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The genomics of prematurity in an era of more precise clinical phenotyping: a review

Tracy A. Manuck[a,b,*]

[a]Department of Obstetrics and Gynecology, Division of Maternal–Fetal Medicine, University of North Carolina – Chapel Hill, Chapel Hill, NC, USA

[b]Department of Obstetrics and Gynecology, Division of Maternal–Fetal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

SUMMARY

Spontaneous preterm birth is a major public health problem, with a clear genetic component. Genetic association studies have evolved substantially in recent years, moving away from the traditional candidate gene analyses to newer approaches utilizing sophisticated analysis platforms to examine sequencing data, and shifting towards functional studies including methylation analysis. It is becoming increasingly evident that careful clinical phenotyping is crucial to high quality genetic association studies regardless of the assay or platform being used. Nonetheless, genetic studies of prematurity are hampered by numerous challenges including small sample sizes, incomplete phenotying, population stratification, and multiple comparisons. As the costs of sequencing and functional analyses continue to decrease, unbiased genome-wide assays will be more widely available. Researchers have met improved success recently when critically applying clinical phenotyping knowledge to group women prior to analyzing genotyping results. Eventually, as the analytic approaches evolve, it is likely that this methodology (combining precisely clinically phenotyped subjects with genome-wide data) will provide key information regarding the pathophysiology of prematurity, and provide potential new avenues for exploring innovative therapeutic strategies.

Keywords

Infant; Premature; Premature birth; Phenotype; Genetic predisposition; Polymorphism

[*]Address: UNC Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, 3010 Old Clinic Building, CB#7516, Chapel Hill, NC 27599-7516, USA. Tel.: +1 919-966-1601; fax: +1 919-966-6377. tmanuck@med.unc.edu.

Conflict of interest statement

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1. Introduction

Approximately 12% of infants born in the USA are preterm at <37 weeks of gestation. Preterm infants account for >70% of the neonatal morbidity and mortality in the USA, and are 40 times more likely to die in the neonatal period than their term counterparts [1]. Despite the magnitude of this clinical problem, preterm birth (PTB) remains a clinical and scientific enigma. Activation of gestational tissues and eventual preterm labor with delivery is likely a common final pathway triggered by multiple mechanisms, including hormonal mediation, inflammation and infection, and genetic factors [2]. There are many steps during the process at which an individual's genotype may affect phenotype in this complex and multistep cascade.

There is strong evidence of a genetic contribution to spontaneous PTB (sPTB). The strongest predictor of sPTB is a previous history of sPTB [3]. sPTB recurs in 35–50% of women, and tends to recur at similar gestational ages [4]. Likewise, the probability of sPTB increases with the number of prior sPTBs a woman has experienced, the most recent birth being the most predictive [5]. Women who themselves were born prematurely are at increased risk of sPTB [6,7]. The heritable nature of this complication is further supported by the findings of Winkvist and colleagues who determined that the risk of sPTB was elevated in women whose sisters had experienced sPTB (odds ratio: 1.94; 95% confidence interval: 1.26–2.99) [8]. Based on twin studies, the heritability of preterm birth is estimated to be 30% [9–11]. The racial disparity in the PTB rate cannot be explained by socio-economic factors alone, suggesting differences in risk-predisposing allele frequencies [12–16].

Numerous studies across a variety of platforms and analytic approaches have examined the relationship between genetics and prematurity. Unfortunately, results have often been inconsistent between populations and difficult to reproduce. Furthermore, though PTB is a multifactorial process leading to a final common pathway resulting in contractions, cervical dilation, and eventual delivery of the neonate, many studies of PTB have limited additional phenotype information, and genetic analyses are based upon relatively heterogeneous groups of women. Recent investigations have shown that women may be grouped into distinct PTB phenotypes (including infection/inflammation, decidual hemorrhage, etc.) using clinical information. These clinical classifications can characterize groups of women (e.g. those delivering very preterm), and may provide further insight beyond the heterogenous PTB categorization [17]. Although significant overlap between phenotypes exists, distinct differences have been observed between phenotypes, as those delivering at the earliest gestational ages and Blacks have notably different phenotypic profiles compared to others [17,18]. It has been hypothesized that suboptimal clinical phenotyping is a major contributing factor to the challenges of reproducibility that have characterized genetic investigations of prematurity.

The purpose of this review is to examine current investigative techniques for genetic studies, and to summarize current knowledge regarding the contribution of genomic studies to PTB, focusing on and highlighting phenotype-specific genetic investigations.

2. Overview of genetic approaches

The study of genomic DNA allows investigators to correlate genotype with phenotype, and has evolved substantially over the past several decades. Traditionally, studies have used candidate gene approaches to evaluate whether certain alleles confer an increased or decreased risk of certain diseases. Candidate gene studies represent the largest body of work across the medical literature with regard to genetic association studies, and involve an a-priori hypothesis regarding biologic function and genetic association. This type of study may be 'hit or miss' depending on whether the 'right' gene was selected by the researchers.

In contrast, examination of the entire exome or entire genome offers a more comprehensive and unbiased approach. High-throughput genotyping, including most genome-wide association study (GWAS) platforms, are now widely accessible to investigators. Although GWAS "scans the genome," this technique examines only a subset of single nucleotide polymorphisms (SNPs) in the genome that are in linkage disequilibrium with other, non-genotyped SNPs. Unfortunately, GWAS has little power to detect rare, potentially causal, genetic variants [19]. The combination of unsuccessful research attempts to find a single causal gene and the multifactorial nature of spontaneous PTB makes it likely that multiple genetic variants and gene–environment interactions that contribute to this disorder have yet to be elucidated. Recently, advanced technology has driven down the costs of sequencing, and it is now feasible for investigators to study every base pair in the human genome. The possibilities with regard to sequencing analyses are endless; the challenges lie in the analysis and interpretation of these large volumes of data [20].

Epigenetic modifications provide another mechanism by which genes may interact with the environment; they affect gene expression by inducing structural changes in DNA that are maintained through cell division, respond to changes in the environment, yet are potentially reversible and can be targets for disease therapy [21]. DNA methylation at cytosine–guanine dinucleotides (CpG sites) – the most commonly studied epigenetic modification in humans – guides temporal and tissue-specific gene expression during fetal development and tissue differentiation. Even subtle environmental changes may induce epigenetic changes and have effects on phenotype. Methylation is tissue specific; results from blood, placental or cervical tissue, for example, typically cannot be directly compared. However, methylation studies in blood may be a reliable correlate of physiologic processes in other tissues [22]. Methylation analyses can be candidate gene and very focused, or can be genome wide. Limited studies of epigenetics in obstetrics have demonstrated identifiable differences between women delivering preterm and those with term deliveries only, across a spectrum of tissue types (placenta, maternal blood, cord blood) [23–28]. Many PTB risk factors result in DNA methylation differences – for example, methylation patterns are associated with stress, diet, smoking, inflammatory cytokine levels, and medication exposure [29–32].

Sophisticated analysis software has become increasingly widespread for researchers to analyze genetic data in the framework of physiologic pathways through systems biology. Such programs include Ingenuity Pathway Analysis (IPA; Qiagen, Valencia, CA, USA), DAVID (National Institute of Allergy and Infectious Diseases, NIH), Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway, and others. The majority of these programs

function by using complex algorithms that analyze the role of a list of genes provided by the user, to search for connected functions and pathways, or overrepresentation of a particular type of gene function (e.g. genes involved in cell signaling) or ontologies.

Additional techniques not directly related to DNA are beyond the scope of this review.

A summary of example gene pathways and representative genes frequently associated with each main preterm birth phenotype, including preterm labor with intact membranes, is shown in Table 1. Each phenotype, with related genetic associations, is discussed in additional detail below.

3. Genetics of preterm labor with intact membranes

Although the largest number of studies has focused on “idiopathic PTB,” this phenotype is the most heterogeneous and should be considered a diagnosis of exclusion. In the most general sense, studies of spontaneous PTB often encompass those with PTB due to cervical insufficiency, preterm premature rupture of membranes (PPROM), placental abruption, uterine overdistension, or a combination of these. Women without any PTB risk factors frequently will have an incomplete phenotypic evaluation during pregnancy. For example, routine endovaginal cervical length screening is not always performed on low risk women. Therefore, it is possible that some women thought to have “idiopathic” PTB may indeed have cervical insufficiency. This may occur if a woman has a clinically unrecognized short cervix, which then progresses to preterm cervical dilation and eventually preterm labor. When the woman presents with advanced dilation, it is then impossible to discern the inciting event leading to the advanced preterm labor. Thus, there is considerable overlap between definitions of sPTB with intact membranes and PPROM, as many studies use different thresholds to define PPROM (minimum interval between rupture and delivery, or minimum interval between rupture and development of frequent uterine contractions). The distinction between sPTB with intact membranes and abruption is also challenging, given that decidual hemorrhage is a recognized risk factor for sPTB, and bloody show may be difficult to distinguish from an early clinical abruption. In all situations, incomplete clinical data collection and clinical phenotyping, particularly in the case of retrospective analyses, may introduce heterogeneity into the analysis and limit statistical power to detect genetic differences.

Nonetheless, despite these limitations, several genetic studies have been conducted using samples from women with clearly phenotyped PTB. These studies have most consistently found associations between inflammatory and coagulation gene polymorphisms and PTB [14,33]. Such genes include tumor necrosis factor (TNF)-α, TNF-β, interleukin (IL)-4, IL-6, IL-10, toll-like receptor (TLR) 2, TLR4, and nucleotide-binding oligomerization domain containing 2 [34]. However, even within these genes, refinement of results may be achieved with proper population stratification and with additional clinical phenotyping. A recent meta-analysis of the association between IL6 genotype and PTB within population strata exemplified this issue. The IL6 SNP rs1800795, genotype CC was associated with a decreased risk for PTB among women of European descent. This association was not significant among women of other ancestries [12]. Another example is the study performed

by Velez and colleagues, which found that IL-12 and IL-12RB polymorphisms (inflammatory pathway) were associated with PTB among African-American women; in contrast, these authors found that polymorphisms in TPA, IL10RA, FV, and FVII (both coagulation and inflammation pathways) to be associated with PTB among Caucasian women [14,33].

Recently, Capece and colleagues performed a pathway analysis of genes associated with sPTB with the goal of identifying maternal genetic markers for stratification of preterm birth due to PPROM or spontaneous PTB with intact membranes, and to differentiate between the mechanisms involved in these clinical endpoints. This study pooled SNP data from individual studies and listed all genes implicated in either sPTB or PPROM by searching for primary source articles as well as established genetic databases (e.g. PTB Gene: http://ric.einstein.yu.edu/ptbgene/index.html) and then used the Ingenuity Pathway Analysis software to determine associations between genes on the final list. Of 185 potentially eligible studies, only 15 could be included in the qualitative synthesis of SNP data, including 10 sPTB and five PPROM reports. In total, 248 SNPs in 102 genes were found to be statistically significantly associated ($P < 0.05$) with sPTB with intact membranes; these genes were uploaded into the IPA for network analysis. The populations were primarily South American, African-American, and Caucasian. The IPA revealed that the top four molecular and cellular functions were cell-to-cell signaling and interaction, cellular movement, lipid metabolism, and small molecule biochemistry, and did not differ when PPROM genes were analyzed. However, more detailed investigation into the pathways revealed that sPTB is associated with the glucocorticoid signaling pathway, inflammatory genes, and matrix-degrading and/or collagen metabolism-related markers [35].

There is a relative paucity of methylation studies of PTB, and most have included cohorts with a large amount of phenotypic heterogeneity. Furthermore, most studies have included samples only collected at the time of delivery; the importance of longitudinal sample collection should not be understated, as this has the potential to provide insight into PTB pathophysiology as it is evolving and also to provide the basis for the development of biomarkers. Parets et al. examined 40 paired maternal and cord blood samples and found that genes involved in metabolic, cardiovascular, and immune pathways differentially methylated. This study was limited to African-Americans, and the authors concluded that this may provide some basis for the higher rates of PTB among African-American women [42]. Another methylation study examined the relationship between methylation and several subtypes of PTB, including spontaneous preterm birth with intact membranes, PPROM, preterm delivery after chorioamnionitis, and medically indicated induction of labor. These investigators found that DNA methylation levels were increased in PLAGL1 among infants with chorioamnionitis ($n = 10$). In this cohort, no methylation changes were noted among infants with PTB or PPROM, but the power to detect differences was limited due to the sample size [43].

Several investigative teams have summarized genetic knowledge of prematurity and generated valuable online resources compiling these results. The ‘Database for Preterm Birth’ is available online at www.ptbdb.cs.brown.edu/dbPTBv1.php and allows for gene, SNP, and keyword searches of a curated aggregated database of prematurity genes [44].

4. Genetics of PPROM

Numerous candidate gene studies focusing on PPROM have also been conducted. PPROM is the most frequently occurring specific prematurity phenotype examined after PTB with intact membranes has been considered. Although many have focused on inflammatory genes as with sPTB with intact membranes, many have also investigated genes involved with collagen or extracellular matrix composition. Romero and colleagues examined 225 mothers and 155 fetuses with PPROM and compared them to 599 mothers and 628 fetuses with normal pregnancies, and reported that genetic variation in the tissue inhibitor of metalloproteinase 2 (TIMP2) gene, alpha 3 type IV collagen isoform precursor (COL4A3), and a three-locus model including collagen type 1 alpha 2 (COL1A2), defensin alpha 5 (DEFA5), and endothelin 1 (ET1) genes were associated with PPROM (approximately doubling the risk) [36].

In the large pathway analysis by Capece and colleagues described above, genes in hematologic/coagulation function disorder, collagen metabolism, matrix degradation, and local inflammation pathways were found in association with PPROM, which was in contrast to an autoimmune/hormonal regulation axis among women with PTB with intact membranes [35]. Furthermore, this analysis also found that although the inflammatory transcription factor NF-κβ is linked to both PTB with intact membranes and PPROM, the inflammatory response is distinctly different. Individual genes found to be associated specifically with PPROM included tumor necrosis factor (TNF) and nitric oxide synthase 2A (NOS2A) [35]. The authors also identified signal transducer and activator of transcription 1 (STAT1) as a PPROM-specific regulator. STAT1 is a major component of the cellular response to interferon-γ, regulating the immune system, cell differentiation, cell growth inhibition, and apoptosis [37]. It is important to note that the PPROM analyses were based primarily on South American (Chilean) subjects.

5. Genetics of cervical insufficiency

Cervical insufficiency is classically defined as painless mid-trimester cervical dilation leading to delivery. A shortened mid-trimester cervical length is now a recognized risk factor for spontaneous preterm birth; the shorter the cervix, the higher the risk. Cervical insufficiency is likely the extreme of this continuum.

Several candidate gene studies of cervical insufficiency have focused on genes involved in connective tissue dynamics, hypothesizing that perturbations in normal homeostasis between collagen, hyaluric acid, and sulfated glycosaminogylcans may influence the development of this clinical phenotype. Second trimester biopsy specimens from women with cervical insufficiency have revealed a high turnover rate of collagen with a high proportion of newly synthesized collagen with low biomechanical strength [38]. Thus, collagen genes are among the most widely investigated candidate genes among women with cervical insufficiency. Within the collagen 1A1 (COL1A1) gene, polymorphisms in the Sp1 binding region affect collagen regulation, and may lead to the formation of weaker collagen homotrimers compared to the normal collagen heterotrimers. SNPs within the transforming growth factor (TGF)-β gene also affect collagen structure by influencing the interaction between cells and

the extracellular matrix. Indeed, polymorphisms in COL1A1 and TGF-β genes have both been associated with cervical insufficiency in limited genetic association studies [39].

6. Genetics of placental abruption

Placental abruption, simply defined, is premature separation of the placenta from the uterine wall prior to the delivery of the fetus. Epidemiologically, it is associated with hypertensive disorders, advanced maternal age, cigarette smoking, illicit drug use, and external trauma to the abdomen. Some investigators have argued that abruption is an entity distinct from sPTB whereas others believe that it is an important sPTB subtype. However, like sPTB, placental abruption aggregates in families. Furthermore, although the diagnosis is difficult to make unless there is large volume blood loss, women with vaginal bleeding during pregnancy are known to be at high risk for preterm birth, suggesting significant overlap between the conditions.

The largest genetic study of abruption was the Peruvian Abruptio Placentae Epidemiology Study. This was a genome-wide association study of 470 placental abruption cases and 473 controls; samples were genotyped using the Illumina Cardio-Metabochip®, and a candidate gene study was performed using the GWAS data focusing on genes involved with mitochondrial biogenesis and oxidative phosphorylation. These researchers found that genes known to regulate mitochondrial biogenesis and oxidative phosphorylation were associated with risk for placental abruption ($P < 0.05$) [45].

In a pilot case–control study of 233 cases and 238 controls (comprised of a subset of subjects from the Peruvian study), real-time quantitative polymerase chain reaction assessed for the relative copy number of mitochondrial DNA in maternal whole blood samples at delivery, and found that a trend towards an association between mitochondrial DNA copy number and placental abruption (among those with the highest quartile of mitochondrial DNA copy number, after adjusting for confounding, $P = 0.09$) [40]. In a GWAS study (also comprised of a subset of women from the Peruvian study) of abruption, no SNPs were significant after false discovery rate correction. However, the top hits were in the CTNNA2, TNFRSF1A, and ZNRF3 genes, and the top 200 SNPs from the GWAS overrepresented genes involved in cell cycle, growth, and proliferation [41].

7. Remaining unresolved challenges, future directions, conclusions

Even the newer pathway analyses such as the study by Capece and colleagues have relied upon candidate gene studies to form the foundation of their investigations. Additional high quality sequencing (both whole exome and whole genome) and functional genetic studies are urgently needed to identify new potential causative genes. As described above, only a limited number of studies have examined the fetal genetic contribution to prematurity. Genetic studies of prematurity are hampered by many challenges, including issues related to population stratification, population differences between different cohorts (even when seemingly similar race/ethnic groups are examined), and the multiple comparisons (particularly with small cohorts). As the cost of sequencing and functional genetic studies continues to decrease, these approaches will be more widely available to more investigators, and the analytic methods will also evolve. Clinician scientists are paying increasing attention

to the ever-important role of clinical phenotyping, which has the great potential to vastly increase the power and effectiveness of subsequent genetic association studies. Indeed, studies of well phenotyped individuals are promising, but must be verified in larger independent cohorts comprised of women from different populations. Eventually, these unbiased genetic association approaches will provide key information regarding the pathophysiology of prematurity, and will supply potential new avenues for exploring innovative therapeutic strategies.

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Research directions

- Refinement of clinical phenotype, followed by large genome-wide investigations of women meeting criteria for each phenotype.
- Investigation of the effect of fetal genotype.
- Integration of maternal and/or fetal genomic data with proteomic data.
- Expansion of analysis efforts into newer analytic techniques, including pathway analysis and systems biology, to understand the broader context of individual gene contributions to prematurity.

Table 1

Gene pathways and representative genes frequently associated with each main preterm birth phenotype.

Phenotype	Phenotype description	Gene pathways or gene categories of interest	Example genes (official gene symbol)	References
Preterm labor with intact membranes	Most general phenotype, often 'catchall' category, may include women with incomplete phenotype evaluation	Inflammatory, coagulation, glucocorticoid signaling, matrix degrading and/or collagen metabolism-related markers	TNF-alpha, TNF-beta, IL4, IL6, IL10, IL10RA, IL12, IL12RB, TLR2, TLR4, NOD2, FV, FVII	[12,14,33–35]
Preterm premature rupture of membranes	Rupture of membranes prior to the onset of labor (time period inconsistently defined between studies)	Inflammatory, collagen, extracellular matrix, immune system regulation	TIMP2, COL4A3, COL1A2, DEFA5, ET1, NOS2A, STAT1	[35,36,37]
Cervical insufficiency	Painless mid-trimester cervical dilation leading to delivery; definition now may include continuum of women with a short cervix	Connective tissue, collagen	COL1A1, TGF-beta	[38,39]
Placental abruption	Premature separation of the placenta from the uterine wall	Mitochondrial biogenesis, oxidative phosphorylation, cell cycle, growth, and proliferaiton	CTNNA2, TNFRSF1A, ZNRF3	[40,41]