Racial disparity in maternal-fetal genetic epistasis in spontaneous preterm birth

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OBJECTIVE: To understand the differences in genetic interactions among tumor necrosis factor-alpha, interleukin-6 and their receptor gene variants between black and white patients in spontaneous preterm birth.

STUDY DESIGN: Maternal and fetal DNA (n = 1195) were collected from cases (preterm birth < 36 weeks' gestation; n = 448), controls (> 37 weeks' gestation; n = 747), and genotyped for single nucleotide polymorphisms in tumor necrosis factor-alpha, tumor necrosis factor receptor 1, and tumor necrosis factor receptor 2, interleukin-6, and interleukin-6 receptor loci. Multifactor dimensionality reduction analysis was used to test all single and multilocus combinations for the ability to predict pregnancy outcome.

RESULTS: In white patients, multilocus interactions in maternal DNA between single nucleotide polymorphisms at −7227 (interleukin-6), 22,215 (interleuki-6 receptor) and −3448 (tumor necrosis factor-alpha) was predictive of approximately 59.1% ($P < .02$; odds ratio, 2.3 [95% confidence interval = 1.6-3.4]) of pregnancy outcome. In white fetal DNA and black maternal DNA, no significant interactive models were observed. In black patients, the best epistatic model was in fetal DNA between single nucleotide polymorphisms at 17,691 (tumor necrosis factor-receptor 1) and at −3448 (tumor necrosis factor-alpha) and was predictive of pregnancy outcome 68.3% of the time ($P < .01$; odds ratio, 5.0 [95% confidence interval = 2.6-9.6]).

CONCLUSION: Analyses of multilocus interactions found/associated different models in black and white patients in both maternal and fetal DNA with preterm birth as outcome. Significant maternal-fetal interactions were not detected in either race.

Key words: African American women, gene-gene interactions, inflammatory cytokines, multifactor dimensionality reduction, prematurity rate, preterm delivery, white women

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The rate of preterm birth has been increasing by as much as 30% during the last 25 years; despite advances in medical care.[1-3] Understanding the causes and consequences of preterm birth is further complicated by disparity observed in the preterm birth rate among various racial groups. The rate changes have reflected an increasing trend in white preterm birth rates and a decreasing trend in black preterm birth rates over the last decade.[2] As of 2003 in the United States, black women had a significantly higher rate of preterm birth (18.4%) compared with white women (11.7%).[4,5]

Many of etiologic factors such as urogenital infections,[6-8] stress,[9,10] socioeconomic,[11] and behavioral issues contribute to the preterm birth rate disparity.[11-15] However, the specific pathophysiologic pathways that are operational in various exposure settings are still unclear. Genetic predispositions in preterm birth pathway candidate genes and gene-environmental interactions have been reviewed as a contributor of disparity in pregnancy outcome.[16-19] Although no direct evidence exists with regard to the functional contributions of genetic variants in pregnancy outcome; recent research has focused on elucidating the role of genetics in preterm birth and racial disparity.[20]

Differences between black and white women in many genetic variants and biomarkers has been reported.[20-25] Tumor necross factor-alpha (TNF-α) and interleukin-6 (IL-6) demonstrated differential immune response in vitro in fetal membranes and in vivo in amniotic fluid in preterm births suggests discrepancy in pathways that lead to preterm birth in each race. Overwhelming TNF-α response and an imbalance between its regulators (soluble and membrane receptors) that may promote TNF-α bioactivity was seen in black preterm births. In contrast, TNF-α response was balanced in white preterm births. Elevated IL-6 was associated with preterm birth in white women (odds ratio [OR], 5.68; 95% confidence interval [CI] = 2.15-15.0) but not in black women. Ge-

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TABLE 1
Demographic characteristics of cases and controls in white and black patients

Variable	Black patients (n = 267)			White patients (n = 360)		
	Cases (n=76) Mean or Median	Controls (n=191) Mean or Median	*P* value[a]	Cases (n=166) Mean or Median	Controls (n=194) Mean or Median	*P* value[a]
Prepregnancy BMI	25.8 [6-5][b]	26.9 [17-56]	.421	25.1 [16-72]	24.4 [15-45]	.06
Pregnancy BMI	32.2 [21-53]	36.6 [21-61]	.141	29.9 [19-73]	30.1 [18-50]	.5
School/Education (y)	12 [6-12]	12 [6-12]	.218	12 [7-12]	12 [7-12]	.002
Gravidity	2 [1-6]	2 [1-13]	.962	2 [1-9]	2 [1-8]	.02
Gestational age (d)	242.5 [154-255]	273 [257-290]	<.001	239 [166-255]	274 [257-296]	<.001
Birthweight (g)	2240 [462-3782]	3190 [1952-4517]	<.001	2150 [370-3790]	3446 [2100-4661]	<.001
Apgar 1	8 [1-9]	8 [3-9]	<.001	8 [1-9]	8 [4-9]	<.001
Apgar 5	9 [6-10]	9 [7-10]	<.001	9 [1-9]	9 [7-10]	<.001
Maternal age (y)	25.3 (5.5)[c]	25.2 (5.2)	.884	27.3 (6.296)	28.3 (5.8)	.1

Brackets = interquartile range; parentheses = standard deviation.

[a] *P* value Mann-Whitney 2-sample rank sum tests analysis comparing cases with controls.

[b] [ ]-interquartile range.

[c] ( )-standard deviation.

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netic differences between black and white preterm births in these genes may partially explain these observations.[24-26] In addition, higher amniotic fluid IL-6 concentration in white preterm births was associated with the IL-6 single nucleotide polymorphism (SNP) at −661 and this result seems to be driven by microbial invasion of the amniotic cavity, suggesting a gene environmental interaction. Such an association was not seen in black preterm births. In addition, SNP analysis documented significant differences between black and white preterm births at allelic, genotypic, and haplotype frequencies.[25,26]

We hypothesize that observed rate disparity in preterm birth rates between black and white women is due to differences in interactions between variants of these preterm birth pathway candidate genes. The objective of this study is to understand the differences in gene-gene interactions (epistasis) among TNF-α and IL-6 and their receptor genes (TNF receptor 1 and 2 [TNFR1 and TNFR2] and IL-6 receptor) based on our in vitro and in vivo findings.

Materials and Methods

This study was approved by the institutional review boards at TriStar, the parent company institutional review board of record for Centennial Women's Hospital, and at Vanderbilt University. Subjects were included in this study after obtaining written consent. All subjects were recruited at Centennial Women's Hospital in Nashville, TN, between Sept. 2003 and Dec. 2006.

Subject recruitment

Pregnant women between the ages of 18-40 years presenting to Centennial Women's Hospital, Nashville, TN, for delivery between Sept. 2003 and June 2006 were eligible. All subjects had contractions (defined as the presence of regular uterine contractions at a minimum frequency of 2 contractions every 10 minutes) that led to delivery. Race was identified by self-report from a set of provided choices and determined by the race of the mother and father of the fetus, their parents and grandparents.[24-27] Subjects of mixed race were excluded from the study. We define mixed race as the presence of more than 1 racial group in the parents and/or grandparents of the mother or father of the infant. Only black and white women of non-Hispanic origin were included. Gestational age was determined by last menstrual period dating and corroborated by ultrasound dating. Patients who delivered preterm (between $22^{0/7}$ weeks and $36^{0/7}$ weeks) were included as cases. We have excluded cases between $36^{1/7}$ and $36^{6/7}$ weeks to minimize overlap between cases and controls. Controls included women with term labor and delivery ($> 37^{0/7}$ weeks) who had intact membranes and no pregnancy-related complications. Subjects with multiple gestations, preeclampsia, placental previa, fetal anomalies, and/or medical (such as gestational diabetes mellitus)/surgical complications of pregnancy were excluded. Subjects who had any surgical procedures during pregnancy or who were treated for preterm labor or for suspected intraamniotic infection and delivered at term were excluded from the control group; but those who were treated and delivered preterm were included as cases.

Demographic characteristics

Our sample included a total of 1195 birth events that includes maternal and fetal DNA samples (448 preterm labor delivered preterm and 747 controls delivered at term).

DNA sampling and genotyping

DNA was isolated from maternal and cord blood (using the Autopure auto-