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Association of genetic ancestry with preterm delivery and related traits among African American mothers

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Abstract

OBJECTIVE—In the United States, the rate of preterm delivery (PTD) is higher in African Americans (17.8%) than non-Hispanic whites (11.5%). Such disparity cannot be fully explained by differences in socioenvironmental factors.

STUDY DESIGN—We genotyped 812 mothers in a case-control PTD study at Boston Medical Center who self-reported their ethnicity as “black.” Regression analysis and Wilcoxon rank-sum test were applied to evaluate ancestral distribution and the association between genetic ancestry and PTD-related traits, as well as the potential confounding effect of population stratification.

RESULTS—The estimated African ancestral proportion was 0.90 ± 0.13 . We found significant associations of ancestral proportion with PTD as a whole and PTD subgrouped by the presence of maternal hypertensive disorders. We did not observe significant confounding as a result of population stratification in this case-control PTD study.

CONCLUSION—Our data underline the need for more intensive investigation of genetic admixture in African Americans to identify novel susceptibility genes of PTD.

Keywords

admixture; genetic ancestry; population stratification

Preterm delivery (PTD) (< 37 weeks of gestation) remains a significant clinical and public health problem. The rate of PTD is high in the United States at about 12.5%¹ and has increased in the past 2 decades.² PTD threatens all ethnic groups, particularly African American women (17.8% compared with 11.5% in non-Hispanic whites).¹ However, socio-demographic risk factors cannot fully explain the racial disparity found in PTD. Compelling evidence suggests that PTD is a complex disease influenced by multiple genetic and

environmental factors and gene-environment interactions.^{1,3,4} However, the role of the genetic influence in PTD remains largely unexplored.

The contemporary African American population is recognized as an admixed population with genetic admixture between Africans and Europeans.⁵ The ethnic definition of African Americans in most PTD studies is based on self-reported ethnicity. Recently, genetic ancestry among African Americans can be estimated by applying advanced statistical methods using a set of ancestry informative markers (AIMs).^{6–9} The degree of estimated European admixture among African Americans has previously been reported between 3.5–25%.^{5,10}

Accurate assessment of genetic ancestry is important for several reasons. First, self-reported ethnicity, which has been a surrogate of individual's ancestral background, may not sufficiently capture genetic variations. This may lead to inadequate adjustment for potential population stratification confounding when studying genetic association of PTD in admixed populations. Alternatively, the use of individual ancestral estimates (IAEs) may more precisely predict individual genetic ancestral variation to disease outcomes.¹¹ Specifically, ancestral information cannot only provide a validation on how well self-reported ethnicity corresponds to ancestral proportion as estimated by AIMs, but it also can be used to evaluate differences in ancestral proportion between cases and controls in genetic association studies. It may also offer the opportunity to assess whether different ethnic definitions (self-report vs ancestral proportion estimate) alter the pattern or associations in epidemiologic and/or genetic studies.

Second, although racial disparities in PTD have been observed for decades, the role of genetic ancestry in PTD among African Americans has remained under investigation. Ancestral information provides a potential opportunity for mapping novel susceptibility genes in diseases with marked ethnic disparity that cannot be fully explained by socioeconomic and/or environmental factors.¹² This approach, known as admixture mapping, has successfully identified candidate regions related to disease of interest, including multiple sclerosis and prostate cancer.^{13–15}

Third, population stratification confounding has been a main concern in case-control genetic association studies in admixed populations, such as African Americans and Latino Americans.^{16,17} Population stratification occurs when there are different allele frequencies between cases and controls as a result of heterogeneity in ancestry, which is unrelated to disease's affection status. Ignoring population stratification in association tests may lead to a potential excess of false-positive and/or false-negative results.^{18,19} With ancestral information, we can evaluate the degree of confounding effect caused by population stratification and apply such information to detect and control for the potential confounding effect.

In this study, we genotyped a panel of 61 AIMs and used 57 of the 61 AIMs to estimate genetic ancestry in 812 mothers enrolled in an ongoing case-control study of PTD at the Boston Medical Center (BMC), who self-reported their ethnicity as "black." We sought to address 3 issues. First, we estimated genetic ancestral proportion by using AIMs data and evaluated whether there was a difference in ancestral proportion between cases and controls. Second, we investigated whether genetic ancestral background was associated with PTD and with pre-term subgroups. Finally, we assessed whether ancestral proportion confounded the association tests between 3 candidate genes (*F5* factor, *CYP11A1*, and *GSTT1*) and PTD.

Materials and Methods

Study population and data collection

In this study, we included the first 812 black mothers (326 preterm cases and 486 matched controls) enrolled in an ongoing case-control study of preterm birth at the BMC.²⁰ Case mothers were those who delivered singleton, live births occurring at < 37 weeks of gestation, and controls were defined as mothers delivering at ≥ 37 weeks of gestation with birthweight appropriate for gestational age as defined by the National Center for Health Statistics/Centers for Disease Control and Prevention guidelines (birthweight 2500–4000 g).²¹ Pregnancies resulting in multiple births and newborns with major birth defects were excluded. Control subjects were matched by race, maternal age, and date of delivery for each case delivery. Detailed description of the study population was published previously.²⁰ Briefly, we collected epidemiologic data, clinical data, and maternal venous blood samples. In addition, placentae were sent for histopathology based on routine indications, including preterm birth.²² The institutional review boards of the BMC, the Massachusetts Department of Public Health, the Chicago Children's Memorial Hospital, and the Harvard School of Public Health approved the study protocol. All participants gave written informed consent.

Definition of phenotypes

PTD was evaluated as both binary (< 37 weeks of gestation vs ≥ 37 weeks of gestation) and continuous (gestational age) variables. Gestational age was assessed using an algorithm based on last menstrual period and the result of early ultrasound (< 20 weeks of gestation). The last menstrual period estimate was used only if confirmed by ultrasound within 7 days or if no ultrasound estimate was obtained; otherwise, the ultrasound estimate was used. This approach has been used in previous studies.^{20,23}

PTD subgroups investigated in this study were defined as follows. (1) By mode of delivery: we categorized PTD cases as spontaneous PTD (vaginally or by cesarean section) that occurred secondary to documented active preterm labor (uterine contractions with cervical effacement and dilation at < 37 weeks), preterm premature rupture of membranes (< 37 weeks without uterine contractions), or by both uterine contractions and preterm premature rupture of membranes occurring simultaneously or as medically induced PTD defined as delivery (vaginally or by cesarean section) that was not preceded by the presence of uterine contractions and/or rupture of membranes. (2) By degree of prematurity: in this study, we used a cut point of < 32 weeks to define very PTD and 34.0–36.86 weeks to define late PTD, which has been used by other groups.^{24,25} (3) By major pregnancy complications: because of sample size constraints, we focused on 2 relatively common pregnancy complications: (a) PTD with intrauterine infection/inflammation using placental histologic chorioamnionitis as a proxy—detailed description on placental collection, pathological methods, definition of maternal and fetal inflammatory responses, and quality control was published previously²² and (b) PTD complicated by maternal hypertensive disorders—this group consisted of PTD cases with an accompanying diagnosis of maternal preeclampsia, eclampsia, gestational hypertension, or HELLP syndrome as defined in our previous publication,²⁶ with or without a history of chronic hypertension.

Selection and genotyping of AIMs

Selection—We selected and genotyped a panel of 61 AIMs with averaged δ (difference of allele frequencies between African and European ancestral populations) equal to 0.54 in 812 black mothers. Detailed information of the 61 AIMs regarding chromosomal location, allele frequencies among different ancestral populations, and difference of allele frequencies between different ancestral populations is provided in Supplemental Table S1. Polymorphic

site, flanking sequence, and other relevant information of these 61 AIMs are available elsewhere.²⁷

Genotyping

DNA was extracted from samples of venous whole blood using a standard protocol.²⁸ Genotyping was performed using the TaqMan genotyping assay (Applied Biosystems, Foster City, CA). Polymerase chain reaction was performed in a 5- μ L reaction containing 10 ng of genomic DNA, 1 $\times$ master mix, 900 nmol/L primers, and two 250 nmol/L TaqMan MGB probes by use of 384-well plates on a PTC-225 Tetrad Thermal Cycler (MJ Research, Waltham, MA) under the following conditions: 95°C for 10 minutes, 50 cycles of 92°C for 15 seconds, and 60°C for 1 minute. After polymerase chain reaction, an endpoint plate read of the fluorescence intensity of each well was performed on an ABI Primer 7900 (Applied Biosystems). Genotypes were called automatically using SDS, version 2.1 (Applied Biosystems) and were inspected visually on the plot.

Statistical analyses

Before data analysis, we computed genotype frequencies of the 61 AIMs and examined whether genotype frequencies of each marker were under Hardy-Weinberg equilibrium (HWE) by using exact tests implemented in the single nucleotide polymorphism-HWE program (<http://www.sph.umich.edu/csg/abecasis/Exact/index.html>).²⁹

To estimate individual admixture, we first retrieved the available data of these 57 AIMs of subjects inherited from African and European ancestral populations (90 Yoruba subjects and 90 CEPH subjects) from the International HapMap Project (<http://www.hapmap.org/>). We then applied an admixture model implemented in the Structure program (<http://pritch.bsd.uchicago.edu/software.html>) using the AIMs data obtained from Hap-Map Project and the 812 African American mothers.^{30,31} Specifically, the admixture model in Structure assumes that each individual inherits some proportion of his or her ancestry from each ancestral population. To compute IAEs, we input genotyping data from both ancestral populations (Africans and Europeans), specified as known populations, and admixed subjects, specified as an unknown population; we assumed an admixture model and used default values for other parameters by Structure with 5000 burn-in and 50,000 further iterations through the Markov chain Monte Carlo algorithm implemented in the Structure program. In addition, to examine whether the distribution of genetic ancestry was similar between cases and controls, a nonparametric approach, the Wilcoxon rank-sum test, was applied because of the skewness of the distribution of individual ancestral proportions.

To examine the impact of genetic ancestry on PTD and related traits, we applied multiple logistic and linear regression models, separately, to test the association between IAEs and PTD-related phenotypes after adjusting covariates. Specifically, we recoded genetic ancestry into 4 groups (first quartile, second plus third quartiles, and fourth quartile of African ancestral proportion) and treated genetic ancestry as an ordinary variable in the model. Trend tests were performed to examine the associations between genetic ancestry and PTD and related traits as well. To evaluate a potential excess of false-positive and false-negative results, multiple logistic and linear regressions were carried out, separately, to test the association of 3 susceptibility genetic polymorphisms (*F5*, *CYP1A1*, and *GSTT1*) with PTD and gestational age, individually, with and without the adjustment of genetic ancestry—specifically, African IAEs.

The covariates adjusted in the analyses included: maternal age (< 20, 20–24, 25–29, 30–34, and $\geq$ 35 years), education ($\leq$ middle school, high school, and > high school), parity (0, 1, and $\geq$ 2), marital status (married, other), maternal prepregnant body mass index (< 20, 20–

24, 25–29, and ≥ 30), maternal smoking during pregnancy (never, quitter, and persistent), alcohol use (yes/no), illicit drug use (yes/no), and infant sex. Data analyses were performed using statistical packages R 2.3.1 (<http://www.r-project.org>) and Intercooled STATA 8.0 (Stata Corp, College Station, TX).

Results

Demographic characteristics and genetic ancestral estimation in BMC cohort

A total of 812 African American mothers (326 with PTD, and 486 with full-term delivery) were included in this study. The demographic characteristics and clinical data are shown in Table 1. The distributions of age, maternal prepregnant body mass index, education, parity, marital status, passive smoking during pregnancy, alcohol use, and infant sex were similar in both groups (Table 1). The rates of maternal smoking during pregnancy and illicit drug use were higher among the PTD cases.

In all, 61 AIMs were genotyped in this study; 4 of 61 AIMs deviated from HWE (Supplemental Table S1) and were excluded in the subsequent analysis. We next applied the Structure program to estimate individual ancestry using the remaining 57 AIMs data. We observed that the average and corresponding SE of African proportion were 0.91 ± 0.13 , 0.91 ± 0.12 , and 0.90 ± 0.13 for all subjects, PTD cases, and controls, respectively. In addition, the results from the Wilcoxon rank-sum test indicated that the distributions of ancestral proportions were only slightly different between PTD cases and controls ($P = .05$; Figure).

Associations between genetic ancestry and PTD and related traits

We examined the associations between IAEs and PTD and related traits with and without the adjustment of covariates. As shown in Table 2, significant associations were found for PTD and related traits, including spontaneous PTD, very PTD, and PTD with maternal hypertensive disorders, respectively. In detail, when comparing subjects in the first quartile of African ancestral proportion (bottom 25%), subjects in the second or third quartile had an increased risk of PTD (odds ratio [OR], 1.5; 95% confidence interval [CI], 1.1–2.2), medically induced PTD (OR, 2.1; 95% CI, 1.1–3.8), near-term PTD (OR, 1.6; 95% CI, 1.0–2.5), and PTD with maternal hypertensive disorders (OR, 2.4; 95% CI, 1.3–4.6). Likewise, subjects in the top 25% distribution of African ancestral proportion had an increased risk of PTD (OR, 1.7; 95% CI, 1.1–2.7), spontaneous PTD (OR, 1.7; 95% CI, 1.1–2.8), very PTD (OR, 2.1; 95% CI, 1.1–4.2), and PTD with maternal hypertensive disorders (OR, 2.2; 95% CI, 1.1–4.5). Moreover, the results from trend test in Table 2 also suggested significant associations of ancestral proportion with PTD ($P = .03$) and PTD with maternal hypertensive disorders ($P = .01$).

Evaluation of potential population stratification confounding effect

To evaluate potential confounding effect caused by population stratification, we examined the associations between 3 PTD candidate genes (*F5*, *CYP1A1*, and *GSTT1*) and PTD and gestational age, separately, with the adjustment of covariates only, and with the adjustment of both covariates and genetic ancestry, respectively. Our data showed that the association results were almost identical with or without adjustment for genetic ancestry (Table 3). In other words, we did not observe an excess in false-positive or false-negative results and did not find significant confounding effect caused by population stratification.

Comment

It has been long observed that the highest rates of PTD in the United States occur among racial minorities, especially African Americans (17.8%). Although the impact of genetic ancestry and its potential confounding effect have been examined in several common complex diseases, such as asthma, breast cancer, and cardiovascular disease, none of the previous studies has assessed the influence of genetic ancestry in PTD and related traits. This study is the first to evaluate whether genetic ancestry is associated with PTD and related traits and whether genetic ancestry may confound association tests of candidate loci with PTD and related traits. Several important findings have been observed in this study.

First, the average estimates of European ancestry were 9.5% in this sample of African American mothers recruited from BMC. The estimates in the study sample were comparable with those reported in previous studies, ranging from 3.5–25%.^{5,32} For instance, Parra et al⁵ in 1998 reported 12% European ancestry estimated from African Americans residing in Charleston, SC, whereas Wassel Fyr et al³³ reported 25% European ancestry estimated from African Americans residing in Pittsburgh, PA. Our results have supported that genetic admixture occurs among contemporary African American populations across different regions of the United States.^{11,34} On the other hand, our results have also suggested high consistency between self-reported ethnicity as “black” and African ancestral background as estimated by AIMs in this sample.

Of note, the accuracy of estimating individual ancestry is affected by the number of AIMs, and the informativeness of AIMs. In this study, we estimated individual ancestry using a set of 57 AIMs with averaged δ equal to 0.54. To assess whether the number and corresponding informativeness of AIMs were sufficient for ancestral estimation, we calculated IAEs by using the first 30, the first 45, and all 57 AIMs, separately. The results in Supplemental Table S2 indicated that IAEs obtained from using ≥ 45 AIMs in estimation were highly similar. This suggested that the potential computing inaccuracy in estimating genetic ancestry may be avoided while genotyping and incorporating a set of ≥ 45 AIMs with averaged $\delta \geq 0.5$. However, previous studies have reported that when sample size of admixed subjects increases, more numbers and more informativeness of AIMs are required for precisely estimating individual ancestry and efficiently controlling for excess of type I error.^{35,36} Therefore, the number of AIMs for precise ancestral estimation should be carefully selected.

Our results suggested that African ancestry was associated with an increased risk of PTD and related traits in African American mothers. Specifically, subjects with higher African ancestry had a higher risk in developing PTD. Furthermore, African ancestry was also associated with PTD subgroups, such as spontaneous PTD, very PTD, and PTD complicated by maternal hypertensive disorders. Consistently, previous studies also reported higher prevalence of spontaneous PTD, very PTD, and PTD complicated by maternal hypertensive disorders among African American mothers than other ethnic groups.^{37,38} Taken together, our findings that subjects carrying higher African ancestral background had a higher risk of developing PTD and certain preterm subgroups lend further support for future studies to conduct admixture mapping of PTD in African Americans.

Admixture mapping has been considered to be a promising method to search for susceptibility genes in a genome scale for complex diseases in admixed populations such as African Americans.³⁹ Suitable diseases for admixture mapping approach are those with marked ethnic disparity that cannot be fully explained by socioeconomic and/or environmental factors. As such, this approach may be a useful tool in determining novel susceptibility genes associated to PTD and related traits.

From an epidemiologic standpoint, great attention has been drawn to whether genetic ancestral estimates can more precisely capture genetic variation than self-reported race.^{40,41} We performed association tests in African American subjects with and without adjusting genetic ancestral proportion. The results were highly consistent in the association tests for 3 candidate genes of PTD. In addition, we also performed the association tests between 57 AIMs and PTD. Similarly, inflation of type I error was not observed in those results (data not shown). Our data supported the findings reported previously that population stratification confounding could be overcome by well-matched case-control study design when conducting genetic association studies in admixed populations.^{16,42,43} Although we did not observe detectable population stratification confounding effect in this study, as mentioned above, when sample size of admixed subjects increases, more numbers and more informativeness of AIMs are required to make the appropriate correction.³⁶

In summary, the estimated average African ancestral proportion was approximately 90% in this BMC sample of African American mothers who self-reported their ethnicity as “black.” Our data did not show a substantial confounding effect caused by population stratification in genetic association tests with PTD. Novel associations were found between African ancestry and PTD as a whole and certain preterm subgroups. The findings have provided strong support for further conducting more intensive investigation of genetic admixture in African Americans, including genome-wide admixture mapping to dissect PTD-related susceptibility genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE.

Distribution of African ancestral proportion in cases and controls

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TABLE 1

Demographic and clinical characteristics of African American mothers, by preterm status

Characteristic	PTD (n = 326)	Control (n = 486)
Demographic characteristics		
Age (y)	28.8 ± 6.8	27.9 ± 6.7
BMI (kg/m ²)	26.7 ± 6.7	26.0 ± 6.1
Education (%)		
≤ Middle school	27.3	29.0
High school	40.5	32.5
> High school	32.2	38.5
Infant sex (%)		
Male	51.5	54.3
Female	48.5	45.7
Parity (%)		
0	37.7	36.2
1	26.4	32.3
≥ 2	35.9	31.5
Marital status (%)		
Married	29.8	36.8
Other	70.2	63.2
Maternal smoking during pregnancy (%)		
Never	75.3	82.7
Quitter	5.6	4.8
Persistent	19.1	12.5
Passive smoking during pregnancy (%)		
No	71.6	77.9
Yes	28.4	22.1
Alcohol use (%)		
No	95.7	96.1
Yes	4.3	3.9
Illicit drug use (%)		
No	84.1	88.3
Yes	15.9	11.7
Clinical characteristics		
Gestational age (wk)	33.1 ± 3.7	39.7 ± 1.0
Infant birthweight (g)	2024.2 ± 762.7	3159.6 ± 551.4

BMI, body mass index; PTD, preterm delivery.

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TABLE 2

Associations between African ancestry and preterm delivery and preterm subgroups

Preterm traits	Crude		Adjusted ^a	
	OR (95% CI)	P	OR (95% CI)	P
PTD				
First quartile	Ref		Ref	
Second + third quartile	1.4 (1.0–2.0)	.05	1.5 (1.1–2.2)	.04 ^b
Fourth quartile	1.6 (1.1–2.3)	.03 ^b	1.7 (1.1–2.7)	.01 ^b
Trend test		.03 ^b		
SPONTANEOUS PTD				
First quartile	Ref		Ref	
Second + third quartile	1.3 (0.9–2.0)	.15	1.3 (0.9–2.0)	.22
Fourth quartile	1.5 (1.0–2.4)	.07	1.7 (1.1–2.8)	.03 ^b
Trend test		.07		
MEDICALLY INDICATED PTD				
First quartile	Ref		Ref	
Second + third quartile	2.0 (1.1–3.7)	.03 ^b	2.1 (1.1–3.8)	.02 ^b
Fourth quartile	1.9 (1.0–3.9)	.06	1.9 (0.9–3.8)	.09
Trend test		.06		
VERY PTD				
First quartile	Ref		Ref	
Second + third quartile	1.3 (0.8–2.3)	.33	1.4 (0.8–2.6)	.29
Fourth quartile	1.7 (0.9–3.2)	.08	2.1 (1.1–4.2)	.03 ^b
Trend test		.08		
NEAR-TERM PTD				
First quartile	Ref		Ref	
Second + third quartile	1.6 (1.1–2.5)	.03 ^b	1.6 (1.0–2.5)	.04 ^b
Fourth quartile	1.5 (0.9–2.4)	.12	1.5 (0.9–2.6)	.13
Trend test		.12		
PTD WITH MATERNAL HYPERTENSIVE DISORDER				
First quartile	Ref		Ref	
Second + third quartile	2.4 (1.3–4.5)	.006 ^b	2.4 (1.3–4.6)	.007 ^b

Preterm traits	Crude		Adjusted ^a	
	OR (95% CI)	P	OR (95% CI)	P
Fourth quartile	2.5 (1.2–4.9)	.009 ^b	2.2 (1.1–4.5)	.03 ^b
Trend test		.01 ^b		
PTD ACCOMPANIED BY HISTOLOGIC CHORIOAMNIONITIS				
First quartile	Ref		Ref	
Second + third quartile	1.0 (0.6–1.6)	.89	1.1 (0.6–1.9)	.72
Fourth quartile	1.2 (0.7–2.1)	.55	1.2 (0.6–2.2)	.65
Trend test		.54		
	β (SE)	P	β (SE)	P
GEAA (WK)				
First quartile	Ref		Ref	
Second + third quartile	−0.40 (0.35)	.24	−0.44 (0.38)	.24
Fourth quartile	−0.60 (0.40)	.13	−0.86 (0.45)	.05
Trend test		.10		

CI, confidence interval; GEAA, gestational age; OR, odds ratio; PTD, preterm delivery; Ref, reference group.

^a Adjusted for maternal age, education, parity, marital status, prepregnant body mass index, maternal smoking during pregnancy, drug use, alcohol use, and infant sex;

^b $P < .05$.

Tsai. Association of genetic ancestry with preterm delivery and related traits among African American mothers. Am J Obstet Gynecol 2009.

Associations of genetic polymorphisms with preterm delivery and length of gestation in 812 African Americans, with and without adjustment of African ancestral proportion

TABLE 3

Variable	PTD (< 37 wk)			Gestational age		
	Unadjusted AIMS		Adjusted AIMS	Unadjusted AIMS		Adjusted AIMS
	OR (95% CI)	P	OR (95% CI)	β (SE)	P	β (SE)
F5 gene (rs6019)						
GG	1.0	—	1.0	—	Ref	—
GC	1.3 (1.0–1.8)	.10	1.3 (0.9–1.8)	.11	–0.5 (0.3)	–0.4 (0.3)
CC	1.8 (1.2–2.8)	.01 ^a	1.7 (1.1–2.7)	.02 ^a	–1.5 (0.4)	–1.4 (0.4)
CYP1A1 Msp I						
AA	1.0	—	1.0	—	Ref	—
Aa/aa	0.9 (0.7–1.3)	.68	0.9 (0.7–1.3)	.73	0.4 (0.3)	0.4 (0.3)
GSTT1						
Present	1.0	—	1.0	—	Ref	—
Delete	0.8 (0.6–1.1)	.18	0.8 (0.6–1.1)	.19	0.6 (0.4)	0.6 (0.4)

All analyses were adjusted for maternal age, education, parity, marital status, prepregnant body mass index, maternal smoking during pregnancy, drug use, alcohol use, and infant sex. *AIM*, ancestry informative markers; *CI*, confidence interval; *OR*, odds ratio; *PTD*, preterm delivery; *Ref*, reference group.

^a *P* < .05.

Tsai. Association of genetic ancestry with preterm delivery and related traits among African American mothers. Am J Obstet Gynecol 2009.