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Polymorphisms in Inflammatory Genes are Associated with Term Small for Gestational Age and Preeclampsia

Quaker E. Harmon¹, Stephanie M. Engel¹, Michael C. Wu², Thomas M. Moran³, Jingchun Luo⁴, Alison M. Stuebe⁵, Christy L. Avery¹, and Andrew F. Olshan¹

¹Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA

²Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA

³Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

⁴Mammalian Genotyping Core, Lineberger Comprehensive Cancer Center, School of Medicine, University of North Carolina, Chapel Hill, NC, USA

⁵Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Abstract

Problem—Inflammatory biomarkers are associated with preeclampsia (PE) and poor fetal growth; however, genetic epidemiologic studies have been limited by reduced gene coverage and the exclusion of African American mothers.

Method of study—Cases and controls ($N = 1646$) from a pregnancy cohort were genotyped for 503 tagSNPs in 40 genes related to inflammation. Gene-set analyses were stratified by race and were followed by a single SNP analysis within significant gene sets.

Results—Gene-level associations were found for *IL6* and *KLRD1* for term small for gestational age (SGA) among African Americans. *LTA/TNF* and *TBX21* were associated with PE among European Americans. The strongest association was for PE among European Americans for an upstream regulator of TNF with RR = 1.8 (95% CI 1.1–2.7).

Conclusion—Although previous studies have suggested null associations, increased tagging and stratification by genetic ancestry suggests important associations between *IL6* and term SGA for African Americans, and a TNF regulator and PE among European Americans ($N = 149$).

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Correspondence Quaker E. Harmon, 2104C McGavran-Greenberg, Campus Box 7435, Chapel Hill, NC 27599-7435, USA. quaker@email.unc.edu

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Keywords

African Americans; genetic association studies; preeclampsia; pregnancy; small for gestational age

Introduction

Hypertensive disorders of pregnancy and poor fetal growth often co-occur¹ and may share underlying pathology.² Hypertensive disorders of pregnancy, including gestational hypertension (GHTN) and preeclampsia (PE), occur in up to 20% of pregnancies³ and are a leading cause of maternal mortality.⁴ Pregnancies complicated by hypertension are at increased risk of stillbirth, poor fetal growth, and preterm birth.^{1,5} The prevalence and health consequences of poor fetal growth depend largely on the metric of assessment⁶ and the specific etiology.⁷ However, low birth weight is consistently associated with increased infant mortality.⁸ Each outcome has also been associated with later risk of cardiovascular disease in the mother.^{9–11}

Hypertension in pregnancy and poor fetal growth may share common placental pathology including shallow or inadequate placentation.^{2,12} Adequate placentation requires remodeling of the spiral arteries in the decidua to allow adequate blood flow to the placenta.^{12,13} With PE, there is poor to absent vascular remodeling in the myometrium and decidua. For pregnancies complicated by poor fetal growth, vascular remodeling is more evident but is diminished in depth and extent.¹⁴ Placental invasion and development are dependent on tightly regulated local inflammatory processes.^{2,15} In particular, the interaction between fetal trophoblasts and maternal decidual cells is mediated by maternal natural killer (NK) and T-cell activity.^{16,17} In addition to mediating placentation, inflammatory cytokines may be released as a result of hypoxia and ischemic–reperfusion injuries which result from inadequate placentation.^{13,18} In fact, women with either outcome exhibit altered inflammatory biomarkers both preceding^{15,19,20} and at the time of diagnosis.^{2,15,21}

The extensive placental growth and uterine wall remodeling that occur during normal gestation may additionally be influenced by cell cycle genes that regulate cell growth and division in rapidly growing tissue such as the placenta.^{22,23} Human and animal placental expression studies suggest that cell cycle genes may differ in expression or function in women with hypertension in pregnancy or small for gestational age (SGA).^{24,25}

Although a fetal genetic component has been identified for both hypertension in pregnancy and fetal growth, these disorders also have a maternal genetic component.^{26,27} Very few candidate gene studies have examined poor fetal growth. Studies of PE, while more numerous, have largely been dominated by genes in the renin angiotensin, coagulation, and angiogenic pathways.²⁸ Candidate gene studies for other pathways have been limited, have focused on relatively few markers per gene without accounting for up- and downstream regions, and have often lacked control for population stratification.²⁹ To address these limitations, we conducted a study nested within the pregnancy, infection, and nutrition (PIN) cohort, a biracial pregnancy cohort in North Carolina. Our focus was on genes related to inflammation and cell cycle pathways.

Methods

Study participants were drawn from the PIN cohort, which was established to assess antenatal risk factors for a variety of reproductive outcomes.³⁰ Women were enrolled between August 1995 and June 2005 from prenatal clinics at Wake County Human Services Department, Wake Medical Center and the University of North Carolina (UNC) Hospital. Women were ineligible if they were less than 16 years old, did not speak English, lacked a telephone, were carrying more than one fetus, or did not plan to continue care at the recruitment hospital.

Outcome and covariate data were collected through self-administered questionnaires, telephone interviews during pregnancy, and abstraction of maternal and infant medical records. Maternal blood for genetic analysis was collected during the first study visit. All participants gave consent, and the study was approved by the Institutional Review Boards of UNC School of Medicine and Wake Medical Center.

Of those enrolled, 3539 women (68.5%) consented to genetic analysis. Eligibility for genotyping in the present study also included collection of a suitable bio-specimen ($N = 3289$), self-reported race as White or African American ($N = 3075$) and recorded date of delivery ($N = 3065$). These eligibility criteria resulted in 3065 (59.3%) women who were eligible for selection. From the eligible population, 1646 pregnancies were selected for genotyping. Attempts were made to genotype all eligible cases. Missing or inadequate samples resulted in (N , % of eligible): 216 (90.4%) SGA, 398 (95.2%) GHTN, and 170 (91.9%) PE cases being included in the study. Although GHTN and PE cases were exclusive case definitions, pregnancies complicated by SGA could also have a diagnosis of GHTN or PE. Control births ($N = 918$) were selected from the remaining eligible women.

Among the 1646 samples genotyped, 11 individuals were dropped due to fewer than 95% of markers successfully called. Exclusions were also made for congenital anomalies ($N = 24$), stillbirths ($N = 10$), and unintentional duplicate samples ($N = 3$). As a result of these exclusions, 1598 women were available for analysis.

Outcome Assessment

Small for gestational age status was defined as birth weight below the 10th percentile for gestational age, stratified by infant race, sex, and maternal parity based on percentiles from 1989 US births.³¹ As a proxy measure for impaired fetal growth, SGA may not appropriately classify preterm infants⁶ and may misidentify constitutionally small infants as SGA. In as much as common causes may exist for preterm birth and poor intra-uterine growth, term SGA was considered as an additional phenotype.

Gestational hypertension and PE were assessed using evidence of new hypertension after 20 weeks and proteinuria abstracted from antenatal charts and discharge diagnoses. Prior to 2002, hypertension during pregnancy was defined using a relative increase of 30 mmHg in systolic blood pressure (BP) or a 15 mmHg increase in the diastolic BP from a woman's baseline blood pressure. Following American College of Obstetrics and Gynecology (ACOG) recommendations in 2002, the definition of hypertension was changed to an

absolute cut point of systolic BP \geq 140 mmHg or diastolic BP \geq 90 mmHg.³ Diagnoses in this study reflect the clinical criteria in use at the time of the pregnancy. While the newer ACOG criteria reduces the number of women who receive a diagnosis of PE, the positive predictive value for adverse maternal and infant outcomes is similar for the two sets of criteria.³² GHTN was defined as new onset hypertension following 20 weeks in the absence of proteinuria. Pregnancies with evidence of GHTN that developed proteinuria later in pregnancy were classified as PE. PE was defined as new onset hypertension (using the criteria appropriate at the time of pregnancy) and evidence of proteinuria. Women with preexisting hypertension, or hypertension before 20 weeks, were excluded from both the case and control groups for all analyses of GHTN and PE.

DNA Extraction and Genetic Analysis

Maternal blood was drawn at a study visit in the second trimester. Buffy coat fractions were isolated from fresh whole blood and stored at -80°C in CPT tubes. DNA was extracted using Applied Biosystems automated DNA extractor and Qiagen (Gentra, Valencia, CA, USA) Puregene chemistry.

Thirty inflammatory and ten cell cycle genes (546 SNPs) were selected as candidate genes. TagSNPs were selected using TagZilla³³ for two population (European and Yoruban, HapMap build 27) with a 20 kb upstream and 10 kb downstream margin, restricting to minor allele frequencies \geq 10% in at least one population and linkage disequilibrium (LD) $r^2 > 0.8$. A custom 1536 Illumina GoldenGate plate was designed which also included SNPs from genes in the angiogenesis and apoptosis pathways.

Genotyping was conducted at the University of North Carolina Mammalian Genotyping Core (Chapel Hill, NC, USA), and genotypes were called with Illumina GenomeStudio software (Illumina, San Diego, CA, USA).

Poor genotyping quality ($<95\%$ of individuals called) resulted in the loss of 43 SNPs. Further quality control was conducted on the remaining 503 SNPs using blinded PIN samples and standardized controls from Corriel Utah family trios. There was one instance of a single base pair genotyping discrepancy found among 199 blind samples, and there were no instances of Mendelian errors among 21 trios examined. Hardy–Weinberg equilibrium was assessed using SAS 9.2³⁴ among non-cases stratified by genetic ancestry. One SNP (IL2: rs10027390) significantly violated HWE ($P < 10^{-5}$) in African American non-cases and was dropped from analysis for this ancestry group.

In tagging two populations, inclusion of redundant tagSNPs with high LD in one ancestral population was necessary to adequately capture variation in the other population. In order to examine the linkage between both typed and untyped markers in this study population, heatmaps were created using Haploview,³⁵ and long-range LD with untyped SNPs was explored using SNAP³⁶ with the 1000 Genomes Project Pilot 1 data.

Genetic Ancestry

Differences in the allelic frequency in genes associated with inflammation have been reported among Whites and African Americans in the United States.³⁷ Birth weight⁸ and the

incidence of PE³ also vary by self-reported race, raising the possibility of confounding by genetic ancestry. Genetic ancestry was therefore assessed using ancestry informative markers (AIMs) ($N = 148$) that have been used in a similar population in North Carolina.³⁸ STRUCTURE was used to calculate a continuous genetic ancestry variable assuming two underlying populations.³⁹ The calculated ancestry variable was used to dichotomize the population into European American and African American ancestry groups using a cut point that corresponded with self-reported race. All analyses were stratified by genetic ancestry and also included continuous percent ancestry.

Statistical Analysis

We employed a two-stage approach to identify associations between inflammatory and cell cycle genes, and the outcomes of SGA, term SGA, GHTN and PE. Stage 1 utilized the SNP set kernel association test (SKAT) with a linear kernel.⁴⁰ This approach is analogous to logistic regression with an additive genetic model. SKAT was chosen because it permits SNP interactions within a gene, allows adjustment for covariates, and accounts for SNPs with opposing effects (protective or risk) within a gene. We included all markers within a given gene as a SNP set, including markers within the upstream and downstream margins. If genes were positioned within 25 kbp of each other, they were analyzed together. Genes with single SNPs (cyclin H (CCNH), transforming growth factor beta 3 (TGFB3), and *beta 1* (TGFB1), *MDM2 oncogene* (MDM2)) or SNPs chosen solely for replication (*interleukin(IL) 1A*, *interleukin 1B*) were not included in the Stage 1 analysis. Individuals with missing genotype information on any SNPs in a set were dropped from the Stage 1 analysis. On average, 99% of genotyped individuals were included in each SNP set, with a minimum of 91%. Analyses were conducted for each outcome with uncomplicated term births as the control group ('Disease Free' column in Tables I and II). For GHTN and PE, women with chronic hypertension were excluded from both the case and control group.

Covariates considered were maternal age, body mass index (BMI), maternal smoking, parity, and a continuous measure of socioeconomic status. A false discovery rate (FDR)⁴¹ of 20% was used to identify SNP sets which advanced to Stage 2 analysis. *P*-values from SKAT were transformed to *Q*⁴² values using R (p.adjust, FDR)⁴³ accounting for the number of SNP sets analyzed ($N = 31$).

Among the genes that advanced to Stage 2 analysis, individual SNP associations were measured. Given the relatively common outcome of GHTN (14% in the underlying PIN cohort, Table S1), associations were measured using risk ratios from a log-linear risk model. Dominant genetic models were used unless the smallest genotype cell size was >5 . Each outcome was compared to a control group, which included all genotyped pregnancies without the outcome of interest ('Control' columns in Tables I and II). For the outcome of term SGA, only term births were included in the control group.

Inverse probability of selection weighting was used so that the estimates are generalizable to the entire eligible population. Briefly, a logistic model was used to calculate the probability that an eligible woman ($N = 3065$) was selected for genotyping ($N = 1646$) based on all covariates in Table I, and other study-related, demographic and pregnancy-related variables.

The inverse of this probability was then used to weight the model. Robust variances were used, although these likely overestimate the true variance.⁴⁴

Top-ranking SNPs from Stage 2 were reported based on the consistency of the observed association across related outcomes (SGA and term SGA) as well as between genetic ancestry groups. Analyses were stratified on genetic ancestry and additionally adjusted for a continuous ancestry variable.

Results

The final analysis dataset included 1598 women. Tables I and II present the demographic characteristics of the case and control groups for SGA and hypertensive disorders of pregnancy, respectively. Women who consented and were successfully geno-typed were similar to the underlying PIN cohort (Table S1) and were predominately White (62.6%), well educated (51.9% with more than high school education), non-smokers (74.4%) with a mean age of 26.1 years, and a mean BMI of 26.5 kg/m². Although the distribution of some covariates differed by self-identified race, the differences were not as pronounced between cases and controls within strata of genetic ancestry (Tables I and II). Adjustment for any or all of the covariates in Table I failed to change the single SNP point estimates more than 10% (results not shown). Therefore, we present estimates adjusted only for genetic ancestry.

Stage 1: Gene-Set Analysis in SKAT

SNPs were combined into 31 SNP sets. Due to proximity on the genome, *tumor necrosis factor (TNF)* and lymphotoxin α (TNF superfamily member 1)(*LTA*), *IL-13 (IL13)* and *IL-4 (IL4)*, and *cyclin-dependent kinase inhibitor 2A (CDKN2A)* and *2B (CDKN2B)* were considered as single SNP sets. Four SNP sets met our FDR criteria of 20% in Stage 1. *IL-6 (IL6)* ($q = 0.17$) and killer cell lectin-like receptor subfamily D, member 1 (*KLRD1*) ($q = 0.17$) were associated with term SGA among African Americans, and *T-box 21 (TBX21)* ($q = 0.05$) and *LTA/TNF* ($q = 0.05$) were associated with PE among European Americans. No SNP sets met the FDR criteria for SGA overall or GHTN (Table III).

Stage 2: Single SNP Analysis

There were 55 individual SNPs within the SNP sets that passed FDR criteria in Stage 1, and eight additional SNPs not included in Stage 1 that were assessed in Stage 2 analyses (Tables IV and V). Variant allele frequencies and genotype frequencies for SNPs reported in Tables IV and V can be found in Tables S2–S5. Single SNP results for all genes and outcomes can be found in Tables S6 and S7.

Term SGA

In Stage 1, *IL6* and *KLRD1* were associated with term SGA in African Americans. Single SNP associations within *IL6*, however, were generally consistent in both ancestral groups, although slightly weaker for European Americans (Table IV). The strongest single SNP association for term SGA for both ancestry groups was seen for a group of three *IL6* SNPs (rs1548216, rs2069843, and rs2069849), all having risk ratios in the range of 1.9–2.4. This group of SNPs is in full LD ($r^2 = 1$) among European Americans and partial LD in African

Americans ($r^2 = 0.72-0.85$) (Fig. 1). An additional group of SNPs upstream of *IL6* was also associated with an increased risk of term SGA of similar magnitude for both African and European Americans (rs6963444, rs7784987, and rs3087221).

For *KLRD1*, however, single SNP associations were not similar across the two ancestry groups. In European Americans, the tagSNPs represent a single block of high LD, except for two SNPs which were quite rare in European Americans (rs10772256 and rs7301562) (Fig. 2, Table S2). Seen as a block, there was an overall null association with term SGA for European Americans. In contrast, among African Americans, a number of SNPs were relatively strongly associated with term SGA. In particular, rs10772256 and rs7301562 (which were in high LD, $r^2 = 1$) were associated with a decreased risk of term SGA (RR = 0.5, 95% CI 0.3–0.9). Additionally, rs3759270 was associated with a substantially decreased risk of term SGA (RR = 0.4, 95% CI 0.3–0.8). Finally, two SNPs in perfect LD (rs3809214 and rs2302489) were associated with an increased risk of term SGA (RR = 1.6) among African Americans.

Preeclampsia

LTA/TNF and *TBX21* were associated at the gene level with PE, but only for European American women. Moreover, the single SNP results were generally null for African Americans (Table V). *LTA* and *TNF* are quite close on chromosome 6 (6p21.3), and tagging for *LTA* also captured regions of the adjacent gene nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibition-like 1 (NFKBIL1). Single SNP results for tags within NFKBIL1 were generally null. Among European Americans, two SNPs in *LTA* that were in high LD ($r^2 = 0.99$) (Fig. 3a), rs909253 and rs1041981, were associated with an increased risk of PE (RR = 1.5 and 1.4). A missense SNP in *LTA* rs2229094 was associated with a decreased risk of PE (RR = 0.6, 95% CI 0.4–1.0). In *TNF*, rs1800629, an upstream SNP that is thought to upregulate *TNF* expression,⁴⁵ was found to increase the risk of PE (RR = 1.8, 95% CI 1.1–2.7).

TagSNPs for *TBX21* captured two upstream SNPs which were closer to an adjacent gene *TBK-binding protein 1 (TBKBP1)* (rs2013383 and rs1808192). These two SNPs are in moderate LD with each other ($r^2 = 0.68$) (Fig. 3b) and have long-range LD extending through *TBKBP1* with very little pairwise or long-range LD with typed or untyped SNPs in *TBX21*. The two *TBKBP1* SNPs were associated with a decreased risk of PE RR = 0.6. For tagSNPs within *TBX21* itself, the associations were null.

Discussion

We examined 40 genes related to inflammation and cell cycle pathways, and their associations with SGA, GHTN and PE in a biracial North Carolina population. There were no significant associations for any of the cell cycle genes. However, a number of interesting and novel associations were found for inflammatory gene variants. Among African American women, *IL6* and *KLRD1* were associated with term SGA. Single SNP associations within *IL6* suggest that a similar, though weaker, association may exist for European Americans. For the outcome of PE, associations within *LTA* and *TNF* were seen for

European American women. Two SNPs within a novel gene, *TBKBP1*, were associated with a decreased risk of PE among European American women only.

We report gene-level associations among African Americans only within the term SGA phenotype, suggesting that these associations are mediated by pathways unrelated to prematurity. It is unclear why distinctive association patterns emerged for African Americans and Whites; however, it may reflect distinct phenotypes, or possibly interactions with social or environmental exposures that are differentially distributed across these two populations. *IL6* was chosen as a candidate gene due to evidence that in early pregnancy *IL6* may influence the ability of the placenta to become adequately implanted.⁴⁶ *IL6* has been examined previously in relation to SGA with null associations, although many fewer SNPs were used to tag the gene,^{21,47,48} and, apart from the Engel study, the populations were White.

KLRD1 (*CD94*) codes for a portion of a receptor on both NK- and T-cells that recognize HLA-E molecules expressed by trophoblasts during pregnancy.⁴⁹ Tight regulation of maternal immunity at the time of implantation mitigates against rejection of the fetal trophoblasts and permits adequate placental development and implantation. Dysregulation of *KLRD1* might result in a heightened inflammatory response to the invading placenta resulting in inadequate placentation impairing fetal growth. In this study, polymorphisms in *KLRD1* were only associated with term SGA among African Americans. Although genetic diversity of HLA-E is much lower than the diversity seen in other major histocompatibility genes, there have been haplotype differences documented between individuals of European and African descent.⁵⁰ Underlying differences in HLA-E haplotypes may explain these discrepant associations across racial groups.

Genes coding for TNF- α (*TNF*) and TNF- β (*LTA*) were associated with an increased risk of PE among European American women. TNF- α has been implicated in the pathogenesis of PE¹ both as a modulator of placental implantation and as a response to the hypoxia created by poor placental perfusion.¹³ Infusion of TNF- α induces hypertension in pregnant rats.²⁹ Despite the credibility of the biology implicating TNF- α with PE, results of genetic epidemiologic studies have been less encouraging. Meta-analyses of the 308A missense mutation (rs18000629)^{51,52} found null pooled estimates. The meta-analyses, however, combined estimates from populations of very different genetic ancestries. It has previously been reported that allele frequencies in *TNF* and its related receptors vary substantially by self-reported race. Moreover, regulation of TNF- α levels during pregnancy appears to differ between White and African American women.⁵³ In our stratified analysis, an association at the gene level was only apparent for European Americans. Despite the null association in the meta-analysis, the complexity of TNF regulation and apparent heterogeneity based on genetic ancestry support further investigation into this gene.

TBX21 is an important regulator of TH1 immunity.⁵⁴ However, the strongest single SNP association in our study may have been with a tagSNP associated with a close upstream gene *TBKBP1* (aka *SINTBAD*). *TBKBP1* was identified in 2004, and its function is still being elucidated. It appears to be related to signaling in the TNF- α /NF κ B pathways and the

activation of interferon.^{55,56} Given the role of TNF- α in PE, further investigation of this novel gene is warranted.

Preeclampsia is a heterogeneous disease and may represent a number of distinct phenotypes with a shared clinical presentation. We did not collect data on the severity of disease or the timing of clinical onset and therefore we were unable to subdivide our case group into more homogeneous phenotypes. In addition, the changing diagnostic criteria over the course of the study resulted in further heterogeneity of phenotype based on the year of diagnosis. Newly released diagnostic criteria present the possibility that there is under ascertainment of PE cases among women with hypertension and other signs of end-organ involvement who do not present with protein-uria.⁵⁷ These shortcomings reduce our power to identify associations that may exist between SNPs and specific subtypes of PE (for example, early onset disease or PE with severe features). Future studies of PE will benefit from increased sample size and additional clinical information that will permit the classification of cases based on gestational age at onset and the presence of severe features.

The heterogeneity in the PE phenotype may also be the result of interactions between genetic susceptibility and environmental exposures such as smoking, infections, nutrition, or exposure to environmental toxicants. Although we were underpowered to explore gene by environment interactions in this study, the strong protective association between smoking and PE offers an opportunity for future genetic association studies to explore gene by environment interactions.

While our study comprises the largest bi-racial study of inflammatory genes in relation to these important obstetric outcomes, it suffers from some notable limitations. This study was limited by the lack of fetal DNA, which is an important genetic factor in both of these reproductive outcomes. However, the results of this study support a role of maternal genes in these outcomes. Although we incorporated genetic variation in upstream and downstream regions, our pre-specified boundaries may be too narrow to capture long-range regulatory elements.⁵⁸ Finally, previous research has demonstrated that a candidate gene approach has been only modestly successful in identifying genetic associations that replicate across populations. Nonetheless, the results presented herein are consistent with current understanding of the biological underpinning of PE and SGA, although verification in an independent population is needed.

Conclusions

This study expanded coverage of candidate inflammatory genes and examined novel cell cycle and NK cell genes while carefully addressing population stratification. The results of this study reveal important differences in the genetic underpinnings of term SGA and PE in European and African Americans while also finding that there may be pathways in common. Novel associations between *KLRD1* and term SGA, and *TBKBPI* and PE warrant further exploration, ideally with enhanced tagging of polymorphisms within *TBKBPI* and consideration of HLA-E haplotypes for *KLRD1*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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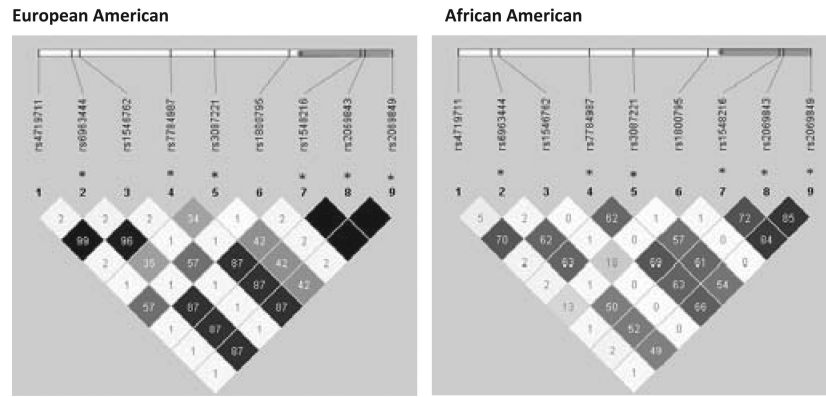


Fig. 1. Linkage disequilibrium (r^2) in *IL6* stratified by genetic ancestry. r^2 is the amount of correlation between two SNPs with empty black cells representing 100% correlation and lighter cells representing less correlation. *SNPs are mentioned in results section. Approximate SNP location (vertical bars) and *IL6* location (grey bar) noted along genome.

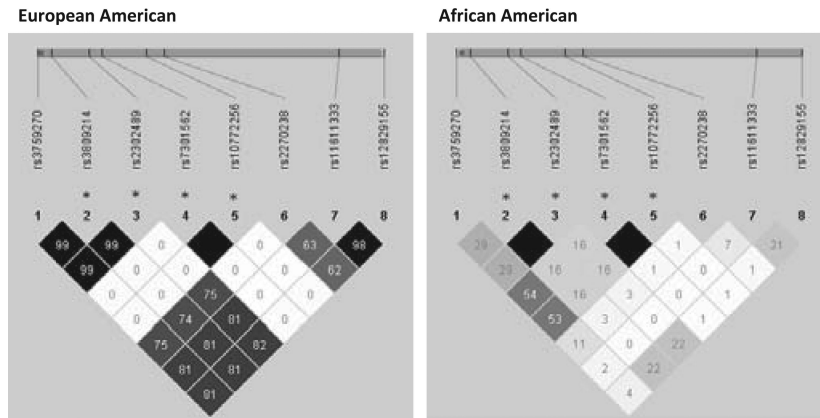


Fig. 2. Linkage disequilibrium (r^2) in KLRD1 stratified by genetic ancestry. r^2 is the amount of correlation between two SNPs with empty black cells representing 100% correlation and lighter cells representing less correlation. *SNPs are mentioned in results section. Approximate SNP location (vertical bars) and KLRD1 location (grey bar) noted along genome.

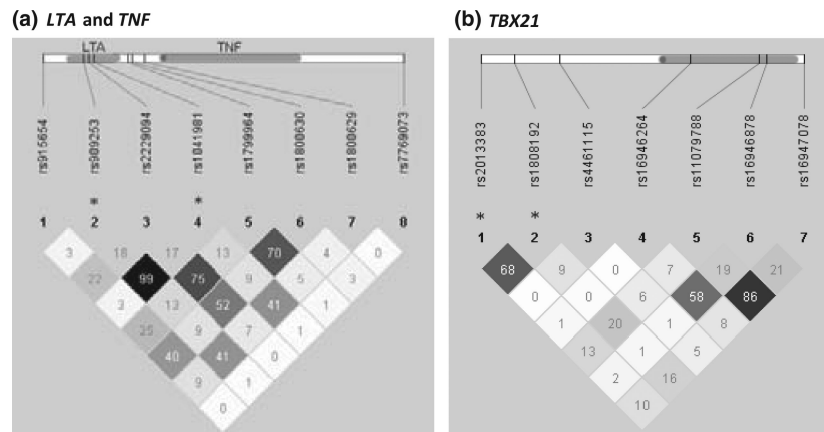


Fig. 3. Linkage disequilibrium (r^2) among European Americans in (a) *LTA*, *TNF*, and (b) *TBX21*. r^2 is the amount of correlation between two SNPs with empty black cells representing 100% correlation and lighter cells representing less correlation. *SNPs are mentioned in results section. Approximate SNP location (vertical bars) and gene location (grey bar) noted along genome.

Table I

Demographic Characteristics of Small for Gestational Age (SGA) Cases and Controls

Genetic ancestry ^a	SGA cases		Disease free		Non-SGA controls ^b	
	European American N = 117 N (%)	African American N = 92 N (%)	European American N = 409 N (%)	African American N = 204 N (%)	European American N = 890 N (%)	African American N = 499 N (%)
Maternal age (years)						
<25	55 (47.0)	27 (29.4)	215 (52.6)	68 (33.3)	440 (49.4)	182 (36.5)
25–34	46 (39.3)	59 (64.1)	133 (32.5)	132 (64.7)	325 (36.5)	295 (59.1)
35+	16 (13.7)	6 (6.5)	61 (14.9)	4 (2.0)	125 (14.0)	22 (4.4)
Smoking ^c						
No	68 (63.6)	58 (72.5)	302 (77.4)	148 (84.6)	588 (71.0)	362 (83.2)
Yes	39 (36.5)	22 (27.5)	88 (22.6)	27 (15.4)	240 (29.0)	73 (16.8)
Missing	10 (8.5)	12 (13.0)	19 (4.6)	29 (14.2)	62 (7.0)	64 (12.8)
BMI (kg/m ²) ^d						
<18.5	11 (9.9)	11 (13.1)	23 (5.7)	16 (8.3)	44 (5.1)	27 (5.8)
18.5–24.9	72 (64.9)	35 (41.7)	250 (62.2)	79 (40.9)	454 (52.7)	166 (35.8)
25–29.9	16 (14.4)	13 (15.5)	71 (17.7)	39 (20.2)	174 (20.2)	100 (21.6)
30+	12 (10.8)	25 (29.8)	58 (14.4)	59 (30.6)	189 (22.0)	171 (36.9)
Missing	6 (5.1)	8 (8.7)	7 (1.7)	11 (5.4)	29 (3.3)	35 (7.0)
Marital status						
Married	77 (65.8)	13 (14.1)	313 (76.5)	32 (15.7)	644 (72.4)	109 (21.9)
Unmarried	40 (34.2)	79 (85.9)	96 (23.5)	172 (84.3)	246 (27.6)	389 (78.1)
Education (years)						
13+	61 (52.1)	27 (29.4)	275 (67.2)	68 (33.3)	542 (60.9)	201 (40.3)
12	56 (47.9)	65 (70.7)	134 (32.8)	136 (66.7)	348 (39.1)	298 (59.7)
Parity						
Nulliparous	49 (41.9)	48 (52.2)	189 (46.4)	88 (43.1)	437 (49.2)	220 (44.2)
Multiparous	68 (58.1)	44 (47.8)	218 (53.6)	116 (56.9)	451 (50.8)	278 (55.8)
Missing	0	0	2 (0.5)	0	2 (0.2)	1 (0.2)
Poverty index						
Mean (S.D.)	310 (237)	119 (85)	367 (238)	144 (123)	345 (237)	148 (124)
Missing	10 (8.6)	26 (28.3)	24 (5.9)	37 (18.1)	70 (7.9)	85 (17.0)
Additional outcomes						
Term SGA	96 (82.1)	64 (69.6)	0	0	717 ^e	393 ^e
Gestational HTN	19 (17.0)	14 (16.9)	0	0	226 (27.2)	131 (28.5)
PE	11 (9.8)	10 (12.1)	0	0	82 (9.9)	62 (13.5)
Preterm birth	21 (18.0)	28 (30.4)	0	0	173 (19.4)	106 (21.2)

^aGenetic ancestry determined using 148 ancestry informative markers and STRUCTURE.

^bNon-SGA controls include uncomplicated births as well as births with other pregnancy outcomes including preterm birth; GHTN, gestational hypertension; and PE, preeclampsia.

^cSelf-reported smoking during months 1–6 of pregnancy.

^dPre-pregnancy body mass index (BMI) calculated from self-reported pre-pregnancy weight and measured height.

^eControls for term SGA are limited to term births.

Table II
Demographic Characteristics of Gestational Hypertension (GHTN) and Preeclampsia (PE) Cases and Controls

	GHTN case		PE case		Disease free ^b		GHTN control ^c		PE control ^c	
	European American N = 245 N (%)	African American N = 145 N (%)	European American N = 93 N (%)	African American N = 72 N (%)	European American N = 394 N (%)	African American N = 190 N (%)	European American N = 699 N (%)	African American N = 397 N (%)	European American N = 851 N (%)	African American N = 470 N (%)
Age (years)										
<25	107 (43.7)	54 (37.2)	52 (55.9)	22 (30.6)	211 (53.6)	64 (33.7)	355 (50.8)	131 (33.0)	410 (48.2)	163 (34.7)
25-34	101 (41.2)	85 (58.6)	36 (38.7)	48 (66.7)	123 (31.2)	122 (64.2)	254 (36.3)	254 (64.0)	319 (37.5)	291 (61.9)
35+	37 (15.1)	6 (4.1)	5 (5.4)	2 (2.8)	60 (15.2)	4 (2.1)	90 (12.9)	12 (3.0)	122 (14.5)	16 (3.4)
Smoking ^d										
No	150 (65.8)	101 (80.2)	57 (71.3)	56 (86.2)	293 (77.5)	135 (83.3)	468 (72.0)	283 (81.6)	561 (70.3)	328 (80.4)
Yes	78 (34.2)	25 (19.8)	23 (28.8)	9 (13.9)	85 (22.5)	27 (16.7)	182 (28.0)	64 (18.4)	237 (29.7)	80 (19.6)
Missing	17 (6.9)	19 (13.1)	13 (14.0)	7 (9.7)	16 (4.1)	28 (14.7)	49 (7.0)	50 (12.6)	53 (6.2)	62 (13.2)
BMI (kg/m ²) ^e										
<18.5	7 (3.0)	6 (4.6)	4 (4.4)	1 (1.5)	22 (5.7)	16 (8.9)	48 (7.0)	32 (8.6)	51 (6.2)	37 (8.5)
18.5-24.9	106 (46.1)	46 (34.9)	41 (45.6)	23 (33.8)	242 (62.2)	74 (41.1)	406 (59.5)	149 (40.1)	471 (57.3)	172 (39.5)
25-29.9	47 (20.4)	29 (22.0)	21 (23.3)	15 (22.1)	69 (17.7)	36 (20.0)	132 (19.4)	74 (19.9)	158 (19.2)	88 (20.2)
30+	70 (30.4)	51 (38.6)	24 (26.7)	29 (42.7)	56 (14.4)	54 (30.0)	96 (14.1)	117 (31.5)	142 (17.3)	139 (31.9)
Missing	15 (6.1)	13 (9.0)	3 (3.2)	4 (5.6)	5 (1.3)	10 (5.3)	17 (2.4)	25 (6.3)	29 (3.4)	34 (7.2)
Marital status										
Married	171 (69.8)	41 (28.3)	58 (62.4)	13 (18.3)	304 (77.2)	30 (15.8)	504 (72.1)	66 (16.7)	617 (72.5)	94 (20.0)
Unmarried	74 (30.2)	104 (71.7)	35 (37.6)	58 (81.7)	90 (22.8)	160 (84.2)	195 (27.9)	330 (83.3)	234 (27.5)	376 (80.0)
Education (years)										
13+	141 (57.6)	62 (42.8)	47 (50.5)	31 (43.1)	267 (67.8)	65 (34.2)	420 (60.1)	140 (35.3)	514 (60.4)	171 (36.4)
12	104 (42.5)	83 (57.2)	46 (49.5)	41 (56.9)	127 (32.2)	125 (65.8)	279 (39.9)	257 (64.7)	337 (39.6)	299 (63.6)
Parity										
Nulliparous	136 (55.5)	70 (48.3)	59 (63.4)	43 (60.6)	181 (46.2)	81 (42.6)	328 (47.1)	181 (45.7)	405 (47.7)	208 (44.3)
Multiparous	109 (44.5)	75 (51.7)	34 (36.6)	28 (39.4)	211 (53.8)	109 (57.4)	369 (52.9)	215 (54.3)	444 (52.3)	262 (55.7)
SGA	19 (7.8)	14 (9.7)	11 (11.8)	10 (13.9)	0	0	93 (13.3)	69 (17.4)	101 (11.9)	73 (15.5)
PTB	19 (7.8)	17 (11.7)	29 (31.2)	19 (26.4)	0	0	160 (22.9)	97 (24.4)	150 (17.6)	95 (20.2)

BMI, body mass index.

^aGenetic ancestry determined using 148 ancestry informative markers and STRUCTURE.

^bDisease-free controls are uncomplicated term births without preexisting hypertension used in Stage 1 for both outcomes.

^cGHTN and PE controls include pregnancies with small for gestational age (SGA) and preterm birth (PTB), but exclude those with pre-existing hypertension. GHTN controls further exclude women with PE.

^dSelf-reported smoking during months 1–6 of pregnancy.

^ePre-pregnancy BMI calculated from self-reported pre-pregnancy weight and measured height.

Table III

 Q^a Values from SKAT Analysis for each SNP Set Stratified by Genetic Ancestry

Pathway/gene	<u>European American</u> ^b		<u>African American</u> ^b		<u>European American</u>		<u>African American</u>	
	SGA	Term SGA	SGA	Term SGA	GHTN	PE	GHTN	PE
Inflammatory								
<i>TBX21</i> ^c	1.00	1.00	0.87	0.83	0.84	0.05	0.83	0.99
<i>LTA&TNF</i> ^c	0.84	0.91	1.00	1.00	0.58	0.05	0.83	0.81
<i>IL6</i> ^c	0.84	1.00	0.87	0.17	0.58	0.91	0.83	0.99
<i>KLRD1</i> ^c	0.84	0.91	0.87	0.17	0.83	0.91	1.00	1.00
<i>IL12B</i>	0.84	1.00	0.87	0.83	0.35	0.91	0.83	1.00
<i>IL2</i>	0.84	1.00	0.87	0.83	0.35	0.91	0.83	0.81
<i>IL10</i>	0.84	1.00	0.87	0.83	0.35	0.91	0.83	0.81
<i>IFNGR2</i>	0.84	1.00	1.00	1.00	0.80	0.39	0.84	0.81
<i>IL12A</i>	0.84	0.91	0.87	0.83	0.80	0.39	0.83	0.99
<i>KIR2DL4</i>	0.84	1.00	0.87	0.87	0.53	0.91	0.83	0.81
<i>IL13&IL4</i>	0.84	1.00	0.87	0.87	0.58	0.81	0.83	0.81
<i>IL6R</i>	0.84	0.91	0.87	0.83	0.58	0.91	0.83	0.81
<i>IL8</i>	0.84	0.91	0.87	0.83	0.62	0.91	0.83	0.81
<i>KIR3DL3</i>	0.84	1.00	0.94	1.00	0.62	0.91	0.83	0.81
<i>IL18</i>	0.84	1.00	0.87	0.83	0.80	0.81	0.83	0.81
<i>CSF2</i>	0.84	1.00	0.87	0.83	0.80	0.91	0.84	1.00
<i>IFNG</i>	1.00	1.00	0.88	1.00	0.80	1.00	0.84	0.81
<i>NFKB1</i>	0.84	0.91	0.89	0.83	0.80	0.81	0.84	1.00
<i>TNFRSF1B</i>	0.84	0.91	0.87	0.83	0.98	0.91	0.83	0.81
<i>IL15</i>	0.84	1.00	0.87	0.83	0.80	0.53	0.83	0.81
<i>KIR3DL2</i>	0.84	1.00	0.87	0.84	0.92	0.81	0.83	0.81
<i>GATA3</i>	0.84	1.00	0.87	0.83	0.84	1.00	0.83	0.81
<i>IL8RB</i>	0.84	0.91	0.87	0.83	1.00	0.91	0.83	0.81
<i>CXCL10</i>	0.84	1.00	0.87	0.83	0.80	0.91	0.84	0.81
Cell cycle								
<i>RASSF1</i>	0.84	1.00	0.79	0.83	0.35	0.23	0.83	0.81
<i>NOV</i>	0.84	1.00	0.87	0.83	0.80	0.81	0.83	0.81
<i>CNNM2</i>	0.84	1.00	0.87	0.83	0.80	0.81	0.83	0.81
<i>GADD45A</i>	0.84	1.00	0.87	0.83	0.80	0.91	0.83	0.88
<i>CDKN2A&CDKN2B</i>	0.84	1.00	0.87	0.83	0.80	0.91	0.84	0.81
<i>CCND1</i>	0.84	1.00	0.87	0.83	1.00	0.91	0.83	0.81
<i>CCNA2</i>	1.00	1.00	0.87	0.83	1.00	1.00	0.83	1.00

Bold values indicate significant ($Q < 0.20$).

SKAT, SNP-set Kernel Association Test; SGA, small for gestational age; GHTN, gestational hypertension; PE, preeclampsia; AIMS, ancestry informative markers; FDR, false discovery rate.

^a Q values represent the proportion of false positives (number of false rejections/total number of rejections).

^b Genetic ancestry determined from 148 AIMS and STRUCTURE.

^c Meets FDR <0.20 for at least one outcome.

Table IV

Single SNP Associations, Risk Ratio, and 95% Confidence Interval for Maternal SNPs for SGA and Term SGA in Infants Stratified by Maternal Genetic Ancestry

Gene/SNP	African American ^a		European American ^a	
	SGA	Term SGA	SGA	Term SGA
<i>IL6</i> ^b				
rs4719711	1.0 (0.7, 1.6)	0.9 (0.5, 1.5)	0.7 (0.4, 0.9)	0.7 (0.4, 1.0)
rs6963444	1.8 (1.2, 2.8)	2.5 (1.5, 4.2)	1.9 (1.0, 3.7)	2.1 (1.0, 4.2)
rs1546762	1.1 (0.7, 1.7)	0.8 (0.5, 1.5)	0.6 (0.4, 0.9)	0.6 (0.4, 1.0)
rs7784987	1.5 (1.0, 2.4)	2.1 (1.2, 3.6)	2.0 (1.0, 3.8)	2.1 (1.1, 4.4)
rs3087221	1.4 (0.9, 2.3)	1.8 (1.1, 3.1)	2.3 (1.0, 5.4)	2.0 (0.8, 5.4)
rs1800795	1.1 (0.6, 2.2)	0.7 (0.3, 1.8)	0.9 (0.6, 1.3)	1.0 (0.7, 1.6)
rs1548216	1.6 (1.0, 2.5)	2.1 (1.2, 3.5)	2.3 (1.2, 4.2)	2.4 (1.2, 4.7)
rs2069843 ^c	1.5 (1.0, 2.3)	2.0 (1.3, 3.1)	2.1 (1.2, 3.8)	2.4 (1.2, 4.6)
rs2069849	1.4 (0.9, 2.3)	1.9 (1.1, 3.2)	2.2 (1.2, 4.1)	2.4 (1.2, 4.6)
<i>KLRD1</i>				
rs3759270	0.6 (0.4, 1.0)	0.4 (0.3, 0.8)	1.3 (0.9, 2.0)	1.3 (0.8, 2.0)
rs3809214 ^c	1.3 (0.9, 1.8)	1.6 (1.1, 2.4)	0.8 (0.6, 1.0)	0.8 (0.6, 1.1)
rs2302489 ^c	1.3 (0.9, 1.8)	1.6 (1.1, 2.4)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)
rs7301562	0.6 (0.4, 1.0)	0.5 (0.3, 0.9)	1.1 (0.2, 7.9)	1.6 (0.2, 11.8)
rs10772256	0.6 (0.4, 1.0)	0.5 (0.3, 0.9)	1.1 (0.2, 7.9)	1.6 (0.2, 11.8)
rs2270238	0.8 (0.4, 1.8)	0.8 (0.3, 2.1)	1.5 (1.0, 2.2)	1.5 (1.0, 2.4)
rs11611333 ^c	1.1 (0.8, 1.5)	1.0 (0.7, 1.5)	1.3 (1.0, 1.6)	1.2 (0.9, 1.7)
rs12829155 ^c	1.3 (0.9, 1.9)	1.5 (0.9, 2.4)	0.8 (0.6, 1.0)	0.8 (0.6, 1.1)

SGA, small for gestational age.

Allele and genotype frequencies presented in Tables S2 and S3.

^aGenetic ancestry determined from 148 ancestry informative markers and STRUCTURE.

^bSelected results for *IL6* presented. Results from all SNPs available in Table S6.

^cAdditive model presented.

Table V

Single SNP Associations, Risk Ratio, and 95% Confidence Interval for Maternal SNPs and PE Stratified by Genetic Ancestry

Gene/SNP	European American ^a	African American ^a
<i>NFKBIL1</i>		
rs2857605	1.1 (0.7, 1.6)	1.0 (0.5, 1.9)
rs2239707	1.0 (0.6, 1.5)	1.4 (0.8, 2.4)
rs2230365	1.0 (0.6, 1.5)	1.5 (0.8, 3.0)
rs3130062	1.2 (0.7, 2.1)	1.7 (0.5, 5.4)
rs4947324	0.6 (0.3, 1.1)	0.9 (0.5, 1.7)
rs2857709	1.0 (0.6, 1.6)	0.8 (0.3, 1.9)
<i>LTA</i>		
rs915654	1.0 (0.6, 1.5)	1.7 (0.9, 3.1)
rs909253 ^b	1.5 (1.1, 2.0)	1.0 (0.7, 1.4)
rs2229094	0.6 (0.4, 1.0)	1.3 (0.8, 2.1)
rs1041981 ^b	1.4 (1.0, 2.0)	1.0 (0.7, 1.5)
Intergenic		
rs1799964	0.7 (0.4, 1.1)	1.0 (0.6, 1.8)
rs1800630	0.8 (0.5, 1.2)	1.4 (0.8, 2.4)
<i>TNF</i>		
rs1800629	1.8 (1.1, 2.7)	0.6 (0.3, 1.2)
rs7769073	0.8 (0.4, 1.8)	0.9 (0.4, 1.7)
<i>TBKBP1</i>		
rs2013383	0.6 (0.4, 0.9)	1.1 (0.7, 1.8)
rs1808192	0.6 (0.4, 0.9)	1.0 (0.6, 1.6)
<i>TBX21</i>		
rs4461115	1.2 (0.8, 1.9)	0.8 (0.3, 2.0)
rs16946264	1.1 (0.6, 1.8)	1.0 (0.6, 1.6)
rs11079788	0.8 (0.5, 1.3)	1.2 (0.7, 1.9)
rs16946878	1.3 (0.7, 2.4)	1.0 (0.5, 1.9)
rs16947078	0.8 (0.5, 1.3)	0.8 (0.5, 1.3)

PE, preeclampsia.

All single SNP estimates are presented in Table S7.

Allele and genotype frequencies presented in Tables S4 and S5.

^a Genetic ancestry determined from 148 ancestry informative markers and STRUCTURE.

^b Additive model presented.