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# Genetics, hormonal influences, and pretertm birth

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ABSTRACT

Prematurity is a devastating disease with high neonatal morbidity and mortality based on gestational age at birth. Genetic and hormonal signals impact directly on the maternal predisposition to preterm birth or sudden onset of myometrial contractility. Candidate gene or genome-wide approaches are beginning to identify potential variants for women at risk for premature delivery or increased responsiveness to hormonal signals including progesterone. However, a majority of these studies have not yielded definitive results to allow for at this stage for development of personalized therapy.



## Genetics

The role of genetics in human parturition is aimed at identifying specific genes that contribute to term and premature activation of normal mechanisms that oversee the timing of birth. The captivating possibility of a genetic predisposition to preterm birth has been proposed and extensively studied. Recent advancements in bioinformatics allowed for genome-wide association studies (GWAS) that queried the whole human genome in a hypothesis-free, discovery fashion. Finding of a particular set of genes with key role in partition may represent a significant step forward toward personalized medicine and therapeutics.

### *Personal and family history of preterm birth (PTB)*

The strong familial clustering of PTB and large epidemiological studies support a genetic component for PTB. Twin studies suggest heritability of PTB is approx. 36-40%.[1,2] Epidemiological analyses support a primary maternal origin, with little effect of paternal or fetal genetic factors. These studies consistently conclude that the best predictor of PTB is a history of a prior PTB, and that subsequent PTBs occur at similar gestational ages.[3,4] In addition, the possibility of having a PTB increases with the number of prior preterm births, with the recent birth being the most predictive.[5]

In the U.S., the Utah Population Database is a unique epidemiologic resource because it links birth with extensive pedigree records for more than 6.4 million individuals. Esplin et al.[5] identified women who had a first live birth and at least one subsequent live birth in Utah during the period 1989–2001. The authors concluded that spontaneous PTB before 34 weeks was the highest risk factor for recurrence of early spontaneous PTB [relative risk (RR): 13.56; 95% confidence interval (CI): 11.5–16.0].

Familial trends in preterm deliveries were also evaluated in a cohort of Swedish women and their personal birth details.[6] The risk of PTB was not affected by the mother being preterm herself. However, the risk was significantly increased if the mother delivered a prior premature infant [odd ratio (OR): 4.11; 95% CI: 3.32–5.09]. Furthermore, women whose sisters experienced a PTB also had an increased risk of prematurity themselves.[7,8] In contrast, Porter et al.[9] reported that the risk of PTB was significantly higher in mothers born preterm than in those who were not (OR: 1.18; 95% CI: 1.02–1.37). This risk

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was inversely correlated to the gestational age of the mother at delivery (<30 weeks; OR: 2.38; 95% CI: 1.37–4.16).

Two large epidemiological studies were aimed at identifying a genetic predisposition to PTB. Bhattacharya et al.,[8] examined data on mother–daughter pairs and found that women who were born spontaneously preterm had significantly higher odds of delivering preterm babies (OR: 1.49; 95% CI: 1.12–1.99). Conversely, Selling et al.[10] analyzed a cohort of more than 38,000 women and published evidence that mothers who themselves were born prematurely were not at significant risk of having PTBs, compared with those who had been born at term (OR: 1.24; 95% CI: 0.95–1.62).

Most recently, Uzun et al.[11] analyzed genetic variants identified in women with 2–3 generations of PTB. Using a meta-analytic, bi-clustering algorithm to identify gene sets associated with PTB, the investigators identified 33 genes including 217 variants from 5 modules significantly different between cases and controls (term delivery no history of PTB). A list of the 33 genes is presented in the original publication.[11] The biological processes impacted by these gene sets included cell motility, migration and locomotion, response to glucocorticoid stimulus, signal transduction, metabolic regulation, and apoptosis.

### *Cytokine and "toll-like receptors" (TLR) polymorphisms*

The availability of a reference sequence of the genome provides the foundation for studying the nature of sequence variation, particularly single nucleotide polymorphisms (SNPs) in human populations. SNP typing is a useful tool for genetic studies and allows us to uncover not only the association of loci at specific sites in the genome with many disease traits, but also genes that may serve as genetic markers for PTB susceptibility. Within the last decade, the panel of investigated polymorphisms has increased to include genes that engage in activating several pathophysiological mechanisms leading to PTB (Table).[12]

Immune and inflammatory-related gene polymorphisms are by far the most studied polymorphisms in relation to PTB. Evidence is increasing for the role that genetic polymorphisms play in the regulation of the maternal and fetal innate immune in response to microbial infections and increased risk of PTB. Interleukins (IL) are cytokines involved in inflammatory response and polymorphisms in IL1α, IL1β and IL6 genes have been associated with PTB. Polymorphisms in the IL1α gene in Japanese women were associated with increased risk of PTB.[13] In contrast, polymorphisms in the promoter region of the IL-6 gene in a cohort of women of European descent and in IL1β gene in Caucasian have been associated with decrease risk of PTB.[14,15] A large meta-analysis by Wu et al.[16] strengthen of the conclusion that IL-6 SNP, rs1800795, located in the IL-6 gene promoter region carries a protective effect for PTB.

IL-10 is a potent anti-inflammatory cytokine.[17] In several inflammatory diseases, IL-10 down-regulates the synthesis of proinflammatory cytokines by monocytes, macrophages, and neutrophils thereby inhibiting the Th1 type immune response. In human pregnancy, it was shown that the IL-10 G13 allele in IL-10.G microsatellite occurs more frequently in women with cervical insufficiency.[18] This data confirms the role of IL-10 in inflammatory processes associated with cervical insufficiency, as a distinct PTB phenotype.

TLRs, a group of cellular receptors that mediate innate immune, play key roles in inflammatory events related to PTB.[19] Polymorphism in TLR-2 variant confers increased risk of PTB.[20] Several authors have reported an increased frequency of TLR-4 polymorphisms (Asp299Gly) in preterm neonates when compared with term infants.[21,22] Interestingly, there was a an increased risk of PTB and preterm premature rupture of membranes (PPROM) in the risk for fetuses carrying the TLR4 Asp299Gly polymorphism, emphasizing the potential role of the fetus in prematurity.

Tumor necrosis factor (TNF)-α is secreted after contact with microbial metabolites by immunocompetent cells and mediates the immunologic response of the host. Polymorphisms at the TNF-a-308 loci is the most recognized SNPs associated with spontaneous PTB.[23–26] Unfortunately, no single polymorphism has been identified as the sole mediator of PTB.

### *Racial predisposition*

There is a significant racial disparity in previable PTBs, with black mothers experiencing a 3–6 fold increased RR compared to white mothers.[27] DeFranco et al. showed that the relationship between spontaneous PTB and GA at the time of occurrence is inversely correlated. In their study the majority, 80%, of previable births (16–22 weeks) were spontaneous, and this was significantly higher compared with 73% in early PTBs (23–33 weeks), 72% in late PTBs (34–36 weeks), and 65% of term births (37–42 weeks). Black mothers are at increased risk of PTB compared to other racial groups, even when controlling for confounders such as socioeconomic and educational influences.[28–30] Recurrent PTB is also more common among black women, when compared to white women with a previous PTB.[31]

Differences in cytokines and SNPs in African-American population have become an area of interest for the persistent racial differences in PTB. An association between the TNF-α-308 A allele and spontaneous PTB has been identified in black women.[32,33] Several interleukins (IL-1, IL-2, IL-6, and IL-10) SNPs and their association with PTB have been investigated with mixed conclusions.[34–39] In addition, SNPs related to genes for protein kinase C-α (*PRKCA*) have been associated with spontaneous PTB in black women.[40]

Recent data demonstrated an association between sleep disturbances and PTB. African-American women exhibit greater inflammation (IL-6, IL-8, IL-1β, and TNF-α) in response to sleep disturbance than European American women.[41] Racial differences in susceptibility to sleep-induced immune response may as well contribute to racial disparities in PTB, as inflammatory pathway is recognized as a converging molecular pathway triggering myometrial contractility.[42]

### *Gene–environment interaction*

A gene–environment interaction is said to be present when the risk of a disease among individuals exposed to both the genotype and environmental triggers is either more severe or less severe than that predicted from the presence of either the genotype or the environmental exposure alone.[43,44] There