Published in final edited form as:

Obstet Gynecol. 2011 May ; 117(5): 1078–1084. doi:10.1097/AOG.0b013e318214e67f.

Admixture Mapping to Identify Spontaneous Preterm Birth Susceptibility Loci in African Americans

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Abstract

Objective—Preterm birth is 1.5 times more common in African American (17.8%) than European American women (11.5%), even after controlling for confounding variables. We hypothesize that genetic factors may account for this disparity and can be identified by admixture mapping.

Methods—This is a secondary analysis of women with at least one prior spontaneous preterm birth enrolled in a multicenter prospective study. DNA was extracted and whole-genome amplified from stored saliva samples. Self-identified African American patients were genotyped with a 1,509 single nucleotide polymorphism (SNP) commercially-available admixture panel. A logarithm of odds locus-genome score of 1.5 or higher was considered suggestive and 2 or higher was considered significant for a disease locus.

Results—One-hundred seventy-seven African American women with one or more prior spontaneous preterm births were studied. One-thousand four-hundred fifty SNPs were in Hardy-Weinberg equilibrium and passed quality filters. Individuals had a mean of 78.3–87.9% African-American ancestry for each SNP. A locus on chromosome 7q21–22 was suggestive of an association with spontaneous preterm birth before 37 weeks of gestation (three SNPs with logarithm of odds scores 1.50–1.99). This signal strengthened when women with at least one

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Financial Disclosure: Dr. Meis is a consultant to a randomized trial of 17P by the Ther-Rx Corporation. The other authors did not report any potential conflicts of interest.

Presented in part at the 57th Society for Gynecologic Investigation Annual Meeting, March 27, 2010, Orlando, FL.

preterm birth before 35.0 (eight SNPs with logarithm of odds scores greater than 1.50) and before 32.0 weeks of gestation were considered (15 SNPs with logarithm of odds scores greater than 1.50). No other areas of the genome had logarithm of odds scores higher than 1.5.

Conclusions—Spontaneous preterm birth in African American women may be genetically mediated by a susceptibility locus on chromosome 7. This region contains multiple potential candidate genes including collagen type 1-alpha-2 gene and genes involved with calcium regulation.

Introduction

Preterm infants account for more than 70% of the neonatal morbidity and mortality in the United States and are 40 times more likely to die in the neonatal period than their term counterparts. More than 12% of infants born in the United States are delivered preterm, defined as less than 37 weeks' gestation. However, preterm birth (PTB) is substantially more common in African-Americans (17.8% vs. 11.5% in European-Americans) even when controlling for social and other confounding factors (1–6). The risk of spontaneous PTB is increased in interracial couples; the risk is higher in couples where the mother is African-American and the father white (compared with couples where the mother is white and the father is African-American), suggesting an increased contribution of maternal genes (7).

Numerous studies have demonstrated that the susceptibility to spontaneous PTB is inherited. It is frequently clustered in families (8). Association studies have identified a number of genes with increased genetic variation among women delivering prematurely (9–12). Other researchers have specifically investigated potential genetic explanations for the overrepresentation of PTB in African-American women and found that the genetic contribution to prematurity varies with race, particularly in pathways related to inflammation and infection (13–15).

Despite evidence regarding the heritability of spontaneous PTB, association studies and family studies have identified very few genes associated with this phenotype. Admixture mapping is an efficient and potentially powerful method to scan the genome and identify genes that cause diseases whose prevalence rates vary among populations (16). This technique is suitable when the frequency of a disease is markedly different in two different populations and when genetic mixture (admixture) has occurred between the populations. The underlying rationale is that one or more disease-associated loci are more common in one ancestral population (in this case, African-Americans) than in the other (Europeans). If so, a region of the genome that contains such a locus is likely to be of recent African (rather than European) origin (17, 18). In a sample of admixed (African-American) individuals with spontaneous PTB, admixture mapping attempts to pinpoint such a region or regions. This is accomplished by assaying single-nucleotide polymorphisms (SNPs) whose frequencies are known to differ strongly in Africans and Europeans. In every admixed individual, some regions of DNA will be of African origin, while others will be of European origin. Regions of potential disease loci may have higher frequencies of "African" SNPs, compared to regions that do not contain a spontaneous PTB locus (16, 18).

Because European and African populations mixed only recently in the United States (within ~ the last 15 generations), stretches of DNA with contiguous European and African ancestry have not had time to undergo extensive recombination. Thus, a relatively small number of polymorphisms are needed to isolate a disease gene-containing region: SNPs covering several million base pairs of DNA are likely to be strongly associated with a disease-causing gene. This is in contrast to traditional linkage disequilibrium mapping, which requires analysis of SNPs every few thousand base pairs. Traditional control subjects are not needed:

the “control” in this case is the average proportion of African ancestry across the entire genome (16, 17, 19–21).

Admixture mapping has been successfully used to identify genes that contribute to other complex diseases, including prostate cancer, type-II diabetes, autoimmune diseases, and obesity (20, 22–24). For example, a strong association between a 3.8 Mb chromosomal region (8q24) and susceptibility to prostate cancer was recently found using this method (25).

We hypothesized that the disparity between rates of PTB in African-American and European-American women is due, at least in part, to genetic differences, and that these differences can be detected using admixture mapping. Finding a disease-associated region through admixture mapping will lead to more in-depth, focused studies aimed at uncovering direct genetic causes of spontaneous PTB.

Methods

This is a secondary analysis of women enrolled in a multi-center, prospective, double blind randomized controlled trial of 17-alpha hydroxyprogesterone caproate (17OHP) for the prevention of recurrent PTB, conducted from 1999 to 2002 by the *Eunice Kennedy Shriver* NICHD Maternal Fetal Medicine Units Network (26). As a part of the original trial protocol, maternal saliva samples were collected for future analyses. Saliva samples were originally labeled with unique, de-identified study codes and frozen at -20°C . DNA was extracted and whole-genome amplified from samples using established methods (Puregene, Qiagen Systems, Valencia, CA) in July and August 2008. Institutional Review Board (IRB) approval and subject consent were obtained at each of the 19 participating Network sites for the original study; IRB approval for this secondary analysis was also obtained.

All women admitted to the original trial had at least one documented spontaneous PTB <37 weeks' gestation. Samples from self-identified African-American women were included. There were no other exclusion criteria. Self-identified African-American women were genotyped with the 1,509 SNP Illumina® African American Admixture Panel. SNPs included on this panel have high minor allele frequency differences between African and European-American populations; allele frequency differences of >0.60 are seen for the majority of SNPs.

Women were analyzed as a group (spontaneous PTB <37.0 weeks') and also stratified by PTB severity. Women with more severe phenotypes – those with one or more spontaneous PTB <35.0 and <32.0 weeks' gestation were also analyzed separately. Women with an early spontaneous PTB <35 or <32 weeks' gestation either prior to entry into, or during their participation in the original trial were included in the severe phenotype groups (26).

The cohort of women in this analysis was compared to the original cohort using chi-square and Student's t-test (SAS® version 8.2, SAS Cary, NC). Genotypes were analyzed using ANCESTRYMAP software version 2.0 (16). A risk parameter of 1.5 was used, because the risk of PTB among African-American women is approximately 1.5 times the risk in European-Americans; this is a conservative estimate (1, 4, 5). Markers were tested for Hardy-Weinberg equilibrium and those with p-values <0.01 were excluded. A logarithm of odds (LOD) locus-genome score was calculated for each SNP marker. A LOD score is based on a likelihood-ratio statistic that compares, for each point on the genome, the likelihood of data being from a disease locus versus the likelihood of data being from a locus unrelated to disease (16). A higher LOD score (2 or higher) represents a higher probability that the point is associated with a disease locus.

Initial results were confirmed with a larger number of burn-in iterations (500) and follow-on iterations (500) per ANCESTRYMAP guidelines. Those areas with LOD scores 1.50–1.99 were considered suggestive of a disease locus, and those areas with scores ≥ 2.00 were considered significant for a disease locus (16, 27).

Results

There were 177 of 271 (65%) self-identified African-American women from the original trial who had DNA available. These 177 women included in our study were similar to the original cohort of African-American women with respect to mean maternal age (25.1 ± 5.0 vs. 24.9 ± 5.0 years, $p=0.48$), randomization to 17OHPC (68.9% vs. 66.8%, $p=0.31$), history of more than 1 prior spontaneous PTB (33.3% vs. 33.6%, $p=0.91$), tobacco use (24.9% vs. 21.8%, $p=0.09$), and mean pre-pregnancy body mass index (28.3 ± 8.4 vs. 27.6 ± 8.1 kg/m², $p=0.06$). However, women in the cohort with DNA available were less likely to have delivered prematurely during the Meis trial compared to the original cohort (PTB < 37 weeks' gestation – 35.0% vs. 41.0%, $p=0.006$ and PTB < 32 weeks' gestation – 11.3% vs. 15.9%, $p=0.005$).

Nine of 1,509 SNPs (<1%) failed and produced no calls; an additional 50 markers (3%) had p -values <0.01 on Hardy-Weinberg Exact testing and were excluded. Thus, 1,450 SNPs (96%) were included in this analysis. The average African ancestry across all markers was 82.5% (median 82.3%, range 78.3–87.9%). To illustrate how ancestry proportions are estimated, consider a single SNP, rs10488004. The minor allele, G, has a frequency of 0.14 in African-Americans and the major allele, A, has a frequency of 0.86. In contrast, for the same SNP, A is the minor allele in European-Americans (frequency = 0.28) and G is the major allele (frequency = 0.72). An individual carrying two copies of A at rs10488004 would be more likely to have inherited this allele because of recent African ancestry, while an individual who carries two copies of G would be more likely to have received it because of recent European ancestry. In practice, thousands of SNPs are used to derive an overall estimate of ancestry proportions.

LOD locus-genome scores were calculated for each SNP marker. Among the entire cohort of 177 women with a prior spontaneous PTB <37 weeks' gestation, 3 SNPs had suggestive LOD locus-genome scores (Table 1). All 3 SNPs correspond to the chromosome region of 7q21. When LOD scores are graphed by physical location in this region of chromosome 7, a distinctive gradual peak is seen (Figure 1). This area is suggestive of a PTB locus.

152 women had one or more spontaneous PTB <35.0 weeks' gestation. Among these women with earlier PTB, the signal strengthened and eight SNPs (all in the 7q21 and 7q22 chromosome region) had LOD scores >1.5; 4 of these LOD scores were >2.0. SNPs with LOD scores >1.5 are shown in Table 2 and chromosome location in Figure 2. Similar to the results for the entire cohort, a distinctive gradual peak is seen, suggestive of a PTB locus.

106 women had one or more spontaneous PTB <32.0 weeks' gestation. These women with the earliest prior spontaneous PTB had the strongest signal, with 15 SNPs with LOD scores >1.5; 6 of these LOD scores were >2.0 (Table 3). In this group with the most severe phenotype (<32.0 weeks' gestation), the majority of the significant results were again seen in the 7q21 and 7q22 region, however, four significant results corresponded to the region of 7q31, located directly adjacent to 7q22 (Figure 3). Again, the peak in Figure 3 represents an area of increased African ancestry in this group of women with very early preterm birth, and is suggestive of one or more PTB loci.

No other significant LOD scores were noted on any other chromosomes for the entire cohort or either of the earlier preterm birth groups.

Discussion

In this admixture mapping study of 177 African-American women with well-documented spontaneous PTB, we found chromosome 7q21 – 7q22 to be an area of potential PTB susceptibility loci. Importantly, the number of significant results increased as the clinical phenotype worsened; women with the earliest spontaneous PTB had the strongest signal in this region (Figures 1–3).

Emerging evidence supports the contribution of genetics to the pathogenesis and pre-disposition to spontaneous PTB. Spontaneous PTB is a complex phenotype and is unlikely to be a ‘single gene’ condition. Given the variation in rates of PTB with self-reported race/ethnicity, it is reasonable to conclude that some of these differences may be due to genetic factors (5). Though genetic differences between African-American and European-American women with spontaneous PTB have been pronounced in other studies, our current knowledge of the exact genetic variants that contribute to PTB is limited (14, 15). Typically, studies have focused on examining variation in specific candidate genes thought to be involved in the pathogenesis of PTB. However, it is clear that a significant knowledge gap exists, because even the strongest case-control studies report population attributable risks of less than 30% (28). One previous small study (examining only 61 ancestry informative markers) of PTB among African-American mothers found significant associations between PTB as a whole and PTB due to maternal hypertensive disorders (1). The authors concluded that more intensive investigations of admixture are needed to identify novel PTB susceptibility genes. Thus, studies such as this one have the potential to make significant contributions to the overall understanding of PTB pathogenesis by identifying different, under-studied genetic areas of interest.

Chromosome 7 in the region of 7q21 and 7q22 is a gene-rich area. While admixture mapping is unable to identify specific genes in this area which may contribute to spontaneous PTB among African-American women, several potential candidate genes are located in this region, including:

- metabolic genes such as:
 - CYP51A1 and CYP3A (cytochrome P450 family 51A1 and 3A)
- inflammatory/ immunomodulatory genes such as:
 - STEAP4 (tumor necrosis factor alpha induced protein 9)
 - TFPI2 (tissue factor pathway inhibitor 2)
 - PILRA and PILRB (paired immunoglobulin-like type 2 receptor alpha and beta)
- calcium regulation genes such as:
 - CALCR (calcitonin receptor)
 - CACNA2D1 (voltage dependent calcium channel alpha)
 - MYLC2PL (myosin light chain 2 precursor)
- collagen genes such as:
 - COL1A2 (alpha-2 type 1 collagen)
 - PCOLCE (procollagen C-endopeptidase enhancer)

Numerous other regulatory and signaling genes are encoded in this region, including zinc-finger proteins and adenosine triphosphate synthases.

Our population, with a median of approximately 82% African ancestry, is consistent with prior reports of other groups of admixed African-Americans (1, 29). Furthermore, the accuracy of self-reported race in our cohort was high; all of the self-identified African-Americans had at least 78.3% African ancestry. All women in this cohort had prospectively collected clinical outcomes and all 'index' PTBs permitting entry into the initial trial were documented and verified by trained researchers. We used a 'cutoff' locus-genome score of 1.5 to consider a marker 'suggestive' of a disease locus, more stringent than the cutoff of 1.0 used in other studies (27). Interestingly, as the analysis was restricted to include only the most 'severe' women (PTB <32 weeks gestation), we noted the strongest signals and the most suggestive and significant results, as illustrated in Figure 3. Additionally, we did not note any 'spurious' results or single SNP 'hits' in other areas of the genome.

The Illumina admixture panel utilized for this study is an established set of SNPs developed by leaders in the field of admixture mapping (Reich and Patterson) (30, 31). The targeted loci on this African-American admixture panel yields approximately 75% of the power for admixture mapping, equivalent to 300,000–1,000,000 loci that would be required for dense, non-specific whole genome scans (31).

It is possible that a few patients may have been excluded from the severe (PTB <35 and <32 weeks) cohorts due to the beneficial effects of 17OHPC, provided to 2/3 of women in the original trial. However, allowing the gestational age of the qualifying PTB (prior to enrollment in the Meis trial) to also classify a women as 'severe' likely minimized this effect.

These results are encouraging and help to isolate the general region of the genome that is different in African-Americans with spontaneous PTB. However, admixture mapping is not able to identify the specific gene or genes in this region that may contribute to spontaneous PTB. All, some, or none of the genes listed above may or may not be involved in the pathogenesis of spontaneous PTB in African-American women. Areas of the genome identified by admixture mapping require more in-depth analysis to isolate specific gene(s) of interest. Though we only found results on chromosome 7, due to the sample size limitations of this study, we cannot definitively exclude the contribution of genes on other chromosomes to the disparity in PTB rates between African- and European-Americans. Although a post-hoc power analysis would not be appropriate, Patterson, et al. estimates that for a population with 80% African ancestry (such as in this study), approximately 200 subjects are necessary to detect loci where the relative risk of disease due to an allele is 2.0 (16). Additionally, because specific genetic variants cannot be identified from admixture mapping, the study design does not permit us to directly assess gene-environment interactions which may confer additional risk to some women.

Future studies should confirm these results in other cohorts of women and should further examine this region of the chromosome using case-control methods to identify specific genetic variants associated with spontaneous PTB.

Acknowledgments

Source(s) of the work:

Supported by grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) [HD27860, HD36801, HD27917, HD21414, HD27861, HD27869, HD27905, HD34208, HD34116, HD21410, HD27915, HD34136, HD34210, HD34122, HD40500, HD40544, HD34116, HD40560, HD40512] and does not necessarily represent the official views of the NICHD or the National Institutes of Health.

The authors thank Allison Northen, MSN, RN, for protocol development and coordination between clinical research centers; Elizabeth Thom, PhD, and Sharon Gilbert, MS, MBA for protocol and data management and

statistical analysis; and Mark A. Klebanoff, MD, MPH, for protocol development and oversight. The authors would also like to thank Dr. Kathleen Jablonski (The George Washington University Biostatistics Center) for her assistance with the statistical analysis.

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Appendix

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Figure 1.

Logarithm of odds locus genome score graph for all 177 African-American women (one or more spontaneous preterm birth before 37 weeks of gestation) along chromosome 7. The y-axis corresponds to the logarithm of odds locus genome score, with values greater than 1.5 considered suggestive of disease. The x-axis represents the physical position along chromosome 7.

Figure 2.

Logarithm of odds locus genome score graph for 152 African American women with earlier spontaneous preterm birth (before 35.0 weeks of gestation) along chromosome 7. The y-axis corresponds to the logarithm of odds locus genome score, with values greater than 1.5 considered suggestive of disease, and values greater than 2.0 considered significant for disease. The x-axis represents the physical position along chromosome 7.

Figure 3.

Logarithm of odds locus genome score graph for 106 African-American women with very early spontaneous preterm birth (before 32.0 weeks of gestation) along chromosome 7. The y-axis corresponds to the logarithm of odds locus genome score, with values greater than 1.5 considered suggestive of disease, and values greater than 2.0 considered significant for disease. The x-axis represents the physical position along chromosome 7.

Table 1

Single Nucleotide Polymorphisms With Logarithm of Odds Locus Genome Scores Higher Than 1.50. Shown are results for all 177 women with one or more spontaneous preterm birth before 37.0 weeks of gestation.

SNP	Physical Position	LOD score *	Chromosome Location
Rs7802588	83132586	1.569	7q21
Rs7807771	84793614	1.577	7q21
Rs10488004	90402887	1.688	7q21

* Logarithm of odds locus genome score

Table 2

Single Nucleotide Polymorphisms With Logarithm of Odds Locus Genome Scores Higher Than 1.50. Shown are results for 152 women with one or more spontaneous preterm birth before 35.0 weeks of gestation.

SNP	Physical Position	LOD score *	Chromosome Location
Rs1322849	81726190	1.807	7q21
Rs7802588	83132586	1.987	7q21
Rs7807771	84793614	2.072	7q21
Rs10488004	90402887	2.332	7q21
Rs9784907	92591107	2.153	7q21
Rs6465387	92798711	2.109	7q21
Rs10256829	103276634	1.525	7q22
Rs6466115	105705623	1.549	7q22

* Logarithm of odds locus genome score

Table 3

Single Nucleotide Polymorphisms With Logarithm of Odds Locus Genome Scores Higher Than 1.50. Shown are results for 106 women with one or more spontaneous preterm birth before 32.0 weeks of gestation.

SNP	Physical Position	LOD score *	Chromosome Location
rs2790012	78354894	1.525	7q21
rs1322849	81726190	1.715	7q21
rs7802588	83132586	1.774	7q21
rs7807771	84793614	1.877	7q21
rs10488004	90402887	2.324	7q21
rs9784907	92591107	2.248	7q21
rs6465387	92798711	2.217	7q21
rs883403	98692629	1.526	7q22
rs10256829	103276634	2.042	7q22
rs6466115	105705623	2.161	7q22
rs17154865	107290240	2.085	7q22
rs1525200	108053867	1.965	7q31
rs10275038	111080977	1.718	7q31
rs12533049	113996284	1.761	7q31
rs2141360	120654124	1.677	7q31

* Logarithm of odds locus genome score