REVIEW ARTICLES

Genetic Contributions to Disparities in Preterm Birth

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ABSTRACT: Ethnic disparity in preterm delivery between African Americans and European Americans has existed for decades, and is likely the consequence of multiple factors, including socioeconomic status, environment, and genetics. This review summarizes existing information on genetic variation and its association with preterm birth in African Americans. Candidate gene-based association studies, in which investigators have evaluated particular genes selected primarily because of their potential roles in the process of normal and pathologic parturition, provide evidence that genetic contributions from both mother and fetus account for some of the disparity in preterm births. To date, most attention has been focused on genetic variation in pro- and anti-inflammatory cytokine genes and their respective receptors. These genes, particularly the pro-inflammatory cytokine genes and their receptors, are linked to matrix metabolism because these cytokines increase expression of matrix degrading metalloproteinases. However, the role that genetic variants that are different between populations play in preterm birth (*e.g.* the *SERPINH1* - G56 SNP) cannot yet be quantified. Future studies based on genome wide association or admixture mapping may reveal other genes that contribute to disparity in prematurity. (*Pediatr Res* 65: 1–9, 2009)

Preterm birth, defined as delivery before 37 wk of gestation, accounts for about 70% of all neonatal morbidity and mortality (1). In 2005, the incidence of preterm delivery among African Americans and European Americans in the United States was 18.4 and 11.7%, respectively (2). This ethnic disparity in preterm delivery between African Americans and European Americans has existed for decades.

Approximately, one third of all preterm births are indicated with the remaining two third being spontaneous. Preterm premature rupture of membranes (PPROM), which accounts for one third of all spontaneous preterm births (3,4), is more likely to precede spontaneous preterm delivery in African Americans than in European Americans (5).

RISK FACTORS FOR PRETERM BIRTH AND ETHNIC DISPARITIES

There are multiple potential risk factors for prematurity including education level, income, physical environment, and

marital status. These factors impact birth outcomes in ethnic subgroups differently (6–11).

The association between cigarette smoking or illicit drug use and preterm delivery is well established. Notably, African American women do not engage in high-risk behaviors, such as cigarette smoking, alcohol and illicit drug use, at a higher rate than European Americans (5,12–14).

Deficiency of iron, folic acid, and vitamin D during pregnancy may increase the risk for a preterm delivery and differences in nutritional status are likely contributors to ethnic/racial disparities in prematurity. African American women are more likely than European Americans to be anemic during pregnancy (15). African American women are also more likely to have lower serum and red blood cell folate concentrations (16). More African American women are vitamin D deficient compared with European American women (17). Poor weight gain during pregnancy has been associated with prematurity and low birth weight (18). African American women are more likely than European Americans to gain inadequate weight during pregnancy (5). Conversely, obesity is independently associated with preterm birth and more African American women have a prepregnancy weight of 200 pounds or more compared with European Americans (19).

Disparities in birth outcomes between African Americans and European Americans in the United States have been attributed, in part to delayed, and inadequate, utilization of prenatal care. However, studies conducted in military settings, where both groups have approximately equal healthcare access, have shown higher preterm birth rate among African Americans (20,21). In other studies, African American women who initiated prenatal care in the first trimester still had higher rates of infant mortality than European American women with late prenatal care (22).

The studies summarized above provide evidence that socioeconomic indicators, nutrition and the environment significantly impact birth outcomes among different ethnic groups, and can contribute, at least in part, to the disparity in preterm birth rates between African Americans and European Americans.

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Abbreviations: LD, linkage disequilibrium; MMP, matrix metalloproteinase; PPROM, preterm premature rupture of membranes; SNP, single nucleotide polymorphism

EPIDEMIOLOGIC EVIDENCE CONSISTENT WITH GENETIC CONTRIBUTIONS TO PRETERM BIRTH

Epidemiologic studies that have included diverse populations are consistent with the notion that genetic factors contribute to disparate rates of prematurity. Adams *et al.* (23) reported a higher rate of a second preterm delivery after a first pregnancy that ended in a spontaneous preterm delivery in African Americans than in European Americans. Both maternal and paternal ethnicities are significant contributors (24). Palomar *et al.* (25) reported an increase in risk of preterm delivery at less than 35 wk of gestation if the mother is European American and the father is African American (odds ratio [OR] = 1.28, 95% confidence interval [CI] 1.13–1.46). Using a United States natality cohort of over 2.8 million singleton births, Simhan *et al.* (26) also reported similar findings. On the basis of the timing of preterm births, and the overrepresentation of preterm births in African American mothers, Kistka *et al.* (27) concluded that genetic factors have a greater etiologic role in prematurity than previously thought.

CANDIDATE GENES AND INCREASED RISK FOR PREMATURE DELIVERY IN AFRICAN AMERICANS

Evidence that genetic factors contribute to preterm birth derives mainly from the association of prematurity with single gene defects (28,29). These rare mutations (*e.g.* those causing Ehlers-Danlos syndrome) make only minor contributions to preterm birth, and do not account for ethnic disparities.

Evidence for genetic contributions to the disparity in preterm birth among ethnic groups comes from candidate gene-based association studies, in which investigators have evaluated particular genes selected primarily because of their potential roles in the process of normal and pathologic parturition. These genes fall into two major groupings including those involved 1) in the host response to infection/inflammation, and 2) those involved in the synthesis and degradation of the extracellular matrix. Candidate genes potentially involved in decidual hemorrhage and activation of uterine contractility have not been investigated in any detail. To date, most attention has been focused on genetic variation in pro- and anti-inflammatory cytokine genes and their respective receptors. These genes, particularly the pro-inflammatory cytokine genes and their receptors, are linked to matrix metabolism because these cytokines increase expression of matrix degrading metalloproteinases.

There are a number of obstacles to pursuing genetic studies on preterm birth. Common conditions like preterm birth are generally influenced by multiple genes. Moreover, the genetics of complex traits do not obey classical Mendelian laws as the impact of these genes is greatly influenced by environmental factors. Additionally, there must be consideration of both the maternal and fetal genetic background, which may independently confer risk of prematurity, or may have synergistic interactions. Recent advances in genome technology and in the corresponding knowledge about the human genome and genetic variation across populations have greatly changed how we can look for genes contributing to complex diseases. A better understanding of relationships among genetic markers,

facilitated by the International Haplotype Map (www.hapmap.org) project, allows genome-wide association studies to be carried out in which large numbers of genetic markers are screened in large samples of patients and unaffected controls. Once population stratification has been controlled (*i.e.*, exclusion of significant differences in ethnic/racial compositions of the control and case groups, which could produce spurious finding because of varying allele frequencies among different racial/ethnic populations that are not associated or linked to the condition under investigation), association between a trait and a genetic marker indicates very close linkage.

Unfortunately, genome-wide association studies of preterm birth have yet to be reported, and the existing literature is based almost exclusively on analysis of candidate genes using the classical case-control study design. Most of these studies have not conformed to recommended guidelines for the conduct of genetic epidemiologic studies (30,31). The majority of the published association studies on preterm birth are based on very small sample sizes, sometimes less than 100, as noted in the subsequent text. Consequently, the statistical power to reject the null hypothesis (no association) is low, challenging the importance of “negative” association results. Replication studies, a necessity when initial reports are based on small sample sizes, have been infrequent. In addition, when positive results have been reported the statistical significance of the associations has been marginal, and usually well below thresholds recommended by critical appraisers. When multiple alleles have been examined, a correction for multiple statistical tests has not routinely been considered. Moreover, the potential confounding effects of population stratification, a particular concern when highly heterogeneous populations like African Americans are being studied, has rarely been addressed in a formal manner. Indeed, in some instances disparate populations, like African Americans and European Americans have been combined in a single analysis. The contribution of genetic variants that are often coupled, or in the parlance of population genetics, in linkage disequilibrium (LD), with the alleles under investigation has only recently been incorporated into studies of prematurity. For example, chromatin immunoprecipitation studies suggest that the tumor necrosis factor alpha (*TNFA*) –308A allele, thought to increase transcriptional activity of the *TNFA* promoter, is in LD with a lymphotoxin- α (*LTA*) haplotype that is associated with increased *LTA* transcription (32). Thus, the reported association between the *TNFA* –308A allele and prematurity may actually reflect the genetic contribution of the *LTA* alleles and the level of *LTA* rather than a causal influence of the *TNFA* gene variant. Few studies have addressed gene-environment (including nutrition) interactions or gene-gene interactions, and those that have are based on very limited sample sizes. Finally, the contribution of epigenetic factors (*e.g.*, DNA methylation), acting on the background of DNA sequence variation, as a contributor to risk of preterm delivery has only recently been described (33). Recognizing these significant shortcomings, we have summarized existing information on genetic variation and its association with preterm birth in African Americans (Table 1).

Table 1. *Studies of genetic polymorphism and risk of preterm birth in African Americans and European Americans*

Reference	Study area, population	Polymorphism	Biological pathway	Clinical condition	Sample		Genotype	Degree of risk
					Cases	Comparison group		
39	U.S., AA	TNF (−308)	Infection/Inflammatory response	PPROM or IPTB	55	110	Maternal	OR = 181 (0.92–3.54)
				PPROM	26			OR = 3.18 (1.33–7.83)
				IPTB	29			OR = 1.04 (0.41–2.49)
46	Africa, Kenya	TNF (−308)	Infection/Inflammatory response	Idiopathic PTB	33	926	Infant	RR = 6.7 (2.0–23.0)
71	U.S., AA	MMP-9 (CA-repeat)	Collagen degradation	PPROM	74	215	Infant	OR = 3.06 (1.77–5.27)
69	U.S., AA	MMP1 (−1607)	Collagen degradation	PPROM	75	255	Infant	OR = 2.29 (1.09–4.82)
41	UK, mixed	TNF (−308)	Infection/Inflammatory response	PPROM or IPTB	48	82	Maternal	OR = 2.2 (1.0–5.0)
		IL-1β (+3953)	Infection/Inflammatory response					<i>p</i> = 0.112
48	U.S., mixed	IL-1β (+3953)	Infection/Inflammatory response	PPROM or IPTB	52	197	Maternal	NA
		IL-1RN*2 (VNTR)		IPTB			Infant	<i>p</i> = 0.033 (AA)
							Maternal	NA
60	U.S., mixed	IL-6 (−174)	Infection/Inflammatory response	IPTB	51	156	Maternal	OR = 0.17 (0.04–0.74)
50	U.S., mixed	F5-α	Uteroplacental	IPTB	300	458	Maternal	<i>p</i> = 0.025
	U.S., AA	F5-α	pathology pathway		193	260		<i>p</i> = 0.023
	U.S., AA	IL-1R2	Infection/Inflammatory response		193	260		<i>p</i> = 0.002
72	U.S., AA	SERPINH1 (−656 T)	Collagen synthesis	PPROM	152	174	Maternal	OR = 3.22 (1.50–7.22)
74	U.S., AA	12-bp deletion in SERPINH1	Collagen synthesis	PPROM	291	403		OR = 0 (0–0.5806)
70	U.S., AA	MMP8 minor alleles	Collagen degradation	PPROM	168	216	Infant	OR = 4.63 (2.01–11.94)
		MMP8 major alleles						OR = 0.52 (0.362–0.751)
		MMP8 minor alleles			171	208	Maternal	adjusted OR = 4.48 (1.90–11.75)
40	U.S., mixed	TNF (−308)	Infection/Inflammatory response	PPROM or PTB	125	250	Maternal	OR = 2.7 (1.7–4.5)
61	U.S., mixed	IL-6 (−174)	Infection/Inflammatory response	PTB				
	AA	IL-6 (−174)			76	321	Maternal	<i>p</i> = 0.09 (Allele); <i>p</i> = 0.34 (Genotype)
	EA	IL-6 (−174)			149	347	Maternal	<i>p</i> = 0.33 (Allele); <i>p</i> = 0.46 (Genotype)
	AA	IL-6 (37672), Allele G			76	321	Maternal	<i>p</i> = 0.04 (Allele); <i>p</i> = 0.05 (Genotype)
	EA	IL-6 (37672), Allele G			149	347	Maternal	<i>p</i> = 0.26 (Allele); <i>p</i> = 0.36 (Genotype)
71	U.S., AA	CARD15 2936insC mutation	Infection/Inflammatory response	PPROM	131	246	Infant	Mutation only detected in controls
		TLR4 896 A>G						NA
49	U.S., mixed	IL-1RN*2	Infection/Inflammatory response	PPROM or IPTB	95	105	Maternal	All: OR = 3.2 (1.68–6.14); EA: OR = 4.66 (1.85–11.74); AA: OR = 1.97 (0.71–5.48)
42	U.S., mixed	TNF-R1 (SNP at 4203)	Infection/Inflammatory response	PTB	49	225	Maternal	Genotype association: <i>p</i> = 0.04
	AA	TNF-R2 (SNP at 19027)						Allele/Genotype association: <i>p</i> = 0.01–0.02
		TNF-R2 (SNP at 35150)						Allele/Genotype association: <i>p</i> = 0.01–0.02
		TNF (−308)						NA
		TNF (−308)			46	224	Infant	NA
	EA	TNF-R1 (SNP at 15227)		PTB	78	184	Maternal	Allele association: <i>p</i> = 0.05
		TNF (−308)			86	191	Infant	Genotype association: <i>p</i> = 0.01
44	U.S., mixed	TNF (−308)	Infection/Inflammatory response	PPROM or PTB	80	80	Maternal	OR = 0.80 (0.34–1.88)
							Infant	OR = 0.85 (0.44–1.65)
		IL-10 (−1082)					Maternal	OR = 1.00 (0.33–3.03)
							Infant	OR = 0.96 (0.35–2.64)
		IFN-γ (+874)					Maternal	OR = 0.56 (0.25–1.25)
							Infant	OR = 2.85 (1.13–7.16)
		IL-6 (−174)					Maternal	OR = 0.73 (0.24–2.19)
							Infant	OR = 0.62 (0.22–1.76)
45	U.S., mixed							
	AA	IL-1α (+4845)			67	238	Maternal	OR = 1.2 (0.6–2.4)
		IL-1β (+3954)						OR = 0.8 (0.4–1.6)
		IL-2 (−385)						OR = 0.7 (0.3–1.6)
		TNF (−488)						OR = 1.4 (0.7–2.9)
	EA	IL-1α (+4845)			69	336		OR = 1.8 (0.9–3.7)
		IL-1β (+3954)						OR = 1.1 (0.5–2.3)

(Continued)

Table 1. (Continued)

Reference	Study area, population	Polymorphism	Biological pathway	Clinical condition	Sample		Genotype	Degree of risk
					Cases	Comparison group		
43	U.S, mixed	IL-2 (−385) TNF (−308)	Infection/Inflammatory response	PTB	158	175	Maternal	OR = 1.0 (0.5–1.9) OR = 2.0 (0.9–4.0)
		TNF- α concentration						$p < 0.001$
	AA	sTNFR1 concentration			52	87		$p = 0.08$
		sTNFR2 concentration						$p = 0.4$
		TNF- α concentration						$p < 0.001$
		sTNFR1 concentration						$p > 0.08$
	EA	sTNFR2 concentration			106	88		$p = 0.2$
		Molar ratio of (TNF- α)/(total sTNFR1 + sTNFR2)						$p < 0.001$
		TNF- α concentration						$p = 0.3$
		sTNFR1 concentration						$p = 0.05$
		sTNFR2 concentration						$p = 0.08$
		Molar ratio of (TNF- α)/(total sTNFR1 + sTNFR2)						$p = 0.3$
43	U.S, mixed		Infection/Inflammatory response	PTB (cases of PPROM were excluded)			Maternal	
	AA	IL-6 concentration IL-10 concentration			49	85		$p = 0.6$ NA
	EA	IL-6 concentration IL-10 concentration			98	89		$p = 0.003$ NA
75	U.S, mixed		Vitamin C metabolism	PPROM or IPTB				
	AA	SLC23A1 SLC23A2-08 SLC23A2-09			129	237		Inconclusive Inconclusive Inconclusive
	EA	SLC23A1 T allele SLC23A2-08 A allele SLC23A2-09			142	335		OR = 0.5 (0.3–0.9) Homozygous: OR = 1.7 (0.9–3.3) Heterozygous: OR = 1.9 (1.0–3.6)

AA, African American; EA, European American. PTB, preterm birth; IPTB, idiopathic preterm birth; PPROM, preterm premature rupture of membrane; NA, No significant association.

Genes Involved in Response to Infection

Toll-like receptor 4 and caspase recruitment domain-containing protein 15. Lipopolysaccharide, a component of the cell wall of Gram-negative bacteria, which is thought to play a key role in eliciting an inflammatory response, is recognized by proteins of the innate immune system, including Toll-like receptor 4 (TLR4) (34) and caspase recruitment domain-containing protein 15 (CARD15) (also referred to as NOD2) (35). Ferrand *et al.* (36) reported similar frequencies of the CARD15 insertion mutation and the hyporesponsive TLR4 allele (896G allele) in African Americans and European Americans. In a case-control study, they found no significant difference in the TLR4 896G allele frequencies among cases and controls, and all carriers of the G allele were heterozygous. The CARD15 2936insC mutation was only detected in controls.

Genes Involved in Inflammation

Tumor necrosis factor- α . TNF- α is a pro-inflammatory cytokine that promotes production of collagen-degrading matrix metalloproteinases (MMPs) while suppressing the biosynthesis of tissue inhibitors of metalloproteinases (37). The MMPs are involved in degradation of fetal membrane colla-

gens and loss of tensile strength. TNF- α also can antagonize the action of progesterone, which may promote uterine contractile activity (38). The TNFA gene is the most studied candidate gene for prematurity.

Association of maternal TNFA –308 alleles and prematurity. Roberts *et al.*, (39) in 1999, reported a significant association between allelic variants of the polymorphism at position –308 in the promoter of the TNFA gene and preterm birth after PPROM in a case-control study of African American women. There were significantly more carriers of the rare –308A allele (homozygous and heterozygous) among women who had preterm delivery after PPROM (58%, $n = 15/26$) than among the controls (30%, $n = 33/110$) ($p = 0.008$; OR = 3.18, 95% CI 1.33–7.83). In women who had idiopathic preterm birth, the rare allele carrier rate among cases and controls was not significantly different.

Macones *et al.* (40) found maternal carriers of the TNFA –308A allele (heterozygous or homozygous) to have a significantly increased risk of spontaneous preterm birth (OR = 2.7, 95% CI 1.7–4.5). The relationship between the TNFA –308A allele and preterm birth was modified by ethnicity. The OR (95% CI) was 2.5 (1.4–4.5) for African Americans, and 1.6 (0.5–5.2) for European Americans. The authors also reported an interaction between carriage of the rare allele and

bacterial vaginosis with preterm birth. Mothers with bacterial vaginosis who carried the rare allele had an increased risk of preterm birth (OR = 6.1, 95% CI 1.9–21.0).

Moore *et al.* (41) described a significant association between the *TNFA* –308A allele and preterm birth. The study sample was 45% black, 44% European, and 11% other races. Forty-eight percent of cases carried the *TNFA* –308A allele compared with 29% of controls ($p = 0.026$; OR = 2.2, 95% CI 1.0–5.0).

In contrast, Menon *et al.* (42) found no significant association between *TNFA* –308 alleles and preterm birth in either African Americans or European Americans. However, these authors found that amniotic fluid TNF- α concentrations were associated with preterm birth in African Americans, but not European Americans (43). Among African Americans, the mean TNF- α concentration in cases (1287 pg/mL) was significantly higher than that in controls (67.3 pg/mL) ($p < 0.001$). There was also a significant difference in the molar ratios of TNF- α /TNF- α receptors between cases and controls among African Americans. Menon *et al.* described a significant genotype association for the TNF- α receptors 1 and 2 (*TNFR1* and *TNFR2*) gene polymorphisms and preterm birth including a *TNFR1* single nucleotide polymorphism (SNP) at +4203 ($p = 0.04$), and a significant allele and/or genotype association (p values 0.01–0.02) for the *TNFR2* SNPs at +19027 and +35150 in African Americans.

Speer *et al.* (44) studied a population that comprised of 21.5% African Americans, 75.5% European Americans, and 3.0% of mixed/other races and found no significant association between the maternal *TNFA* –308A allele and preterm birth.

Engel *et al.* (45) examined polymorphisms in the *TNFA* and *LTA* genes as part of a common haplotype configuration and did not find any differences in haplotype frequency distribution between spontaneous preterm birth cases and control subjects.

Association of fetal *TNFA* –308 alleles and prematurity.

In a study in western Kenya, Aidoo *et al.* (46) reported that fetal carriage of the –308A allele was significantly associated with preterm birth. The relative risks (95% CI) were 7.3 (2.85–18.9) and 6.7 (2.0–23.0) for homozygotic and heterozygotic genotypes, respectively.

Menon *et al.* (42) reported a significant association between fetal carriage of the *TNFA* –308 genotype and preterm birth in European Americans, but not in African Americans.

Interleukin-1 β . Infusion of interleukin-1 β (IL-1 β) into the amniotic cavity of pregnant rhesus monkeys resulted in the production of TNF- α and prostaglandins with subsequent preterm uterine contractions (47).

Genc *et al.* (48) reported that among children of African descent, absence of homozygous carriage of *IL1B* (+3953*2) was associated with spontaneous preterm delivery ($p = 0.033$). The carriage rate among children delivered at term was 40.71% ($n = 11/27$) compared with 7.1% ($n = 1/14$) among preterm babies. Mothers of African descent also showed a similar trend in carriage rate 55.6% ($n = 15/27$) for term delivery, and 28.6% ($n = 4/14$) for preterm delivery but the difference was not statistically significant. There was also

no significant association between fetal and maternal carriage of IL-1 receptor antagonist allele 2 (*IL1RN**2) and preterm delivery.

Murtha *et al.* (49) found maternal carriage of at least one copy of the *IL1RN**2 to be associated with increased risk of preterm birth. The racial breakdown of the study population was 45.5% European American, 42.5% African American, and 12% were of other races. After adjusting for maternal age and race, the OR (95% CI) for the association between *IL1RN**2 and preterm birth was 3.2 (1.68–6.14) for the whole sample and 4.66 (1.85–11.74) for European Americans. A similar pattern of increased *IL1RN**2 allele frequency was observed among African American subjects (cases: 17.4% vs. controls: 9.7%), but the difference was not statistically significant.

Hao *et al.* (50) reported a significant association between IL-1 receptor 2 (*IL1R2*) gene haplotypes and preterm birth in African Americans ($p = 0.002$).

Engel *et al.* (45) found no differences in *IL1B* haplotype frequencies between preterm birth cases and controls, among both African Americans and European Americans. They also found no differences in *IL1A* haplotype frequencies among African Americans. Moore *et al.* (41) reported no significant difference in the carriage of the *IL1B* (+3953) allelic variants between cases and controls in a study in which blacks comprised of 45% of population.

Interleukin-2. Engel *et al.* (45) concluded that an *IL2* –385 SNP did not influence the risk of spontaneous preterm birth in African Americans or European Americans.

Interleukin-4. IL-4 induces differentiation of T lymphocytes along the T_H2 pathway, blocking production of interferon- γ , thereby leading to reduction in pro-inflammatory cytokine synthesis (51). IL-4, which increases during normal pregnancy, also activates B lymphocytes leading to B-cell proliferation and antibody synthesis (52). A –590 C>T SNP in the promoter of the *IL4* gene increases gene transcription and elevates IL-4 levels (53,54). This polymorphism has been associated with elevated serum immunoglobulin levels and increased severity of asthma and atopic dermatitis (53,55).

Interleukin-6. IL-6 is a pro-inflammatory agent that induces T lymphocytes, C-reactive protein synthesis and B-cell differentiation to activate the acute phase inflammatory response. Intra-amniotic inflammation and microbial invasion of the intrauterine compartment, elevates IL-6 concentrations in amniotic fluid, cervical fluid, and cord plasma (56–59). A polymorphism at –174 (G>C) in the promoter region of the *IL6* gene, which results in decreased cytokine production, has been associated with decreased risk of preterm birth (60). Significant differences between European Americans and African Americans, in both genotype and allele frequencies in the *IL6* gene and its receptor gene (*IL6R*), have been reported (60,61).

Simhan *et al.* (60) reported that the homozygous *IL6* (–174C/C) genotype was significantly less frequent among women with spontaneous preterm birth. Thirty (19.2%) of the control subjects and 2 (6.3%) of the cases were homozygous for the *IL6* (–174C/C) genotype (OR = 0.17, 95% CI 0.04–0.74). No African American woman carried the C/C genotype.

Velez *et al.* (61) examined the association of polymorphisms in the *IL6* gene and its receptor gene (*IL6R*) with preterm birth, and reported a significant association between the SNP at +37672 for *IL6R* from maternal samples (allele frequency $p = 0.04$; genotype $p = 0.05$) among African Americans. No significant association was found between the polymorphism at position -174 of *IL6* and preterm birth in either African Americans or European Americans.

Velez *et al.* (62) also reported a significant association between maternal *IL6R* SNP (rs4553185) and preterm birth among African Americans (allele $p = 0.00449$, and genotype $p = 0.01$). In African Americans, analysis of maternal samples showed an association of two SNPs, rs1800795, and rs2069840, which have alleles that form a haplotype, with preterm birth. Relative to the common C-C haplotype, the A-G haplotype showed a significant protective effect (OR = 0.32, 95% CI 0.12–0.73; $p = 0.004$). In analyses of IL-6 amniotic fluid concentrations the strongest associations were observed in *IL6R* haplotypes formed by alleles of the rs4601580-rs4845618-rs7549338 SNPs, from African American maternal samples ($p = 0.0023$), and rs4601580-rs4845618 SNPs, from European American fetal samples ($p = 0.0016$).

Speer *et al.* (44) found no significant difference in *IL6* (-174) genotype frequencies between spontaneous preterm birth cases and controls, in either maternal or fetal samples. However, absence of the low-producer *IL6* C/C genotype was noted in African Americans.

Menon *et al.* (59) compared amniotic fluid concentrations of IL-6 in preterm and term subjects and found significant differences only in European Americans ($p = 0.003$). The median IL-6 concentration in preterm birth cases was significantly higher in European Americans compared with African Americans ($p = 0.03$).

Interleukin-10. IL-10 is an endogenous cytokine that promotes development of the T_H2 type of immune response. IL-10 may be produced by T_H1 , T_H2 , and non-T cells (63). IL-10 is also produced by maternal decidua cells and, to a lesser extent, fetal membranes (64). In most pregnancies, IL-10 is present in amniotic fluid in detectable levels, at all gestational ages (65). Amniotic fluid IL-10 concentrations have been reported to be significantly higher in women with preterm labor and associated intrauterine infection (65). IL-10 has also been shown to be an autocrine inhibitor of MMP-9 production, in human cytotrophoblasts (66).

A study of 80 mother and infant pairs that was comprised of 21.5% African Americans, 75.5% European Americans, and 3% other ethnicities, found no association between *IL10* polymorphisms and preterm birth in either maternal or infant sample (44). The authors, however, reported a significantly higher frequency of the *IL10* A-T-A haplotype (low IL-10 producer) among African American women ($p = 0.004$).

Interferon- γ . In a study in which 21.5% of the participants were African Americans, Speer *et al.* (44) reported the fetal interferon- γ gene (*IFNG*) polymorphism (+874T) to be associated with spontaneous preterm birth, conditioned on maternal *IFNG* genotype.

Genes Involved in Matrix Metabolism

The fetal membranes derive tensile strength from interstitial collagen, and membrane rupture has been attributed, in part, to collagen degradation, which is mediated by MMPs. Fetal membrane MMP activity increases at the time of parturition and elevated levels have been associated with PPRM (67). MMP-1 is one of the collagenases involved in the first step of interstitial collagen catabolism. Fibrillar collagen cleaved by MMP-1 is further broken down by other MMPs, including the gelatinases MMP-2 and MMP-9. Other enzymes associated with the degradation process are collagenases MMP-8 and MMP-13 (68).

Matrix metalloproteinase-1. Fujimoto *et al.* (69) examined the relationship between the -1607 matrix metalloproteinase-1 (*MMP1*) promoter polymorphism (rs1799750) and PPRM in African Americans and reported significant differences in neonatal allele and genotype frequencies between cases and controls. The authors found the frequency of 1G/2G heterozygotes and 2G/2G homozygotes to be significantly higher in cases (88%, $n = 66/75$) than in controls (76.2%, $n = 179/235$) ($p = 0.028$; OR 2.29, 95% CI 1.09–4.82). Alternatively said, the 1G/1G genotype protects against PPRM, as does a -935C allele of a T>C promoter SNP described by Wang *et al.* (33).

Matrix metalloproteinase-8. In a case-control study of 168 cases and 216 controls, in African Americans, Wang *et al.* (70) reported that neonatal (*i.e.*, fetal) carriage of the three minor allele haplotype (-799T, -381G, +17G) in the *MMP8* promoter region was significantly associated with PPRM ($p < 0.0001$; OR = 4.63, 95% CI 2.01–11.94). The individual SNPs did not, however, show any significant association with PPRM. The minor allele haplotype increased *MMP8* promoter activity in cytotrophoblasts. In this study, population stratification was excluded through an analysis of genetic ancestry estimated with ancestry informative markers. Percent African ancestry among cases was 0.847 ± 0.141 , and 0.827 ± 0.149 in controls ($p = 0.487$).

Matrix metalloproteinase-9. A case-control study of African American neonates showed higher carriage rate of the 14 CA-repeat allele in the *MMP9* promoter in offspring of women who had PPRM (63.5%, $n = 47/74$) compared with those delivered at term (36.2%, $n = 78/207$) (OR = 3.06, 95% CI 1.77–5.27; $p < 0.0001$) (71). The authors found that the low number 14 CA-repeat allele confers greater promoter activity in amnion epithelial cells. They also noted that previous studies have reported that African Americans have a lower 14 CA-repeat allele frequency compared with European Americans, suggesting that the higher PPRM incidence in African Americans cannot be attributed to the 14 CA-repeat allele frequency differences between the ethnic groups.

Heat shock protein 47 (SERPINH1). The *SERPINH1* gene encodes a heat shock protein (Hsp47), localized to the endoplasmic reticulum, that serves as a chaperone stabilizing the collagen triple helix. Reduced amounts of nascent *SERPINH1* transcripts and mRNA have been found in amnion samples carrying the minor *SERPINH1* -656T allele (72). Hsp47 is essential for collagen synthesis. Increasing levels of Hsp47

increases type I collagen production. The reduced collagen content in PPROM fetal membranes may be due partly to reduced synthesis or increased degradation. Wang *et al.* (72) concluded that the *SERPINH1* –656T allele is the first example of an ancestry-informative marker associated with preterm birth in African Americans. The T allele is enriched in persons of African descent (73).

Wang *et al.* found the minor *SERPINH1* –656T allele was significantly more frequent in African American neonates born from pregnancies complicated by PPROM compared with controls ($p < 0.0009$; OR = 3.22, 95% CI 1.50–7.22). Cases and controls showed no significant differences in ancestry. A replication case-control study conducted on a separate sample gave similar results.

Wang *et al.* (74) later identified a relatively infrequent 12-bp deletion in the 5'-flanking region of the *SERPINH1* gene that increases promoter activity and protects against PPROM in African Americans. The 12-bp deletion is adjacent to and in LD with the minor *SERPINH1* –656T allele. The allele frequency of the 12-bp deletion was 9/403 (2.3%) among controls and 0/291 (0%) among PPROM cases ($p = 0.0124$).

Other Genes

Significant association between factor V haplotypes and preterm birth has been reported in African Americans (50). Erichsen *et al.* (75) examined the association between haplotypes in the sodium-dependent vitamin C transporters, SLC23A1 and SLC23A2, and preterm birth. The sample consisted of 366 African Americans (129 cases and 237 controls) and 477 European Americans (142 cases and 335 controls). African Americans showed no consistent pattern of association between the five common haplotypes in spontaneous preterm birth. However, significant associations were found for European Americans.

OPPORTUNITIES TO IDENTIFY OTHER GENES CONTRIBUTING TO DISPARITIES IN PRETERM BIRTH

Admixture mapping, an alternative to traditional linkage analysis, can be used to localize disease-causing genes that differ in frequency across populations. It has particular value when used in populations that have undergone recent admixture such as African Americans, and when applied to conditions with distinct prevalence differences between populations, like preterm birth. Admixture mapping gains its power from the fact that the LD between linked loci of previously isolated populations can be detected even after 20 generations. Thus, near a disease gene there will be enrichment of ancestry-informative genetic markers representing the population with the greater disease risk. The intermixing of Western European, Indigenous American, and West African populations started over 500 y ago during the European Colonial period. Because of the slow decay of admixture LD, it has been estimated (and observed) that admixture LD exists at large genetic recombination distances up to 10–20 cm in African Americans. This means studies to be conducted with many fewer genetic

markers and fewer subjects than needed for genome scans using genetic association in unadmixed populations where genetic recombination distances are as small. Panels of markers for admixture mapping have been identified by several groups (76–78) and admixture LD has been used to study associations with resting metabolic rate and obesity, insulin-related phenotypes, and skin pigmentation among other traits (77). Moreover, informative markers have been established for other populations including Indigenous Americans, allowing for admixture calculations that can encompass Western European, African, and Indigenous American. This methodology has yet to be applied to the identification of genes contributing to ethnic disparities in prematurity, and consequently represents a major research opportunity.

CONCLUSIONS

Ethnic disparities in preterm birth may result from multiple factors. Although existing studies can be criticized based on study design, there is accumulating evidence that genetic contributions from both mother and fetus account for some of the disparity in preterm birth between African Americans and European Americans. Ethnic differences in allele and/or haplotype frequencies have been reported for the *TNFA*, and *IL6* genes, and genes encoding their receptors, but the inconsistent finding on their association with preterm birth suggests that independently, these genes are not strong determinants of preterm birth. It is possible that any effects that these genes have on prematurity results from interaction with other genes or with environmental factors. The *SERPINH1* –656T allele, which is enriched in African populations and African Americans, is an example of an ancestry-informative marker associated with preterm birth in African Americans. Future studies based on genome-wide association or admixture mapping may reveal other genes that contribute to disparity in prematurity.

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