coordinate multi-investigator and multisite large-scale genetic studies of PTB, it is essential to ensure that phenotype definitions are compatible. Here, we briefly review some basic phenotypic definitions. PTB has been defined by the World Health Organization (WHO) as a birth occurring before 37 completed weeks or 259 days of gestation.\(^{24}\) This definition has also been accepted by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists.\(^{25}\) However, insofar as the subgroups of PTB are concerned, there is some ambiguity. This poses problems for assessing etiologic and presumably genetic heterogeneity.\(^{26}\) The subgrouping, based on clinical presentation, is the one most commonly used. It divides PTB into: preterm labor (PTL), preterm premature rupture of membranes (pPROM), and medically indicated (iatrogenic) PTB. Other subdivisions have been proposed\(^{27}\) and a recent article concluded that it is necessary to split and lump these categories when studying the cause of this complex trait.\(^{28}\) This may be appropriate for an epidemiologic survey of PTB; however, etiologic, pathologic, and physiologic heterogeneities will complicate the Genome-Wide Association (GWA) analysis, making any significant associations difficult to replicate. Such failure to replicate is not only a concern for PTB researchers but also for investigators in most other complex disease areas. Therefore, we argue that 1 of the reasons for these rather disappointing findings is the fact that previous studies of the genetic aspects of PTB have not devoted enough effort to defining the phenotype. PTB, in epidemiologic and biologic studies has been treated as a single dichotomous trait when in reality it is not.

The reason to devote large-scale genotyping efforts to address the genetic basis of PTB is compelling. This will serve as a means of developing better predictive models and lead to a better understanding of disease pathophysiology. To assure adequate resources and the necessary number of samples, we require an assembly of investigators who have collected samples with appropriate phenotype data and are willing to join in a Preterm Birth Genome Project (PGP) consortium. This consortium has already been established at a meeting held at WHO headquarters in September 2007. The goal of the PGP is to pool resources with the intent of increasing sample sizes for both the initial GWA studies, as well as for the follow-up studies. This will be carried out as part of an international effort to define risk factors common to all populations and those that are unique for specific populations.

Therefore, we invite all investigators who have DNA samples from studies of pregnancy outcome to join the PGP. The project will be coordinated by investigators at the WHO, Geneva, Switzerland, March of Dimes USA, and Preterm Birth International Collaborative (PREBIC). Michael Katz, MD, (Senior Vice President for Research and Global Programs, March of Dimes Birth Defect Foundation) is the director of the consortium. Those investigators who have a shared interest in identifying genetic risks for PTB risk should contact either Mario Merialdi (mmerialdi@who.int), Project Chairman, Ramkumar Menon, Management committee (fortunat@edge.net), or Scott Williams, Scientific committee (smwilliams@chgr.mc.vanderbilt.edu) with the subject heading “PGP Consortium.”

The consortium has considered the rights of all investigators with respect to their intellectual property, the authorship of publications, and independence. These rules are available for perusal by all who express their interest in this important endeavor. We encourage them to contact us as soon as possible.

REFERENCES


