VARIATIONS IN INFLAMMATORY AND CELL CYCLE GENES AND PRETERM BIRTH, SMALL FOR GESTATIONAL AGE AND HYPERTENSIVE DISORDERS OF PREGNANCY

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ABSTRACT

QUAKER HARMON: Variations in Inflammatory and Cell Cycle Genes and Preterm Birth, Small for Gestational Age and Hypertensive Disorders of Pregnancy
(Under the direction of Stephanie Engel)

The maternal outcome of preeclampsia and the fetal outcomes of preterm birth and poor intrauterine growth often occur together, share placental pathology and are marked by changes in inflammatory biomarkers. Genetic polymorphisms in inflammatory genes have been investigated with respect to all of these outcomes with conflicting results. In previous studies case groups have been small or non-representative of US populations, and coverage of candidate genes has been sparse. We sought to expand coverage of inflammatory genes related to natural killer cells and T cells and in addition included candidate genes related to cell cycle function. In a sample of 1646 women from a bi-racial prospective pregnancy cohort, we examined the relationship between 503 tagSNPs in 40 genes and the outcomes of preterm birth, small for gestational age, gestational hypertension and preeclampsia.

Six genes involved in natural killer cell function (*IL12A, CSF2, IFNGR2* and *KIR3DL2*) and Th2 immunity (*IL13* and *IL4*) were associated with preterm birth among European Americans with some evidence of an association for African Americans as well (*IL12A* and *CSF2*). *IL6* and *KLRD1* were associated with term small for gestational age births among African Americans with similar results for *IL6* alone among European Americans. *LTA*, *TNF* and *TBKBP1* were associated with preeclampsia among European Americans only. There were no associations with any cell cycle genes or with the outcome of gestational hypertension.

In summary, this study found novel associations with a number of genes related to natural killer cells, Th2 immunity and TNF signaling pathways and the outcomes of preterm birth, poor fetal growth and preeclampsia among both European and African Americans.

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LIST OF ABBREVIATIONS

ABI	Applied Biosystems
ACOG	American College of Obstetricians and Gynecologists
BMI	body mass index (kg/m2)
CES-D	Center for Epidemiologic Studies Depression Scale
CEPH	Centre d'Etude du Polymorphism Humain, Northern and Western European Ancestry
CEU	Northern and Western Europe Ancestry
CI	confidence interval
CVD	cardio vascular disease
DAG	directed acyclic graph
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
GDM	gestational diabetes mellitus
GHTN	gestational hypertension
HWE	Hardy Weinberg Equilibrium
IOM	Institute of Medicine

IPW inverse probability weighting

IQR inter-quartile range

IUGR intrauterine growth restriction

kg kilogram

LD linkage disequilibrium

MAF minor allele frequency

MOS Medical Outcomes Study

OR odds ratio

PE preeclampsia

PIN Pregnancy Infection and Nutrition

PPROM preterm premature rupture of amniotic membranes

PPV positive predictive value

PTB preterm birth

PTL preterm labor

QC quality control

SBP systolic blood pressure

SGA small for gestational age

SNP Single Nucleotide Polymorphism

UNC University of North Carolina

US United States

YRI Yoruba from Ibadan, Nigeria

CHAPTER 1 BACKGROUND

Introduction

Pregnancy is a state of altered inflammatory function.[1, 2] In the majority of pregnancies, the altered inflammatory function works to the benefit of both mother and fetus by mitigating the immune rejection of fetal tissue[3, 4] while restricting the extent of invasion of the fetally derived placenta.[5] As the pregnancy progresses, the balance of pro and anti-inflammatory cytokines may act as a determinant of the timing of delivery.[4] Perturbations in inflammatory pathways from pre-conception through delivery have significant impacts on the success of the pregnancy and the health of both the mother and the fetus. Increased inflammation has been implicated in preterm birth,[2, 6] poor fetal growth as measured at birth (Small for Gestational Age, SGA)[4, 7] and Hypertensive Disorders of Pregnancy including Preeclampsia (PE) and Gestational Hypertension without proteinuria (GHTN).[1, 8]

Previous studies have identified a number of inflammatory biomarkers that are altered in PE and SGA.[1, 7-10] Studies of heredity have established a genetic component in PE,[11] preterm birth[12-14] and SGA.[15] Genetic epidemiology studies to date have found some associations with preterm birth, SGA and PE and polymorphisms in inflammatory pathway genes (see Section 1.6). Although there have been some large studies for preterm birth, studies for PE in US populations

have been limited and only a handful of studies have measured associations with SGA, covering fewer than 10 inflammatory genes in total.

Given the dramatic growth of the placenta during pregnancy and the pivotal role it plays in sustaining the fetus, factors that limit placental growth or function may be involved in SGA, PE and preterm birth. In addition to placental growth, remodeling of the uterine wall and vasculature is extensive and must occur for a successful pregnancy. Cell cycle processes are fundamental for cell proliferation, and genetic polymorphisms in cell cycle genes may result in reduced cell proliferation and poor placental development, leading to poor fetal growth and/or preeclampsia. Genetic polymorphisms in cell cycle genes have not been extensively studied for the outcomes of PE, SGA or preterm birth. A few studies have found associations with other reproductive outcomes such as missed abortion[16] and gestational diabetes.[17] Additionally, a number of cell cycle genes have been implicated in related outcomes such as cardiovascular disease[18] and type 2 diabetes.[19] Animal and human placental expression studies have also suggested that cell cycle genes are differentially expressed in placental tissue[20, 21] and may differ in expression, quantity or function in women with PE or SGA. Therefore cell cycle genes contribute to a novel pathway that may be important in the outcomes of PE, SGA and preterm birth.

The Pregnancy Infection and Nutrition Cohort offers a good opportunity to study polymorphisms in a panel of candidate genes in the inflammatory and cell cycle pathways in a biracial population with well-measured covariates. Knowledge about these genetic variants will improve our knowledge about these heterogeneous phenotypes, aide in the identification of susceptible populations and identify target genes for further study.

Descriptive epidemiology of Preterm, SGA/IUGR and Preeclampsia/Gestational Hypertension

Preterm birth, poor fetal growth and gestational hypertension are maternal and infant outcomes that often co-occur. Hypertensive disorders of pregnancy (including both preeclampsia and gestational hypertension) are maternal conditions that result in preterm birth in up 60% of pregnancies complicated by preeclampsia and poor fetal growth in up 25%.[22] Preterm birth due to medical indications, which may include maternal disease due to gestational hypertension, only accounts for 30% of preterm births[23] with the majority of preterm births having an etiology unrelated to gestational hypertension. While poor fetal growth is present in some pregnancies complicated by gestational hypertension, the association with preterm birth is more complicated. While there is evidence that infants born preterm may be smaller than their *in utero* peers at a given gestational age,[24] a measure of fetal growth such as SGA (small for gestational age) that is adjusted for gestational age, should have a similar proportion of 'small' infants at each gestational age.

Despite the similarities and co-occurrence of these outcomes, they share distinct risk factors and etiologies, which will be explored below. In studying closely associated outcomes such as these, similarities in genetic associations must be examined for confounding, and phenotypes should be adjusted when appropriate. By examining this group of outcomes in the same population, it is our hope that identification of both similar and distinct genetic associations will inform knowledge of important biologic pathways and identify opportunities for both primary and secondary prevention.

1.2.1 Preterm Birth

Descriptive Epidemiology

Preterm birth is defined as delivery before 37 completed weeks of gestation. In the United States, preterm birth occurs in approximately 12% of births. Although it is primarily defined by the timing of delivery, preterm birth is a heterogeneous outcome with multiple pathways leading to a birth before term. Preterm birth has been divided into subtypes based on the indication for delivery, the timing of delivery, or the presumed underlying pathology. Preterm birth is of importance due to the significant medical and societal impacts borne by the infants and their families throughout the life course.[25]

Classification

Based on indication for delivery, preterm birth can be characterized as preterm labor, preterm premature rupture of the fetal membranes or a medically indicated delivery for the health of the mother or infant. Although these subtypes are commonly used and may have different risk factors, the distinction between the indications for preterm delivery may not always be etiologically important.[26-28]

Timing of delivery is also used to classify preterm births. Extremely preterm (delivery before 28 weeks), very preterm (delivery before 32 weeks) and late preterm (34 to 36 weeks) have all been used as gestational age classifications of preterm birth. The severity of preterm birth with regard to gestational age may be most important for predicting the mortality and morbidity of the infant. Infants born extremely preterm have the highest risk of both neonatal

and infant mortality as well as the highest risk of later complications.[25] There is some indication that early preterm birth may have distinct risk factors.[26]

A classification of preterm based on the underlying pathology resulting in preterm birth would be most interesting from an etiologic perspective. While specific maternal medical conditions (preeclampsia, underlying chronic disease), fetal conditions (severely low amniotic fluid, fetal distress, and certain congenital defects), maternal trauma or serious illness may often be an apparent cause of preterm birth, many etiologies of preterm birth (subclinical placental abruption, placental pathology, subclinical uterine infection or inflammation) are neither apparent, nor susceptible to diagnosis prior to delivery.

Time Trends

Although the preterm birth rate had appeared to be steadily increasing from 8.9% in 1980[29] to a high of 12.8% in 2006,[30] recent data suggest that the rate may be plateauing or even decreasing with the preterm birth rate declining for two consecutive years to 12.3% in 2008.[31, 32] Changes since the 1980s in the preterm birth rate have been attributed to changes in maternal demographics, increasing use of reproductive technologies and medical interventions such as cesarean section in the late preterm period.[33] The greatest increases in the preterm birth rate were seen among late preterm births with medical indications. The decline in the preterm birth rate observed in 2008 was evident among all maternal age groups below 40, in White, African American and Hispanic mothers, in almost all US states and in both cesarean and vaginal births.[32] Although the preterm birth rate has generally been increasing, fetal outcomes have been improving over the same time period, with increased survival among the earliest preterm infants.[25]

Sequelae

Infant

Neonatal and infant death is the most serious consequences of preterm birth. In 2006 the U.S. the infant mortality rate for preterm was 35 per 1,000, compared with 2 per 1,000 among term infants. Among preterm infants, the risk of mortality is highest for those born earliest with very preterm infants (less than 32 weeks) having an infant mortality rate of 176 per 1,000, compared with 7 per 1,000 among late (34-36 week) preterm infants.[34] Although preterm birth, and in particular very preterm birth, is relatively uncommon, the high death rate among preterm infants results in infant mortality among preterm infant accounting for 68% of total infant mortality in 2006.

In addition to mortality, preterm infants are at increased risk for significant morbidity. Acute complications include respiratory distress, necrotizing enterocolitis, feeding intolerance, apnea, infection, cardiac abnormalities, anemia, and brain injury (intraventricular hemorrhage and periventricular leukomalacia). Chronic health concerns include chronic lung disease, gastro-espohageal reflux, vulnerability to infection (particularly respiratory syncitial virus), hearing loss, eye disorders (retinopathy of prematurity), cerebral palsy, cognitive deficits, behavioral problems and epilepsy.[25, 35] Follow-up studies have also shown an association between gestational age at birth and educational attainment and income later in life.[35, 36] As with mortality, the risk and severity of acute and chronic morbidity is associated with the severity of preterm, with infants born before 28 weeks at highest risk.[33]

Although very preterm infants face the highest risks of mortality and morbidity, there is an increasing awareness of the risk associated with late preterm birth. Infants born between 34 and 36 weeks continue to have an elevated neonatal mortality rate compared with full term

infants, and these infants also had increased respiratory distress syndrome, sepsis, intraventricular hemorrhage and NICU admission.[37] Although there are fewer long-term studies among late preterm infants specifically, there is some indication that there may be a risk of long term behavioral problems as well.[38]

Maternal

Maternal health consequences from preterm birth are fewer compared with infant sequelae, and they may be attributable to shared pathways between preterm delivery and later health outcomes, rather than early delivery itself. Women with a previous preterm birth are more likely to have subsequent preterm births.[23, 39] Many of the medical sequelae for women with preterm delivery are related to the underlying pathology that necessitated the preterm birth such as complications from preeclampsia, gestational diabetes, coagulation disorders or underlying cardiac or respiratory conditions. As such, the preterm delivery is associated with subsequent maternal health complications, but the preterm delivery is not causative.

There is some suggestion that women with a previous preterm delivery are at increased risk of later cardiovascular disease;[40] however, this may be due to shared vascular and metabolic risk factors which predispose to both preterm delivery and later CVD risk.

Risk Factors

Apart from pre-existing or emergent maternal medical conditions and previous preterm birth, few strong risk factors for preterm birth have been identified. Table 1.1 highlights the most commonly identified risk factors. Heritability will be discussed in Section 1.5.

Table 1.1 Risk factors for preterm birth[23, 25, 41, 42]

Behavioral and Psychosocial	**Pregnancy Complications**	**Maternal Medical Condition**
Smoking	Infection	Assisted Reproduction
High psychological or social stress	Vaginal bleeding	Short inter-pregnancy interval
Long work hours, hard physical labor.	Placental abruption	History of thyroid, renal,
Cocaine, heroin use	High or low amniotic fluid	respiratory, cardiac, diabetes,
Heavy alcohol use	Placenta previa	auto-immune conditions,
Depression	Abdominal surgery	hypertension.
Poor nutrition	Multiple gestation	Cervical cone biopsy or LEEP
	Pre eclampsia	Previous preterm
Demographic and Anthropometric		Short cervical length
African American race	**Environmental Exposures**	Uterine abnormalities
Low socio-economic status	Lead	
Low education	Occupational exposure to PCB	
Extremes of age	DDT	
Unmarried status	Environmental tobacco smoke	
Low pre-pregnancy BMI	Air pollution	

1.2.2 Hypertensive Disorders of Pregnancy

Descriptive Epidemiology

Pregnancy is a state of great physiologic change for the mother. Measures such as blood pressure vary throughout pregnancy with a usual pattern that includes a decrease in blood pressure during the second trimester.[43, 44] Hypertensive disorders of pregnancy, as used here, encompass three conditions of increased blood pressure that emerge after the 20th week of gestation. The estimates of incidence of hypertensive disease in pregnancy range from a low of 2%-7% for preeclampsia in healthy nulliparous women[22] to a high of 12-22% for hypertensive

disorders overall.[45] Although the exact incidence may be uncertain, hypertensive disorders of pregnancy are a leading cause of maternal mortality. In the United States, from 1991 to 1999 hypertensive disorders of pregnancy was the identified cause of death in 15.7% of maternal deaths[46] while from 1998 to 2005 hypertensive disorders of pregnancy were identified as cause of death in 12.3% of maternal deaths.[47]

Classification

Although there is some variation in the nomenclature used to describe the specific conditions,[45] the following terminology will be used. Gestational hypertension (GHTN) is an increase in blood pressure after 20 weeks of gestation without proteinuria (protein in urine). Preeclampsia (PE) is an increase in blood pressure after 20 weeks gestation with evidence of proteinuria. Women with preeclampsia may also have edema, visual disturbances, headache and abdominal pain. Severe preeclampsia includes a blood pressure above 160 mmHg systolic or 110 mmHg diastolic, proteinuria in excess of 5 grams per 24 hours (3+ dipstick), low urine output, pulmonary edema, low platelets and elevated liver enzymes. Eclampsia is diagnosed when a woman with preeclampsia experiences a new-onset seizure. In a woman with pre-existing hypertension or renal impairment, a diagnosis of superimposed preeclampsia can be made with worsening of hypertension or proteinuria or the new involvement of other systems (neurological, liver, hematologic).[22,45]

Recent guidelines[45] suggest that an elevation in blood pressure should be defined as a blood pressure above 140mmHg systolic or 90 mmHg diastolic at least twice after 20 weeks gestation in women who were previously normotensive. Proteinuria can be defined as more than 300mg of protein in a 24 hour collection of urine or a protein dipstick value of >=1+ (300mg/L) on two random urine samples taken more than 24 hours apart. Previous definitions

of preeclampsia used a “30-15” rule; an increase in systolic blood pressure of 30 mmHg or an increase in 15 mmHg in the diastolic blood pressure over baseline.[45]

There is some suggestion that preeclampsia is a heterogeneous disorder with different pathophysiology for those cases arising early in pregnancy with impaired fetal growth compared to cases arising later in pregnancy with little fetal compromise.[48]

Time Trends

The changing and differing diagnostic criteria for hypertensive disorders of pregnancy, as well as poor data quality on birth certificates, has complicated the analysis of these disorders over time. Using data from the National Hospital Discharge Survey, Wallis found an increase in both gestational hypertension and preeclampsia over the period from 1987 to 2004. GHTN increased from 10.7 per 1,000 deliveries in 1987-1988 to 30.6 per 1,000 deliveries in 2003-2004. Over the same time period preeclampsia increased from 23.6 per 1,000 deliveries to 29.4 per 1,000.[49] An analysis of preeclampsia in Norway, which has had more stable diagnostic criteria and universal access to care, over the period of 1967-2003 suggested a gradual increase in the incidence of preeclampsia in first pregnancies from 3.1% in the first decade of the study to 5.5% in the final decade.[50] Currently, rising rates of obesity, a risk factor for preeclampsia, have led to concerns that the incidence of preeclampsia may continue to increase.[22, 43]

Sequelae

<u>Fetal</u>

Up to one quarter of infants in pregnancies complicated by a hypertensive disorders of pregnancy will have poor intrauterine growth, and up to two-thirds will be delivered preterm for

fetal or maternal indications.[22] Preterm birth can be indicated due to intrauterine growth restriction, placental abruption, low amniotic fluid or non-reassuring fetal testing. Acute and chronic sequelae from preterm birth and poor fetal growth are covered in Sections 1.2.1 and 1.2.3. Still birth and infant death are rare fetal outcomes, which are elevated compared with non-hypertensive pregnancies.[22, 50]

Maternal

Many of the symptoms of hypertensive disorders of pregnancy resolve with the delivery of the infant. In severe cases, there can be longer lasting sequelae including neurologic deficits as a result of seizure or stroke, renal failure, liver failure or hemorrhage.[45] Hypertensive disorders of pregnancy are one of the leading causes of maternal mortality.

Women with a prior pregnancy complicated by hypertension are more likely to have recurrent gestational hypertension and preterm birth.[22, 45] There is also evidence that women with gestational hypertension or preeclampsia are at increased risk for cardiovascular disease (CVD) and diabetes later in life,[51, 52] with some evidence to suggest that early preeclampsia or recurrent preeclampsia are stronger risk factors for later CVD.

Risk Factors

The strongest known risk factor for preeclampsia is the presence of antiphospholipid antibodies and a previous pregnancy with preeclampsia.[53] These are associated with a more than 5 fold increase in risk. However preeclampsia is most often associated with first pregnancies, and antiphospholipid antibodies are rare. Heritability will be discussed in Section 1.5. Additional risk factors are outlined in Table 1.2.

Table 1.2 Risk factors for hypertensive disorders of pregnancy [22, 45, 53]

Maternal Medical Conditions	Pregnancy Related Conditions	Demographic and Anthropometric Factors
Antiphospholipid syndrome Chronic Hypertension Diabetes Pre-existing disease; renal, autoimmune, vascular, connective tissue, rheumatic, thrombophilias	Previous PE First birth Multiple Gestations Long Inter pregnancy Interval Infection New Father*	Increased BMI Extremes of age Family History of PE African American race **Behavioral** Smoking (protective)

*The risk associated with novel sperm exposure is quite controversial

Smoking

Of note, smoking has an accepted and seemingly robust, if weak, protective association with preeclampsia. Multiple studies and systematic reviews have shown an association between smoking and both gestational hypertension and preeclampsia in the range of OR 0.5-0.7[54-56] with some suggestion that heavy smokers, women who smoke until the end of pregnancy and lean women[57] have more protection.

1.2.3 Fetal Growth

Fetal Growth as a Reproductive Outcome

Fetal growth over the course of pregnancy is a result of genetically determine growth potential, maternal ability to meet the nutritional needs of the fetus through adequate nutrients and adequate delivery of the nutrients, fetal nutritional demands, which may be influenced by fetal pathology, and the length of gestation, which provides time for growth. Maternal, fetal and environmental factors may act at any of these levels to influence how well a fetus grows over the course of pregnancy. Given the individual variation of growth potential, the strong association of birth weight with gestational age, difficulty in accurately defining gestational age

and the inability to obtain a true fetal weight until the time of delivery, assessment of fetal growth is quite difficult.

Despite the difficulties in assessing the trajectory of fetal growth, the final product of fetal growth, birth weight, is a well-measured and well recorded outcome. Low birth weight (<2500 g) in particular, is associated with a number of important neonatal outcomes including neonatal mortality and morbidity. However, focusing simply on birth weight obscures important individual level and population associations. Historically, given the difficulty is assessing gestational age accurately, preterm birth was sometimes equated with low birth weight. However, not all preterm births are also low birth weight. Additionally small term infants may have undergone restricted growth *in utero*, and so-called "normal" birth weight infants may not have reached their full potential. At the population level, factors such as altitude that result in a lower mean birth weight may not be pathological.

Within the population of "small" infants, only a fraction are small for reasons that will result in meaningful health consequences. Yet attempts to identify small infants who are also high risk for other outcomes have had only limited success. At a population level with large numbers, the residual distribution of birth weight can help identify populations at risk for higher infant mortality by identifying a surplus of small preterm infants.[58] At the individual level, birth weight adjusted for gestational age through a small for gestational age (SGA) or z-score measurement overcomes some of the difficulty with looking solely at low birth weight by taking time *in utero* available for growth into account.

However, an SGA measure based on live births only identifies the lowest fraction (often 5th or 10th percentile) of infants at a given gestational age. Preterm infants are often smaller than their *in utero* counterparts who go on to deliver at term.[24, 59] The SGA measure fails to capture

this discrepancy and may fail to capture many preterm infants who have been growth restricted in utero.[60] Use of ultrasound-based measures of fetal growth has been offered as a possible solution to the difficulties of a live birth standard.[60] Ultrasound-based measures however are algorithms that also have inherent errors and can only be established and validated in a select population, inviting bias and non-generalizabilty .

For purposes of this study, the outcome of interest is intrauterine or placental conditions that prevent the fetus from attaining maximal growth. While frequent longitudinal ultrasound measurements starting at a very early in pregnancy for cohort members along with a comparable population sample would be ideal, these data were not available for this secondary analysis. The SGA variable collected for the study cohort may under-represent growth restricted preterm infants, but the cut-point of 10% offers a reasonable balance between more stringent definitions, which would further bias the preterm infants, and a more permissive definition, which would identify more constitutionally small infants.

Types

Poor fetal growth has sometimes been characterized as proportional or symmetric and non-proportional or asymmetric. Symmetrically small infants have reduced weight, length and head circumference while asymmetrically small infants have reduced weight but "normal" length and head circumference. Theoretically, complications or maternal malnutrition arising at conception will result is symmetrically small infants while complications that arise later in pregnancy will impact final weight but spare bone and head growth, which have already neared completion. Studies that have been able to accurately determine gestational age and account for confounding variables however have failed to find etiologic differences between these two groups of small infants.[61, 62]

Time trend

As measured by SGA, poor fetal growth will, by definition, remain stable over time. Therefore continuous measures such as the distribution of birth weights, residual distributions of small preterm infants, or mean birth weight over time will provide more information about temporal trends in birth weight. National statistics from the US suggest a fairly stable birth weight distribution between 1950 and 2000 with a very slight shift towards heavier births.[33] A study in Norway examined birth weights from 1860 to 1984, a time period that included both industrialization and periods of industrial collapse, World Wars and modern times with a strong social support system, all of which all affect the livelihood, nutrition and general health of women. Over this period of time in Norway birth weights increased just under 200g over the course of 120 years.[63] These data suggest that population-level birth weight has remained fairly stable over time.

Sequelae

<u>Infant</u>

Low birth weight is consistently associated with increased neonatal mortality[33] although it is difficult to ascribe causation given the number of causes of low birth weight (preterm birth in particular) and the possibility of an unknown common cause of low birth weight and neonatal mortality.[64] The immediate neonatal sequelae of low birth weight are often intertwined with the sequelae of early gestational age, although the association between infant mortality and birth weight is evident at all gestational ages.[58]

The long term effects of low birth weight on subsequent health and mortality can also be difficult to assess given the implausibility that birth weight *per se* is causally related to later

health outcomes.[65] However, while birth weight may not be causally linked to subsequent outcomes, there are a number of observed associations between birth weight and later health outcomes.

The Barker Hypothesis[66-68] suggests that impaired growth and development in fetal life and infancy programs persistent changes in metabolic, physiologic and structural processes that influence the development of chronic disease later in life. In particular, heart disease and diabetes have been associated with lower weight at birth. While the association with all-cause mortality has been less clear cut, there is the suggestion of higher cardiovascular and all-cause mortality among low birth weight infants compared with their "normal" birth weight peers.[69]

Maternal

Delivery of a small fetus is often less physically difficult for women with lower incidence of perineal damage and need for c-section due to fetal size. As with preterm delivery, the immediate maternal sequelae depend on the cause of the low birth weight. There is some suggestion that women who deliver low birth weight infants may be at increased risk for later CVD. The association with later CVD seems to be driven by the preterm aspect of low birth weight and is likely due to common cause between CVD and poor fetal growth or preterm birth.[40, 70] There is however suggestive evidence that a biologic process activated during pregnancy that results in a low birth weight infant may persist and result in later CVD.[71]

Risk Factors

In general, fetal growth, as measured at birth, is considered as a possible negative outcome at both ends of the birth weight distribution. Both small and large infants have increased risk of

negative sequelae. Although this study is focused on poor fetal growth as a marker of placental dysfunction, large infants also can have poor outcomes.

Risk factors for poor or excessive fetal growth are complex. Birth weight is the culmination of fetal, maternal and environmental factors. Potential for infant height and weight is determined by fetal genetics. Attainment of that potential is influenced by maternal ability to supply the necessary nutrients and the intervention of many possibly environmental insults.

A number of natural experiments in maternal malnutrition, such as severe famines during times of war, have shown that acute maternal malnutrition, below 1,500 calories a day, especially during the third trimester, is associated with birth weight decrements of approximately 300g. However, above this minimum level, maternal adaptation appears to protect the fetus from significant weight loss.[63]

Table 1.3 lists a number of factors that are associated with birth weight across the range of birth weight with some conditions increasing the risk for large infants (diabetes) and others associated with small infants (smoking). Heritability and recurrence of low birth weight will be explored in Section 1.5.

Table 1.3 Factors associated with fetal growth [33, 41, 61]

Maternal/Paternal	Pregnancy Related	Environmental (all limited evidence)
Ethnicity/ Race	Parity	Lead
Social Class	Plurality	DDT/DDE
Maternal height and weight	Smoking	Environmental Tobacco Smoke
Parental birth weight	Fetal sex	Outdoor air pollution
Previous LBW infant	Gestational hypertension	Disinfection by products
	Gestational diabetes	Nitrate in water
	Gestational weight gain	

1.3 Role of Inflammation in Adverse Pregnancy Outcomes

Pregnancy is a state of altered inflammatory function.[1] During an uncomplicated pregnancy, there are distinct changes in maternal immunity that result in an enhancement of defensive or innate immunity and a decrease in adaptive immunity through reduced natural kill cell and T cell inflammatory activity. Compared with post-partum levels, there are marked changes in cytokine concentrations, activity and response to stimulation.[72, 73] In the majority of pregnancies, the altered inflammatory function benefits both mother and fetus by mitigating the immune rejection of fetal tissue[3] while restricting the extent of invasion of the fetally-derived placenta.[5] As the pregnancy progresses, the balance of pro- and anti-inflammatory cytokines may act as a determinant of the timing of delivery.[74] Dysregulation in inflammatory pathways from pre-conception through delivery may impact the success of the pregnancy and the health of both the mother and the fetus.

1.3.1 Preterm Birth

Although the biological pathways behind the initiation of labor, whether at term or preterm, are still poorly understood, inflammatory cytokines are integral to a number of processes that occur at the time of delivery. As reviewed by Bowen,[74] pro-inflammatory cytokines tend to increase towards term, and labor itself is a pro-inflammatory state. Inflammatory cytokines (*IL-1, TNFα, IL-6*) in addition to anti-inflammatory cytokines (*IL-4* and *IL-10*) influence the production and metabolism of prostaglandins which enhance uterine contractility.[75] *TNFα, IL-1β, IL-6, CSF1, TGFβ* and *IL-8* influence the secretion of metalloproteinases that degrade fetal membranes at the time of birth. *IL-8* has been implicated in cervical ripening.

Given the role of infection in preterm delivery, evidence of elevated inflammatory cytokines in preterm deliveries may be due to underlying acute or chronic infection. However pregnancies uncomplicated by infection show elevated levels of *IL-8* and *IL-1β,* suggesting an independent role of inflammatory cytokines.[75]

1.3.2 Hypertensive Disorders of Pregnancy and SGA

Although distinct outcomes, Hypertensive Disorders of Pregnancy and SGA share certain common biologic process and will be considered together. Among the similarities, Ness[9] and others[3, 7, 10] note that many cases of SGA and PE share common placental pathology that includes shallow placentation. In normal pregnancy, fetal cytotrophoblasts invade the maternal tissue and orchestrate remodeling of the maternal vasculature. Maternal spiral arteries that had previously been narrow and contractile become wider with erosion of the muscular lining so that resistance to placental blood flow is reduced and no longer subject to vasomotor contraction.[3, 8] The process of changes in the maternal uterine wall (myometrium and decidua) is referred to as remodeling. Part of the pathology associated with both preeclampsia and poor fetal growth is shallow placentation, with both the myometrium and decidua showing reduced transformation. For PE there is sometimes evidence of absence of vascular remodeling in the myometrium and reduced remodeling in the decidua. For pregnancies that result in poor fetal growth, however, there is some, but still diminished, remodeling in both the myometrium and decidua.[76]

Inflammatory cytokines play a role in successful placental invasion and development[74] and may influence the invasive phenotype of trophoblasts. The interaction between fetal trophoblasts and maternal decidual cells may be mediated by maternal natural killer cells. These NK cells create a local “microenvironment” which, while permitting placental implantation and

remodeling, limits the extent of the invasion.[5] Inflammatory cytokines may also play a role in placental development by influencing the hypoxia inducible factor (HIF), a transcription factor which is central in placental angiogenesis.[9]

The later manifestations of poor placentation can be maternal, fetal or both, with SGA and PE occurring both concurrently and in isolation.[77] Fetal effects of poor placentation include SGA. With inadequate transformation of spiral arteries, the resistance to placental blood flow remains high, and as a result there is inadequate delivery of both oxygen and other nutrients to the fetus. While some degree of maternal and fetal adaptation can occur (increased maternal cardiac function and increased erythropoiesis to improve oxygen carrying capacity and delivery, and fetal shunting of blood, decreased fetal movement and tone), in SGA these adaptations are insufficient to overcome the restricted oxygen and nutrients available to the fetus.[78]

Maternal effects of poor placentation can include symptoms of gestational hypertension including increased blood pressure, decreased renal function and endothelial dysfunction. As result of shallow placentation, hypoxia and ischemic-reperfusion injuries occur with increased levels of inflammatory cytokines. These inflammatory cytokines may act directly to create the symptoms of preeclampsia or may act through other biological pathways including angiogenesis, the rennin-angiotensin system, endothelial activation, or clotting system disturbances.[1, 8, 9] Ness also hypothesizes that the inflammatory cytokines may interact with preexisting risk factor for metabolic syndrome (adiposity, hyperglycemia, insulin resistance, hyperlipidemia, coagulopathy) to predispose some women with poor placentation to exhibit symptoms of PE.[9]

Animal models of preeclampsia are limited by differences in placental structure. However LaMarca[8] was able to reproduce some of the maternal symptoms of preeclampsia (increased

blood pressure, decrease blood flow and renal function) by infusing rats with pro-inflammatory cytokines.

Inflammatory cytokines have been measured in the serum of women with gestational hypertension, preeclampsia and SGA. Increases in pro-inflammatory cytokines (*TNFα, IL-6, IL-8*) have been identified in women with PE[8] and SGA (*IL-6, TNFα, IL-1, IL-8*) [1, 4, 7, 9] and in women who will go onto develop PE. [74, 79, 80] Decreased levels of anti-inflammatory cytokines (*IL-10*) has also been associated with PE [8] and SGA.[4, 74] Although not all studies are consistent and vary with respect to timing of sample collection, sample tissue, outcome definition and comparison groups, there is sufficient evidence to implicate inflammatory cytokines in the outcomes of GHTN and SGA.

1.3.3 Selection of Inflammatory Genes

The inflammatory pathway is complex and interconnected with a number of other biologic pathways. Review of existing genetic studies (Section 1.6) suggested some genes that are important to consider (TNFα*, LTA (TNFβ), IL6, IL6R, IL1A, IL1B, IL10, IL2, IL4, IL13*). Some of the genes found in previous studies (*TNFR1, TNFR2, IL5, IL1RA*) were not included in the current panel due to design issues, including identification of more biologically relevant genes, poor tag design scores, difficulty tagging the gene in a combined CEU and YRI population, too many SNPs required to tag the gene, or previous findings based solely on tags with poor replication.

In order to expand on candidate genes, we considered the underlying immune system and links to cardiovascular outcomes. Although the three outcomes under consideration have different underlying pathology, the inflammatory genes involved may be similar. The inflammatory pathway in preeclampsia has received the most attention with numerous *in vitro*

and placental studies. Saito[81, 82] provides a conceptual framework for preeclampsia that highlights the delicate balance between different arms of the immune system during pregnancy.

The human immune system can be divided into the innate immune system and the adaptive immune system.[83] The innate immune system is non-specific and acts quickly in response to multiple insults (injury, pathogens) by recruiting immune cells, activating cells to identify pathogens and remove dead cells, and activating the adaptive immune system. Inflammation is one of the first responses in the innate immune system and can be induced by infection or injury to prevent the spread of infection and promote healing. Cytokines released as a part of the innate immune system (*IL1, IL6, IL8, IFNγ, TNFα*) induce local reactions (swelling, redness, warmth) and recruit additional immune cells to the site. Innate immunity is non-specific and does not produce long-term immune memory or protection.

The adaptive immune system, while slower to respond compared with the innate immune system, results in the creation of antibodies and generates specific immune responses based on the type of pathogen present. The adaptive system is responsible for immunologic memory and longer-term immune protection. The adaptive immune system functions through T cells and B cells and can produce Type 1 (Th1) or Type 2 (Th2) cytokines.

In general, Th1 cytokines induce cell-mediated immunity. Type 1 cytokines (*IL2, TNF, IFNγ*) drive the production of cytotoxic T cells and activated macrophages. Cytotoxic T cells lyse cells expressing specific antigens and also play a role in graft rejection when cells are recognized as 'non-self'. Activated macrophages engulf invading organisms, dead cells, immune complexes and antigens. Macrophages also release cytokines (*TNF* and *IL1*).

The Th2 response results in humoral immunity. Type 2 cytokines (*IL4, IL5, IL6, IL10, IL13*) recruit and stimulate B cells, which produce antibodies. These antibodies are responsible for marking pathogens for death and for immune memory. Type 2 cytokines also activate phagocytic cells (macrophages and neutrophils) to remove antigen, bacteria and complement, which can destroy organisms or make it easier to be spotted as foreign so that other cells will destroy it.

The mechanism that drives the differentiation of naïve T cells to Th1 or Th2 is unknown and is thought to depend on the local cytokine milieu. *IFNγ* and *IL12* drive Th1 cell production while *IL10* and *IL4* inhibit Th1. *IL4*, along with *IL6* and *IL1*, drives Th2 production while *IFNγ* inhibits Th2 cells. Therefore the two cells lines act to inhibit the other and, in as much as both Th1 and Th2 are needed for complete immunity, the two cell lines compete for dominance depending on the unique situation.

Saito suggests that while pregnancy is generally a pro-inflammatory state, the balance of inflammation during pregnancy is in favor of Th2 cells as opposed to Th1 cells. In pregnancy an over expression of the Th1 response may result in rejection of the semi-foreign fetus and trophoblast cells, which are necessary for placental development.

Saito posits that an excessive Th1 response results in the rejection of the fetus (miscarriage) or poor placentation (preeclampsia), while an increased Th2 response allows for a successful pregnancy.[82] Given the nature of biological systems however, inflammatory cytokines are not uniquely situated in a single pathway and have both autocrine and paracrine activity, making the true pathways complex.

In choosing genes to include on the panel, we considered both the role of the gene in inflammation as well as evidence that the gene might be associated with cardiovascular disease or conditions associated with metabolic syndrome (diabetes, obesity, and hypertension). In addition, changes in immune function over the course of uncomplicated pregnancy was considered.[72, 73] Cytokines that normally change over the course of pregnancy may influence these outcomes if polymorphisms result in the alteration of expected ratios between different cytokines. Table 1.4 outlines the genes chosen, the immune function, association with reproductive outcomes and association with other CVD of metabolic syndrome diseases.

Table 1.4 Candidate genes involved in inflammation

Gene	Role in Immune System	Association with Reproductive Outcomes	Association with CVD and Metabolic Syndrome
IL1A	Innate	Preeclampsia,[84, 85] PTB.[86] Increased in response to hypoxia[22]	
IL1B	Innate	Recurrent Fetal Loss,[87] PTB,[88, 89] PE,[85] Increased in response to hypoxia[22]	
TNFα	Innate/ Th1	PE with IUGR.[90] PTB[6, 91] Increased in response to hypoxia.[22] In rat models infusion mimics PE[8]	SBP, Cholesterol ratios, CVD risk factors.[92] Diabetes[93]
IL6	Innate/Th2	Recurrent pregnancy loss.[87] PTB[6, 91, 94, 95] PE[1] Increased in response to reduced placental blood flow[22]	Type 1 and Type 2 Diabetes[93] MI[96]
IL6R	Innate/Th2	Associated with PTB[94, 97, 98]	CRP levels.[99] CRP levels and risk of CHD.[100] Type 2 diabetes[101]
IL8	Innate	Increased in response to reduced placental blood flow.[22] Levels increased in PE[8] Increased placental expression with hypoxia (Thomas Moran)	
IL8RB	Innate	Receptor for IL8	
CSF2	Innate (5q31 cluster)	Shows variable expression over the course of pregnancy (Thomas Moran)	
LTA	Innate/Th1	Recurrent pregnancy loss.[102] PTB[6]	MI[103, 104]
IL10 (Tr1)	Blocks excessive inflammation	Associated with PTB[105] PE[106-108] Levels decreased in PE[8]	Graft v host disease[109]
TGFB1, TGFB3 (Th3)	Block excessive inflammation	May regulate T cell differentiation[110] PTB.[4, 111] Involved in trophoblast differentiation[112]	
TNFRSF1B	Innate/Th1	PTB[113, 114]	Hypertension[115]
IL2	Th1	Increased expression in placenta[9]	Type 1 Diabetes[116]
TBX21 (TBET)	Th1	Key transcription factor in Th1[110]	
IFNγ	Th1	Associated with PTB[111]	
IFNGR2	Th1	Recommended by Thomas Moran (Mt. Sinai Immunologist)	
IL12A/IL12B	Th1	Influences release of IFNγ by NK cells[22] Plays a role in T cell differentiation[82]	Type 1 Diabetes[117, 118]
IL18	Th1	Plays a role in T cell differentiation[82]	Obesity, diabetes, CHD[119] CVD and CVD mortality[120]
CXCL10	Th1	Closely associated with IFNγ.	
IL4	Th2	Associated with PTB[4, 105] SGA[4] PE[121]	MI[122]
IL13	Th2	Associated with PTB[4]	
GATA3	Th2	Key transcription factor in Th2 cells[110]	Asthma[123]
IL15	Th1/ NK	Associated with PTB[98]	
NFκB1	Transcription factor implicated in many pathways	NFκB signaling in involved in the inflammatory excess seen in obesity[124]	Diabetes[125]

Abbreviations: PTB (preterm birth), PE (preeclampsia), IUGR (intrauterine growth restriction), SBP (systolic blood pressure), CVD (cardiovascular disease), MI (myocardial infarction), CRP (c-reactive protein), CHD (coronary heart disease), SGA (small for gestational age), NK (Natural Killer Cells)

In addition we had an interest in Natural Killer cells and their role in these outcomes given placental expression data.[73] Natural Killer (NK) cells are a part of the innate immune system although they play an important role in adaptive immunity as well. They induce apoptosis in cells and can be activated by mitogens (chemical substance that triggers mitosis), *INFγ* and *IL12* in the absence of antigen or antibody.[83] As a response to NK cells, inhibitory KIR cells bind to specific receptors on MHC class 1 molecules and provide protection against cell destruction. Uterine NK cells are the predominate leukocyte in the uterine mucosa and are most abundant in early pregnancy, less conspicuous after 20 weeks and nearly absent at term.[126] The fetus and invading trophoblasts are in a sense semi-foreign tissue and are at risk of being destroyed by the maternal immune system. In order to evade detection and destruction, trophoblasts only express the MHC molecules (HLA-C, HLA-E and HLA-G) which have specific ligands for NK cell receptors such as KIRs. Inhibitory KIR binding to the HLA-G expressed by the trophoblast may protect these cells from maternal immune detection and destruction by NK cells.[127] There is some evidence that the KIR haplotypes maybe implicated in recurrent miscarriage and PE.[128, 129]

KIR haplotypes vary in the number and specific genes present. Individuals have between 7 and 12 KIR genes expressed on a single haplotype. However the genes 2DL4, 3DP1, 3DL2 and 3DL3 are present in virtually all haplotypes and have been called framework loci. For this study the framework KIRs *KIR3DL3, KIR3DL2* and *KIR2DL4* were chosen along with *CD94 (KLRD1*) which was shown to vary during pregnancy.

1.4 Role of Cell Cycle in Outcomes

1.4.1 Description of the Cell Cycle

The cell cycle refers to the processes that occur within a cell that leads to duplication of the genetic material and the division of the cell into two daughter cells. Cell cycle functions are vital for the growth of embryonic, fetal and placental tissue and continue to play a role throughout the life cycle in the maintenance and renewal of human tissues and organs.

The cell cycle can be divided into two periods: interphase, during which genetic material is replicated, and mitosis, when the cell splits into two daughter cells each with a full complement of genetic material.

Interphase is composed of G1, S and G2 phase. Briefly, G1 and G2 are periods of cell growth and maintenance during which time biochemical processes ready the cell for DNA synthesis (G1) or mitosis (G2). During S phase, DNA replication occurs and the cell temporarily has two sister chromatids. Since accurate DNA replication and successful cell division is critical to an organism's survival, regulation of the cell cycle is tightly controlled. Transitions between the phases of the cell cycle are controlled by checkpoint proteins, which ensure that the cell is prepared to enter the next phase. When factors that might be damaging to the cell, such as UV radiation, reactive oxygen species, and inflammation, are present, and/or DNA damage is detected, arrest of cell cycle progression allows time for a variety of processes, including DNA repair and reduction of cellular stress. If damage is irreparable, arrest of cell cycle progression may result in the cell entering apoptosis (cell death) as opposed to replication.

Two important checkpoints occur before S phase and before mitosis. Groups of cyclins and cyclin dependent kinases form activated units that regulate the orderly progression through the

cell cycle. Disruptions of these cell cycle regulatory proteins can result in cells that are arrested in G1 or G2 and cease replication and/or division. In addition, inhibitory proteins, including cyclin-dependent kinase inhibitors and protein 53 (*p53*), can block progression of the cell cycle and arrest the cell in a specific phase.

M phase includes both mitosis and cytokinesis. Mitosis is the process by which the chromosomes are separated into two identical sets of chromosomes in two nuclei. Following mitosis, cytokinesis occurs, and the single cell with two nuclei is divided into two daughter cells that are each diploid. M phase accounts for approximately 10% of the cell cycle. Although M phase is vital for cell division, this project will focus on genes associated with interphase and the checkpoint proteins that regulate the entry into S and M phase.

1.4.2 Relevance of cell cycle processes

Epidemiologic studies have noted a strong correlation between placental weight and birth weight and SGA.[130-132] Placentas from pregnancies complicated by PE also tend to be smaller, although small placentas are more likely in preterm PE and in PE complicated by SGA.[131, 133] As the placenta is essentially an organ that grows *de novo* over the course of pregnancy, fundamental cell growth processes maybe influence placental growth. Poor cell cycle function due to genetic polymorphisms may result in reduced cell proliferation and poor placental development with the ultimate outcome of poor fetal growth and/or preeclampsia.

Genetic polymorphisms in cell cycle genes have not been extensively studied for the outcomes of preterm birth, GHTN or SGA. A few studies have documented associations with missed abortion[16] and gestational diabetes.[17] However, a number of cell cycle genes have been implicated in cardiovascular disease[18] and type 2 diabetes.[19] Animal and human placental

expression studies have also suggested that cell cycle genes are differentially expressed in placental tissue[20, 21] and may differ in expression, quantity or function in women with PE or SGA.[134-138] Therefore cell cycle genes comprise a novel pathway that may be important in the outcomes of preterm birth, GHTN, PE and SGA.

1.4.3 Selection of Candidate Cell Cycle Genes

Candidate genes were chosen to represent a number of important check points in the cell-cycle. In addition, placental expression studies and associations with reproductive, metabolic or cardiovascular outcomes were used to focus on genes that may be relevant (Table 1.4.3).

Table 1.5 Overview of role and supporting evidence for cell cycle genes

Gene	*Alias*	*Role*	*Evidence*
CCNA2	Cyclin A2, CCN1, CCNA	G1/S and G2/M transition	Plays a role in trophoblast differentiation[112]
NOV	Neuroblastoma overexpressed gene	Regulate cellular migration, invasion and differentiation	Lower expression in placentas with early onset PE.[138] Trophoblast levels altered with hypoxia, regulated by HIF-1α and TGFB3.[139]
CCND1	Cyclin D1	G1/S transition	Decreased placental expression in PE and IUGR.[136] Differential placental expression throughout pregnancy.[20]
CDKN2A/2B	Cyclin dependent kinase inhibitor 2A/2B	G1 control, interacts with p53	Associated with Type 2 diabetes[140] Gestational diabetes[17] MI, CHD[18]
RASSF1	Ras associated domain family member 1	Tumor suppressor function, induce cell cycle arrest through cyclin D1	
CNNM2	Cyclin M2		Downregulated in mouse placenta with hypoxia.[141, 142] SBP.[143]
MDM2	p53 binding protein homolog	G1 and apoptosis through interaction with p53	Associated with spontaneous miscarriage[16] and subfertility[144]
CCNH	Cyclin H	G1/S and G2/M transition	Associated with transplant rejection[145]
GADD45A	Growth arrest and DNA-damage-inducible, alpha	Respond to stress by activating inflammation and innate immunity	Important upstream regulator in preeclampsia (correlated with sFlt-1)[135]

1.5 Evidence of Genetic Component

Preterm Birth

One of the stronger risk factors for preterm birth is a previous preterm pregnancy.[33] In addition to the high risk of recurrence, twin studies suggest a heritability of 34% for birth timing.[146] The genetic risk of preterm birth is complicated by the contributions of three genetic lineages -- maternal, paternal and fetal -- as well as the role of shared environment within a single woman or within her family of birth. Recent population based studies in Norway,[12] Denmark[13] and Sweden[14] have attempted to assess the role of maternal genes in the outcome of preterm birth.

The study in Sweden[14] used three generations to generate pairwise odds ratios between siblings and within siblings to assess familial aggregation. Modeling also allowed the estimation of maternal and fetal genetic effects and environmental effects of the couple, sibling environment and non-shared environment. The Swedish study found an increased risk of preterm birth among sisters (OR 1.9, 95% CI 1.6, 2.2) but not among brothers or mixed sibling pairs. The increased risk among sisters could reflect maternal or fetal genetic effects or a shared sibling environment. The modeling of environmental as well as genetic effects suggested no role for shared sibling environment but a significant effect for maternal genes (25%), fetal genes (5%), couple environment (18%) and unshared environmental effects (52%). The effect of maternal genes was stronger in spontaneous preterm birth while the effect of fetal genes increased in medically indicated births.

In Denmark,[13] Boyd identified women with a singleton birth between 1978 and 2004 and assessed her family history and her partner's family history with respect to preterm birth.

Cohorts for each type of family history (personal, family, partner and partner family history) were constructed to assess the risk of preterm birth for each type of family history. While a woman with a previous preterm birth had an increased risk of subsequent preterm birth (RR 5.9, 95% CI 5.7, 6.1), having a partner with a previous preterm birth (with a different woman) did not increase her risk (OR 1.1, 95% CI 1.0, 1.2). Family history of preterm birth was also associated with preterm birth. Women with a history of preterm birth among their mothers, full sisters or maternal half-sisters were 55% more likely to deliver preterm. There was no increased risk due to a preterm birth in a woman's paternal half-sisters, female partners of the woman's male relatives and any relation in the biological father's family. In addition to documenting the high recurrence of preterm birth, this study suggests a strong heritable factor that is transmitted through female relatives. The paternal effect, which may also be considered an effect of fetal genes, was generally absent. The authors suggest that imprinting or mitochondrial genes may explain some of the distinctly female transmission seen. This study was unable to assess environmental risk factors.

The Norwegian study[12] examined 2 generations of singleton births without preeclampsia for recurrence of preterm birth in a first birth among mothers and fathers born preterm themselves. While women born preterm had an increased risk of preterm birth in their first pregnancy (RR 1.5, 95% CI 1.4, 1.7), men born preterm had only a small increase in preterm birth for their first child (RR 1.1, 95% CI 1.0, 1.2). In women the association was stronger if she had been born in the early (<34 weeks) preterm period.

These three population based studies support a role for maternal genes in the risk of preterm birth while failing to find evidence of an association with fetal genotype. The role of

imprinted genes, mitochondrial genes and shared environmental factors has not been fully explored and may explain some of the patterns observed.

SGA

History of a previous SGA infant is a strong risk factor for SGA, and women who were born SGA themselves are more likely to have an SGA infant.[15] Twin studies suggest a heritability of 34%. A population-based study in Sweden[18] compared the risk of SGA between full and half siblings looking at sisters, brothers, sister-brother pairs and successive pregnancies within couples. The methods used allowed for the examination of maternal, fetal, couple environment, sibling environment and non-shared environment. Among full siblings there was a stronger effect among sisters (OR 1.8, 95% CI 1.7, 1.9) than among brothers or sister-brother pairs (OR 1.3, 95% CI 1.2-1.4). The association among brothers suggests a fetal genetic component, while the stronger association among sisters suggests an additional maternal genetic component. Among half-siblings there was only an association between sisters (OR 1.2, 95% 1.1, 1.4) although half-sisters were not classified by maternal or paternal sharing. An analysis of the discrete genetic and environmental components suggests that the fetal genetic effect explains 37% of the variance while the maternal genes explain an additional 9% (a total of 27.5%) while the couple environment (18%) and non-shared environment (36%) are also important.

Preeclampsia

The genetic component of preeclampsia is complex due to the possible contributions of fetal, maternal and paternal genes.[147] One twin study estimated the heritability of preeclampsia (54%) and gestational hypertension (24%), although the rarity of the outcome and the restriction to female twins has limited the number of twin studies with sufficient power.[148]

A large population based study in Norway[11] using two generations of birth certificate data showed that both a maternal and a fetal mode of transmission is implicated in preeclampsia. Women who had been born in a pregnancy complicated by preeclampsia had an increased risk of preeclampsia in their own pregnancies (OR 2.2, 95% CI 2.0, 2.4). Men who had been born in a pregnancy complicated by preeclampsia also had an increased risk of fathering a pregnancy complicated by preeclampsia (OR 1.5, 95% CI 1.3, 1.7). While the women could be expressing genes in a maternal or fetal pathway, fathers can only contribute to the fetal pathway. In addition, siblings from normal pregnancies in families with a history of preeclampsia were also examined. The sisters in this situation could possess maternal genes but not fetal genes, and the brothers could also possess the maternal gene but this would not contribute to the preeclampsia risk in their partner. The findings supported the hypothesis of a dual genetic pathway, with the sisters having an increased (but attenuated) risk for PE (OR 2.0, 95% 1.7, 2.3) and the brothers having no increase in risk (OR 1.1, 95% CI 0.9, 1.4).

A study in Sweden[148] looked at mother-daughters pairs, full sisters, maternal half-sisters and paternal half-sisters. The inclusion of paternal half-sisters along with the assumption that children live with their mothers, allowed the authors to attempt to disentangle genetic and environmental contributions. The Swedish study found an increased risk among women who had a full sister with PE (OR 3.3, 95% CI 3.0, 3.6) or who had a mother with PE (OR 2.6, 95% CI 1.6, 4.3). However the risk among maternal half-sisters was reduced (OR 1.4, 95% CI 0.9, 2.2) and absent in paternal half-sisters (OR 1.0, 95% CI 0.6, 1.6). A small sample of monozygotic twins showed a substantially increased (and imprecise) increased risk. Gestational hypertension showed a similar association, although the strength of the effect was stronger and maternal half-sisters had an increased risk (OR 2.7, 95% CI 1.2, 6.0). An analysis of the risk of gestational hypertension among pairs where the primary diagnosis was preeclampsia (and vice versa)

suggested that each outcome was a risk factor for the other. They estimated that the genetic component of preeclampsia is approximately 30%.

Both studies note the possible role of shared environmental risk factors, in particular obesity and smoking. The Swedish study was able to model shared environment under a strong assumption regarding family dynamics and found that shared environmental factors were not significant. However the possibility for shared environment playing a role in the apparent heritability of gestational hypertension is still possible.

These studies suggest that both preeclampsia and gestational hypertension have genetic causes. Although it is clear that there are both fetal and maternal components to the genetic risk, the maternal portion is substantial.

Summary

The studies of heritability in preterm birth, SGA and GHTN suggest that a genetic etiology is plausible. While preterm birth shows a predominately maternal genetic effect, both SGA and PE suggest the addition of a fetal genetic effect. Given the role of fetal genes in the development of the placenta, the presence of a fetal genetic effect in SGA and PE is not surprising. Reproductive outcomes must always consider the role of three distinct genetic contributions- maternal, fetal and paternal. While this study only has access to maternal DNA, the maternal genetic effect is substantial enough in all three outcomes to consider the maternal effect in isolation.

1.6 Review of Genetic Epidemiologic Studies

Compared with cancer or cardiovascular outcomes, genetic epidemiologic studies in reproductive outcomes are still limited. Although pregnancy can be considered a critical event in

genetic evolution, large-scale reproductive cohorts similar to the genetic cohorts for chronic disease do not exist. Most of the reproductive epidemiology studies looking at PE or preterm birth have been small, with fewer than a few hundred cases. The genes used in these studies have often been limited to a few SNPs for a few genes, with only a couple of studies using a larger, candidate gene approach. One of the difficulties that the existing studies share with almost all diseases is the definition of the outcome of interest. For preeclampsia, although guidelines exist for diagnosis, many studies use different classification or exclusion criteria, resulting in phenotypes that vary from study to study. Given the differences in allelic frequencies among groups of different genetic ancestry, existing studies from Europe or South America may not be generalizable to US populations. Given these difficulties, the current study will be able to add to what is currently known about genetic determinants of adverse pregnancy outcome. Given the size of the study population, the depth of the genetic panel, and the inclusion of US Whites and African Americans, this study is well positioned to advance the knowledge of these important outcomes.

Preterm Birth

A HuGE[91] review of genetic variation in preterm birth reviewed 18 studies published before June, 2004 and concluded that inflammatory cytokines (*TNFα* in particular) showed the most consistent increase in the risk of PTB. In addition matrix metalloproteinase genes (involved in the degradation of fetal membranes) such as *MMP1* and *MMP9*, Toll-like receptor 4 (*TLR4* involved in the response to certain bacteria), Beta-2-adrenergic receptor (*ADRB2* links the sympathetic nervous system to the immune system), Vascular endothelial growth factor (*VEGF*; angiogenesis), Methylene tetrahydrofolate reductase (*MTHFR;* folate metabolism) and Factor 5 (*FV;* coagulation pathway) genes may all be implicated in preterm birth.

A search of the Genetics Association Database (http://geneticassociationdb.nih.gov/cgi-bin/index.cgi) as well as a review of PubMed revealed 20 genetic epidemiology studies that considered preterm birth as an outcome. The review was limited to studies that considered maternal DNA and had included at least one gene in the inflammatory pathway. The studies revealed quite a bit of heterogeneity with the outcome of interest with respect to the timing of preterm birth, the subtypes of preterm birth (preterm labor, PPROM, indicated delivery) included and the genetic ancestry of the populations studied. Most studies were small (largest had 300 cases and most had fewer than 200 cases) and the findings of early studies did not always replicate in subsequent studies. Table 1.6 has an overview of all the studies.

Overall *IL6, IL6R, TNFα* (with or without *LTA*) and its receptors *TNFR1* and *TNFR2*, *IL1A, IL1B, IL1RN, IL5* and *TGFβ1* showed the most consistent associations with preterm birth. Genetic associations often varied between White and African-American mothers, with each population showing different associations when stratified.

A number of candidate gene approaches using a 1536 panel have been conducted in the US,[98, 149] Chile,[150, 151] and Norway.[152] While these studies examined a wider range of genes in the inflammatory pathway, coverage of each gene was less intense with fewer tagSNPs per gene.

Table 1.6 Review of Genetic Epidemiology Studies of Preterm Birth

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
Dizon-Townson, DS[153]	1997	Women possibly recruited in Utah	Case-control	203 mothers, 44 infants	41 multips	SPTB (PTL, PPROM) < 37 wks	TNFα	None
Simhan, HN[95]	2003	Women recruited at Magee-Women's Hospital, Pittsburg, PA. Black and White women included. Subset of Prenatal Exposures and PE Prevention Study.	Case-control	51 cases (39 white, 12 African American)	156 controls (110 White, 46 African American)	PTL < 34 wks (no PPROM)	IL6	Genotypic association among white mothers OR 0.14 (0.01-0.62)
Hartel CH[154]	2004	Retrospective study in Germany of VLBW infants and their mothers. Non-white births excluded.	Case-control	466 mothers of PTB VLBW infants	281 mothers of term infants	PTB VLBW not defined	IL6 CD14 NOD2 TLR2 TLR4	One genotypic (p=0.018) and one allelic (p=0.02) association. Strengthened among spontaneous PTB None None None None
Hao, K[155]	2004	Women delivered at Boston Medical Center. Cases and controls matched for maternal age and ethnicity. Includes African American (453), Hispanic (194) and White (111) mothers.	Case-control	300 cases	458 controls term >=2500g	PTB <37 wks	31 genes (111 SNPs) F5 IL1R2 NOS2A OPRM1	Haplotype association p=0.025 Haplotype association in Blacks (p=0.0002) Haplotype association in Whites (p<0.001) Haplotype association in Hispanics (p=0.0004)

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
Annells, MF[105]	2004	Women with a previous preterm birth from North Adelaide, Australia. All of European descent.	Case-control	202 cases	185 term, no history of PTB	SPTB (PTL, PPROM) <35 wks	TNFα (3 SNPs)	Haplotype association with early PTB OR 2.4 (1.1-5.5)
							IL1A	None
							IL1B (2 SNPs)	None
							IL4	Genotypic association with early PTB OR 3.4 (1.2-9.6)
							IL10 (3 SNPs)	Haplotype association with early PTB OR 2.1 (1.0-4.1) with a strengthening seen for PPROM
							TGFβ1 (2 SNPs)	None
							MBL2 (5 SNPs)	Allelic association with early PTB 2.3 (1.1-5.0)
							IL6	None
							IL1RN	None
							IL1R1	None
							TNFRSF6 (2 SNPs)	None
Engel, SA[6]	2004	Women recruited from hospitals in Wake and Orange County, NC. Restricted to African American and White.	Nested case-control	67 African American, 69 White	238 African American, 336 White	SPTB (PTL, PPROM) < 37wks	IL1A (2 SNPs)	Association in white mothers OR 1.8 (0.9-3.7)
							IL1B (3 SNPs)	Association in white mothers for 2 haplotypes OR 1.7 (0.9-3.2) and OR 2.1 (0.9-5.2)
							IL2	None

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
							IL6 TNFα LTA (2 SNPs) TNFα/LTA	Association in both Whites and African Americans Association in white mothers OR 2.9 (0.9-4.0) One SNP showed an increased risk of PTB in white mothers OR 2.6 (1.3-5.5) Association in white mothers for two haplotypes OR 1.5 (0.8-2.6) and OR 1.6 (0.9-2.9)
Engel, SA[4]	2005	Women recruited from hospitals in Wake and Orange County, NC. Restricted to African American and White.	Nested case-control	67 African American, 69 White	238 African American, 336 White	SPTB (PTL, PPROM) < 37wks	IL4 (3 SNPs) IL5 IL13 (3 SNPs) IL10 (3 SNPs) TGFβ1 (2 SNPs)	Haplotype association in African American mothers OR 2.9 (1.2-7.4) Possible association in white mothers combined in haplotype with IL13 OR 0.5 (0.3-1.0) Haplotype association in African American mothers OR 2.7 (1.0-7.2) None Haplotype association in white mothers OR 3.0 (0.9-9.9)

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
Speer, EM[111]	2006	Women recruited at Magee-Women's Hospital in Pittsburg, PA from consecutive eligible deliveries. Term controls matched by maternal age, race, infant sex. African American 20%.	Case-control	80 mother-infant pairs	80 mother infant spont term	SPTB (PTL or PPROM) < 35 wks	TNFα IFNγ IL6 & IL10 (1 & 3 SNPs) TGFβ1	None Conditional on fetal IFNγ genotype, maternal T allele negatively associated with PTB OR 0.5 (0.3-0.98) None Genotypic association with gestational age of preterm deliveries p=0.025
Menon, R[114]	2006	White women recruited from 2 academic hospitals in Nashville, TN and Pittsburg, PA	Case-control	101 Cases	321 Controls	PTL< 36 (0/7)	TNFα (6 SNPs) TNFR1 (6 SNPs) TNFR11 (7 SNPs) IL6, IL6R (5&3 SNPs) TNFα/IL6/IL6R	None Allelic and genotypic association with PTB Genotypic association with PTB None Multilocus association OR 3.5 (2.52-4.87)
Velez, DR[156]	2007	Women recruited from 2 academic hospitals in Nashville, TN & Pittsburg, PA.	Race stratified case-control	White 149, African American 76	White 347, African American 321	PTL <36(0/7) wks	IL6 (5 SNPs) IL6R (3 SNPs)	None One SNP; African American mothers both genotypic and allelic (p=0.05, p=0.04)

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
Stonek, F[157 158]	2008 2008	Consecutive Caucasian women present to antenatal clinic before 12 wks GA in Vienna, Austria	Case cohort (analyzed as case control)	259 (Fetal Death 13, PE 14, PTB 87, SGA 146)	1367 with no outcome	PTB (<37 wks). Also PE, SGA and Fetal Death	IL10 IL6	None None
Moura, E[159]	2008	Two independent case-control samples (Mulatto, White and Mulatto) from two hospitals in Brazil. Women matched on ethnicity within each hospital.	2 case-control studies	Cases 122 and 82	Controls 101 and 105 (multips)	SPTB < 37 wks	TNFα IL10 (3 SNPs) IL6 IFNγ TNFα/IL6/ IFNγ	None None None None Genotype combination associated with PTB 2.26 (1.32-3.91) p=0.002
Hollegaard MV[88]	2008	Women selected from the Copenhagen First Trimester Study based on availability of blood spots for DNA extraction.	Case-control	62 cases	55 term	SPTB <37 wks	TNFα (5 SNPs) IL1B (2 SNPs) IL6 (3 SNPs)	Genotypic association OR 3.1 (1.0-10.3) with 2 haplotypes also showing an association (p=0.04 and p=0.05) Genotypic association with PTB 6.4 (1.3-60.5) None
Fortunato, SJ[94]	2008	Women recruited at a single hospital in Nashville, TN. Only included women of self-reported African American or White race (non-Hispanic). For white women adds to case group in Menon 2006	Case-control stratified by race	242 cases (166 White, 76 African American)	385 controls (194 White, 191 African American)	PTL <36 wks	TNFα (5 SNPs) TNFR1 (5 SNPs)	None Genotypic and allelic association in white mothers (p=0.001, p=0.002) for one SNP

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
							TNFR2 (7 SNPs)	Genotypic and allelic association in white mothers (p=0.04, p=0.02) for 1 SNP. Allelic association for 2 SNPs in black mothers.
							IL6 (7 SNPs)	None
							IL6R (3 SNPs)	Allelic association with 2 SNPs in black mothers.
							IL6/IL6R/TNFα	Multilocus association in white mothers OR 2.3 (1.6-3.4)
Velez, DR[149]	2008	Women recruited at Centennial Medical Center in Nashville, TN. This paper is only White women with a single reported racial ancestry through 2 generations. Maternal and fetal DNA collected. Only maternal reported here.	Case-control	172 White	198 White	PTL <36(0/7) wks	130 genes (1536 panel)	
							CRHBP	Allelic and genotypic
							FV	Allelic and genotypic
							IL5	Allelic and genotypic
							PTGER3	Allelic and genotypic
							tPA	Allelic and genotypic
Velez, DR[98]	2009	Women recruited at Centennial Medical Center in Nashville, TN. This paper is only African American with only a single reported racial ancestry through 2 generations. Maternal and fetal DNA collected. Only maternal reported here.	Case-control	76 African American	191 African American	PTL < 36(0/7) wks	130 genes (1536 panel)	
							IL15	Genotypic association
							IL1RAP	Allelic and genotypic
							IL2A	Allelic and genotypic
							IL6R	Allelic, genotypic and haplotype
							TNFRSF1B	Allelic, genotypic and haplotype

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
Gebhardt S[160]	2009	Consecutive low-risk obstetrical primip in Western Cape, South Africa. Restricted to Coloured and Black women	Prospective cohort of 450 low risk women	Preterm 33, PE 35, IUGR 2	421 controls	Preterm Labor <37 wks	IL4 IL1B IL1RN IL10 (3 SNPs) TNFα (3 SNPs) LGALS13 (10 SNPs)	None None Genotypic 2.28 (1.17-4.44) None Genotypic and allelic 2.09 (1.01-4.31) Allelic 2.27 (1.20-4.29)
Sata, F[86]	2009	Consecutive women recruited postpartum from a university hospital in Sapporo, Japan	Case-control	73 cases	341 term	PTB <37 wks	IL1A (2 SNPs) IL1B (2 SNPs) IL2 IL6	Genotypic and haplotype associations with PTB overall with larger estimates for PTL. Permutation p =0.01 for haplotype associations with all PTB combined Suggestion of a haplotype association None None
Kalinka, J[161]	2009	Abstract only. Polish Caucasian women	Case-control	62 cases	63 controls	SPTB (PTL, PPROM) <36 wks	ILIRN IL1B IL6 TNFα	Increased risk of PTB OR 2.75 (1.02-4.13) None Genotypic association when coincident with IL1RN genotype OR 3.0 (1.0-8.9) None

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
Romero, R[151]	2010	Women recruited from a single site in Puento Alto, Chile. All women of Hispanic origin	Case-control	223 cases	599 controls	PTL < 37 wks	190 genes (775 SNPs)	
							IL6R	Allelic and haplotype
							COL4A3	Allelic and haplotype
							LTF	Allelic and haplotype
							FGF1	Allelic and haplotype
							GNB3	Allelic association
							IGF1	Allelic association
							TIMP2	Allelic association
Romero, R[150]	2010	Women recruited from a single hospital in Santiago Chile, all mothers Hispanic	Case-Control	225 mothers	599 mothers	PPROM <37 weeks	190 genes (775 SNPs)	
							TIMP2	Allelic association
							ANG	Allelic association
							TLR1	Allelic association
							NOS3	Allelic association
							COL4A3	Allelic and haplotype association.
							PTGER1	Allelic association
Gomez, LM[162]	2010	Women recruited from prenatal clinics in Philadelphia. 85% African American	Case-control (post-hoc merger of RCT)	68 cases	675 controls	SPTB <37 wks	1536 Plate but full results not reported	
							PRKCA	6 risk alleles among women with BV
							FLT1	among BV+ OR 1.9 (1.1-3.3)
							IL6	among BV+ OR 3.5 (1.6-7.8)
Liang, M[163]	2010	Han Chinese from Anqing Hospital	Hybrid (Triad and Control parents)	250 case families	247 control families	SPTB delivery <37 wks	TNFα	Heterozygote RR 0.46 (0.2-1.04)
							Interaction	RR 0.20 (0.07-0.58) mother and fetus het

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
Ryckman, KK[164]	2010	MoBA and Centennital (TN, USA) Study See Velez 2009 for details on Centennial Study	Case-control	MoBA 207	MoBA 217	PPTB<36 (6/7) MoBA	1430 SNPs in MoBA Maternal. "Suggestive" Inflammatory Results	
							COL1A2	Allelic and genotypic
							IL18	Genotypic association
							IL1B	Allelic and genotypic
							IL1R1 (2 SNPs)	Allelic and genotypic
							IL1R2 (3 SNPs)	Allelic and genotypic Replicated
							IL1RAP (3 SNPs)	Allelic and genotypic. One replicated
							IL1RN (3 SNPs)	Allelic and genotypic
							IL2RA (5 SNPs)	Allelic and genotypic. One replicated
							IL2RB (3 SNPs)	Allelic and genotypic
							IL4R (2 SNPs)	Allelic and genotypic. Replicated
							IL6R (2 SNPs)	Allelic and genotypic. Replicated
							IL8RA	Allelic and genotypic
							TNFRSF1A	Association in pooled results
Myking, S[152]	2011	MoBA (Ryckman Data)	Hybrid (triad, control dyads)	196 triads	211 control dyads	PTB <36 (6/7) Term 39 (0/7) - 40 (6/7)	Maternal genotype results not available	
							IL10RA	Significant when maternal and fetal alleles combined

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
							IL1A	Significant when maternal and fetal alleles combined
							IL10RB	Significant when maternal and fetal alleles combined
Jones, NM[165]	2011	Women recruited from community clinics in Michigan	Sub-cohort stratified by self reported race	131 Non-Hispanic white, 49 African American	356 non-Hispanic white, 239 African American	PTB <37 wks with subtype analysis	IL1-RN	(CEU) PTB OR 1.9 (1.2-2.9) sPTB OR 2.0 (1.2-3.3) additive interaction with fetal genotype
							MMP-9	(CEU) sPTB OR 1.7 (1.0-2.8)
							TNFR2	(YRI) sPTB OR 2.3 (1.1-4.6) mulitplicative interaction with fetal genotype
							IL-1β	No association
							TNFα	No association
							TNFRSF6	No association
							MBL (2 SNPs)	No association
							CD14	No association
							TLR4	No association
Nuk, M[166]	2012	Women recruited from a single Hospital in Graz, Austria	Correlation	106 cases	200	PTB <37 wks	TNFα	No correlation
							IL10	No correlation

Abbreviations: SPTB spontaneous preterm birth; PTL preterm labor; PPROM preterm premature rupture of membranes; wks weeks; OR odds ratio; VLBW very low birth weight; g grams; GA gestational age; SGA small for gestational age; IUGR intrauterine growth restriction.

Hypertensive Disorders of Pregnancy

A review by Mutze in 2008 of genes and the preeclampsia syndrome notes that up to 70% of the candidate gene research has focused on eight genes in the rennin-angiotensin system (angiotensinogen *AGT*, angiotensin converting enzyme *ACE*, and angiotensin receptors), inherited thrombophilias (factor V, prothrombin, methylene tetrahydrofolate reductase), *NOS3* genes, and *TNFα*.[167] Among the immunogenetics research, which includes natural killer cells (*KIRs*) and cytokines on the inflammatory pathway, she notes the conflicting evidence in support of 10 cytokines (*TNFα, IL1A, IL1B, IL1RA, IL6, IL10, IFNγ, TGFβ, CD14* receptor and *CTLA-4*) with most SNPs showing more evidence against an association or only a single study showing an association. She notes that outcome classification is heterogeneous; the studies have focused on white European women, and the likely interaction between maternal and fetal genotypes and the small sample size of most studies are limitations that must be addressed. Among the more promising associations, she highlights the placental genes *ACVR2* and *STOX1* and genes involved in angiogenesis (*PIGF, VEGF, Flt-1, ENG*).

A review of the Genetics Association Database and PubMed revealed 20 genetic epidemiology studies of preeclampsia using maternal DNA. Studies that included at least one inflammatory gene were selected and studies focusing on coagulation pathway or angiogenesis were not reviewed. As noted by Mutze, there was a good deal of outcome heterogeneity with variation in the diagnostic criteria for preeclampsia, the inclusion of severe PE, and restrictions based on parity. While some of the studies were based in the US, many were European, with additional studies from Brazil, Chile, Iran, South Africa and Australia. Apart from a study utilizing the HUNT cohort in Norway, most studies were small with fewer than 200 cases. Overall there has been little consistency in results, with some genes showing an association in some

populations but not others. *TNFα, IL1A, IL1B, IL10* showed associations in at least two studies, although there were also negative results for each gene. The diversity of genetic ancestry and the differences in association among women in the US studies suggests the possibility of heterogeneity by race. Table 1.7 provides an overview of the studies.

A case group at the Hospital of the University of Pennsylvania[168, 169] ran a 50,000 SNP panel designed for cardiovascular, metabolic and inflammatory syndromes. While they have reported on angiogenic and solute carrier genes, results from the inflammatory genes have not yet been published.

Table 1.7 Review of Genetic Epidemiology Studies of Preeclampsia

Study	Year	Population	Study Design	Cases	Controls	Outcome Criteria*	Genes	Association
Dizon-Townson, DS[170]	1998	Mothers admitted for delivery (94% Caucasian) from a common referral population. Possibly Utah.	Case-control	131 severe PE, 75 HELLP	41 multips	Severe PE [BP (8 or 9) and Pr (7, 8) with PC (1)]	TNFα (2 SNPs)	None
Livingston, JC[171]	2001	Mothers and infants recruited at delivery in Memphis, TN and Lexington KY. 57% African America.	Prospective cross-sectional	112 severe PE	106 matched for GA	Severe PE [BP (7 or 6) and Pr] HELLP	TNFα (2 SNPs)	None
Lachmeijer, AMA[172]	2002	Affected sisters and their parents from discharge records, obstetrical charts and advertisements in The Netherlands	Family based	150 sib-pairs	104 healthy blood donors (male and female)	PIH [BP (4)] PE [BP (4) Pr (1 or 3)] Severe PE [BP (5) Pr (6)]	IL1B (2 SNPs) IL1RN	None None
Lachmeijer, AMA[173]	2001	Affected sisters and their parents from discharge records, obstetrical charts and advertisements in The Netherlands	Family based	150 sib pairs divided into 'strict' 'index' 'sister' PE HELLP	98 men and women from Vrije University (same as above missing 6 men)	PIH [BP (4)] PE [BP (4) Pr (1 or 3)] Severe PE [BP (5) Pr (6)]	TNFα and LTA (5 markers)	Haplotype association in 'strict index' group OR 1.9 (1.1, 3.3)
Witt, CS[174]	2002	Not stated. Authors associated with Royal Perth Hospital, Western Australia	Comparison of frequency	45 primips	48 primips	PE [BP (3) Pr (1)	KIR2DL4	None
de Groot, CJM[108]	2004	Cases selected from database and patient charts at 2 hospitals in The Netherlands. Controls were matched for maternal age and delivery date.	Case-control	163 primips	163 primips	PE [BP (11) or (2) Pr (11)	IL10 (4 SNPs)	Genotypic OR 0.29 (0.10-0.83) for 1 SNP

Study	Year	Population	Study Design	Cases	Controls	Outcome Criteria*	Genes	Association
Haggerty, CL[85]	2005	Sub-sample of the PEPP study at Magee-Women's Hospital in Pittsburg, PA.	Case-control stratified by race	150 primips	661 primips	PE [BP (12) and (10) Pr (1) or (9) and (10)]	TNFα	Genotypic association among white women
							IL1A	Genotypic association among black and white women
							IL1B	Haplotype with IL1A association in all women
							IL10	Suggestion of association in White women OR=1.7
Goddard, KA[84]	2006	Mothers and Infants from a hospital based population in Puerto Alto, Chile	Case-control	394 mothers	602 Full term "hyper healthy"	PE [BP(1) Pr(1 or 2)]	190 genes, 775 SNPs	
						Additive model maternal		
							IL1A	1.60 (1.19, 2.07)
							IL12RB1	2.85 (1.29, 6.26)
						Additive global haplotype based		
							IL4R	p=0.0006
							IL1A	p=0.0193
							IL1B	p=0.0272
						Maternal Fetal Interaction Model		
							IL4R	p=0.0036

Study	Year	Population	Study Design	Cases	Controls	Outcome Criteria*	Genes	Association
Kamali-Sarvestani, EK[175]	2006	Women who had delivered at a single hospital in Iran. Controls matched on age and race.	Case-control	134 primips	164 multips (all 'normal')	PE [BP(2) Pr(1 or 3)] Severe PE [BP(9) Pr(4 or 2)]	IFNγ IL10 (3 SNPs)	None SNP (-1082 G) differed significantly between cases and controls p=0.045.
Daher, S[107]	2006	Cases and controls ascertained consecutively at study hospital in Sao Paulo, Brazil.	Case-control	White primips 56 Non White primips 95	White multips 92 Non White multips 97	PE [BP(2) Pr(1)]	TNFα TGFβ1 IL10 IL6 IFNγ	None None Lower frequency in White women with PE p=0.02 None None
Saarela, T[176]	2006	Retrospective case ascertainment at a single hospital in Finland.	Case-control	133 primips	115 multips	PE [BP (1) Pr (1)]	IL6 HL CAPN-10	None. None None
Mirahmadian, M[106]	2008	Consecutive patient with PE at 2 hospitals in Tehran, Iran	Case-control	160 cases	100 healthy pregnancies during same time period	PE [PC (2)]	TNFα (2 SNPs) IL10 (3 SNPs)	Allelic and genotypic different p=0.0001 Genotypic and alleliic differences.

Study	Year	Population	Study Design	Cases	Controls	Outcome Criteria*	Genes	Association
Fraser, R[121]	2008	Cases and Controls selected from the GOPEC cohort. All white Europeans.	Case-control	117 cases	146 controls with uncomplicated term deliveries	PE [BP (2) Pr (1)]	IL4 TLR2 MMP9	Genotypic association OR 4.5 (1.3-15.4) None None
Molvarec, A[90]	2008	Caucasian women from a single hospital in Budapest, Hungary	Case-control	140 PE, 69 HELLP	144 healthy pregnancies	PE [BP (1) Pr (1)] HELLP. Also IUGR.	TNFα	Increased allelic frequency in women with both PE and severe IUGR.
Stonek. F[157] 2008[158]	2008	Consecutive Caucasian women at antenatal clinic before 12 wks GA in Vienna, Austria	Case cohort (analyzed as case control)	259 with at least one outcome (Fetal Death 13, PE 14, PTB 87, SGA 146)	1367 with no outcome	PE [PC (1)]. Also PTB, SGA and Fetal death	IL10 IL6	None None
de Lima, TH[177]	2009	Mulatto women recruited from a single maternity hospital in NE Brazil	Case-control	92 with PE, 73 with Eclampsia	101 multips	PE and Severe PE [PC (2)]	TNFα IL6 IFNγ IL10 (3 SNPs) TGFβ1 (2 SNPs)	None None Higher allelic frequency in severe PE p=0.02 None None

Study	Year	Population	Study Design	Cases	Controls	Outcome Criteria*	Genes	Association
Tan, CY[178]	2009	Malay women recruited from maternity hospitals in Singapore or Malaysia	Case-control	83 cases	240 controls	PE [BP (1) Pr (1)]	KIR2DL4 (23 SNPs)	None
							HLA-G	Interaction of fetal HLA-G*0160 and maternal KIR2DL4
Johnson, MP[179]	2009	Australian Family Cohort and Norwegian Case Control (from HUNT cohort and biobank)	Family based and case-control	74 Aust/NZ families with 140 affected women, Norway 1,139	Aust/NZ 90 unaffected, Norway 2,269 controls	PE [PC (3) in Aust/NZ and PC (2) in Norway]	10 genes (56 SNPs) within a previously identified 5q critical region	
							IL4 (3 SNPs)	None
							CSF2 (2 SNPs)	None
							IL13 (7 SNPs)	None
							IL3 (1 SNPs)	None
							IL5 (2 SNPs)	None
Gebhardt, S[160]	2009	Consecutive low-risk obstetrical primips in Western Cape, South Africa. Restricted to Coloured and Black women	Prospective cohort of 450 low risk women	Preterm 33, PE 35, IUGR 2	421 controls	PE [BP (13) Pr (1) or (2)]	IL4	None
							IL1B	None
							IL1RN	Genotypic OR 2.6 (1.4-5)
							IL10 (3 SNPs)	None
							TNFα (3 SNPs)	None
							LGALS13 (10 SNPs)	None

Study	Year	Population	Study Design	Cases	Controls	Outcome Criteria*	Genes	Association
Fenstad, MH[180]	2010	Familes from Austrailia and NewZealand, mothers from Norway	Family linkage design, and case-control	74 Aus/NZ familes with 140 affected women and 851 women in Norway	Aus/NZ 146 unaffected, 1440 controls in Norway	PE [PC (3) in Aus/NZ and PC (2) in Norway)	TNFSF13B (7 SNPs Aus/NZ, 3 SNPs Norway	3 rare SNPs associated in Aus/NZ familes but not in Norway
Hill, LD[181]	2011	Mothers and infants from Santiago Chile, Philidelphia, PA and Detroit, MI	Case control	Chilean: 528 dyads, African American (unpaired): 424 mothers, 375 infants	Chilean: 575 dyads, African American (unpaired): 412 mothers, 462 infants. All term	PE [PC (1, 2)]	ERAP2 (2 SNPs)	Association for fetal SNP in African American infants only

Abbreviations: HELLP hemolysis, elevated liver enzymes, low platelets; PE preeclampsia; PTB preterm birth; SGA small for gestational age; NE northeast; IUGR intrauterine growth restriction; primip primiparous; multip multiparous.

LEGEND

BP: Blood pressure criteria

1. >=140 mmHg SBP or >=90 mmHg DBP
2. >=140/90 mmHg SBP
3. >140/90 mmHg
4. >=90 mmHg DBP with increment of at least 20mmHg
5. >=110 mmHg DBP
6. >110 mmHg DBP
7. >160 mmHg SBP
8. >=160 mmHg SBP or >=110 mmHg DBP
9. >=160/110 mmHg
10. Increase of >15 mmHg diastolic or >30 mmHg systolic
11. Increase of >=15 mmHg diastolic or >=30 mmHg systolic
12. >140 mmHg SBP or >90 mmHg DBP
13. >=90 mmHg DBP

Pr: Proteinuria criteria

1. >=300mg/24h
2. 2+ dip
3. 1+ dip
4. 2g/24h
5. >=2+ dip
6. >=1g/24h
7. >500mg/24h
8. 3+ or 4+
9. 0.3 protein/creatinine ratio
10. Hyperuricemia >1SD for GA
11. >=2+ voided or >=1+ catheter sample

PC: Published Criteria

1. ACOG
2. 2000 National Working Group on Hypertension in Pregnancy
3. Australasian Society for the Study of Hypertension in Pregnancy

SGA

Very few genetic epidemiology studies have been conducted looking at SGA. While fetal growth potential is considered to be genetically influenced, SGA as an outcome has yet to be comprehensively studied from a genetic perspective. Only 6 studies (from four case groups) were found that looked at SGA as an outcome. In all but the Edwards study,[182] case groups were small (<200), and SGA was considered along with other outcomes (PE, PTB, Fetal Death). The Molvarec[90] study was primarily interested in the intersection of IUGR and PE, and all SGA cases also had concurrent PE. The Edwards[182] study was the largest of the group with 530 case mothers and 190 genes examined. The population was drawn from Puente Alto, Chile and may not be generalizable to White and African American populations in the US. Table 1.8 provides overview of the studies.

IL1B and *IL10* were the only genes to replicate in White US mothers and Chilean mothers. *TNFα, IL2, IL4, IL13, IL6R, CSF1, CSF2, IL4R* and *IL12B* each showed an association in at least one population.

A European consortium, NESTEGG[183] with 800 children born SGA along with parents, siblings and control, will be conducting candidate gene analysis. The children have been followed up to 11 years, and the focus of the study is on genetic factors influencing both fetal and childhood growth in SGA and idiopathic short stature children. A single result for the association between polymorphisms in growth hormone receptor and response to growth hormone treatment has been published. Further candidate gene results are hopefully forthcoming.

Table 1.8 Review of Genetic Epidemiology Studies of Small for Gestational Age

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
Engel, SA[6]	2004	Women recruited from hospitals in Wake and Orange County, NC. Restricted to African American and White.	Nested case-control	87 African American, 93 White	240 African American, 323 White	SGA (below 10th percentile for GA for race, sex and parity)	IL1A (2 SNPs) IL1B (3 SNPs) IL2 IL6 TNFα LTA (2 SNPs)	No association Haplotype association in white mothers OR 0.6 (0.3-1.0) Allelic association in white mothers OR 1.6 (1.0-2.6) No association No association No association
Engel, SA[4]	2004	Women recruited from hospitals in Wake and Orange County, NC. Restricted to African American and White.	Nested case-control	87 African American, 93 White	240 African American, 323 White	SGA (below 10th percentile for GA for race, sex and parity)	IL4 (3 SNPs) IL5 IL13 (3 SNPs) IL10 (3 SNPs) TGFβ1 (2 SNPs)	Haplotype association in white mothers OR 0.2 (0.2-1.2). Possible allelic association for both Whites and African Americans. No association Possible allelic association in African American mothers Haplotype association in white mothers OR 0.5 (0.3-0.8) None
Molvarec, A[90]	2008	Caucasian women from a single hospital in Budapest, Hungary	Case control	140 PE, 69 HELLP 94 cases of SGA	144 healthy pregnancies	IUGR (<10th or 3rd percentile for GA and gender using Hungarian percentiles)	TNFα	Increased allelic frequency in women with both PE and severe IUGR

Study	Year	Population	Study Design	Cases	Controls	Outcome	Genes	Association
Stonek, F[157]	2008 2008[158]	Consecutive Caucasian women present to antenatal clinic before 12 wks GA in Vienna, Austria	Case cohort (analyzed as case control)	259 with at least one outcome (Fetal Death 13, PE 14, PTB 87, SGA 146)	1367 with no outcome	SGA (<10th percentile) also PE, PTB and Fetal Death	IL10 IL6	No association with all outcomes grouped or singly No association with all outcomes grouped or singly
Edwards, DR[182]	2011	Chilean women from Puente Alto	Case control	530 mothers and 436 infants	599 mothers and 628 term infants	SGA (<10th percintile for Chile)	190 genes (775 SNPs)	
							IL6R	OR 1.57 (1.18-2.1)
							CSF1	OR 1.22 (1.00-1.48)
							CSF2	OR 0.79 (0.65-0.97)
							IL10	OR 1.25 (1.04-1.50)
							IL1B	OR 0.73 (0.57-0.93)
							IL4R	OR 0.80 (0.67-0.95)
							IL12B	OR 2.28 (1.01-5.14)

Abbreviations: SGA Small for gestational age, OR Odds ratio, GA gestational age, PE preeclampsia, HELLP hemolysis, elevated liver enzymes, low platelets, IUGR intrauterine growth restriction.

CHAPTER 2 METHODS

2.1 Specific Aims

Preterm birth, hypertensive disorders of pregnancy and SGA are important maternal and fetal outcomes with acute and chronic sequelae for both mother and infant. In addition to increased fetal morbidity and mortality, there is some indication that women who experience these reproductive outcomes are also at risk for future cardiovascular disease. Inflammatory biomarkers and genetic variation in inflammatory genes have been found to be associated with all of these reproductive outcomes as well as with later cardiovascular outcomes. Cell cycle genes have been shown to play a role in placentation and fetal growth and have also been linked with diabetes and cardiovascular disease. These two pathways offer insight into the biological process of both reproductive outcomes and later chronic disease.

The Pregnancy Infection and Nutrition Cohort offers an opportunity to study polymorphisms in a panel of candidate genes in the inflammatory and cell cycle pathways in a biracial population with well-measured covariates. Knowledge about these genetic variants will improve our knowledge about these heterogeneous phenotypes, aide in the identification of susceptible populations and identify target genes for further study.

Specific Aim #1: Evaluate the association between variation in genes associated with inflammation and the outcomes of preterm birth, preeclampsia, isolated gestational

hypertension and SGA. We will used a gene based test to evaluate SNPs, grouped by gene, in 31 genes chosen to represent the innate and adaptive (Th1 and Th2) immune system, and their association with preterm birth, small for gestational age, gestational hypertension and preeclampsia.

Hypothesis #1 Pro-inflammatory genes will be associated with preterm birth. A pro-inflammatory state may arise through variation in pro-inflammatory genes or anti-inflammatory genes.

Hypothesis #2 Genes that are associated with poor placentation will be associated with GHTN and SGA. This includes genes associated with trophoblast invasion (*IL10*), maternal semi-allograft rejection (*KIRs*) and inflammatory cytokines that are stimulated by hypoxia (*IL1A, IL1B, TNFα, IL8, TNFRSF1B, IL6*).

Hypothesis #3 Genes that have shown previous association with co-morbid diseases in the metabolic syndrome (hypertension, CVD, diabetes) are associated with GHTN (*IL6R, IL6, TNFα, TNFRSF1B, IL18, NFkB1*).

Hypothesis #4 Genes that promote a shift towards Th1 by mutations in Th1 genes (*IL2, IFNγ, TNFα, LTA, Il12A, IL12B, IL18, CSF2, TBX21, CXCL10, IL15*) or Th2 genes (*IL6, Il6R, GATA3, IL4, IL13*) will be associated with hypertensive disorders of pregnancy more so than SGA or preterm birth.

Specific Aim#2: Evaluate the association between genetic variation in cell-cycle regulation genes and the outcomes of GHTN, SGA and preterm birth. We will use a gene based test to evaluate SNPs, grouped by gene, in 10 cell cycle genes and their association with gestational hypertension, small for gestational age and preterm birth.

Hypothesis #1 Cell cycle genes will show a stronger associated with placental and fetal growth outcomes (GHTN and SGA) as opposed to preterm birth.

Few studies have evaluated the association between cell cycle variants and preterm birth, hypertensive disorders of pregnancy or small for gestational age. Furthermore, this study is one of the most comprehensive efforts to date of variants in the inflammatory pathway and the outcome of SGA. This study will add to the growing set of studies of inflammation and the outcomes of GHTN and PTB by including novel inflammatory genes and studying two well-defined racial groups.

2.2 Study Population

2.2.1 Pregnancy Infection and Nutrition Study

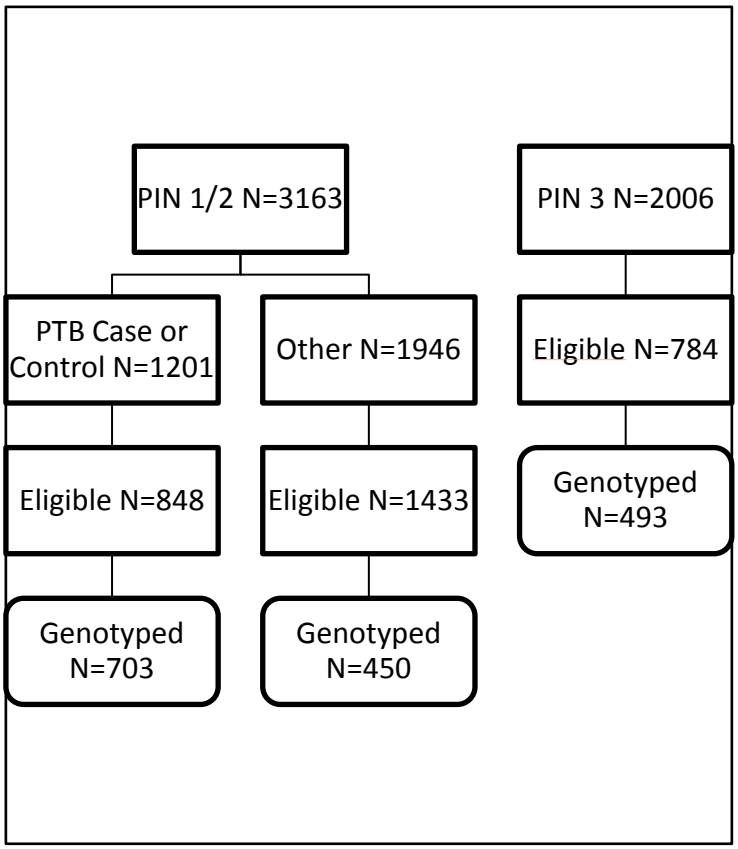
The Pregnancy, Infection and Nutrition (PIN) Study recruited women from August 1995 through June 2005. Three distinct cohorts make up the study population for this analysis. Recruitment for PIN 1 and 2 cohorts occurred between August 1995 and June 2000 in Wake and Orange Counties, North Carolina. Recruitment at prenatal clinics at Wake County Human Services Department and the Wake Medical Center occurred between February 1996 and June 1998. Recruitment from prenatal clinics at University of North Carolina (UNC) Hospitals occurred between August 1995 and June 2000.[184, 185] Recruitment for PIN 3 occurred between January 2001 and June 2005 at the prenatal clinics at UNC Hospitals. Potential subjects were identified through a chart review of all prenatal patients and recruited between 24 and 29 weeks for PIN1 and 2 (N=3163). PIN 3 women were recruited at their second prenatal visit if they were 20 weeks gestation or less (N=2006). Exclusion criteria at enrollment were similar between cohorts:

less than age 16, non-English speaking, not planning to continue care or deliver at the recruitment hospital, carrying multiple gestations, or lacking a telephone.

Data collection protocols varied slightly between the early and later cohorts. For PIN 1 and 2, data collection occurred at the recruitment visit (weeks 24-29), during a telephone interview within 2 weeks of recruitment, and through abstraction of the medical record following delivery. PIN 3 started recruitment earlier in pregnancy and include data collection at the recruitment visit (<=20 weeks), two self-administered questionnaires (<=20 weeks and 24-29 weeks), two telephone interviews (17-22 weeks and 27-30 weeks), and abstraction of the medical record following delivery. All participants gave informed consent at the time of recruitment, and the institutional review boards of the University of North Carolina School of Medicine and Wake Medical Center (for PIN 1) approved the study.

Figure 2.1 graphically displays the sample selection used in this project. Overall demographic and relevant covariate information was very similar in the entire cohort (N=5169) those eligible for genotyping (N=3065) and those genotyped (N=1646) (Table 2.1)

Figure 2.1 Flow Chart of sample selection



Eligibility criteria included maternal self-reported race of White or African American, consent for DNA analysis, suitable DNA sample available and non-missing preterm status. Some women contributed more than 1 birth to the original cohort. Only one birth per woman is represented in the final genotyping sample.

Table 2.1 Comparison of the entire PIN cohort, eligible for genotyping and genotyped

	All N=5169 N(%)	***Eligible N=3065 N(%)***	***Genotyped N=1646 N(%)***
Age yrs Mean (SD)	26.8 (6.2)	26.2 (6.3)	26.1 (6.3)
White	3035 (58.7)	1918 (62.6)	1031 (62.6)
African American	1746 (33.8)	1147 (37.4)	615 (37.4)
Other	387 (7.5)	0	0
Missing race	1	0	0
Poverty mean (median, IQR)	305 (223, 109-476)	284 (198, 96-473)	273 (179, 95-464)
Missing poverty	741	375	199
Married	2959 (57.4)	1646 (53.7)	868 (52.8)
Single	1843 (35.8)	1199 (39.1)	658 (40.0)
Other	352 (6.8)	218 (7.1)	119 (7.2)
Missing marital	15	2	1
BMI Mean (median, IQR)	26.0 (24,21-29)	25.8 (24, 21-29)	26.5 (24, 21-30)
Missing BMI	364	188	82
Height inches Mean (SD)	64.8 (2.7)	65.0 (2.7)	64.9 (2.7)
Missing height	304	147	61
Smoker	935 (20.8)	657 (23.6)	383 (25.6)
Missing smoking	670	0	152
First birth	2347 (45.6)	1400 (45.8)	769 (46.8)
Multiparous	2803 (54.4)	1659 (54.2)	873 (53.1)
Missing parity	19	5	4
Male Infant	2560 (50.6)	1530 (50.1)	818 (49.7)
Missing gender	106	14	1
GDM	312 (6.6)	190 (6.7)	127 (8.0)
Missing GDM	442	235	58
Preterm	686 (13.5)	377 (12.3)	347
Missing PTB	80	0	0
Preterm Labor (% PTB)	214 (33.9)	120 (35.2)	111 (35.5)
PPROM (% PTB)	127 (20.1)	66 (19.4)	63 (20.1)
Medically Indicated (% PTB)	290 (46.0)	155 (45.5)	139 (44.4)
Missing preterm subtype	137	38	36
Chronic Hypertension	263 (5.6)	139 (4.9)	113 (7.1)
Isolated GHTN	777 (15.0)	479 (15.6)	454
PE	393 (8.3)	239 (8.4)	217
Missing chronic hypertension	442	235	59
Missing PE	440	233	57
SGA	371 (8.2)	239 (8.3)	216
Missing SGA	658	167	105

Abbreviations: SD standard deviation, IQR interquartile range, BMI Body Mass index (kg/m^2), GDM Gestational Diabetes Mellitus, PTB Preterm Birth, GHTN Gestational Hypertension, PE Preeclampsia, SGA Small for gestational age.

2.2.2 Selection of Cases and Controls

Cases and controls were selected from eligible women from the entire PIN cohort. Initial eligibility criteria included consent for DNA analysis, availability of a suitable biospecimen, non-missing preterm outcome and self reported maternal race of White or Black. Overall 3539 (68.5%) of the women in all three PIN cohorts provided consent for genetic analysis. These eligibility criteria resulted in 3065 (59.3%) women who were eligible for selection into our study. Case distributions among the entire cohort and the eligible cohort were very similar (Table 2.2).

Table 2.2 Case distribution in the entire PIN cohort and the Eligible PIN sample

	All N=5169 *N(%)*	***Eligible N=3065*** *N(%)*	***Genotyped N=1646*** *N (% of eligible genotyped)*
Preterm	686 (13.5)	377 (12.3)	347 (92.0)
SGA	371 (8.2)	239 (8.2)	216 (90.4)
PE	393 (8.3)	238 (8.4)	217 (91.2)
Isolated GHTN	777 (15.0)	479 (15.6)	454 (94.8)
No case status	3335 (64.5)	1973 (64.4)	629 (31.9)

Percents do not sum to 100% due to multiple case definitions for some women
Abbreviations: SGA small for gestational age, PE preeclampsia, GHTN gestational hypertension

Case selection

Women with a preterm delivery, an infant with SGA or identified as having preeclampsia or gestational hypertension were identified as cases as described below (Section 2.3.1). Attempts were made to genotype all cases, however poor or insufficient biospecimens resulted in a lack of suitable DNA for some women. Between 90% and 95% of all eligible cases were genotyped (Table 2.2).

Non-case Selection

Only 32% of eligible non-cases (N=629) were genotyped (Table 2.2). During selection of non-cases priority was given to non-cases with existing extracted DNA. Extracted DNA was available for women who were a part of a PIN subcohort or who had been included in previous genetic studies.

Sources of DNA (Figure 2.2)

The PIN subcohort was randomly chosen at the time of enrollment into PIN1/2 using an automated system that selected the subcohort in a one-to-one ratio to preterm cases delivering at 35-36 weeks and a two-to-one ratio for preterm cases delivering prior to 35 weeks. The randomization resulted in a subcohort of 1201 women including 921 women selected as controls (122 of whom became preterm cases) and 280 additional preterm cases. While most specimens were collected and stored for all women in PIN, specimens from women who were in the subcohort were assayed with priority. Women in the subcohort also had additional biospecimens collected at the time of delivery and were re-interviewed within 2 months of delivery.

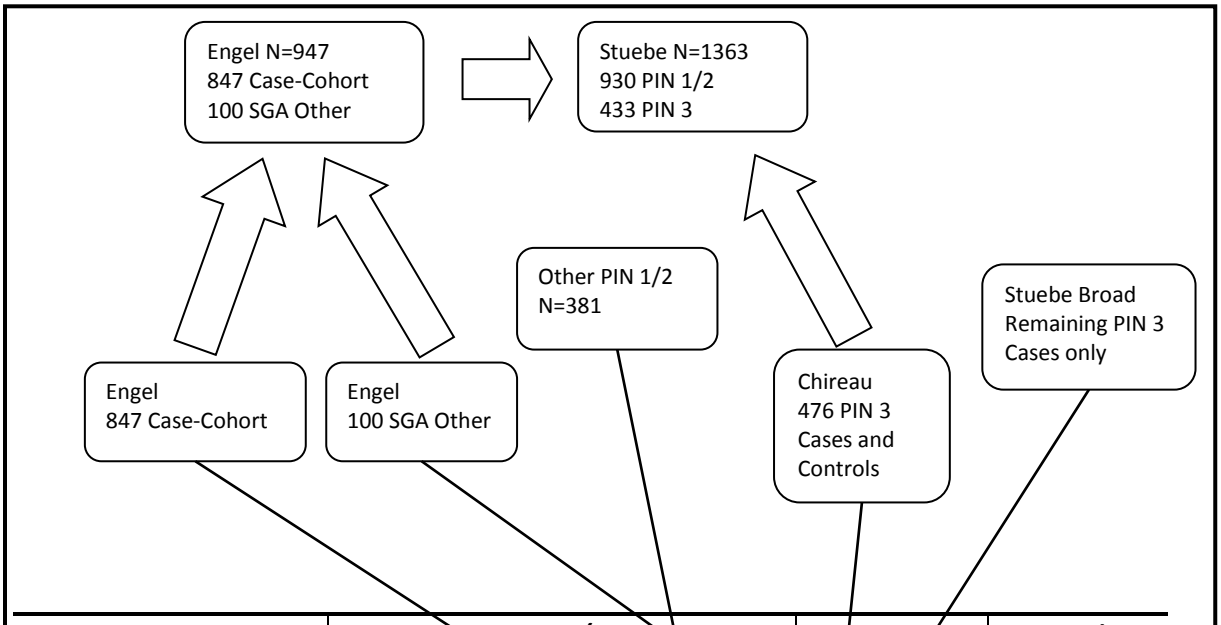
The subcohort had been used in previous genetic studies[4, 6] investigating the outcomes of spontaneous preterm birth and SGA. For these studies, non-cases were randomly selected from the subcohort for DNA extraction and genotyping.

One additional study extracted DNA using the PIN biospecimens. Monique Chireau extracted DNA from 476 women from PIN 3 who had available biospecimens and had consented to participate in genetic analysis. Selection into this study also required the successful collection of a placenta at the time of delivery. Selection into Dr. Chireau's sample was based on timing of

entry into PIN and likely represents a random selection of women enrolled in PIN 3 at the time. Further description of the births included in Dr. Chireau's study is provided in Section 2.5.1

In addition to existing extracted DNA, additional cases of PE and GHTN were identified in PIN 1/2 women outside the subcohort. Additional non-cases were also drawn from this population. Additional PIN 3 cases (all outcomes) were identified and extracted at the Broad Institute as a part of an ongoing genetic study being conducted by Dr. Stuebe.

Figure 2.2 Sources of DNA for the current study



	PIN 1/2		***PIN 3***	**Total**
	Case-Cohort	*Other*		
Total	703	450	493	1646
Preterm	255 (36.3%)	0	92 (18.7%)	347 (21.1%)
SGA	69 (9.8%)	94 (20.9%)	53 (10.8%)	216 (13.1%)
Isolated GHTN	97 (13.8%)	215 (47.8%)	142 (28.8%)	454 (27.6%)
PE	83 (11.8%)	79 (17.6%)	55 (11.2%)	217 (13.2%)
No case status	324 (46.1%)	87 (19.3%)	218 (44.2%)	629 (38.2%)

Abbreviations: SGA Small for Gestational Age, GHTN Gestational Hypertension, PE preeclampsia

2.3 Variable Measurement

2.3.1 Outcomes

2.3.1.1 Preterm Birth

Gestational age at delivery was calculated based on the first ultrasound performed prior to 22 weeks' gestation. For women without an early ultrasound, self-reported Last Menstrual Period (LMP) was used to determine gestational age at delivery. Preterm birth was defined as a live birth before 37 complete weeks of gestation. Subtypes of preterm birth were classified as spontaneous preterm labor (PTL), preterm premature rupture of membranes (rupture of membranes preceded onset of uterine contractions by at least 4 hours, PPROM) or medical indication based on chart review by a collaborating obstetrician.

Medically indicated preterm births are sometimes a result of worsening hypertension or poor fetal growth. In order to isolate the preterm births due to other causes, Spontaneous Preterm Birth (including PTL and PPROM) was considered as an additional outcome.

2.3.1.2 Hypertensive Disorders of Pregnancy

PIN collected information on three gestational hypertension variables; chronic hypertension, gestational hypertension (GHTN) and preeclampsia (PE). While chronic hypertension was collected similarly for all women, the GHTN and PE variables were collected in a variety of ways depending on the cohort and the data sources available.

Chronic Hypertension: Chronic hypertension was evaluated based on diagnoses in the discharge summary or labor and delivery charts. In addition, for some women, individual values

in the prenatal chart (before 20 weeks) were examined for evidence of hypertension. Women were assigned a binary outcome of chronic hypertension present or absent.

Gestational Hypertension (GHTN): For PIN 1 and PIN 3, two different GHTN variables were created. One variable (PIN Discharge) was based on diagnoses in the labor and delivery chart or discharge record. Another variable (PIN Prenatal ACOG) was abstracted using ACOG criteria[45] and clinical variables (blood pressure, proteinuria) from the prenatal record. For PIN 2 women, data abstractors inspected the prenatal and labor and delivery record and used the following criteria (PIN Prenatal non-ACOG): After 20 weeks gestation, SBP increase >=30 mmHg or DBP increase >= 15mmHg or BP>=140/90 mmHg on two occasions >=6 hrs apart to indicate the presence or absence of GHTN. The criteria used for PIN 2 reflect clinical practice before the 2002 ACOG guidelines.

Preeclampsia (PE): For PIN 1 and PIN 3, two different PE variables were created. One variable (PIN Discharge) was based on diagnoses in the labor and delivery chart or discharge record. Another variable (PIN Prenatal ACOG) was abstracted using ACOG criteria[45] and clinical variables (blood pressure, proteinuria) from the prenatal record. For PIN 2 women, data abstractors inspected the prenatal and labor and delivery record and used the following criteria (PIN Prenatal non-ACOG): After 20 weeks gestation SBP increase >=30 mmHg or DBP increased >= 15mmHg or BP>=140/90 mmHg on two occasions >=6 hrs apart PLUS the presence of proteinuria (>=0.3g/24 hrs or >=30 mg/dl [1+dipstick] on two occasions >6hrs apart) OR Edema (1+ 2+ 3+) to indicate the presence or absence of PE. The criteria used for PIN 2 reflect clinical practice before the 2002 ACOG guidelines.

ACOG Criteria for Preeclampsia:[45]

Criteria for Diagnosis of Preeclampsia
• Blood pressure of 140 mm Hg systolic or higher or 90 mm Hg diastolic or higher that occurs after 20 weeks of gestation in a woman with previously normal blood pressure • Proteinuria, defined as urinary excretion of 0.3 g protein or higher in a 24-hour urine specimen

Validation Study

For GHTN and PE the presence of two variables creates a challenge in case definition. The PIN Discharge variables are not based on standardized criteria and reflect physician diagnostic practices. These diagnostic practices may include noting a diagnosis when there is a poor maternal or fetal outcome and failing to make a diagnosis when a healthy term infant is delivered. On the other hand, the variables based solely on prenatal records were assessed using 2 different sets of standardized criteria. Additionally the prenatal record abstraction does not capture events following the last prenatal visit and disease onset at the time of delivery will have been missed. While term deliveries may have prenatal visits at weekly or biweekly intervals preceding delivery, preterm births may occur during pregnancy intervals when routine prenatal visits are less frequent.

Given the presence of up to two variables for case definition, a validation study was conducted using the UNC Perinatal Database to determine the utility of using both PIN variables to identify cases. The UNC Perinatal Database is a clinical database containing pregnancy information for all deliveries at UNC after April 1996. Clinical nurse researchers enter standardized data into the database from a woman's complete medical record. While in theory this should capture both prenatal and delivery time periods, in practice, the database contains mostly clinical information from the time of delivery. 1626 women from PIN who were eligible for the genetic study who had discordant diagnoses based on the PIN variables (discordant for

GHTN or discordant for PE) OR who were missing one or both of the PIN variables, were compared to the UNC database. 1223 women were matched in the database.

Results of Validation Study (Table 2.3)

Chronic hypertension was present in the UNC database and showed strong agreement with the PIN variable with a kappa of 0.92 (0.89, 0.95). Although the case group for the validation study was comprised of women who were discordant on other variables related to hypertension, the good agreement of the chronic hypertension variable is reassuring.

The PIN Discharge variables had strong agreement with the UNC database. This reflects the reliance of both variables on the labor and delivery and discharge records.

The PIN variable based on non-ACOG criteria and abstracted from the complete medical record also had strong agreement with the UNC database.

The PIN Prenatal variable based on ACOG criteria does not have good agreement with the UNC database. While the PIN variable captures 10 times more cases of isolated GHTN compared to the UNC database, <1% of the PIN GHTN variables are validated by the UNC Database. For PE the agreement is also quite poor (Kappa=0.20) and many of the cases missed by the PIN variable are cases of late onset disease that arose at the time of delivery.

Table 2.3: Agreement between PIN variables and the UNC Perinatal Database for 1223 women with discordant PIN values

	PE			***Isolated GHTN***		
PIN Variable	PIN Cases	UNC Cases	Kappa (95% CI)	PIN Cases	UNC Cases	Kappa (95% CI)
Discharge	161	148	0.93 (0.89, 0.96)	39	41	0.89 (0.82, 0.97)
non-ACOG	41	42	0.91 (0.84, 0.98)	28	20	0.82 (0.71, 0.94)
ACOG	114	148	0.20 (0.11, 0.28)	466	41	-0.12 (-0.16, -0.08)

Conclusions based on the validation study

The initial PIN protocol released data solely based on the PIN ACOG assessment due to increased confidence in the standardized criteria used for ascertainment. The strong correlation of the Discharge and non-ACOG variables with the UNC Database however gives support for their use as well. Discussions with UNC OB/GYN Dr. Thorpe revealed that clinical practice at the time was in flux with changes in criteria for both PE and GHTN. In fact until 2002, gestational hypertension had been called pregnancy-induced hypertension [45] which further complicates the MD diagnosis of GHTN. Given the fact that the PIN ACOG variables were not able to assess disease onset at the time of delivery and that the Discharge and non-ACOG variables correlated with one other clinical source of information, all three variables were used to determine case and control status in this study.

Case status Definition for GHTN and PE

- Women who were found to have PE by any of the PIN variables are considered PE cases.
- Women who were found to have GHTN by any of the GHTN variables and did not progress to PE are identified as cases of isolated GHTN.
- Women with chronic hypertension will be initially considered as cases if they also have PE or isolated GHTN. They will be removed from the case definition as part of a sensitivity analysis.

Table 2.4 Case definitions for Preeclampsia (PE) and Isolated Gestational Hypertension (GHTN)

	PIN Discharge	*PIN nonACOG*	*PIN ACOG*	*Chronic Hypertension*
Preeclampsia	PE=Yes, GHTN= Yes or No	Or PE= Yes, GHTN= Yes or No	Or PE=Yes, GHTN= Yes or No	Yes or No
Isolated GHTN	PE=No and GHTN=Yes	Or PE=No and GHTN=Yes	Or PE=No and GHTN=Yes	Yes or No

Additional validation

In order to clarify the validity of the PIN diagnoses, 125 records for women who were both genotyped and had discordant PIN diagnoses were validated against UNC antenatal and delivery records.

Blood pressure and proteinuria data were abstracted from the medical record and preeclampsia and gestational hypertension were assessed using ACOG criteria. For women that PIN identified as having PE by any measure, the validation suggested a sensitivity of 77%, specificity of 62% and a positive predictive value of 63%. The low PPV was due to women that PIN identified with PE for whom there was only evidence of isolated gestational hypertension in the chart (24/70, 34%).

For isolated gestational hypertension the sensitivity was 63%, specificity 75% and positive predictive value 73%. The low positive predictive value was due primarily to women who PIN identified as having gestational hypertension but in fact had preeclampsia (13/55 24%).

Given the underlying data set included only women with discordant diagnoses of either gestational hypertension or preeclampsia, the PPV is the most informative value. For both diagnoses the PPV is fairly low, with PIN PE diagnoses including a large proportion of women with gestational hypertension, and PIN gestational hypertension diagnoses including a smaller proportion of women with preeclampsia.

Given the changing diagnostic criteria over the course of the study, those women who were diagnosed by PIN prior to publication and acceptance of the ACOG rules might not meet current PE diagnostic criteria and their inclusion as PE cases will increase the heterogeneity of the case group and perhaps limit our ability to find associations.

Within the analysis, refinement of the PE case definition is possible based on the results of the chart abstraction to assess the sensitivity of the estimates to stricter case definitions. The single SNP analysis will be conducted using a refined case group that includes; 1. Concordant PIN diagnoses of preeclampsia or 2. Validated PE diagnosis based on the UNC chart review. Although this will be a small group, the direction of the association can be assessed to determine how the change in case definition will alter inference about the SNPs.

2.3.1.3 Small for gestational age

Birth weight was recorded at time of delivery for all infants. SGA was defined as below the 10th percentile for weight for gestational age stratified by race, sex and parity. The percentiles used were developed by Zhang[186] based on 1989 United States births.

Women with PE are more likely to have infants born SGA.[132] This association may be stronger among women with early onset PE and preterm birth.[133] In addition, infants born preterm for any reason are more likely to have impaired fetal growth compared to infants who go on to a term delivery. For these reasons term SGA was also considered as a discreet outcome in order to capture pathways independent of prematurity and sever preeclampsia.

2.3.2 Main Exposures

2.3.2.1 Sample Collection and DNA Extraction

Whole blood was collected from PIN participants, centrifuged and the buffy coat fraction was stored in CPT tubes and placed in -80˚C storage. DNA was extracted using various protocols for each study. For PIN1/2 women used in Dr. Engel's study, DNA was extracted using the

Applied Biosystems (ABI) automated DNA extractor.[6] DNA extraction for PIN3 women at Wake Forest University (Winston-Salem, NC) and PIN3 cases at the Broad Institute (Cambridge, MA) was performed using Qiagen AutoPure chemistry. In addition to previously extracted DNA, some cases and controls had DNA extracted specifically for this study at the Biospecimen Processing Laboratory at UNC (Chapel Hill, NC). DNA was extracted from the buffy coat sample using similar Qiagen (Gentra) Puregene chemistry.

2.3.2.2 Tag Selection

For each gene, the Illumina database was queried for all polymorphism design scores within our genes of interest, allowing for 20kb upstream and 10kb downstream margins. Genes in close proximity were analyzed together. A scoring algorithm for each SNP was created, taking into account Illumina design score, Illumina error codes, DNA coding changes, and presence in a possible 5' promoter site. This composite SNP database consisting of over 30,000 polymorphisms was analyzed using TagZilla for multiple populations (populations consisting of more than one racial group), to select an optimal tagSNP within each bin.[187] Given power considerations, we selected an R^2 = 80% and limited tags to minor allele frequencies ≥ 10%. Due to the inclusion of two genetic ancestry groups, some tagSNPs chosen were unique to a specific genetic ancestry group.

In addition to tagSNPs, some SNPs that had previously shown an association in the literature were forced onto the panel.

SNPs selected for both inflammatory and cell cycle genes are in the Appendix (Tables S1 and S2). Minor allele frequencies were obtained from the Illumina database and supplemented with data from NCBI (http://www.ncbi.nlm.nih.gov/projects/SNP/) when Illumina data was

missing. MAF are noted for CEU (Northern and Western European Ancestry) and YRI (Yoruba n Ibadan, Nigeria). Some SNPs are non-polymorphic in a given genetic ancestry group (MAF=0.0).

2.3.2.3 GoldenGate Process

The DNA sample is first activated for binding to paramagnetic particles. Three oligonucleotides are designed for each SNP locus. Two oligos are specific to each allele of the SNP site and a third that hybridizes several bases downstream is the locus-specific oligo. All three contain regions of genomic complementarity and universal PCR primer sites. During the primer hybridization process, the assay oligonucleotides hybridize to the genomic DNA sample bound to the paramagnetic particles. Following hybridization, several wash steps are performed to reduce noise by removing excess oligos. Extension of the appropriate allele-specific oligos and ligation of the extended product to the locus-specific oligo joins information about the genotype present at the SNP site to the address sequence of the locus. These provide the template for PCR using universal PCR primers P1-P3. Universal primers P1 and P2 are Cy3 and Cy5-labeled. The single-stranded, labeled DNAs are hybridized to their complement bead type through the locus-specific oligo. Hybridization of the GoldenGate assay products onto the array matrix or beadchip allows for the separation of the assay products in solution, onto a solid surface for individual SNP genotype readout. The intensities of the beads' fluorescence are detected by the Illumina BeadArray Reader and are in turn analyzed using Illumina's software for automated genotype calling. Genotyping results will be reported as allele sizes of the polymorphic markers of called alleles as well as values normalized to a CEPH individual.

2.3.2.4 Quality Control

Genotyping

Genotyping was performed by the University of North Carolina Mammalian Genotyping Core using the Illumina GoldenGate assay. Assay intensity and genotype cluster images for all SNPs were reviewed individually. Of the 1536 makers on the panel, 1430 were successfully genotyped with 106 markers (6.9%) excluded due to low signal intensity or inability to distinguish between genotype clusters. Seven QC samples were included on each plate. Three blind duplicates and 4 'open' CEPH controls (a family trio and one family member repeated). Blind duplicates were chosen at random from all genotyped samples (approximately 3% of all samples) with sufficient quantity of DNA. Blinded duplicates were examined for inconsistency between genotypes and SNPs were excluded if they have >2 genotype call errors between duplicates. The open controls were examined for mendelian inheritance errors or inconsistencies across plates, which may be evidence of genotyping errors or batch effects.

Hardy Weinberg

HWE was examined using Plink among non-cases stratified by race to detect possible genotyping errors ($p<0.01$). SNPs which show evidence HW disequilibrium were reviewed with the UNC Lab to determine possible reasons for discrepancies (difficulty distinguishing clusters, close proximity to another SNP) and they were dropped if the genotyping results remain inconsistent.

Participants

1649 PIN samples were plated. In the initial run 99.1% of the samples had a call rate >=95%. Following the initial genotyping an additional plate was run to capture samples (N=19) that initially failed genotyping. The additional plate had 73.7% with a call rate >=95%. Ultimately 1646 unique individuals were successfully genotyped. Given the very low failure rate for individuals, those individuals failing genotyping were individually inspected with regards to case status to exclude any major systematic issues. Markers for gender were also genotyped and were inspected. Given that all cases and controls gave birth, non-female gender among subjects would be a sign of sample contamination. Subjects were also examined for 100% concordance of genotype to identify unintended duplicates.

2.3.3 Genetic Ancestry

Previous studies[188] suggest that there may be important differences between allelic frequencies in genes related to inflammatory cytokines between self-reported African-Americans and Caucasians in the United States. As race has also been associated with all three outcomes, the potential for confounding by population stratification is possible.

Self-reported race was collected for all PIN mothers, and maternal race for this study was restricted to self-reported race as “White” or “Black or African American”. Women who reported mixed race including African-American or White were not selected for genotyping.

In addition to self-reported race, a panel of 157 ancestry informative markers (AIMs) were chosen based on AIMs that have performed well on the same platform and in a similar (North Carolina) population.[189] The selected AIMs maximize the difference in allele frequency between the assumed ancestral populations, Yorban individuals from Ibadan in Nigeria and the HapMap

CEPH population representing Northern and Western Europe populations. For the Carolina Breast Cancer Study (CBCS), AIMs were selected based on δ and Fisher's Information Criteria across three possible admixture proportions; 10% European/90%African, 50%European/50%African and 90%European/10%African. Previous assessment of admixture among contemporary women in North Carolina suggests proportion of European Ancestry is approximately 15-20% for African Americans and 90% for Whites.[189, 190]

2.3.4 Additional covariates

2.3.4.1 Smoking

Women reported the duration and amount smoked during the telephone interview between 24 and 30 weeks gestation. The variable captures the average number of cigarettes smoked during the first 6 months of pregnancy. Previous analysis in the early cohorts in PIN showed a high correlation between smoking in this interval and in later intervals in pregnancy. Urinary cotinine (a metabolite of nicotine) was analyzed for a subset of the women in PIN 1 and 2 between 24 and 29 weeks and shortly after delivery. A previous analysis[185] suggested that postpartum cotinine levels were somewhat more strongly associated with preterm birth compared to self-report, however cotinine levels at 24-29 weeks showed a similar pattern of association. Given that only a small fraction on the entire cohort had measured cotinine levels, self-reported smoking was used.

2.3.4.2 Height and Body Mass Index

Women were measured for height at their recruitment visit and they provided a self-reported pre-pregnancy weight. Maternal weight throughout the pregnancy was abstracted

from the medical record and the date of the last reported weight was noted to determine gestational weight gain. Self reported pre-pregnancy weight was corrected if it was not consistent with the first measured weight. Body Mass Index (BMI) was categorized based on the 2009 IOM Guidelines[191] (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2 and >=30.0kg/m^2).

2.3.4.4 Parity

Number of previous pregnancies was self reported by women at the recruitment visit. Parity was calculated was calculated as number of live born infants plus number of still born.

2.3.4.5 Age

Maternal age at conception was self-reported and collected at the recruitment visit.

2.3.4.6 Poverty

Percent poverty was constructed based on self report of total family income adjusted for the total number of adults and children relying on the income. The adjusted income was compared to regional values for poverty. For PIN 1/ 2 the benchmark was 1996 poverty levels while for PIN 3 the benchmark is 2001.

2.4 Analysis Plan

Analysis proceeded in stages with the analysis and study design dictated by the goals of each stage. The following section will discuss the specifics of each stage in detail.

In general Stage 1 was focused on gene level associations with the outcomes and was a case control design using SNPs which are grouped at the level of the gene. The analysis was

stratified by genetic ancestry and adjusted for continuous genetic ancestry. As a discovery phase, a false discovery rate of 20% was used to identify gene sets which proceed to Stage 2.

Stage 2 focused on identifying the specific SNPs within the genes that are driving the relationship seen in Stage 1. Inverse probability weighting was used to include the entire genotyped cohort to estimate risk ratios for each SNP. Robust variance estimators were used to construct confidence intervals. SNPs within gene sets were ranked based on strength and precision of the association. Investigation of LD was used to further understand the relative importance of each SNP. Stage 2 was also stratified by genetic ancestry and adjusted for ancestry. Additional covariates were explored based on DAGs for the specific outcomes.

Stage 3 was exploratory and involved a Stage 2 analysis of all SNPs in both pathways regardless of the results of Stage 1.

2.4.1 Stage 1

Traditional analysis of candidate gene panels usually includes a SNP-based analysis with the possible addition of a haplotype analysis. For outcomes with strong associations with a single polymorphism, this approach has resulted in some meaningful discoveries. However for complex disorders, current SNP by SNP approaches are often finding modest effects with single SNPs, and these associations are often hard to replicate.

For complex disorders, analysis at the level of the gene may be more relevant. Particularly when analyzing tag SNPs, multiple SNPs on a given gene may be in LD with causal SNPs. Although each individual SNP may have a weak association, epistatic interactions may result in individual SNPs showing little effect while their interactions may have a larger effect.[192, 193] A gene based analysis approach also has the potential to reduce the multiple testing issues

associated with large numbers of SNPs, especially in the context of genome wide association studies (GWAS).

Advantages of gene based analyses include improved reproducibility, power and interpretability. Since different studies often genotype different SNPs, reproducibility may be hampered if different tag SNPs or different genetic panels are assayed by different study groups. Gene based results allow for the assessment of genes across study centers and may help more quickly focus fine mapping of relevant genes. Power is improved due to the reduction in the number of tests and a lowering of a panel-wise significance level. Gene based associations are also likely to be stronger than the individual SNP associations. Finally, interpretations at the gene level can be made based on known biomarkers and gene products as opposed to speculation about the functional implication of an unknown causal SNP which is being captured by a tagSNP.[194]

Michael Wu[194] has developed an attractive method (SKAT- SNP-set Kernel Association Test) for performing a gene based analysis which offers a powerful and flexible framework that allows for complex SNP interactions and non-linear effects. In addition, the method allows for inclusion of covariates and does not penalized SNPs with opposing effects (risk or protective) within a single gene. Although SKAT allows for any biologically informed method for grouping SNPs into sets; gene, pathway, conserved regions, haplotype blocks or windows, gene based sets with a suitable upstream and downstream regulatory region will be used for this analysis.

SKAT initially assumes an additive model and uses a logistic kernel-machine regression model. This model form assesses the influence of all the SNPs in a given SNP set through a semidefinite kernel function. The kernel can be specified to accommodate different model forms from linear kernels, which represent the logistic model, to highly non-linear kernels.

Kernel functions convert information for each pair of subjects to a value that represents their similarity. As all possible pairs are integrated into the function, the resulting matrix must be positive semidefinite (a positive semidefinite matrix has only non-negative eigenvalues and possesses properties which facilitate the calculation of optimal solutions).[195]

Kernel choice is important as it drives the modeling of the association between the SNPs in the SNP-set and disease status. A number of kernels exist and many more are being developed.[196] SKAT incorporates 6 predefined kernels (linear, linear weighted, IBS, IBS weights, quadratic and a product kernel which allows for interactions). Through simulation, Wu suggests use of a linear kernel (comparable to a usual logistic model) or the identical by state (IBS) kernel. The IBS kernel compares the number of alleles shared IBS at the SNPs within the SNP-set. The IBS kernel can be augmented by weights based on MAF or on prior information regarding expected associations between specific tags and the trait of interest.[193] The logistic model can also be weighted by the MAF which allows for rare variants to be up-weighted relative to common variants.

Hypothesis testing is conducted using a variance component score test of the null hypothesis that the general function for the SNP set equals 0.[197] The degrees of freedom are adjusted for the correlation of the SNPs within the SNP set with higher correlation between SNPs resulting in fewer degrees of freedom.

Compared to other existing multi-SNP tests, SKAT has several advantages.[194] Compared to tests which rely on the most significant p-value for an individual SNP within a given SNP-set, this method allows for interaction between SNPs within a SNP-set. When a given SNP is not in LD with a causal SNP, this method borrows power across a number of SNPs that may each be correlated to the causal SNP. Omnibus tests for multiple SNPS allow for simultaneous analysis of

all SNPs within a given SNP-set, but are crippled by a large number of degrees of freedom and cannot account for opposing directions of effect. Omnibus methods also do not allow for the incorporation of covariates.

In Stage 1 a gene based analysis was used to identify genes of interest. Stage 1 was conducted as a stratified analysis. For each racial group, defined by genetic ancestry, the appropriate SNP set was assembled for each gene. As tag SNPs were chosen using a 20kb upstream and 10kb downstream region, the gene set included all tag SNPs within this region. Tag SNPs which are only polymorphic in a single genetic ancestry group were excluded from the analysis in the other group. Genes that are tightly clustered with overlapping upstream and downstream regions were considered as a single gene set. Rare SNPs were included as long as the SNP is truly rare in the population in general (as confirmed by HapMap) and there was at least one individual with the variant allele in the case or non-case group. Given that missing genotypes in a single SNP removed an individual from analysis in the entire geneset, individuals included for analysis varied by outcome and geneset. While imputation could be used to fill in those alleles that failed to genotype, using a complete case analysis captures greater than 90% of individuals for each outcome/ genetic ancestry combination. Given the logistical difficulties of imputing the missing alleles and the high coverage of a complete case approach, imputation was not attempted. Tables 2.7 through 2.9 provide information on each geneset in terms of the number of individuals and SNPs included in analysis.

For Stage 1 cases included all genotyped cases with non-missing genotypes for the specific outcome. As this is a case-control design, controls were genotyped women who are free from any outcome of interest (Table 2.10).

Table 2.5 Number of SNPs in each gene set for inflammatory genes

GENE	SNPs	SNPs dropped (outcome)*
TNFRSF1B	9	
IL6R	31	rs12060250 (all) rs12096944 (all)
IL10	17	
IL1A	2	Replication SNPs
IL1B	2	Replication SNPs
IL8RB	6	
IL12A	26	
IL8	17	rs16849893 rs4694634 rs7693566 (SGA, PE, tSGA, nPE) rs16849896 rs16849907 (GHTN, PE, tSGA, nGHTN, nPE)
CXCL10	9	
NFKB1	28	
IL2	9	rs10034410 (PE, nPE) rs10027390 out of HWE (YRI)
IL15	22	rs17007476 (PE, sPTB nPE) rs17007480 rs17007503 (PTB, SGA, PE, sPTB tSGA nPE)
CSF2	18	rs743677 (PE, tSGA, nPE)
IL13;IL4	26	rs2243240 rs2243246 rs2243261 (PE, sPTB, nPE) rs4621555 (PE, sPTB, tSGA, nPE), rs2243253 (SGA, tSGA, nPE)
IL12B	19	
LTA;TNF	14	
IL6	26	rs2069842 (SGA, PE, sPTB, tSGA, nPE)
GATA3	34	rs12262237 (PTB, SGA, GHTN, sPTB, tSGA, nGHTN) rs263425 (SGA, GHTN, tSGA, nGHTN)
IL18	12	rs11214098 non-polymorphic (all)
KLDR1	8	
IFNG	12	rs17104856 (PTB, SGA, GHTN, sPTB, tSGA, nGHTN, nPE)
TGFB3	2	rs4252345 non-polymorphic (all)
TBX21	7	
TGFB1	1	
KIR3DL3	14	
KIR2DL4	2	
KIR3DL2	6	
IFNGR2	14	

*All SNPs dropped from European Americans except for IL2 rs10027390 which was out of HWE in African Americans and was dropped for all analyses in this genetic ancestry group

Table 2.6 Number of SNPs in each gene set for cell cycle genes

GENE	SNPs	SNPs dropped* (outcome)
GADD45A	20	rs1511686 (PTB, SGA, PE, sPTB, tSGA)
RASSF1	7	
CCNA2	9	rs3217760 (PTB, GHTN, PE, sPTB, sGHTN, sPE)
CCNH	1	
NOV	14	
CDKN2A;CDKN2B	24	
CNNM2	16	rs7902220 (PTB, SGA, PE, sPTB, tSGA, nPE)
CCND1	18	rs7106515 non-polymorphic (all)
MDM2	1	

Table 2.7 Number of individuals with complete genotype information for each gene set and outcome stratified by genetic ancestry group

	PRETERM		SPONTANEOUS PRETERM		SGA		Term SGA		GHTN		GHTN w/o CHTN		PE		GHTN w/o CHTN	
	EA	AA	EA	AA	EA	AA	EA	AA	EA	AA	EA	AA	EA	AA	EA	AA
Total	603	338	512	269	526	296	505	268	688	371	650	347	524	301	498	274
Inflammation Genes																
TNFRSF1B	598	333	507	266	521	290	500	263	682	365	644	342	520	298	494	271
IL6R	592	329	504	261	521	285	500	258	680	356	642	335	518	293	492	266
IL10	600	335	509	266	523	295	502	267	686	368	648	345	522	300	496	273
IL1A	603	338	512	269	526	296	505	268	688	371	650	347	524	301	498	274
IL1B	603	338	512	269	526	296	505	268	688	371	650	347	524	301	498	274
IL8RB	603	338	512	269	526	296	505	268	688	371	650	347	524	301	498	274
IL12A	594	317	504	253	520	277	499	250	683	342	645	319	520	282	494	256
IL8	599	311	509	247	522	271	502	247	680	343	642	325	519	281	493	256
CXCL10	602	336	511	267	525	295	504	267	687	370	649	346	523	300	497	273
NFKB1	598	321	507	255	522	280	501	253	683	355	645	333	520	287	495	262
IL2	601	337	510	268	524	295	503	267	685	370	647	347	521	301	495	274
IL15	580	325	492	261	507	284	486	259	658	362	622	339	505	293	480	268
CSF2	590	330	503	262	516	287	495	260	676	364	639	341	515	294	489	267
IL13;IL4	583	335	502	267	512	293	491	266	670	368	633	344	517	299	491	272
IL12B	594	335	504	266	520	294	499	266	679	369	642	345	518	298	493	271
LTA;TNF	580	332	495	264	505	290	484	263	662	362	625	338	504	296	478	270
IL6	599	337	509	268	522	292	501	264	684	366	646	343	520	299	494	272
GATA3	586	332	497	263	513	288	492	261	663	361	626	337	509	293	484	266
IL18	603	337	512	268	526	295	505	267	688	369	650	345	524	299	498	273
KLDR1	601	335	511	266	525	294	504	266	686	368	648	344	523	299	497	272
IFNG	585	331	498	264	514	292	496	264	673	365	638	342	515	297	489	270
TGFB3	603	338	512	269	526	296	505	268	688	371	650	347	524	301	498	274
TBX21	602	338	511	269	526	296	505	268	687	371	649	347	524	301	498	274
TGFB1	602	338	511	269	525	296	504	268	687	371	649	347	523	301	497	274
KIR3DL3	584	327	496	259	510	286	489	258	668	359	632	337	506	291	480	265

	PRETERM		SPONTANEOUS PRETERM		SGA		Term SGA		GHTN		GHTN w/o CHTN		PE		GHTN w/o CHTN	
	EA	AA	EA	AA	EA	AA	EA	AA	EA	AA	EA	AA	EA	AA	EA	AA
KIR2DL4	600	335	509	268	522	293	501	267	683	370	646	346	520	298	494	272
KIR3DL2	600	332	509	266	523	292	502	265	682	367	644	344	521	297	495	271
IFNGR2	597	336	508	268	523	294	503	267	683	369	645	345	521	301	495	274
Cell Cycle Genes																
GADD45A	587	311	498	247	509	270	488	246	668	336	632	316	508	278	483	252
RASSF1	602	338	511	269	525	296	504	268	687	370	649	346	523	301	497	274
CCNA2	598	338	508	269	521	296	500	268	682	371	644	347	520	301	494	274
CCNH	603	338	512	269	525	296	504	268	688	371	650	347	524	301	498	274
NOV	595	336	504	268	518	295	497	268	678	369	640	345	516	301	490	274
CDKN2A; CDKN2B	594	329	503	263	516	286	495	261	678	362	640	339	518	292	493	266
CNNM2	599	337	508	268	523	294	502	267	684	368	646	344	521	301	495	274
CCND1	600	335	509	267	523	292	502	265	684	368	646	345	521	298	495	272
MDM2	603	338	512	269	526	296	505	268	688	371	650	347	524	301	498	274

Abbreviations: SGA Small for Gestational Age, GHTN Gestational Hypertension, CHTN Chronic Hypertension, PE Preeclampsia, EA European American, AA African American

Multiple Comparisons

While use of SKAT in Stage 1 will limit the number of hypotheses being tested, there is still a concern with multiple comparisons. The Bonferroni correction has traditionally been used to correct for multiple comparisons. This correction provides a straightforward way to ensure global error rate by correcting the per test alpha by dividing alpha by the total number of statistical tests being performed. While Bonferroni correction works well for a relatively small number of independent tests, it does not take into account that linkage disequilibrium between SNPs, complex biologic interactions between genes and similarities between genetic models that will result in correlation between tests. Ignoring this correlation makes Bonferroni too conservative and may result in an unacceptable Type II error rate[198, 199] especially in the context of small effects in relatively small studies.

The False Discovery Rate (FDR) is less conservative than the Bonferroni Correction and may be more appropriate when discovery is the goal. When implemented, FDR results in alpha (α Type I errors) to be the expected proportion of errors among all of the rejected hypotheses. For example an FDR alpha of 0.05 will result in 5% of identified SNPs being false positive discoveries. The FDR method ranks all the p-values and considers each in a decreasing fashion by searching for the first for which the p-value is ≤ the rank of the SNP/total number of SNPs tested *alpha. All SNPs with that p value and smaller are then considered significant. In this way the degree of correction is more stringent for smaller p-values.[199]

Use of FDR is appropriate in this situation as Stage 1 is being used to identify genes which are associated with the outcomes and underwent further investigation in Stage 2. Given the discovery nature of Stage 1, a generous FDR of 20% was used. This can be interpreted as 20% of the genes which enter Stage 2 are false positive. Genes with a single SNP, or with SNPs that

were chosen purely for replication, were considered only in Stage 2. As a result there were be 24 genes ranked for FDR in the inflammatory pathway (IL1A and IL1B are replication SNPs, TGFB1 and TGFB3 have single SNPs) while 7 genes were ranked in the cell cycle pathway (CCNH and MDM2 have single SNPs) for a total of 31 genesets in Stage 1.

2.4.2 Stage 2

While SKAT offers an attractive method for assessment of significance at the gene-level it does not quantify the strength or direction of the association and does not identify the SNPs within the gene that may be associated with the outcome. Although covariate adjustment is possible in SKAT, model reduction methods are not practical given lack of fit statistics and the absence of a single measure of effect for the SNP-set. Given the low power of this study however, SKAT remains a very desirable approach.

While information at the level of the gene is relevant from a biologic perspective and allows for guidance of future studies, identification of the specific genetic changes within the gene is also desirable. Associations between specific SNPs and the outcomes of interest were examined in Stage 2 based on strength of association, precision of the estimate and association with other SNPs in the set (LD).

Stage 2 focused on identifying the SNPs which are likely associated with the observed gene effect and further explored possible confounding. As the data for Stage 2 is the same as the data used in Stage 1, the two stages are not independent and interpretations of the results from Stage 2 were cautious. Although measures of effect and p-values were calculated, this stage was used to generally assess direction of effect and the relative rank of the SNPs within the genes for

a given outcome. Also, specific regions of interest within each gene were identified. These regions can be targeted in future fine mapping studies.

2.4.2.1 Study Design

Stage 2 assessed the association between each SNP and the outcomes of interest. Given the frequency of preterm birth, SGA and gestational hypertension in this population (Table 2.1) estimation of an odds ratio could not be considered a valid estimate of a risk ratio. While a common non-case group was valid for the estimation of an odds ratio in Stage 1, the genotyped population is not a suitable "cohort" for the estimation of a relative risk. The genotyped population includes an excess of "cases" relative to the underlying PIN cohort. Given that the biology, and therefore the SNPs, underlying these outcomes are related, a straightforward estimation of a relative risk using the entire genotyped population will misrepresent the distribution of the exposure in the base PIN population.

An approach that allowed estimation of a risk ratio, while accounting for the over representation of cases in the genotyped population, is Inverse Probability Weighting (IPW) using a log linear model. IPW allows the entire genotyped population to be used as a cohort while representing the case (and covariate) distribution of the entire eligible population. While generalizing to the original PIN Cohort would be ideal, selection criteria for eligibility precluded a reasonable estimation of the variance of the point estimates using the base PIN Cohort as the reference population.

The analysis of Stage 2 proceeded as a two-stage selection design. Considering the entire eligible population (N=3065), the probability of being selected for genotyping was calculated. Probability of selection was modeled using the following variables: general birth outcome

(liveborn v. all other outcomes), PIN cohort (two indicator variables), any case status (yes/no), selection into original PIN subcohort (yes/no), presence of a second birth in the cohort (yes/no), maternal age (indicator variables for <25 yrs, >=35yrs), parity (multiparous or nulliparous), any smoking in months 1-6 (yes/no), maternal education (<=12 yrs or 13+ years), pre-pregnancy BMI (indicator variables for underweight <18.5, overweight 25-29.9, obese >=30), percent of poverty level (continuous and standardized), marital status (married or non-married), site of PIN recruitment (UNC or Wake), self reported race (White or African American). Given missing in some of the covariates, values were imputed using means for specific PIN cohort/Site/Self-reported Race groups.

Selection probabilities were calculated for each individual in the eligible cohort. The inverse of the selection probability was used as a weight for each individual in the genotyped population who was included in analysis. Cases were identified for each outcome, and controls were all those without the specific case definition as outlined in Table 2.10.

Table 2.8 Breakdown of Cases and Controls by outcome and genetic ancestry

	Stage 1		Stage 2	
	Cases	Non-Cases	Cases	Controls
Preterm EA	194	409	194	813
Preterm AA	134	204	134	457
Spont. Preterm EA	103	409	103	813
Spont. Preterm AA	65	204	65	457
SGA EA	117	409	117	890
SGA AA	92	204	92	499
Term SGA* EA	96	409	96	717
Term SGA* AA	64	204	64	393
GHTN EA	279	409	279	728
GHTN AA	167	204	167	424
GHTN (sens)† EA	245	405	245	699
GHTN (sens)† AA	145	202	145	397
Preeclampsia EA	115	409	115	892
Preeclampsia AA	97	204	97	494
Preeclampsia (sens)† EA	93	405	93	851
Preeclampsia (sens)† AA	72	202	72	470

*Controls include only term births
†Cases and controls have women with pre-existing hypertension excluded
Abbreviations: Spont. Spontaneous, EA European American, AA African American, sens Sensitivity

While usual log linear models using IPW will produce valid point estimates, calculation of the variance of the estimates is more problematic. In SAS the usual variance estimator (here reported as "naïve") will underestimate the variance and result in confidence intervals that are overly precise. Other options for calculation of variance for a model that includes selection weights, three levels of exposure (additive genetic model) and a continuous covariate (percent African American ancestry) include use of a robust variance estimator and use of bootstrapping. While a naïve SE may be overly small, a robust estimator is usually overly conservative. The true SE is likely between the two estimates.[200]

To explore the impact of different models on both point estimates and variance, point estimates and SE were generated using three different methods. For each analysis, models were stratified by genetic ancestry and continuous percent African American ancestry was included as a covariate. Genotype was modeled as additive with the variant allele harmonized

between the ancestry groups. Odds ratios were generated using PLINK for each SNP and each outcome using the same case-control group that was used in Stage 1. SAS was used to generate RR and SE for each SNP and each outcome using a log linear risk model. Two models were generated. While both used IPW, one used the "naïve" variance while the other used a robust variance estimator.

A fourth model was generated using boot strapping. All 3065 women eligible for genotyping were sampled with replacement for 1,000 iterations. Each iteration was used to calculate an individual selection probability that represented the probability of being selected into the genotyping sample in the specific iteration. Each of the 1,000 iterations was used to generate a point estimate using a log linear model. The 1,000 point estimates were then used to generate a point estimate (mean) and a distribution (2.5^{th} and 97.5^{th} percentile of the 1,000 estimates).

Comparing these 4 models suggested that in general the RR estimates were slightly closer to the null compared to the OR for PTB and GHTN. The SE for the naïve models were smaller than the SE from the robust models although the magnitude of difference was generally small. Boot strapping results did not differ from the standard analysis using naïve or robust SE equations. Point estimates and precision were comparable while analysis time was greatly increased.

As the true SE is likely between the naïve estimate and the robust estimate and the difference between these two was not great, the robust SE was chosen for analysis. Although this may be a slightly conservative estimate leading to slightly less precision, the Stage 2 analysis is designed to rank SNPs within genes. The decrease in precision will not alter ranking while

avoiding overly optimistic interpretations. Models will be adjusted for genetic ancestry and additional covariates as outlined in Section 2.4.2.

An additive genetic model was assumed in Stage 2 although cell counts for the homozygote variant were monitored and dominant models were used when small cell counts (<5) result in unstable estimates.

Reporting of SNPs from Stage 2 was based on the observed strength of association as well as the precision of the estimate. Unstable estimates were not reported. Estimates were examined across related outcomes and between ancestry groups to identify single SNPs and genomic regions which appeared relevant.

Linkage disequilibrium between SNPs within each gene in this population was calculated and visualized using Haploview.[201] In addition, long range LD was used to assess the association between typed SNPs and untyped SNPs in adjacent genes. The tagging process included both upstream and downstream regions and other genes were captured by the chosen tagSNPs. Visualizing long range LD also helped identify different LD patterns between ancestry groups. SNAP[202] allows for the visualization of long range LD between typed and untyped SNPs using various reference populations. The 1000 Genomes Project CEU and YRI reference groups were used when possible.

Sensitivity analysis in Stage 2 included exploration of covariates in the top ranking SNPs. Nested models adjusted for all possible covariates as well as each covariate singly[203] were compared with models adjusted only for continuous ancestry. Adjustments that change the estimate >10% were considered for inclusion in the models.

2.4.3 Stage 3

Given the novelty of this multistage SKAT approach in a population with suspected heterogeneity, a sensitivity analysis was conducted in Stage 3. All SNPs were assessed using the Stage 2 analysis. Of interest were SNPs with a p-value below a Bonferroni correction (using the number of SNPs for each pathway) that were missed by the Stage 1 analysis.

2.4.4 Covariate analysis

Overview of procedures common to both pathways and all outcomes

A number of covariates were considered in this analysis. While covariates related to race were considered for all outcomes, other covariates were considered specifically for each outcome and pathway. Complex biological processes such as the ones under consideration are hard to capture completely in a DAG leading to possible misspecification. Simulations of misspecified DAGs suggest that a full model based on a conservative DAG (inclusion of variables when there is doubt) followed by a change-in-estimate using the fully adjusted model as the reference, provides the best outcome with respect to bias and precision.[203] In this study, model constraints, missing data on covariates, and power must also be taken into consideration.

2.4.4.1 Cell cycle

Very little information regarding possible confounders exists for cell cycle genes. Smoking may be associated with cell cycle function through the downstream gene *p53,* which is involved in the regulation of apoptosis. Among the genes under consideration, smoking may act directly through *MDM2*. Additionally *CDKN2a* is an upstream regulator of *p53* while *GADD45a* has its expression regulated by *p53*. This association is tentative however. Given the amount of missing

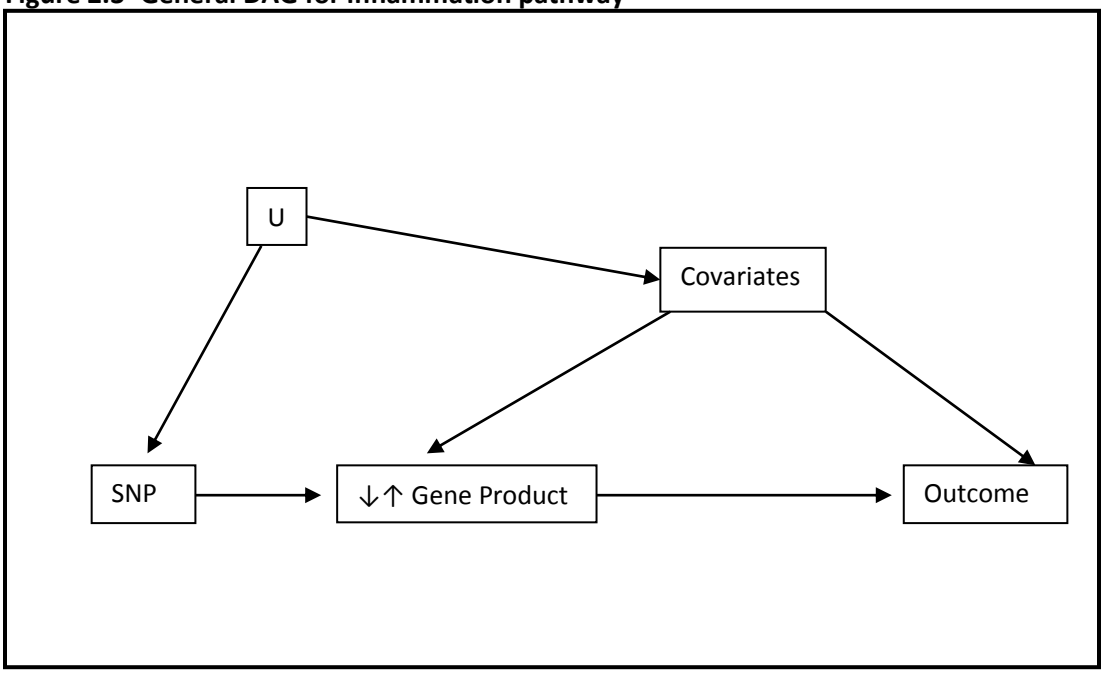
in smoking (Table 2.4.2.2a), and the possibility that the association is an interaction, smoking was not considered as a covariate in initial assessments. If *MDM2, CDKN2A* or *GADD45A* had been found to be significant genes in Stage 1 of the analysis, a sensitivity analysis of the individual SNPs would have been conducted using smoking as a covariate to identify if the ranking of the SNPs would have changed by the addition of smoking to the model.

2.4.4.2 Inflammation

All outcomes

A general DAG of the form that follows (Figure 2.4.2.2) can be drawn for each of the outcomes. The covariates may vary for each of the outcomes; however, barring the presence of an unmeasured confounder, these pathways are blocked by the gene product which is a collider.[204] Unmeasured covariates could include other genetic polymorphisms that are correlated with the measured SNPs and the covariate of interest. At the level of the Stage 1 gene analysis, "U" would need to be associated with the entire gene and not just single SNPs which may decrease the likelihood that "U" will introduce considerable bias. Unmeasured confounding cannot, by definition, be controlled. If "U" does exist, adjusting for the "covariates" in Figure 2.4.2.2 would block the back door path through "U".

Figure 2.3- General DAG for inflammation pathway



However given the high degree of missing data in a number of covariates in this data set (Table 2.11), the potential improvement in bias by adjusting would be offset by a significant decrease in power and precision.

Table 2.9 Missing in possible covariates stratified by self-reported race

Variable	African American (N=615) Missing (N)	White (N=1031) Missing (N)	Total (N=1646) Missing (N)
Smoking	80	72	152
Age	0	0	0
BMI	48	34	82
SES	115	84	199
Parity	1	2	3
Height	37	24	61

Abbreviations: BMI body mass index kg/m^2; SES socioeconomic status represented by percent poverty

Adjustment for covariates will result in a reduction of both the case and control groups due to missing in the covariates. The possible covariate sets vary by the outcome of interest, however case groups would decrease by 12% to 41% and non-case group would decrease by 9% to 28% if all possible covariates were included in the model. Decreases are higher in African

Americans and highest for the SGA outcome, which also suffers from missing in the outcome (N=85) (Table 2.12).

Table 2.10 Impact of adjustment for all possible covariates for each case group and the non-case group

Outcome	Adjustment set*	Complete Data Available (N)		
		African American N=615	White N=1031	Total N=1646
Preterm	None	145	202	347
	All	111	165	276
SGA	None	96	120	216
	All	57	98	155
Isolated GHTN	None	171	283	454
	All	135	248	383
Preeclampsia	None	100	117	217
	All	81	100	181
Non Case	None	210	419	629
	Adjusted for PTB	159	378	537
	Adjusted for SGA	150	367	517
	Adjusted for GHTN	164	380	544

*Adjustment sets: None (no covariates included). All (adjusted for all covariates as follows):
Preterm birth (PTB): Smoking, age, body mass index, percent poverty (Total non-missing N=1341)
SGA (small for gestational age): Smoking, body mass index, percent poverty, parity, gestational diabetes, height (Total non-missing N=1301) 83 missing SGA
GHTN (gestational hypertension): Smoking, age, body mass index, parity, previous diabetes (Total non-missing N=1380)

Due to missing data, a conservative approach to adjustment by including all possible covariates would have result in an unacceptable loss of power. Absent "U", all covariates in Figure 2.3 are on blocked paths and do not require adjustment. For these reasons, only covariates which do not fit into the covariate box in Figure 2.3 in each subsequent DAG will be considered for inclusion in models. For the remaining DAGs "U" will be left off the DAG although the discussion will assume that the "U" association described here is a possibility.

To explore the possibility of confounding, I will conduct a sensitivity analysis on high ranking SNPs in the Stage 2 analysis comparing the change in estimate between unadjusted models (adjusted for ancestry), fully adjusted and single adjusted models.[203]

Preterm Birth

Covariates for consideration

Risk factors for preterm birth which are also associated with SNPs in inflammatory genes are likely acting through gene products of cytokines (Figure 2.4). For instance, the effect of psychosocial stress may influence pregnancy outcomes through changes in inflammatory biomarkers.[205] BMI and active infection will also increase the circulating levels of inflammatory biomarkers.

Of the covariates listed here, smoking, BMI and age are well measured in our cohort although both suffer from missing data. A number of psychosocial and infection related variables were collected in portions of the PIN cohort. Socioeconomic status (SES) can be captured using a variety of variables in PIN including percent poverty.

Infection and stress are less well characterized in the PIN cohort. The presence of bacterial vaginosis was assessed for only a fraction of the cohort.[6, 206] Self-reported sexually transmitted infections, as well as yeast infections, were collected for PIN1 and 2 but not for PIN 3. Measures of depression (CES-D) and social support (MOS Social Support Scale) were assessed for all three PIN cohorts, but these measures were not among the psychosocial measures which have previously been associated with preterm birth.[207] Measures of perceived stress, state trait

anxiety and life events were collected for some of the PIN cohorts, however the timing varied enough to make construction of a valid variable across cohorts difficult.

Possible covariates on the causal pathway

An alternate DAG (Figure 2.5) for preterm is possible with the covariates separated into those that are likely associated with the gene product (age, stress, and smoking) and those that may be caused by the gene product (BMI, infection). The first group is associated with the gene product in the sense that stress or smoking may increase inflammatory cytokines. However inflammatory cytokines themselves will not cause psychosocial stress nor smoking during pregnancy. For this set of covariates, the gene product is a collider unless there is a "U". For the second group of covariates however the relationship is not as clear. BMI, as a measure of adipose tissue, may result in higher circulating cytokines as the adipose tissue provides substrate for cytokine production (red arrow). Alternately genetic polymorphisms may influence inflammatory cytokines and result in an increased BMI (green arrow). In the first case BMI would be considered a possible confounder only in the presence of "U". In the second case BMI would be on the causal pathway between the SNP and the outcome of interest and should not be considered as a confounder.

The direction of the "arrow" for these covariates will depend largely on the gene product under consideration. In sensitivity analyses where these covariates are kept in the model, closer examination of the biology involved will help inform the decision about inclusion or exclusion of the covariate.

Figure 2.4 DAG for Preterm Birth

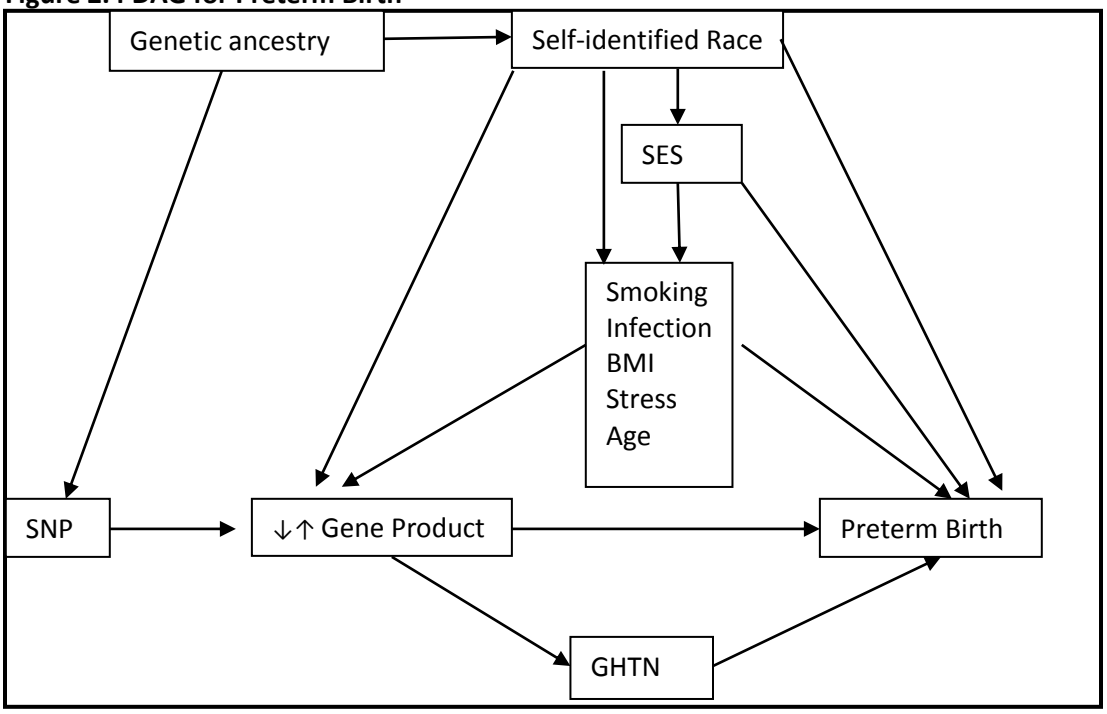
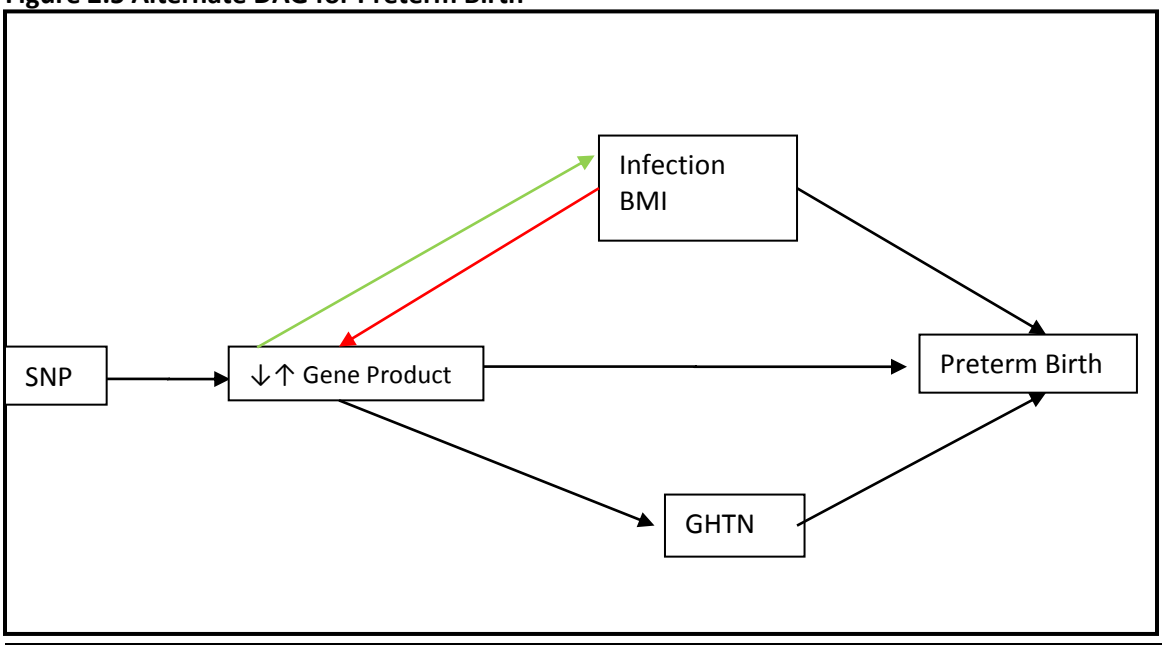
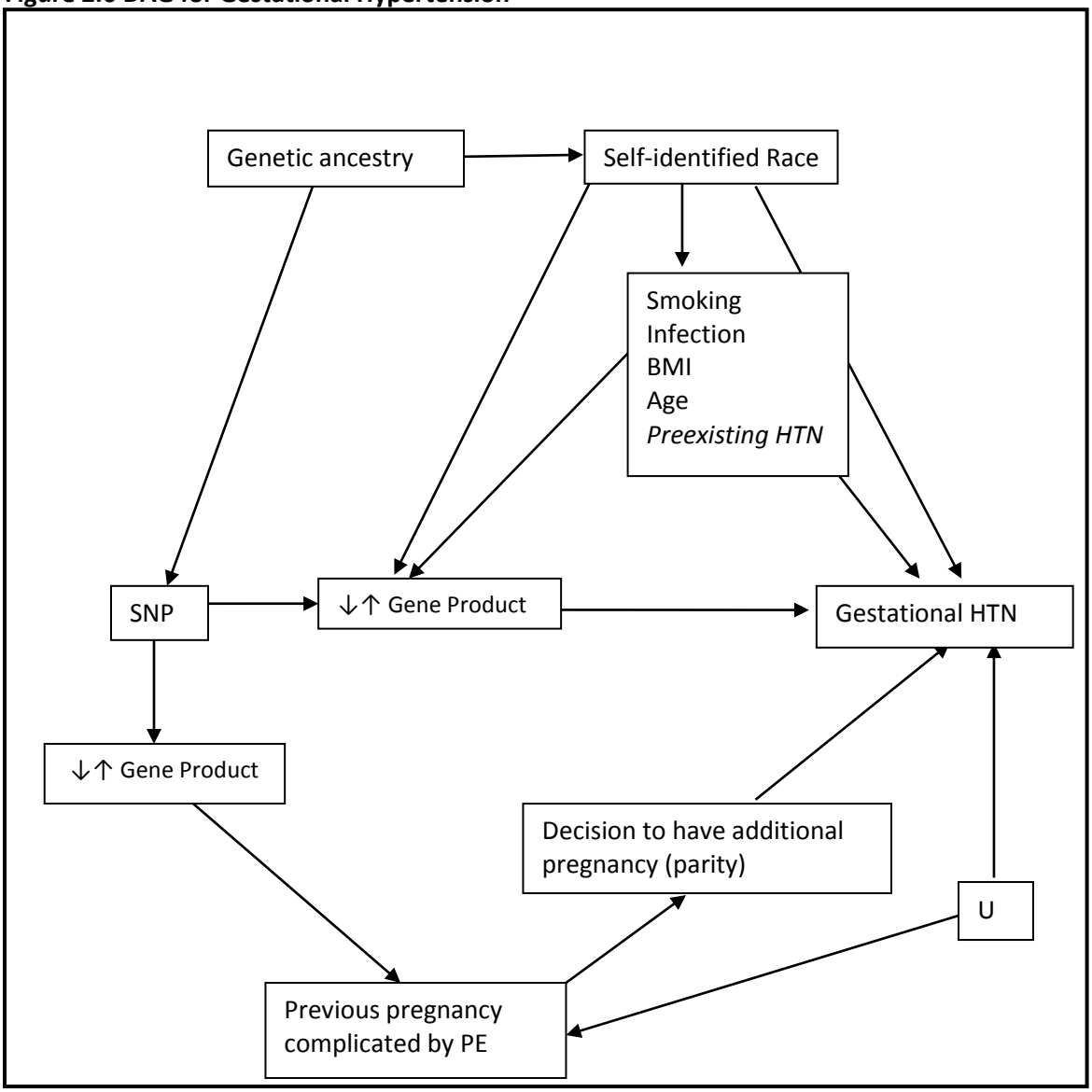


Figure 2.5 Alternate DAG for Preterm Birth



Gestational Hypertension

Figure 2.6 DAG for Gestational Hypertension



Covariates for consideration

Although PE and GHTN were considered as discrete outcomes, the risk factors for both are similar and can be represented by a single DAG (Figure 2.6). Hypertensive disorders of pregnancy share many similar covariates with preterm birth. Smoking, BMI age, chronic hypertension and both pre-existing and gestational diabetes are well measured. Although some

sources suggest that infection during pregnancy may be associated with preeclampsia, the stronger associations are with urinary tract infections and periodontal diseases and not the STDs measured in PIN.[208]

Confounding by previous reproductive outcomes

Unlike preterm birth, preeclampsia has a strong association with parity. First births are more likely to be complicated by preeclampsia. Difficult first pregnancies may influence family planning choices and limit subsequent pregnancies resulting in fewer high-risk mothers with higher parity. Parity is well documented in PIN. Data was also collected on self-report of a previous pregnancy complicated by preeclampsia for multiparous women. As can be seen on the DAG, adjusting for parity is a better choice given the likelihood that unmeasured variables influence the outcomes in serial pregnancies. Parity is not missing for any observations in the data set (Table 2.11).

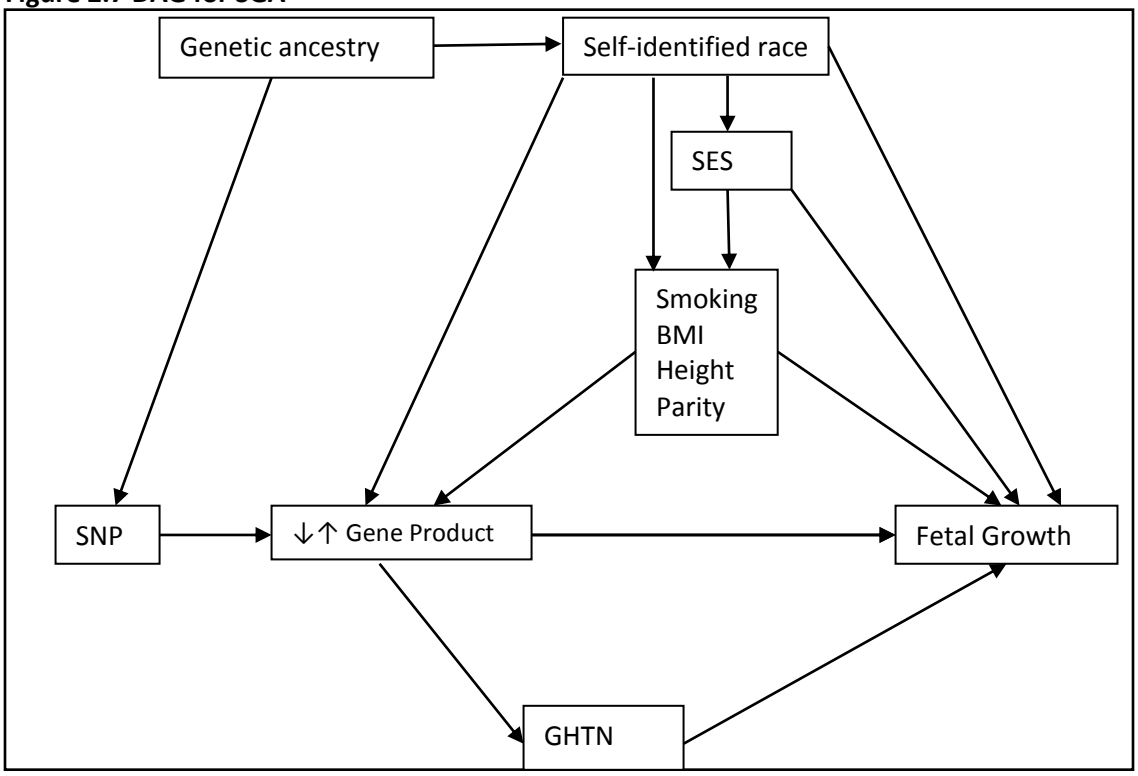
The special case of chronic hypertension

Preexisting hypertension makes the diagnosis of GHTN and PE difficult. Older diagnostic criteria included an increase in blood pressure of 15mmHg DBP or 30mmHg SBP after 20 weeks of pregnancy. Current guidelines restrict the diagnosis of GHTN or PE to women with a normal blood pressure before 20 weeks and recognize the diagnosis of superimposed PE or GHTN for women with preexisting hypertension who have a worsening of hypertension or develop new onset proteinuria (or worsening proteinuria) during pregnancy.[209] However in PIN 1 and 2 some women were not enrolled until after 20 weeks and an elevated BP after 20 weeks may be either chronic hypertension or GHTN. Additionally there is a tendency for BP to drop slightly in the first trimester of pregnancy.[210] Women who do not obtain routine medical care outside of

pregnancy may present for prenatal care with a 'normal' blood pressure even in the presence of undetected chronic hypertension. Given these factors, chronic hypertension was approached as outcome misclassification by conducting a sensitivity analysis with exclusion of women with self-reported chronic hypertension.

SGA

Figure 2.7 DAG for SGA



Covariates for consideration

SGA shares many similar possible covariates with preterm birth with the addition of maternal anthropometric parameters such as height that influence growth potential. Parity is also associated with SGA. Unlike gestational hypertension however, there is not as much of a

concern that subsequent pregnancies will be limited. Infants born to multiparous women tend to be slightly heavier compared to nulliparous births.[61]

2.4.5 Population Stratification

Population stratification has been defined as differences in allele frequencies between cases and controls due to systematic differences in ancestry rather than associations of genes with disease. In genetic epidemiology studies, population stratification may result in biased results when the outcome of interest also varies based on genetic ancestry. Population stratification can result in both false positive and false negative results and the strength of the bias will depend on the magnitude of allelic variation among ancestry groups and differences in disease among those same groups.[211] In non-genetic epidemiologic studies race is often considered as a confounder for similar reasons. Self-reported race is considered a marker for a wide variety of social, cultural, dietary, economic, stress, and educational experiences. In genetic epidemiologic studies however, race is also seen as a marker of genetic ancestry which will have practical consequences for LD structure, haplotypes, and allelic frequencies. In this setting self-reported race is often an inadequate surrogate for genetic ancestry. Not only are individuals poor reporters of their genetic ancestry[212] at a level necessary for genetic studies, self-reported race may not adequately capture the genetic heterogeneity among self-reported racial groups.[213, 214]

While population stratification can be quite complex when dealing with large metropolitan populations with a wide variety of genetic ancestry, the concern still remains in largely biracial populations as present in this study. In the United States, among those who self-report as African American, the percent of European genetic ancestry is quite variable. As measured in metropolitan centers across the US, estimated European ancestral proportion ranged from

11.6% in Charleston, SC to 22.5% in New Orleans, LA[215] with geographically isolated areas showing even more extreme values.[216]

A number of methods have been proposed for addressing population stratification in genetic epidemiology studies. Genomic control was an early method which used random markers to estimate an inflation factor which was used to adjust all test statistics. Genomic control only protects against false positives and tends to overcorrect when non-random markers are used.[211]

More recent work has focused on choosing informative markers called ancestry informative markers (AIMs), which are independent markers throughout the genome that have large allele differences between the ancestral populations of interest. Although allele differences between ancestral populations (δ) is important in selecting AIMs, factors such as the allele frequency in the ancestral population irrespective of δ (*p*) and the respective genetic contribution of each ancestral population to the admixed population (*m*) also influence the precision of ancestral estimates.[217] Pfaff's Fisher Information Criterion[217] captures δ, *p*, and *m* into a single information estimate which allows for marker selection to optimize precision based on the actual, or hypothesized, ancestral populations and admixture proportions.

Estimating genetic ancestry using AIMs can be accomplished using a number of different methods. Consensus on the optimal method of calculating genetic ancestry has not yet emerged. Commonly used methods include maximum likelihood estimation (MLE) methods, structured association and principal component analysis.[218] Under situations with informative markers and large and accurate ancestral group information, both MLE and structured association methods perform well.[219] MLE methods have been shown to be superior when marker information is low and there is little information on the allelic frequency in the ancestral

population. MLE methods are generally faster and less computationally intensive, however, when the assumption of independence among markers is violated, the confidence intervals may be too narrow.[219] Structured association methods use Bayesian and MCMC methods to assign individuals to clusters or sub-populations. Structured association methods are dependent on the number of ancestral populations specified. This specification is at the discretion of the investigator and can be difficult to both determine and interpret in cosmopolitan populations.[211]

Principal Component Analysis (PCA) is also used to correct for population stratification. PCA methods infer continuous axes of genetic variation by using eigenvectors of the covariance matrix of SNPs between samples.[220] Unlike structured association methods, which are dependent on the correct choice of the number of clusters, PCA techniques are invariant to the number of axes chosen. Although many PCA techniques employ all the SNPs genotyped in GWAS panels, work has shown that well-chosen AIMs panels of 50-200 SNPs are equally good at controlling bias and optimizing power.[221]

Software exists for both MLE (FRAPPE), Structured Association (STRUCTURE) and PCA (Eigenstrat) methods. Given the informativeness of the AIMs used, the relatively small size of the study population, the presence of only two ancestral populations, ease of use and familiarity of the software and previous work using similar populations in North Carolina[189] which has found high correlation between MLE and Structure methods, Structure will be used initially for calculation of ancestry.

Additional issues with ancestry

While adjustment for genetic ancestry will address confounding by population stratification, there is also the possibility of heterogeneity between the two genetic ancestry groups included in this study. Previous genetic epidemiologic studies looking at preterm birth[4, 6, 97, 98, 113, 114, 149, 155, 156] found that genetic associations varied by genetic ancestry. Pathway analysis in one cohort composed of US Whites and African Americans with the outcome of spontaneous preterm birth suggested that different pathways were operating in the two racial groups.[97] Tag selection for this study resulted in some SNPs that are polymorphic in a single ancestry group (Table S1 and S2 in Appendix). While these private SNPs may be important for a specific ancestry group, they will provide no additional information for the other group.

Although an analysis with all women combined would have more power due to an increased case and control group, differences in the size of the racial groups, the likelihood that different genes and SNPs are acting in different genetic ancestry groups, and the presence of private SNPs, increases the likelihood that associations would be missed in a combined analysis of both genetic ancestry groups. For this reason all analyses were performed within strata of genetic ancestry and additionally adjusted for continuous percent ancestry.

2.4.6 Power

Power will depend on the study design used -- case-cohort v. case-control -- due to the differences in the number of "controls". As the proposed method for this study (SKAT) does not conform to a typical power calculation, certain simplifying assumptions are used.

Given the lack of a power model for SKAT, an unmatched case-control design was simulated within Quanto (http://hydra.usc.edu/gxe/) to calculate power. For all calculations a

log-additive, gene only, unmatched case-control model was assumed. Two-sided Type 1 error of 0.05 was used for both study designs. Initial calculations also included a Bonferroni correction using the assumed number of genes in each pathway. For inflammatory genes the Bonferroni corrected p value= 0.002 and for cell cycle genes p=0.006. Baseline risk was calculated in the cohort.

The case:control ratio was estimated using a hypothetical case-cohort study design. For the hypothetical study a 'cohort' was constructed by using the N=523 women in the existing PIN1/2 subcohort and adding the non-cases and an appropriate number of cases from each of the two (PIN1/2 non-subcohort, PIN 3) remaining sampling groups. The appropriate number of cases was chosen to reflect the distribution of cases in the established subcohort (PIN1/2= 87 non-cases and 53 cases, PIN3= 218 non-cases and 134 cases). The total reconstructed cohort was composed of 1015 women. Table 2.12 outlines the criteria used for each outcome for the power calculations.

Table 2.11 Criteria used in power calculations

Outcome	*Risk*	*Cases*	*Case:Control Ratio Case-Cohort N=1015*
Preterm birth	12%	347	3
SGA	10%	216	5
Isolated PIH	15%	454	2
PE	8%	217	5

Table 2.12 Range of odds ratios with 80% power for each outcome with the specified type 1 error

	PTB			***SGA***			***GHTN***			***PE***		
	Type 1 error			Type 1 error			Type 1 error			Type 1 error		
MAF	0.002	0.005	0.05	0.002	0.005	0.05	0.002	0.005	0.05	0.002	0.005	0.05
10%	1.7	1.7	1.5	1.9	1.8	1.6	1.7	1.6	1.5	1.9	1.8	1.6
20%	1.5	1.5	1.4	1.7	1.6	1.5	1.5	1.5	1.4	1.7	1.6	1.5
30%	1.5	1.4	1.3	1.6	1.5	1.4	1.5	1.4	1.3	1.6	1.5	1.4
40%	1.5	1.4	1.3	1.6	1.5	1.4	1.4	1.4	1.3	1.6	1.5	1.4

Abbreviations: PTB preterm birth, SGA small for gestational age, GHTN gestational hypertension, PE preeclampsia, MAF minor allele frequency.

For the more common outcomes of PTB and GHTN power is adequate at or below OR 1.7 within the full range of MAF. For the less common outcomes however power is adequate only below an OR of 1.9 (Table 2.13).

The applicability of this approach to power calculations is limited given the study design.

The SKAT model will be based on genes and not on single SNPs. While this should increase the overall power to detect a relevant gene, the association between MAF for a single SNP and the resulting power is not as clear.

The Quanto program used for the power calculation relies on an unmatched case-control design. Due to the presence of cases in both the case group and the control group in a case-cohort design, the Quanto method likely under estimates power for the case-cohort design.

The outcomes above are not mutually exclusive and non-independent. “Pure” case groups would be quite small with much lower power.

The above calculations include women of both races. Racially stratified analyses will have much lower power.

The assumption of the Quanto power calculation is that there is a single causative SNP. The power calculated reflects the ability to detect the single causative SNP among a large number of null SNPs.

An alternative approach to power calculation assumes that there exists more than one causative SNP and seeks to assess power to find one of many causative SNPs.[222] Under this framework, Table 2.14 outlines the number of causative SNPs which must be assumed to be present to have 80% to find one of them given the range of power to find a single SNP if only 1

SNP is causative. For instance if the power to find a single causative SNP is 2%, the presence of 80 causative SNPs would result in 80% power to find one of them.

Table 2.13 Power to detect multiple risk alleles

Power for a single allele assuming only 1 risk allele	*Number of risk alleles needed to have 80% power to find 1 SNP*
0.01	>100
0.02	80
0.03	53
0.04	40
0.05	32
0.06	27
0.08	***20***
0.10	***16***
0.12	13
0.15	10
0.20	8
0.25	6
0.30	5

In this study an assumption of 15-20 underlying risk alleles seems reasonable. This would place the target single SNP power in the range of 8% to 10%. Although the previous power calculation suggested adequate single SNP power below OR 1.7-1.9, SNP effects are likely to be much more modest.

Given that sample size, baseline risk and MAF are fixed in this study, the only variable which can be modified to influence power is the Type 1 error. Type 1 error can be considered as a function of the number of tests conducted, with more tests resulting in a lower type 1 error due to multiple comparisons.

Quanto was again used to estimate power for an OR of 1.4 at a range of MAF given four different type 1 errors. Specifications within Quanto were the same as presented in Table 2.12. Given the similarity between power calculations for SGA and PE, only SGA is presented. The

candidate type 1 errors were chosen based on convenient Bonferroni corrections. The Bonferroni correction for the number of genes in the inflammatory pathway is 0.002. At the other extreme the Bonferroni correction for the total number of SNPs is 0.0001. Midway between these values, assuming 200 SNPs for analysis would result in a Bonferroni correction of 0.0002 and assuming 100 SNPs would result in a Bonferroni correction of 0.0005.

Table 2.14 Power with OR 1.4 to find one allele with a range of MAF and Type 1 error

	PTB				***SGA***				***GHTN***			
	Type 1 error				Type 1 error				Type 1 error			
MAF	0.0001	***0.0002***	0.0005	0.002	0.0001	***0.0002***	0.0005	0.002	0.0001	***0.0002***	0.0005	0.002
10%	0.08	***0.10***	0.15	0.26	0.03	***0.05***	0.07	0.15	0.10	***0.13***	0.19	0.31
20%	0.25	***0.30***	0.39	0.54	0.11	***0.15***	0.21	0.34	0.32	***0.38***	0.48	0.63
30%	0.38	***0.45***	0.55	0.69	0.19	***0.27***	0.32	0.46	0.49	***0.56***	0.65	0.78
40%	0.46	***0.53***	0.62	0.76	0.23	***0.29***	0.37	0.53	0.57	***0.64***	0.72	0.84

Abbreviations: PTB preterm birth, SGA small for gestational age, GHTN gestational hypertension, PE preeclampsia, MAF minor allele frequency.

Table 2.15 suggests that for the more common outcomes of PTB and GHTN, the study has 80% power to detect a single SNP with OR 1.4 assuming that there are at least 20 causative SNPs on the panel. With a MAF >10% the number of causative SNPs falls to 6. For SGA an assumption of 53 causative SNPs would be needed at the most stringent type 1 error and lowest MAF. However at less stringent type 1 error levels the assumptions about the number of causative SNPs becomes more reasonable (fewer than 30 and often fewer than 10).

As a way of informing the number of SNPs which could reasonably proceed to Stage 2, a goal of a single SNP power of 8%-10% suggests that a type 1 error of 0.0002 to 0.0005 would be a reasonable choice. This type 1 error corresponds to the analysis of 100-200 SNPs in Stage 2. The number of genes that would result in this number of SNPs will depend on the gene.

2.4.7 Strengths and Limitations

This study offers an innovative approach to studying genetic associations with these important reproductive outcomes in a number of ways.

At its inception, this study was the largest candidate gene analysis for the outcome of SGA. Since the study was designed, however, another 1536 panel was completed with an SGA outcome.[182] Nevertheless, the Edwards study was in a Chilean population that may not be generalizable to African Americans. Additionally, while the Edwards study examined more genes related to inflammation, the number of SNPs per gene was limited. This study expanded coverage of the genes investigated, was conducted within a population of African Americans and considered novel genes within both inflammation and cell cycle pathways.

For the outcomes of gestational hypertension and preeclampsia, this study assessed the largest number of genes related to inflammation in a North American population. Although some of the inflammatory genes have been examined in other populations, this study includes African Americans and expanded the breadth of genes examined with the addition of cell cycle genes and novel inflammatory genes identified through placental expression studies.

For preterm birth, a study of similar breadth in a US bi-racial population has already been conducted. While many of the genes will overlap, this panel expanded the tagSNP coverage of most genes and added additional candidate genes in the inflammatory pathway, considered novel genes in the cell-cycle pathway and doubled the number of African American women in the preterm case group.

For all outcomes, the choice of candidate genes reflects careful consideration of the complexity of the inflammatory pathway. Candidate genes were chosen to reflect important components of the innate and adaptive (both Th1 and Th2) pathways. In addition genes related to natural killer cells were included based on emerging *in vitro* studies of placental expression.

For all outcomes, cell cycle genes represent a novel pathway and this will be the first study of these genes in relation to reproductive outcomes.

The methods of analysis (see Section 2.4.4) represent an emerging approach to analysis of genetic data with a focus on the gene as opposed to individual SNPs. A gene based approach is both more powerful and has more relevance for directing future in vitro and clinical studies which focus on gene products as opposed to SNPs which may simply be associated.

Despite the many strengths, there are a number of limitations.

1. The study has low power for a single SNP analysis, especially given the need to stratify by genetic ancestry. While single SNP analysis may have low power, study design and analysis strategies are designed to enhance power. The use of SKAT enhanced power by decreasing the number of tests (reducing multiple comparison corrections) and leveraging small SNP effects across a gene. Despite low power, this study still surpasses most existing studies with respect to the number of cases and controls.

2. Reproductive outcomes are a combination of maternal, paternal and fetal genetic effects. Maternal genes influence the intrauterine environment, comprise half of the fetal genome and have the possibility of interacting with the fetal genes. Paternal genes comprise the remaining half of the fetal genome. Fetal genes not only determine the fetal potential for growth but are also expressed in trophoblasts and influence placental development. Although heritability studies suggest that maternal genes are primarily responsible for preterm birth,[12-14] SGA appears to have a stronger fetal genetic

association[15] while hypertensive disorders of pregnancy have both maternal and fetal genetic effects.[11, 148] In particular the role of cell cycle genes in placental development may be most influenced by fetal genes as opposed to maternal genes.

The PIN study did not collect paternal or fetal DNA. Null findings for genes of interest in this study should be followed up in datasets with mother-infant, or trio, data given the possibility that fetal genes, or a maternal-fetal interaction are important.

3. Preeclampsia and gestational hypertension are difficult outcomes to assess. While PIN attempted to collect clinical data throughout pregnancy, clinician reporting bias, changing study and clinical criteria, and differential outcome assessment based on other maternal and fetal outcomes, makes misclassification possible. Attempts to validate the GHTN and PE variables against an existing database provided reasonable support for the use of the existing variables. Further chart abstraction of a subset of women provided a subset of "validated" cases for sensitivity analysis.

CHAPTER 3 QUALITY CONTROL RESULTS

3.1 Quality Control Summary

Individual Samples

Genotyping was conducted on an Illumina custom GoldenGate platform with 1824 samples typed for 1536 SNPs. Samples included in the genotyping included women for this study, samples for additional projects, and quality control samples

Of these 1824 samples, only 1795 were related to the present study, including quality control samples. During initial genotyping 8 samples were excluded for genotyping call rates <=95% resulting in 1787 PIN samples entering the QC phase.

From these 1787 samples the following were removed during the QC process:

83 CEPH trio samples included for duplicate and mendelian inheritance QC
64 blind PIN duplicates included for QC
5 mislabeled samples
10 still births
24 births with congenital anomalies
3 individuals with >5% missing in genotype data

In total of 189 samples were dropped from the original genotyping and 1598 PIN women available for analysis. Figure X reflects the sample process and Section 3.3 explores each exclusion criteria.

SNPs

The GoldenGate platform contained 1536 SNPs. One hundred and six (106) failed initial genotyping (Table X in Appendix). In addition one SNP (rs11119449) was missing genotype information for all individual and was excluded. This resulted in 1429 SNPs that entered the QC process. Section 3.2 explores the SNP quality control in more detail

3.2 Quality Control for SNPs

3.2.1 Blinds

Inclusion of duplicate blinded samples allows for the identification of genotyping errors by identifying SNPs, plates, or run batches, with discordant alleles. For purposes of this analysis, both PIN duplicates and CEPH duplicates were included. PIN duplicates were chosen randomly when sufficient sample was available and will allow for the identification of problems during the process of DNA isolation, purification and plating. CEPH replicates were more plentiful and represented fewer individuals overall. This allowed for plating to detect both intra and inter-plate quality control.

Blind PIN and CEPH replicates were included on the 20 genotyping plates. Sixty-four (64) PIN samples were included in duplicate on the 20 genotyping plates. In addition 2 PIN samples were inadvertently plated in duplicate (Table S4). In addition, 67 sets of CEPH controls (representing 15 different individuals and 71 unique samples) were included on the 20 genotyping plates. Nineteen (19)

of these CEPH duplicate sets were present on the same plate and 48 were on different plates. In total 199 unique samples were a part of the blind assessment.

The assessment of blinds was conducted for the 1429 SNPs that passed initial genotyping quality control. Among these 1429 SNPs, there were 622 missing genotypes from 257 unique SNPs. This represents 622/(1429*199) = 0.22% missing. The majority (N=200) of SNPs were missing in 2 or fewer samples (77.8%). All duplicate sets were inspected for concordance. When genotypes were non-missing, only two instances of non-concordant genotypes were identified. SNPs rs1538537 (possible allele A/T- gene CA9) and rs2243250 (possible allele C/T- gene IL4) each had one instance of mismatch. Otherwise all duplicate pairs had identical genotypes. (For the purposes of analysis, each set (Blind/ Non-blind PIN sample) was inspected to identify the sample with the least missing. In 15 sets, the blind sample had the least missing and was retained for analysis. In 6 sets, the sample retained for analysis had missing allele data which could be filled in from the duplicate. For the inadvertent duplicates, the most complete sample was retained for analysis. (Table S5)

Overall the missing was low in the blinds and the assessment of concordance did not reveal any serious genotyping problems. No SNPs were dropped from analysis based on this quality control step.

3.2.2 Trios

In addition to providing information for duplicates, CEPH trios were included to allow for quality control assessment by confirming mendelian inheritance. Five families from the Coriell Institute CEPH/Utah pedigrees were included in the genotyping (Table S6). For the trios analysis trios with all three members on the same plate (N=20) were chosen for analysis. For a single trio the members were on two plates (N=1) (Table S7). Overall 21 trio sets were analyzed representing covering all 20 genotyping plates and representing 15 unique individuals and 63 samples.

PLINK version 1.07[223] was used to assess mendelian inheritance in 1429 SNPs which had passed initial quality control screening (plink –file trios –compound-genotypes –mendel). Overall genotyping was 0.999367 with no mendelian errors detected. Based on this assessment no SNPs were dropped from the analysis based on this quality control step.

3.2.3 Hardy Weinberg Equilibrium

Deviations from Hardy Weinberg Equilibrium (HWE) can indicate poor genotyping quality. Assessment of HWE was assessed in all 1429 SNPs that passed initial genotyping quality control using non-cases stratified by genetic ancestry. Genetic ancestry was determined using STRUCTURE (see Section 3.5). For purposes of HWE, individuals with >=40% African ancestry were considered as one genetic ancestry group (African American). This cut point kept all individuals with genetic ancestry proportions between 40% and 60% African American ancestry within their self-described racial group.

HWE was assessed using SAS 9.2.[224] Exact p-values for HWE were calculated using 10,000 permutations. Given the large number of SNPs assessed, a p-value of 0.05/1429= $3.5*10^{-5}$ (Bonferroni correction) was used to identify SNPs with possible HW disequilibrium.

The distribution of p-values for HWE in the entire panel of 1429 SNPs was as expected with only a small excess of p-values <0.001 (Table 3.1).

Table 3.1. Distribution of p-values for 1429 SNPs

European Ancestry (1390 polymorphic SNPs)		*African Ancestry (1424 polymorphic SNPs)*	
HWE exact p-value	N SNPs (%)	HWE exact p-value	N SNPs (%)
< 0.001	4 (0.3%)	<0.001	6 (0.4%)
<0.01	17 (1.2%)	<0.01	16 (1.1%)
<0.05	59 (4.2%)	<0.05	67 (4.7%)

For the 503 SNPs specific to this study, a single SNP (IL2: rs10027390) had a p-value $<10^{-5}$. This SNP will be excluded from analysis for the YRI ancestry group. All SNPs with p-values <0.01 are in Table 3.2. Although not meeting the p-value criteria, the low HWE p-value may be noted if these SNPs prove significant in further analysis. Of note only one of these low p-value SNPs (KIR3DL2 rs3745900) is in common between the ancestry groups. This suggests that assay wide genotyping quality per say may not be an issue for these SNPs. Instead the departures from HWE in these SNPs may represent population specific concerns (non-random mating, selection or migration, mutation, residual population stratification or small population size).

Table 3.2 SNPs with exact p-value for HWE <0.01 among non-cases stratified by genetic ancestry

European American Ancestry		**African American Ancestry**	
Gene/ SNP	P exact	Gene/ SNP	P exact
CDKN2A;CDKN2B rs1063192	0.0006	IL2 rs10027390	<.000001
CDKN2A;CDKN2B rs3217989	0.0027	IL12A rs12492730	0.0027
NFKB1 rs12648696	0.0028	IFNGR2 rs9978223	0.0033
KIR3DL3 rs4441391	0.003	IL4 rs2243283	0.004
KIR3DL3 rs11883241	0.0036	KIR3DL2 rs3745900	0.0045
IL12A rs13064168	0.004	KIR2DL4 rs17771961	0.0077
LTA;TNF rs915654	0.007	KIR3DL3 rs270775	0.0099
NFKB1 rs11733293	0.0083	IL6 rs6949149	0.0111
KIR3DL3 rs1325155	0.0087	CSF2 rs246844	0.0155
CDKN2A rs3088440	0.0112		
IL12B rs2546890	0.0132		
NFKB1 rs3817685	0.0134		

3.2.4 Additional SNP considerations

Despite and effort in the planning stage, a handful of SNPs which were genotyped were non-polymorphic in our sample. There was 1 non-polymorphic SNPs dropped from the sample.

In addition, among those with <=40% YRI ancestry there were an additional 3 non-polymorphic SNPs. These will be dropped from analysis in models stratified by genetic ancestry. (Tables S8 and S9)

Figure 3.1 outlines the QC process with regard to SNPs.

3.3 Quality Control for Individuals

3.3.1 Cryptic Associations

Given the limited geographical area used for subject recruitment in PIN (Orange, Durham and Wake Counties, NC) the possibility exists for individuals to be related to each other. Given the small number of SNPs and the residual LD in the SNPs, there was no easy method to test for cryptic relatedness. PLINK[223] offers tools to assess for Identical by descent (IBD) among unrelated individuals. However their method need a minimum of 1,000 independent SNPs and is only recommended for genome wide size assays. Given the relatively small number of SNPs in this sample, PLINK tended to overestimate relatedness. As an example, the CEPH trios with known relatedness were assessed using PLINK's pairwise IBD estimation. PLINK provides an estimate of pi hat (proportion IBD) for each pair in the sample. Identical samples (or monozygotic twins would have an expected pi hat=1, parents and offspring, siblings and dizygotic twins would have pi hat=0.5, uncle-nephew relations would have pi hat=0.25, and first cousins would be expected to have pi hat=0.125. In the CEPH trios we can identify with certainty parent-child relations (expected pi hat 0.5) and unrelated individuals (married couples and individuals from different pedigrees (expected pi hat=0). Plink however estimated pi hate for parent-offspring from 0.53-0.62 and unrelated individuals had estimated pi hat from 0-0.30. Although PLINK overestimated relatedness it did correctly call pi hat=1 for all individuals paired with themselves.

Given this shortcoming with PLINK cryptic relatedness was not formally assessed in this sample. The pairs with the highest PLINK estimates of relatedness (pi hat >=0.5, 13 sister pairs including 23 individuals) were examined in MERLIN (a pedigree based program) and confirmed as unrelated (kinship coefficient=0 for all markers). PLINK did identify two sets of mis-labeled duplicates (samples with different IDs but identical genotypes).

In the first set (PINID 10042 and 21027) the samples appear to be from the same individual (age and interpregnancy intervals match, delivered at both UNC and Wake which may explain the lack of a duplicate flag in the PIN database) and two distinct pregnancies. The first pregnancy was kept (PINID=10042).

In the second set (PINID 12682 and 25217) the samples appear to come from different women (different ages, and recruitment site) who were recruited within 3 days of each other. This may represent a labeling problem. Both samples were excluded from analysis.

Although a formal test of cryptic relatedness was not possible, this step identified two unexpected duplicates. Three women were dropped from the analysis based on this step, Table S10 lists the participant IDs of all women excluded.

3.3.2 Missing Genotype Information

Genotyping failure (<95% of genotypes called) resulted in the loss of 8 PIN participants. These participants were not included in the QC process. In addition, 3 PIN participants were found to have >=5% missing genotype data after the completion of the QC process. These women were dropped from further analysis. Table S10 lists the participant IDs that were dropped due to poor or incomplete genotyping.

3.3.3 Exclusions based on pregnancy outcome

Women with two pregnancy outcomes were excluded from analysis. Pregnancies ending in still birth (N=24) were excluded for a number of reasons. Birth weight in still born infants is unreliable due to tissue necrosis in the interval between intrauterine death and birth. The interval between time of death and date of birth can vary and result in inaccurate assessment of time at risk. The pathology which

results in still birth may result in unique causes of preterm birth and hypertension disorders of pregnancy. Pregnancies with congenital anomalies identified at birth were also excluded from analysis. The primary reason for exclusion is that early delivery (preterm birth) may be induced for reasons related to the congenital anomaly and thus represent a different causal process. In addition birth weight may be related to the congenital anomaly and again represent a different causal process. While some birth defects (cleft lip or palate, hypospadias etc) may be relevant to include in this analysis, the type of congenital anomaly noted at birth is included in the data set.

Table S10 provides the IDs of women excluded for still birth or congenital anomaly.

3.4 Flow charts of Individual and SNP exclusions

Figure 3.1 Flow Chart of Exclusions of Individuals

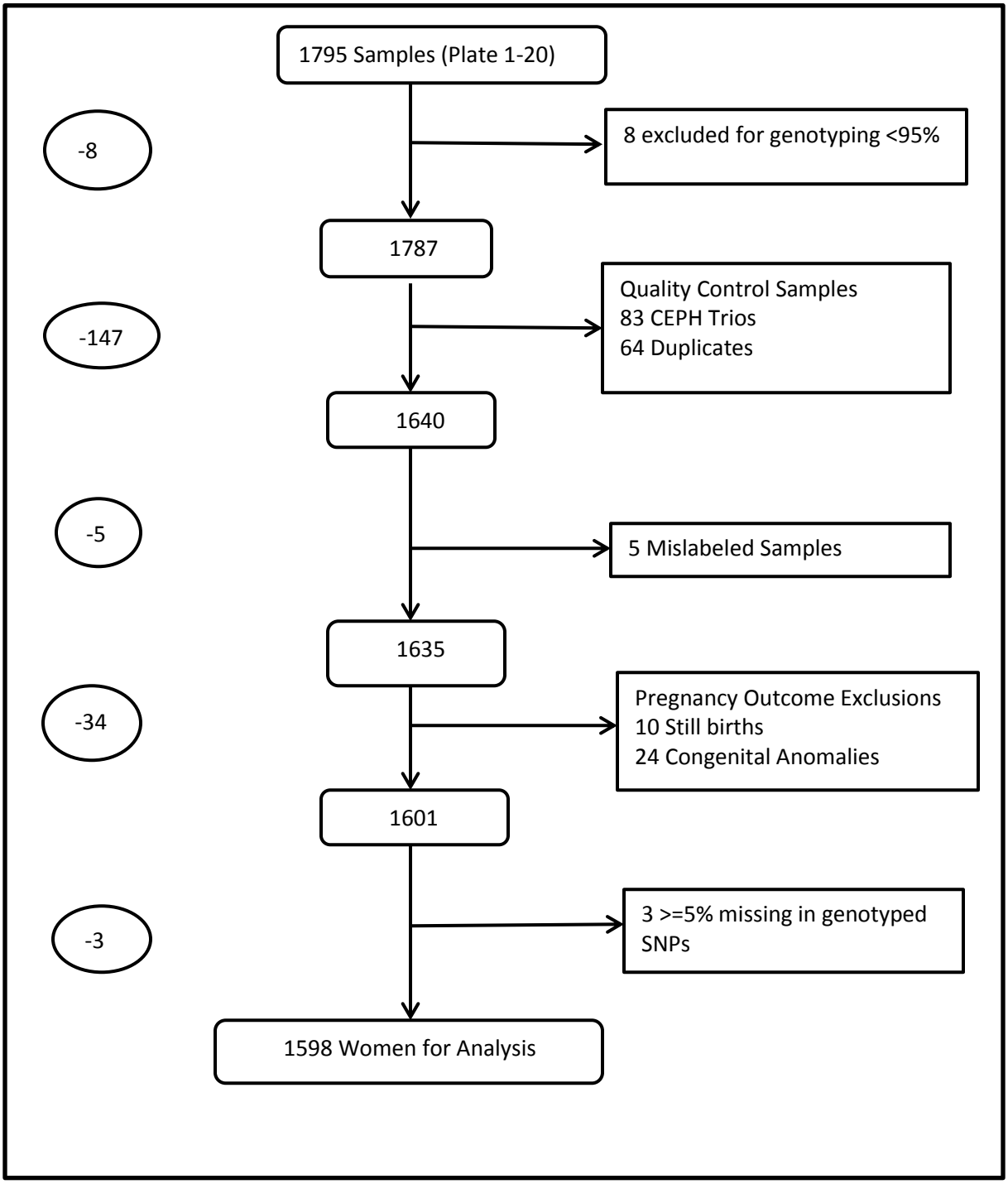
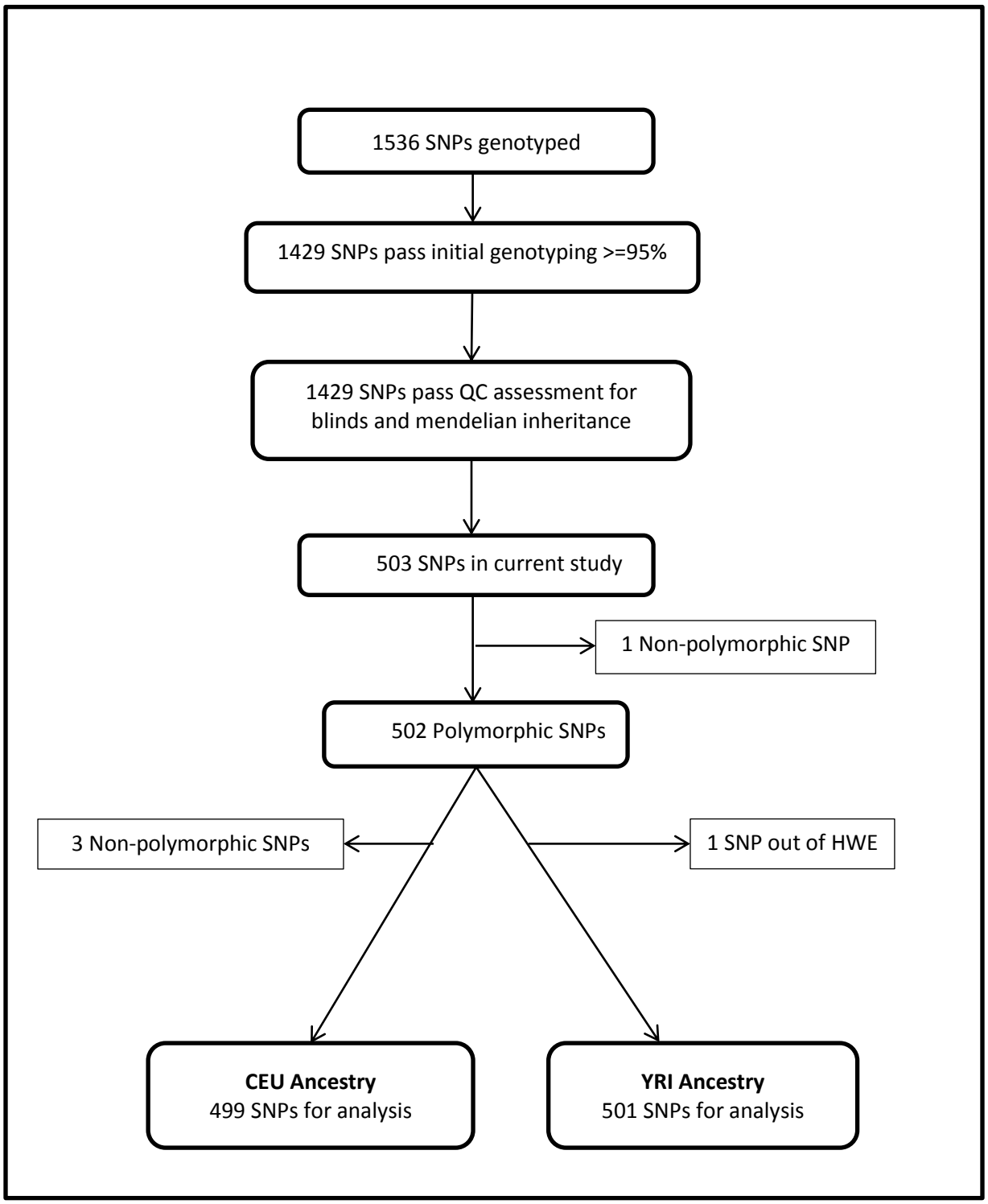


Figure 3.2 Flow Chart of SNP Exclusions



3.5 Assessment of genetic ancestry

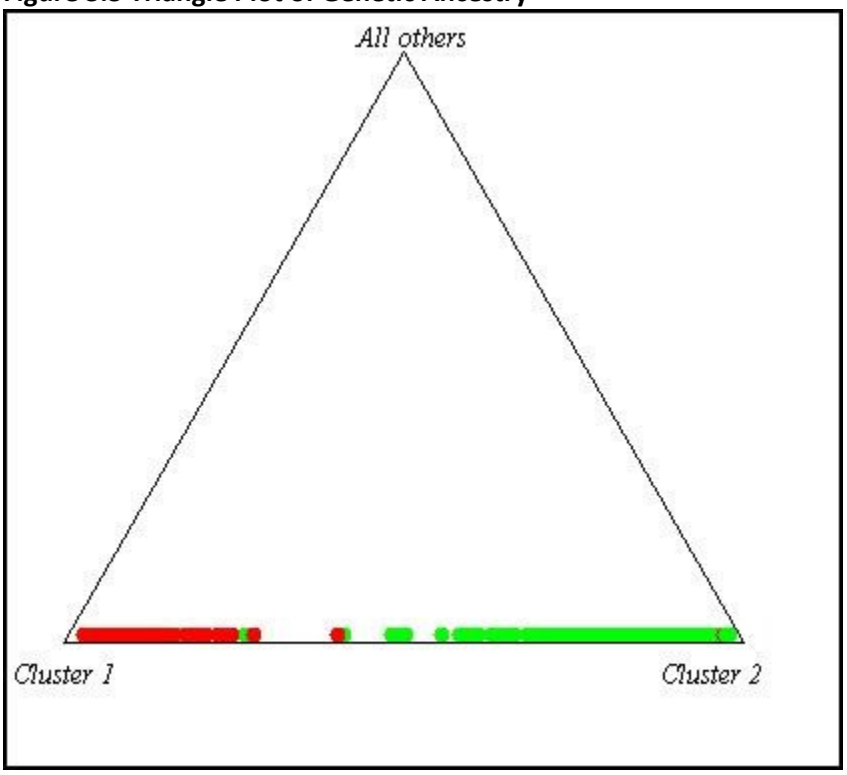
Structure[225] was used to determine genetic ancestry in the individuals for analysis. One hundred and forty-nine (149) AIMs were successfully genotyped. Initial Hardy-Weinberg analysis in the original PIN cohort suggested possible genotyping problems with two AIMS (rs11150219 p=0.0042 in self-reported African Americans and rs11652805 p=0.0083 in self-reported Whites) so these SNPs were dropped from analysis in their respective race. As a result 148 AIMS were used for the assessment of genetic ancestry.

Structure was used with the following parameters:

Ancestry Model: Admixture
Allele Frequency Model: Independent
Number of populations: 2
Burn-In: 10,000
Iterations: 100,000

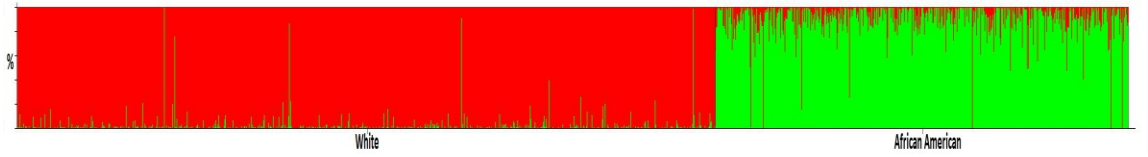
Alterations in the model assumptions (ancestry model and allele frequency model did not change the results). Red is c_mrace=1 (White) and Green is c_mrace=2 (African American). The triangle plot suggests a greater spread in ancestry among individuals who self report as African American (Figure 3.3)

Figure 3.3 Triangle Plot of Genetic Ancestry



The bar plot (Figure 3.4) suggests that while most individuals are clearly associated with a single genetic ancestry, a number of individuals show an even mixture of the two ancestry groups and some individuals have a conflict between self-reported race and genetic ancestry.

Figure 3.4 Bar plot of %ancestry for all individuals by self-reported race



Following assessment of genetic ancestry two groups emerged as problematic. Individuals who have an even mixture of ancestry do not fall neatly into either group. Among the PIN sample, 13 individuals had evenly mixed genetic ancestry (Table S12). All but one of these individuals self-identified

as African American. A cut point of 0.40% African American was chosen as the cut point for genetic ancestry. This places all individuals in this middle area with their self-identified race.

In addition, assessment of genetic ancestry identified individuals with a clear discrepancy between self-reported race and genetic ancestry (N=12) (Table S13). For purposes of analysis when the concern is population stratification, these individuals will be included in the group corresponding to their genetic ancestry. For analyses where self-reported race (as a measure of the lived experience of race in the United States) is a concern as a confounder, these individuals will be dropped from the analysis.

CHAPTER 4 RESULTS

Summary Paper 1

Polymorphisms in Natural Kill Cell Related Genes are Associated with Preterm Birth

Harmon QE, Engel SM, Olshan A, Moran T, Stuebe AM, Luo J, Wu MC, Avery C

Background: Inflammation is implicated in preterm birth; however genetic studies of inflammatory genes have yielded inconsistent results. We expanded coverage of genes related to T-cell and natural killer cell mediated immunity while addressing population stratification in a biracial pregnancy cohort.

Methods: We utilized maternal genetic samples from the Pregnancy Infection and Nutrition Cohort which enrolled women in North Carolina between 1995 and 2005. Preterm cases and term controls (N=1646) were genotyped for 432 tagSNPs in 30 candidate genes. Gene-level and single SNP associations were modeled in strata of genetic ancestry defined by ancestry informative markers.

Results: Six genes were associated with preterm birth among European Americans; IL12A*, CSF2, IFNGR2, KIR3DL2, IL4* and *IL13*. Among the four genes related to Natural Killer cell function, two (*IL12A* and *CSF2*) showed consistent protective associations for both European and African Americans. *IFNGR2* and *KIR3DL2* showed single SNP associations for European Americans only with a strengthening of

the association for spontaneous preterm birth for *IFNGR2* (rs2268241 RR=0.57 95% CI 0.3-0.9). *IL4* and *IL13* are associated with TH2 immunity and SNPs tagging a locus control region have an increased risk of spontaneous preterm birth for European Americans (rs3091307 RR=1.9 95% CI 1.4-2.5).

Conclusions: Although gene level associations were found in European Americans only, single SNP associations among African Americans were often similar in direction although estimated with less precision. In particular, genes related to Natural Killer cells and SNPs tagging a control region for IL13 and IL4 are associated with the risk of preterm birth.

Summary Paper 2

Polymorphisms in Inflammatory Genes are Associated with Term SGA and Preeclampsia

Harmon QE, Engel SM, Wu MC, Moran T, Luo J, Stuebe AM, Avery CL, Olshan A

Background: Poor fetal growth and hypertensive disorders of pregnancy frequently co-occur and are related to measured levels of inflammatory biomarkers. Genetic epidemiologic studies of poor fetal growth in particular have been limited in scope and inclusion of African Americans in the United States. We sought to expand coverage of inflammatory genes, explore novel cell cycle genes in a bi-racial pregnancy cohort from North Carolina, USA.

Methods: Women who enrolled in the Pregnancy, Infection and Nutrition cohort between 1995 and 2005 were eligible for genotyping. Cases of gestational hypertension, preeclampsia and poor fetal growth were identified based on abstraction of antenatal and hospital records. A total of 1646 women were genotyped for 503 tagSNPs in 40 genes and a panel of ancestry informative markers. Gene-set analyses were stratified by race and were followed by a single SNP analysis within significant (FDR<0.2) candidate genes.

Results: Gene level associations were found for African Americans and term SGA for *IL6* and *KLRD1* while *LTA/TNF* and *TBX21* were associated with preeclampsia among European Americans only. Single SNP analyses for *IL6* showed consistent increased risk of term small for gestational age for both African and European Americans with risk ratios ranging from 1.8 to 2.5. For *KLRD1* however the single SNP associations were apparent only for African Americans with rs3759270 having an RR=0.4 (95%CI 0.3-0.8). For preeclampsia single SNP associations were seen only among European Americans and implicate *LTA*, *TNF* and a gene upstream from *TBX21*, *TBKBP1*. The strongest association was for an upstream regulator of TNF with RR=1.8 (95% CI 1.1-2.7).

Conclusion: Novel associations with *TBX21* & *TBKBP1* were found for preeclampsia among European Americans, while among African Americans, variation within *KLRD1* was associated with term SGA. 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 preeclampsia among European Americans.

Paper #1: Polymorphisms in Natural Kill Cell Related Genes are Associated with Preterm Birth

Harmon QE, Engel SM, Olshan A, Moran T, Stuebe AM, Luo J, Wu MC, Avery C

Introduction

Preterm birth affects approximately 12% of US births.[31] Significant medical and societal impacts are borne by the infants and their families due do the increased risk of mortality as well as both acute and chronic medical and neurocognitive disease.[25] While the earliest preterm births result in the most severe outcomes, late preterm births are also associated with increased risk of mortality and respiratory difficulties.[37]

Having a previous preterm birth is one of the strongest risk factors for a subsequent preterm birth and may reflect innate susceptibility factors, including maternal genes.[12, 13] Although a number of candidate pathways have been identified,[226] inflammatory pathways have been a particular focus. Pregnancy is a state of altered inflammatory and immune function. Changes in both gene expression and measured levels of inflammatory cytokines have been documented during the course of uncomplicated pregnancies.[72-74, 227] In particular, T-cells and Natural Killer cells (NK) decrease in both number and function over the course of pregnancy, while defensive immunity is enhanced.[72] Candidate inflammation genes have been examined in a number of diverse populations,[6, 88, 94, 98, 105, 114, 149-151, 156, 160, 164] although many of the studies have had small case groups and few address issues of population stratification despite very racially diverse study populations. Studies with larger case groups[98, 149-152, 164] focused on exploring more genes with limited single nucleotide polymorphisms (SNP) coverage per gene. In addition, studies conducted among US populations have identified differences in the genes and biologic pathways associated with preterm birth in Whites and African Americans, [94, 97, 98, 149, 156] reinforcing the need to consider ancestry in the context of this outcome.

Using the Pregnancy, Infection and Nutrition Cohort (PIN), we attempted to: replicate previous associations; broaden the inflammation gene coverage to include lesser studied genes in the critical T-cell and NK cell pathways; and deepen the per-gene SNP coverage, while carefully addressing issues of population stratification in this well-characterized biracial cohort. We additionally improve upon previous studies by incorporating novel statistical methodology to identify gene-based associations, and using inverse probability of selection modeling to account for any differences between the genotyped and parent cohort. In this paper, we describe our findings for polymorphisms in 30 candidate genes and the risk for preterm birth.

Methods

Study population

We utilized a nested case-control subset of the Pregnancy Infection and Nutrition Study (PIN), a prospective pregnancy cohort designed to assess antenatal risk factors for preterm birth, fully described by Savitz.[185] Women were recruited between August 1995 and June 2005 through Wake County Human Services Department, Wake Medical Center and University of North Carolina (UNC) prenatal clinics. Exclusion criteria at enrollment included age less than 16 years, non-English speaking, not planning to deliver at the recruitment hospital, carrying multiple gestations, or lacking a telephone.

Outcome information was abstracted from the medical record following delivery. Maternal blood for genetic analysis was obtained during the first study visit. Covariates were collected through self-administered questionnaires or telephone interviews. All participants gave informed consent, and the institutional review boards of the UNC School of Medicine and Wake Medical Center approved the study.

Cases and controls for this study were selected among eligible women from the entire PIN cohort (N=5169). Initial eligibility criteria included consent for DNA analysis (N=3539), collection of a suitable biological specimen (N=3289), self-reported maternal race of White or African American (N=3075) and known birth date, resulting in 3065 (59.3%) women who were eligible for selection into our study. Of the eligible women, all preterm cases with sufficient DNA were genotyped (N=347, 92%). Term births (N=1299) selected for genotyping included births with other reproductive outcomes of interest (gestational hypertension, small for gestational age) as well as women with uncomplicated pregnancies. In total 1646 women were genotyped.

Outcome Assessment

Gestational age at delivery was calculated based on the first ultrasound performed prior to 22 weeks gestation. For women without an early ultrasound, self-reported last menstrual period was used. Preterm birth was defined as a live birth before 37 complete weeks of gestation. Subtype of preterm birth was assessed by physician review.185 While this study does not have sufficient power to consider each subtype of preterm birth, spontaneous preterm birth, which includes both preterm labor and preterm prelabor rupture of membranes, was considered as an additional outcome.

Gene Selection

Thirty candidate genes were selected from the innate and adaptive immune system with a focus on representing Th1 and Th2 cytokines and their regulators, inflammatory mediators (including TNF signaling), selected chemokines and NK cells. In particular, we aimed to represent inflammatory genes for which marked changes in protein concentrations across trimesters have been demonstrated, because dysregulation in these genes could result in initiation of parturition before term.[72, 73]

SNP analysis

Whole blood was collected, centrifuged and the buffy coat fraction was stored in CPT tubes and placed in -80˚C storage. DNA was extracted using various protocols including the Applied Biosystems automated DNA extractor and Qiagen (Gentra) Puregene chemistry.

A custom 1536 Illumina GoldenGate plate was designed which included the 30 genes (432 SNPs) from this study as well as genes from angiogenesis, apoptosis and cell cycle pathways. TagSNPs were chosen using TagZilla for multiple populations allowing for 20kb upstream and 10kb downstream margins and restricting to tags with minor allele frequencies of at least 10% and linkage disequilibrium (LD) with r^2<80%. Genotyping was conducted at the University of North Carolina Genomics Core (Chapel Hill, NC) and genotypes were called by the Illumina BeadArray Reader and software for automated genotype calling.

Genotyping was performed on 1646 PIN samples. Individuals were dropped when fewer than 95% of SNPs were successfully called (N=11). We further excluded unintentional duplicate samples (N=3), congenital anomalies (N=24) and stillbirths (N=11), resulting in 1598 women included in the analysis.

Poor genotyping quality (<95% call rate) resulted in the loss of 39 SNPs. Quality control included duplicate PIN samples and standardized samples from Corriel CEPH trios on each plate. Of the 393 SNPs that entered quality control, there was one instance of a single base pair genotyping discrepancy found in 199 blind samples and no instances of Mendelian errors among 21 trios examined. HWE was assessed using SAS 9.2 (Cary, NC) 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.

Tagging for two genetic ancestry populations resulted in redundant (LD>0.8) tagSNPs in the European American population. Haploview (Cambridge, MA)[201] was used to calculate LD (using r^2) and generate LD heatmaps.

Confounding by population stratification

Previous studies suggest that there may be important differences between allelic frequencies in genes related to inflammatory cytokines between self-reported African-Americans and Whites in the United States.[188] As race has also been associated with preterm birth,[25] there is potential for confounding by population stratification.

A panel of 157 ancestry informative markers was chosen to estimate genetic ancestry using SNPs identified in a similar North Carolina bi-racial population.[189] STRUCTURE (Chicago, IL)[228] was used to quantify genetic ancestry assuming two underlying populations. Genetic ancestry was then used to stratify the analyses by race (European American and African American), and continuous percent African American ancestry was included in all models.

Additional covariates

Covariates were selected based on previous studies and an examination of a directed acyclic graph (DAG). Possible covariates included self-reported maternal smoking during the first 6 months of pregnancy (yes/no), maternal age (<25 yrs, 25-34 yrs, >=35 yrs), pre-pregnancy body mass index (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2 and >=30.0 kg/m^2), and socio-economic status, as represented by total family income adjusted for the number of individuals in the household relative to contemporary local poverty levels. In addition, a number of additional demographic, pregnancy health and study characteristics were included for the calculation of selection probabilities. All values were self-reported with the exception of measured height.

Statistical Analysis

We used a 2-stage analysis approach to examine the influence of inflammatory genes on both preterm and spontaneous preterm birth. Stage 1 was a gene-level analysis using the SNP-set Kernel Association Test (SKAT)[194] with a linear kernel (analogous to logistic regression with an additive genetic effect). Gene level analysis is particularly useful in genetically diverse populations where different SNPs are in LD with the causal SNPs. SKAT also allows for complex SNP interactions, permits covariate adjustment, and does not penalized SNPs with opposing associations (increased or decreased risk) within a single gene. SNPs were grouped by gene into SNP-sets and genes in close proximity (within 25 kbp) were analyzed together. Individuals with at least one missing genotype were dropped from the relevant SNP-set but were included in other SNP-sets where they had complete data. On average, 98% of individuals were included in each SNP-set with a range of 92-100% (Table S14). Hypothesis testing in SKAT was conducted using a variance component score test of the null hypothesis that the general function for the SNP-set equals 0.[197] Analyses were performed within strata defined by genetic ancestry and additionally adjusted for percent African American ancestry. A false discovery rate (FDR) of 20% was used to identify genes which progressed to Stage 2. The FDR was calculated as a Q value[229] using R (p.adjust, FDR). Cases included all preterm births with a subset analysis of spontaneous preterm birth. Controls included term births without gestational hypertension or small for gestational age complications (Table 4.1, "Disease Free").

The goal of Stage 2 was to identify the SNPs in each gene responsible for the significant SNP-set association p-values estimated in Stage 1. Given the prevalence of preterm birth in this population (13.5%), risk ratios were estimated using the entire genotyped cohort and a log-linear risk model. Inverse probability weighting was used so that the estimates reflect the eligible population. Cases were all preterm births with a subset analysis of spontaneous preterm births. Controls were all genotyped

term births (Table 4.1 Term Births). Briefly, the probability of being selected into the genotyped sample (N=1646) was calculated for all eligible women (N=3065) using a logistic model including all covariates in Table 1 as well as additional demographic and study related characteristics. The inverse of these selection probabilities was used to weight the analysis. Robust variance estimators were used. Given the dependence between Stage 1 and Stage 2, top ranking SNPs from Stage 2 were reported based on the consistency of the observed association in both preterm birth and spontaneous preterm birth, as well consistency across genetic ancestry groups.

Results

The final analysis set included N=1598 individuals. Women were predominantly White (62.6%), non-smoking (74.4%), well-educated (52% with at least high school education) with a mean BMI of 26.5 kg/m^2 and a mean age at the start of pregnancy of 26.1 years (Table 4.1). In the underlying cohort, preterm birth occurred in 13.5% of births, and 62.1% of these were spontaneous. The eligible and genotyped population did not differ appreciably from the entire cohort (Table S15).

Stage 1: Gene Set Analysis

Proximity of genes resulted in 24 gene-sets with *IL13* and *IL4,* and *LTA* and *TNF,* respectively, considered jointly in the SKAT analysis. Genes with a single SNP (*TGFB1, TGFB3*) or with SNPs genotyped solely for replication purposes (*IL1A* and *IL1B* each with 2 SNPs) were not included in the Stage 1, gene-level analysis.

For preterm birth, four gene-sets (*IFNGR2, IL12A, KIR3DL2, CSF2)* associated with Natural Killer Cells and one gene associated with Th2 immunity (*IL13/IL4*) met the FDR criteria of 20% (Table 4.2) among European Americans. *IFNGR2* and *IL13/IL4* also met the FDR criteria for spontaneous preterm birth. No

gene-sets were significantly associated with preterm birth or spontaneous preterm birth among African American participants.

Stage 2: Single SNP Analysis

The five gene-sets identified in Stage 1 (90 SNPs) and 7 SNPs not included in Stage 1, were examined in Stage 2 in both European and African Americans. Table 3 presents the RR and 95% CI for the strongest single SNP results. All of the single SNP results can be found in Table S16. In the assessment of covariates, nested models adjusted only for percent genetic ancestry were compared with fully and singly adjusted models for a subset of the SNPs with the strongest associations. Adjustment for all, or any, of the covariates failed to change the point estimates (>10%) (Results not shown).

IL12A

Two SNPs (rs6441282 and rs692890) showed consistent associations (RR 0.7-0.8) for both ancestry groups and both outcomes, with the variant allele conferring reduced risk of both preterm and spontaneous preterm birth. The variant alleles were the minor alleles for European American women (allele frequency: 0.47 and 0.33) but were more common in African American women (allele frequency: 0.66 and 0.63). These two SNPs were in strong LD among African American women but not among European American women (Figure 4.1).

In European American women, another SNP in moderate LD with rs692890 (rs609907) (Figure 4.1) also conferred a reduced risk (RR=0.6-0.7) for total and spontaneous preterm birth. A number of SNPs had consistent results for both outcomes among European American women only: rs503582, rs7653097 and rs755004 (RR 1.3- 1.5), rs13064168 (RR 0.6) and rs17826053 (RR 0.8). SNP rs4680536 showed an increased risk with spontaneous preterm only (RR=1.3, 95% CI 1.0-1.7).

CSF2 and IL3

Two LD blocks in European American women (Figure 4.2) show an association between *CSF2* and preterm birth. A group of three SNPs (rs25881, rs25882, rs27438 r^2>0.8), including one intron variant and one missense variant, conferred increased risk (RR=1.3-1.4) for preterm birth only.

As second LD block (rs721121, rs4705916, rs743564, rs6898270, r^2>0.85 in European American women) was associated with generally reduced risk of preterm for both European and African American women. For African American women there was a strengthening of the risk reduction for spontaneous preterm birth for rs721121 and rs4705916 (RR=0.57, 95% CI 0.4, 0.9).

Upstream tags for *CSF2* also captured SNPs which are more closely associated with *IL3*. One intronic variant in *IL3* (rs31481) was associated with an increased risk for preterm birth among both ancestry groups (RR 1.3-1.4). Among white women only, a downstream SNP (rs11575022) was associated with an increased risk for both preterm and spontaneous preterm birth (RR 1.6 and 1.4 respectively).

IL13 and IL4

IL13 and *IL4* are very close on Chromosome 5 and were considered together for Stage 1. In both genes, associations were generally found for European American women only, and these associations were strongest for spontaneous preterm birth. For *IL13*, a cluster of 3 SNPs in strong LD (r^2>0.8) (Figure 4.3) (rs7737470, rs3091307, rs1881457) had RR from 1.8-1.9 for spontaneous preterm birth. A second cluster in LD (r^2>0.7) (rs2243204, rs2243210, rs2243218, rs2243219) had RR from 1.3-1.5. The results for *IL4* were more varied with both protective and risk alleles. One cluster of SNPs in strong LD (r^2>0.8) (rs2243267, rs2243270, rs11242123) showed both risk (RR 1.6-1.8) and protective variants (rs2243250) (RR 0.6). A single SNP (rs11242122) downstream of *IL4* showed a particularly strong protective association for spontaneous preterm birth with an RR=0.5 (95% CI 0.4-0.7).

KIR3DL2

Results for SNPs in *KIR3DL2* were found only for European American women. Two downstream SNPs (rs11672983, rs3816051) showed consistent increased risk for both preterm and spontaneous preterm births (RR 1.3-1.4). A single SNP rs4806457 which is an intron variant showed a risk association with preterm birth only (RR=1.7, 95% CI 1.1-2.7).

IFNGR2

Among European American women, two LD clusters in *IFNGR2* were seen (Figure 4.4). Rs9978223, rs2268241 and rs9808753 (r^2>0.9) all showed a reduced risk, with a strengthening of the association for spontaneous preterm (RR 0.6-0.7). An additional cluster of two SNPs (rs9808685, rs2834210 r^2=0.97) showed a consistent risk association with both preterm and spontaneous preterm births (RR 1.3).

Discussion

We undertook an investigation of T-cell and NK-cell related gene variants in a biracial pregnancy cohort. In addition to novel findings in *KIR* genes, we found important associations for genes associated with NK cells and Th2 immunity.

In our study a number of the genes which showed a gene level association are related to Natural Killer (NK) cells and their function (*IL12A, IFNGR2, CSF2 and KIR3DL2*). NK cells and the cytokines associated with them *(IL12, IL15, IL6, IFNγ, TNFα* and *CSF2*) have been documented to change dramatically over the course of pregnancy[72, 73] and may be closely involved in immune tolerance to the developing placenta and adequate placental implantation early in pregnancy. Related to NK Cells, killer cell immunoglobulin-like receptor (KIR) genes may be particularly important in allowing trophoblast cells

to evade destruction by NK cells during placental development. Indeed, KIR genes have been implicated in both recurrent miscarriage and preeclampsia.[128]

While this is the first study to examine the association between KIRs and preterm birth, previous studies have genotyped *IL12A, IFNGR2, CSF2* , *IL13* and *IL4* with fewer than 8 SNPs per gene and often 5 or fewer SNPs, which vastly underestimates the underlying genetic variation. The positive findings in this study relative to the previous null findings may be due to more extensive coverage of the gene, and additionally the enhanced power of our Stage 1 gene level analysis.

IL12A and *CSF2* showed single SNP associations in both ancestry groups suggesting common pathways. *IL12A* is an important stimulator of NK cells and results in production of both TNF-α and IFN-γ.[22] As an upstream regulator of NK cells, IL12 can stimulate the release of TNF-α which increases in amniotic fluid with the onset of labor. TNF-α is associated with membrane degradation, cervical ripening and uterine contractions.[74] Upstream changes in the regulation of Natural Killer cells could have significant impact on TNF-α levels in women with an otherwise normally functioning *TNF* gene.

CSF2 is also released from NK cells and levels are suppressed in the 2nd and 3rd trimester in uncomplicated pregnancies.[72] Of interest, two of the *CSF2* SNPs (rs4705916 and rs721121) with consistent associations with spontaneous preterm birth in both European and African Americans, flank a possible regulatory region on chromosome 5 that regulates both *CSF2* and *IL3*.[230]

The two remaining NK associated genes (*KIR3DL2* and *IFNGR2*) were associated with preterm birth only among European Americans. *IFNGR2* is the receptor for IFN-γ which is an important NK cell cytokine. *IFNGR2* expression changes over the course of normal pregnancy[227] and dysregulation of *IFNGR2* through polymorphisms may influence the timing of parturition through its role in multiple immune related cell lines. Although *KIR3DL2* may be implicated directly in placental implantation,[128] two

SNPs which were used to tag *KIR3DL2* are closer to a gene related to IgA response (*FCAR*). *FCAR* has shown altered expression over the course of pregnancy[227] although the significance of this change is unknown. More extensive examination of *FCAR* is warranted to distinguish which gene these tags are capturing.

In addition to the genes related to NK cells, Th2 cytokines *IL13* and *IL4* had strong gene level and single SNP associations. These genes, and *IL5*, are quite close together on chromosome 5 and share regulatory elements located between *RAD50* and *IL13*.[231] The strongest associations for *IL13* appear for three SNPs which are in strong LD (r^2=0.9) with each other and share strong LD with a number of untyped SNPs within both *RAD50* and an intergenic locus control region. As this regulatory region has the potential to influence expression of *IL13, IL4* and *IL5*, further investigation of this region would be worthwhile.

Both gene and SNP level results differed for groups stratified by genetic ancestry. It is possible that fewer African American participants, weaker patterns of LD, and population substructure which reduces effective sample size, could explain the lack of an association with any of the candidate genes we explored. However, despite our inability to detect a significant gene level association for African Americans, the similar single SNP results for *CSF2* and *IL12A* suggest that similar genes are important for both groups.

Apart from power issues, evidence suggests that different genes and biological pathways may be associated with preterm birth in US Whites and African Americans.[97, 113] Reproductive outcomes such as preterm birth have strong selective pressures.[232] While the negative selective pressure of increased neonatal mortality is clear, positive selective pressure may also act on genes related to preterm birth. Decreased cephalopelvic disproportion[232] and hostile intrauterine environments in the presence of uterine or placental infection[233] may make preterm delivery a lifesaving event for both infant and

mother. In the face of different infectious and environmental exposures over generations and across populations, divergent genes and biological pathways may have emerged in geographically and genetically distinct ancestral groups.[234] Given the possibility that the biologic and genetic underpinnings of preterm birth vary by ancestral origins, stratification by ancestry is essential. And additionally, it may not be reasonable to assume that results from geographically distinct populations are generalizable, especially if the social and environmental exposures among these populations can differentially activate the relevant pathways. It would follow, then, that gene by environment studies which account for differences in both genetic structure and socio-environmental exposures and are needed to clarify disparate associations across studies.

This study has several limitations that should be considered in future studies examining genetic associations with preterm and spontaneous preterm birth. Fetal genes may also play a role in preterm birth. This study did not have access to fetal DNA and was unable to explore main effects or interactions with fetal DNA. While inclusion of fetal DNA is important to understand all possible pathways to preterm birth, the findings of this study support population based studies which suggest that maternal genetics may play an independent role in the risk of preterm birth. Additionally, tagSNPs themselves are not expected to be the causal SNP and further fine mapping of genomic regions identified by this study is necessary to identify the causal SNPs.

In summary, this study broadened coverage of polymorphisms in genes related to inflammation and explored novel genes related to NK cells. Using a larger population of African American women compared with previous candidate gene studies also allowed us to identify common risk alleles for both genetic ancestry groups. Genes associated with NK cells (*IL12A, IFNGR2* and *KIR3DL2*) were novel findings, and results suggest that further examination of the regulatory regions associated with cytokines on 5q31 (*IL4, IL13, IL3, CSF2*) may be fruitful.

Table 4.1: Demographic Characteristics of PIN Mothers

	Preterm Case		Disease Free		Term Birth[a]	
Genetic Ancestry[b]	European American N=194	African American N=134	European American N=409	African American N=204	European American N=813	African American N=457
Maternal Age						
<25 yrs	94 (48.5)	50 (37.3)	215 (52.6)	68 (33.3)	401 (49.3)	159 (34.8)
25-34 yrs	77 (39.7)	73 (54.5)	133 (32.5)	132 (64.7)	294 (36.2)	281 (61.5)
35+ yrs	23 (11.9)	11 (8.2)	61 (14.9)	4 (2.0)	118 (14.5)	17 (3.7)
Smoking[c]						
No	115 (66.5)	95 (80.5)	302 (77.4)	148 (84.6)	541 (71.0)	325 (81.9)
Yes	58 (33.5)	23 (19.5)	88 (22.6)	27 (15.4)	221 (29.0)	72 (18.1)
Missing	21 (10.8)	16 (11.9)	19 (4.6)	29 (14.2)	51 (6.3)	60 (13.1)
BMI (kg/m^2)[d]						
<18.5	14 (7.5)	8 (6.5)	23 (5.7)	16 (8.3)	41 (5.2)	30 (7.1)
18.5-24.9	95 (50.8)	43 (34.7)	250 (62.2)	79 (40.9)	431 (54.9)	158 (37.3)
25-29.9	44 (23.5)	28 (22.6)	71 (17.7)	39 (20.2)	146 (18.6)	85 (20.1)
30+	34 (18.2)	45 (36.3)	58 (14.4)	59 (30.6)	167 (21.3)	151 (35.6)
Missing	7 (3.6)	10 (7.5)	7 (1.7)	11 (5.4)	28 (3.4)	33 (7.2)
Poverty Index						
Mean (SD)	331 (254)	132 (94)	367 (238)	144 (123)	343 (234)	148 (126)
Missing	23 (11.9)	17 (12.7)	24 (5.9)	37 (18.1)	57 (7.0)	94 (20.6)
Marital Status						
Married	134 (69.1)	39 (29.3)	313 (76.5)	32 (15.7)	587 (72.2)	83 (18.2)
Unmarried	60 (30.9)	94 (70.7)	96 (23.5)	172 (84.3)	226 (27.8)	374 (81.8)
Missing	0	1 (0.7)	0	0	0	0
Education						
13+ yrs	105 (54.1)	56 (41.8)	275 (67.2)	68 (33.3)	498 (61.3)	172 (37.6)
<=12 yrs	89 (45.9)	78 (58.2)	134 (32.8)	136 (66.7)	315 (38.8)	285 (62.4)
Parity						
Nulliparous	88 (45.4)	49 (36.8)	189 (46.4)	88 (43.1)	398 (49.1)	219 (47.9)
Multiparous	106 (54.6)	84 (63.2)	218 (53.6)	116 (56.9)	413 (50.9)	238 (52.1)
Missing	0	1 (0.7)	2 (0.5)	0	2 (0.2)	0
Spontaneous Preterm						
Yes	103 (53.1)	65 (48.5)				

a Term births include disease free term births plus term births with other outcomes of interest: small for gestational age, gestational hypertension and preeclampsia.

b Genetic ancestry determined using 148 AIMs and STRUCTURE.

c Self-reported smoking during months 1-6 of pregnancy.

d Pre-pregnancy BMI calculated from self-reported pre-pregnancy weight and measured height.

Table 4.2: Q[a] values from SKAT analysis for each geneset stratified by genetic ancestry

	European American[b]		African American[b]	
Gene	Preterm	Spontaneous	Preterm	Spontaneous
IFNGR2	**0.06***	**0.18**	0.93	1.00
IL13 & IL4	**0.10**	**0.01***	1.00	1.00
KIR3DL2	**0.10**	0.43	0.89	1.00
IL12A	**0.10**	0.44	0.89	0.64
CSF2	**0.14**	0.67	0.89	0.82
IL18	0.40	0.44	0.93	1.00
GATA3	0.40	0.48	0.89	1.00
IL10	0.40	0.48	0.89	0.82
IL12B	0.54	0.81	0.93	1.00
IL6	0.54	0.79	0.93	0.92
KIR2DL4	0.54	0.43	0.89	1.00
IL15	0.66	0.67	0.93	0.89
LTA & TNF	0.70	0.70	0.48	1.00
IFNG	0.75	1.00	0.89	0.64
TBX21	0.75	1.00	0.89	0.92
NFKB1	0.75	1.00	0.93	1.00
TNFRSF1B	0.75	0.67	0.89	0.64
IL8	0.75	0.67	0.93	0.82
KIR3DL3	0.75	0.67	0.89	0.64
KLDR1	0.85	1.00	0.89	1.00
IL6R	0.88	0.67	0.93	1.00
IL2	0.89	0.81	0.89	0.82
IL8RB	1.00	0.81	0.93	1.00
CXCL10	1.00	0.81	0.89	1.00

a Genetic ancestry determined from 148 AIMS and STRUCTURE

b Q values represent the proportion of false positives (number of false rejections/total number of rejections)

*Bonferroni p-value for p=0.05 and 24 genesets= 0.002. The p-value for IL13&IL4 met this criterion for spontaneous preterm among White mothers. The p-value for IFNGR2 met this criterion for preterm among White mothers.

Bold meets FDR <0.2

Table 4.3: Single SNP Relative Risk and 95% Confidence Intervals for Preterm and Spontaneous Preterm Birth among Mothers Stratified by Genetic Ancestry

	European American [a]		African American [a]	
Gene/SNP [b]	Preterm	Spont. Preterm	Preterm	Spont. Preterm
IL12A				
rs503582	1.3 (1.1, 1.7)	1.3 (1.0, 1.7)	1.1 (0.8, 1.4)	1.0 (0.7, 1.4)
rs7653097	1.5 (1.0, 2.1)	1.4 (0.9, 2.3)	1.0 (0.7, 1.4)	0.9 (0.6, 1.5)
rs13064168	0.6 (0.4, 0.8)	0.7 (0.4, 1.0)	1.1 (0.7, 1.7)	1.3 (0.7, 2.4)
rs609907*	0.6 (0.5, 0.8)	0.7 (0.5, 1.0)	1.1 (0.8, 1.6)	1.2 (0.7, 2.0)
rs2647929	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	1.1 (0.8, 1.6)	1.6 (1.0, 2.4)
rs9811792	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	1.1 (0.8, 1.4)	1.5 (1.0, 2.2)
rs7372767	1.1 (0.9, 1.4)	1.1 (0.9, 1.5)	1.3 (0.9, 1.7)	1.7 (1.1, 2.6)
rs6441282	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)	0.7 (0.5, 1.0)
rs692890	0.7 (0.6, 0.9)	0.7 (0.5, 0.9)	0.8 (0.6, 1.1)	0.7 (0.5, 1.0)
rs755004	1.3 (1.0, 1.7)	1.5 (1.1, 2.1)	0.6 (0.3, 1.2)	0.6 (0.2, 1.7)
rs17826053	0.7 (0.5, 1.0)	0.7 (0.5, 1.1)	1.0 (0.7, 1.4)	0.7 (0.4, 1.2)
rs4680536	1.1 (0.9, 1.4)	1.3 (1.0, 1.7)	1.1 (0.8, 1.4)	1.0 (0.7, 1.4)
IFNGR2				
rs6517167	1.3 (1.0, 1.7)	1.1 (0.7, 1.6)	1.1 (0.8, 1.4)	0.9 (0.6, 1.3)
rs9978223	0.7 (0.5, 0.9)	0.6 (0.4, 1.0)	1.1 (0.8, 1.4)	1.1 (0.7, 1.5)
rs2268241	0.6 (0.5, 0.9)	0.6 (0.3, 0.9)	1.2 (0.9, 1.6)	1.3 (0.9, 1.8)
rs9808685	1.3 (1.1, 1.7)	1.3 (1.0, 1.8)	1.0 (0.8, 1.3)	0.9 (0.6, 1.3)
rs2834210	1.3 (1.0, 1.6)	1.3 (0.9, 1.7)	1.0 (0.8, 1.4)	0.9 (0.6, 1.3)
rs9808753	0.7 (0.5, 1.0)	0.6 (0.4, 1.0)	1.2 (0.9, 1.6)	1.1 (0.7, 1.8)
rs2834213	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	1.2 (0.7, 2.1)	1.8 (0.9, 3.5)
KIR3DL2				
rs4806457	1.7 (1.1, 2.7)	1.5 (0.7, 3.1)	1.0 (0.5, 1.8)	0.7 (0.3, 1.7)
rs11672983	1.3 (1.0, 1.5)	1.3 (1.0, 1.7)	0.8 (0.6, 1.0)	0.9 (0.6, 1.4)
rs3816051	1.4 (1.2, 1.7)	1.4 (1.1, 1.9)	0.9 (0.6, 1.1)	0.9 (0.6, 1.3)
IL3				
rs31481	1.4 (1.1, 1.8)	1.0 (0.7, 1.5)	1.3 (0.9, 1.8)	1.2 (0.7, 2.0)
rs11575022	1.6 (1.1, 2.3)	1.5 (0.9, 2.6)	1.1 (0.7, 1.5)	1.0 (0.6, 1.7)
CSF2				
rs721121	0.8 (0.7, 1.0)	0.9 (0.7, 1.2)	0.7 (0.5, 1.0)	0.6 (0.4, 0.9)
rs4705916	0.8 (0.6, 1.0)	0.8 (0.6, 1.1)	0.7 (0.5, 1.0)	0.6 (0.4, 0.9)
rs743564	0.8 (0.6, 1.0)	0.9 (0.6, 1.2)	0.7 (0.5, 1.0)	0.8 (0.5, 1.2)
rs25881	1.4 (1.0, 1.8)	1.2 (0.8, 1.7)	1.0 (0.8, 1.4)	0.9 (0.6, 1.4)
rs25882	1.3 (1.0, 1.7)	1.1 (0.7, 1.6)	1.1 (0.8, 1.5)	1.0 (0.7, 1.6)
rs27438	1.3 (1.0, 1.7)	1.1 (0.8, 1.6)	0.9 (0.7, 1.1)	0.8 (0.6, 1.2)
rs6898270	0.8 (0.6, 1.0)	0.9 (0.6, 1.2)	0.8 (0.6, 1.2)	0.8 (0.5, 1.3)

Table 4.3 continued

	European American[a]		African American[a]	
	Preterm	Spont. Preterm	Preterm	Spont. Preterm
IL13				
rs7737470*	1.4 (1.1, 1.8)	1.9 (1.4, 2.5)*	1.1 (0.8, 1.4)	1.0 (0.6, 1.5)
rs3091307*	1.4 (1.1, 1.8)	1.9 (1.4, 2.6)*	1.0 (0.7, 1.3)	0.9 (0.7, 1.3)
rs1881457*	1.5 (1.1, 1.9)	1.8 (1.3, 2.5)*	1.0 (0.7, 1.3)	1.1 (0.7, 1.8)
rs1295686	0.8 (0.6, 1.1)	0.7 (0.5, 1.0)	1.1 (0.9, 1.5)	1.2 (0.8, 1.7)
rs20541	1.2 (0.9, 1.6)	1.5 (1.1, 2.1)	0.9 (0.6, 1.2)	0.8 (0.5, 1.3)
rs848	1.2 (0.9, 1.6)	1.5 (1.0, 2.0)	1.1 (0.8, 1.4)	1.1 (0.8, 1.4)
rs1295683	1.3 (0.9, 1.7)	1.5 (1.0, 2.2)	0.8 (0.5, 1.3)	0.7 (0.4, 1.4)
rs2243204	1.2 (0.9, 1.8)	1.5 (0.9, 2.3)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs2243210	1.0 (0.7, 1.6)	1.3 (0.8, 2.2)	0.8 (0.6, 1.1)	0.8 (0.5, 1.3)
rs2243218	1.2 (0.8, 1.7)	1.5 (1.0, 2.3)	1.0 (0.7, 1.3)	1.0 (0.7, 1.5)
rs2243219	1.2 (0.9, 1.8)	1.5 (1.0, 2.3)	1.0 (0.8, 1.3)	0.9 (0.7, 1.3)
IL4				
rs2243250	0.7 (0.5, 0.9)	0.6 (0.4, 0.9)	1.0 (0.8, 1.4)	1.0 (0.7, 1.5)
rs2243263	1.2 (0.9, 1.7)	1.6 (1.1, 2.3)	1.1 (0.8, 1.5)	1.2 (0.8, 1.9)
rs2243267	1.5 (1.1, 2.0)	1.8 (1.2, 2.6)	1.1 (0.8, 1.5)	1.2 (0.8, 1.9)
rs2243270	1.4 (1.1, 1.9)	1.7 (1.1, 2.5)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs11242122*	0.7 (0.6, 0.9)	0.5 (0.4, 0.7)*	1.0 (0.8, 1.3)	0.8 (0.5, 1.2)
rs11242123	1.4 (1.0, 1.9)	1.7 (1.2, 2.6)	1.0 (0.8, 1.4)	1.1 (0.7, 1.6)

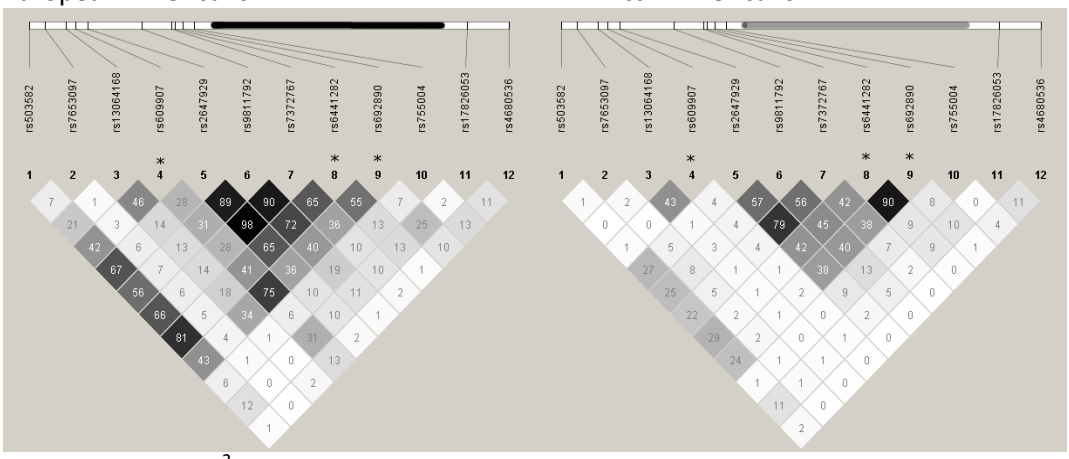
a Based on genetic ancestry

b SNPs arranged by base pair position within each gene

*SNPs and estimates have p-value <0.0005 (Bonferroni correction for 100 SNPs in Stage 2)

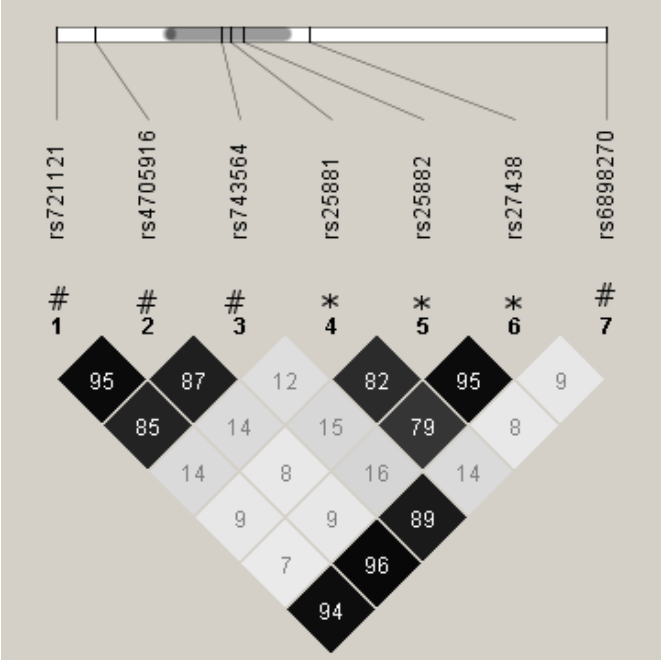
Figure 4.1: Linkage Disequilibrium in *IL12A* within European and African Americans

European Americans African Americans



Values represent r^2 for pairs of SNPs with darker boxes having stronger correlation. Grey bar represent approximate location of *IL12A*. * highlights blocks of LD for SNPs discussed in results.

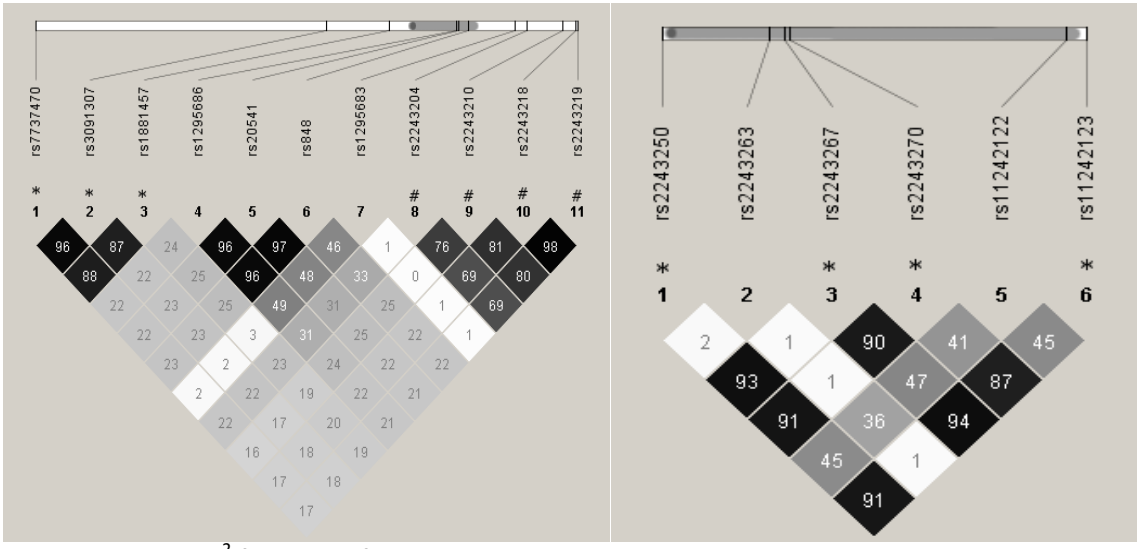
Figure 4.2: Linkage Disequilibrium in *CSF2* in European Americans



Values represent r2 for pairs of SNPs with darker boxes having stronger correlation. Grey bar represent approximate location of CSF2. * and # highlight blocks of LD for SNPs discussed in results.

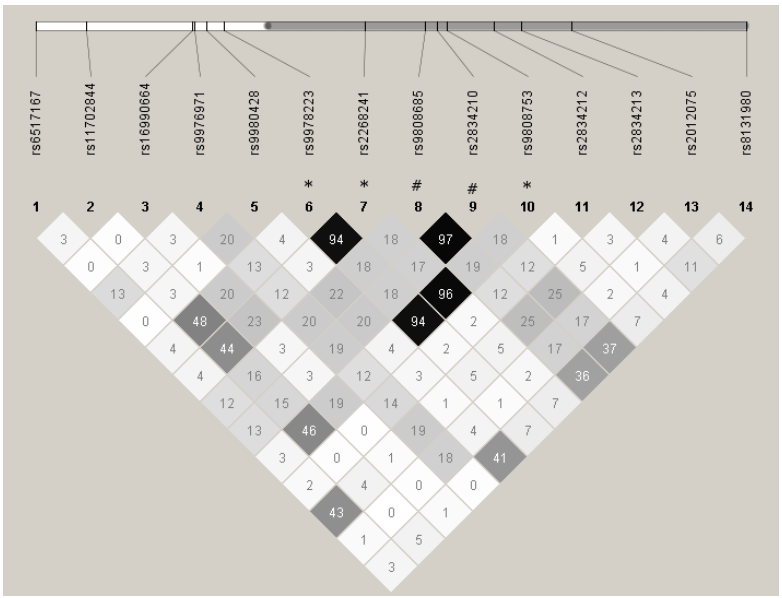
Figure 4.3: Linkage Disequilibrium within *IL13* and *IL4* within European Americans

IL13 **IL4**



Values represent r^2 for pairs of SNPs with darker boxes having stronger correlation. Grey bar represent approximate location of *IL13* and *IL4*. * and # highlight blocks of LD for SNPs discussed in results.

Figure 4.4: Linkage Disequilibrium within *IFNGR2* for European Americans



Values represent r^2 for pairs of SNPs with darker boxes having stronger correlation. Grey bar represent approximate location of *IFNGR2*. * and # indicate blocks of LD for SNPs discussed in results.

Paper #2: Polymorphisms in Inflammatory Genes are Associated with Term SGA and Preeclampsia

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Introduction

Hypertensive disorders of pregnancy and poor fetal growth often co-occur[22] and may share underlying pathology.[9] Hypertensive disorders of pregnancy, including gestational hypertension (GHTN) and preeclampsia (PE), occur in up to 20% of pregnancies[45] and are a leading cause of maternal mortality.[47] Pregnancies complicated by hypertension are at increased risk of stillbirth, poor fetal growth and preterm birth.[22, 50] The prevalence and health consequences of poor fetal growth depend largely on the metric of assessment[60] and the specific etiology.[64] However, low birth weight is consistently associated with increased infant mortality.[33] Each outcome has also been associated with later risk of cardiovascular disease in the mother.[40, 51, 52, 70]

Hypertension in pregnancy and poor fetal growth often share common placental pathology including shallow or inadequate placentation.[3, 7, 9, 10] In addition, women with either outcome exhibit altered inflammatory biomarkers both preceeding[74, 79, 80] and at the time of diagnosis.[1, 4, 7, 9, 74] Adequate placentation is to a large degree dependent on tightly regulated local inflammatory processes[9, 74]-- in particular natural kill (NK)[5] and T cell[82] activity. Placental growth and uterine wall remodeling may additionally be influenced by cell cycle genes that regulate cell growth and division in rapidly growing tissue such as the placenta.[20, 21] 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).[134-138]

Although a fetal genetic component has been identified for both hypertension in pregnancy[11, 148] and fetal growth,[15] these disorders also have a maternal genetic component. However, sparse gene

coverage, small case groups and lack of control for population stratification have limited previous studies of genetic associations in small for gestational age infants and preeclampsia. To address these limitations, we examined the associations between both inflammatory and cell cycle gene and preeclampsia and SGA with increased gene coverage and measured genetic ancestry. Here we report on the association between 40 genes and the outcomes of SGA, gestational hypertension and preeclampsia in a well characterized biracial pregnancy cohort in North Carolina.

Methods

Study participants were drawn from the Pregnancy, Infection and Nutrition (PIN) cohort,[184, 185] which was established to assess antenatal risk factors for a variety of reproductive outcomes. Briefly, 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.[184, 185] 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%) allowed their DNA to be used for genetic analysis. Eligibility for genotyping in the current 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. Control births (N=918) were selected from the remaining eligible women.

Outcome assessment

SGA status was defined as birth weight below the 10th percentile for gestational age, stratified by infant race and sex and maternal parity based on percentiles from 1989 US births.[186] As a proxy measure for impaired fetal growth, SGA may not appropriately classify preterm infants[59, 60] and may misidentify constitutionally small infants as SGA. In as much as common causes may exist for preterm birth and poor intrauterine growth,[24] term SGA was considered as an additional phenotype.

Gestational hypertension and preeclampsia were assessed using clinical records. Prior to 2002, hypertension during pregnancy was defined using a relative increase of 30mmHg in Systolic Blood Pressure (BP) or a 15mmHg increase in the Diastolic Blood Pressure from a woman's baseline blood. 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 >=140 mmHg or Diastolic BP >=90 mmHg.[45] 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 preeclampsia, however the positive predictive value for adverse maternal and infant outcomes is similar for the two sets of criteria.[235] Preexisting hypertension, onset of hypertension after 20 weeks and evidence of proteinuria were abstracted from antenatal charts and discharge diagnoses. Gestational hypertension was defined as new onset hypertension following 20 weeks in the absence of proteinuria. Preeclampsia 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 gestational hypertension and preeclampsia.

Additional Covariates

Covariates of interest were selected based on previous studies and explored as potential confounders using directed acyclic graphs.[236] All values were self-reported, with the exception of measured height. Covariates included maternal age (<25 yrs, 25-34 yrs, >=35 yrs), body mass index[191] (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2 and >=30.0 kg/m^2), any maternal smoking during the first 6 months of pregnancy (yes/no), parity (nulliparous, multiparous) and a continuous measure of socio-economic status based on contemporary levels of poverty indexed to household income and household size. In addition, study related variables, and additional demographic and pregnancy health characteristics were included for the calculation of selection probabilities.

Single Nucleotide Polymorphisms: Selection and Assessment

Thirty inflammatory and 10 cell cycle genes (546 SNPs) were selected as candidate genes. Tag SNPs were selected using TagZilla[187] for two population with a 20kb upstream and 10kb downstream margin restricting to minor allele frequencies >=10% and linkage disequilibrium (LD) <0.8 (r^2) . A custom 1536 Illumina GoldenGate plate was designed which also included SNPs from genes associated with angiogenic and apoptosis pathways.

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[6] and Qiagen chemistry.

Genotyping was conducted at the University of North Carolina Genomics Core (Chapel Hill, NC) and alleles were read using the Illumina BeadArray Reader and were analyzed using Illumina's software for automated genotype calling.

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 in 199 blind samples (IL4: rs2243250), and there were no instances of mendelian errors among 21 trios examined. Hardy Weinberg Equilibrium was assessed using SAS 9.2[224] 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, redundant SNPs (Linkage Disequilibrium with $r^2>0.8$) were included for European Americans, and use of a Yoruban reference population also resulted in some redundant SNPs for our African American population. Linkage Disequilibrium (LD) in the study population was calculated and heatmaps were created using Haploview.[201] In addition to pairwise LD in this population, long range LD with untyped SNPs was explored using SNAP[202] with the 1000 Genomes Project Pilot 1.

Genetic ancestry

Differences in the allelic frequency in genes associated with inflammation have been reported among Whites and African Americans in the United States.[188] The incidence of preeclampsia[45] and birth weight[33] also vary by self-reported race presenting the possibility of confounding by genetic ancestry. Genetic ancestry was therefore assessed using ancestry informative markers (N=157) that have previously been used in a similar population in North Carolina.[189] STRUCTURE[228] was used to calculate a

continuous genetic ancestry variable. All analyses were stratified by genetic ancestry (European and African American) and also included continuous percent African ancestry.

Statistical analysis

We employed a two-stage approach to identify associations between inflammatory and cell cycle genes and the outcomes of SGA, GHTN and PE. Stage 1 utilized the SNP-set Kernel Association Test[194] (SKAT) with a linear kernel (analogous to logistic regression with an additive genetic model). SKAT was chosen as it permits SNP interactions within a gene, allows adjustment for covariates and accounts for SNPs with opposing effects (protective or risk) within a gene. SNP-sets were constructed based on candidate genes and genes within 25kBP were analyzed together. Genes with single SNPs (*CCNH, TGFB3, TGFB1, MDM2*) or SNPs chosen solely for replication (*IL1A, IL1B*) were not included in the Stage 1 analysis. Individuals with missing genotype information on any SNPs in a set were dropped from the analysis. On average 99% of individuals were included in each SNP-set with a minimum of 91% (Supplemental Table 1). Analyses were conducted for each outcome with uncomplicated term births as the control group. For GHTN and PE, women with chronic hypertension were removed from the control group. The null hypothesis that the general function for the SNP-set equals zero is tested using a variance component score test in SKAT.[197] A false discovery rate (FDR)[199] of 20% was used to identify SNP-sets which advanced to Stage 2 analysis. P-values from SKAT were transformed to Q[229] values using R(p.adjust, FDR)[237] accounting for the number of SNP-sets analyzed (N=31).

The Stage 2 analysis was used to quantify the individual SNP associations within the SNP-sets identified as significant in Stage 1. GHTN was not rare in this population (15% in the underlying PIN cohort); therefore, we estimated risk ratios for all outcomes using a log-linear risk model. Given a high proportion of small cell (<5) counts of homozygous recessives in some of the case groups, dominant genetic models were used unless the smallest cell was >5. Inverse probability of selection weighting was

used so that the estimates are generalizable to the 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 1 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 they are likely overestimate the true variance.[200] Stage 2 is not independent of Stage 1, therefore top ranking SNPs from Stage 2 were reported based on the consistency of the observed association in associated outcomes (SGA and Term SGA) as well as between groups based genetic ancestry groups. Analyses were stratified based on genetic ancestry and additionally adjusted for a continuous ancestry variable. In a limited subset of high priority models (N=15) we also examined the influence of maternal age, smoking, BMI, parity and socio economic status on point estimates and precision.

Results

The final analysis dataset included 1598 women. Tables 4.4 and 4.5 presents the demographic characteristics of the case and control groups for SGA and hypertensive disorders of pregnancy respectively. Women who consented and were successfully genotyped were similar to the underlying PIN cohort 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/m^2 (Table S17). Although demographics differed between European and African Americans, the differences were not as pronounced between cases and controls within strata of genetic ancestry. Adjustment for any or all of the covariates in Table 4.4 failed to change the single SNP point estimates more than 10% (results not shown). Therefore we only present estimates adjusted for genetic ancestry.

Stage 1: Gene-set analysis

SNPs were combined into 31 SNP-sets. Due to proximity on the genome *LTA* and *TNF*, *IL13* and *IL4*, and *CDKN2A* and *CDKN2B* were considered as single SNP-sets. Four SNP-sets met the FDR criteria of 20% in Stage 1: *IL6* and *KLRD1* were associated with term SGA among African Americans and *TBX21* and *LTA/TNF* were associated with PE among European Americans. No SNP-sets met the FDR criteria for SGA or GHTN (Table 4.6).

Stage 2: Single SNP analysis

The 55 SNPs associated with the SNP-sets identified in Stage 1 and the 8 SNPs not included in Stage 1 were assessed in Stage 2 in both ancestral groups (Table 4.7 and Table 4.8). Single SNP results for all genes and outcomes can be found in Tables S18 and S19.

SGA

IL6 and *KLRD1* were associated with Term SGA only among African Americans. Single SNP associations within *IL6* however were generally consistent in both ancestry groups, although slightly weaker for European Americans (Table 4.7). The strongest single SNP associations for Term SGA (RR 1.9-2.4) for both ancestry groups were seen for a group of 3 intronic *IL6* SNPs (rs1548216, rs2069843, rs2069849). 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) (Figure 4.5). Another group of SNPs upstream from *IL6* was also associated with an increased risk of Term SGA (RR 1.8-2.5) for both African and European Americans (rs6963444, rs7784987, rs3087221).

For *KLRD1* however, single SNP associations were dissimilar across the two ancestry groups. The tagSNPs chosen represent a single block of high LD among European Americans, except for two SNPs

which were quite rare in European Americans (rs10772256, rs7301562) (Figure 4.6). Seen as a block, there was an overall null association with both SGA and Term SGA for European Americans. In contrast, among African Americans, a number of SNPs were relatively strongly associated with Term SGA. In particular, rs10772256 (missense) and rs7301562 (r^2=1), were associated with a decreased risk of Term SGA (RR= 0.5, 95% CI 0.3-0.9). Additionally rs3759270 was also associated with a fairly substantial decreased risk of Term SGA (RR=0.4, 95%CI 0.3-0.8). Finally two SNPs in perfect LD (rs3809214, rs2302489) were associated with an increased risk of Term SGA (RR=1.6) among African Americans.

Preeclampsia

LTA/TNF and *TBX21* were associated with preeclampsia, but only for European American women. Moreover, the single SNP results were generally null for African Americans (Table 4.8). *LTA* and *TNF* are quite close on chromosome 6 (6p21.3) and tagging for *LTA* also captured intronic regions of *NFKBIL1*. Single SNP results for tags within *NFKBIL1* were generally null. In *LTA* two SNPs in high LD (r^2=0.99) (Figure 4.7), rs909253 and rs1041981 (missense) were associated with an increased risk of preeclampsia (RR=1.5 and 1.4). Another missense SNP in *LTA* rs2229094 was associated with a decreased risk of preeclampsia (RR=0.6, 95% CI 0.4-1.0). In *TNF,* rs1800629 an upstream SNP that is thought to upregulate *TNF* expression,[85] was found to increase the risk of preeclampsia (RR=1.8, 95% CI 1.1-2.7).

TagSNPs for *TBX21* captured two upstream SNPs which were closer to another gene *TBKBP1* (rs2013383, rs1808192). These two SNPs are in moderate LD with each other (r^2=0.68) (Figure 4.8) 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 preeclampsia RR=0.6. For tagSNPs within *TBX21* itself, the associations were null.

Preeclampsia exists on a spectrum and clinical diagnostic criteria changed over the course of participant recruitment. In addition, diagnostic criteria were abstracted from both antenatal records and discharge records, which sometimes conflicted and were not always both available. Given these challenges a validation of the preeclampsia diagnosis was performed in a subset. Among women who had discordant PE diagnoses (antenatal record differed from discharge diagnosis) we were able to review the complete antenatal and delivery record of a subsample (N=125). A sensitivity analysis of the single SNP estimates for SNPs in *LTA/TNF* and *TBX21* was conducted using a more refined PE diagnosis on the basis of this validation work. Women were considered a validated PE case if they had both an antenatal record and discharge diagnosis of PE, or if they were included in the chart review and were found to have PE using ACOG criteria. Among the 76 validated cases, the single SNP results for *LTA* and *TNF* were generally consistent in strength and direction. For *TBKBP1* the estimates were attenuated and, although in the same direction, the overall effect was null. However SNPs in *TBX21,* which were null using the entire PE case group, were strengthened and, although imprecise, suggest a possible risk association.

Discussion

We examined 40 genes related to inflammation and cell-cycle pathways and their association with SGA, GHTN and PE in a biracial North Carolina population. There were no significant associations for any of the cell cycle genes. 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 preeclampsia, associations within *LTA* and *TNF* were seen for European American women. Two SNPs within a novel gene, *TBKP1*, were associated with a decreased risk of preeclampsia 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* has been examined previously in relation to SGA with null associations, although many fewer SNPs were used to tag the gene[6, 158, 182] and apart from the Engel study[6] the populations were white. *IL6* expression decreases over the course of uncomplicated pregnancy[72] and *IL6* early in pregnancy may influence the ability of the placenta to become adequately implanted.[238]

KLRD1 (*CD94*) codes for a portion of receptor on both NK and T cells that recognizes HLA-E molecules expressed by trophoblasts during pregnancy[239]. Tight regulation of maternal immunity at the time of implantation mitigates against rejection of fetal trophoblasts. Dysregulation of *KLRD1* therefore could result in poor placental implantation due to low levels of maternal rejection. 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 MHC genes, there have been haplotype differences documented between individuals of European and African descent.[240] Underlying differences in HLA-E haplotypes may explain the different results seen in ancestry groups.

Genes coding for TNF-α (*TNF*) and TNF-β (*LTA*) were associated with an increased risk of preeclampsia among European American women. TNF-α has been implicated in the pathogenesis of preeclampsia[22] both as a modulator of placental implantation and as a response to the hypoxia created by poor placental perfusion.[8] Infusions of TNF induce hypertension in pregnant rats.[241] Despite the credibility of the biology implicating TNF with preeclampsia, results of genetic epidemiologic studies have been less encouraging. A meta-analysis of the -308A missense mutation (rs1808192) by Bombell[87]

found a null pooled RR. The Bombell study however combined estimates from populations of very different genetic ancestry. Work in US populations suggest that allele frequencies for *TNF* and its related receptors vary by self-reported race, and regulation of TNF-α levels during pregnancy appears to be different between White and African American women.[113] 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.

A gene level association was found for *TBX21* which is an important regulator of TH1 immunity.[242] However the single SNP analysis revealed that the association was most likely 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/NFκB pathways and the activation of interferon.[243, 244] Given the role of TNF-α in preeclampsia, further investigation of this novel gene is warranted.

Diagnosis of preeclampsia is difficult both clinically and from a research perspective. Preeclampsia exists on a spectrum and lacks a gold standard biomarker. Our study also spans a period of time when the diagnostic criteria were in flux. Some subset of women diagnosed with PE prior to 2002 may now be considered to only have had gestational hypertension if they met the relative increase in blood pressure criteria but did not exceed the current threshold of a blood pressure of 140/90. Although our PE case definition is heterogeneous, our ability to exclude women with preexisting hypertension was a strength. Our validation study supported our initial findings for *LTA/TNF* with conflicting results for *TBX21/TBKBP1*. Admittedly, heterogeneity still exists within our case definition, however, and future studies will need to improve case ascertainment.

This study was limited by the lack of fetal DNA, which is an important genetic factor in both of these reproductive outcomes. While examination of fetal DNA may have identified additional important

pathways or highlighted interactions with maternal DNA, the results of this study support population based studies that identify an independent role of maternal genes in these outcomes. Although we incorporated genetic variation in up and downstream regions, our pre-specified boundaries may be too narrow to capture long range regulatory elements.[245] 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 biology underpinning preeclampsia and SGA although verification in an independent population is needed.

In summary, this study expanded coverage of known candidate inflammatory genes and examined novel cell cycle and natural kill cell genes while carefully addressing population stratification. The results of this study reveal important differences in the genetic underpinnings of term SGA and preeclampsia in European and African Americans while also finding that there may be pathways in common. Novel associations between *KLRD1* and term SGA and *TBKBP1* and preeclampsia need further exploration with more dense tagging of polymorphisms within *TBKBP1* and consideration of HLA-E haplotypes for *KLRD1*. Associations for *IL6* and *TNF/LTA* in the face of previous null results, highlight the difficulty in studying these important outcomes that have both phenotypic complexity and multiple environmental and social risk factors that are likely interacting with biologic pathways.

Table 4.4 Paper #2 Demographic characteristics of small for gestational age (SGA) cases and controls

	SGA Cases		Disease Free		Non-SGA Controls[a]	
Genetic Ancestry[b]	European American N=117	African American N=92	European American N=409	African American N=204	European American N=890	African American N=499
Maternal Age						
<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)
Muliparous	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 (SD)	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)
Term SGA	96 (82.1)	64 (69.6)	0	0	0	0
Gestational HTN	19 (17.0)	14 (16.9)	0	0	226 (27.2)	131 (28.5)
Preeclampsia	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)

a. Non-SGA controls include non-SGA births with other outcomes of interest: preterm birth (PTB), gestational hypertension (GHTN) and preeclampsia (PE).

b. Genetic ancestry determined using 148 AIMs and STRUCTURE.

c. Self-reported smoking during months 1-6 of pregnancy.

d. Pre-pregnancy BMI calculated from self-reported pre-pregnancy weight and measured height.

Table 4.5 Paper #2 Demographic characteristics of gestational hypertension (GHTN) and preeclampsia (PE) cases and controls

	GHTN Case		PE Case		Non Case[a]		GHTN Control[b]		PE Control[b]	
Genetic Ancestry[c]	European American N=245	African American N=145	European American N=93	African American N=72	European American N=394	African American N=190	European American N=699	African American N=397	European American N=851	African American N=470
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 (14.3)	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)
Muliparous	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)

a. Non case controls are uncomplicated term births without preexisting hypertension used in Stage 2 for both outcomes. b. GHTN and PE controls include pregnancies with SGA and Preterm Birth, but exclude those with pre-existing hypertension. GHTN controls further exclude women with PE. c. Genetic ancestry determined using 148 AIMs and STRUCTURE. d. Self-reported smoking during months 1-6 of pregnancy. e. Pre-pregnancy BMI calculated from self-reported pre-pregnancy weight and measured height.

Table 4.6 Paper #2 Q[a] values from SKAT analysis for each SNP-set stratified by genetic ancestry

	European American[b]		African American[b]		European American		African American	
Pathway/Gene	SGA	Term SGA	SGA	Term SGA	GHTN	PE	GHTN	PE
TH1								
TBX21*	1.00	1.00	0.87	0.83	0.84	0.05	0.83	0.99
IFNGR2	0.84	1.00	1.00	1.00	0.80	0.39	0.84	0.81
IL12A	0.84	0.91	0.87	0.83	0.80	0.39	0.83	0.99
IL18	0.84	1.00	0.87	0.83	0.80	0.81	0.83	0.81
CSF2	0.84	1.00	0.87	0.83	0.80	0.91	0.84	1.00
IL12B	0.84	1.00	0.87	0.83	0.35	0.91	0.83	1.00
IL2	0.84	1.00	0.87	0.83	0.35	0.91	0.83	0.81
IFNG	1.00	1.00	0.88	1.00	0.80	1.00	0.84	0.81
Inflammatory Mediators								
LTA&TNF*	0.84	0.91	1.00	1.00	0.58	0.05	0.83	0.81
IL6*	0.84	1.00	0.87	0.17	0.58	0.91	0.83	0.99
NFKB1	0.84	0.91	0.89	0.83	0.80	0.81	0.84	1.00
TNFRSF1B	0.84	0.91	0.87	0.83	0.98	0.91	0.83	0.81
IL6R	0.84	0.91	0.87	0.83	0.58	0.91	0.83	0.81
Natural Killer Cell								
KLRD1*	0.84	0.91	0.87	0.17	0.83	0.91	1.00	1.00
IL15	0.84	1.00	0.87	0.83	0.80	0.53	0.83	0.81
KIR3DL2	0.84	1.00	0.87	0.84	0.92	0.81	0.83	0.81
KIR2DL4	0.84	1.00	0.87	0.87	0.53	0.91	0.83	0.81
KIR3DL3	0.84	1.00	0.94	1.00	0.62	0.91	0.83	0.81
TH2								
IL13&IL4	0.84	1.00	0.87	0.87	0.58	0.81	0.83	0.81
GATA3	0.84	1.00	0.87	0.83	0.84	1.00	0.83	0.81
Anti-Inflammatory								
IL10	0.84	1.00	0.87	0.83	0.35	0.91	0.83	0.81
Chemokine								
IL8	0.84	0.91	0.87	0.83	0.62	0.91	0.83	0.81
IL8RB	0.84	0.91	0.87	0.83	1.00	0.91	0.83	0.81
CXCL10	0.84	1.00	0.87	0.83	0.80	0.91	0.84	0.81
Cell Cycle								
RASSF1	0.84	1.00	0.79	0.83	0.35	0.23	0.83	0.81
NOV	0.84	1.00	0.87	0.83	0.80	0.81	0.83	0.81
CNNM2	0.84	1.00	0.87	0.83	0.80	0.81	0.83	0.81
GADD45A	0.84	1.00	0.87	0.83	0.80	0.91	0.83	0.88
CDKN2A&CDKN2B	0.84	1.00	0.87	0.83	0.80	0.91	0.84	0.81
CCND1	0.84	1.00	0.87	0.83	1.00	0.91	0.83	0.81
CCNA2	1.00	1.00	0.87	0.83	1.00	1.00	0.83	1.00

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

*Meets FDR <0.20 for at least one outcome

Abbreviations: SGA small for gestational age, GHTN gestational hypertension, PE preeclampsia

Table 4.7 Paper #2 Single SNP associations, risk ratio and 95% confidence interval for maternal SNPs for SGA and Term SGA in infants stratified by maternal genetic ancestry

	African American[a]		European American[a]	
Gene/SNP	SGA	Term SGA	SGA	Term SGA
IL6[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)
KLRD1				
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)

a Genetic ancestry determined from 148 AIMS and STRUCTURE

b Selected results for *IL6* presented. Results from all SNPs available in Supplemental Table 2

c Additive model presented

Table 4.8 Paper #2 Single SNP associations, risk ratio and 95% confidence interval for maternal SNPs and Preeclampsia stratified by genetic ancestry

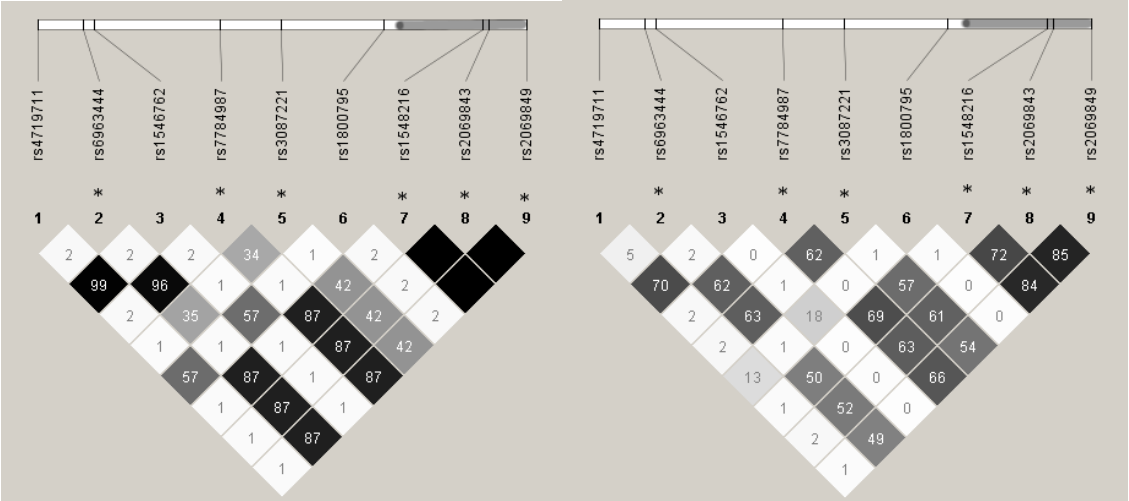
Gene/SNP	European American[a]	African American[a]
NFKBIL1		
rs2857605	1.1 (0.7, 1.6)	1.0 (0.5, 1.9)
rs2239707	1.0 (0.6, 1.5)	1.4 (0.8, 2.4)
rs2230365	1.0 (0.6, 1.5)	1.5 (0.8, 3.0)
rs3130062	1.2 (0.7, 2.1)	1.7 (0.5, 5.4)
rs4947324	0.6 (0.3, 1.1)	0.9 (0.5, 1.7)
rs2857709	1.0 (0.6, 1.6)	0.8 (0.3, 1.9)
LTA		
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)
TNF		
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)
TBKBP1		
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)
TBX21		
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)

a Genetic ancestry determined from 148 AIMS and STRUCTURE

b Additive model presented

Figure 4.5 Linkage disequilibrium (r^2) in *IL6* stratified by genetic ancestry

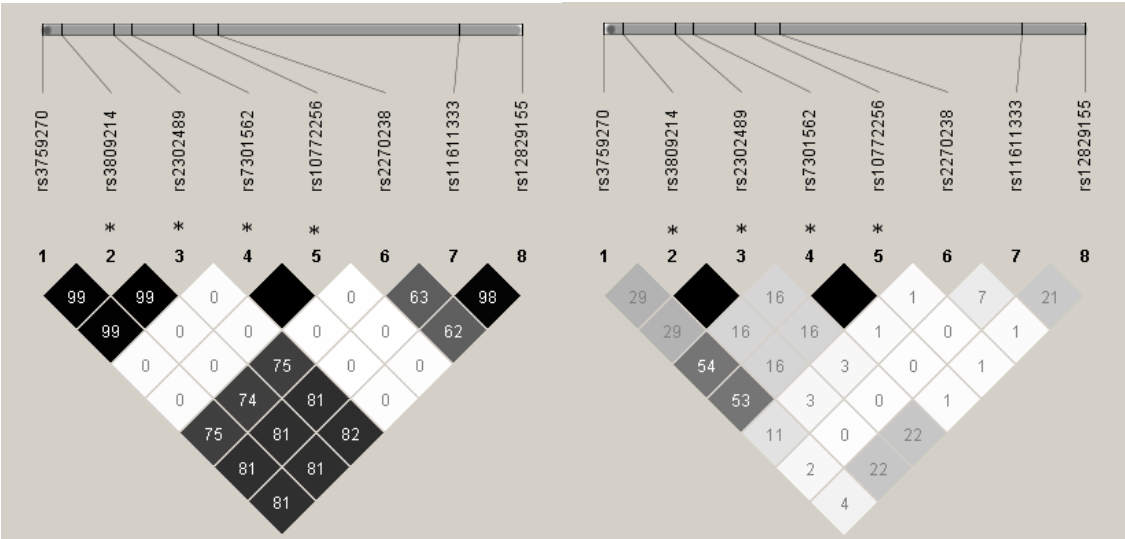
European American **African American**



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.

Figure 4.6 Linkage disequilibrium (r^2) in KLRD1 stratified by genetic ancestry

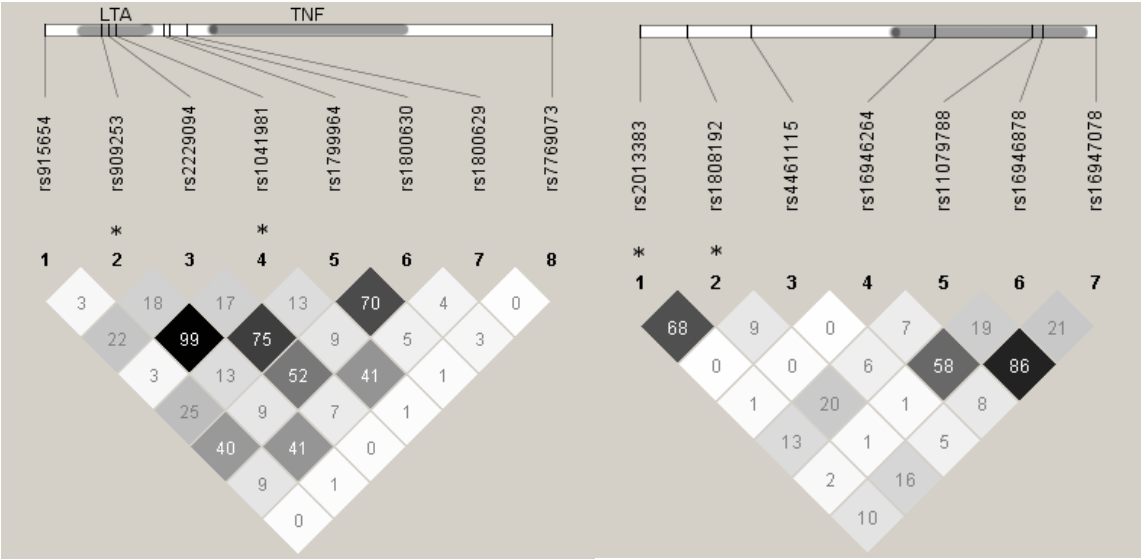
European American **African American**



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.

Figure 4.7 Linkage disequilibrium (r^2) among European Americans in *LTA*, *TNF* and *TBX21*

LTA* and *TNF ***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.

Additional results

Results for cell cycle SNPs and the outcome of preterm birth and spontaneous preterm birth were null and were not reported in Paper #1. The full results for these SNPs can be found in Table S20.

CHAPTER 5 DISCUSSION

Summary of results

This was an ambitious project that considered 40 genes and three distinct yet related reproductive outcomes. At the core, the specific aims were to evaluate the associations between inflammatory and cell cycle genes and the outcomes of Preterm Birth, Poor Fetal Growth, Gestational Hypertension and Preeclampsia.

Cell cycle genes were identified as candidates given the rapid placental and fetal growth that occurs during pregnancy and the observed association between these genes and the related outcomes of cardiovascular disease and metabolic syndrome. No gene level associations were seen for any of the cell cycle genes and any of the outcomes. Single SNP results were intriguing for CDKN2A/2B with a few SNPs showing strong associations with preterm and preeclampsia for European American women. A number of SNPs in CNNM2 showed strong associations with all outcomes for both European and African Americans. Although follow-up on CDKN2A/2B and CNNM2 may be warranted in larger populations, cell cycle genes as a whole show little promise as causative genes.

There were more interesting results in the inflammatory genes. For preterm and spontaneous preterm, genes involved in natural killer cell function (*IL12A, CSF2, KIR3DL2* and *IFNGR2*) and the Th2 cytokines *IL13* and *IL4* showed associations with preterm birth. Although gene level associations were seen for European American women only, single SNP associations revealed similar, if less precise, associations for African Americans for *IL12A* and *CSF2*. The genes identified with preterm birth highlight the important role of NK cells during pregnancy and warrant further investigation. In addition, tagSNPs for *IL13*, *IL4* and *CSF2* were closely associated with long range regulatory regions on chromosome 5. These regulatory regions have the potential to influence additional cytokines (IL3 and IL5) and should be further investigated with fine mapping.

For SGA, gene level associations were seen only for term SGA among African Americans for *IL6* and *KLRD1*. Single SNP results suggest a similar but weaker association for *IL6* and Term SGA among European Americans as well. *IL6* may be involved in early placentation and is known to decrease in concentration over the course of normal pregnancy. Its role in poor fetal growth appears to be independent of a pathway through prematurity and may involve poor placental development. *KLRD1* has not been explored before with SGA and showed essentially null results for European Americans. *KLRD1* is involved in the mitigation of maternal rejection of fetal trophoblasts during early gestation and may influence fetal growth through inadequate placental invasion or function.

Results for hypertensive disorders of pregnancy were isolated to the most refined phenotype of preeclampsia without evidence of chronic hypertension. The inflammatory cytokines *LTA* and *TNF* were associated with preeclampsia for European American women only. These cytokines play multiple roles in early placentation and in maternal response to hypoxia. In addition tagSNPs meant to capture variation in *TBX21* instead identified an association with *TBKBP1,* a gene involved in TNF signaling and interferon

production. *TNF*, *LTA* and *TBKBP1* warrant further investigation with careful attention to both genetic ancestry and phenotype definition.

We found associations in genes (*TNF, IL13, IL6*) that had previous null findings for these same outcomes. While this may point to spurious findings, it may also be a result of the methods used in this analysis. By focusing on the gene-level in a stratified analysis, we were able to assess related SNPs across the length of the gene with both risk and protective associations contributing to the overall association of the gene. In the single SNP analysis, the use of log-linear risk models protected us from overestimating the association for the more common outcomes (Preterm birth and Gestational Hypertension both exceeded 10% in the underlying cohort). Use of inverse probability weighting allowed the use of the entire genotyped cohort, while use of the more conservative robust variance estimator mitigates over interpretation of the results. In comparison to other studies, we also used more tagSNPs for many of the genes capturing more of the genetic variation present in each gene.

Heterogeneity by genetic ancestry

One of the more intriguing results was the heterogeneity of results between ancestry groups. Our lower power among African Americans could explain some of the observed differences. In fact, the similarity of single SNP associations for *IL12A* and *CSF2* support the hypothesis that low power was a factor in not identifying an association between these genes and preterm birth in African Americans. However the same argument cannot be made for gene-level associations with term SGA among African Americans, particularly for *KLRD1*. We had more power to detect an association among European Americans and yet the single SNP results were null. Although differences in the genetic structure of *KLRD1* and its biologic interaction with HLA-E may explain the differences between African and

European Americans for this gene, growing evidence suggests that there are true differences in the genetic and biological pathways leading to these reproductive outcomes.

Previous work by Menon and Velez has suggested that not only do the pathways responsible for preterm birth differ between US Whites and African Americans, but that the actual function and response of critical cytokines (TNF and its receptors) may vary by self-reported race.[97] This biological diversity based on race leads to two important questions; 1. Is it credible that genetically based causal pathways vary by race? 2. What are the implications for future genetic and general epidemiologic studies of these outcomes?

It is generally accepted that allele frequencies vary by genetic ancestry due to differences in the underlying genetic structure based on human migration patterns, genetic recombination and population admixture. These differences are generally thought to impact studies through population stratification (confounding) and the possibility that linkage between tagSNPs and causal SNP may differ in populations with different genetic ancestry. The results of this and other studies of reproductive outcomes however, suggest that not only is the genetic structure different, but that the biologic pathways that result in these reproductive outcomes may vary by genetic ancestry.

Are reproductive outcomes so different from other outcomes that evolutionary pressure has resulted in different causative genes based on genetic ancestry? Reproductive outcomes differ from diseases with later onset in two important ways. There is strong selective pressure on genetic variants that favor conception and fetal survival regardless of potential negative side effects of these variants that emerge past reproductive age. Additionally, selection acts on both the fetus and the mother, although their interests may not always be congruent. From an evolutionary perspective, an individual's

goal is to reproduce and to have their biological progeny reproduce. The optimal result, for both mother and fetus, is a live born infant with a mother that survives delivery. In an evolutionary context a small, but live born, infant is a good outcome whereas a large infant that results in an obstructed labor and maternal death is a very bad outcome. Maternal and fetal death is a genetic dead end. A small infant with a living mother allows for future pregnancies and, despite increased perinatal mortality and morbidity, the infant's genes have the potential to continue. The reproductive outcomes investigated here all result in smaller infants, and as such may have been the result of selective pressures acting on fetal growth to enhance infant and maternal survival.

Maternal and fetal interests (from an evolutionary perspective) may not always be congruent during pregnancy, and this results in a maternal-fetal conflict.[233] The mother balances her expenditures for the current pregnancy with her need to have sufficient reserve for potential future pregnancies. The fetus however is concerned primarily with being born alive. Under this hypothesis of maternal-fetal conflict, both mother and fetus must have a biological "escape hatch" that allows the pregnancy to respond to varying exposures during gestation that may make continuation of the pregnancy less desirable for the fetus or the mother. How the mother and fetus respond to environmental exposures will vary based on the timing of the exposure during gestation, the severity of the exposure and the type of exposure. Early miscarriage, poor fetal growth and preterm birth are all examples of an "escape hatch" outcome where there is early pregnancy termination or a reduced investment in the pregnancy.

If both maternal and fetal pathways exist to influence the success and timing of delivery, why would these vary by genetic ancestry? These pathways evolved in response to specific environmental and pathogenic conditions that vary by geographic region. Malaria provides an example of a geographically isolated selective pressure that influences selection of specific polymorphisms. Maternal

malaria can have devastating results for both the fetus and the mother.[234, 246] A study in Tanzania showed that during the rainy season when malaria was most prevalent, infants were more likely to be born with a specific *FLT1* haplotype. In a non-malaria pregnancy the FLT1 haplotype is associated with fetal growth and maternal polymorphisms in FLT1 are associated with preeclampsia. Taken to the scale of the entire human population over the length of human evolution, specific geographic exposures (infection, nutritional, climactic) may have influenced the specific genetic variants that allow mothers and fetuses to negotiate the maternal-fetal conflict. While malaria exposure in specific regions of African may have promoted pathways which function through angiogenesis, exposures in other regions may have promoted immunologic or coagulation pathways.

The hypothesis that different biological pathways are acting during pregnancy can also be explored by examining differences in gene expression during pregnancy and in response to infection. Menon[113] examined cytokine levels and the response of *TNF* and its receptors in the amniotic fluid of African American and White women at the time of delivery. In addition to finding an excess of minor allele frequency differences, Menon also found that regulation of TNF-α levels varied by self-reported race and that cytokine response to signs of intrauterine infection also varied by race. Although the selective pressure that acted to influence the allelic frequency of variants in these genes cannot be discerned, there do seem to be important differences in the regulation and response of this important cytokine during pregnancy based on self-reported race.

While this study does not provide conclusive evidence that that the pathways underlying these reproductive outcomes vary by race, it does provide support to this hypothesis. If there are differences in the genetic underpinnings and biological pathways of reproductive outcomes based on genetic ancestry, what are the implications for the study of these outcomes? The conclusion should not be that

since these outcomes are genetically influenced that there is no way of modifying the outcome. The conclusion also should not be that observed disparities are based in biology and therefore should be accepted as inevitable. Although the exposures which gave rise to the underlying pathways may no longer be relevant-- malaria is no longer a threat to African Americans in the United States-- the underlying biologic pathways are still responsive to contemporary exposures. The underlying pathways evolved in response to environmental and pathogenic exposures and it is through identification and control of these exposures that we will be able to reduce the prevalence of these outcomes.

If the underlying pathways are in fact different, this has important implications for how we study these outcomes. Instead of treating race as a confounder, studies should be stratified and exposure-outcome relationships should be examined within the specific population of interest. Genetic associations with preterm birth from a Chilean population may not be relevant to a Polish population. Given the importance of interactions with exposures, there must also be increased attention to gene by environment interactions with studies that have adequate power and exposure assessment to consider interactions.

This study did not have the power to explore interactions between women with specific genetic susceptibility and measured exposures. However, interactions which would be relevant in this evolutionary context would include exposures which could be interpreted by the body as a threat to mother or child. These exposures would include infections (especially ones such as influenza which historically have a high mortality rate), malnutrition or an abrupt decline in nutrition or extreme psychosocial stress. Additionally, exposures which vary by self-reported race could have potential interactions including poor air quality, chronic stress from poverty and racism, poor nutritional quality, and toxic exposures related to urban environments or poor housing.

In non-genetic studies the possibility of differing biology would also translate into studies stratified by self-reported race so that exposures that are only relevant in a subset of susceptible individuals can be identified. While stratified studies will require increased enrollment of the populations of interest, and will therefore require additional funding, we will miss the opportunity to identify important exposures if all mothers are assumed to be equally susceptible to every exposure. Preterm birth and preeclampsia are important outcomes, and while we have improved our ability to treat women and infants, we have failed to identify successful interventions to reduce the initial incidence of these outcomes. A study of the scale of the National Children's Study would provide a wonderful opportunity to study these outcomes in adequately sized populations. The threated long term viability of the National Children's Study is a great loss. More studies in US populations need to be designed with the scale to address these issues.

Future approaches

To date there have been a number of candidate gene studies for these outcomes, although replication and consistent findings have been elusive. Despite evidence of a genetic component for all of these outcomes, candidate gene studies on their own do not appear to be providing the answers. Further attention to stratification by ancestry, larger case groups, and the exploration of gene by environment interactions may provide more insight in future candidate gene studies. However more advanced methodological approaches are also worth pursuing.

Given the complexity of the underlying pathways, GWAS may reveal associations beyond the usual suspects of candidate genes. Findings in this study of associations in intergenic regions, which may correspond to regulatory regions, argue for GWAS studies that focus on the entire genome and not

panels restricted to exonic regions. GWAS studies however will require even larger case groups to have adequate power. Additionally, due to underlying differences in both genetic architecture and biologic pathways, GWAS panels should be designed to specifically capture the diversity of the genome in US African Americans. GWAS studies should specifically enroll sufficient African American cases to assess associations in this population.

Epigenetic associations may also be important consideration in these outcomes. The activation of specific pathways that allow for maternal and fetal adaptation throughout the course of gestation may function through epigenetic changes. Differential methylation of the fetal genome at the time of implantation and over the course of early embryonic life may be a critical window when environmental exposures act to enhance or silence specific biologic functions. Epigenetic studies of these outcomes are more difficult due to the need for larger case groups, access to both maternal and fetal genetic material and the question of tissue specific methylation.

Mitochondria are also a potential source of genetic variation that maybe implicated in these outcomes. Mitochondria are only present in the maternal ovum and are inherited exclusively through the maternal line. A population based study[13] showed an increased risk of preterm birth among maternal but not paternal half-sisters, suggesting that mitochondrial genes may be involved. Given the diversity of mitochondria within cells and the differences in mitochondrial genetics between target tissues, studies of mitochondrial genetics and reproductive outcomes may be limited by difficulty ascertaining and obtaining the target tissue (placenta, placental bed, fetal blood, amniotic fluid).

Public Health Implications

While research into preterm birth and preeclampsia in particular has been active for decades, our understanding of the underlying biological pathways remains limited. Although we have improved our ability to delay some preterm deliveries and care for infants born preterm, small or after a pregnancy complicated by preeclampsia, we have relatively few clinical interventions to accurately predict risk or prevent these outcomes. One of the hurdles to identification of effective interventions, or preventive strategies, is the heterogeneous phenotype captured by our relatively crude clinical definitions of these outcomes. Heterogeneous phenotypes may represent multiple causal pathways which cannot be discerned when considered as a group. We are further limited in our ability to identify modifiable risk factors when susceptibility to specific exposures varies among specific target populations.

Genetic studies such as this help clarify phenotype and provide additional information to identify susceptible populations. Despite smaller case groups, gene level associations were found for the more distinct phenotypes of Term SGA and Preeclampsia suggesting that these outcomes are distinct from the more general SGA or Gestational Hypertension. On the other hand, spontaneous preterm birth did not improve the detection of associations, suggesting that either this outcome remains heterogeneous or that phenotypic distinction based on precipitating cause may be less etiologically important in preterm birth outcomes.

The identified genes provide novel targets for further mapping, *in vitro* and *in vivo* investigation. Mapping of the regulatory regions identified for *IL13* and *IL4* as well as *CSF2* and *IL3* may provide insight into ways in which these cytokines become dysregulated during pregnancy. *In vitro* work with placental tissue and maternal serum could elucidate the role of these cytokines over the course of pregnancy, during placental implantation and in response to infectious exposures. Measurement of these cytokines

throughout pregnancy is needed to understand the changing concentrations, both absolute and relative to other cytokines, over the duration of both complicated and uncomplicated pregnancies. Further understanding of these genes will possibly identify measurable gene products which can predict risk or identify susceptible subpopulations.

The differences in gene-level associations by genetic ancestry provides additional insight into the identification of susceptible populations. Racial disparity in preterm birth undoubtedly reflects different exposure distributions in US populations as defined by race. However differences in the underlying biological pathways suggest that the search for relevant exposures should be explored within studies stratified by race.

In summary this work provides insight into both phenotype and susceptibility. This knowledge will inform future studies and enhance our ability to find the modifiable risk factors which will allow us to decrease the prevalence of these important outcomes.

APPENDIX: SUPPLEMENTAL TABLES

Table S1: Placental Pathology in PIN 3

	Entire Cohort N=2006		*Eligible N=784*		*Genotyped N =493*	
Pathology	**All**	**Non-case**	**All**	**Non-case**	**All**	**Non-Case**
Fetal Vascular	1269	779	607	365	440	218
Absent	593 (46.7)	379 (48.7)	286 (47.1)	181 (49.6)	208 (47.3)	112 (51.4)
Mild	352 (27.7)	216 (27.7)	168 (27.7)	103 (28.2)	113 (25.7)	55 (25.2)
Mild/Mod	255 (20.1)	155 (19.9)	121 (19.9)	71 (19.5)	92 (20.9)	44 (20.2)
Mod/Severe	65 (5.1)	27 (3.5)	29 (4.8)	9 (2.5)	25 (5.7)	7 (3.2)
Severe	4 (0.3)	2 (0.3)	3 (0.5)	1 (0.3)	2 (0.5)	0
Maternal Vascular	1269	779	607	365	440	218
Absent	212 (16.7)	128 (16.4)	100 (16.5)	57 (15.6)	76 (17.3)	35 (16.1)
Mild	683 (53.8)	450 (57.8)	330 (54.4)	219 (60.0)	221 (50.2)	119 (54.6)
Mild/Mod	307 (24.2)	176 (22.6)	140 (23.1)	75 (20.5)	113 (25.7)	55 (25.2)
Mod/Severe	66 (5.2)	25 (3.2)	37 (6.1)	14 (3.8)	30 (6.8)	9 (4.1)
Severe	1 (0.1)	0	0	0	0	0
Fetal Acute Inflamm	1269	779	607	365	440	218
0	1124 (88.6)	683 (87.7)	540 (89.0)	321 (87.9)	388 (88.2)	188 (86.2)
1	53 (4.2)	41 (5.3)	20 (3.3)	16 (4.4)	15 (3.4)	11 (5.0)
2	54 (4.3)	33 (4.2)	27 (4.4)	17 (4.7)	20 (4.5)	11 (5.0)
3	35 (2.8)	21 (2.7)	18 (3.0)	10 (2.7)	15 (3.4)	7 (3.2)
4	3 (0.2)	1 (0.1)	2 (0.3%)	1 (0.3)	2 (0.5)	1 (0.5)
Mat Acute Inflamm	1269	779	607	365	440	218
0	965 (76.0)	576 (73.9)	451 (74.3)	264 (72.3)	320 (72.7)	153 (70.2)
1	223 (17.6)	152 (19.5)	120 (19.8)	79 (21.6)	89 (20.2)	48 (22.0)
2	59 (4.6)	39 (5.0)	23 (3.8)	15 (4.1)	19 (4.3)	11 (5.0)
3	19 (1.5)	12 (1.5)	13 (2.1)	7 (1.9)	12 (2.7)	6 (2.8)
4	3 (0.2)	0	0	0	0	0
Chronic Inflamm	1272	781	609	367	440	218
No	1037 (81.5)	636 (81.4)	504 (82.8)	307 (83.7)	366 (83.2)	186 (85.3)
Yes	235 (18.5)	145 (18.6)	105 (17.2)	60 (16.3)	74 (16.8)	32 (14.7)

*Cases were also drawn from additional sources and were not required to have a placenta.

Table S2 RS number and minor allele frequency for SNPs in Inflammatory Genes

RS #	Gene Name	MAF* CEU	MAF* YRI	Location	RS #	Gene Name	MAF* CEU	MAF* YRI	Location
rs2069626	CSF2	0.02	0.13	intron	rs12412241	GATA3	0.33	0.26	flanking 3UTR
rs25879	CSF2	0.21	0.31	flanking 5UTR	rs1244186	GATA3	0.25	0.22	3UTR
rs25881	CSF2	0.16	0.25	intron	rs1269486	GATA3	0.28	0.19	flanking 5UTR
rs25882	CSF2	0.19	0.41	coding	rs1399180	GATA3	0.18	0.40	intron
rs25887	CSF2	0.39	0.46	flanking 3UTR	rs1778058	GATA3	0.42	0.38	flanking 3UTR
rs27438	CSF2	0.21	0.38	flanking 3UTR	rs1877739	GATA3	0.23	0.18	flanking 3UTR
rs31474	CSF2	0.20	0.43	flanking 5UTR	rs2275806	GATA3	0.37	0.12	5UTR
rs4705916	CSF2	0.38	0.19	flanking 5UTR	rs2280015	GATA3	0.21	0.17	intron
rs6898270	CSF2	0.43	0.16	flanking 3UTR	rs263419	GATA3	0.17	0.41	flanking 3UTR
rs721121	CSF2	0.47	0.26	flanking 5UTR	rs263423	GATA3	0.23	0.45	flanking 3UTR
rs743564	CSF2	0.43	0.25	intron	rs263425	GATA3	0.00	0.25	flanking 3UTR
rs743677	CSF2	0.00	0.32	intron	rs369421	GATA3	0.18	0.14	intron
rs10031051	CXCL10	0.02	0.10	3UTR	rs376397	GATA3	0.32	0.26	intron
rs10518143	CXCL10	0.20	0.10	flanking 5UTR	rs3781093	GATA3	0.10	0.18	intron
rs12504339	CXCL10	0.25	0.47	flanking 5UTR	rs3781094	GATA3	0.33	0.19	intron
rs12651276	CXCL10	0.17	0.03	flanking 5UTR	rs379568	GATA3	0.09	0.38	flanking 3UTR
rs3733236	CXCL10	0.13	0.26	3UTR	rs388957	GATA3	0.02	0.29	intron
rs4508917	CXCL10	0.23	0.21	flanking 5UTR	rs406103	GATA3	0.23	0.28	intron
rs7670156	CXCL10	0.12	0.47	flanking 5UTR	rs406571	GATA3	0.28	0.43	flanking 3UTR
rs867562	CXCL10	0.16	0.03	flanking 5UTR	rs422628	GATA3	0.21	0.22	intron
rs4302486	CXCL10	0.50	0.39	flanking 3UTR	rs434645	GATA3	0.12	0.18	flanking 3UTR
rs1058240	GATA3	0.17	0.37	3UTR	rs444929	GATA3	0.20	0.21	intron
rs10752126	GATA3	0.39	0.32	intron	rs477461	GATA3	0.15	0.33	flanking 3UTR
rs10795588	GATA3	0.48	0.17	flanking 3UTR	rs528778	GATA3	0.19	0.19	intron
rs10905284	GATA3	0.42	0.09	intron	rs532854	GATA3	0.28	0.38	flanking 3UTR
rs11255509	GATA3	0.00	0.06	3UTR	rs556960	GATA3	0.26	0.13	intron
rs11567934	GATA3	0.00	0.18	intron	rs569421	GATA3	0.19	0.48	intron
rs12262237	GATA3	0.00	0.11	flanking 3UTR	rs570613	GATA3	0.35	0.43	intron
rs578268	GATA3	0.47	0.47	flanking 3UTR	rs10494879	IL10	0.46	0.28	flanking 5UTR

RS #	Gene Name	MAF* CEU	MAF* YRI	Location	RS #	Gene Name	MAF* CEU	MAF* YRI	Location
rs7100967	GATA3	0.00	0.13	flanking 3UTR	rs11119449	IL10	0.35	0.42	flanking 3UTR
rs10878760	IFNG	0.15	0.00	intron	rs11119451	IL10	0.34	0.25	flanking 3UTR
rs11177074	IFNG	0.03	0.18	flanking 3UTR	rs13376708	IL10	0.12	0.33	flanking 3UTR
rs12306852	IFNG	0.20	0.48	flanking 5UTR	rs17015767	IL10	0.21	0.09	flanking 5UTR
rs17104856	IFNG	0.00	0.04	intron	rs1800871	IL10	0.17	0.46	flanking 5UTR
rs1861494	IFNG	0.32	0.21	intron	rs1800872	IL10	0.20	0.48	flanking 5UTR
rs2041864	IFNG	0.39	0.32	flanking 3UTR	rs1800890	IL10	0.38	0.20	flanking 5UTR
rs2069727	IFNG	0.42	0.13	flanking 3UTR	rs1878672	IL10	0.48	0.27	intron
rs2193047	IFNG	0.38	0.48	3UTR	rs3024490	IL10	0.22	0.48	intron
rs2216163	IFNG	0.32	0.08	intron	rs3024491	IL10	0.39	0.27	intron
rs3181032	IFNG	0.00	0.18	flanking 5UTR	rs3024493	IL10	0.17	0.02	intron
rs3181035	IFNG	0.04	0.28	flanking 3UTR	rs3024496	IL10	0.48	0.37	3UTR
rs6581794	IFNG	0.32	0.14	flanking 3UTR	rs4390174	IL10	0.32	0.29	flanking 3UTR
rs7302488	IFNG	0.32	0.13	flanking 5UTR	rs6658896	IL10	0.02	0.18	flanking 3UTR
rs11702844	IFNGR2	0.12	0.00	flanking 5UTR	rs6673928	IL10	0.27	0.12	flanking 3UTR
rs16990664	IFNGR2	0.06	0.33	flanking 5UTR	rs6686931	IL10	0.18	0.39	flanking 5UTR
rs2012075	IFNGR2	0.08	0.09	intron	rs6692511	IL10	0.34	0.26	flanking 3UTR
rs2268241	IFNGR2	0.19	0.42	intron	rs6699203	IL10	0.33	0.25	flanking 3UTR
rs2284556	IFNGR2	0.48	0.19	intron	rs7539748	IL10	0.26	0.00	flanking 3UTR
rs2834210	IFNGR2	0.48	0.28	intron	rs7548373	IL10	0.07	0.25	flanking 3UTR
rs2834212	IFNGR2	0.13	0.00	intron	rs1014486	IL12A	0.30	0.26	flanking 5UTR
rs2834213	IFNGR2	0.25	0.02	intron	rs12492730	IL12A	0.00	0.15	flanking 3UTR
rs6517167	IFNGR2	0.16	0.28	flanking 5UTR	rs13064168	IL12A	0.09	0.08	flanking 5UTR
rs8131980	IFNGR2	0.25	0.12	flanking 3UTR	rs16830946	IL12A	0.00	0.14	flanking 5UTR
rs9808685	IFNGR2	0.46	0.48	intron	rs16830949	IL12A	0.00	0.16	flanking 5UTR
rs9808753	IFNGR2	0.10	0.20	coding	rs17826053	IL12A	0.18	0.20	flanking 3UTR
rs9976971	IFNGR2	0.41	0.05	flanking 5UTR	rs2243115	IL12A	0.08	0.07	flanking 5UTR
rs9978223	IFNGR2	0.19	0.49	flanking 5UTR	rs2243123	IL12A	0.24	0.13	intron
rs9980428	IFNGR2	0.17	0.24	flanking 5UTR	rs2243131	IL12A	0.19	0.17	intron

RS #	Gene Name	MAF* CEU	MAF* YRI	Location	RS #	Gene Name	MAF* CEU	MAF* YRI	Location
rs2243151	IL12A	0.33	0.36	flanking 3UTR	rs2546890	IL12B	0.47	0.29	flanking 5UTR
rs2243154	IL12A	0.13	0.00	flanking 3UTR	rs2546893	IL12B	0.48	0.24	intron
rs2647929	IL12A	0.49	0.20	flanking 5UTR	rs2569253	IL12B	0.48	0.20	intron
rs2886666	IL12A	0.17	0.00	flanking 5UTR	rs2853694	IL12B	0.46	0.27	intron
rs4608735	IL12A	0.07	0.12	flanking 3UTR	rs3212220	IL12B	0.23	0.43	intron
rs4680536	IL12A	0.42	0.28	flanking 3UTR	rs3212227	IL12B	0.23	0.30	3UTR
rs479952	IL12A	0.47	0.40	flanking 5UTR	rs4921466	IL12B	0.06	0.11	flanking 3UTR
rs485497	IL12A	0.46	0.15	flanking 3UTR	rs6868898	IL12B	0.34	0.16	flanking 5UTR
rs503582	IL12A	0.48	0.46	flanking 5UTR	rs7709212	IL12B	0.37	0.24	flanking 5UTR
rs532953	IL12A	0.18	0.12	flanking 5UTR	rs7730126	IL12B	0.23	0.18	flanking 3UTR
rs583911	IL12A	0.48	0.10	intron	rs919766	IL12B	0.08	0.33	intron
rs598638	IL12A	0.22	0.00	flanking 3UTR	rs3091307	IL13	0.22	0.25	flanking 5UTR
rs609907	IL12A	0.27	0.13	flanking 5UTR	rs4621555	IL13	0.00	0.15	flanking 3UTR
rs6441282	IL12A	0.43	0.38	flanking 5UTR	rs7737470	IL13	0.22	0.26	intron
rs692890	IL12A	0.35	0.38	flanking 5UTR	rs1295683	IL13; IL4	0.10	0.08	flanking 3UTR
rs7372767	IL12A	0.49	0.21	flanking 5UTR	rs1295686	IL13; IL4	0.23	0.28	intron
rs755004	IL12A	0.15	0.01	flanking 5UTR	rs1881457	IL13;IL4	0.16	0.30	flanking 5UTR
rs7653097	IL12A	0.05	0.12	flanking 5UTR	rs20541	IL13;IL4	0.23	0.17	coding
rs9811792	IL12A	0.48	0.30	flanking 5UTR	rs2069744	IL13;IL4	0.00	0.31	intron
rs9852519	IL12A	0.36	0.21	flanking 3UTR	rs2243204	IL13;IL4	0.12	0.28	flanking 3UTR
rs10052709	IL12B	0.11	0.20	flanking 5UTR	rs2243210	IL13;IL4	0.10	0.16	flanking 3UTR
rs10072923	IL12B	0.23	0.34	flanking 3UTR	rs2243218	IL13;IL4	0.08	0.33	flanking 3UTR
rs11574790	IL12B	0.08	0.28	intron	rs2243219	IL13;IL4	0.09	0.32	flanking 3UTR
rs1368439	IL12B	0.22	0.03	3UTR	rs848	IL13;IL4	0.24	0.41	3UTR
rs1433048	IL12B	0.18	0.00	intron	rs10519610	IL15	0.21	0.33	intron
rs1549922	IL12B	0.46	0.37	flanking 3UTR	rs10833	IL15	0.40	0.09	3UTR
rs2099327	IL12B	0.23	0.07	flanking 3UTR	rs12498901	IL15	0.20	0.10	intron
rs2195940	IL12B	0.08	0.21	intron	rs12508866	IL15	0.27	0.03	intron
rs12508955	IL15	0.28	0.17	intron	rs5744223	IL18	0.00	0.18	flanking 5UTR

RS #	Gene Name	MAF* CEU	MAF* YRI	Location	RS #	Gene Name	MAF* CEU	MAF* YRI	Location
rs13117878	IL15	0.43	0.49	intron	rs5744238	IL18	0.00	0.13	intron
rs1519551	IL15	0.48	0.47	intron	rs5744280	IL18	0.41	0.35	intron
rs1519552	IL15	0.29	0.36	intron	rs578784	IL18	0.00	0.27	flanking 3UTR
rs1589241	IL15	0.30	0.13	intron	rs17561	IL1A	0.31	0.13	coding
rs17007476	IL15	0.00	0.18	intron	rs1800587	IL1A	0.31	0.44	5UTR
rs17007480	IL15	0.00	0.10	intron	rs1143627	IL1B	0.37	0.36	flanking 5UTR
rs17007503	IL15	0.00	0.14	intron	rs1143634	IL1B	0.29	0.11	coding
rs17007508	IL15	0.00	0.20	intron	rs16944	IL1B	0.35	0.43	flanking 5UTR
rs17007610	IL15	0.42	0.42	intron	rs10027390	IL2	0.31	0.20	flanking 3UTR
rs17364630	IL15	0.20	0.12	intron	rs10034410	IL2	0.00	0.11	flanking 3UTR
rs17461269	IL15	0.29	0.01	intron	rs11932411	IL2	0.00	0.42	flanking 3UTR
rs1907949	IL15	0.09	0.14	intron	rs17454584	IL2	0.18	0.08	flanking 3UTR
rs2087849	IL15	0.28	0.29	intron	rs2069762	IL2	0.29	0.07	flanking 5UTR
rs2857261	IL15	0.42	0.48	intron	rs2069776	IL2	0.31	0.13	flanking 3UTR
rs3775597	IL15	0.15	0.17	intron	rs2069778	IL2	0.19	0.00	intron
rs6837991	IL15	0.30	0.18	intron	rs35914000	IL2	0.34	0.01	flanking 3UTR
rs6850492	IL15	0.49	0.25	intron	rs4833248	IL2	0.11	0.00	flanking 5UTR
rs7671458	IL15	0.21	0.23	intron	rs40401	IL3	0.21	0.30	coding
rs7698675	IL15	0.28	0.23	intron	rs11575022	IL3/CSF2	0.10	0.20	flanking 3UTR
rs11214098	IL18	0.00	0.14	flanking 3UTR	rs168681	IL3; CSF2	0.36	0.23	flanking 3UTR
rs11214105	IL18	0.21	0.19	flanking 5UTR	rs2069801	IL3; CSF2	0.00	0.12	flanking 3UTR
rs1946518	IL18	0.35	0.34	flanking 5UTR	rs246841	IL3; CSF2	0.10	0.01	flanking 3UTR
rs2043055	IL18	0.44	0.50	intron	rs246844	IL3; CSF2	0.17	0.24	flanking 3UTR
rs360714	IL18	0.02	0.10	intron	rs3091335	IL3; CSF2	0.00	0.42	flanking 5UTR
rs4937075	IL18	0.25	0.27	flanking 3UTR	rs31400	IL3; CSF2	0.37	0.46	flanking 5UTR
rs543810	IL18	0.11	0.25	flanking 3UTR	rs31481	IL3; CSF2	0.18	0.20	intron
rs5744222	IL18	0.22	0.00	flanking 5UTR	rs2069842	IL6	0.00	0.04	intron
rs11242122	IL4	0.26	0.33	flanking 3UTR	rs2069843	IL6	0.02	0.18	intron
rs11242123	IL4	0.16	0.49	flanking 3UTR	rs2069845	IL6	0.46	0.30	intron

RS #	Gene Name	MAF* CEU	MAF* YRI	Location	RS #	Gene Name	MAF* CEU	MAF* YRI	Location
rs2243240	IL4	0.01	0.13	flanking 5UTR	rs2069849	IL6	0.06	0.20	coding
rs2243246	IL4	0.00	0.28	flanking 5UTR	rs3087221	IL6	0.01	0.21	flanking 5UTR
rs2243248	IL4	0.09	0.12	flanking 5UTR	rs4719711	IL6	0.43	0.16	flanking 5UTR
rs2243250	IL4	0.10	0.29	flanking 5UTR	rs6949149	IL6	0.05	0.13	flanking 5UTR
rs2243253	IL4	0.00	0.19	intron	rs6954681	IL6	0.12	0.40	flanking 5UTR
rs2243261	IL4	0.00	0.28	intron	rs6954897	IL6	0.31	0.19	flanking 5UTR
rs2243263	IL4	0.11	0.14	intron	rs6963444	IL6	0.02	0.22	flanking 5UTR
rs2243267	IL4	0.17	0.38	intron	rs6969927	IL6	0.20	0.18	flanking 5UTR
rs2243270	IL4	0.17	0.23	intron	rs7776857	IL6	0.43	0.00	flanking 5UTR
rs2243283	IL4	0.00	0.15	intron	rs7784987	IL6	0.02	0.15	flanking 5UTR
rs2243292	IL4	0.00	0.12	flanking 3UTR	rs7805828	IL6	0.38	0.36	flanking 5UTR
rs9282745	IL4	0.00	0.11	intron	rs11265607	IL6R	0.28	0.29	flanking 5UTR
rs10156056	IL6	0.07	0.29	flanking 5UTR	rs11265608	IL6R	0.12	0.09	flanking 5UTR
rs10242595	IL6	0.24	0.49	flanking 3UTR	rs11265610	IL6R	0.00	0.36	intron
rs12700386	IL6	0.23	0.10	flanking 5UTR	rs11265618	IL6R	0.16	0.38	intron
rs1474347	IL6	0.48	0.08	intron	rs11265621	IL6R	0.41	0.29	flanking 3UTR
rs1546762	IL6	0.43	0.11	flanking 5UTR	rs12060250	IL6R	0.00	0.08	intron
rs1548216	IL6	0.00	0.22	intron	rs12083537	IL6R	0.14	0.23	intron
rs1800795	IL6	0.47	0.00	flanking 5UTR	rs12090237	IL6R	0.01	0.10	intron
rs1800797	IL6	0.48	0.00	flanking 5UTR	rs12096944	IL6R	0.00	0.14	intron
rs1880241	IL6	0.43	0.43	flanking 5UTR	rs1386821	IL6R	0.17	0.09	intron
rs2056576	IL6	0.30	0.36	flanking 5UTR	rs1552481	IL6R	0.00	0.25	flanking 5UTR
rs2069824	IL6	0.03	0.12	flanking 5UTR	rs17654071	IL6R	0.45	0.22	flanking 5UTR
rs2069827	IL6	0.11	0.02	flanking 5UTR	rs2054855	IL6R	0.09	0.31	flanking 5UTR
rs2069835	IL6	0.00	0.04	intron	rs2229238	IL6R	0.26	0.21	3UTR
rs2069840	IL6	0.38	0.17	intron	rs1951240	IL8	0.40	0.48	flanking 3UTR
rs4072391	IL6R	0.25	0.34	3UTR	rs1951242	IL8	0.40	0.16	flanking 3UTR
rs4329505	IL6R	0.16	0.47	intron	rs4694634	IL8	0.00	0.35	flanking 5UTR
rs4341355	IL6R	0.29	0.44	intron	rs4694635	IL8	0.00	0.19	flanking 5UTR

RS #	Gene Name	MAF* CEU	MAF* YRI	Location	RS #	Gene Name	MAF* CEU	MAF* YRI	Location
rs4537545	IL6R	0.34	0.31	intron	rs7654490	IL8	0.00	0.25	flanking 5UTR
rs4553185	IL6R	0.49	0.49	intron	rs7658422	IL8	0.00	0.28	flanking 3UTR
rs4601580	IL6R	0.49	0.39	intron	rs7693566	IL8	0.00	0.32	flanking 5UTR
rs4845374	IL6R	0.16	0.31	intron	rs11676348	IL8RB	0.46	0.37	flanking 3UTR
rs4845615	IL6R	0.00	0.16	flanking 5UTR	rs11677534	IL8RB	0.48	0.19	flanking 3UTR
rs4845617	IL6R	0.39	0.37	5UTR	rs4674258	IL8RB	0.48	0.45	flanking 5UTR
rs4845618	IL6R	0.49	0.43	intron	rs4674259	IL8RB	0.48	0.12	5UTR
rs4845623	IL6R	0.35	0.43	intron	rs4674261	IL8RB	0.42	0.37	flanking 3UTR
rs4845626	IL6R	0.16	0.45	intron	rs6761387	IL8RB	0.05	0.25	intron
rs6427627	IL6R	0.40	0.38	flanking 5UTR	rs9797797	KIR2DL3	0.32	0.22	intron
rs6427641	IL6R	0.40	0.27	intron	rs17771961	KIR2DL4	0.18	0.05	flanking 5UTR
rs6684439	IL6R	0.05	0.01	intron	rs35950908	KIR2DL4	0.20	0.06	flanking 3UTR
rs7518199	IL6R	0.35	0.10	intron	rs649216	KIR2DL4	0.48	0.21	flanking 5UTR
rs7526293	IL6R	0.24	0.42	flanking 3UTR	rs10407958	KIR3DL2	0.18	0.20	intron
rs7549250	IL6R	0.49	0.46	intron	rs11672983	KIR3DL2	0.41	0.14	flanking 5UTR
rs10805066	IL8	0.33	0.40	flanking 5UTR	rs1654644	KIR3DL2	0.37	0.33	intron
rs11729759	IL8	0.00	0.24	flanking 3UTR	rs17771967	KIR3DL2	0.41	0.35	flanking 3UTR
rs11730667	IL8	0.39	0.20	flanking 5UTR	rs3745900	KIR3DL2	0.19	0.16	intron
rs12506479	IL8	0.23	0.19	flanking 5UTR	rs3816051	KIR3DL2	0.46	0.30	5UTR
rs13142454	IL8	0.00	0.16	flanking 3UTR	rs4806457	KIR3DL2	0.28	0.29	intron
rs16849893	IL8	0.00	0.20	flanking 5UTR	rs4806585	KIR3DL2	0.16	0.12	intron
rs16849896	IL8	0.00	0.22	flanking 5UTR	rs11671355	KIR3DL3	0.26	0.00	intron
rs16849907	IL8	0.00	0.12	flanking 5UTR	rs11880171	KIR3DL3	0.31	0.34	intron
rs16849928	IL8	0.40	0.42	flanking 5UTR	rs11882659	KIR3DL3	0.36	0.49	intron
rs16849958	IL8	0.41	0.12	flanking 3UTR	rs2256974	TNF	0.15	0.41	intron
rs11883241	KIR3DL3	0.27	0.40	flanking 3UTR	rs7769073	TNF	0.02	0.11	intron
rs12151161	KIR3DL3	0.15	0.34	flanking 5UTR	rs1041981	LTA	0.30	0.48	coding
rs12982080	KIR3DL3	0.36	0.28	flanking 3UTR	rs1799964	LTA;TNF	0.25	0.20	flanking 3UTR
rs12982559	KIR3DL3	0.26	0.15	flanking 3UTR	rs1800629	LTA;TNF	0.17	0.08	flanking 5UTR

RS #	Gene Name	MAF* CEU	MAF* YRI	Location	RS #	Gene Name	MAF* CEU	MAF* YRI	Location
rs1325155	KIR3DL3	0.42	0.31	flanking 5UTR	rs1800630	LTA;TNF	0.21	0.02	flanking 3UTR
rs1325156	KIR3DL3	0.19	0.41	flanking 5UTR	rs2229094	LTA;TNF	0.26	0.29	coding
rs1325158	KIR3DL3	0.30	0.36	flanking 3UTR	rs2230365	LTA;TNF	0.13	0.03	coding
rs16985907	KIR3DL3	0.04	0.15	coding	rs2239707	LTA;TNF	0.37	0.11	intron
rs2296370	KIR3DL3	0.31	0.33	flanking 3UTR	rs2516479	LTA;TNF	0.39	0.28	flanking 3UTR
rs2296371	KIR3DL3	0.32	0.41	flanking 3UTR	rs2857605	LTA;TNF	0.28	0.08	intron
rs270775	KIR3DL3	0.43	0.26	intron	rs2857709	LTA;TNF	0.00	0.05	flanking 3UTR
rs4441391	KIR3DL3	0.23	0.16	flanking 5UTR	rs3130062	LTA;TNF	0.12	0.00	coding
rs6509899	KIR3DL3	0.05	0.20	flanking 3UTR	rs4947324	LTA;TNF	0.09	0.11	flanking 3UTR
rs7249048	KIR3DL3	0.00	0.25	UTR	rs909253	LTA;TNF	0.29	0.45	intron
rs7249176	KIR3DL3	0.15	0.42	intron	rs915654	LTA;TNF	0.35	0.40	flanking 5UTR
rs3809214	KLRD1/CD94	0.35	0.38	5UTR	rs10489113	NFKB1	0.23	0.48	flanking 3UTR
rs7301562	KLRD1/CD94	0.00	0.26	Intron	rs11733293	NFKB1	0.35	0.34	flanking 3UTR
rs10772256	KLRD1/CD94	0.00	0.25	Nonsynon	rs12648696	NFKB1	0.31	0.37	flanking 3UTR
rs11611333	KLRD1/CD94	0.39	0.39	Intron	rs1598861	NFKB1	0.30	0.01	intron
rs12829155	KLRD1/CD94	0.42	0.21	3UTR	rs1599961	NFKB1	0.46	0.41	intron
rs2270238	KLRD1/CD94	0.28	0.00	Intron	rs17032705	NFKB1	0.38	0.33	intron
rs2302489	KLRD1/CD94	0.38	0.37	5UTR	rs17032740	NFKB1	0.00	0.11	intron
rs3759270	KLRD1/CD94	0.35	0.30	5UTR	rs17032779	NFKB1	0.02	0.16	intron
rs7980604	KLRD1/CD94	0.00	0.25	Intron	rs10514934	TBX21	0.13	0.00	intron
rs17032815	NFKB1	0.00	0.13	intron	rs11079788	TBX21	0.23	0.24	intron
rs17033015	NFKB1	0.30	0.10	flanking 3UTR	rs16946264	TBX21	0.07	0.14	intron
rs1801	NFKB1	0.40	0.25	intron	rs16946878	TBX21	0.03	0.11	intron
rs230493	NFKB1	0.36	0.13	intron	rs16947078	TBX21	0.21	0.20	flanking 3UTR
rs230515	NFKB1	0.38	0.06	intron	rs1808192	TBX21	0.35	0.13	flanking 3UTR
rs230529	NFKB1	0.47	0.44	intron	rs2013383	TBX21	0.44	0.17	flanking 3UTR
rs230530	NFKB1	0.36	0.11	intron	rs4461115	TBX21	0.29	0.02	flanking 3UTR
rs230533	NFKB1	0.37	0.16	intron	rs4794067	TBX21	0.27	0.14	flanking 5UTR
rs230547	NFKB1	0.06	0.14	intron	rs9910408	TBX21	0.45	0.28	flanking 5UTR

RS #	Gene Name	MAF* CEU	MAF* YRI	Location	RS #	Gene Name	MAF* CEU	MAF* YRI	Location
rs3755867	NFKB1	0.39	0.33	intron	rs1800471	TGFB1	0.11	0.10	Nonsynon
rs3774933	NFKB1	0.46	0.30	intron	rs11466414	TGFB3	0.06	0.01	5UTR
rs3817685	NFKB1	0.33	0.33	intron	rs4252345	TGFB3	0.00	0.02	Synonymous
rs4648058	NFKB1	0.39	0.30	intron	rs1061622	TNFRSF1B	0.24	0.16	Nonsynon
rs4648090	NFKB1	0.12	0.17	intron	rs1061624	TNFRSF1B	0.48	0.33	3UTR
rs4648110	NFKB1	0.29	0.22	intron	rs1061628	TNFRSF1B	0.38	0.48	3UTR
rs4648127	NFKB1	0.10	0.00	intron	rs1201157	TNFRSF1B	0.43	0.36	Intron
rs4648135	NFKB1	0.08	0.18	intron	rs235214	TNFRSF1B	0.16	0.20	flanking 3UTR
rs4648141	NFKB1	0.20	0.44	intron	rs3766730	TNFRSF1B	0.16	0.00	Intron
rs7674640	NFKB1	0.43	0.29	flanking 3UTR	rs496888	TNFRSF1B	0.34	0.32	Intron
rs909332	NFKB1	0.07	0.10	intron	rs5746051	TNFRSF1B	0.17	0.03	Intron
rs9790601	NFKB1	0.37	0.21	intron	rs5746053	TNFRSF1B	0.18	0.15	Intron
rs980455	NFKB1	0.46	0.47	flanking 5UTR	rs816050	TNFRSF1B	0.20	0.24	Intron

* MAF Source CEU/YRI: Data from Illumina or NCBI when Illumina data was missing. Populations include: PGA University of Washington; Perlgen; HapMap; SNP500 Cancer

Abbreviations: MAF minor allele frequency, CEU Northern and Western European ancestry; YRI Yoruban ancestry; UTR untranslated region.

Table S3 RS number and minor allele frequency for SNPs in Cell Cycle Genes

RS #	Gene Name	MAF CEU	MAF YRI	Location	RS #	Gene Name	MAF CEU	MAF YRI	Location
rs1507994	CCNA2	0.44	0.35	intron	rs2266690	CCNH	0.20	0.05	coding
rs1803183	CCNA2	0.02	0.25	coding	rs10757261	CDKN2A	0.38	0.28	flanking 3UTR
rs2071486	CCNA2	0.33	0.35	intron	rs10757262	CDKN2A	0.12	0.14	intron
rs3217760	CCNA2	0.00	0.13	coding	rs2027938	CDKN2A	0.26	0.25	flanking 3UTR
rs3217770	CCNA2	0.00	0.13	intron	rs2518722	CDKN2A	0.22	0.47	flanking 3UTR
rs3217771	CCNA2	0.31	0.06	intron	rs2811708	CDKN2A	0.25	0.23	intron
rs3217773	CCNA2	0.42	0.17	intron	rs2811720	CDKN2A	0.15	0.40	flanking 3UTR
rs6815050	CCNA2	0.33	0.24	intron	rs3088440	CDKN2A	0.05	0.23	3UTR
rs6825926	CCNA2	0.06	0.48	flanking 5UTR	rs3731239	CDKN2A	0.38	0.00	intron
rs11827026	CCND1	0.05	0.34	flanking 5UTR	rs3731257	CDKN2A	0.27	0.08	flanking 3UTR
rs1192925	CCND1	0.38	0.30	flanking 5UTR	rs4074785	CDKN2A	0.10	0.18	intron
rs12281701	CCND1	0.00	0.28	flanking 5UTR	rs717326	CDKN2A	0.11	0.14	flanking 3UTR
rs1352075	CCND1	0.48	0.22	intron	rs2811711	CDKN2A;CDKN2B	0.14	0.19	intron
rs1982774	CCND1	0.39	0.16	flanking 5UTR	rs3217989	CDKN2A;CDKN2B	0.00	0.33	3UTR
rs2450254	CCND1	0.40	0.36	flanking 5UTR	rs3217992	CDKN2A;CDKN2B	0.46	0.20	3UTR
rs3212860	CCND1	0.00	0.18	flanking 5UTR	rs3217999	CDKN2A;CDKN2B	0.00	0.15	flanking 3UTR
rs3212891	CCND1	0.41	0.49	intron	rs3218002	CDKN2A;CDKN2B	0.09	0.23	flanking 3UTR
rs3212922	CCND1	0.02	0.34	intron	rs3218009	CDKN2A;CDKN2B	0.10	0.00	flanking 3UTR
rs3862792	CCND1	0.07	0.26	coding	rs3218020	CDKN2A;CDKN2B	0.36	0.12	flanking 5UTR
rs3918298	CCND1	0.03	0.30	intron	rs3218022	CDKN2A;CDKN2B	0.00	0.12	flanking 5UTR
rs592483	CCND1	0.38	0.19	flanking 5UTR	rs3731191	CDKN2A;CDKN2B	0.00	0.30	intron
rs603965	CCND1	0.48	0.16	coding	rs3731194	CDKN2A;CDKN2B	0.00	0.11	intron
rs611003	CCND1	0.46	0.30	flanking 5UTR	rs3731204	CDKN2A;CDKN2B	0.15	0.11	intron
rs649392	CCND1	0.38	0.35	intron	rs3731206	CDKN2A;CDKN2B	0.00	0.19	intron
rs655089	CCND1	0.44	0.40	flanking 5UTR	rs1063192	CDKN2B	0.35	0.14	3UTR
rs667515	CCND1	0.35	0.35	flanking 5UTR	rs11191457	CNNM2	0.22	0.08	flanking 3UTR
rs7106515	CCND1	0.00	0.14	flanking 5UTR	rs11191512	CNNM2	0.21	0.16	intron
rs7121246	CCND1	0.00	0.40	flanking 5UTR	rs11191527	CNNM2	0.10	0.03	intron
rs7177	CCND1	0.43	0.15	3UTR	rs11191537	CNNM2	0.13	0.15	intron

RS #	Gene Name	MAF CEU	MAF YRI	Location	RS #	Gene Name	MAF CEU	MAF YRI	Location
rs11191549	CNNM2	0.33	0.24	flanking 3UTR	rs646652	GADD45A	0.24	0.31	flanking 5UTR
rs12264034	CNNM2	0.00	0.48	intron	rs674425	GADD45A	0.18	0.23	flanking 3UTR
rs17787717	CNNM2	0.12	0.00	intron	rs675327	GADD45A	0.24	0.13	flanking 3UTR
rs2296569	CNNM2	0.18	0.00	intron	rs685724	GADD45A	0.31	0.38	flanking 3UTR
rs2297787	CNNM2	0.08	0.33	intron	rs7414246	GADD45A	0.37	0.30	flanking 3UTR
rs4917991	CNNM2	0.22	0.23	intron	rs7546055	GADD45A	0.17	0.47	flanking 3UTR
rs4917995	CNNM2	0.18	0.09	flanking 3UTR	rs769412	MDM2	0.06	0.13	coding
rs6584535	CNNM2	0.22	0.00	intron	rs10505358	NOV	0.03	0.16	flanking 3UTR
rs7087944	CNNM2	0.00	0.13	intron	rs11538929	NOV	0.12	0.02	coding
rs7897654	CNNM2	0.28	0.20	flanking 3UTR	rs11775043	NOV	0.12	0.18	3UTR
rs7902220	CNNM2	0.00	0.10	intron	rs13261466	NOV	0.31	0.01	flanking 5UTR
rs7914558	CNNM2	0.42	0.28	intron	rs1381337	NOV	0.00	0.12	intron
rs10889710	GADD45A	0.47	0.08	flanking 5UTR	rs1461693	NOV	0.15	0.38	flanking 3UTR
rs11583718	GADD45A	0.37	0.39	flanking 3UTR	rs16892531	NOV	0.02	0.19	3UTR
rs12405855	GADD45A	0.13	0.00	flanking 5UTR	rs16892578	NOV	0.02	0.26	flanking 3UTR
rs12408005	GADD45A	0.50	0.07	flanking 3UTR	rs16892586	NOV	0.03	0.21	flanking 3UTR
rs1511686	GADD45A	0.00	0.14	flanking 5UTR	rs1870779	NOV	0.04	0.35	flanking 3UTR
rs2055904	GADD45A	0.01	0.15	flanking 5UTR	rs2071526	NOV	0.17	0.45	flanking 5UTR
rs2815266	GADD45A	0.05	0.19	flanking 5UTR	rs7001184	NOV	0.01	0.17	flanking 3UTR
rs344916	GADD45A	0.18	0.33	flanking 5UTR	rs7014927	NOV	0.17	0.32	intron
rs344934	GADD45A	0.23	0.41	flanking 5UTR	rs7834596	NOV	0.13	0.33	intron
rs3783468	GADD45A	0.42	0.13	intron	rs1989839	RASSF1	0.17	0.33	intron
rs4655749	GADD45A	0.01	0.13	flanking 5UTR	rs2073498	RASSF1	0.16	0.00	UTR
rs532446	GADD45A	0.30	0.38	intron	rs2073499	RASSF1	0.20	0.31	intron
rs598602	GADD45A	0.25	0.15	flanking 3UTR	rs2236947	RASSF1	0.48	0.27	intron
rs604043	GADD45A	0.24	0.19	flanking 5UTR	rs35455589	RASSF1	0.00	0.25	coding
rs607375	GADD45A	0.28	0.48	flanking 3UTR	rs6446203	RASSF1	0.01	0.39	intron
rs624790	GADD45A	0.12	0.38	flanking 5UTR	rs709210	RASSF1	0.33	0.03	coding

Table S4 List of PIN blinds and corresponding PIN ID

Blind	*PIN ID*	*Blind*	*PIN ID*
BLIND_1	10018	BLIND_41	21546
BLIND_2	10370	BLIND_40	21384
BLIND_3	21406	BLIND_42	21588
BLIND_4	10025	BLIND_43	10004
BLIND_5	10439	BLIND_44	10053
BLIND_6	20750	BLIND_45	10082
BLIND_7	10378	BLIND_46	10319
BLIND_8	14359	BLIND_47	10329
BLIND_9	14742	BLIND_48	10448
BLIND_10	14839	BLIND_49	12445
BLIND_11	15095	BLIND_50	12888
BLIND_12	21009	BLIND_51	14183
BLIND_13	10925	BLIND_52	14234
BLIND_14	11655	BLIND_53	20589
BLIND_15	21730	BLIND_54	21323
BLIND_16	14386	BLIND_55	10092
BLIND_17	20568	BLIND_56	21370
BLIND_18	21416	BLIND_57	24269
BLIND_19	21872	BLIND_58	11268
BLIND_20	21910	BLIND_59	11380
BLIND_21	22051	BLIND_60	11416
BLIND_22	22150	dup_22641	22641
BLIND_23	22213	dup_11294	11294
BLIND_24	22379	dup_21365	21365
BLIND_25	10745	dup_23840	23840
BLIND_26	24552	dup_12220	12220
BLIND_27	24803	dup_14971	14971
BLIND_28	11621	dup_14356	14356
BLIND_29	21344	*Inadvertent*	*Duplicates*
BLIND_30	21602	31616_R	31616
BLIND_34	10694	13584A	13584B
BLIND_35	10658		
BLIND_36	10677		
BLIND_37	11004		
BLIND_38	20590		
BLIND_39	21341		

Table S5 Summary of disposition of blinds and corresponding original sample

Set	*ID*	*Blind*	*Action*	*Note*
2	10370	BLIND_2	Take Blind	
3	21406	BLIND_3	Take Blind	
11	15095	BLIND_11	Take Blind	
14	11655	BLIND_14	Take Blind	
21	22051	BLIND_21	Take Blind	
35	10658	BLIND_35	Take Blind	
38	20590	BLIND_38	Take Blind	
44	10053	BLIND_44	Take Blind	
53	20589	BLIND_53	Take Blind	
59	21344	BLIND_29	Take Blind	
60	21602	BLIND_30	Take Blind	
62	11294	Dup_11294	Take Blind	
63	21365	Dup_21365	Take Blind	
64	23840	Dup_23840	Take Blind	
12	21009	BLIND_12	Take Blind	Fill in rs10407958, rs3794400 from original
40	21384	BLIND_40	Keep original	Fill in rs35950908 from Blind
61	22641	Dup_22641	Keep original	Fill in rs17623313, rs4529792 from dup_
65	12220	Dup_12220	Keep original	Fill in rs4879923 from dup_
66	14971	Dup_14971	Keep original	Fill in rs17085265, rs2025804, rs6691346 from dup_
67	14356	Dup_14356	Keep original	Fill in rs17086497, rs1870379, rs2297141, rs2359192, rs3025035 from dup_
90	31616	31616_R	Keep 31616	31616_R had more missing
91	13584A	13584B	Keep 13584B	13584A had more missing

Table S6 Identification of trio members from five Utah families*

Family ID	*Child ID (gender)*	*Paternal ID*	*Maternal ID*
1347	10859 (F)	11881	11882
1362- A#	10860 (M)	11992	11993
1408	10831 (F)	12155	12156
1362- B#	10861 (F)	11994	11995
1341	06991 (F)	06993	06985

*Pedigree information can be found at the Coriell website:
http://ccr.coriell.org/sections/collections/nigms/CEPHFamilies.aspx?PgId=49&coll=GM
Familes 1362-A and 1362-B are two different branches of a single pedigree. The individuals used are unrelated beyond the expected parent/child relation.

Table S7 Trio IDs and plate assignment

Child	*Parent1/ Father*	*Parent2/ Mother*	*Plate*
NA_10859_01E04	NA_11881_01C03	NA_11882_01E07	1
NA_10860_02D01	NA_11992_02B12	NA_11993_19H12	2,19
NA_10831_03B04	NA_12155_03G12	NA_12156_03D01	3
NA_10861_04F09	NA_11994_04B01	NA_11995_04F02	4
NA_06991_05F05	NA_06993_05D10	NA_06985_05B09	5
NA_10861_06F08	NA_11994_06A01	NA_11995_06H06	6
NA_10831_07C10	NA_12155_07D07	NA_12156_07F01	7
NA_10859_08G09	NA_11881_08G06	NA_11882_08D12	8
NA_10860_09D08	NA_11992_09E05	NA_11993_09A07	9
NA_06991_10D06	NA_06993_10F11	NA_06985_10F10	10
NA_10831_11B01	NA_12155_11D10	NA_12156_11B07	11
NA_10860_12A10	NA_11992_12G05	NA_11993_12A02	12
NA_10859_13H02	NA_11881_13B12	NA_11882_13D07	13
NA_10861_14H05	NA_11994_14F02	NA_11995_14B08	14
NA_06991_15D11	NA_06993_15D04	NA_06985_15A01	15
NA_10831_16F02	NA_12155_16E05	NA_12156_16H07	16
NA_10861_17H06	NA_11994_17C11	NA_11995_17B08	17
NA_06991_18E06	NA_06993_18F10	NA_06985_18G01	18
NA_10859_19H02	NA_11881_19G05	NA_11882_19E08	19
NA_10859_20D06	NA_11881_20F10	NA_11882_20F11	20
NA_10831_20H03	NA_12155_20H11	NA_12156_20H12	20

Note: All CEPH samples in this study have the following naming protocol: NA_CoriellID_Plate number, well number.

Table S8 SNPs (N=106) deleted for poor genotyping

rs7548373	**rs9910408**	**rs12982080**
rs1800872	rs10889568	**rs17771967**
rs235214	rs10434	rs4769604
rs6660481	rs4795051	rs674425
rs7177	rs1052576	rs1625895
rs40401	**rs2256974**	rs4309
rs10833	rs3789679	rs3212922
rs3807373	rs4478599	rs4675801
rs857440	rs2072324	**rs2516479**
rs4601580	**rs9282745**	rs1484994
rs16871960	rs2779251	rs734936
rs3900115	rs7575147	rs11653716
rs556960	**rs2069827**	**rs16944**
rs2284556	**rs833057**	**rs4794067**
rs2078486	**rs2243123**	**rs12700386**
rs638889	**rs2216163**	rs4359744
rs3934834	rs13173738	rs11077350
rs6697014	**rs578268**	rs2154381
rs2239680	rs3769823	rs998584
rs9436299	rs3729508	**rs11880171**
rs480568	**rs7980604**	**rs3731714**
rs11223503	rs9436740	**rs9790601**
rs11752276	rs8135345	rs3790433
rs1800682	**rs11882659**	rs4350528
rs31474	**rs11255509**	rs9551462
rs4795050	rs11603042	rs7136446
rs6718026	rs4318	rs4489979
rs7414246	rs4459610	rs2296799
rs13376708	**rs10514934**	**rs7249176**
rs12405556	**rs2243131**	rs6556352
rs7208775	**rs1598861**	rs4902083
rs944725	rs9554311	**rs1589241**
rs7149935	rs7097467	**rs479952**
rs7915610	rs11912889	rs11900753
rs649216	**rs25879**	
rs4806585	rs870300	

Bold are inflammatory genes

Table S9 SNPs excluded for being non-polymorphic

Non-polymorphic in All
KIR3DL3 rs9797797
Non-polymorphic in Europeans
CCND1 rs7106515
IL18 rs11214098
TGFB3 rs4252345

Table S10 PIN participant IDs excluded from analysis (N=48)

<95% genotyping call (N=8)	***Congenital Anomaly (N=24)***
13109	10048
13290	10085
13790	10634
20446	10892
21034	11052
24845	11158
31820	11301
32438	11409
>=5% missing after QC	11554
31905	11845
10760	11907
33354	11954
Unknown Duplicate	12137
21027	12341
Mislabeled Samples	13390
12682	13773
25217	13983
Still births (N=10)	14912
11201	14983
11262	15164
12441	23974
12645	24096
12647	24098
12655	24785
12856	
13174	
15336	
24235	

Table S11 List of AIMS Genotyped (N=156)

rs11223503*	rs12900552	rs2246695	rs6414248
rs13173738*	rs12926237	rs228768	rs645510
rs4350528*	rs12945601	rs2416791	rs6491743
rs4489979*	rs12997060	rs2426515	rs6494466
rs6556352*	rs1303629	rs2451563	rs6535244
rs857440*	rs13080353	rs2488465	rs6666101
rs7575147*	rs13169284	rs2593595	rs6765491
rs11150219†	rs13178470	rs2596793	rs6820509
rs11652805†	rs13261248	rs2660769	rs6937164
rs10028057	rs13318432	rs2687427	rs7021690
rs10041728	rs1335826	rs2777804	rs7086
rs10056388	rs1372115	rs316598	rs710052
rs1011643	rs1372894	rs328744	rs7107482
rs10124991	rs1380014	rs33957	rs7111814
rs10195705	rs1412521	rs344454	rs7134682
rs10202705	rs1415723	rs3755446	rs7161
rs10254729	rs1426654	rs3759171	rs7187359
rs10255169	rs1462309	rs3791896	rs7189172
rs1043809	rs1470608	rs385194	rs735480
rs10806263	rs1477921	rs3861709	rs7424137
rs10842753	rs1490728	rs4143633	rs7512316
rs10908312	rs1508061	rs4149436	rs7689609
rs10952147	rs155409	rs4506877	rs7788641
rs10962612	rs16891982	rs4529792	rs7810554
rs11000419	rs17049450	rs4602918	rs798443
rs1117382	rs17261772	rs4619931	rs8113143
rs1125217	rs17269594	rs4659762	rs833282
rs11264110	rs1733731	rs4789070	rs870272
rs11607932	rs17520733	rs4792105	rs897351
rs11901793	rs1862819	rs4793237	rs9297712
rs12094678	rs1870571	rs4811651	rs9306906
rs12129648	rs1885167	rs4823460	rs9416026
rs1256197	rs1911999	rs4859147	rs9416972
rs1257010	rs1917028	rs4885162	rs9525462
rs12594483	rs1982235	rs4896780	rs9530646
rs12612040	rs1991818	rs4923940	rs9543532
rs12640848	rs2075902	rs503677	rs9806307
rs12676654	rs2184033	rs567357	rs9849733
rs12900262	rs222674	rs6023376	rs9923864

* Failed to genotype

†Out of HWE in one genetic ancestry group

Table S12 Individuals with ambiguous genetic ancestry

PIN ID	*Self Reported Race*	*%YRI*
10803	African American	0.5
11184	African American	0.592
12613	African American	0.587
21370	African American	0.583
24187	African American	0.476
24535	African American	0.492
24578	African American	0.495
24827	African American	0.553
30936	African American	0.477
32257	African American	0.404
21984	African American	0.604
23496	African American	0.61
32875	White	0.394

Table S13 Individuals with discordant self-reported race and genetic ancestry

PIN ID	*Self Reported Race*	*%YRI*
12909	White	0.758
20750	White	0.869
31439	White	0.909
34545	White	0.99
12644	White	0.994
23299	African American	0.002
11513	African American	0.003
34522	African American	0.003
33822	African American	0.006
10863	African American	0.008
12818	African American	0.156
15215	African American	0.253

Table S14 Paper #1 Number of individuals included in each SNP-set for SKAT analysis

	PRETERM		SPONTANEOUS PRETERM	
	European American	African American	European American	African American
Total N	603	338	512	269
GENE	N	N	N	N
CSF2	590	330	503	262
CXCL10	602	336	511	267
GATA3	586	332	497	263
IFNG	585	331	498	264
IFNGR2	597	336	508	268
IL10	600	335	509	266
IL12A	594	317	504	253
IL12B	594	335	504	266
IL13&IL4	583	335	502	267
IL15	580	325	492	261
IL18	603	337	512	268
IL2	601	337	510	268
IL6	599	337	509	268
IL6R	592	329	504	261
IL8	599	311	509	247
IL8RB	603	338	512	269
KIR2DL4	600	335	509	268
KIR3DL2	600	332	509	266
KIR3DL3	584	327	496	259
KLDR1	601	335	511	266
LTA&TNF	580	332	495	264
NFKB1	598	321	507	255
TBX21	602	338	511	269
TNFRSF1B	598	333	507	266

Table S15 Paper #1 Demographics for entire PIN cohort, eligible cohort and genotyped cohort

	All N=5169	*Eligible N=3065*	*Genotyped N=1646*
Self-Reported Race: White	3035 (58.7)	1918 (62.6)	1031 (62.6)
African American	1746 (33.8)	1147 (37.4)	615 (37.4)
Other	387 (7.5)	0	0
Missing race	1	0	0
Age years: Mean (SD)	26.8 (6.2)	26.2 (6.3)	26.1 (6.3)
Smoker[a]	935 (20.8)	657 (23.6)	383 (25.6)
Missing smoking	670	0	152
BMI: Mean (median, IQR)[b]	26.0 (24, 21-29)	25.8 (24, 21-29)	26.5 (24, 21-30)
Missing BMI	364	188	82
Poverty: Mean (median, IQR)	305 (223, 109-476)	284.0 (198, 96-473)	273.0 (179, 95-464)
Missing poverty	741	375	199
Married	2959 (57.4)	1646 (53.7)	868 (52.8)
Single	1843 (35.8)	1199 (39.1)	658 (40.0)
Other	352 (6.8)	218 (7.1)	119 (7.2)
Missing marital	15	2	1
Education: 13+ years	3013 (58.5)	1663 (54.3)	854 (51.9)
Missing Education	19	4	0
First birth	2347 (45.6)	1400 (45.8)	769 (46.8)
Multiparous	2803 (54.4)	1659 (54.2)	873 (53.1)
Missing parity	19	5	4
Preterm	686 (13.5)	377 (12.3)	347
Missing PTB	80	0	0
Preterm Labor (% PTB)	214 (33.9)	120 (35.2)	111 (35.5)
PPROM (% PTB)	127 (20.1)	66 (19.4)	63 (20.1)
Medically Indicated (% PTB)	290 (46.0)	155 (45.5)	139 (44.4)
Missing preterm subtype	137	38	36

a Self-reported smoking during months 1-6 of pregnancy.

b Pre-pregnancy BMI calculated from self-reported pre-pregnancy weight and measured height.

Abbreviations: SD standard deviation, IQR interquartile range, BMI Body Mass index (kg/m^2), PTB Preterm Birth, PPROM preterm prelabor rupture of membranes

Table S16 Paper #1 Risk Ratio and 95% Confidence Interval for all SNPs stratified by genetic ancestry

Gene/SNP[b]	Variant Allele[c]	European American[a]		African American[a]	
		Preterm	Spont. Preterm	Preterm	Spont. Preterm
IL12A					
rs503582	T	1.3 (1.1, 1.7)	1.3 (1.0, 1.7)	1.1 (0.8, 1.4)	1.0 (0.7, 1.4)
rs532953	C	0.8 (0.6, 1.2)	0.9 (0.6, 1.4)	1.2 (0.8, 1.8)	1.2 (0.7, 2.1)
rs7653097	C	1.5 (1.0, 2.1)	1.4 (0.9, 2.3)	1.0 (0.7, 1.4)	0.9 (0.6, 1.5)
rs1014486	G	1.0 (0.8, 1.2)	0.9 (0.7, 1.3)	1.0 (0.8, 1.3)	0.9 (0.6, 1.4)
rs13064168	A	0.6 (0.4, 0.8)	0.7 (0.4, 1.0)	1.1 (0.7, 1.7)	1.3 (0.7, 2.4)
rs609907	C	0.6 (0.5, 0.8)	0.7 (0.5, 1.0)	1.1 (0.8, 1.6)	1.2 (0.7, 2.0)
rs2647929	A	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	1.1 (0.8, 1.6)	1.6 (1.0, 2.4)
rs2886666	T	1.2 (0.9, 1.6)	1.1 (0.8, 1.6)	0.7 (0.3, 1.4)	0.6 (0.2, 1.7)
rs9811792	C	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	1.1 (0.8, 1.4)	1.5 (1.0, 2.2)
rs16830946	G			1.1 (0.7, 1.6)	0.8 (0.4, 1.5)
rs7372767	G	1.1 (0.9, 1.4)	1.1 (0.9, 1.5)	1.3 (0.9, 1.7)	1.7 (1.1, 2.6)
rs6441282	T	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)	0.7 (0.5, 1.0)
rs692890	T	0.7 (0.6, 0.9)	0.7 (0.5, 0.9)	0.8 (0.6, 1.1)	0.7 (0.5, 1.0)
rs755004	T	1.3 (1.0, 1.7)	1.5 (1.1, 2.1)	0.6 (0.3, 1.2)	0.6 (0.2, 1.7)
rs16830949	T	4.1 (1.3, 13.2)	0.0 (0.0, 0.0)	0.8 (0.5, 1.2)	0.9 (0.6, 1.5)
rs2243115	G	1.2 (0.9, 1.7)	1.3 (0.8, 1.9)	1.1 (0.8, 1.6)	0.8 (0.5, 1.5)
rs583911	G	1.0 (0.8, 1.3)	1.0 (0.7, 1.4)	0.9 (0.7, 1.2)	1.2 (0.8, 1.8)
rs2243151	T	1.2 (1.0, 1.5)	1.2 (0.9, 1.7)	1.1 (0.8, 1.4)	1.0 (0.7, 1.5)
rs2243154	A	0.9 (0.6, 1.3)	0.7 (0.4, 1.2)	1.3 (0.6, 2.8)	1.8 (0.7, 4.7)
rs4608735	C	1.3 (0.9, 1.7)	1.3 (0.8, 1.9)	1.2 (0.9, 1.7)	1.0 (0.6, 1.7)
rs17826053	G	0.7 (0.5, 1.0)	0.7 (0.5, 1.1)	1.0 (0.7, 1.4)	0.7 (0.4, 1.2)
rs485497	A	1.1 (0.9, 1.3)	1.0 (0.8, 1.4)	1.0 (0.7, 1.3)	1.2 (0.8, 1.9)
rs4680536	G	1.1 (0.9, 1.4)	1.3 (1.0, 1.7)	1.1 (0.8, 1.4)	1.0 (0.7, 1.4)
rs12492730	G	0.8 (0.2, 3.0)	0.8 (0.1, 5.5)	1.1 (0.8, 1.5)	0.7 (0.4, 1.2)
rs9852519	T	0.9 (0.7, 1.1)	0.8 (0.6, 1.2)	1.0 (0.7, 1.3)	1.2 (0.8, 1.7)
rs598638	T	1.0 (0.8, 1.4)	0.8 (0.5, 1.2)	1.1 (0.5, 2.4)	1.3 (0.5, 3.8)
IFNGR2					
rs6517167	T	1.3 (1.0, 1.7)	1.1 (0.7, 1.6)	1.1 (0.8, 1.4)	0.9 (0.6, 1.3)
rs11702844	G	0.8 (0.6, 1.1)	0.7 (0.5, 1.2)	1.2 (0.6, 2.4)	0.6 (0.2, 2.5)
rs16990664	T	0.7 (0.4, 1.3)	0.6 (0.3, 1.4)	1.1 (0.8, 1.4)	0.9 (0.6, 1.3)
rs9976971	A	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	1.0 (0.6, 1.7)	1.0 (0.5, 2.1)
rs9980428	T	1.2 (0.9, 1.6)	1.3 (1.0, 1.9)	0.8 (0.6, 1.2)	0.8 (0.5, 1.3)
rs9978223	A	0.7 (0.5, 0.9)	0.6 (0.4, 1.0)	1.1 (0.8, 1.4)	1.1 (0.7, 1.5)
rs2268241	A	0.6 (0.5, 0.9)	0.6 (0.3, 0.9)	1.2 (0.9, 1.6)	1.3 (0.9, 1.8)
rs9808685	G	1.3 (1.1, 1.7)	1.3 (1.0, 1.8)	1.0 (0.8, 1.3)	0.9 (0.6, 1.3)
rs2834210	A	1.3 (1.0, 1.6)	1.3 (0.9, 1.7)	1.0 (0.8, 1.4)	0.9 (0.6, 1.3)
rs9808753	G	0.7 (0.5, 1.0)	0.6 (0.4, 1.0)	1.2 (0.9, 1.6)	1.1 (0.7, 1.8)

Gene/SNP[b]	Variant Allele[c]	European American[a]		African American[a]	
		Preterm	Spont. Preterm	Preterm	Spont. Preterm
rs2834212	C	0.9 (0.7, 1.3)	1.1 (0.7, 1.8)	1.0 (0.4, 2.6)	1.7 (0.6, 4.8)
rs2834213	G	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	1.2 (0.7, 2.1)	1.8 (0.9, 3.5)
rs2012075	C	1.0 (0.7, 1.3)	0.9 (0.6, 1.3)	1.0 (0.7, 1.4)	1.1 (0.7, 1.8)
rs8131980	A	1.2 (1.0, 1.6)	1.3 (0.9, 1.7)	1.0 (0.7, 1.5)	0.9 (0.5, 1.6)
KIR3DL2					
rs10407958	A	0.8 (0.5, 1.1)	0.7 (0.4, 1.1)	1.2 (0.8, 1.6)	1.4 (0.9, 2.2)
rs1654644	G	1.2 (1.0, 1.5)	1.2 (0.9, 1.6)	0.9 (0.7, 1.2)	1.1 (0.7, 1.5)
rs4806457	C	1.7 (1.1, 2.7)	1.5 (0.7, 3.1)	1.0 (0.5, 1.8)	0.7 (0.3, 1.7)
rs3745900	T	1.2 (0.9, 1.5)	1.2 (0.9, 1.7)	0.8 (0.6, 1.1)	0.8 (0.6, 1.2)
rs11672983	A	1.3 (1.0, 1.5)	1.3 (1.0, 1.7)	0.8 (0.6, 1.0)	0.9 (0.6, 1.4)
rs3816051	C	1.4 (1.2, 1.7)	1.4 (1.1, 1.9)	0.9 (0.6, 1.1)	0.9 (0.6, 1.3)
IL3					
rs31400	T	1.1 (0.9, 1.3)	1.2 (0.9, 1.6)	1.0 (0.8, 1.3)	1.1 (0.8, 1.6)
rs3091335	G	2.5 (1.1, 5.9)	2.2 (0.5, 8.6)	0.9 (0.7, 1.2)	0.9 (0.6, 1.4)
rs31481	A	1.4 (1.1, 1.8)	1.0 (0.7, 1.5)	1.3 (0.9, 1.8)	1.2 (0.7, 2.0)
rs2069801	G			0.8 (0.5, 1.3)	0.7 (0.4, 1.3)
rs246844	A	1.2 (0.9, 1.5)	0.9 (0.6, 1.3)	1.1 (0.8, 1.6)	1.2 (0.7, 1.9)
rs11575022	C	1.6 (1.1, 2.3)	1.5 (0.9, 2.6)	1.1 (0.7, 1.5)	1.0 (0.6, 1.7)
rs246841	T	1.0 (0.7, 1.5)	0.8 (0.5, 1.4)	1.1 (0.5, 2.3)	1.7 (0.7, 4.0)
rs168681	A	1.0 (0.8, 1.3)	1.1 (0.8, 1.4)	1.1 (0.8, 1.6)	1.3 (0.9, 2.0)
rs721121	G	0.8 (0.7, 1.0)	0.9 (0.7, 1.2)	0.7 (0.5, 1.0)	0.6 (0.4, 0.9)
CSF2					
rs4705916	A	0.8 (0.6, 1.0)	0.8 (0.6, 1.1)	0.7 (0.5, 1.0)	0.6 (0.4, 0.9)
rs743677	G	1.8 (0.4, 7.6)	2.1 (0.3, 14.8)	1.1 (0.7, 1.6)	0.8 (0.4, 1.5)
rs2069626	G	1.2 (0.5, 3.0)	1.5 (0.5, 4.6)	1.1 (0.7, 1.8)	1.3 (0.7, 2.5)
rs743564	G	0.8 (0.6, 1.0)	0.9 (0.6, 1.2)	0.7 (0.5, 1.0)	0.8 (0.5, 1.2)
rs25881	T	1.4 (1.0, 1.8)	1.2 (0.8, 1.7)	1.0 (0.8, 1.4)	0.9 (0.6, 1.4)
rs25882	C	1.3 (1.0, 1.7)	1.1 (0.7, 1.6)	1.1 (0.8, 1.5)	1.0 (0.7, 1.6)
rs27438	A	1.3 (1.0, 1.7)	1.1 (0.8, 1.6)	0.9 (0.7, 1.1)	0.8 (0.6, 1.2)
rs25887	C	1.0 (0.8, 1.3)	1.0 (0.8, 1.4)	1.1 (0.9, 1.5)	1.2 (0.8, 1.7)
rs6898270	T	0.8 (0.6, 1.0)	0.9 (0.6, 1.2)	0.8 (0.6, 1.2)	0.8 (0.5, 1.3)
IL13					
rs7737470	A	1.4 (1.1, 1.8)	1.9 (1.4, 2.5)	1.1 (0.8, 1.4)	1.0 (0.6, 1.5)
rs4621555	C			1.1 (0.8, 1.6)	1.2 (0.7, 1.9)
rs3091307	G	1.4 (1.1, 1.8)	1.9 (1.4, 2.6)	1.0 (0.7, 1.3)	0.9 (0.7, 1.3)
rs1881457	C	1.5 (1.1, 1.9)	1.8 (1.3, 2.5)	1.0 (0.7, 1.3)	1.1 (0.7, 1.8)
rs2069744	T	0.7 (0.2, 3.2)	0.8 (0.1, 5.8)	1.0 (0.7, 1.3)	1.0 (0.7, 1.5)
rs1295686	G	0.8 (0.6, 1.1)	0.7 (0.5, 1.0)	1.1 (0.9, 1.5)	1.2 (0.8, 1.7)
rs20541	T	1.2 (0.9, 1.6)	1.5 (1.1, 2.1)	0.9 (0.6, 1.2)	0.8 (0.5, 1.3)

Gene/SNP[b]	Variant Allele[c]	European American[a]		African American[a]	
		Preterm	Spont. Preterm	Preterm	Spont. Preterm
rs848	T	1.2 (0.9, 1.6)	1.5 (1.0, 2.0)	1.1 (0.8, 1.4)	1.1 (0.8, 1.4)
rs1295683	T	1.3 (0.9, 1.7)	1.5 (1.0, 2.2)	0.8 (0.5, 1.3)	0.7 (0.4, 1.4)
rs2243204	T	1.2 (0.9, 1.8)	1.5 (0.9, 2.3)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs2243210	A	1.0 (0.7, 1.6)	1.3 (0.8, 2.2)	0.8 (0.6, 1.1)	0.8 (0.5, 1.3)
rs2243218	A	1.2 (0.8, 1.7)	1.5 (1.0, 2.3)	1.0 (0.7, 1.3)	1.0 (0.7, 1.5)
rs2243219	G	1.2 (0.9, 1.8)	1.5 (1.0, 2.3)	1.0 (0.8, 1.3)	0.9 (0.7, 1.3)
IL4					
rs2243240	T	3.6 (0.7, 18.7)		1.1 (0.7, 1.9)	0.9 (0.4, 2.1)
rs2243246	C	3.5 (0.7, 18.6)		0.8 (0.6, 1.2)	0.8 (0.4, 1.3)
rs2243248	G	1.0 (0.6, 1.5)	1.2 (0.7, 2.0)	1.2 (0.9, 1.7)	1.3 (0.9, 2.0)
rs2243250	C	0.7 (0.5, 0.9)	0.6 (0.4, 0.9)	1.0 (0.8, 1.4)	1.0 (0.7, 1.5)
rs2243253	T	6.1 (3.6, 10.4)	9.5 (2.9, 31.8)	1.2 (0.8, 1.7)	1.3 (0.8, 2.1)
rs2243261	T	3.5 (0.7, 18.6)		0.9 (0.6, 1.3)	0.8 (0.4, 1.4)
rs2243263	C	1.2 (0.9, 1.7)	1.6 (1.1, 2.3)	1.1 (0.8, 1.5)	1.2 (0.8, 1.9)
rs2243267	C	1.5 (1.1, 2.0)	1.8 (1.2, 2.6)	1.1 (0.8, 1.5)	1.2 (0.8, 1.9)
rs2243270	G	1.4 (1.1, 1.9)	1.7 (1.1, 2.5)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs2243283	G	1.5 (0.6, 4.0)	1.9 (0.5, 7.8)	1.1 (0.7, 1.5)	1.1 (0.6, 1.8)
rs2243292	C	1.2 (0.3, 5.3)	0.0 (0.0, 0.0)	0.9 (0.5, 1.5)	0.6 (0.3, 1.5)
rs11242122	G	0.7 (0.6, 0.9)	0.5 (0.4, 0.7)	1.0 (0.8, 1.3)	0.8 (0.5, 1.2)
rs11242123	T	1.4 (1.0, 1.9)	1.7 (1.2, 2.6)	1.0 (0.8, 1.4)	1.1 (0.7, 1.6)
Single SNPs					
IL1A					
rs17561	T	1.2 (0.9, 1.5)	1.2 (0.9, 1.6)	0.8 (0.6, 1.2)	0.7 (0.5, 1.2)
rs1800587	T	1.2 (0.9, 1.5)	1.2 (0.9, 1.7)	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)
IL1B					
rs1143634	T	1.2 (0.9, 1.5)	1.2 (0.8, 1.6)	0.8 (0.5, 1.1)	0.7 (0.4, 1.2)
rs1143627	T	1.1 (0.8, 1.3)	0.9 (0.7, 1.3)	0.9 (0.7, 1.1)	0.8 (0.6, 1.3)
TGFB3					
rs4252345	G			1.0 (0.5, 2.0)	1.0 (0.4, 2.6)
rs11466414	T	1.2 (0.8, 1.8)	1.3 (0.7, 2.2)	1.1 (0.4, 2.9)	0.4 (0.1, 3.4)
TGFB1					
rs1800471	C	0.7 (0.4, 1.1)	0.4 (0.2, 0.9)	0.8 (0.5, 1.5)	0.6 (0.2, 1.5)
TNFRSF1B					
rs496888	G	1.1 (0.9, 1.3)	1.1 (0.8, 1.5)	0.9 (0.6, 1.1)	0.8 (0.5, 1.2)
rs3766730	T	0.8 (0.6, 1.1)	0.7 (0.5, 1.1)	0.4 (0.1, 0.9)	0.1 (0.0, 1.0)
rs816050	T	1.1 (0.9, 1.5)	1.1 (0.8, 1.6)	0.8 (0.6, 1.1)	0.7 (0.4, 1.1)
rs1201157	T	1.0 (0.8, 1.2)	0.9 (0.7, 1.2)	1.0 (0.7, 1.3)	0.8 (0.5, 1.1)
rs1061622	G	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)	0.9 (0.6, 1.2)	0.7 (0.5, 1.2)
rs5746051	G	0.9 (0.7, 1.2)	0.8 (0.5, 1.2)	0.7 (0.4, 1.3)	0.4 (0.1, 1.2)

Gene/SNP[b]	Variant Allele[c]	European American[a]		African American[a]	
		Preterm	Spont. Preterm	Preterm	Spont. Preterm
rs5746053	A	0.9 (0.7, 1.2)	0.7 (0.5, 1.1)	0.9 (0.6, 1.3)	0.7 (0.4, 1.2)
rs1061624	G	0.9 (0.7, 1.1)	1.0 (0.7, 1.3)	1.0 (0.8, 1.3)	0.9 (0.6, 1.4)
rs1061628	T	1.3 (1.0, 1.6)	1.4 (1.1, 1.8)	0.8 (0.6, 1.1)	0.8 (0.6, 1.3)
IL6R					
rs11265607	G	1.0 (0.8, 1.3)	1.2 (0.9, 1.6)	0.9 (0.7, 1.2)	1.2 (0.8, 1.7)
rs6427627	C	1.0 (0.8, 1.3)	1.2 (0.9, 1.6)	0.9 (0.7, 1.1)	1.0 (0.7, 1.4)
rs11265608	A	1.0 (0.7, 1.4)	1.0 (0.6, 1.6)	0.9 (0.6, 1.4)	0.9 (0.5, 1.6)
rs17654071	G	0.9 (0.7, 1.2)	0.8 (0.6, 1.0)	1.1 (0.8, 1.5)	0.9 (0.6, 1.5)
rs2054855	T	1.1 (0.8, 1.5)	1.4 (0.9, 2.1)	1.1 (0.9, 1.5)	1.1 (0.7, 1.7)
rs4845615	A	0.9 (0.1, 7.0)	2.4 (0.3, 18.5)	0.7 (0.4, 1.2)	0.9 (0.5, 1.6)
rs1552481	G	0.7 (0.1, 5.2)	1.7 (0.2, 12.3)	1.0 (0.7, 1.4)	1.0 (0.6, 1.5)
rs4845617	A	1.0 (0.8, 1.3)	1.2 (0.9, 1.6)	0.8 (0.6, 1.1)	0.9 (0.6, 1.3)
rs6427641	G	1.1 (0.9, 1.3)	1.2 (0.9, 1.6)	0.8 (0.6, 1.0)	0.8 (0.6, 1.2)
rs11265610	C	1.2 (0.3, 5.2)	1.8 (0.3, 13.6)	1.1 (0.8, 1.4)	1.2 (0.8, 1.8)
rs12083537	G	1.0 (0.8, 1.3)	1.1 (0.8, 1.6)	0.9 (0.6, 1.2)	1.0 (0.7, 1.5)
rs1386821	C	1.0 (0.8, 1.3)	1.1 (0.8, 1.6)	0.9 (0.6, 1.4)	0.9 (0.5, 1.7)
rs12090237	A	1.1 (0.5, 2.6)	0.9 (0.3, 3.5)	0.9 (0.6, 1.4)	0.9 (0.5, 1.5)
rs6684439	T	1.0 (0.8, 1.2)	1.1 (0.8, 1.5)	1.0 (0.7, 1.3)	1.0 (0.6, 1.4)
rs12096944	T			1.0 (0.6, 1.6)	0.9 (0.5, 1.9)
rs12060250	G			1.0 (0.6, 1.6)	1.0 (0.5, 1.9)
rs4845618	G	1.1 (0.8, 1.3)	1.0 (0.7, 1.3)	1.0 (0.7, 1.2)	0.9 (0.7, 1.4)
rs7549250	C	1.1 (0.9, 1.4)	1.0 (0.7, 1.3)	0.9 (0.7, 1.2)	0.9 (0.6, 1.4)
rs7518199	C	0.9 (0.7, 1.2)	1.0 (0.8, 1.4)	0.9 (0.7, 1.3)	0.9 (0.6, 1.3)
rs4553185	C	1.1 (0.9, 1.3)	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)	1.0 (0.6, 1.4)
rs4845623	G	0.9 (0.7, 1.2)	1.0 (0.8, 1.4)	1.0 (0.8, 1.4)	1.1 (0.7, 1.7)
rs4537545	T	1.0 (0.8, 1.2)	1.1 (0.8, 1.5)	0.9 (0.7, 1.3)	1.0 (0.7, 1.6)
rs4845626	T	1.0 (0.8, 1.4)	1.1 (0.7, 1.5)	0.9 (0.7, 1.1)	1.0 (0.7, 1.4)
rs4845374	A	1.0 (0.8, 1.3)	1.0 (0.7, 1.5)	1.2 (0.9, 1.7)	1.4 (0.9, 2.1)
rs11265618	T	1.0 (0.8, 1.4)	1.1 (0.7, 1.5)	0.9 (0.7, 1.2)	1.1 (0.8, 1.6)
rs4329505	C	1.0 (0.8, 1.3)	1.0 (0.7, 1.5)	1.2 (0.9, 1.5)	1.3 (0.9, 1.9)
rs4341355	C	1.1 (0.8, 1.4)	1.0 (0.7, 1.4)	1.0 (0.7, 1.2)	1.0 (0.7, 1.4)
rs2229238	T	1.0 (0.8, 1.4)	1.0 (0.7, 1.5)	1.1 (0.8, 1.5)	0.9 (0.6, 1.4)
rs4072391	T	1.0 (0.8, 1.3)	1.1 (0.7, 1.5)	1.1 (0.8, 1.4)	0.9 (0.6, 1.3)
rs11265621	G	1.0 (0.8, 1.3)	1.0 (0.7, 1.4)	1.1 (0.9, 1.5)	1.1 (0.7, 1.6)
rs7526293	T	1.0 (0.8, 1.3)	1.0 (0.7, 1.5)	1.0 (0.8, 1.3)	0.9 (0.7, 1.3)
IL10					
rs7539748	A	1.0 (0.8, 1.3)	1.1 (0.8, 1.5)	1.5 (0.9, 2.7)	2.0 (0.9, 4.2)
rs11119451	C	1.2 (0.9, 1.5)	1.1 (0.8, 1.5)	1.0 (0.8, 1.4)	1.1 (0.7, 1.6)
rs6658896	T	0.6 (0.2, 1.4)		0.9 (0.6, 1.4)	0.7 (0.3, 1.3)

Gene/SNP[b]	Variant Allele[c]	European American[a]		African American[a]	
		Preterm	Spont. Preterm	Preterm	Spont. Preterm
rs6692511	T	0.9 (0.7, 1.2)	1.0 (0.8, 1.4)	1.1 (0.8, 1.5)	1.0 (0.6, 1.6)
rs6699203	A	0.9 (0.8, 1.2)	1.0 (0.8, 1.4)	1.1 (0.8, 1.5)	1.1 (0.7, 1.7)
rs4390174	G	1.0 (0.8, 1.2)	0.8 (0.6, 1.0)	1.1 (0.9, 1.5)	1.1 (0.8, 1.7)
rs6673928	T	1.1 (0.9, 1.4)	1.1 (0.9, 1.5)	1.1 (0.8, 1.6)	1.5 (0.9, 2.4)
rs3024496	C	1.1 (0.9, 1.4)	1.2 (0.9, 1.6)	1.1 (0.9, 1.4)	1.2 (0.8, 1.7)
rs1878672	G	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)	1.0 (0.8, 1.4)	1.1 (0.7, 1.6)
rs3024493	T	1.1 (0.9, 1.5)	1.1 (0.7, 1.6)	0.9 (0.4, 2.0)	0.5 (0.1, 2.2)
rs3024491	T	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)	1.0 (0.8, 1.4)	1.1 (0.7, 1.6)
rs3024490	T	0.9 (0.7, 1.1)	0.8 (0.6, 1.2)	0.8 (0.6, 1.1)	0.8 (0.5, 1.1)
rs1800871	T	0.9 (0.7, 1.1)	0.8 (0.6, 1.2)	0.8 (0.6, 1.1)	0.7 (0.5, 1.1)
rs1800890	A	1.2 (0.9, 1.4)	1.1 (0.9, 1.5)	1.1 (0.8, 1.4)	1.2 (0.8, 1.8)
rs17015767	C	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	1.2 (0.8, 1.7)	1.6 (1.0, 2.6)
rs10494879	G	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	1.1 (0.9, 1.5)	1.4 (1.0, 1.9)
rs6686931	T	0.8 (0.6, 1.1)	0.8 (0.5, 1.1)	0.8 (0.6, 1.1)	0.7 (0.5, 1.0)
IL8RB					
rs4674258	C	1.0 (0.8, 1.3)	1.1 (0.8, 1.5)	1.1 (0.8, 1.3)	1.1 (0.8, 1.5)
rs4674259	G	1.0 (0.8, 1.3)	1.1 (0.8, 1.5)	1.0 (0.7, 1.3)	1.0 (0.7, 1.5)
rs6761387	T	1.0 (0.6, 1.6)	0.9 (0.4, 1.9)	0.9 (0.6, 1.3)	0.9 (0.6, 1.5)
rs4674261	C	1.0 (0.8, 1.2)	0.9 (0.7, 1.3)	0.9 (0.7, 1.2)	0.8 (0.6, 1.2)
rs11677534	T	1.0 (0.8, 1.3)	1.1 (0.8, 1.5)	1.1 (0.9, 1.5)	1.2 (0.8, 1.6)
rs11676348	C	1.0 (0.8, 1.3)	1.1 (0.8, 1.5)	0.9 (0.7, 1.2)	1.0 (0.7, 1.4)
IL8					
rs7654490	T	2.2 (0.3, 17.9)		0.9 (0.6, 1.3)	1.1 (0.7, 1.7)
rs16849893	A			0.7 (0.5, 1.0)	0.6 (0.4, 1.1)
rs16849896	T			0.8 (0.5, 1.1)	1.0 (0.6, 1.5)
rs4694634	C			0.9 (0.7, 1.2)	0.9 (0.6, 1.4)
rs16849907	T			0.8 (0.5, 1.3)	1.1 (0.6, 1.8)
rs12506479	C	0.9 (0.7, 1.1)	1.0 (0.7, 1.4)	0.8 (0.6, 1.1)	0.8 (0.5, 1.2)
rs10805066	G	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	1.0 (0.8, 1.3)	1.3 (0.9, 2.0)
rs7693566	C			0.9 (0.6, 1.3)	1.1 (0.7, 1.8)
rs4694635	T	1.6 (0.6, 4.1)	1.1 (0.3, 5.3)	1.2 (0.8, 1.7)	1.2 (0.8, 2.0)
rs16849928	A	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	1.1 (0.9, 1.4)	1.3 (1.0, 1.9)
rs11730667	A	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	1.1 (0.8, 1.4)	1.2 (0.9, 1.8)
rs13142454	G	1.1 (0.2, 8.1)		1.1 (0.8, 1.6)	1.2 (0.7, 2.0)
rs11729759	A	1.1 (0.2, 8.1)		1.0 (0.7, 1.4)	1.2 (0.8, 1.9)
rs1951240	G	1.0 (0.8, 1.3)	1.1 (0.8, 1.4)	1.0 (0.8, 1.3)	0.8 (0.5, 1.2)
rs16849958	C	1.0 (0.8, 1.3)	1.1 (0.8, 1.4)	1.2 (0.9, 1.7)	0.8 (0.5, 1.3)
rs1951242	T	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	1.0 (0.7, 1.3)	1.1 (0.8, 1.7)
rs7658422	C	1.1 (0.2, 8.1)		1.1 (0.8, 1.5)	1.4 (0.9, 2.1)

Gene/SNP[b]	Variant Allele[c]	European American[a]		African American[a]	
		Preterm	Spont. Preterm	Preterm	Spont. Preterm
CXCL10					
rs3733236	T	1.0 (0.6, 1.5)	1.0 (0.5, 1.8)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs10031051	C	1.0 (0.4, 2.5)	1.2 (0.4, 3.3)	0.9 (0.6, 1.5)	0.8 (0.4, 1.6)
rs7670156	A	0.9 (0.6, 1.4)	1.0 (0.6, 1.8)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs12651276	G	1.0 (0.7, 1.2)	0.9 (0.6, 1.2)	1.1 (0.6, 1.9)	1.7 (0.9, 3.3)
rs10518143	C	0.9 (0.7, 1.2)	1.1 (0.8, 1.5)	0.9 (0.6, 1.3)	0.8 (0.4, 1.5)
rs867562	A	1.0 (0.7, 1.3)	0.9 (0.6, 1.3)	1.1 (0.6, 2.2)	1.5 (0.7, 3.5)
rs4508917	G	0.9 (0.7, 1.2)	1.1 (0.8, 1.5)	1.0 (0.7, 1.4)	1.1 (0.7, 1.7)
rs12504339	C	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)	0.9 (0.7, 1.1)	1.0 (0.7, 1.4)
rs4302486	A	1.1 (0.9, 1.4)	1.0 (0.8, 1.4)	1.2 (0.9, 1.6)	1.0 (0.6, 1.5)
NFKB1					
rs980455	G	0.9 (0.8, 1.2)	1.0 (0.8, 1.3)	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)
rs3774933	C	1.0 (0.8, 1.2)	1.0 (0.8, 1.4)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs17032705	A	1.0 (0.8, 1.2)	1.0 (0.8, 1.4)	0.8 (0.6, 1.1)	0.8 (0.5, 1.2)
rs1599961	A	1.0 (0.8, 1.2)	1.0 (0.8, 1.4)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs17032740	G	0.7 (0.1, 4.9)		0.8 (0.5, 1.3)	0.9 (0.5, 1.7)
rs230533	T	1.0 (0.8, 1.2)	1.0 (0.8, 1.4)	1.0 (0.7, 1.3)	0.9 (0.6, 1.4)
rs230530	C	1.0 (0.8, 1.3)	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	0.9 (0.6, 1.5)
rs230529	A	0.9 (0.8, 1.2)	1.1 (0.8, 1.4)	1.1 (0.8, 1.4)	1.1 (0.7, 1.5)
rs17032779	C	0.9 (0.3, 2.7)	1.5 (0.5, 4.7)	1.2 (0.8, 1.8)	1.1 (0.6, 2.0)
rs230515	C	0.9 (0.7, 1.2)	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)	0.9 (0.5, 1.4)
rs230493	A	1.0 (0.8, 1.2)	1.1 (0.8, 1.4)	1.1 (0.8, 1.5)	1.1 (0.7, 1.7)
rs17032815	A	0.9 (0.3, 2.6)	1.5 (0.5, 4.6)	1.0 (0.7, 1.6)	0.8 (0.4, 1.6)
rs909332	T	0.8 (0.5, 1.4)	0.7 (0.3, 1.6)	0.9 (0.6, 1.5)	1.2 (0.6, 2.3)
rs1801	C	0.9 (0.8, 1.2)	1.1 (0.8, 1.4)	1.2 (0.9, 1.6)	1.2 (0.8, 1.7)
rs4648058	C	0.9 (0.7, 1.2)	1.1 (0.8, 1.4)	1.3 (1.0, 1.6)	1.3 (0.9, 1.8)
rs3755867	G	0.9 (0.7, 1.2)	1.1 (0.8, 1.4)	1.2 (0.9, 1.5)	1.2 (0.8, 1.7)
rs4648090	A	1.1 (0.9, 1.5)	1.1 (0.8, 1.7)	1.1 (0.7, 1.6)	1.1 (0.6, 1.9)
rs4648110	A	1.0 (0.8, 1.3)	1.0 (0.7, 1.5)	1.0 (0.7, 1.3)	0.9 (0.6, 1.3)
rs3817685	G	0.9 (0.8, 1.2)	1.1 (0.8, 1.4)	1.0 (0.8, 1.4)	1.1 (0.7, 1.7)
rs4648127	T	0.8 (0.5, 1.3)	0.8 (0.5, 1.5)	1.5 (0.4, 5.6)	1.6 (0.2, 10.7)
rs230547	T	1.2 (0.8, 1.7)	1.4 (0.8, 2.3)	1.1 (0.8, 1.6)	1.1 (0.7, 1.9)
rs4648135	G	1.0 (0.6, 1.6)	1.0 (0.5, 1.9)	1.1 (0.7, 1.5)	1.3 (0.8, 2.1)
rs4648141	A	1.0 (0.8, 1.3)	1.1 (0.8, 1.5)	1.1 (0.9, 1.5)	1.0 (0.7, 1.5)
rs7674640	C	1.1 (0.8, 1.3)	1.0 (0.7, 1.3)	1.0 (0.8, 1.4)	1.2 (0.8, 1.7)
rs10489113	G	1.1 (0.9, 1.4)	1.1 (0.8, 1.6)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs11733293	T	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	1.1 (0.8, 1.4)	1.0 (0.7, 1.6)
rs17033015	A	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)	0.9 (0.7, 1.4)	0.9 (0.5, 1.5)
rs12648696	C	0.9 (0.7, 1.1)	1.0 (0.7, 1.3)	1.0 (0.8, 1.3)	1.0 (0.7, 1.5)

Gene/SNP[b]	Variant Allele[c]	European American[a]		African American[a]	
		Preterm	Spont. Preterm	Preterm	Spont. Preterm
IL2					
rs17454584	G	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	0.5 (0.2, 1.1)	0.5 (0.1, 1.6)
rs35914000	A	1.1 (0.8, 1.3)	1.0 (0.7, 1.4)	0.5 (0.3, 1.1)	0.3 (0.1, 1.1)
rs10034410	T	2.0 (0.3, 11.6)	4.2 (0.8, 21.7)	0.8 (0.5, 1.2)	0.5 (0.3, 1.1)
rs10027390	C	0.9 (0.8, 1.2)	0.9 (0.7, 1.3)		
rs11932411	C	1.5 (0.4, 5.4)	1.4 (0.2, 9.6)	1.1 (0.8, 1.4)	0.9 (0.6, 1.4)
rs2069776	C	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	1.1 (0.8, 1.5)	1.1 (0.7, 1.7)
rs2069778	T	0.9 (0.7, 1.3)	0.8 (0.5, 1.2)	0.8 (0.3, 2.0)	0.4 (0.1, 2.7)
rs2069762	G	1.1 (0.9, 1.4)	1.2 (0.9, 1.6)	1.2 (0.8, 1.9)	1.1 (0.6, 2.2)
rs4833248	A	1.1 (0.9, 1.4)	1.2 (0.9, 1.6)	1.2 (0.7, 1.9)	1.0 (0.5, 2.0)
IL15					
rs6837991	T	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)	1.1 (0.8, 1.5)	1.2 (0.8, 1.9)
rs12508866	C	1.0 (0.8, 1.3)	0.9 (0.7, 1.3)	1.1 (0.7, 1.9)	0.5 (0.2, 1.5)
rs17007476	C			1.3 (0.9, 1.9)	1.3 (0.8, 2.0)
rs17007480	A			1.4 (0.9, 2.3)	1.6 (0.9, 3.1)
rs1519551	G	0.9 (0.7, 1.1)	0.9 (0.6, 1.2)	1.2 (0.9, 1.6)	1.0 (0.7, 1.5)
rs17461269	A	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)	0.8 (0.4, 1.6)	0.9 (0.3, 2.2)
rs17007503	C			1.2 (0.8, 1.8)	1.4 (0.8, 2.5)
rs1519552	A	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)	1.2 (0.9, 1.6)	1.3 (0.9, 1.9)
rs17007508	G			1.0 (0.7, 1.5)	1.3 (0.8, 2.2)
rs7698675	T	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)	1.2 (0.9, 1.7)	1.2 (0.8, 1.9)
rs13117878	C	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	1.2 (0.9, 1.5)	1.0 (0.7, 1.5)
rs17364630	G	1.0 (0.7, 1.3)	1.1 (0.8, 1.6)	1.0 (0.6, 1.5)	0.7 (0.3, 1.3)
rs12498901	C	1.0 (0.7, 1.3)	1.1 (0.8, 1.6)	0.9 (0.6, 1.4)	0.7 (0.3, 1.3)
rs7671458	G	0.9 (0.7, 1.2)	1.1 (0.7, 1.5)	0.9 (0.7, 1.3)	0.7 (0.4, 1.2)
rs10519610	C	0.9 (0.7, 1.2)	1.0 (0.7, 1.4)	0.9 (0.7, 1.2)	0.7 (0.5, 1.1)
rs6850492	A	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	1.0 (0.8, 1.4)	0.8 (0.5, 1.3)
rs2087849	T	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	1.2 (0.9, 1.5)	1.2 (0.8, 1.8)
rs2857261	G	1.2 (0.9, 1.4)	1.2 (0.9, 1.6)	1.0 (0.8, 1.3)	1.2 (0.9, 1.8)
rs1907949	T	1.0 (0.7, 1.4)	1.0 (0.6, 1.5)	1.0 (0.7, 1.5)	0.7 (0.4, 1.3)
rs3775597	C	1.0 (0.7, 1.4)	0.9 (0.6, 1.5)	1.0 (0.7, 1.5)	0.8 (0.4, 1.6)
rs12508955	T	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	1.2 (0.9, 1.7)	1.2 (0.7, 1.9)
rs17007610	T	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	1.0 (0.8, 1.3)	0.8 (0.6, 1.2)
IL12B					
rs7730126	T	0.9 (0.7, 1.2)	1.0 (0.7, 1.4)	0.9 (0.7, 1.3)	0.9 (0.6, 1.5)
rs2099327	C	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)	1.1 (0.7, 1.8)	1.1 (0.6, 2.0)
rs1549922	G	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)	0.9 (0.7, 1.3)	1.0 (0.7, 1.6)
rs4921466	C	0.9 (0.6, 1.2)	1.1 (0.7, 1.6)	0.9 (0.6, 1.3)	0.8 (0.5, 1.5)
rs10072923	C	1.0 (0.8, 1.4)	1.0 (0.7, 1.5)	1.2 (0.9, 1.5)	1.0 (0.7, 1.5)

Gene/SNP[b]	Variant Allele[c]	European American[a]		African American[a]	
		Preterm	Spont. Preterm	Preterm	Spont. Preterm
rs1368439	G	1.3 (1.0, 1.8)	1.3 (0.9, 1.8)	0.9 (0.5, 1.5)	1.0 (0.5, 2.1)
rs3212227	C	1.1 (0.8, 1.4)	1.1 (0.7, 1.6)	1.0 (0.8, 1.4)	1.0 (0.7, 1.5)
rs11574790	T	0.9 (0.6, 1.2)	1.0 (0.7, 1.5)	1.0 (0.8, 1.4)	1.1 (0.8, 1.6)
rs2195940	T	0.8 (0.6, 1.2)	1.0 (0.6, 1.5)	0.9 (0.6, 1.2)	0.9 (0.6, 1.5)
rs919766	C	0.9 (0.6, 1.2)	1.0 (0.7, 1.5)	1.0 (0.7, 1.3)	1.1 (0.7, 1.6)
rs2853694	C	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)	0.8 (0.6, 1.2)	0.7 (0.4, 1.2)
rs2569253	C	0.9 (0.7, 1.1)	0.9 (0.6, 1.1)	1.0 (0.7, 1.3)	0.9 (0.6, 1.5)
rs3212220	T	1.0 (0.8, 1.4)	1.0 (0.7, 1.5)	1.1 (0.8, 1.4)	1.0 (0.6, 1.5)
rs1433048	G	1.2 (0.9, 1.6)	1.1 (0.7, 1.6)	0.9 (0.5, 1.7)	1.3 (0.6, 2.7)
rs2546893	A	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)	1.2 (0.9, 1.6)	1.2 (0.8, 1.8)
rs2546890	A	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs10052709	G	0.9 (0.6, 1.2)	0.8 (0.5, 1.3)	1.0 (0.7, 1.5)	0.8 (0.5, 1.4)
rs7709212	C	1.2 (0.9, 1.5)	1.2 (0.9, 1.7)	1.1 (0.8, 1.4)	1.1 (0.7, 1.7)
rs6868898	C	0.9 (0.7, 1.1)	0.9 (0.6, 1.2)	0.9 (0.6, 1.2)	0.9 (0.6, 1.5)
LTA&TNF (*NFKBIL1*)					
rs2857605	G	0.9 (0.7, 1.2)	0.8 (0.5, 1.1)	0.8 (0.5, 1.5)	1.4 (0.8, 2.6)
rs2239707	G	1.0 (0.8, 1.3)	0.8 (0.6, 1.1)	0.9 (0.6, 1.3)	1.1 (0.7, 1.9)
rs2230365	T	1.1 (0.8, 1.5)	0.8 (0.5, 1.3)	0.9 (0.6, 1.6)	0.8 (0.4, 1.9)
rs3130062	C	1.1 (0.8, 1.7)	0.9 (0.5, 1.5)	0.6 (0.1, 2.6)	1.2 (0.3, 5.2)
rs4947324	T	0.9 (0.6, 1.3)	1.0 (0.6, 1.5)	1.0 (0.7, 1.6)	1.0 (0.5, 1.8)
rs2857709	T	1.0 (0.7, 1.3)	0.9 (0.6, 1.3)	0.6 (0.3, 1.4)	1.0 (0.4, 2.4)
LTA&TNF (*LTA*)					
rs915654	T	1.0 (0.8, 1.3)	0.9 (0.7, 1.2)	1.1 (0.8, 1.4)	0.8 (0.6, 1.2)
rs909253	C	1.1 (0.9, 1.4)	1.2 (0.9, 1.7)	1.1 (0.8, 1.4)	1.0 (0.7, 1.4)
rs2229094	C	1.0 (0.8, 1.2)	0.9 (0.6, 1.2)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs1041981	A	1.1 (0.9, 1.4)	1.2 (0.9, 1.7)	1.1 (0.8, 1.4)	1.0 (0.7, 1.4)
LTA&TNF (intergenic)					
rs1799964	C	0.9 (0.7, 1.2)	0.8 (0.5, 1.1)	0.9 (0.6, 1.2)	0.8 (0.5, 1.3)
rs1800630	A	1.0 (0.8, 1.4)	0.9 (0.6, 1.3)	1.0 (0.7, 1.5)	0.9 (0.5, 1.6)
LTA&TNF (*TNF*)					
rs1800629	A	1.0 (0.7, 1.4)	1.2 (0.8, 1.8)	1.0 (0.7, 1.5)	1.0 (0.6, 1.7)
LTA&TNF (*LST1*)					
rs7769073	A	1.1 (0.7, 1.9)	1.3 (0.6, 2.4)	1.0 (0.7, 1.5)	0.9 (0.5, 1.6)
IL6					
rs6949149	T	1.7 (1.2, 2.4)	1.8 (1.1, 2.9)	0.7 (0.4, 1.0)	0.8 (0.5, 1.3)
rs6954897	G	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	0.9 (0.7, 1.2)	0.9 (0.6, 1.4)
rs6954681	T	1.4 (1.1, 1.8)	1.2 (0.8, 1.8)	1.0 (0.7, 1.2)	0.9 (0.7, 1.3)
rs6969927	A	0.8 (0.6, 1.1)	1.0 (0.7, 1.4)	1.2 (0.9, 1.7)	1.5 (1.0, 2.3)
rs10156056	C	1.2 (0.9, 1.6)	0.9 (0.5, 1.5)	1.0 (0.8, 1.4)	0.9 (0.6, 1.3)

Gene/SNP[b]	Variant Allele[c]	European American[a]		African American[a]	
		Preterm	Spont. Preterm	Preterm	Spont. Preterm
rs7776857	G	1.0 (0.8, 1.3)	1.1 (0.8, 1.6)	1.1 (0.6, 2.0)	1.3 (0.6, 2.6)
rs4719711	C	1.2 (1.0, 1.5)	1.2 (0.9, 1.7)	1.1 (0.8, 1.4)	1.2 (0.8, 1.8)
rs6963444	G	1.0 (0.5, 2.0)	0.7 (0.2, 2.2)	0.9 (0.6, 1.3)	0.7 (0.4, 1.2)
rs1546762	C	1.2 (0.9, 1.5)	1.2 (0.9, 1.7)	1.1 (0.8, 1.5)	1.2 (0.8, 1.8)
rs7805828	A	0.8 (0.7, 1.0)	0.9 (0.7, 1.2)	1.1 (0.9, 1.5)	1.3 (0.9, 1.8)
rs1880241	G	1.0 (0.8, 1.2)	1.1 (0.8, 1.4)	1.2 (0.9, 1.5)	1.4 (1.0, 2.0)
rs2056576	T	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	0.9 (0.7, 1.1)	0.9 (0.6, 1.3)
rs7784987	A	0.9 (0.4, 1.9)	0.5 (0.1, 1.9)	0.9 (0.6, 1.3)	0.9 (0.5, 1.5)
rs3087221	T	0.9 (0.4, 2.4)	1.0 (0.3, 3.5)	0.8 (0.6, 1.2)	0.7 (0.4, 1.2)
rs2069824	C	1.0 (0.7, 1.6)	0.7 (0.4, 1.5)	1.0 (0.7, 1.4)	1.1 (0.7, 1.7)
rs1800797	A	1.0 (0.8, 1.2)	1.1 (0.8, 1.4)	1.2 (0.7, 2.0)	1.3 (0.7, 2.6)
rs1800795	C	1.0 (0.8, 1.2)	1.0 (0.8, 1.4)	1.2 (0.7, 1.9)	1.3 (0.7, 2.6)
rs2069835	C	1.0 (0.6, 1.6)	0.8 (0.3, 1.7)	0.8 (0.5, 1.2)	0.6 (0.3, 1.2)
rs1474347	G	1.0 (0.8, 1.2)	1.0 (0.7, 1.3)	0.9 (0.6, 1.3)	0.7 (0.4, 1.3)
rs2069840	G	0.8 (0.7, 1.0)	0.9 (0.6, 1.2)	1.4 (1.1, 1.9)	1.6 (1.1, 2.5)
rs2069842	A	4.1 (1.6, 10.7)		1.2 (0.8, 1.8)	1.3 (0.7, 2.3)
rs1548216	C	1.4 (0.8, 2.4)	1.3 (0.5, 3.2)	0.9 (0.6, 1.3)	0.8 (0.4, 1.3)
rs2069843	A	1.4 (0.8, 2.4)	1.3 (0.5, 3.2)	1.0 (0.6, 1.5)	0.9 (0.5, 1.6)
rs2069845	G	1.0 (0.8, 1.2)	1.0 (0.8, 1.4)	0.8 (0.6, 1.1)	0.7 (0.5, 1.1)
rs2069849	T	1.4 (0.8, 2.4)	1.3 (0.5, 3.2)	0.9 (0.6, 1.4)	0.8 (0.5, 1.4)
rs10242595	G	1.0 (0.8, 1.2)	1.0 (0.7, 1.4)	1.0 (0.7, 1.3)	0.9 (0.6, 1.4)
GATA3					
rs406571	C	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)	0.8 (0.6, 1.1)	0.7 (0.5, 1.1)
rs1877739	C	0.9 (0.7, 1.1)	0.8 (0.6, 1.2)	1.0 (0.7, 1.3)	1.2 (0.8, 1.7)
rs532854	C	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)	0.8 (0.7, 1.1)	0.9 (0.6, 1.3)
rs10795588	G	1.0 (0.8, 1.3)	1.0 (0.8, 1.4)	1.0 (0.8, 1.4)	1.0 (0.6, 1.5)
rs263425	T			0.9 (0.6, 1.3)	1.1 (0.7, 1.9)
rs263423	A	1.0 (0.8, 1.3)	0.8 (0.5, 1.1)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs1244186	T	0.9 (0.7, 1.1)	0.7 (0.5, 1.0)	1.0 (0.7, 1.4)	0.7 (0.4, 1.2)
rs2275806	A	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	1.0 (0.7, 1.4)	0.9 (0.6, 1.4)
rs1269486	A	0.9 (0.7, 1.1)	0.7 (0.5, 1.0)	0.9 (0.6, 1.3)	0.6 (0.3, 1.0)
rs1399180	T	0.9 (0.7, 1.2)	0.8 (0.6, 1.2)	1.0 (0.7, 1.3)	1.0 (0.7, 1.5)
rs369421	C	0.9 (0.7, 1.2)	0.8 (0.5, 1.2)	0.9 (0.6, 1.5)	0.6 (0.3, 1.3)
rs3781094	G	1.1 (0.9, 1.4)	1.0 (0.7, 1.3)	1.1 (0.8, 1.5)	1.0 (0.7, 1.5)
rs3781093	G	1.0 (0.7, 1.3)	1.3 (0.9, 1.8)	0.8 (0.6, 1.1)	0.9 (0.6, 1.4)
rs376397	A	0.9 (0.7, 1.1)	1.0 (0.7, 1.3)	1.0 (0.8, 1.4)	0.9 (0.6, 1.4)
rs570613	G	0.9 (0.7, 1.1)	1.0 (0.8, 1.4)	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)
rs10752126	G	0.9 (0.7, 1.1)	1.0 (0.8, 1.4)	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)
rs569421	C	1.0 (0.8, 1.3)	1.2 (0.9, 1.7)	0.8 (0.6, 1.1)	1.0 (0.7, 1.4)

Gene/SNP[b]	Variant Allele[c]	European American[a]		African American[a]	
		Preterm	Spont. Preterm	Preterm	Spont. Preterm
rs444929	C	0.8 (0.6, 1.1)	0.8 (0.6, 1.2)	1.2 (0.9, 1.6)	0.9 (0.6, 1.4)
rs2280015	A	1.1 (0.8, 1.4)	1.3 (0.9, 1.8)	0.8 (0.6, 1.2)	1.1 (0.7, 1.7)
rs422628	C	0.8 (0.6, 1.1)	0.8 (0.6, 1.2)	1.1 (0.8, 1.5)	0.8 (0.5, 1.2)
rs406103	T	1.0 (0.8, 1.3)	1.3 (0.9, 1.7)	0.9 (0.7, 1.1)	1.0 (0.7, 1.4)
rs528778	T	0.9 (0.7, 1.1)	0.9 (0.6, 1.3)	1.3 (0.9, 1.7)	0.9 (0.5, 1.4)
rs11567934	A			1.0 (0.7, 1.4)	1.0 (0.6, 1.7)
rs388957	T	0.7 (0.3, 1.4)	0.9 (0.4, 2.3)	1.0 (0.7, 1.4)	1.0 (0.7, 1.6)
rs10905284	A	1.1 (0.9, 1.3)	0.9 (0.7, 1.2)	1.2 (0.9, 1.7)	1.2 (0.8, 1.9)
rs1058240	G	0.8 (0.6, 1.1)	0.8 (0.6, 1.2)	1.1 (0.8, 1.4)	0.7 (0.4, 1.0)
rs263419	T	1.0 (0.8, 1.3)	1.3 (0.9, 1.8)	0.9 (0.7, 1.2)	1.2 (0.8, 1.7)
rs12262237	A			1.1 (0.7, 1.8)	1.3 (0.7, 2.5)
rs7100967	A			0.8 (0.5, 1.3)	1.2 (0.7, 2.1)
rs477461	G	1.0 (0.8, 1.4)	1.3 (0.9, 1.9)	0.8 (0.6, 1.1)	1.1 (0.8, 1.7)
rs434645	A	0.8 (0.6, 1.1)	0.9 (0.6, 1.3)	1.0 (0.8, 1.4)	0.7 (0.5, 1.2)
rs379568	T	1.1 (0.8, 1.6)	1.2 (0.8, 1.9)	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)
rs1778058	A	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	1.1 (0.9, 1.5)	1.2 (0.8, 1.8)
rs12412241	A	0.8 (0.6, 1.1)	0.9 (0.6, 1.2)	1.0 (0.8, 1.4)	0.9 (0.6, 1.3)
IL18					
rs4937075	G	1.2 (1.0, 1.5)	1.2 (0.9, 1.6)	1.0 (0.8, 1.4)	1.0 (0.6, 1.4)
rs578784	T	1.2 (1.0, 1.6)	1.1 (0.8, 1.5)	1.0 (0.8, 1.4)	1.0 (0.6, 1.6)
rs11214098	A			1.0 (0.6, 1.5)	0.8 (0.4, 1.6)
rs543810	G	0.9 (0.6, 1.3)	0.9 (0.6, 1.5)	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)
rs5744280	T	0.8 (0.7, 1.1)	0.7 (0.5, 1.0)	1.1 (0.8, 1.4)	1.1 (0.7, 1.5)
rs5744238	A	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.2 (0.7, 2.3)	1.1 (0.5, 2.6)
rs2043055	G	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	1.1 (0.8, 1.4)	1.0 (0.7, 1.5)
rs360714	G			0.8 (0.6, 1.3)	1.1 (0.7, 1.9)
rs1946518	T	1.0 (0.8, 1.3)	0.9 (0.7, 1.2)	0.8 (0.6, 1.1)	0.9 (0.6, 1.4)
rs5744223	G	2.7 (0.7, 10.3)	0.0 (0.0, 0.0)	1.0 (0.7, 1.5)	1.0 (0.5, 1.8)
rs5744222	A	1.1 (0.9, 1.4)	1.4 (1.0, 1.8)	0.8 (0.4, 1.5)	0.9 (0.4, 2.2)
rs11214105	A	1.1 (0.9, 1.4)	1.0 (0.7, 1.3)	0.9 (0.6, 1.2)	0.9 (0.6, 1.4)
KLDR1					
rs3759270	C	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)	1.1 (0.8, 1.4)	1.1 (0.8, 1.7)
rs3809214	T	1.0 (0.8, 1.2)	1.0 (0.8, 1.4)	0.9 (0.6, 1.1)	0.8 (0.6, 1.3)
rs2302489	A	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)	1.2 (0.9, 1.5)	1.2 (0.8, 1.7)
rs7301562	C	2.2 (0.8, 6.3)		0.9 (0.6, 1.3)	1.0 (0.6, 1.7)
rs10772256	T	2.2 (0.8, 6.3)		0.9 (0.6, 1.3)	1.1 (0.6, 1.8)
rs2270238	T	1.0 (0.8, 1.2)		0.9 (0.5, 1.7)	
rs11611333	G	1.0 (0.8, 1.2)	0.9 (0.7, 1.2)	1.2 (0.9, 1.5)	1.1 (0.8, 1.6)
rs12829155	G	1.0 (0.8, 1.2)	1.1 (0.8, 1.4)	0.7 (0.5, 1.0)	0.8 (0.5, 1.3)

Gene/SNP[b]	Variant Allele[c]	European American[a]		African American[a]	
		Preterm	Spont. Preterm	Preterm	Spont. Preterm
IFNG					
rs10878760	T	1.2 (0.9, 1.6)	1.0 (0.7, 1.5)	1.2 (0.7, 2.2)	1.4 (0.7, 2.9)
rs17104856	T			1.3 (0.8, 1.9)	1.4 (0.8, 2.6)
rs2193047	T	1.1 (0.9, 1.4)	1.0 (0.7, 1.3)	1.3 (1.0, 1.7)	1.4 (1.0, 2.0)
rs2041864	T	0.9 (0.7, 1.1)	1.0 (0.7, 1.3)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)
rs11177074	C	1.0 (0.7, 1.5)	1.1 (0.7, 1.9)	1.3 (0.9, 1.8)	1.3 (0.8, 2.0)
rs6581794	T	1.1 (0.9, 1.4)	0.9 (0.7, 1.3)	1.0 (0.7, 1.5)	1.1 (0.7, 1.8)
rs3181035	A	1.0 (0.7, 1.5)	1.1 (0.7, 1.9)	1.4 (1.0, 1.8)	1.4 (1.0, 2.1)
rs2069727	G	1.0 (0.8, 1.2)	1.1 (0.8, 1.4)	0.8 (0.6, 1.2)	0.6 (0.3, 1.1)
rs1861494	C	1.1 (0.9, 1.4)	0.9 (0.7, 1.3)	1.1 (0.8, 1.6)	1.2 (0.7, 2.0)
rs3181032	G	1.2 (0.6, 2.6)	1.1 (0.3, 4.0)	1.1 (0.7, 1.5)	1.0 (0.6, 1.6)
rs7302488	G	1.1 (0.9, 1.4)	0.9 (0.7, 1.3)	1.2 (0.8, 1.6)	1.2 (0.7, 1.9)
rs12306852	C	0.8 (0.6, 1.1)	0.9 (0.6, 1.4)	1.0 (0.8, 1.3)	1.2 (0.8, 1.7)
TBX21					
rs2013383	A	0.9 (0.7, 1.1)	1.0 (0.7, 1.3)	0.9 (0.7, 1.2)	1.1 (0.7, 1.6)
rs1808192	T	0.9 (0.7, 1.2)	1.1 (0.8, 1.5)	1.0 (0.7, 1.4)	1.3 (0.9, 2.1)
rs4461115	C	1.0 (0.8, 1.3)	1.0 (0.7, 1.4)	1.1 (0.6, 2.1)	1.5 (0.7, 3.4)
rs16946264	A	0.9 (0.6, 1.3)	1.1 (0.6, 1.7)	1.3 (1.0, 1.8)	1.2 (0.8, 1.8)
rs11079788	T	0.9 (0.7, 1.2)	1.0 (0.7, 1.4)	1.1 (0.8, 1.5)	1.2 (0.8, 1.7)
rs16946878	C	1.2 (0.8, 1.9)	1.4 (0.8, 2.4)	1.5 (1.0, 2.2)	1.3 (0.8, 2.2)
rs16947078	G	0.9 (0.7, 1.2)	0.9 (0.7, 1.4)	1.2 (0.9, 1.6)	1.1 (0.7, 1.7)
KIR3DL3					
rs4441391	A	1.0 (0.8, 1.2)	1.1 (0.8, 1.4)	0.8 (0.6, 1.2)	1.0 (0.6, 1.7)
rs1325155	T	1.1 (0.9, 1.4)	1.1 (0.8, 1.4)	1.0 (0.8, 1.3)	0.8 (0.5, 1.2)
rs1325156	A	0.8 (0.6, 1.1)	0.8 (0.6, 1.2)	1.1 (0.8, 1.4)	1.2 (0.9, 1.8)
rs12151161	G	1.0 (0.7, 1.3)	0.8 (0.5, 1.3)	1.1 (0.8, 1.4)	1.4 (0.9, 2.0)
rs7249048	G			1.1 (0.8, 1.6)	1.4 (0.9, 2.2)
rs270775	G	1.0 (0.8, 1.2)	0.9 (0.7, 1.2)	1.1 (0.8, 1.5)	0.8 (0.5, 1.2)
rs2296370	A	1.1 (0.9, 1.4)	1.1 (0.9, 1.5)	0.9 (0.7, 1.2)	0.8 (0.6, 1.3)
rs2296371	A	1.0 (0.8, 1.2)	1.1 (0.8, 1.4)	1.2 (0.9, 1.6)	1.4 (1.0, 2.1)
rs12982559	A	1.1 (0.9, 1.3)	1.1 (0.8, 1.4)	1.2 (0.9, 1.6)	1.2 (0.8, 1.9)
rs11883241	T	1.0 (0.8, 1.3)	1.1 (0.8, 1.4)	1.0 (0.8, 1.3)	1.2 (0.9, 1.7)
rs6509899	A	0.8 (0.6, 1.1)	0.9 (0.6, 1.4)	1.1 (0.8, 1.4)	1.3 (0.9, 1.9)
rs1325158	T	1.0 (0.8, 1.2)	1.0 (0.8, 1.4)	1.2 (0.9, 1.6)	1.6 (1.1, 2.3)
rs11671355	C	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	0.7 (0.4, 1.3)	0.5 (0.2, 1.3)
rs16985907	C	1.0 (0.6, 1.7)	0.8 (0.4, 1.8)	1.0 (0.7, 1.6)	1.0 (0.6, 1.8)
KIR2DL4					
rs35950908	A	1.2 (0.9, 1.6)	1.2 (0.8, 1.7)	0.6 (0.3, 1.1)	1.0 (0.5, 1.8)
rs17771961	G	1.4 (1.1, 1.7)	1.7 (1.2, 2.3)	0.9 (0.6, 1.3)	0.8 (0.5, 1.4)

a Based on genetic ancestry
b SNPs arranged by base pair position within each gene. Following the Stage 2 genes, genes are arranged from Chromosome 1- 19 according to position on the chromosome with SNPs arranged by base pair position within gene.
c Variant allele chosen as the minor allele if the minor allele was the same in both ancestry groups. Otherwise variant is the Global Minor Allele from dbSNP.
Empty cells are non-polymorphic for that ancestry group, were out of HWE, or had no cases.

Table S17: Paper#2 Demographics for entire PIN cohort, eligible cohort and genotyped cohort

	All N=5169	***Eligible N=3065***	***Genotyped N=1646***
Self-Reported Race: White	3035 (58.7)	1918 (62.6)	1031 (62.6)
African American	1746 (33.8)	1147 (37.4)	615 (37.4)
Other	387 (7.5)	0	0
Missing race	1	0	0
Age (years): Mean (SD)	26.8 (6.2)	26.2 (6.3)	26.1 (6.3)
Smoker[a]	935 (20.8)	657 (23.6)	383 (25.6)
Missing smoking	670	0	152
BMI[b] (m^2/kg): Mean (IQR)	26.0 (21-29)	25.8 (21-29)	26.5 (21-30)
Missing BMI	364	188	82
Poverty: Mean (median, IQR)	305 (223, 109-476)	284.0 (198, 96-473)	273.0 (179, 95-464)
Missing poverty	741	375	199
Married	2959 (57.4)	1646 (53.7)	868 (52.8)
Single	1843 (35.8)	1199 (39.1)	658 (40.0)
Other	352 (6.8)	218 (7.1)	119 (7.2)
Missing marital	15	2	1
Education: 13+ years	3013 (58.5)	1663 (54.3)	854 (51.9)
Missing Education	19	4	0
First birth	2347 (45.6)	1400 (45.8)	769 (46.8)
Multiparous	2803 (54.4)	1659 (54.2)	873 (53.1)
Missing parity	19	5	4
Prexisting Hypertension	263 (5.6)	139 (4.9)	112 (7.0)
Gestational Hypertension	673 (14.2)	418 (14.8)	398
Preeclampsia	294 (6.2)	185 (6.5)	170
Missing	440	233	57
Small for gestational age	371 (8.2)	239 (8.3)	216
Missing SGA	658	167	105
Preterm	686 (13.5)	377 (12.3)	347
Missing PTB	80	0	0

a Self-reported smoking during months 1-6 of pregnancy.

b Pre-pregnancy BMI calculated from self-reported pre-pregnancy weight and measured height.

Abbreviations: SD standard deviation, IQR interquartile range, BMI Body Mass index (kg/m^2)

Table S18: Paper #2 Risk ratio and 95% confidence interval for all genotyped SNPs for SGA and Term SGA stratified by genetic ancestry

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
IL6		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
rs6949149	T	0.7 (0.3, 1.5)	0.6 (0.2, 1.6)	1.0 (0.6, 1.8)	1.3 (0.7, 2.4)
rs6954897	G	1.4 (0.8, 2.5)	1.4 (0.7, 2.6)	1.4 (0.9, 2.1)	1.4 (0.8, 2.4)
rs6954681	T	1.0 (0.7, 1.5)	1.0 (0.6, 1.6)	0.8 (0.5, 1.3)	0.7 (0.4, 1.2)
rs6969927	A	1.0 (0.7, 1.5)	1.0 (0.7, 1.6)	0.9 (0.5, 1.4)	1.0 (0.5, 1.7)
rs10156056	C	1.1 (0.7, 1.8)	1.1 (0.7, 1.9)	0.9 (0.6, 1.5)	0.7 (0.4, 1.1)
rs7776857	G	0.8 (0.5, 1.1)	0.8 (0.5, 1.2)	1.2 (0.6, 2.5)	0.7 (0.2, 2.0)
rs4719711	C	0.6 (0.4, 0.9)	0.7 (0.4, 1.0)	1.0 (0.7, 1.6)	0.9 (0.5, 1.5)
rs6963444	G	1.9 (1.0, 3.7)	2.1 (1.0, 4.2)	1.8 (1.2, 2.8)	2.5 (1.5, 4.2)
rs1546762	C	0.6 (0.4, 0.9)	0.6 (0.4, 1.0)	1.1 (0.7, 1.7)	0.8 (0.5, 1.5)
rs7805828*	A	1.2 (0.9, 1.5)	1.1 (0.8, 1.4)	0.9 (0.6, 1.2)	0.9 (0.6, 1.3)
rs1880241*	G	1.0 (0.8, 1.4)	0.9 (0.7, 1.3)	0.8 (0.6, 1.1)	0.8 (0.5, 1.2)
rs2056576	T	1.1 (0.7, 1.5)	0.9 (0.6, 1.4)	1.1 (0.7, 1.7)	1.0 (0.6, 1.7)
rs7784987	A	2.0 (1.0, 3.8)	2.1 (1.1, 4.4)	1.5 (1.0, 2.4)	2.1 (1.2, 3.6)
rs3087221	T	2.3 (1.0, 5.4)	2.0 (0.8, 5.4)	1.4 (0.9, 2.3)	1.8 (1.1, 3.1)
rs2069824	C	1.2 (0.7, 2.0)	1.1 (0.6, 2.1)	1.1 (0.7, 1.8)	0.8 (0.4, 1.5)
rs1800797	A	1.0 (0.6, 1.4)	1.1 (0.7, 1.7)	1.2 (0.6, 2.3)	0.7 (0.3, 1.8)
rs1800795	C	0.9 (0.6, 1.3)	1.0 (0.7, 1.6)	1.1 (0.6, 2.2)	0.7 (0.3, 1.8)
rs2069835	C	1.0 (0.5, 1.9)	0.8 (0.4, 1.7)	0.8 (0.4, 1.3)	0.7 (0.3, 1.4)
rs1474347	G	0.9 (0.6, 1.3)	1.0 (0.6, 1.5)	0.9 (0.6, 1.5)	0.7 (0.4, 1.3)
rs2069840	G	1.0 (0.7, 1.4)	1.0 (0.6, 1.5)	0.9 (0.6, 1.5)	1.1 (0.6, 2.0)
rs2069842	A			1.1 (0.6, 1.9)	1.4 (0.7, 2.6)
rs1548216	C	2.3 (1.2, 4.2)	2.4 (1.2, 4.7)	1.6 (1.0, 2.5)	2.1 (1.2, 3.5)
rs2069843	A	2.2 (1.2, 4.1)	2.4 (1.2, 4.6)	1.5 (1.0, 2.5)	2.0 (1.2, 3.5)
rs2069845*	G	1.0 (0.8, 1.3)	1.1 (0.8, 1.5)	1.3 (0.9, 1.8)	1.4 (0.9, 2.1)
rs2069849	T	2.2 (1.2, 4.1)	2.4 (1.2, 4.6)	1.4 (0.9, 2.3)	1.9 (1.1, 3.2)
rs10242595*	G	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)	1.2 (0.8, 1.6)	1.3 (0.9, 2.0)
KLRD1					
rs3759270	C	1.3 (0.9, 2.0)	1.3 (0.8, 2.0)	0.6 (0.4, 1.0)	0.4 (0.3, 0.8)
rs3809214*	T	0.8 (0.6, 1.0)	0.8 (0.6, 1.1)	1.3 (0.9, 1.8)	1.6 (1.1, 2.4)
rs2302489*	T	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	1.3 (0.9, 1.8)	1.6 (1.1, 2.4)
rs7301562	C	1.1 (0.2, 7.9)	1.6 (0.2, 11.8)	0.6 (0.4, 1.0)	0.5 (0.3, 0.9)
rs10772256	T	1.1 (0.2, 7.9)	1.6 (0.2, 11.8)	0.6 (0.4, 1.0)	0.5 (0.3, 0.9)
rs2270238	T	1.5 (1.0, 2.2)	1.5 (1.0, 2.4)	0.8 (0.4, 1.8)	0.8 (0.3, 2.1)
rs11611333*	G	1.3 (1.0, 1.6)	1.2 (0.9, 1.7)	1.1 (0.8, 1.5)	1.0 (0.7, 1.5)
rs12829155*	G	0.8 (0.6, 1.0)	0.8 (0.6, 1.1)	1.3 (0.9, 1.9)	1.5 (0.9, 2.4)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
TNFRSF1B					
rs496888*	G	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	1.0 (0.7, 1.4)	1.0 (0.6, 1.4)
rs3766730	T	0.8 (0.5, 1.3)	0.7 (0.4, 1.2)	0.6 (0.3, 1.5)	0.5 (0.2, 1.6)
rs816050	T	1.2 (0.8, 1.8)	1.1 (0.7, 1.8)	1.1 (0.7, 1.7)	1.1 (0.6, 1.9)
rs1201157*	T	0.9 (0.7, 1.1)	1.0 (0.7, 1.3)	0.9 (0.7, 1.3)	0.9 (0.6, 1.4)
rs1061622	G	0.8 (0.5, 1.1)	0.7 (0.4, 1.1)	0.9 (0.5, 1.4)	0.8 (0.4, 1.4)
rs5746051	G	0.7 (0.5, 1.1)	0.6 (0.4, 1.0)	0.6 (0.3, 1.4)	0.5 (0.2, 1.3)
rs5746053	A	0.7 (0.4, 1.0)	0.6 (0.4, 1.0)	0.6 (0.4, 1.1)	0.6 (0.3, 1.2)
rs1061624*	G	1.0 (0.8, 1.3)	0.9 (0.7, 1.3)	1.0 (0.7, 1.3)	0.9 (0.6, 1.3)
rs1061628*	T	1.1 (0.8, 1.4)	1.1 (0.8, 1.4)	0.8 (0.6, 1.2)	0.9 (0.6, 1.3)
IL6R					
rs11265607	G	0.8 (0.6, 1.2)	0.9 (0.6, 1.4)	0.6 (0.4, 1.0)	0.5 (0.3, 0.8)
rs6427627*	C	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.7 (0.5, 1.0)	0.6 (0.4, 0.9)
rs11265608	A	0.9 (0.6, 1.5)	0.7 (0.4, 1.3)	0.8 (0.5, 1.5)	0.8 (0.4, 1.6)
rs17654071	G	1.5 (1.0, 2.4)	0.0 (0.0, 0.0)	1.1 (0.7, 1.6)	1.2 (0.7, 2.0)
rs2054855	T	0.8 (0.5, 1.3)	0.8 (0.4, 1.3)	1.1 (0.7, 1.8)	1.3 (0.8, 2.2)
rs4845615	A	2.6 (0.5, 12.2)	3.0 (0.6, 15.3)	1.0 (0.6, 1.8)	1.0 (0.5, 2.0)
rs1552481	G	3.0 (0.9, 10.5)	3.4 (0.9, 12.6)	1.1 (0.7, 1.7)	1.0 (0.6, 1.8)
rs4845617	A	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)	1.1 (0.7, 1.8)	1.3 (0.7, 2.3)
rs6427641*	G	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	0.8 (0.6, 1.2)	0.8 (0.6, 1.1)
rs11265610	C	2.0 (0.4, 8.7)	2.5 (0.5, 11.4)	0.9 (0.6, 1.3)	0.7 (0.4, 1.2)
rs12083537	G	1.1 (0.7, 1.6)	1.1 (0.7, 1.7)	0.9 (0.6, 1.3)	0.7 (0.4, 1.1)
rs1386821	C	1.0 (0.7, 1.5)	1.0 (0.6, 1.6)	0.7 (0.4, 1.3)	0.5 (0.2, 1.1)
rs12090237	A	1.5 (0.6, 3.9)	1.9 (0.7, 4.9)	1.3 (0.8, 2.1)	1.0 (0.5, 1.8)
rs6684439	T	1.5 (1.0, 2.3)	1.9 (1.2, 3.1)	1.3 (0.8, 2.1)	1.4 (0.8, 2.5)
rs12096944	T			0.9 (0.5, 1.7)	1.2 (0.6, 2.4)
rs12060250	G			1.0 (0.5, 1.8)	1.2 (0.6, 2.4)
rs4845618*	G	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)	1.0 (0.7, 1.5)
rs7549250*	C	1.0 (0.8, 1.4)	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)	0.9 (0.6, 1.4)
rs7518199	C	1.3 (0.9, 2.0)	1.5 (0.9, 2.5)	1.0 (0.7, 1.6)	1.0 (0.6, 1.7)
rs4553185*	C	1.1 (0.8, 1.4)	1.0 (0.8, 1.4)	0.9 (0.7, 1.3)	0.9 (0.6, 1.3)
rs4845623*	G	1.1 (0.8, 1.4)	1.2 (0.9, 1.5)	1.2 (0.9, 1.6)	1.3 (0.9, 2.0)
rs4537545*	T	1.2 (0.9, 1.5)	1.3 (1.0, 1.8)	1.0 (0.7, 1.4)	1.1 (0.8, 1.7)
rs4845626	T	0.9 (0.6, 1.3)	0.8 (0.5, 1.2)	0.7 (0.5, 1.1)	0.9 (0.5, 1.6)
rs4845374	A	0.8 (0.5, 1.3)	0.8 (0.5, 1.2)	1.0 (0.6, 1.5)	0.8 (0.4, 1.3)
rs11265618	T	0.9 (0.6, 1.3)	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)	1.0 (0.6, 1.6)
rs4329505	C	0.8 (0.5, 1.3)	0.8 (0.5, 1.2)	1.4 (0.9, 2.3)	1.4 (0.8, 2.4)
rs4341355*	C	1.2 (0.8, 1.6)	1.2 (0.8, 1.7)	0.9 (0.6, 1.2)	0.9 (0.6, 1.3)
rs2229238	T	0.9 (0.6, 1.3)	0.9 (0.6, 1.5)	1.1 (0.7, 1.7)	1.0 (0.6, 1.8)
rs4072391	T	0.9 (0.6, 1.4)	1.0 (0.6, 1.5)	1.3 (0.8, 2.0)	1.3 (0.8, 2.2)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
rs11265621*	G	0.9 (0.6, 1.2)	0.8 (0.6, 1.1)	0.9 (0.7, 1.3)	1.0 (0.7, 1.4)
rs7526293	T	1.0 (0.7, 1.5)	1.0 (0.6, 1.5)	1.0 (0.6, 1.6)	1.0 (0.6, 1.7)
IL10					
rs7539748	A	0.9 (0.6, 1.4)	1.0 (0.6, 1.5)	1.7 (0.9, 3.3)	1.9 (0.9, 4.2)
rs11119451*	C	1.2 (0.9, 1.7)	1.1 (0.8, 1.6)	1.0 (0.7, 1.5)	1.0 (0.7, 1.5)
rs6658896	T	1.4 (0.6, 2.9)	1.3 (0.6, 3.1)	0.7 (0.4, 1.2)	0.6 (0.3, 1.3)
rs6692511*	T	0.9 (0.7, 1.2)	1.0 (0.7, 1.4)	1.0 (0.7, 1.6)	1.0 (0.6, 1.7)
rs6699203*	A	0.8 (0.6, 1.1)	1.0 (0.7, 1.3)	1.0 (0.7, 1.6)	1.0 (0.6, 1.7)
rs4390174*	G	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	1.2 (0.9, 1.7)	1.3 (0.9, 1.9)
rs6673928	T	0.9 (0.6, 1.4)	1.0 (0.6, 1.5)	1.3 (0.8, 2.1)	1.8 (1.0, 3.1)
rs3024496*	C	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)	1.1 (0.8, 1.4)	1.0 (0.7, 1.5)
rs1878672	G	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)	1.3 (0.8, 2.0)	1.2 (0.7, 2.1)
rs3024493	T	0.9 (0.6, 1.4)	0.8 (0.5, 1.3)	1.2 (0.5, 2.8)	1.0 (0.3, 2.8)
rs3024491	T	0.9 (0.6, 1.3)	0.8 (0.5, 1.3)	1.2 (0.8, 1.9)	1.1 (0.7, 1.8)
rs3024490*	T	0.8 (0.6, 1.1)	0.9 (0.6, 1.4)	1.0 (0.8, 1.4)	1.0 (0.7, 1.5)
rs1800871*	T	0.8 (0.6, 1.1)	0.9 (0.6, 1.4)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)
rs1800890	A	0.9 (0.6, 1.4)	1.0 (0.6, 1.5)	1.3 (0.9, 2.1)	1.4 (0.9, 2.4)
rs17015767	C	1.0 (0.7, 1.5)	1.0 (0.7, 1.6)	1.2 (0.7, 2.0)	1.6 (0.9, 2.9)
rs10494879*	G	1.1 (0.9, 1.5)	1.1 (0.8, 1.5)	1.2 (0.8, 1.6)	1.2 (0.8, 1.8)
rs6686931*	T	0.9 (0.7, 1.3)	1.0 (0.7, 1.4)	0.9 (0.7, 1.3)	0.9 (0.7, 1.4)
IL1A					
rs17561	T	1.0 (0.6, 1.4)	1.0 (0.6, 1.5)	1.1 (0.7, 1.8)	1.0 (0.6, 1.7)
rs1800587	T	1.0 (0.7, 1.4)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	0.9 (0.5, 1.6)
IL1B					
rs1143634	T	0.9 (0.6, 1.4)	1.0 (0.6, 1.5)	0.7 (0.4, 1.3)	0.6 (0.3, 1.2)
rs1143627*	T	1.1 (0.8, 1.6)	1.0 (0.7, 1.4)	0.9 (0.7, 1.3)	0.8 (0.5, 1.2)
IL8RB					
rs4674258*	C	0.8 (0.6, 1.0)	0.8 (0.6, 1.1)	1.0 (0.7, 1.3)	0.9 (0.6, 1.2)
rs4674259	G	0.8 (0.5, 1.2)	0.9 (0.5, 1.4)	0.7 (0.5, 1.2)	0.7 (0.4, 1.2)
rs6761387	T	1.4 (0.7, 2.5)	1.3 (0.6, 2.5)	1.0 (0.6, 1.6)	0.8 (0.5, 1.5)
rs4674261*	C	1.3 (1.0, 1.7)	1.2 (0.9, 1.7)	1.1 (0.8, 1.5)	1.2 (0.8, 1.7)
rs11677534	T	0.8 (0.5, 1.2)	0.9 (0.5, 1.4)	1.0 (0.6, 1.5)	1.0 (0.6, 1.6)
rs11676348*	C	0.8 (0.6, 1.0)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.7 (0.5, 1.0)
IL12A					
rs503582*	T	0.9 (0.7, 1.1)	0.9 (0.6, 1.2)	0.9 (0.7, 1.2)	0.8 (0.6, 1.2)
rs532953	C	0.8 (0.5, 1.2)	0.7 (0.4, 1.2)	1.4 (0.8, 2.2)	1.3 (0.7, 2.5)
rs7653097	C	0.8 (0.5, 1.5)	0.8 (0.4, 1.6)	1.2 (0.7, 1.8)	1.1 (0.6, 1.9)
rs1014486*	G	1.1 (0.9, 1.5)	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	1.1 (0.8, 1.6)
rs13064168	A	0.8 (0.5, 1.3)	1.0 (0.6, 1.5)	1.4 (0.8, 2.5)	1.3 (0.6, 2.7)
rs609907	C	0.7 (0.5, 1.1)	0.7 (0.5, 1.1)	1.2 (0.7, 1.9)	1.1 (0.6, 2.0)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
rs2647929	A	1.1 (0.7, 1.6)	1.0 (0.6, 1.5)	0.7 (0.4, 1.1)	0.7 (0.4, 1.3)
rs2886666	T	1.8 (1.2, 2.6)	1.7 (1.1, 2.7)	0.6 (0.2, 1.6)	0.7 (0.2, 2.0)
rs9811792	C	1.3 (0.8, 2.0)	1.2 (0.8, 2.0)	0.9 (0.6, 1.3)	0.9 (0.5, 1.5)
rs16830946	G			0.8 (0.5, 1.4)	0.8 (0.4, 1.6)
rs7372767	G	1.1 (0.7, 1.6)	1.0 (0.6, 1.6)	0.7 (0.4, 1.1)	0.7 (0.4, 1.3)
rs6441282*	T	1.0 (0.8, 1.3)	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)	0.9 (0.6, 1.3)
rs692890*	T	0.8 (0.6, 1.1)	0.9 (0.6, 1.2)	1.0 (0.7, 1.4)	0.9 (0.6, 1.4)
rs755004	T	1.1 (0.8, 1.7)	1.2 (0.8, 2.0)	1.2 (0.6, 2.4)	1.5 (0.7, 3.2)
rs16830949	T			1.1 (0.7, 1.7)	1.1 (0.6, 1.9)
rs2243115	G	1.0 (0.6, 1.7)	0.9 (0.5, 1.6)	1.3 (0.8, 2.2)	1.4 (0.7, 2.6)
rs583911	G	1.5 (0.9, 2.3)	1.5 (0.9, 2.4)	0.9 (0.6, 1.4)	1.2 (0.7, 2.0)
rs2243151*	T	0.9 (0.7, 1.2)	0.8 (0.6, 1.1)	1.0 (0.8, 1.4)	0.9 (0.6, 1.4)
rs2243154	A	1.0 (0.6, 1.7)	1.2 (0.7, 2.0)	0.7 (0.2, 2.7)	1.0 (0.3, 4.0)
rs4608735	C	1.0 (0.6, 1.6)	0.9 (0.5, 1.6)	1.4 (0.9, 2.2)	1.3 (0.7, 2.3)
rs17826053	G	0.8 (0.5, 1.2)	0.8 (0.5, 1.3)	0.9 (0.5, 1.4)	0.7 (0.4, 1.3)
rs485497	A	1.4 (0.9, 2.3)	1.5 (0.9, 2.4)	0.9 (0.6, 1.4)	1.1 (0.6, 1.8)
rs4680536*	G	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	1.1 (0.8, 1.6)	1.0 (0.7, 1.5)
rs12492730	G			1.4 (0.9, 2.3)	1.4 (0.8, 2.5)
rs9852519	T	1.3 (0.9, 2.0)	1.3 (0.9, 2.1)	0.8 (0.5, 1.2)	1.0 (0.5, 1.7)
rs598638	T	1.0 (0.7, 1.5)	0.9 (0.6, 1.5)	1.3 (0.5, 3.1)	1.5 (0.5, 4.2)
IL8					
rs7654490	T	4.0 (0.5, 30.7)		0.8 (0.5, 1.3)	0.8 (0.5, 1.5)
rs16849893	A			1.0 (0.6, 1.6)	0.9 (0.5, 1.6)
rs16849896	T			0.7 (0.4, 1.1)	0.7 (0.4, 1.3)
rs4694634	C			1.1 (0.7, 1.7)	0.8 (0.5, 1.4)
rs16849907	T			1.0 (0.6, 1.8)	1.1 (0.6, 2.1)
rs12506479	C	0.9 (0.6, 1.3)	0.8 (0.5, 1.2)	0.9 (0.6, 1.4)	0.9 (0.5, 1.5)
rs10805066*	G	1.4 (1.0, 1.8)	1.6 (1.2, 2.1)	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)
rs7693566	C			0.7 (0.4, 1.1)	0.6 (0.3, 1.0)
rs4694635	T	1.8 (0.6, 5.6)	1.2 (0.3, 5.4)	1.3 (0.8, 2.0)	1.4 (0.8, 2.5)
rs16849928*	A	1.1 (0.8, 1.4)	1.2 (0.9, 1.6)	1.3 (0.9, 1.7)	1.4 (1.0, 2.0)
rs11730667	A	1.3 (0.8, 2.1)	1.7 (1.0, 3.1)	1.4 (0.9, 2.2)	1.5 (0.9, 2.5)
rs13142454	G			1.3 (0.8, 2.1)	1.6 (0.9, 2.7)
rs11729759	A			1.4 (0.9, 2.2)	1.9 (1.1, 3.2)
rs1951240*	G	0.9 (0.7, 1.2)	0.8 (0.6, 1.1)	1.0 (0.7, 1.4)	1.1 (0.7, 1.6)
rs16849958	C	1.0 (0.6, 1.5)	0.9 (0.6, 1.4)	0.8 (0.5, 1.3)	0.7 (0.4, 1.3)
rs1951242	T	1.4 (0.8, 2.3)	1.8 (1.0, 3.2)	1.1 (0.7, 1.8)	1.2 (0.7, 2.0)
rs7658422	C			1.3 (0.9, 2.1)	1.8 (1.1, 3.0)
CXCL10					
rs3733236	T	1.5 (0.9, 2.4)	1.5 (0.9, 2.6)	1.2 (0.8, 1.8)	1.4 (0.9, 2.4)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
rs10031051	C	0.8 (0.3, 2.5)	0.7 (0.2, 2.7)	1.1 (0.6, 1.9)	1.1 (0.5, 2.1)
rs7670156	A	1.3 (0.8, 2.0)	1.3 (0.8, 2.2)	1.2 (0.7, 2.0)	1.5 (0.8, 2.8)
rs12651276	G	1.0 (0.7, 1.5)	1.0 (0.6, 1.5)	0.5 (0.2, 1.3)	0.3 (0.1, 1.2)
rs10518143	C	0.7 (0.5, 1.1)	0.7 (0.4, 1.0)	0.6 (0.3, 1.1)	0.5 (0.2, 1.1)
rs867562	A	1.0 (0.7, 1.5)	0.9 (0.6, 1.4)	0.9 (0.4, 2.1)	0.6 (0.2, 2.1)
rs4508917	G	0.7 (0.5, 1.0)	0.7 (0.4, 1.0)	0.8 (0.5, 1.2)	0.8 (0.5, 1.4)
rs12504339*	C	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)	1.0 (0.8, 1.4)	1.2 (0.8, 1.7)
rs4302486	A	1.1 (0.7, 1.6)	1.1 (0.7, 1.8)	1.0 (0.7, 1.6)	0.9 (0.5, 1.6)
NFKB1					
rs980455*	G	0.8 (0.6, 1.1)	0.9 (0.6, 1.2)	0.9 (0.6, 1.2)	1.0 (0.7, 1.5)
rs3774933*	C	0.9 (0.6, 1.1)	0.9 (0.6, 1.2)	1.0 (0.7, 1.5)	1.2 (0.8, 1.9)
rs17032705*	A	0.8 (0.6, 1.1)	0.9 (0.6, 1.2)	1.2 (0.8, 1.7)	1.4 (0.9, 2.2)
rs1599961*	A	0.9 (0.6, 1.1)	0.9 (0.6, 1.2)	1.1 (0.8, 1.6)	1.3 (0.8, 2.0)
rs17032740	G	1.1 (0.2, 8.4)	1.3 (0.2, 9.9)	0.9 (0.5, 1.5)	1.2 (0.7, 2.2)
rs230533	T	0.9 (0.6, 1.3)	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)	1.0 (0.6, 1.7)
rs230530	C	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.2 (0.7, 1.8)	1.1 (0.6, 1.9)
rs230529	A	0.8 (0.5, 1.1)	0.8 (0.5, 1.2)	0.9 (0.6, 1.4)	0.9 (0.5, 1.6)
rs17032779	C	1.4 (0.4, 4.2)	1.6 (0.5, 5.1)	1.1 (0.6, 1.8)	1.1 (0.6, 2.1)
rs230515	C	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	0.8 (0.5, 1.4)	0.8 (0.5, 1.5)
rs230493	A	0.8 (0.6, 1.2)	0.8 (0.6, 1.3)	1.0 (0.6, 1.5)	0.9 (0.5, 1.5)
rs17032815	A	1.8 (0.7, 4.7)	2.1 (0.8, 5.7)	0.9 (0.5, 1.6)	1.0 (0.5, 1.9)
rs909332	T	1.0 (0.5, 2.1)	1.2 (0.6, 2.6)	1.2 (0.7, 2.1)	1.0 (0.5, 2.0)
rs1801*	C	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	1.1 (0.8, 1.5)	1.1 (0.7, 1.7)
rs4648058*	C	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	1.1 (0.7, 1.5)	1.1 (0.7, 1.7)
rs3755867*	G	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	1.0 (0.7, 1.5)	1.1 (0.7, 1.7)
rs4648090	A	1.0 (0.6, 1.5)	0.9 (0.5, 1.5)	0.8 (0.5, 1.3)	0.7 (0.4, 1.3)
rs4648110*	A	1.2 (0.9, 1.6)	1.1 (0.8, 1.6)	0.8 (0.6, 1.1)	0.7 (0.5, 1.1)
rs3817685	G	0.8 (0.5, 1.1)	0.8 (0.5, 1.2)	1.1 (0.7, 1.7)	1.2 (0.7, 2.0)
rs4648127	T	1.5 (0.9, 2.5)	1.6 (1.0, 2.7)	1.2 (0.2, 8.1)	1.9 (0.3, 11.9)
rs230547	T	0.8 (0.4, 1.4)	0.7 (0.4, 1.5)	1.2 (0.7, 1.9)	1.2 (0.6, 2.2)
rs4648135	G	0.9 (0.4, 1.8)	1.1 (0.5, 2.3)	1.1 (0.7, 1.7)	0.9 (0.5, 1.5)
rs4648141*	A	1.2 (0.9, 1.7)	1.3 (0.9, 1.8)	0.8 (0.6, 1.1)	0.7 (0.5, 1.1)
rs7674640*	C	1.0 (0.8, 1.3)	1.0 (0.8, 1.4)	1.1 (0.8, 1.6)	1.0 (0.7, 1.6)
rs10489113*	G	1.4 (1.0, 1.9)	1.4 (1.0, 2.0)	0.8 (0.6, 1.1)	0.8 (0.5, 1.2)
rs11733293*	T	0.7 (0.6, 1.0)	0.7 (0.5, 1.0)	1.1 (0.8, 1.6)	1.2 (0.8, 1.8)
rs17033015	A	1.0 (0.7, 1.5)	1.0 (0.6, 1.5)	1.0 (0.6, 1.6)	0.9 (0.5, 1.6)
rs12648696*	C	0.8 (0.6, 1.0)	0.8 (0.5, 1.0)	1.2 (0.8, 1.6)	1.3 (0.9, 2.0)
IL2					
rs17454584	G	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	0.9 (0.4, 2.0)	1.0 (0.4, 2.5)
rs35914000	A	0.8 (0.6, 1.2)	0.8 (0.5, 1.2)	1.1 (0.5, 2.1)	1.0 (0.5, 2.3)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
rs10034410	T	7.1 (2.5, 19.8)	9.7 (3.9, 24.4)	0.8 (0.4, 1.4)	0.5 (0.2, 1.0)
rs10027390	C	1.0 (0.7, 1.5)	1.1 (0.7, 1.7)		
rs11932411	C	2.4 (0.7, 9.1)	3.2 (0.9, 11.9)	0.8 (0.5, 1.3)	0.6 (0.4, 1.0)
rs2069776	C	1.0 (0.7, 1.5)	1.1 (0.7, 1.6)	1.2 (0.7, 1.8)	1.3 (0.8, 2.3)
rs2069778	T	0.7 (0.4, 1.0)	0.7 (0.4, 1.1)	1.4 (0.6, 3.2)	1.6 (0.6, 4.3)
rs2069762	G	1.3 (0.9, 2.0)	1.4 (0.9, 2.1)	1.5 (0.9, 2.6)	1.2 (0.6, 2.5)
rs4833248	A	1.3 (0.9, 2.0)	1.4 (0.9, 2.1)	1.5 (0.9, 2.6)	1.2 (0.6, 2.5)
IL15					
rs6837991	T	0.8 (0.5, 1.1)	0.7 (0.5, 1.1)	1.0 (0.7, 1.6)	1.2 (0.7, 2.1)
rs12508866	C	1.0 (0.7, 1.5)	1.0 (0.7, 1.6)	1.2 (0.7, 2.3)	0.9 (0.4, 2.2)
rs17007476	C	5.0 (1.0, 24.3)	5.4 (1.1, 26.4)	1.1 (0.6, 1.7)	0.7 (0.4, 1.4)
rs17007480	A	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.7 (0.4, 1.5)	0.8 (0.3, 1.9)
rs1519551*	G	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	0.7 (0.5, 1.0)
rs17461269	A	0.9 (0.6, 1.3)	0.9 (0.6, 1.4)	1.2 (0.6, 2.3)	1.2 (0.5, 2.8)
rs17007503	C			0.7 (0.4, 1.4)	0.7 (0.3, 1.6)
rs1519552	A	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)	1.2 (0.8, 2.0)	1.2 (0.7, 2.0)
rs17007508	G	2.2 (0.4, 14.1)	2.4 (0.4, 14.9)	0.9 (0.6, 1.5)	1.0 (0.6, 1.8)
rs7698675	T	0.8 (0.5, 1.1)	0.8 (0.5, 1.2)	1.2 (0.8, 1.9)	1.2 (0.7, 2.0)
rs13117878*	C	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)	1.1 (0.8, 1.4)	0.8 (0.6, 1.2)
rs17364630	G	1.0 (0.7, 1.6)	1.2 (0.8, 1.9)	0.9 (0.5, 1.6)	0.7 (0.3, 1.3)
rs12498901	C	1.0 (0.7, 1.6)	1.2 (0.8, 1.9)	1.0 (0.6, 1.7)	0.8 (0.4, 1.6)
rs7671458	G	1.0 (0.7, 1.5)	1.2 (0.8, 1.9)	0.9 (0.6, 1.5)	0.8 (0.4, 1.4)
rs10519610	C	1.0 (0.7, 1.5)	1.2 (0.8, 1.8)	0.9 (0.6, 1.3)	0.7 (0.4, 1.2)
rs6850492	A	0.8 (0.6, 1.2)	0.9 (0.6, 1.4)	1.1 (0.7, 1.7)	0.8 (0.5, 1.4)
rs2087849	T	0.8 (0.6, 1.2)	0.8 (0.5, 1.3)	1.4 (0.9, 2.2)	1.5 (0.9, 2.6)
rs2857261*	G	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)	1.0 (0.7, 1.3)	1.2 (0.9, 1.8)
rs1907949	T	1.2 (0.8, 1.9)	1.0 (0.6, 1.7)	0.6 (0.3, 1.0)	0.4 (0.2, 0.9)
rs3775597	C	1.1 (0.7, 1.8)	0.9 (0.5, 1.6)	1.0 (0.6, 1.8)	0.9 (0.5, 1.8)
rs12508955	T	0.9 (0.6, 1.2)	0.8 (0.5, 1.3)	1.5 (0.9, 2.3)	1.2 (0.7, 2.2)
rs17007610*	T	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	0.7 (0.5, 1.1)
CSF2					
rs31400*	T	1.0 (0.8, 1.4)	1.0 (0.7, 1.3)	0.9 (0.7, 1.2)	0.9 (0.6, 1.3)
rs3091335	G	3.3 (1.2, 8.8)	2.5 (0.6, 10.2)	1.2 (0.7, 1.8)	1.0 (0.6, 1.6)
rs31481	A	1.3 (0.9, 1.9)	1.2 (0.7, 1.8)	1.4 (0.9, 2.2)	1.5 (0.8, 2.5)
rs2069801	G	3.9 (0.5, 28.4)	4.0 (0.6, 29.1)	0.6 (0.3, 1.1)	0.5 (0.2, 1.1)
rs246844	A	1.1 (0.7, 1.7)	0.9 (0.6, 1.5)	0.9 (0.6, 1.4)	1.0 (0.6, 1.6)
rs11575022	C	1.3 (0.7, 2.3)	1.0 (0.4, 2.1)	0.9 (0.6, 1.4)	1.0 (0.6, 1.8)
rs246841	T	1.2 (0.7, 1.9)	1.1 (0.6, 1.8)	1.9 (0.9, 3.9)	1.8 (0.7, 4.5)
rs168681	A	1.2 (0.8, 1.9)	1.2 (0.8, 2.0)	1.0 (0.6, 1.5)	1.0 (0.6, 1.7)
rs721121*	G	0.9 (0.7, 1.1)	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)	1.0 (0.6, 1.4)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
rs4705916	A	0.9 (0.6, 1.4)	1.0 (0.6, 1.6)	0.6 (0.4, 1.0)	0.6 (0.3, 1.0)
rs743677	G	1.4 (0.2, 10.7)		1.8 (1.2, 2.9)	1.5 (0.9, 2.6)
rs2069626	G	0.8 (0.2, 3.3)	0.5 (0.1, 3.9)	1.5 (0.9, 2.5)	1.5 (0.8, 2.9)
rs743564*	G	0.8 (0.6, 1.1)	0.9 (0.6, 1.2)	0.6 (0.4, 1.0)	0.6 (0.3, 1.0)
rs25881	T	1.1 (0.8, 1.7)	1.0 (0.6, 1.6)	1.0 (0.6, 1.5)	1.0 (0.6, 1.7)
rs25882	C	1.1 (0.8, 1.7)	1.0 (0.6, 1.6)	1.4 (0.9, 2.3)	1.4 (0.8, 2.3)
rs27438	A	1.2 (0.8, 1.8)	1.1 (0.7, 1.7)	1.2 (0.6, 2.2)	1.0 (0.5, 2.2)
rs25887*	C	1.1 (0.8, 1.4)	1.2 (0.9, 1.6)	1.3 (1.0, 1.9)	1.4 (0.9, 2.1)
rs6898270	T	0.9 (0.6, 1.4)	1.0 (0.6, 1.5)	0.6 (0.4, 0.9)	0.5 (0.3, 0.9)
IL13					
rs7737470	A	1.1 (0.7, 1.6)	1.1 (0.7, 1.8)	1.1 (0.7, 1.7)	1.1 (0.6, 1.8)
rs4621555	C			1.1 (0.7, 1.8)	1.0 (0.6, 1.9)
rs3091307	G	1.1 (0.7, 1.6)	1.1 (0.7, 1.8)	1.2 (0.6, 2.4)	1.4 (0.6, 3.5)
rs1881457	C	1.1 (0.8, 1.7)	1.2 (0.7, 1.8)	1.1 (0.7, 1.7)	1.0 (0.6, 1.8)
rs2069744	T	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.0 (0.6, 1.5)	1.2 (0.7, 2.0)
rs1295686	G	0.7 (0.3, 1.7)	0.7 (0.2, 1.8)	1.1 (0.7, 1.6)	1.2 (0.7, 2.0)
rs20541	T	0.9 (0.6, 1.4)	0.9 (0.5, 1.4)	0.9 (0.6, 1.4)	0.9 (0.5, 1.5)
rs848	T	1.0 (0.6, 1.4)	0.8 (0.5, 1.4)	0.9 (0.5, 1.4)	0.8 (0.5, 1.5)
rs1295683	T	1.1 (0.7, 1.8)	1.0 (0.6, 1.7)	0.6 (0.3, 1.1)	0.8 (0.4, 1.6)
rs2243204	T	0.7 (0.4, 1.3)	0.6 (0.3, 1.3)	1.5 (0.8, 2.8)	1.4 (0.6, 2.9)
rs2243210	A	0.9 (0.5, 1.7)	1.0 (0.5, 1.8)	1.0 (0.7, 1.6)	1.0 (0.6, 1.7)
rs2243218	A	0.9 (0.5, 1.7)	1.0 (0.6, 1.9)	1.3 (0.8, 2.0)	1.1 (0.6, 1.9)
rs2243219	G	1.1 (0.6, 1.8)	1.1 (0.6, 2.0)	1.2 (0.7, 2.2)	1.0 (0.5, 2.0)
IL4					
rs2243240	T			1.4 (0.8, 2.6)	1.3 (0.6, 2.8)
rs2243246	C			0.9 (0.5, 1.4)	0.8 (0.4, 1.4)
rs2243248	G	0.9 (0.5, 1.6)	0.8 (0.4, 1.6)	1.2 (0.8, 1.9)	1.1 (0.6, 1.9)
rs2243250	C	0.3 (0.1, 0.8)	0.3 (0.1, 0.7)	1.2 (0.8, 1.9)	1.3 (0.7, 2.1)
rs2243253	T			1.7 (1.1, 2.7)	1.7 (1.0, 3.0)
rs2243261	T			0.9 (0.5, 1.5)	0.8 (0.4, 1.4)
rs2243263	C	1.1 (0.7, 1.7)	1.1 (0.7, 1.9)	1.1 (0.7, 1.7)	1.1 (0.6, 1.9)
rs2243267	C	1.0 (0.6, 1.6)	1.0 (0.6, 1.7)	1.1 (0.7, 1.7)	1.1 (0.7, 1.9)
rs2243270	G	1.1 (0.7, 1.7)	1.1 (0.7, 1.9)	1.1 (0.5, 2.1)	1.0 (0.5, 2.4)
rs2243283	G	1.3 (0.3, 5.2)	0.8 (0.1, 5.6)	0.8 (0.5, 1.2)	0.7 (0.4, 1.3)
rs2243292	C	3.1 (0.9, 10.6)	2.6 (0.6, 11.9)	1.0 (0.5, 1.8)	1.3 (0.6, 2.6)
rs11242122*	G	0.9 (0.7, 1.3)	0.9 (0.6, 1.3)	1.1 (0.8, 1.5)	1.2 (0.8, 1.7)
rs11242123	T	1.0 (0.6, 1.6)	1.1 (0.6, 1.8)	0.7 (0.4, 1.0)	0.5 (0.3, 0.9)
IL12B					
rs7730126	T	1.1 (0.8, 1.6)	1.0 (0.7, 1.5)	0.9 (0.5, 1.3)	0.7 (0.4, 1.3)
rs2099327	C	1.4 (0.9, 2.1)	1.4 (0.9, 2.1)	0.8 (0.4, 1.6)	0.7 (0.3, 1.7)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
rs1549922*	G	0.8 (0.6, 1.1)	0.9 (0.7, 1.2)	0.8 (0.6, 1.2)	1.0 (0.6, 1.5)
rs4921466	C	0.7 (0.4, 1.1)	0.6 (0.3, 1.1)	1.0 (0.6, 1.7)	0.8 (0.4, 1.5)
rs10072923	C	1.3 (0.8, 1.9)	1.3 (0.8, 2.0)	1.3 (0.8, 2.1)	1.2 (0.7, 2.1)
rs1368439	G	0.8 (0.5, 1.3)	0.9 (0.6, 1.5)	0.8 (0.4, 1.6)	0.9 (0.4, 2.0)
rs3212227	C	1.2 (0.8, 1.8)	1.3 (0.8, 2.0)	1.1 (0.7, 1.7)	1.1 (0.6, 1.8)
rs11574790	T	0.7 (0.4, 1.1)	0.7 (0.4, 1.2)	1.0 (0.6, 1.5)	0.8 (0.5, 1.4)
rs2195940	T	0.7 (0.4, 1.1)	0.7 (0.4, 1.2)	1.0 (0.6, 1.5)	0.9 (0.5, 1.6)
rs919766	C	0.7 (0.4, 1.1)	0.7 (0.4, 1.2)	1.0 (0.7, 1.6)	1.0 (0.6, 1.7)
rs2853694	C	0.8 (0.5, 1.2)	0.9 (0.6, 1.5)	0.6 (0.4, 1.0)	0.7 (0.4, 1.2)
rs2569253	C	1.1 (0.7, 1.7)	1.0 (0.6, 1.6)	0.8 (0.5, 1.3)	0.9 (0.5, 1.5)
rs3212220	T	1.3 (0.9, 1.9)	1.3 (0.9, 2.0)	1.1 (0.7, 1.8)	1.1 (0.7, 1.9)
rs1433048	G	0.8 (0.5, 1.3)	0.9 (0.5, 1.4)	0.3 (0.1, 0.9)	0.4 (0.1, 1.3)
rs2546893	A	1.4 (0.9, 2.3)	1.3 (0.8, 2.2)	0.9 (0.6, 1.4)	1.0 (0.6, 1.7)
rs2546890*	A	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	1.0 (0.7, 1.4)	1.2 (0.8, 1.8)
rs10052709	G	0.8 (0.5, 1.3)	0.7 (0.4, 1.2)	1.0 (0.6, 1.7)	0.9 (0.5, 1.7)
rs7709212*	C	1.1 (0.9, 1.5)	1.2 (0.9, 1.6)	1.0 (0.7, 1.5)	1.0 (0.7, 1.6)
rs6868898	C	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)	1.0 (0.6, 1.6)	1.2 (0.7, 2.1)
LTA & TNF					
rs2857605	G	0.8 (0.6, 1.2)	0.9 (0.6, 1.4)	0.8 (0.4, 1.5)	1.0 (0.5, 2.2)
rs2239707	G	1.1 (0.8, 1.7)	1.2 (0.8, 1.9)	0.9 (0.5, 1.5)	1.1 (0.6, 2.1)
rs2230365	T	1.4 (0.9, 2.1)	1.5 (1.0, 2.4)	1.0 (0.5, 2.0)	1.0 (0.5, 2.3)
rs3130062	C	0.9 (0.5, 1.6)	0.9 (0.5, 1.7)	1.0 (0.2, 4.4)	1.3 (0.3, 6.1)
rs4947324	T	0.6 (0.4, 1.1)	0.7 (0.4, 1.2)	1.0 (0.6, 1.7)	1.1 (0.6, 2.0)
rs2857709	T	0.9 (0.6, 1.3)	0.9 (0.6, 1.5)	0.6 (0.2, 1.6)	0.9 (0.3, 2.3)
rs915654*	T	1.1 (0.8, 1.4)	1.2 (0.9, 1.5)	1.0 (0.8, 1.4)	0.9 (0.6, 1.3)
rs909253*	C	1.1 (0.8, 1.5)	1.2 (0.8, 1.6)	1.1 (0.8, 1.5)	1.1 (0.7, 1.6)
rs2229094	C	1.0 (0.7, 1.4)	1.1 (0.7, 1.7)	0.9 (0.6, 1.4)	0.9 (0.5, 1.5)
rs1041981*	A	1.1 (0.8, 1.5)	1.2 (0.8, 1.6)	1.1 (0.8, 1.5)	1.1 (0.7, 1.6)
rs1799964	C	0.9 (0.6, 1.4)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	0.9 (0.5, 1.6)
rs1800630	A	1.2 (0.8, 1.8)	1.3 (0.8, 2.0)	1.1 (0.7, 1.8)	1.0 (0.6, 1.9)
rs1800629	A	1.3 (0.8, 1.9)	1.3 (0.8, 2.1)	1.1 (0.6, 1.8)	1.2 (0.7, 2.2)
rs7769073	A	0.8 (0.4, 1.7)	0.8 (0.4, 1.8)	0.9 (0.5, 1.7)	0.9 (0.4, 1.8)
GATA3					
rs406571*	C	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)
rs1877739	C	0.8 (0.5, 1.2)	0.8 (0.5, 1.3)	1.0 (0.6, 1.6)	1.0 (0.6, 1.8)
rs532854*	C	1.0 (0.7, 1.3)	0.9 (0.7, 1.3)	0.7 (0.5, 1.0)	0.8 (0.6, 1.2)
rs10795588*	G	0.9 (0.7, 1.2)	0.8 (0.6, 1.0)	1.4 (1.0, 1.9)	1.6 (1.1, 2.3)
rs263425	T			0.5 (0.3, 1.0)	0.7 (0.4, 1.2)
rs263423*	A	1.2 (0.9, 1.7)	1.3 (0.9, 1.9)	1.0 (0.7, 1.4)	1.0 (0.7, 1.5)
rs1244186	T	1.2 (0.8, 1.7)	1.2 (0.8, 1.8)	0.9 (0.5, 1.4)	0.7 (0.4, 1.3)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
rs2275806	A	1.0 (0.6, 1.6)	0.9 (0.5, 1.5)	1.3 (0.9, 2.1)	1.5 (0.9, 2.5)
rs1269486	A	1.2 (0.8, 1.7)	1.2 (0.7, 1.8)	0.9 (0.5, 1.4)	0.7 (0.4, 1.3)
rs1399180	T	1.1 (0.7, 1.7)	1.1 (0.7, 1.8)	0.7 (0.5, 1.1)	0.7 (0.4, 1.1)
rs369421	C	1.2 (0.8, 1.9)	1.2 (0.8, 1.9)	0.9 (0.5, 1.6)	0.8 (0.4, 1.6)
rs3781094*	G	1.0 (0.8, 1.3)	0.9 (0.7, 1.2)	1.6 (1.2, 2.2)	1.6 (1.1, 2.4)
rs3781093	G	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)	0.9 (0.6, 1.4)	1.1 (0.6, 1.8)
rs376397	A	1.0 (0.7, 1.5)	1.0 (0.7, 1.6)	0.7 (0.5, 1.1)	0.6 (0.4, 1.1)
rs570613*	G	1.0 (0.8, 1.3)	1.1 (0.8, 1.4)	0.8 (0.6, 1.0)	0.8 (0.6, 1.2)
rs10752126*	G	1.1 (0.8, 1.4)	1.1 (0.8, 1.5)	0.7 (0.5, 1.0)	0.6 (0.4, 0.9)
rs569421	C	1.2 (0.8, 1.7)	1.2 (0.8, 1.9)	0.8 (0.5, 1.3)	0.8 (0.5, 1.4)
rs444929	C	0.8 (0.6, 1.2)	0.9 (0.5, 1.3)	1.1 (0.7, 1.8)	1.1 (0.7, 1.9)
rs2280015	A	1.1 (0.8, 1.7)	1.1 (0.7, 1.8)	0.7 (0.4, 1.1)	0.9 (0.5, 1.5)
rs422628	C	0.9 (0.6, 1.3)	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)	0.8 (0.5, 1.4)
rs406103	T	1.3 (0.9, 1.9)	1.3 (0.9, 2.0)	0.6 (0.4, 1.0)	0.6 (0.4, 1.0)
rs528778	T	0.8 (0.6, 1.2)	0.8 (0.5, 1.3)	1.2 (0.8, 1.8)	1.1 (0.7, 1.9)
rs11567934	A			0.7 (0.4, 1.2)	0.5 (0.2, 1.0)
rs388957	T	1.3 (0.6, 2.7)	1.3 (0.6, 2.9)	0.7 (0.4, 1.1)	0.5 (0.3, 0.9)
rs10905284	A	1.1 (0.7, 1.9)	1.0 (0.6, 1.7)	1.7 (1.1, 2.6)	1.5 (0.9, 2.6)
rs1058240	G	0.9 (0.6, 1.3)	0.9 (0.5, 1.4)	1.2 (0.7, 1.8)	1.1 (0.6, 1.8)
rs263419	T	1.2 (0.8, 1.8)	1.1 (0.7, 1.8)	0.9 (0.6, 1.4)	0.9 (0.5, 1.5)
rs12262237	A			0.9 (0.4, 1.9)	0.7 (0.3, 1.9)
rs7100967	A			1.0 (0.6, 1.8)	1.4 (0.8, 2.6)
rs477461	G	1.0 (0.7, 1.6)	1.0 (0.6, 1.6)	0.9 (0.6, 1.4)	0.9 (0.6, 1.6)
rs434645	A	0.8 (0.5, 1.3)	0.9 (0.5, 1.4)	1.0 (0.7, 1.6)	0.9 (0.5, 1.6)
rs379568	T	1.5 (1.0, 2.3)	1.7 (1.0, 2.7)	0.6 (0.4, 1.0)	0.6 (0.4, 1.1)
rs1778058*	A	1.1 (0.8, 1.4)	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)	1.4 (0.9, 2.0)
rs12412241*	A	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)	1.1 (0.8, 1.5)	1.2 (0.8, 1.7)
IL18					
rs4937075*	G	1.1 (0.8, 1.5)	1.2 (0.8, 1.6)	1.2 (0.8, 1.7)	1.3 (0.8, 2.0)
rs578784*	T	1.1 (0.8, 1.5)	1.1 (0.8, 1.6)	1.3 (0.9, 1.9)	1.5 (1.0, 2.4)
rs11214098	A			1.4 (0.9, 2.2)	1.8 (1.1, 3.2)
rs543810	G	0.8 (0.5, 1.3)	0.7 (0.4, 1.3)	1.2 (0.8, 1.8)	1.3 (0.8, 2.2)
rs5744280	T	0.9 (0.6, 1.3)	0.8 (0.5, 1.3)	1.4 (0.9, 2.2)	1.2 (0.7, 2.0)
rs5744238	A			1.2 (0.6, 2.3)	1.5 (0.7, 3.4)
rs2043055*	G	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)	1.2 (0.9, 1.5)	1.0 (0.7, 1.4)
rs360714	G	0.6 (0.1, 2.4)	0.6 (0.1, 2.5)	0.6 (0.4, 1.1)	0.6 (0.3, 1.2)
rs1946518*	T	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)	0.8 (0.6, 1.1)	0.8 (0.5, 1.1)
rs5744223	G			1.2 (0.7, 2.1)	1.2 (0.6, 2.2)
rs5744222	A	1.0 (0.7, 1.5)	1.1 (0.7, 1.7)	0.6 (0.2, 1.4)	0.3 (0.1, 1.3)
rs11214105	A	1.2 (0.8, 1.8)	1.3 (0.8, 1.9)	0.8 (0.5, 1.3)	0.8 (0.5, 1.4)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
IFNG					
rs10878760	T	1.3 (0.8, 1.9)	1.4 (0.9, 2.2)	1.1 (0.5, 2.7)	1.4 (0.5, 3.7)
rs17104856	T			1.1 (0.6, 2.0)	1.3 (0.7, 2.6)
rs2193047*	T	1.1 (0.8, 1.4)	1.1 (0.8, 1.5)	1.0 (0.7, 1.4)	1.0 (0.7, 1.5)
rs2041864*	T	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	0.9 (0.6, 1.2)	0.9 (0.6, 1.3)
rs11177074	C	1.1 (0.6, 1.8)	1.0 (0.5, 1.8)	0.9 (0.6, 1.5)	0.8 (0.5, 1.5)
rs6581794	T	1.1 (0.8, 1.6)	1.2 (0.8, 1.9)	1.0 (0.6, 1.6)	1.0 (0.6, 1.7)
rs3181035	A	1.1 (0.6, 1.8)	1.0 (0.5, 1.8)	0.9 (0.6, 1.3)	0.8 (0.5, 1.4)
rs2069727	G	0.7 (0.5, 1.1)	0.7 (0.4, 1.1)	0.8 (0.5, 1.3)	0.7 (0.4, 1.2)
rs1861494	C	1.1 (0.8, 1.6)	1.2 (0.8, 1.9)	1.0 (0.6, 1.6)	0.9 (0.5, 1.6)
rs3181032	G	2.2 (1.0, 4.8)	1.7 (0.6, 4.6)	0.9 (0.5, 1.5)	0.8 (0.4, 1.5)
rs7302488	G	1.1 (0.8, 1.7)	1.3 (0.8, 1.9)	1.0 (0.6, 1.6)	0.9 (0.5, 1.6)
rs12306852	C	1.3 (0.9, 2.0)	1.3 (0.8, 2.0)	1.1 (0.7, 1.8)	1.0 (0.6, 1.8)
TGFB3					
rs4252345	G			1.0 (0.4, 2.4)	0.7 (0.2, 2.4)
rs11466414	T	1.0 (0.6, 1.8)	1.1 (0.6, 2.1)	0.8 (0.2, 2.9)	0.0 (0.0, 0.0)
TBX21					
rs2013383	A	1.1 (0.8, 1.7)	1.2 (0.8, 1.9)	1.0 (0.6, 1.5)	0.9 (0.5, 1.4)
rs1808192	T	1.1 (0.7, 1.6)	1.1 (0.7, 1.7)	1.0 (0.6, 1.5)	0.8 (0.5, 1.4)
rs4461115	C	0.9 (0.6, 1.3)	0.8 (0.5, 1.3)	1.5 (0.8, 2.9)	1.8 (0.9, 4.0)
rs16946264	A	1.0 (0.6, 1.6)	0.9 (0.5, 1.5)	1.2 (0.7, 1.9)	1.2 (0.7, 2.1)
rs11079788	T	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)	1.3 (0.9, 2.0)	1.5 (0.9, 2.5)
rs16946878	C	1.2 (0.7, 2.1)	0.9 (0.5, 1.9)	1.2 (0.7, 2.1)	1.5 (0.8, 2.9)
rs16947078	G	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)	1.3 (0.9, 2.0)	1.6 (1.0, 2.7)
TGFB1					
rs1800471	C	0.7 (0.4, 1.2)	0.8 (0.4, 1.5)	1.2 (0.7, 2.2)	1.2 (0.6, 2.4)
KIR3DL3					
rs4441391	A	0.7 (0.5, 1.1)	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)	0.8 (0.4, 1.4)
rs1325155*	T	1.3 (1.0, 1.6)	1.3 (1.0, 1.7)	1.1 (0.8, 1.4)	1.1 (0.8, 1.7)
rs1325156	A	1.0 (0.7, 1.6)	1.1 (0.7, 1.7)	1.2 (0.8, 1.9)	1.1 (0.6, 1.8)
rs12151161	G	1.4 (0.9, 2.1)	1.4 (0.9, 2.3)	1.1 (0.7, 1.7)	1.1 (0.7, 1.9)
rs7249048	G	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.3 (0.8, 2.1)	1.3 (0.8, 2.3)
rs270775*	G	1.3 (1.0, 1.6)	1.2 (0.9, 1.6)	1.2 (0.9, 1.7)	1.3 (0.9, 1.9)
rs2296370*	A	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)	0.9 (0.7, 1.3)	0.8 (0.6, 1.3)
rs2296371*	A	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)	1.0 (0.7, 1.4)	1.0 (0.7, 1.5)
rs12982559	A	1.0 (0.7, 1.4)	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)	0.9 (0.5, 1.6)
rs11883241	T	0.9 (0.6, 1.3)	0.8 (0.5, 1.2)	1.1 (0.7, 1.7)	1.0 (0.6, 1.7)
rs6509899	A	0.7 (0.4, 1.3)	0.9 (0.5, 1.6)	1.1 (0.7, 1.7)	1.1 (0.7, 1.9)
rs1325158*	T	0.8 (0.6, 1.0)	0.7 (0.5, 1.0)	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)
rs11671355	C	1.2 (0.8, 1.8)	1.3 (0.8, 2.0)	1.0 (0.5, 1.9)	1.3 (0.6, 2.6)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
rs16985907	C	1.5 (0.8, 2.7)	1.6 (0.8, 3.0)	1.3 (0.8, 2.1)	1.0 (0.6, 1.9)
KIR2DL4					
rs35950908	A	1.0 (0.7, 1.5)	1.0 (0.6, 1.6)	0.8 (0.4, 1.5)	0.9 (0.4, 1.8)
rs17771961	G	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)	1.4 (0.9, 2.4)	1.5 (0.8, 2.8)
KIR3DL2					
rs10407958	A	1.0 (0.7, 1.7)	1.1 (0.6, 1.8)	1.1 (0.7, 1.8)	1.2 (0.7, 2.1)
rs1654644*	G	1.0 (0.8, 1.4)	1.0 (0.8, 1.4)	1.0 (0.7, 1.3)	0.9 (0.6, 1.3)
rs4806457	C	1.1 (0.5, 2.3)	1.3 (0.6, 2.9)	0.6 (0.2, 1.3)	0.7 (0.3, 1.7)
rs3745900	T	0.8 (0.6, 1.2)	0.9 (0.6, 1.4)	0.8 (0.5, 1.3)	0.8 (0.4, 1.4)
rs11672983	A	1.0 (0.7, 1.5)	1.0 (0.6, 1.5)	0.7 (0.5, 1.1)	0.7 (0.4, 1.2)
rs3816051*	C	1.1 (0.8, 1.4)	1.0 (0.7, 1.3)	0.9 (0.6, 1.2)	0.8 (0.5, 1.2)
IFNGR2					
rs6517167	T	1.0 (0.6, 1.4)	0.9 (0.6, 1.5)	1.0 (0.6, 1.5)	1.1 (0.7, 1.9)
rs11702844	G	1.0 (0.7, 1.6)	1.0 (0.6, 1.6)	0.6 (0.2, 2.1)	0.6 (0.1, 2.6)
rs16990664	T	1.2 (0.6, 2.2)	1.5 (0.8, 2.8)	1.1 (0.7, 1.8)	1.2 (0.7, 2.1)
rs9976971	A	1.2 (0.8, 1.9)	1.3 (0.8, 2.1)	1.0 (0.5, 1.8)	1.1 (0.6, 2.3)
rs9980428	T	1.1 (0.7, 1.6)	1.0 (0.6, 1.5)	0.9 (0.6, 1.4)	0.9 (0.5, 1.4)
rs9978223	A	0.9 (0.6, 1.5)	1.0 (0.6, 1.6)	1.0 (0.6, 1.7)	0.9 (0.5, 1.7)
rs2268241	A	1.0 (0.6, 1.5)	1.0 (0.6, 1.6)	1.1 (0.7, 1.8)	1.2 (0.7, 2.1)
rs9808685*	G	1.0 (0.8, 1.3)	1.0 (0.8, 1.4)	1.1 (0.8, 1.5)	1.0 (0.7, 1.4)
rs2834210	A	1.0 (0.6, 1.6)	1.1 (0.7, 1.8)	1.1 (0.7, 1.8)	1.0 (0.6, 1.6)
rs9808753	G	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)	1.2 (0.8, 1.8)	1.5 (0.9, 2.5)
rs2834212	C	1.4 (0.9, 2.2)	1.4 (0.9, 2.3)	0.9 (0.3, 3.0)	1.3 (0.4, 4.5)
rs2834213	G	0.9 (0.6, 1.3)	0.9 (0.6, 1.4)	1.3 (0.7, 2.7)	1.6 (0.7, 3.4)
rs2012075	C	1.2 (0.8, 1.9)	1.2 (0.7, 1.8)	0.9 (0.5, 1.5)	0.7 (0.4, 1.4)
rs8131980	A	1.1 (0.7, 1.5)	1.1 (0.7, 1.7)	1.0 (0.6, 1.6)	0.8 (0.5, 1.6)
GADD45A					
rs12405855	T	0.8 (0.6, 1.3)	0.8 (0.5, 1.3)	1.2 (0.5, 2.7)	0.6 (0.1, 2.6)
rs344934*	C	0.9 (0.7, 1.2)	1.1 (0.8, 1.5)	1.2 (0.9, 1.6)	1.2 (0.8, 1.8)
rs4655749	G	0.6 (0.3, 1.3)	0.7 (0.3, 1.5)	1.2 (0.8, 2.0)	1.3 (0.7, 2.3)
rs344916	C	0.7 (0.5, 1.1)	0.9 (0.6, 1.4)	1.3 (0.7, 2.3)	1.2 (0.6, 2.4)
rs10889710	A	1.1 (0.6, 1.9)	0.9 (0.5, 1.7)	0.6 (0.4, 1.0)	0.6 (0.4, 1.1)
rs646652	C	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)	1.1 (0.7, 1.8)	1.2 (0.7, 2.0)
rs2055904	T	0.6 (0.3, 1.3)	0.6 (0.3, 1.4)	1.3 (0.8, 2.1)	1.4 (0.8, 2.5)
rs604043	G	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)	1.4 (0.9, 2.1)	1.2 (0.7, 2.0)
rs2815266	A	1.0 (0.6, 1.8)	1.3 (0.7, 2.2)	1.2 (0.7, 1.9)	1.3 (0.7, 2.3)
rs624790	C	1.0 (0.6, 1.5)	1.2 (0.8, 1.9)	1.0 (0.7, 1.6)	0.9 (0.6, 1.6)
rs1511686	T			1.1 (0.7, 1.8)	0.8 (0.4, 1.6)
rs3783468	A	1.1 (0.7, 1.8)	0.9 (0.6, 1.6)	1.0 (0.6, 1.5)	0.9 (0.5, 1.6)
rs532446*	C	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)	1.0 (0.8, 1.4)	1.1 (0.7, 1.6)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
rs607375*	C	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)	1.2 (0.9, 1.6)	1.2 (0.8, 1.8)
rs685724*	G	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)	0.8 (0.6, 1.0)	0.8 (0.5, 1.1)
rs675327	T	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)	1.5 (1.0, 2.3)	1.4 (0.8, 2.5)
rs11583718*	C	1.0 (0.7, 1.3)	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)	1.1 (0.8, 1.7)
rs7546055	C	0.8 (0.5, 1.1)	0.9 (0.6, 1.3)	0.8 (0.5, 1.2)	0.7 (0.4, 1.3)
rs598602	T	0.9 (0.6, 1.4)	0.9 (0.5, 1.4)	1.3 (0.8, 2.0)	1.3 (0.8, 2.3)
rs12408005	T	1.2 (0.7, 2.0)	1.0 (0.6, 1.7)	1.0 (0.6, 1.5)	1.0 (0.6, 1.7)
RASSF1					
rs35455589	C			0.6 (0.4, 1.1)	0.7 (0.4, 1.2)
rs709210	T	1.4 (0.9, 2.0)	1.4 (0.9, 2.2)	1.0 (0.6, 1.8)	0.9 (0.5, 1.8)
rs2073498	A	1.1 (0.7, 1.7)	1.1 (0.7, 1.8)	1.4 (0.5, 3.4)	0.9 (0.2, 3.6)
rs2236947*	A	0.8 (0.6, 1.0)	0.8 (0.6, 1.1)	1.5 (1.1, 2.0)	1.4 (0.9, 2.1)
rs2073499	G	1.0 (0.6, 1.5)	0.9 (0.6, 1.5)	0.5 (0.3, 0.8)	0.6 (0.3, 1.0)
rs6446203	T	1.0 (0.4, 2.4)	0.7 (0.2, 2.1)	0.7 (0.4, 1.0)	0.7 (0.4, 1.2)
rs1989839	C	1.0 (0.6, 1.6)	1.0 (0.6, 1.7)	0.8 (0.5, 1.3)	0.9 (0.5, 1.5)
CCNA2					
rs6825926	T	0.9 (0.5, 1.6)	1.0 (0.6, 1.9)	0.9 (0.5, 1.4)	0.8 (0.5, 1.4)
rs1803183	G	0.7 (0.2, 2.2)	0.5 (0.1, 2.3)	0.7 (0.5, 1.1)	0.7 (0.4, 1.2)
rs6815050*	C	1.1 (0.9, 1.5)	1.2 (0.8, 1.6)	0.7 (0.5, 1.0)	0.8 (0.5, 1.2)
rs3217773	C	1.0 (0.7, 1.5)	1.1 (0.7, 1.6)	1.2 (0.7, 1.9)	1.0 (0.6, 1.8)
rs3217771	T	1.0 (0.7, 1.5)	1.1 (0.7, 1.6)	1.2 (0.7, 1.9)	1.0 (0.6, 1.8)
rs3217770	C			0.9 (0.5, 1.5)	1.1 (0.6, 2.0)
rs2071486*	G	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)	1.1 (0.8, 1.5)	1.3 (0.9, 1.8)
rs3217760	A			1.2 (0.5, 2.4)	0.7 (0.2, 2.0)
rs1507994*	A	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)	0.9 (0.7, 1.2)	0.8 (0.6, 1.2)
CCNH					
rs2266690	C	1.4 (1.0, 2.1)	1.4 (0.9, 2.2)	1.6 (0.9, 2.7)	1.7 (0.9, 3.3)
NOV					
rs13261466	T	1.0 (0.7, 1.5)	1.0 (0.7, 1.5)	0.7 (0.3, 1.8)	0.6 (0.2, 1.8)
rs2071526	A	1.0 (0.7, 1.4)	1.0 (0.7, 1.6)	0.7 (0.4, 1.1)	0.7 (0.4, 1.2)
rs7834596	T	1.0 (0.7, 1.5)	1.1 (0.7, 1.7)	0.9 (0.6, 1.4)	0.9 (0.6, 1.6)
rs7014927	C	1.0 (0.6, 1.4)	1.0 (0.7, 1.6)	0.7 (0.4, 1.3)	0.7 (0.4, 1.5)
rs11538929	A	0.8 (0.5, 1.3)	0.7 (0.4, 1.3)	1.7 (0.8, 3.4)	1.6 (0.7, 3.9)
rs1381337	G	4.2 (0.7, 24.6)	4.5 (0.9, 23.7)	1.7 (1.1, 2.6)	1.6 (0.9, 2.7)
rs16892531	G	0.9 (0.3, 2.4)	1.1 (0.4, 3.1)	0.8 (0.4, 1.4)	0.8 (0.4, 1.5)
rs11775043	G	1.0 (0.7, 1.4)	1.0 (0.7, 1.5)	0.6 (0.4, 1.1)	0.7 (0.4, 1.3)
rs10505358	G	0.8 (0.3, 2.1)	1.0 (0.4, 2.6)	1.2 (0.7, 2.1)	1.2 (0.6, 2.3)
rs1870779	C	0.8 (0.4, 1.7)	1.0 (0.5, 2.1)	1.0 (0.6, 1.5)	0.9 (0.5, 1.5)
rs1461693	T	0.9 (0.6, 1.4)	1.0 (0.6, 1.5)	0.6 (0.4, 0.9)	0.6 (0.4, 1.1)
rs16892578	T	1.4 (0.6, 3.4)	1.7 (0.7, 4.2)	1.4 (0.9, 2.1)	1.4 (0.8, 2.3)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
rs16892586	A	0.6 (0.2, 1.7)	0.7 (0.2, 2.1)	0.8 (0.4, 1.3)	0.7 (0.4, 1.4)
rs7001184	A	2.5 (0.7, 8.7)	3.7 (1.1, 11.9)	1.3 (0.8, 2.0)	1.2 (0.7, 2.2)
CDKN2A					
rs2811720	G	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	0.9 (0.6, 1.4)	0.9 (0.5, 1.6)
rs2518722*	T	1.2 (0.9, 1.6)	1.3 (1.0, 1.8)	0.9 (0.6, 1.2)	0.8 (0.5, 1.2)
rs10757261*	A	1.2 (0.9, 1.5)	1.2 (0.9, 1.7)	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)
rs2027938	A	1.2 (0.8, 1.7)	1.2 (0.8, 1.8)	1.0 (0.6, 1.5)	1.0 (0.6, 1.7)
rs717326	G	1.2 (0.7, 1.9)	1.2 (0.7, 2.0)	0.9 (0.5, 1.5)	0.8 (0.4, 1.6)
rs3731257	T	1.0 (0.7, 1.5)	0.9 (0.6, 1.4)	1.2 (0.7, 2.0)	1.6 (0.9, 2.9)
rs3088440	A	1.1 (0.6, 1.8)	1.0 (0.6, 1.8)	0.9 (0.5, 1.4)	0.9 (0.5, 1.6)
rs2811708	T	1.3 (0.9, 1.9)	1.4 (0.9, 2.2)	1.0 (0.6, 1.5)	1.0 (0.6, 1.8)
rs3731239	C	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)	1.4 (0.8, 2.4)	1.2 (0.6, 2.5)
rs4074785	A	1.4 (0.8, 2.2)	1.4 (0.8, 2.4)	0.9 (0.5, 1.5)	0.8 (0.4, 1.5)
CDKN2B					
rs3731206	A	0.6 (0.1, 2.5)	0.7 (0.2, 3.0)	0.8 (0.5, 1.3)	0.7 (0.4, 1.3)
rs3731204	G	1.4 (1.0, 2.1)	1.6 (1.0, 2.4)	0.8 (0.4, 1.5)	0.9 (0.4, 1.8)
rs10757262	T	1.1 (0.7, 1.6)	1.1 (0.7, 1.8)	1.1 (0.7, 1.8)	1.1 (0.7, 2.0)
rs3731194	C	0.7 (0.2, 2.9)	0.8 (0.2, 3.5)	0.8 (0.4, 1.4)	0.8 (0.4, 1.6)
rs3731191	T	0.6 (0.1, 2.5)	0.7 (0.2, 3.0)	0.9 (0.6, 1.4)	0.9 (0.5, 1.5)
rs2811711	C	1.3 (0.9, 2.0)	1.5 (0.9, 2.3)	1.4 (0.9, 2.1)	1.2 (0.7, 2.1)
rs3218022	G	1.6 (0.4, 6.0)	1.9 (0.5, 7.2)	1.5 (0.9, 2.4)	1.5 (0.8, 2.8)
rs3218020	T	1.2 (0.8, 1.8)	1.3 (0.8, 2.0)	0.7 (0.4, 1.2)	0.7 (0.4, 1.3)
rs3218009	C	1.0 (0.6, 1.6)	1.0 (0.6, 1.7)	1.0 (0.4, 2.9)	0.8 (0.2, 2.9)
rs3218002	T	1.0 (0.6, 1.5)	1.0 (0.6, 1.7)	1.1 (0.7, 1.8)	1.1 (0.7, 1.9)
rs3217999	C	1.5 (0.4, 5.7)	1.8 (0.5, 6.7)	1.3 (0.8, 2.2)	1.3 (0.7, 2.3)
rs3217992	A	1.2 (0.8, 1.8)	1.3 (0.8, 2.0)	0.6 (0.4, 1.1)	0.5 (0.3, 1.1)
rs1063192	C	1.2 (0.8, 1.8)	1.2 (0.7, 1.8)	1.2 (0.7, 2.2)	1.2 (0.6, 2.5)
rs3217989	G			1.2 (0.8, 1.8)	1.6 (0.9, 2.7)
CNNM2					
rs11191457	T	0.8 (0.5, 1.2)	0.9 (0.6, 1.4)	0.8 (0.5, 1.4)	1.0 (0.5, 1.9)
rs7897654	C	0.9 (0.6, 1.3)	1.0 (0.7, 1.6)	1.2 (0.7, 1.8)	1.3 (0.8, 2.2)
rs2297787	A	1.3 (0.8, 2.2)	1.4 (0.8, 2.4)	1.0 (0.7, 1.6)	1.4 (0.8, 2.3)
rs17787717	G	1.1 (0.7, 1.8)	1.0 (0.6, 1.8)	2.3 (1.2, 4.2)	2.8 (1.4, 5.6)
rs7902220	C	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	2.1 (1.1, 3.7)	1.5 (0.6, 3.6)
rs6584535	T	1.3 (0.9, 2.0)	1.4 (0.9, 2.1)	0.3 (0.1, 1.0)	0.2 (0.0, 1.1)
rs11191512	G	0.8 (0.5, 1.2)	0.9 (0.6, 1.4)	1.3 (0.8, 2.1)	1.3 (0.8, 2.3)
rs7914558*	A	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)	1.2 (0.9, 1.6)	1.3 (0.9, 1.8)
rs4917991*	C	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)	1.2 (0.9, 1.6)	1.2 (0.8, 1.7)
rs11191527	T	0.8 (0.5, 1.3)	0.9 (0.6, 1.4)	0.7 (0.4, 1.2)	0.8 (0.4, 1.6)
rs12264034	T	2.1 (0.3, 12.9)	2.3 (0.4, 14.0)	1.0 (0.6, 1.5)	1.1 (0.7, 1.9)

Gene/SNP	Variant Allele	European American		African American	
		SGA	Term SGA	SGA	Term SGA
rs11191537	G	1.1 (0.7, 1.7)	1.2 (0.8, 1.9)	1.2 (0.8, 2.0)	1.3 (0.7, 2.3)
rs7087944	T	4.7 (0.9, 24.2)	5.0 (1.0, 26.4)	1.0 (0.6, 1.7)	1.0 (0.6, 1.8)
rs2296569	C	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)	0.8 (0.3, 2.2)	1.1 (0.4, 2.9)
rs4917995	A	1.0 (0.7, 1.6)	0.9 (0.6, 1.5)	1.3 (0.8, 2.0)	1.2 (0.7, 2.1)
rs11191549*	T	1.0 (0.8, 1.4)	1.1 (0.8, 1.5)	1.2 (0.9, 1.7)	1.2 (0.8, 1.7)
CCND1					
rs7106515	G			0.8 (0.5, 1.3)	0.7 (0.4, 1.4)
rs1982774	T	0.9 (0.6, 1.3)	0.8 (0.5, 1.3)	1.5 (0.9, 2.3)	1.7 (1.0, 2.9)
rs592483	C	0.8 (0.6, 1.2)	0.8 (0.5, 1.3)	1.5 (1.0, 2.3)	1.6 (0.9, 2.7)
rs611003*	A	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)	1.1 (0.7, 1.6)
rs11827026	A	0.9 (0.4, 1.8)	0.8 (0.3, 1.9)	0.8 (0.5, 1.2)	0.8 (0.5, 1.4)
rs655089*	G	1.0 (0.8, 1.4)	1.0 (0.8, 1.4)	0.9 (0.7, 1.2)	0.8 (0.6, 1.2)
rs667515*	C	1.1 (0.8, 1.4)	1.1 (0.8, 1.5)	1.0 (0.8, 1.4)	1.3 (0.9, 1.8)
rs2450254*	T	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)	0.9 (0.7, 1.2)	1.2 (0.8, 1.6)
rs3212860	T	2.7 (0.4, 17.8)	4.7 (0.7, 33.4)	0.9 (0.6, 1.5)	0.9 (0.5, 1.6)
rs1352075	T	0.9 (0.6, 1.3)	0.8 (0.5, 1.3)	0.9 (0.6, 1.4)	0.9 (0.5, 1.5)
rs3862792	T	0.9 (0.4, 2.3)	0.7 (0.2, 2.1)	0.7 (0.4, 1.3)	0.7 (0.4, 1.4)
rs603965	A	1.0 (0.6, 1.5)	0.9 (0.6, 1.5)	0.8 (0.5, 1.2)	0.8 (0.4, 1.3)
rs3918298	A	1.1 (0.5, 2.6)	0.9 (0.3, 2.4)	0.7 (0.5, 1.1)	0.7 (0.4, 1.2)
rs649392*	G	0.9 (0.7, 1.3)	0.9 (0.7, 1.3)	1.0 (0.7, 1.4)	1.0 (0.7, 1.5)
rs3212891*	C	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)	1.0 (0.8, 1.4)	1.1 (0.7, 1.6)
rs7121246	T	2.6 (0.2, 27.3)	2.6 (0.2, 28.8)	0.8 (0.5, 1.3)	0.9 (0.5, 1.5)
rs12281701	C	2.6 (0.2, 27.3)	2.6 (0.2, 28.8)	0.8 (0.5, 1.4)	0.8 (0.4, 1.5)
rs1192925*	C	1.0 (0.7, 1.3)	0.9 (0.7, 1.3)	1.1 (0.8, 1.6)	1.2 (0.8, 1.9)
MDM2					
rs769412	G	1.3 (0.8, 2.1)	1.2 (0.7, 2.2)	0.8 (0.4, 1.4)	0.7 (0.4, 1.5)

Empty cell reflect non-polymorphic SNPs, zero cell counts or deviation from HWE (IL2:rs10027390).

*Additive model presented

Minor allele chosen as minor for both ancestry groups or the Global Minor Allele noted in dbSNP

Table S19: Paper #2 Risk ratios and 95% confidence intervals for all genotyped SNPs and Preeclampsia and Gestational Hypertension stratified by genetic ancestry (dominant model)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
NFKBIL1		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
rs2857605	G	1.1 (0.7, 1.6)	0.8 (0.6, 1.1)	1.0 (0.5, 1.9)	1.0 (0.6, 1.6)
rs2239707	G	1.0 (0.6, 1.5)	0.9 (0.7, 1.2)	1.4 (0.8, 2.4)	1.1 (0.7, 1.7)
rs2230365	T	0.9 (0.6, 1.5)	1.3 (0.9, 1.7)	1.5 (0.8, 3.0)	1.2 (0.7, 2.0)
rs3130062	C	1.2 (0.7, 2.1)	0.8 (0.5, 1.2)	1.7 (0.5, 5.4)	1.0 (0.3, 2.8)
rs4947324	T	0.6 (0.3, 1.1)	0.7 (0.5, 1.1)	0.9 (0.5, 1.7)	1.2 (0.8, 1.9)
rs2857709	T	1.0 (0.6, 1.6)	0.7 (0.5, 1.0)	0.8 (0.3, 1.9)	0.8 (0.4, 1.6)
LTA					
rs915654*	T	0.9 (0.7, 1.2)	1.1 (0.9, 1.4)	1.4 (1.0, 2.0)	1.1 (0.9, 1.4)
rs909253*	C	1.5 (1.1, 2.0)	1.1 (0.9, 1.4)	1.0 (0.7, 1.4)	0.8 (0.6, 1.1)
rs2229094	C	0.6 (0.4, 1.0)	1.1 (0.8, 1.4)	1.3 (0.8, 2.1)	1.4 (1.0, 2.0)
rs1041981*	A	1.4 (1.0, 2.0)	1.1 (0.9, 1.3)	1.0 (0.7, 1.5)	0.8 (0.7, 1.1)
TNF					
rs1799964	C	0.7 (0.4, 1.1)	1.0 (0.8, 1.4)	1.0 (0.6, 1.8)	1.4 (1.0, 2.0)
rs1800630	A	0.8 (0.5, 1.2)	1.2 (0.9, 1.7)	1.4 (0.8, 2.4)	1.4 (0.9, 2.1)
rs1800629	A	1.8 (1.1, 2.7)	1.1 (0.8, 1.4)	0.6 (0.3, 1.2)	1.0 (0.7, 1.6)
rs7769073	A	0.8 (0.4, 1.8)	0.6 (0.4, 1.1)	0.9 (0.4, 1.7)	1.2 (0.8, 2.0)
TBKBP1					
rs2013383	A	0.6 (0.4, 0.9)	1.1 (0.8, 1.5)	1.1 (0.7, 1.8)	1.0 (0.7, 1.5)
rs1808192	T	0.6 (0.4, 0.9)	1.1 (0.8, 1.4)	1.0 (0.6, 1.6)	1.1 (0.8, 1.6)
TBX21					
rs4461115	C	1.2 (0.8, 1.9)	1.2 (0.9, 1.5)	0.8 (0.3, 2.0)	1.3 (0.8, 2.2)
rs16946264	A	1.1 (0.6, 1.8)	0.9 (0.6, 1.3)	1.0 (0.6, 1.6)	1.1 (0.8, 1.7)
rs11079788	T	0.8 (0.5, 1.3)	0.9 (0.7, 1.2)	1.2 (0.7, 1.9)	1.1 (0.8, 1.6)
rs16946878	C	1.3 (0.7, 2.4)	0.8 (0.5, 1.4)	1.0 (0.5, 1.9)	1.2 (0.8, 1.9)
rs16947078	G	0.8 (0.5, 1.3)	0.9 (0.7, 1.2)	0.8 (0.5, 1.3)	1.1 (0.8, 1.6)
TNFRSF1B					
rs496888*	G	0.8 (0.6, 1.1)	1.0 (0.8, 1.2)	0.9 (0.6, 1.3)	0.8 (0.6, 1.1)
rs3766730	T	1.3 (0.8, 2.0)	0.9 (0.7, 1.3)	0.9 (0.4, 2.0)	0.8 (0.4, 1.5)
rs816050	T	1.3 (0.8, 2.0)	1.1 (0.8, 1.4)	0.5 (0.3, 0.9)	0.9 (0.6, 1.3)
rs1201157*	T	0.8 (0.6, 1.1)	1.0 (0.8, 1.2)	1.3 (0.9, 1.8)	1.1 (0.8, 1.4)
rs1061622	G	1.0 (0.6, 1.5)	1.0 (0.7, 1.3)	0.7 (0.4, 1.3)	0.9 (0.6, 1.3)
rs5746051	G	1.3 (0.8, 1.9)	1.0 (0.7, 1.3)	0.7 (0.3, 1.6)	0.9 (0.5, 1.5)
rs5746053	A	1.2 (0.8, 1.9)	1.0 (0.7, 1.3)	1.1 (0.6, 1.9)	0.9 (0.6, 1.4)
rs1061624*	G	1.0 (0.7, 1.3)	0.8 (0.7, 1.0)	1.0 (0.7, 1.4)	0.8 (0.6, 1.0)
rs1061628*	T	1.1 (0.8, 1.4)	1.0 (0.8, 1.3)	1.0 (0.7, 1.5)	0.9 (0.7, 1.2)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
IL6R					
rs11265607*	G	1.2 (0.8, 1.6)	1.0 (0.8, 1.2)	0.9 (0.6, 1.3)	0.9 (0.7, 1.2)
rs6427627*	C	1.2 (0.9, 1.7)	0.9 (0.8, 1.1)	0.8 (0.6, 1.1)	0.9 (0.7, 1.2)
rs11265608	A	1.2 (0.7, 2.1)	0.8 (0.6, 1.2)	0.9 (0.5, 1.6)	1.0 (0.7, 1.6)
rs17654071	G	0.8 (0.5, 1.3)	1.1 (0.8, 1.5)	1.1 (0.7, 1.8)	1.1 (0.8, 1.6)
rs2054855	T	0.7 (0.4, 1.2)	1.0 (0.7, 1.4)	1.6 (1.0, 2.7)	1.3 (0.9, 1.9)
rs4845615	A		1.7 (0.4, 7.2)	1.3 (0.7, 2.4)	1.0 (0.6, 1.6)
rs1552481	G		2.6 (1.0, 6.4)	1.3 (0.8, 2.1)	1.0 (0.7, 1.4)
rs4845617	A	1.0 (0.6, 1.6)	0.9 (0.7, 1.3)	0.8 (0.5, 1.2)	0.7 (0.5, 1.0)
rs6427641*	G	1.1 (0.8, 1.5)	1.1 (0.9, 1.3)	0.9 (0.6, 1.2)	0.8 (0.6, 1.1)
rs11265610	C		2.0 (0.6, 6.1)	0.9 (0.6, 1.5)	1.0 (0.7, 1.4)
rs12083537	G	1.0 (0.6, 1.5)	1.7 (1.3, 2.2)	0.8 (0.5, 1.3)	0.8 (0.6, 1.2)
rs1386821	C	1.0 (0.6, 1.6)	1.7 (1.3, 2.2)	1.3 (0.7, 2.2)	1.0 (0.7, 1.5)
rs12090237	A	1.3 (0.4, 3.9)	1.5 (0.8, 2.8)	0.6 (0.3, 1.1)	0.8 (0.6, 1.3)
rs6684439	T	0.9 (0.6, 1.4)	1.0 (0.8, 1.3)	0.8 (0.5, 1.3)	1.0 (0.7, 1.4)
rs12096944	T			0.9 (0.5, 1.9)	0.9 (0.5, 1.5)
rs12060250	G			0.9 (0.5, 1.9)	0.9 (0.6, 1.5)
rs4845618*	G	1.1 (0.8, 1.5)	1.0 (0.8, 1.2)	1.0 (0.7, 1.5)	1.0 (0.8, 1.3)
rs7549250*	C	1.1 (0.8, 1.5)	1.0 (0.8, 1.3)	1.0 (0.6, 1.4)	1.1 (0.8, 1.4)
rs7518199*	C	1.0 (0.7, 1.4)	1.0 (0.8, 1.2)	1.2 (0.8, 1.9)	1.3 (1.0, 1.8)
rs4553185*	C	1.1 (0.8, 1.5)	1.0 (0.8, 1.3)	1.1 (0.8, 1.7)	1.2 (0.9, 1.5)
rs4845623*	G	1.0 (0.7, 1.4)	1.0 (0.8, 1.2)	0.9 (0.6, 1.3)	1.1 (0.9, 1.5)
rs4537545*	T	1.0 (0.7, 1.4)	1.0 (0.8, 1.2)	0.8 (0.6, 1.2)	1.1 (0.8, 1.4)
rs4845626	T	0.9 (0.6, 1.5)	1.1 (0.8, 1.5)	0.9 (0.6, 1.5)	0.8 (0.6, 1.2)
rs4845374	A	0.8 (0.5, 1.4)	1.2 (0.9, 1.6)	0.8 (0.5, 1.3)	0.7 (0.5, 0.9)
rs11265618	T	0.9 (0.6, 1.5)	1.1 (0.8, 1.5)	0.9 (0.6, 1.5)	0.9 (0.6, 1.2)
rs4329505	C	0.8 (0.5, 1.3)	1.2 (0.9, 1.5)	0.8 (0.5, 1.3)	0.9 (0.7, 1.4)
rs4341355	C	1.1 (0.7, 1.6)	0.9 (0.7, 1.2)	1.2 (0.6, 2.2)	0.9 (0.6, 1.4)
rs2229238	T	1.0 (0.7, 1.6)	0.8 (0.6, 1.1)	1.4 (0.8, 2.2)	1.1 (0.7, 1.5)
rs4072391	T	1.0 (0.7, 1.6)	0.8 (0.6, 1.1)	1.2 (0.8, 2.0)	1.1 (0.8, 1.6)
rs11265621*	G	1.0 (0.7, 1.4)	0.9 (0.7, 1.1)	1.0 (0.7, 1.4)	0.8 (0.6, 1.0)
rs7526293	T	1.2 (0.8, 1.8)	0.9 (0.6, 1.2)	1.3 (0.8, 2.1)	1.1 (0.8, 1.6)
IL10					
rs7539748	A	1.0 (0.6, 1.5)	0.9 (0.7, 1.2)	1.5 (0.7, 3.2)	1.0 (0.6, 1.9)
rs11119451	C	0.9 (0.6, 1.4)	1.0 (0.8, 1.4)	0.9 (0.6, 1.5)	1.2 (0.9, 1.8)
rs6658896	T	0.5 (0.1, 1.9)	0.7 (0.4, 1.5)	1.0 (0.6, 1.9)	0.9 (0.6, 1.4)
rs6692511	T	0.9 (0.6, 1.4)	0.8 (0.6, 1.0)	1.2 (0.7, 1.9)	1.1 (0.8, 1.6)
rs6699203	A	0.9 (0.6, 1.4)	0.8 (0.6, 1.0)	1.2 (0.7, 1.9)	1.1 (0.8, 1.6)
rs4390174*	G	1.1 (0.8, 1.4)	1.0 (0.8, 1.2)	1.0 (0.7, 1.4)	1.1 (0.9, 1.5)
rs6673928	T	1.3 (0.9, 2.1)	1.0 (0.8, 1.3)	0.7 (0.4, 1.4)	1.1 (0.7, 1.6)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
rs3024496*	C	0.9 (0.7, 1.3)	1.2 (1.0, 1.4)	1.0 (0.7, 1.4)	1.2 (0.9, 1.5)
rs1878672*	G	0.9 (0.7, 1.3)	1.2 (1.0, 1.4)	0.9 (0.6, 1.4)	1.2 (0.9, 1.5)
rs3024493	T	0.8 (0.5, 1.3)	1.5 (1.1, 2.0)	1.0 (0.4, 2.5)	1.1 (0.6, 2.0)
rs3024491*	T	1.0 (0.7, 1.3)	1.2 (1.0, 1.4)	0.9 (0.6, 1.4)	1.1 (0.9, 1.5)
rs3024490	T	1.0 (0.6, 1.5)	0.8 (0.6, 1.1)	0.6 (0.4, 0.9)	1.1 (0.8, 1.6)
rs1800871	T	0.9 (0.6, 1.5)	0.8 (0.6, 1.1)	0.6 (0.4, 0.9)	1.1 (0.8, 1.7)
rs1800890	A	1.0 (0.7, 1.6)	1.2 (0.9, 1.5)	0.8 (0.5, 1.2)	1.1 (0.8, 1.6)
rs17015767	C	1.4 (0.9, 2.1)	1.0 (0.8, 1.4)	0.8 (0.5, 1.5)	1.0 (0.7, 1.5)
rs10494879*	G	1.0 (0.7, 1.3)	1.2 (1.0, 1.4)	0.8 (0.5, 1.2)	1.0 (0.8, 1.4)
rs6686931	T	1.1 (0.7, 1.7)	0.8 (0.6, 1.1)	0.8 (0.5, 1.2)	1.1 (0.8, 1.6)
IL1A					
rs17561	T	0.9 (0.6, 1.4)	1.1 (0.9, 1.5)	0.8 (0.5, 1.4)	0.8 (0.5, 1.2)
rs1800587*	T	0.9 (0.7, 1.3)	1.2 (1.0, 1.5)	0.7 (0.5, 1.0)	0.8 (0.6, 1.0)
IL1B					
rs1143634	T	1.1 (0.7, 1.7)	1.3 (1.0, 1.7)	0.7 (0.4, 1.3)	0.9 (0.6, 1.3)
rs1143627*	T	0.8 (0.6, 1.2)	0.9 (0.8, 1.2)	1.3 (0.9, 1.8)	0.9 (0.7, 1.2)
IL8RB					
rs4674258*	C	0.9 (0.7, 1.2)	1.0 (0.8, 1.2)	1.1 (0.8, 1.5)	0.9 (0.7, 1.1)
rs4674259	G	0.7 (0.5, 1.2)	1.0 (0.7, 1.4)	1.3 (0.8, 2.1)	0.8 (0.6, 1.2)
rs6761387	T	0.9 (0.4, 2.1)	1.1 (0.7, 1.7)	0.6 (0.3, 1.0)	1.0 (0.6, 1.4)
rs4674261*	C	1.0 (0.8, 1.4)	1.0 (0.8, 1.3)	1.1 (0.8, 1.6)	1.1 (0.9, 1.4)
rs11677534*	T	0.9 (0.6, 1.2)	1.0 (0.8, 1.2)	1.4 (1.0, 2.0)	0.9 (0.7, 1.2)
rs11676348*	C	0.9 (0.6, 1.2)	1.0 (0.8, 1.2)	0.8 (0.6, 1.1)	0.8 (0.7, 1.1)
IL12A					
rs503582*	T	1.3 (0.9, 1.7)	1.0 (0.8, 1.2)	0.9 (0.6, 1.3)	1.1 (0.9, 1.4)
rs532953	C	0.5 (0.3, 0.9)	1.1 (0.8, 1.4)	1.0 (0.6, 1.8)	0.9 (0.6, 1.4)
rs7653097	C	1.3 (0.7, 2.2)	0.9 (0.6, 1.4)	1.3 (0.8, 2.1)	0.8 (0.6, 1.2)
rs1014486*	G	1.0 (0.8, 1.4)	1.0 (0.8, 1.2)	1.2 (0.8, 1.6)	1.1 (0.8, 1.4)
rs13064168	A	0.9 (0.6, 1.4)	0.9 (0.7, 1.2)	0.7 (0.3, 1.6)	0.9 (0.5, 1.5)
rs609907	C	0.7 (0.4, 1.0)	0.9 (0.7, 1.1)	0.9 (0.5, 1.6)	0.9 (0.6, 1.3)
rs2647929	A	1.2 (0.7, 1.8)	1.0 (0.7, 1.3)	1.2 (0.7, 2.0)	1.0 (0.7, 1.5)
rs2886666	T	1.2 (0.8, 1.8)	1.2 (0.9, 1.6)	0.8 (0.3, 2.0)	1.4 (0.8, 2.5)
rs9811792*	C	1.2 (0.9, 1.6)	1.0 (0.8, 1.3)	1.2 (0.8, 1.8)	1.0 (0.8, 1.3)
rs16830946	G		1.3 (0.3, 6.1)	1.0 (0.6, 1.8)	0.8 (0.5, 1.2)
rs7372767	G	1.2 (0.7, 1.9)	1.0 (0.7, 1.3)	1.0 (0.6, 1.6)	1.0 (0.7, 1.4)
rs6441282*	T	0.8 (0.6, 1.1)	1.0 (0.8, 1.2)	1.0 (0.7, 1.5)	0.9 (0.7, 1.1)
rs692890	T	0.7 (0.5, 1.1)	0.9 (0.7, 1.2)	0.7 (0.4, 1.4)	0.8 (0.5, 1.3)
rs755004	T	1.3 (0.8, 2.0)	1.1 (0.8, 1.5)	0.7 (0.2, 1.7)	1.2 (0.7, 2.1)
rs16830949	T			0.9 (0.5, 1.6)	0.7 (0.5, 1.1)
rs2243115	G	0.8 (0.4, 1.4)	1.0 (0.7, 1.5)	0.6 (0.3, 1.2)	1.2 (0.8, 1.8)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
rs583911	G	1.2 (0.7, 1.8)	1.1 (0.8, 1.5)	1.3 (0.8, 2.1)	0.9 (0.6, 1.4)
rs2243151*	T	1.2 (0.8, 1.6)	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	1.1 (0.8, 1.4)
rs2243154	A	1.6 (1.0, 2.6)	0.9 (0.6, 1.3)	1.8 (0.8, 4.5)	1.2 (0.6, 2.5)
rs4608735	C	0.7 (0.4, 1.3)	1.0 (0.7, 1.5)	0.9 (0.5, 1.7)	1.3 (0.9, 2.0)
rs17826053	G	0.5 (0.3, 0.9)	0.9 (0.7, 1.3)	0.9 (0.5, 1.6)	0.9 (0.6, 1.3)
rs485497	A	1.2 (0.7, 1.9)	1.2 (0.9, 1.6)	1.1 (0.7, 1.8)	0.8 (0.6, 1.2)
rs4680536*	G	1.0 (0.8, 1.4)	0.9 (0.7, 1.1)	1.3 (0.9, 1.8)	0.8 (0.6, 1.1)
rs12492730	G	1.0 (0.1, 7.2)	2.5 (1.2, 5.2)	1.0 (0.5, 1.7)	1.3 (0.9, 2.0)
rs9852519	T	1.0 (0.6, 1.5)	0.9 (0.7, 1.2)	1.2 (0.7, 2.0)	1.0 (0.7, 1.5)
rs598638	T	0.7 (0.4, 1.2)	1.2 (0.9, 1.6)	0.8 (0.3, 2.5)	1.0 (0.5, 2.0)
IL8					
rs7654490	T			1.2 (0.7, 2.0)	0.7 (0.5, 1.1)
rs16849893	A		1.5 (0.3, 8.6)	0.7 (0.4, 1.3)	0.7 (0.5, 1.1)
rs16849896	T		0.0 (0.0, 0.0)	1.1 (0.6, 1.9)	0.7 (0.4, 1.1)
rs4694634	C		1.5 (0.3, 8.6)	0.5 (0.3, 0.9)	0.7 (0.5, 1.1)
rs16849907	T			1.0 (0.5, 1.9)	0.7 (0.4, 1.2)
rs12506479	C	1.0 (0.6, 1.5)	1.0 (0.8, 1.4)	0.8 (0.5, 1.3)	1.2 (0.9, 1.7)
rs10805066	G	0.9 (0.6, 1.4)	1.0 (0.8, 1.3)	0.9 (0.5, 1.7)	1.0 (0.6, 1.6)
rs7693566	C		1.5 (0.3, 8.5)	0.8 (0.5, 1.4)	0.7 (0.5, 1.0)
rs4694635	T	0.5 (0.1, 4.3)	1.5 (0.6, 4.0)	1.7 (1.0, 2.8)	1.3 (0.9, 2.0)
rs16849928*	A	0.9 (0.7, 1.2)	0.9 (0.7, 1.1)	1.4 (1.0, 2.0)	1.2 (0.9, 1.5)
rs11730667	A	0.9 (0.6, 1.5)	0.8 (0.6, 1.2)	1.3 (0.8, 2.1)	1.2 (0.8, 1.7)
rs13142454	G		3.8 (1.5, 9.9)	1.5 (0.9, 2.6)	1.3 (0.9, 1.9)
rs11729759	A		3.8 (1.5, 9.9)	1.3 (0.8, 2.1)	1.3 (0.9, 1.8)
rs1951240*	G	1.1 (0.8, 1.4)	1.1 (0.9, 1.4)	0.9 (0.7, 1.3)	1.1 (0.9, 1.4)
rs16849958	C	1.2 (0.8, 2.0)	1.2 (0.9, 1.7)	1.0 (0.6, 1.6)	1.2 (0.8, 1.8)
rs1951242	T	0.9 (0.6, 1.5)	0.9 (0.6, 1.2)	1.2 (0.8, 2.0)	1.1 (0.8, 1.6)
rs7658422	C	0.0 (0.0, 0.0)	3.8 (1.5, 9.9)	1.1 (0.7, 1.9)	1.2 (0.8, 1.7)
CXCL10					
rs3733236	T	0.8 (0.4, 1.5)	0.7 (0.5, 1.1)	0.9 (0.5, 1.5)	1.0 (0.7, 1.4)
rs10031051	C	1.1 (0.4, 3.5)	1.1 (0.5, 2.4)	1.3 (0.7, 2.4)	0.7 (0.4, 1.1)
rs7670156	A	0.9 (0.5, 1.6)	0.8 (0.5, 1.2)	1.0 (0.6, 1.7)	0.9 (0.6, 1.3)
rs12651276	G	1.2 (0.8, 1.8)	1.0 (0.7, 1.3)	0.4 (0.1, 1.2)	1.4 (0.8, 2.3)
rs10518143	C	0.8 (0.5, 1.3)	1.1 (0.8, 1.4)	1.3 (0.7, 2.2)	0.8 (0.5, 1.2)
rs867562	A	1.3 (0.8, 2.0)	1.0 (0.7, 1.4)	0.3 (0.1, 1.3)	1.1 (0.6, 2.0)
rs4508917*	G	0.8 (0.6, 1.2)	1.1 (0.9, 1.3)	1.1 (0.7, 1.6)	1.1 (0.8, 1.5)
rs12504339	C	1.1 (0.7, 1.8)	1.0 (0.7, 1.3)	0.9 (0.5, 1.5)	1.0 (0.7, 1.4)
rs4302486*	A	1.1 (0.8, 1.5)	0.9 (0.8, 1.2)	1.2 (0.8, 1.7)	1.0 (0.8, 1.3)
NFKB1					
rs980455*	G	0.8 (0.6, 1.1)	1.0 (0.8, 1.2)	1.2 (0.8, 1.7)	0.9 (0.7, 1.1)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
rs3774933*	C	0.8 (0.6, 1.1)	1.0 (0.8, 1.2)	0.9 (0.6, 1.3)	1.0 (0.8, 1.3)
rs17032705*	A	0.8 (0.6, 1.1)	1.0 (0.8, 1.2)	0.9 (0.6, 1.4)	1.1 (0.8, 1.5)
rs1599961*	A	0.8 (0.6, 1.1)	1.0 (0.8, 1.2)	0.9 (0.6, 1.3)	1.0 (0.8, 1.3)
rs230533*	T	0.9 (0.6, 1.2)	1.0 (0.2, 4.3)	1.1 (0.6, 2.0)	0.9 (0.6, 1.4)
rs230530	C	1.2 (0.8, 1.9)	1.0 (0.9, 1.3)	0.8 (0.5, 1.3)	0.9 (0.7, 1.3)
rs230529*	A	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	1.2 (0.7, 1.9)	1.2 (0.9, 1.8)
rs17032779	C	1.1 (0.3, 4.2)	1.0 (0.8, 1.2)	0.9 (0.6, 1.3)	0.9 (0.7, 1.2)
rs230515	C	0.7 (0.5, 1.1)	1.4 (0.7, 3.0)	1.1 (0.6, 2.0)	0.7 (0.4, 1.1)
rs230493	A	0.8 (0.5, 1.2)	1.1 (0.9, 1.5)	0.8 (0.5, 1.3)	1.0 (0.7, 1.5)
rs17032815	A	1.0 (0.3, 4.1)	1.1 (0.8, 1.5)	0.8 (0.5, 1.4)	1.1 (0.7, 1.5)
rs909332	T	0.6 (0.2, 1.8)	1.6 (0.8, 3.2)	1.2 (0.6, 2.1)	0.9 (0.5, 1.4)
rs1801*	C	0.9 (0.6, 1.2)	1.0 (0.6, 1.7)	0.9 (0.5, 1.8)	1.1 (0.7, 1.7)
rs4648058	C	0.9 (0.6, 1.4)	1.0 (0.8, 1.2)	1.0 (0.7, 1.4)	1.0 (0.8, 1.3)
rs3755867*	G	0.9 (0.7, 1.3)	1.2 (0.9, 1.6)	0.9 (0.5, 1.4)	1.1 (0.8, 1.6)
rs4648090	A	1.0 (0.6, 1.6)	1.1 (0.9, 1.3)	0.8 (0.5, 1.3)	1.0 (0.8, 1.3)
rs4648110	A	0.9 (0.6, 1.4)	1.1 (0.8, 1.5)	0.9 (0.5, 1.6)	0.9 (0.6, 1.4)
rs3817685	G	0.9 (0.6, 1.4)	1.1 (0.8, 1.5)	1.0 (0.6, 1.6)	0.8 (0.6, 1.1)
rs4648127	T	0.8 (0.4, 1.5)	1.2 (0.9, 1.6)	0.8 (0.5, 1.3)	1.2 (0.8, 1.7)
rs230547	T	1.1 (0.6, 1.9)	1.2 (0.8, 1.7)	2.3 (0.6, 8.5)	1.6 (0.6, 4.5)
rs4648135	G	0.9 (0.4, 2.0)	1.0 (0.7, 1.5)	0.9 (0.5, 1.7)	1.1 (0.7, 1.6)
rs4648141	A	0.9 (0.6, 1.5)	0.9 (0.6, 1.6)	0.8 (0.5, 1.4)	0.9 (0.6, 1.4)
rs7674640*	C	1.2 (0.9, 1.7)	1.3 (1.0, 1.7)	1.3 (0.7, 2.3)	0.9 (0.6, 1.3)
rs10489113	G	0.9 (0.6, 1.4)	0.8 (0.7, 1.0)	0.9 (0.6, 1.3)	1.2 (0.9, 1.5)
rs11733293*	T	1.0 (0.7, 1.3)	1.3 (1.0, 1.7)	1.0 (0.6, 1.8)	0.8 (0.5, 1.1)
rs17033015	A	1.1 (0.7, 1.8)	1.0 (0.8, 1.2)	0.9 (0.6, 1.4)	1.0 (0.8, 1.4)
rs12648696*	C	0.9 (0.7, 1.3)	0.8 (0.6, 1.1)	1.0 (0.6, 1.8)	1.2 (0.9, 1.8)
rs12648696*	C		1.0 (0.9, 1.3)	0.8 (0.6, 1.3)	1.0 (0.8, 1.3)
IL2					
rs17454584	G	1.0 (0.7, 1.6)	1.2 (0.9, 1.6)	0.8 (0.3, 2.0)	0.7 (0.4, 1.4)
rs35914000	A	0.9 (0.6, 1.4)	1.1 (0.8, 1.5)	0.8 (0.4, 1.7)	0.8 (0.5, 1.4)
rs10034410	T		2.1 (0.3, 13.3)	0.8 (0.4, 1.6)	0.6 (0.4, 1.1)
rs10027390	C	1.4 (0.9, 2.2)	0.7 (0.6, 1.0)		
rs11932411	C	0.0 (0.0, 0.0)	1.9 (0.7, 5.4)	0.9 (0.6, 1.5)	0.8 (0.6, 1.1)
rs2069776	C	1.4 (0.9, 2.1)	0.7 (0.6, 1.0)	1.0 (0.6, 1.7)	1.1 (0.8, 1.7)
rs2069778	T	1.3 (0.8, 2.0)	0.7 (0.5, 0.9)	0.5 (0.1, 2.0)	0.6 (0.3, 1.6)
rs2069762	G	1.1 (0.7, 1.6)	1.3 (1.0, 1.7)	1.9 (1.1, 3.3)	1.4 (0.9, 2.2)
rs4833248	A	1.1 (0.7, 1.6)	1.3 (1.0, 1.7)	1.9 (1.1, 3.4)	1.4 (0.9, 2.2)
IL15					
rs6837991	T	0.9 (0.6, 1.3)	1.0 (0.8, 1.3)	1.5 (0.9, 2.4)	0.8 (0.6, 1.2)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
rs12508866	C	0.9 (0.6, 1.4)	0.8 (0.6, 1.1)	1.3 (0.6, 2.6)	0.9 (0.5, 1.6)
rs17007476	C		4.2 (1.8, 10.0)	0.9 (0.5, 1.7)	1.4 (1.0, 2.0)
rs17007480	A			1.0 (0.5, 2.1)	1.5 (1.0, 2.4)
rs1519551*	G	0.7 (0.5, 1.0)	0.9 (0.7, 1.1)	1.0 (0.7, 1.4)	1.0 (0.8, 1.3)
rs17461269	A	1.6 (1.0, 2.5)	1.0 (0.7, 1.3)	0.6 (0.3, 1.5)	0.6 (0.3, 1.2)
rs17007503	C			1.1 (0.6, 2.1)	1.3 (0.8, 2.0)
rs1519552	A	0.9 (0.6, 1.3)	1.0 (0.8, 1.3)	1.4 (0.8, 2.4)	1.1 (0.7, 1.6)
rs17007508	G	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.8 (0.4, 1.3)	0.9 (0.6, 1.3)
rs7698675	T	0.9 (0.6, 1.4)	1.0 (0.8, 1.3)	1.3 (0.8, 2.2)	1.0 (0.7, 1.5)
rs13117878*	C	0.7 (0.6, 1.0)	0.9 (0.8, 1.2)	1.1 (0.8, 1.5)	1.0 (0.8, 1.3)
rs17364630	G	0.7 (0.4, 1.2)	0.9 (0.7, 1.3)	0.8 (0.4, 1.5)	0.6 (0.4, 1.1)
rs12498901	C	0.7 (0.4, 1.2)	0.9 (0.7, 1.3)	0.8 (0.4, 1.5)	0.6 (0.4, 1.1)
rs7671458	G	0.7 (0.4, 1.2)	0.9 (0.7, 1.3)	0.9 (0.5, 1.5)	0.8 (0.6, 1.2)
rs10519610	C	0.7 (0.4, 1.1)	0.9 (0.7, 1.2)	1.1 (0.7, 1.8)	0.9 (0.6, 1.3)
rs6850492*	A	0.7 (0.5, 1.0)	1.0 (0.8, 1.2)	0.9 (0.6, 1.3)	0.9 (0.7, 1.2)
rs2087849	T	0.9 (0.6, 1.4)	1.1 (0.8, 1.4)	1.4 (0.9, 2.3)	1.2 (0.8, 1.7)
rs2857261*	G	1.3 (1.0, 1.7)	1.0 (0.8, 1.2)	1.0 (0.8, 1.4)	1.1 (0.8, 1.4)
rs1907949	T	1.1 (0.6, 1.8)	0.9 (0.7, 1.4)	0.8 (0.5, 1.5)	1.0 (0.7, 1.5)
rs3775597	C	1.1 (0.6, 1.8)	1.0 (0.7, 1.4)	1.0 (0.6, 1.9)	1.2 (0.8, 1.8)
rs12508955	T	0.9 (0.6, 1.4)	1.1 (0.8, 1.4)	1.2 (0.7, 2.0)	1.1 (0.8, 1.6)
rs17007610*	T	0.8 (0.6, 1.0)	1.0 (0.8, 1.2)	1.0 (0.8, 1.4)	0.9 (0.7, 1.2)
CSF2					
rs31400*	T	1.1 (0.9, 1.5)	1.0 (0.8, 1.2)	0.8 (0.6, 1.2)	0.8 (0.6, 1.0)
rs3091335	G	0.0 (0.0, 0.0)	0.9 (0.2, 3.6)	1.0 (0.6, 1.6)	0.9 (0.7, 1.3)
rs31481	A	1.4 (0.9, 2.2)	1.2 (0.9, 1.6)	0.8 (0.5, 1.5)	1.1 (0.7, 1.6)
rs2069801	G	0.0 (0.0, 0.0)	2.4 (0.3, 18.3)	1.1 (0.6, 2.0)	1.0 (0.6, 1.5)
rs246844	A	1.4 (0.9, 2.1)	1.3 (1.0, 1.8)	0.8 (0.5, 1.3)	1.2 (0.8, 1.6)
rs11575022	C	1.2 (0.6, 2.4)	1.7 (1.2, 2.5)	1.0 (0.6, 1.6)	1.1 (0.7, 1.6)
rs246841	T	1.4 (0.8, 2.2)	0.9 (0.7, 1.3)	0.4 (0.1, 1.6)	0.7 (0.3, 1.6)
rs168681	A	1.0 (0.6, 1.5)	0.9 (0.7, 1.2)	0.7 (0.4, 1.2)	0.9 (0.6, 1.3)
rs721121*	G	0.9 (0.7, 1.3)	0.9 (0.8, 1.2)	1.2 (0.8, 1.7)	1.1 (0.9, 1.5)
rs4705916	A	0.8 (0.5, 1.3)	0.8 (0.6, 1.1)	1.1 (0.7, 1.8)	1.0 (0.7, 1.4)
rs743677	G	0.0 (0.0, 0.0)	0.7 (0.1, 5.0)	1.2 (0.7, 2.0)	0.9 (0.6, 1.3)
rs2069626	G	1.1 (0.3, 4.5)	0.8 (0.3, 2.1)	1.2 (0.7, 2.3)	0.8 (0.5, 1.3)
rs743564*	G	0.9 (0.6, 1.2)	0.9 (0.8, 1.1)	1.0 (0.7, 1.4)	0.8 (0.6, 1.1)
rs25881	T	1.3 (0.8, 2.0)	1.1 (0.8, 1.5)	0.9 (0.6, 1.6)	1.2 (0.8, 1.7)
rs25882	C	1.0 (0.6, 1.6)	1.1 (0.8, 1.4)	1.3 (0.8, 2.2)	1.0 (0.7, 1.5)
rs27438*	A	1.2 (0.8, 1.9)	1.1 (0.8, 1.4)	1.0 (0.7, 1.6)	1.2 (0.9, 1.6)
rs25887*	C	0.9 (0.7, 1.2)	1.0 (0.8, 1.2)	0.9 (0.7, 1.3)	1.0 (0.7, 1.2)
rs6898270	T	0.7 (0.5, 1.2)	0.8 (0.6, 1.1)	1.0 (0.6, 1.7)	0.9 (0.6, 1.3)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
IL13					
rs7737470	A	1.1 (0.7, 1.7)	1.4 (1.1, 1.9)	1.5 (1.0, 2.5)	0.8 (0.6, 1.1)
rs4621555	C		0.0 (0.0, 0.0)	1.1 (0.6, 1.9)	1.2 (0.8, 1.7)
rs3091307	G	1.0 (0.7, 1.6)	1.4 (1.1, 1.9)	1.5 (0.7, 3.3)	1.1 (0.6, 1.8)
rs1881457	C	1.0 (0.6, 1.6)	1.4 (1.1, 1.9)	1.1 (0.7, 1.9)	0.7 (0.5, 1.1)
rs2069744	T		0.6 (0.1, 2.3)	1.3 (0.8, 2.1)	1.1 (0.8, 1.5)
rs1295686	G	1.1 (0.3, 3.4)	0.9 (0.5, 1.8)	0.7 (0.4, 1.1)	1.1 (0.8, 1.6)
rs20541	T	0.8 (0.5, 1.3)	1.1 (0.8, 1.5)	1.2 (0.7, 1.9)	1.2 (0.8, 1.7)
rs848	T	0.8 (0.5, 1.3)	1.1 (0.8, 1.5)	1.5 (0.8, 2.8)	1.4 (0.9, 2.2)
rs1295683	T	0.7 (0.4, 1.3)	1.1 (0.8, 1.5)	1.1 (0.6, 1.9)	0.9 (0.6, 1.4)
rs2243204	T	0.7 (0.4, 1.5)	1.0 (0.7, 1.5)	1.0 (0.5, 1.9)	1.0 (0.6, 1.5)
rs2243210	A	0.8 (0.4, 1.6)	0.9 (0.5, 1.3)	1.3 (0.8, 2.1)	1.1 (0.7, 1.5)
rs2243218	A	0.8 (0.4, 1.6)	0.9 (0.6, 1.3)	1.3 (0.8, 2.2)	1.0 (0.7, 1.4)
rs2243219	G	0.8 (0.4, 1.6)	0.9 (0.6, 1.3)	1.0 (0.5, 1.7)	1.0 (0.6, 1.5)
IL4					
rs2243240	T			0.9 (0.4, 2.1)	1.1 (0.7, 1.9)
rs2243246	C			0.9 (0.6, 1.6)	0.8 (0.5, 1.1)
rs2243248	G	0.7 (0.4, 1.5)	0.9 (0.6, 1.3)	1.0 (0.6, 1.7)	1.1 (0.7, 1.6)
rs2243250*	C	0.7 (0.5, 1.0)	0.9 (0.7, 1.2)	0.8 (0.5, 1.1)	1.1 (0.9, 1.5)
rs2243253	T		2.5 (0.5, 12.9)	1.0 (0.6, 1.8)	1.3 (0.9, 1.9)
rs2243261	T			0.6 (0.3, 1.0)	0.8 (0.5, 1.2)
rs2243263	C	0.8 (0.5, 1.4)	1.2 (0.8, 1.6)	0.8 (0.5, 1.4)	1.1 (0.8, 1.7)
rs2243267	C	1.4 (0.9, 2.3)	1.1 (0.8, 1.5)	1.4 (0.8, 2.3)	0.8 (0.6, 1.2)
rs2243270	G	1.4 (0.9, 2.2)	1.1 (0.8, 1.5)	1.7 (0.7, 4.0)	0.8 (0.5, 1.3)
rs2243283	G	1.0 (0.1, 7.7)	1.5 (0.6, 4.0)	1.1 (0.7, 1.8)	0.9 (0.6, 1.4)
rs2243292	C	2.7 (0.6, 12.3)	0.5 (0.1, 3.8)	1.4 (0.7, 2.6)	1.0 (0.6, 1.6)
rs11242122*	G	0.9 (0.6, 1.3)	0.9 (0.7, 1.1)	1.0 (0.7, 1.4)	1.2 (1.0, 1.6)
rs11242123	T	1.3 (0.8, 2.1)	1.2 (0.9, 1.6)	0.9 (0.6, 1.6)	0.6 (0.4, 0.9)
IL12B					
rs7730126*	T	0.9 (0.7, 1.3)	1.2 (1.0, 1.5)	1.1 (0.7, 1.6)	0.9 (0.7, 1.2)
rs2099327	C	0.9 (0.6, 1.5)	1.3 (1.0, 1.8)	1.7 (0.9, 3.1)	0.6 (0.4, 1.1)
rs1549922*	G	1.1 (0.8, 1.4)	0.8 (0.6, 0.9)	0.9 (0.6, 1.3)	1.0 (0.8, 1.3)
rs4921466	C	0.9 (0.5, 1.5)	0.9 (0.6, 1.3)	0.8 (0.5, 1.5)	1.1 (0.7, 1.7)
rs10072923	C	1.0 (0.7, 1.6)	1.2 (0.9, 1.5)	1.1 (0.7, 1.8)	1.1 (0.8, 1.5)
rs1368439	G	1.1 (0.7, 1.8)	0.7 (0.5, 1.0)	0.9 (0.4, 1.9)	1.0 (0.6, 1.8)
rs3212227	C	1.1 (0.7, 1.7)	1.1 (0.9, 1.5)	0.9 (0.6, 1.5)	0.9 (0.6, 1.2)
rs11574790	T	0.8 (0.5, 1.4)	0.9 (0.7, 1.3)	0.9 (0.5, 1.5)	1.2 (0.8, 1.7)
rs2195940	T	0.8 (0.5, 1.4)	0.9 (0.6, 1.3)	0.7 (0.4, 1.2)	1.2 (0.8, 1.8)
rs919766	C	0.8 (0.5, 1.4)	0.9 (0.7, 1.3)	0.9 (0.5, 1.4)	1.2 (0.9, 1.7)
rs2853694*	C	1.0 (0.8, 1.4)	0.8 (0.6, 1.0)	1.0 (0.6, 1.5)	1.0 (0.7, 1.3)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
rs2569253	C	1.2 (0.7, 2.0)	1.0 (0.7, 1.4)	1.2 (0.8, 2.0)	0.8 (0.6, 1.1)
rs3212220	T	1.1 (0.7, 1.7)	1.1 (0.9, 1.5)	0.9 (0.6, 1.5)	1.0 (0.7, 1.4)
rs1433048	G	1.2 (0.8, 1.9)	0.9 (0.7, 1.2)	0.6 (0.2, 1.6)	1.1 (0.6, 1.9)
rs2546893	A	1.2 (0.7, 2.1)	1.0 (0.8, 1.4)	1.3 (0.8, 2.1)	0.8 (0.6, 1.2)
rs2546890*	A	1.0 (0.7, 1.4)	0.8 (0.7, 1.0)	1.0 (0.7, 1.4)	0.9 (0.7, 1.2)
rs10052709	G	0.8 (0.5, 1.4)	0.8 (0.6, 1.1)	1.1 (0.6, 2.0)	1.0 (0.7, 1.6)
rs7709212*	C	1.0 (0.8, 1.4)	1.3 (1.0, 1.6)	1.2 (0.8, 1.7)	1.0 (0.7, 1.3)
rs6868898	C	0.9 (0.6, 1.4)	0.8 (0.6, 1.1)	1.0 (0.6, 1.7)	1.3 (0.9, 1.8)
IL6					
rs6949149	T				
rs6954897	G	1.6 (0.9, 2.9)	1.5 (1.0, 2.2)	1.2 (0.7, 2.1)	1.0 (0.7, 1.6)
rs6954681	T	0.8 (0.5, 1.4)	1.0 (0.7, 1.5)	0.8 (0.5, 1.4)	0.9 (0.6, 1.3)
rs6969927	A	1.3 (0.9, 2.1)	1.6 (1.2, 2.1)	1.0 (0.6, 1.7)	1.0 (0.6, 1.5)
rs10156056	C	0.9 (0.6, 1.4)	0.8 (0.6, 1.1)	1.2 (0.7, 2.0)	1.5 (1.0, 2.1)
rs7776857	G	1.0 (0.6, 1.7)	1.5 (1.1, 2.0)	0.9 (0.5, 1.4)	0.9 (0.6, 1.3)
rs4719711	C	1.0 (0.7, 1.6)	0.9 (0.7, 1.2)	1.2 (0.6, 2.5)	0.8 (0.4, 1.4)
rs6963444	G	0.9 (0.6, 1.5)	0.9 (0.7, 1.2)	1.4 (0.9, 2.3)	0.7 (0.5, 1.1)
rs1546762	C	1.8 (0.8, 3.9)	1.5 (0.9, 2.5)	0.7 (0.4, 1.3)	0.9 (0.6, 1.4)
rs7805828*	A	1.0 (0.6, 1.5)	0.9 (0.7, 1.2)	1.2 (0.7, 1.9)	0.7 (0.5, 1.1)
rs1880241*	G	0.8 (0.6, 1.2)	0.9 (0.7, 1.0)	1.1 (0.8, 1.5)	1.3 (1.0, 1.6)
rs2056576*	T	0.9 (0.7, 1.3)	0.9 (0.8, 1.1)	1.1 (0.8, 1.5)	1.2 (0.9, 1.5)
rs7784987	A	0.8 (0.6, 1.1)	1.0 (0.8, 1.3)	1.0 (0.7, 1.4)	1.1 (0.8, 1.3)
rs3087221	T	1.9 (0.9, 4.0)	1.4 (0.9, 2.4)	1.0 (0.5, 1.7)	1.0 (0.6, 1.5)
rs2069824	C	1.5 (0.5, 4.5)	1.0 (0.4, 2.5)	0.6 (0.4, 1.2)	1.0 (0.7, 1.5)
rs1800797	A	1.1 (0.6, 2.0)	1.5 (1.1, 2.2)	1.1 (0.6, 1.9)	1.2 (0.8, 1.8)
rs1800795	C	0.8 (0.5, 1.2)	0.8 (0.6, 1.1)	0.9 (0.5, 1.9)	0.6 (0.3, 1.1)
rs2069835	C	0.8 (0.5, 1.3)	0.8 (0.6, 1.0)	0.9 (0.5, 1.9)	0.6 (0.3, 1.1)
rs1474347	G	1.4 (0.7, 2.6)	1.4 (0.9, 2.1)	1.1 (0.6, 2.0)	0.8 (0.5, 1.2)
rs2069840	G	0.8 (0.5, 1.3)	0.8 (0.6, 1.1)	0.7 (0.4, 1.3)	0.8 (0.5, 1.2)
rs2069842	A	0.7 (0.4, 1.0)	0.9 (0.7, 1.2)	1.6 (1.0, 2.7)	1.2 (0.8, 1.7)
rs1548216	C			1.5 (0.9, 2.7)	1.4 (0.9, 2.2)
rs2069843	A	1.7 (0.8, 3.7)	1.6 (1.0, 2.6)	0.9 (0.5, 1.5)	1.0 (0.6, 1.4)
rs2069845*	G	1.7 (0.8, 3.7)	1.6 (1.0, 2.6)	0.8 (0.4, 1.5)	0.8 (0.5, 1.3)
rs2069849	T	0.9 (0.7, 1.3)	0.9 (0.7, 1.1)	0.7 (0.5, 1.1)	0.9 (0.6, 1.2)
rs10242595*	G	1.7 (0.8, 3.7)	1.6 (1.0, 2.6)	0.9 (0.5, 1.6)	0.9 (0.6, 1.4)
GATA3		1.0 (0.7, 1.4)	0.8 (0.7, 1.0)	1.0 (0.7, 1.4)	0.9 (0.7, 1.2)
rs406571*	C				
rs1877739	C	1.0 (0.7, 1.4)	1.1 (0.9, 1.4)	0.9 (0.6, 1.2)	1.3 (1.0, 1.7)
rs532854*	C	1.0 (0.7, 1.6)	0.9 (0.7, 1.2)	0.8 (0.5, 1.3)	0.9 (0.6, 1.3)
rs10795588	G	1.2 (0.9, 1.6)	1.0 (0.8, 1.2)	0.9 (0.6, 1.3)	1.0 (0.8, 1.2)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
rs263425	T	1.2 (0.8, 2.0)	0.8 (0.6, 1.1)	1.3 (0.8, 2.1)	0.9 (0.7, 1.3)
rs263423	A			0.4 (0.2, 0.8)	1.1 (0.8, 1.7)
rs1244186	T	1.4 (0.9, 2.2)	1.3 (1.0, 1.7)	1.0 (0.6, 1.7)	0.8 (0.6, 1.2)
rs2275806	A	1.2 (0.8, 1.9)	1.1 (0.8, 1.5)	1.0 (0.6, 1.7)	1.4 (1.0, 2.0)
rs1269486	A	1.0 (0.6, 1.8)	1.0 (0.7, 1.3)	0.7 (0.4, 1.2)	1.0 (0.7, 1.5)
rs1399180	T	1.2 (0.8, 1.9)	1.2 (0.9, 1.5)	1.2 (0.7, 1.9)	1.4 (0.9, 1.9)
rs369421	C	1.7 (1.1, 2.5)	1.3 (0.9, 1.7)	0.6 (0.4, 1.0)	1.1 (0.8, 1.7)
rs3781094*	G	1.5 (1.0, 2.3)	1.3 (1.0, 1.7)	0.9 (0.5, 1.7)	1.3 (0.8, 1.9)
rs3781093	G	0.9 (0.7, 1.1)	0.9 (0.8, 1.1)	1.1 (0.8, 1.6)	1.1 (0.8, 1.5)
rs376397*	A	0.9 (0.6, 1.5)	0.9 (0.7, 1.2)	1.4 (0.9, 2.3)	0.8 (0.5, 1.1)
rs570613*	G	1.0 (0.8, 1.4)	1.0 (0.9, 1.3)	0.9 (0.6, 1.4)	1.0 (0.8, 1.3)
rs10752126*	G	1.0 (0.8, 1.4)	1.0 (0.9, 1.3)	1.1 (0.8, 1.5)	0.9 (0.7, 1.1)
rs569421	C	1.1 (0.8, 1.4)	1.0 (0.9, 1.2)	1.0 (0.7, 1.5)	0.8 (0.6, 1.1)
rs444929	C	1.0 (0.7, 1.6)	0.9 (0.7, 1.3)	1.0 (0.6, 1.7)	0.7 (0.5, 1.1)
rs2280015	A	1.4 (0.9, 2.1)	1.0 (0.8, 1.3)	1.2 (0.7, 2.0)	1.2 (0.9, 1.8)
rs422628	C	1.2 (0.8, 1.9)	1.0 (0.8, 1.4)	1.2 (0.8, 2.0)	0.7 (0.5, 1.0)
rs406103	T	1.2 (0.8, 1.9)	1.0 (0.7, 1.3)	1.3 (0.8, 2.0)	1.2 (0.8, 1.7)
rs528778	T	1.2 (0.8, 1.9)	1.0 (0.8, 1.4)	1.0 (0.6, 1.6)	0.5 (0.4, 0.8)
rs11567934	A	1.2 (0.8, 1.9)	1.0 (0.7, 1.3)	1.2 (0.7, 1.9)	1.3 (0.9, 1.8)
rs388957	T	4.3 (0.7, 26.7)		1.1 (0.6, 1.9)	0.7 (0.4, 1.1)
rs10905284	A	1.0 (0.4, 2.6)	0.8 (0.4, 1.5)	0.8 (0.5, 1.4)	0.7 (0.5, 1.0)
rs1058240	G	1.5 (0.8, 2.8)	1.3 (0.9, 1.8)	1.4 (0.9, 2.3)	1.4 (1.0, 2.0)
rs263419	T	1.1 (0.7, 1.7)	0.9 (0.7, 1.2)	1.0 (0.6, 1.7)	1.4 (1.0, 2.0)
rs12262237	A	1.2 (0.7, 1.8)	1.1 (0.8, 1.4)	1.0 (0.6, 1.7)	0.8 (0.6, 1.2)
rs7100967	A			1.7 (0.9, 3.2)	1.1 (0.7, 1.9)
rs477461	G		0.8 (0.1, 10.3)	1.1 (0.6, 2.1)	0.8 (0.5, 1.3)
rs434645	A	1.2 (0.7, 1.9)	1.1 (0.8, 1.5)	0.9 (0.5, 1.4)	0.7 (0.5, 1.1)
rs379568	T	1.0 (0.6, 1.6)	0.9 (0.7, 1.3)	0.9 (0.5, 1.5)	1.1 (0.7, 1.5)
rs1778058*	A	1.2 (0.7, 1.9)	1.2 (0.9, 1.7)	0.9 (0.5, 1.4)	1.1 (0.7, 1.5)
rs12412241*	A	1.0 (0.8, 1.4)	1.1 (0.9, 1.4)	0.9 (0.6, 1.2)	1.1 (0.9, 1.4)
IL18		0.9 (0.6, 1.3)	1.1 (0.9, 1.4)	1.0 (0.7, 1.5)	1.3 (1.0, 1.7)
rs4937075*	G				
rs578784	T	1.2 (0.8, 1.6)	1.0 (0.8, 1.2)	1.2 (0.8, 1.8)	0.8 (0.6, 1.0)
rs11214098	A	1.2 (0.8, 1.8)	0.9 (0.7, 1.2)	1.3 (0.8, 2.2)	0.9 (0.6, 1.3)
rs543810	G			0.8 (0.4, 1.5)	0.8 (0.5, 1.3)
rs5744280*	T	1.1 (0.7, 1.8)	1.3 (0.9, 1.7)	0.9 (0.6, 1.5)	0.9 (0.6, 1.3)
rs5744238	A	1.0 (0.7, 1.3)	1.0 (0.8, 1.2)	1.0 (0.7, 1.4)	1.1 (0.9, 1.5)
rs2043055*	G			1.0 (0.5, 2.3)	1.2 (0.6, 2.1)
rs360714	G	1.0 (0.8, 1.4)	1.0 (0.8, 1.2)	1.0 (0.7, 1.5)	1.1 (0.8, 1.4)
rs1946518*	T	1.1 (0.3, 3.6)	1.2 (0.6, 2.5)	0.7 (0.4, 1.4)	1.0 (0.7, 1.5)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
rs5744223	G	1.3 (1.0, 1.8)	1.0 (0.8, 1.3)	0.8 (0.6, 1.2)	0.8 (0.6, 1.1)
rs5744222	A		2.5 (0.5, 11.6)	1.0 (0.5, 1.8)	0.7 (0.4, 1.1)
rs11214105	A	0.7 (0.5, 1.1)	1.0 (0.8, 1.4)	1.1 (0.5, 2.4)	1.1 (0.6, 2.0)
KLRD1		1.3 (0.8, 2.0)	0.9 (0.7, 1.3)	0.8 (0.5, 1.4)	0.8 (0.6, 1.2)
rs3759270	C				
rs3809214*	T	1.0 (0.6, 1.5)	1.0 (0.8, 1.3)	0.9 (0.5, 1.4)	0.9 (0.6, 1.3)
rs2302489*	T	0.9 (0.7, 1.3)	1.0 (0.8, 1.2)	0.9 (0.6, 1.4)	1.1 (0.8, 1.4)
rs7301562	C	1.0 (0.7, 1.3)	1.0 (0.8, 1.2)	0.9 (0.6, 1.4)	1.1 (0.8, 1.4)
rs10772256	T	1.7 (0.2, 11.7)	1.3 (0.3, 5.2)	0.9 (0.6, 1.6)	1.1 (0.8, 1.6)
rs2270238	T	1.7 (0.2, 11.7)	1.3 (0.3, 5.2)	0.9 (0.6, 1.6)	1.1 (0.8, 1.6)
rs11611333*	G	1.0 (0.7, 1.6)	1.1 (0.8, 1.4)	1.0 (0.4, 2.2)	0.8 (0.4, 1.5)
rs12829155	G	1.0 (0.8, 1.4)	1.0 (0.8, 1.2)	1.0 (0.7, 1.5)	1.1 (0.8, 1.4)
IFNG		0.9 (0.5, 1.5)	1.0 (0.7, 1.5)	1.3 (0.8, 2.2)	0.9 (0.6, 1.3)
rs10878760	T	1.1 (0.7, 1.7)	1.0 (0.7, 1.3)	0.4 (0.1, 1.9)	1.1 (0.6, 2.2)
rs17104856	T			1.0 (0.5, 1.9)	1.0 (0.6, 1.7)
rs2193047*	T	1.1 (0.8, 1.5)	0.9 (0.7, 1.1)	0.9 (0.6, 1.3)	0.9 (0.7, 1.2)
rs2041864*	T	1.0 (0.7, 1.3)	1.0 (0.9, 1.3)	1.1 (0.8, 1.5)	1.0 (0.7, 1.2)
rs11177074	C	0.9 (0.5, 1.6)	0.8 (0.6, 1.3)	1.0 (0.6, 1.6)	0.9 (0.6, 1.4)
rs6581794	T	1.0 (0.7, 1.6)	1.0 (0.7, 1.3)	0.7 (0.4, 1.2)	0.9 (0.6, 1.3)
rs3181035	A	0.9 (0.5, 1.6)	0.8 (0.6, 1.3)	1.0 (0.6, 1.6)	0.9 (0.6, 1.3)
rs2069727	G	0.9 (0.6, 1.4)	1.2 (0.9, 1.7)	1.1 (0.6, 1.7)	1.0 (0.7, 1.4)
rs1861494	C	1.0 (0.7, 1.6)	1.0 (0.7, 1.3)	0.6 (0.3, 1.1)	0.9 (0.6, 1.4)
rs3181032	G	2.3 (1.0, 5.6)	1.0 (0.5, 2.3)	1.2 (0.7, 2.0)	0.9 (0.6, 1.4)
rs7302488	G	1.0 (0.7, 1.6)	1.0 (0.7, 1.3)	0.5 (0.3, 1.0)	1.0 (0.6, 1.4)
rs12306852	C	1.2 (0.7, 1.9)	0.9 (0.7, 1.3)	1.7 (0.9, 3.0)	1.1 (0.8, 1.7)
TGFB3					
rs4252345	G			2.5 (1.3, 5.0)	0.9 (0.4, 1.8)
rs11466414	T	1.7 (1.0, 3.0)	1.0 (0.7, 1.5)	0.9 (0.2, 3.1)	0.4 (0.1, 1.4)
TGFB1					
rs1800471	C	0.8 (0.4, 1.5)	0.8 (0.5, 1.2)	0.9 (0.4, 1.9)	1.0 (0.6, 1.7)
KIR3DL3					
rs4441391	A	1.0 (0.6, 1.5)	0.8 (0.6, 1.0)	1.0 (0.6, 1.7)	0.7 (0.5, 1.1)
rs1325155*	T	1.1 (0.9, 1.5)	1.2 (1.0, 1.4)	1.2 (0.9, 1.6)	0.8 (0.6, 1.1)
rs1325156	A	0.9 (0.6, 1.5)	1.3 (0.9, 1.7)	0.9 (0.6, 1.5)	1.2 (0.9, 1.8)
rs12151161	G	1.0 (0.6, 1.7)	1.4 (1.0, 1.9)	0.9 (0.6, 1.5)	1.4 (1.0, 2.0)
rs7249048	G	4.6 (0.6, 37.3)	0.0 (0.0, 0.0)	0.6 (0.4, 1.2)	1.6 (1.1, 2.3)
rs270775*	G	0.9 (0.7, 1.3)	1.0 (0.8, 1.2)	1.1 (0.8, 1.6)	1.1 (0.8, 1.4)
rs2296370*	A	1.0 (0.8, 1.4)	0.9 (0.7, 1.1)	1.0 (0.7, 1.4)	0.8 (0.6, 1.0)
rs2296371*	A	1.1 (0.8, 1.5)	0.8 (0.7, 1.0)	1.0 (0.6, 1.4)	1.1 (0.8, 1.4)
rs12982559	A	1.3 (0.8, 2.0)	0.8 (0.6, 1.1)	1.4 (0.8, 2.2)	1.1 (0.8, 1.6)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
rs11883241*	T	0.9 (0.7, 1.3)	0.8 (0.7, 1.0)	1.3 (0.9, 1.7)	1.1 (0.9, 1.5)
rs6509899	A	1.0 (0.6, 1.7)	1.1 (0.8, 1.5)	0.6 (0.3, 1.0)	1.2 (0.8, 1.7)
rs1325158*	T	1.0 (0.7, 1.3)	0.8 (0.7, 1.0)	1.1 (0.8, 1.5)	1.3 (1.0, 1.6)
rs11671355	C	1.2 (0.8, 1.9)	0.9 (0.7, 1.2)	1.3 (0.7, 2.5)	0.9 (0.5, 1.5)
rs16985907	C	1.3 (0.7, 2.6)	1.0 (0.7, 1.7)	0.4 (0.2, 0.9)	0.7 (0.5, 1.2)
KIR2DL4					
rs35950908	A	1.2 (0.7, 1.8)	1.2 (0.9, 1.6)	0.6 (0.3, 1.2)	0.7 (0.4, 1.2)
rs17771961	G	0.9 (0.5, 1.4)	0.8 (0.6, 1.1)	1.1 (0.6, 2.1)	1.3 (0.9, 1.9)
KIR3DL2					
rs10407958	A	0.7 (0.4, 1.2)	1.2 (0.9, 1.6)	1.0 (0.6, 1.7)	1.1 (0.8, 1.6)
rs1654644*	G	1.1 (0.8, 1.4)	1.0 (0.8, 1.3)	0.9 (0.6, 1.3)	0.8 (0.6, 1.0)
rs4806457	C	1.9 (0.9, 3.7)	1.0 (0.6, 1.8)	0.6 (0.2, 1.5)	1.0 (0.6, 1.7)
rs3745900	T	1.3 (0.8, 1.9)	1.0 (0.7, 1.3)	0.8 (0.5, 1.4)	1.4 (1.0, 2.0)
rs11672983	A	1.4 (0.9, 2.2)	1.2 (0.9, 1.6)	0.8 (0.5, 1.3)	0.7 (0.5, 1.0)
rs3816051*	C	1.3 (0.9, 1.7)	1.1 (0.9, 1.3)	0.8 (0.5, 1.1)	0.7 (0.5, 0.9)
IFNGR2					
rs6517167	T	1.3 (0.9, 2.1)	0.8 (0.6, 1.1)	0.7 (0.4, 1.2)	1.2 (0.8, 1.7)
rs11702844	G	1.4 (0.9, 2.2)	1.1 (0.8, 1.5)	1.7 (0.8, 3.9)	1.1 (0.6, 2.2)
rs16990664	T	0.5 (0.2, 1.4)	0.7 (0.4, 1.2)	0.8 (0.5, 1.4)	1.0 (0.7, 1.4)
rs9976971	A	0.8 (0.5, 1.2)	1.1 (0.8, 1.5)	1.5 (0.8, 2.7)	1.4 (0.9, 2.1)
rs9980428	T	1.5 (1.0, 2.3)	0.9 (0.7, 1.2)	0.8 (0.5, 1.2)	0.8 (0.6, 1.2)
rs9978223	A	1.1 (0.7, 1.8)	0.9 (0.7, 1.3)	1.0 (0.6, 1.8)	0.6 (0.4, 0.9)
rs2268241	A	1.1 (0.7, 1.8)	0.9 (0.7, 1.3)	1.3 (0.8, 2.2)	0.9 (0.6, 1.3)
rs9808685*	G	1.3 (1.0, 1.8)	1.1 (0.9, 1.3)	0.7 (0.5, 1.0)	1.1 (0.8, 1.4)
rs2834210	A	1.5 (0.8, 2.5)	0.9 (0.7, 1.2)	0.8 (0.5, 1.2)	1.2 (0.9, 1.8)
rs9808753	G	1.0 (0.7, 1.7)	0.9 (0.7, 1.3)	1.3 (0.8, 2.1)	0.9 (0.6, 1.3)
rs2834212	C	0.7 (0.4, 1.3)	1.1 (0.8, 1.5)	2.0 (0.8, 4.9)	0.9 (0.3, 2.1)
rs2834213	G	1.3 (0.8, 1.9)	1.0 (0.8, 1.4)	1.5 (0.7, 3.0)	1.4 (0.8, 2.4)
rs2012075	C	0.9 (0.6, 1.5)	0.7 (0.5, 1.0)	1.0 (0.6, 1.7)	0.9 (0.6, 1.3)
rs8131980	A	1.2 (0.8, 1.8)	1.0 (0.7, 1.3)	0.7 (0.4, 1.2)	1.0 (0.7, 1.5)
GADD45A					
rs12405855	T	0.9 (0.5, 1.4)	1.1 (0.8, 1.4)	1.1 (0.5, 2.8)	1.1 (0.5, 2.2)
rs344934*	C	1.0 (0.7, 1.4)	1.1 (0.9, 1.3)	0.9 (0.7, 1.3)	0.9 (0.7, 1.2)
rs4655749	G	1.0 (0.5, 2.0)	0.9 (0.6, 1.4)	0.7 (0.4, 1.3)	1.1 (0.7, 1.6)
rs344916	C	0.9 (0.5, 1.3)	1.1 (0.9, 1.5)	0.7 (0.4, 1.2)	0.7 (0.5, 1.1)
rs10889710	A	1.1 (0.6, 2.2)	1.3 (0.8, 2.0)	1.1 (0.7, 1.8)	0.9 (0.6, 1.2)
rs646652	C	0.9 (0.5, 1.4)	0.8 (0.6, 1.1)	1.0 (0.6, 1.7)	1.1 (0.8, 1.6)
rs2055904	T	1.1 (0.6, 2.1)	0.9 (0.6, 1.4)	0.7 (0.4, 1.3)	1.0 (0.7, 1.6)
rs604043	G	0.8 (0.5, 1.3)	0.8 (0.6, 1.1)	1.4 (0.9, 2.3)	1.1 (0.7, 1.5)
rs2815266	A	1.1 (0.6, 1.9)	1.1 (0.8, 1.6)	1.3 (0.7, 2.1)	0.9 (0.6, 1.4)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
rs624790	C	0.9 (0.6, 1.5)	1.3 (0.9, 1.7)	1.0 (0.6, 1.6)	0.8 (0.6, 1.1)
rs1511686	T			1.3 (0.7, 2.2)	1.4 (0.9, 2.0)
rs3783468	A	1.1 (0.6, 1.9)	1.1 (0.8, 1.7)	1.1 (0.7, 1.8)	1.0 (0.7, 1.5)
rs532446*	C	1.0 (0.7, 1.4)	0.9 (0.7, 1.1)	0.8 (0.6, 1.2)	1.0 (0.8, 1.3)
rs607375*	C	1.0 (0.7, 1.3)	0.9 (0.7, 1.1)	1.0 (0.7, 1.4)	1.0 (0.8, 1.2)
rs685724*	G	1.0 (0.7, 1.4)	1.1 (0.9, 1.4)	1.0 (0.7, 1.4)	1.1 (0.8, 1.3)
rs675327	T	0.8 (0.5, 1.3)	0.9 (0.6, 1.2)	1.2 (0.7, 2.0)	1.3 (0.9, 1.9)
rs11583718*	C	1.0 (0.7, 1.3)	0.9 (0.8, 1.1)	1.0 (0.7, 1.4)	1.0 (0.7, 1.2)
rs7546055	C	1.0 (0.7, 1.6)	1.0 (0.7, 1.3)	0.6 (0.4, 1.0)	0.9 (0.6, 1.3)
rs598602	T	0.8 (0.5, 1.4)	0.9 (0.6, 1.2)	1.6 (1.0, 2.6)	1.2 (0.8, 1.8)
rs12408005	T	1.4 (0.8, 2.5)	1.0 (0.7, 1.4)	1.1 (0.7, 1.8)	0.9 (0.6, 1.2)
RASSF1					
rs35455589	C	2.8 (0.4, 19.2)	1.3 (0.3, 5.6)	0.8 (0.5, 1.4)	1.1 (0.8, 1.6)
rs709210	T	1.5 (0.9, 2.3)	0.9 (0.6, 1.1)	1.6 (0.9, 2.8)	0.7 (0.4, 1.1)
rs2073498	A	0.8 (0.5, 1.4)	0.7 (0.5, 1.0)	0.9 (0.3, 2.9)	0.9 (0.4, 2.0)
rs2236947	A	0.7 (0.4, 1.0)	1.4 (1.0, 2.0)	0.8 (0.5, 1.3)	1.1 (0.7, 1.5)
rs2073499	G	1.0 (0.6, 1.6)	0.8 (0.6, 1.1)	1.1 (0.5, 2.1)	0.9 (0.6, 1.4)
rs6446203	T	1.8 (0.8, 4.0)	1.2 (0.6, 2.2)	1.3 (0.8, 2.1)	0.7 (0.5, 1.1)
rs1989839	C	0.9 (0.5, 1.4)	0.7 (0.5, 1.1)	1.1 (0.7, 1.9)	1.2 (0.8, 1.7)
CCNA2					
rs6825926	T	1.1 (0.6, 2.0)	1.0 (0.7, 1.5)	1.1 (0.6, 1.9)	0.8 (0.6, 1.2)
rs1803183	G	0.8 (0.2, 2.8)	1.0 (0.4, 2.1)	1.3 (0.8, 2.1)	0.8 (0.6, 1.1)
rs6815050*	C	0.9 (0.6, 1.2)	1.0 (0.8, 1.2)	1.0 (0.7, 1.5)	0.8 (0.6, 1.1)
rs3217773	C	1.0 (0.6, 1.5)	1.1 (0.8, 1.4)	1.2 (0.7, 2.0)	1.2 (0.8, 1.8)
rs3217771	T	1.0 (0.6, 1.5)	1.1 (0.8, 1.4)	1.2 (0.7, 2.0)	1.2 (0.8, 1.8)
rs3217770	C	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.7 (0.4, 1.3)	1.2 (0.8, 1.8)
rs2071486*	G	1.0 (0.7, 1.3)	1.0 (0.8, 1.2)	0.9 (0.7, 1.3)	1.1 (0.9, 1.4)
rs3217760	A			1.0 (0.4, 2.4)	0.9 (0.5, 1.8)
rs1507994*	A	1.0 (0.7, 1.4)	1.0 (0.8, 1.2)	1.1 (0.8, 1.6)	0.9 (0.7, 1.1)
CCNH					
rs2266690	C	1.4 (0.9, 2.2)	1.1 (0.9, 1.5)	0.8 (0.4, 1.6)	1.2 (0.7, 1.9)
NOV					
rs13261466	T	0.8 (0.5, 1.2)	1.3 (1.0, 1.7)	0.1 (0.0, 1.0)	1.0 (0.5, 1.8)
rs2071526	A	1.2 (0.8, 1.8)	0.8 (0.6, 1.0)	0.7 (0.5, 1.2)	0.9 (0.6, 1.3)
rs7834596	T	1.1 (0.7, 1.7)	0.8 (0.6, 1.1)	1.0 (0.6, 1.7)	1.1 (0.8, 1.6)
rs7014927	C	1.2 (0.8, 1.8)	0.8 (0.6, 1.0)	1.0 (0.5, 1.9)	1.0 (0.6, 1.7)
rs11538929	A	0.8 (0.5, 1.4)	1.1 (0.8, 1.5)	2.2 (1.1, 4.7)	0.5 (0.2, 1.3)
rs1381337	G			1.2 (0.7, 2.0)	1.0 (0.7, 1.4)
rs16892531	G	1.1 (0.4, 3.3)	1.0 (0.5, 2.1)	0.6 (0.3, 1.3)	0.9 (0.6, 1.4)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
rs11775043	G	1.1 (0.7, 1.8)	0.8 (0.6, 1.1)	1.1 (0.7, 1.9)	1.3 (0.9, 1.9)
rs10505358	G	0.9 (0.3, 2.5)	0.6 (0.3, 1.3)	0.9 (0.5, 1.7)	0.8 (0.5, 1.3)
rs1870779	C	1.0 (0.5, 2.1)	0.7 (0.4, 1.3)	0.7 (0.4, 1.2)	0.9 (0.6, 1.2)
rs1461693	T	1.1 (0.7, 1.8)	0.8 (0.6, 1.1)	0.9 (0.5, 1.4)	1.1 (0.7, 1.5)
rs16892578	T	1.2 (0.4, 3.5)	0.9 (0.4, 2.1)	1.1 (0.7, 1.8)	0.8 (0.6, 1.2)
rs16892586	A	0.8 (0.3, 2.3)	0.6 (0.3, 1.3)	0.6 (0.3, 1.2)	1.0 (0.6, 1.5)
rs7001184	A	5.2 (1.8, 14.7)		1.2 (0.7, 2.1)	0.8 (0.6, 1.3)
CDKN2A					
rs2811720	G	0.9 (0.5, 1.4)	0.9 (0.6, 1.2)	0.9 (0.6, 1.5)	1.0 (0.7, 1.4)
rs2518722*	T	1.0 (0.7, 1.4)	0.9 (0.7, 1.1)	1.2 (0.9, 1.7)	1.0 (0.8, 1.2)
rs10757261*	A	0.8 (0.6, 1.1)	0.9 (0.7, 1.1)	1.0 (0.7, 1.5)	0.9 (0.7, 1.2)
rs2027938*	A	1.0 (0.7, 1.4)	0.9 (0.7, 1.1)	1.3 (0.9, 1.9)	1.1 (0.8, 1.4)
rs717326	G	0.5 (0.2, 1.0)	0.8 (0.6, 1.2)	0.8 (0.4, 1.4)	0.8 (0.5, 1.3)
rs3731257	T	1.6 (1.1, 2.5)	1.0 (0.7, 1.3)	0.7 (0.3, 1.4)	1.3 (0.8, 2.0)
rs3088440	A	0.5 (0.2, 1.0)	0.9 (0.6, 1.4)	1.0 (0.6, 1.7)	0.9 (0.6, 1.3)
rs2811708*	T	1.0 (0.7, 1.3)	0.9 (0.7, 1.1)	1.2 (0.8, 1.9)	1.1 (0.8, 1.5)
rs3731239	C	0.8 (0.5, 1.3)	1.2 (0.9, 1.6)	1.2 (0.6, 2.2)	1.1 (0.7, 1.8)
rs4074785	A	0.5 (0.2, 1.1)	0.9 (0.6, 1.4)	0.7 (0.4, 1.3)	0.8 (0.5, 1.2)
CDKN2B					
rs3731206	A	1.2 (0.3, 3.9)	1.2 (0.5, 2.7)	1.0 (0.6, 1.7)	1.0 (0.7, 1.5)
rs3731204	G	1.2 (0.8, 1.9)	0.9 (0.7, 1.3)	1.4 (0.8, 2.5)	0.8 (0.5, 1.4)
rs10757262	T	0.8 (0.5, 1.3)	0.8 (0.6, 1.1)	1.1 (0.6, 1.9)	1.4 (1.0, 2.0)
rs3731194	C	1.3 (0.4, 4.6)	1.1 (0.5, 2.7)	1.3 (0.7, 2.3)	1.1 (0.7, 1.8)
rs3731191	T	1.3 (0.4, 4.4)	1.6 (0.8, 3.5)	1.0 (0.6, 1.6)	0.8 (0.6, 1.2)
rs2811711	C	1.1 (0.7, 1.8)	0.9 (0.7, 1.2)	1.5 (0.9, 2.5)	1.3 (0.9, 1.8)
rs3218022	G	2.4 (0.6, 9.1)	2.5 (1.2, 5.1)	1.5 (0.8, 2.7)	1.0 (0.6, 1.5)
rs3218020	T	1.8 (1.1, 2.8)	1.1 (0.8, 1.4)	0.8 (0.5, 1.3)	1.3 (0.9, 1.9)
rs3218009	C	0.9 (0.5, 1.6)	1.4 (1.0, 1.9)	1.0 (0.4, 3.1)	1.2 (0.6, 2.6)
rs3218002	T	0.7 (0.4, 1.2)	1.0 (0.7, 1.3)	1.2 (0.7, 2.0)	1.1 (0.8, 1.6)
rs3217999	C	2.2 (0.6, 8.5)	2.8 (1.5, 5.3)	1.3 (0.8, 2.3)	0.9 (0.6, 1.4)
rs3217992	A	2.0 (1.3, 3.2)	1.0 (0.8, 1.3)	0.9 (0.5, 1.6)	1.3 (0.9, 1.9)
rs1063192	C	1.1 (0.7, 1.8)	1.0 (0.7, 1.3)	1.3 (0.7, 2.5)	1.3 (0.8, 2.0)
rs3217989	G		1.5 (0.2, 9.2)	0.8 (0.5, 1.3)	1.0 (0.7, 1.4)
CNNM2					
rs11191457	T	0.8 (0.5, 1.3)	1.0 (0.8, 1.3)	1.2 (0.7, 2.1)	0.9 (0.6, 1.4)
rs7897654	C	0.7 (0.5, 1.1)	1.0 (0.8, 1.3)	1.2 (0.7, 1.9)	0.9 (0.6, 1.3)
rs2297787	A	0.9 (0.5, 1.7)	0.9 (0.6, 1.4)	1.0 (0.6, 1.6)	1.0 (0.7, 1.4)
rs17787717	G	0.5 (0.3, 1.0)	1.3 (0.9, 1.8)	1.2 (0.5, 2.9)	1.7 (1.0, 2.8)
rs7902220	C			1.0 (0.4, 2.4)	1.3 (0.8, 2.3)
rs6584535	T	1.4 (0.9, 2.1)	1.0 (0.8, 1.4)	0.8 (0.4, 2.0)	1.5 (0.9, 2.5)

Gene/SNP	Variant Allele	European American		African American	
		PE	GHTN	PE	GHTN
rs11191512	G	0.8 (0.5, 1.3)	1.0 (0.8, 1.3)	1.2 (0.7, 2.0)	0.9 (0.6, 1.3)
rs7914558*	A	0.7 (0.5, 1.0)	1.1 (0.9, 1.4)	0.9 (0.6, 1.2)	1.1 (0.8, 1.4)
rs4917991*	C	0.7 (0.5, 1.0)	1.1 (0.9, 1.4)	0.8 (0.6, 1.2)	1.0 (0.8, 1.3)
rs11191527	T	0.7 (0.4, 1.2)	1.2 (0.9, 1.5)	1.1 (0.6, 2.0)	0.7 (0.4, 1.2)
rs12264034	T	5.4 (1.6, 17.8)	3.2 (1.4, 7.3)	0.9 (0.6, 1.4)	1.0 (0.7, 1.5)
rs11191537	G	1.0 (0.6, 1.6)	0.8 (0.6, 1.1)	1.7 (1.0, 2.9)	1.0 (0.6, 1.5)
rs7087944	T	0.0 (0.0, 0.0)	4.1 (1.7, 9.9)	1.1 (0.7, 2.0)	1.3 (0.9, 1.9)
rs2296569	C	0.9 (0.6, 1.4)	1.1 (0.8, 1.4)	1.1 (0.5, 2.7)	0.4 (0.2, 1.0)
rs4917995	A	0.7 (0.4, 1.1)	1.1 (0.8, 1.5)	0.6 (0.3, 1.1)	1.3 (0.9, 1.9)
rs11191549*	T	0.7 (0.5, 1.0)	1.1 (0.9, 1.4)	0.8 (0.5, 1.1)	1.0 (0.8, 1.3)
CCND1					
rs7106515	G			0.9 (0.5, 1.6)	0.7 (0.5, 1.2)
rs1982774*	T	0.9 (0.7, 1.3)	1.1 (0.9, 1.3)	1.0 (0.7, 1.5)	1.0 (0.7, 1.3)
rs592483*	C	0.9 (0.6, 1.2)	1.1 (0.9, 1.3)	1.1 (0.7, 1.6)	1.1 (0.8, 1.5)
rs611003*	A	1.2 (0.9, 1.7)	0.9 (0.8, 1.1)	0.8 (0.6, 1.3)	1.1 (0.9, 1.5)
rs11827026	A	0.8 (0.3, 1.8)	1.2 (0.7, 1.9)	1.3 (0.8, 2.1)	1.1 (0.7, 1.5)
rs655089*	G	1.3 (0.9, 1.7)	0.9 (0.8, 1.1)	0.8 (0.6, 1.2)	0.9 (0.7, 1.1)
rs667515*	C	1.3 (0.9, 1.7)	0.9 (0.8, 1.2)	1.1 (0.8, 1.5)	0.9 (0.7, 1.2)
rs2450254*	T	1.2 (0.9, 1.6)	1.0 (0.8, 1.2)	1.2 (0.8, 1.6)	1.0 (0.8, 1.2)
rs3212860	T			0.7 (0.4, 1.3)	0.8 (0.5, 1.2)
rs1352075	T	1.0 (0.6, 1.7)	0.8 (0.6, 1.1)	1.5 (0.9, 2.5)	1.4 (1.0, 2.0)
rs3862792	T	0.6 (0.2, 2.1)	1.0 (0.5, 1.9)	1.3 (0.8, 2.2)	0.9 (0.6, 1.4)
rs603965	A	1.1 (0.7, 1.8)	0.9 (0.7, 1.2)	1.2 (0.8, 2.0)	1.3 (0.9, 1.8)
rs3918298	A	0.6 (0.2, 2.1)	1.0 (0.5, 1.9)	0.8 (0.5, 1.3)	1.0 (0.7, 1.4)
rs649392*	G	1.0 (0.7, 1.4)	1.0 (0.8, 1.2)	0.9 (0.7, 1.4)	0.9 (0.7, 1.2)
rs3212891*	C	1.0 (0.7, 1.3)	1.0 (0.8, 1.2)	1.0 (0.7, 1.4)	1.1 (0.8, 1.4)
rs7121246	T	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.1 (0.7, 1.8)	0.9 (0.6, 1.3)
rs12281701	C	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.0 (0.6, 1.7)	1.1 (0.7, 1.6)
rs1192925*	C	1.3 (1.0, 1.8)	1.0 (0.8, 1.2)	1.0 (0.6, 1.4)	0.9 (0.7, 1.2)
MDM2					
rs769412	G	0.8 (0.4, 1.5)	1.0 (0.7, 1.6)	0.7 (0.4, 1.3)	1.3 (0.9, 2.0)

Empty cells reflect non-polymorphic SNP, null cell counts or out of HWE (IL2:rs10027390).
*Additive model displayed
Minor allele is the common minor allele for both ancestry groups or the Global Minor Allele as noted in dbSNP

Table S20 Single SNP results [RR (95 %Confidence Interval)] for cell cycle genes and preterm

	European American[†]		African American[†]	
Gene/SNP	**Preterm**	**Spontaneous Preterm**	**Preterm**	**Spontaneous Preterm**
GADD45A				
rs12405855	1.1 (0.8, 1.4)	1.1 (0.8, 1.6)	1.6 (0.9, 2.8)	0.7 (0.2, 2.8)
rs344934	1.0 (0.8, 1.2)	0.8 (0.6, 1.1)	1.2 (0.9, 1.6)	1.4 (1.0, 2.0)
rs4655749	1.0 (0.7, 1.6)	0.7 (0.3, 1.4)	1.1 (0.8, 1.6)	1.1 (0.7, 1.8)
rs344916	1.0 (0.8, 1.4)	0.9 (0.6, 1.3)	1.0 (0.8, 1.3)	1.2 (0.8, 1.8)
rs10889710	1.0 (0.8, 1.3)	1.1 (0.8, 1.4)	0.9 (0.6, 1.2)	0.7 (0.4, 1.1)
rs646652	0.9 (0.7, 1.3)	1.0 (0.7, 1.5)	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)
rs2055904	1.0 (0.6, 1.6)	0.7 (0.3, 1.4)	1.1 (0.7, 1.5)	0.9 (0.6, 1.6)
rs604043	0.9 (0.7, 1.2)	1.0 (0.6, 1.5)	0.9 (0.7, 1.3)	0.8 (0.5, 1.3)
rs2815266	1.2 (0.8, 1.7)	1.2 (0.7, 1.9)	1.1 (0.8, 1.5)	1.3 (0.8, 2.0)
rs624790	1.1 (0.8, 1.5)	1.0 (0.7, 1.5)	1.0 (0.8, 1.3)	1.1 (0.8, 1.6)
rs1511686	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.9 (0.6, 1.4)	0.6 (0.3, 1.2)
rs3783468	1.1 (0.9, 1.4)	1.2 (0.9, 1.6)	1.2 (0.9, 1.7)	1.0 (0.6, 1.6)
rs532446	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.9 (0.6, 1.3)
rs607375	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.8 (0.5, 1.1)
rs685724	1.2 (0.9, 1.5)	1.2 (0.9, 1.7)	1.2 (0.9, 1.5)	1.3 (0.9, 1.9)
rs675327	0.9 (0.6, 1.2)	1.0 (0.6, 1.5)	1.2 (0.8, 1.7)	1.2 (0.7, 2.0)
rs11583718	0.9 (0.7, 1.1)	0.9 (0.6, 1.2)	0.9 (0.7, 1.3)	1.0 (0.7, 1.6)
rs7546055	0.9 (0.7, 1.1)	0.7 (0.4, 1.0)	0.8 (0.6, 1.1)	1.0 (0.7, 1.4)
rs598602	0.9 (0.7, 1.2)	1.0 (0.7, 1.5)	0.8 (0.5, 1.2)	0.7 (0.4, 1.3)
rs12408005	1.1 (0.9, 1.4)	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)	0.9 (0.6, 1.4)
RASSF1				
rs35455589	0.9 (0.2, 3.5)	1.0 (0.1, 11.4)	0.9 (0.6, 1.3)	0.8 (0.5, 1.5)
rs709210	0.9 (0.7, 1.1)	0.9 (0.6, 1.2)	1.0 (0.7, 1.5)	1.1 (0.6, 1.8)
rs2073498	1.0 (0.7, 1.4)	1.1 (0.7, 1.7)	1.6 (0.8, 3.2)	1.5 (0.5, 4.3)
rs2236947	1.2 (0.9, 1.5)	1.2 (0.9, 1.7)	1.1 (0.8, 1.5)	1.3 (0.9, 2.0)
rs2073499	0.9 (0.6, 1.2)	0.9 (0.6, 1.5)	0.9 (0.7, 1.2)	0.8 (0.5, 1.1)
rs6446203	0.6 (0.2, 1.4)	0.2 (0.0, 1.7)	0.9 (0.7, 1.2)	0.7 (0.5, 1.1)
rs1989839	1.0 (0.7, 1.4)	1.1 (0.7, 1.7)	1.1 (0.8, 1.4)	1.0 (0.7, 1.6)
CCNA2				
rs6825926	0.8 (0.5, 1.2)	0.6 (0.3, 1.2)	1.0 (0.7, 1.3)	0.8 (0.6, 1.2)
rs1803183	0.9 (0.4, 2.0)	0.5 (0.1, 2.2)	0.8 (0.6, 1.1)	0.7 (0.4, 1.0)
rs6815050	1.1 (0.8, 1.3)	0.9 (0.7, 1.3)	1.0 (0.8, 1.4)	1.2 (0.8, 1.9)
rs3217773	1.0 (0.8, 1.3)	1.3 (0.9, 1.7)	1.1 (0.7, 1.5)	0.8 (0.5, 1.4)
rs3217771	1.0 (0.8, 1.3)	1.2 (0.9, 1.7)	1.0 (0.7, 1.5)	0.8 (0.5, 1.4)
rs3217770	3.9 (0.9, 18.0)	8.1 (2.2, 30.4)	1.3 (0.9, 1.8)	1.8 (1.1, 2.7)
rs2071486	1.0 (0.8, 1.3)	0.8 (0.6, 1.1)	1.0 (0.8, 1.3)	1.4 (1.0, 2.0)
rs3217760	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.8 (0.4, 1.7)	0.7 (0.2, 2.0)
rs1507994	1.0 (0.8, 1.3)	1.2 (0.9, 1.6)	1.0 (0.8, 1.3)	0.7 (0.5, 1.0)

	European American†		African American†	
Gene/SNP	**Preterm**	**Spontaneous Preterm**	**Preterm**	**Spontaneous Preterm**
CCNH				
rs2266690	1.0 (0.7, 1.2)	0.9 (0.6, 1.2)	1.0 (0.6, 1.6)	1.0 (0.5, 1.9)
NOV				
rs13261466	1.0 (0.8, 1.3)	0.7 (0.5, 1.1)	0.4 (0.2, 1.0)	0.5 (0.1, 1.5)
rs2071526	0.8 (0.6, 1.0)	0.9 (0.6, 1.3)	0.9 (0.7, 1.2)	0.8 (0.5, 1.2)
rs7834596	0.8 (0.6, 1.0)	0.9 (0.6, 1.4)	1.0 (0.8, 1.4)	1.0 (0.6, 1.5)
rs7014927	0.8 (0.6, 1.0)	0.9 (0.6, 1.3)	0.9 (0.7, 1.1)	0.9 (0.6, 1.3)
rs11538929	1.2 (0.9, 1.6)	1.0 (0.7, 1.5)	1.0 (0.5, 2.1)	0.5 (0.1, 2.0)
rs1381337			0.9 (0.6, 1.3)	0.9 (0.5, 1.6)
rs16892531	1.0 (0.5, 2.2)	0.7 (0.2, 2.3)	0.8 (0.5, 1.3)	0.9 (0.5, 1.6)
rs11775043	0.7 (0.5, 1.0)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	1.0 (0.6, 1.6)
rs10505358	0.9 (0.5, 1.9)	1.0 (0.4, 2.6)	1.2 (0.9, 1.8)	1.0 (0.6, 1.7)
rs1870779	1.0 (0.6, 1.6)	0.9 (0.4, 1.8)	1.0 (0.8, 1.4)	0.9 (0.6, 1.4)
rs1461693	0.8 (0.6, 1.0)	0.9 (0.6, 1.3)	0.9 (0.6, 1.2)	1.0 (0.7, 1.6)
rs16892578	0.9 (0.4, 2.1)	0.7 (0.2, 2.4)	1.0 (0.7, 1.3)	0.8 (0.5, 1.3)
rs16892586	1.0 (0.5, 1.8)	1.0 (0.4, 2.4)	1.0 (0.6, 1.5)	1.1 (0.6, 2.0)
rs7001184	2.1 (0.7, 5.9)	4.3 (1.5, 12.6)	1.2 (0.9, 1.6)	0.9 (0.6, 1.6)
CDKN2A/2B				
rs2811720	0.9 (0.7, 1.2)	0.8 (0.5, 1.2)	1.0 (0.8, 1.4)	1.2 (0.8, 1.8)
rs2518722	1.0 (0.8, 1.2)	0.9 (0.6, 1.2)	1.1 (0.8, 1.4)	1.1 (0.8, 1.7)
rs10757261	0.9 (0.7, 1.1)	0.8 (0.6, 1.0)	1.1 (0.9, 1.5)	1.2 (0.8, 1.8)
rs2027938	0.9 (0.7, 1.2)	0.8 (0.6, 1.2)	1.1 (0.8, 1.5)	1.0 (0.7, 1.6)
rs717326	0.9 (0.6, 1.3)	0.7 (0.4, 1.3)	1.1 (0.7, 1.6)	1.1 (0.6, 1.9)
rs3731257	1.1 (0.8, 1.3)	1.1 (0.8, 1.5)	1.1 (0.7, 1.7)	1.2 (0.7, 2.2)
rs3088440	0.9 (0.6, 1.3)	0.8 (0.5, 1.4)	1.0 (0.7, 1.4)	0.9 (0.6, 1.5)
rs2811708	1.0 (0.8, 1.2)	0.9 (0.7, 1.3)	1.1 (0.8, 1.4)	1.0 (0.6, 1.5)
rs3731239	1.0 (0.8, 1.3)	1.2 (0.9, 1.5)	0.6 (0.4, 1.0)	0.6 (0.3, 1.3)
rs4074785	0.9 (0.6, 1.3)	0.9 (0.5, 1.5)	1.1 (0.7, 1.6)	1.0 (0.6, 1.8)
rs3731206	0.7 (0.3, 1.9)	1.0 (0.3, 3.1)	1.1 (0.8, 1.5)	1.2 (0.8, 1.9)
rs3731204	1.0 (0.7, 1.3)	0.9 (0.6, 1.3)	1.2 (0.8, 1.8)	0.9 (0.5, 1.8)
rs10757262	0.9 (0.7, 1.2)	0.8 (0.5, 1.3)	1.0 (0.7, 1.4)	0.9 (0.6, 1.5)
rs3731194	0.8 (0.3, 2.3)	1.2 (0.4, 4.1)	1.2 (0.8, 1.8)	1.5 (0.9, 2.4)
rs3731191	0.9 (0.4, 2.3)	1.2 (0.3, 3.9)	0.8 (0.6, 1.1)	0.7 (0.4, 1.1)
rs2811711	0.9 (0.7, 1.3)	0.9 (0.6, 1.3)	1.4 (1.0, 1.9)	1.3 (0.8, 2.1)
rs3218022	0.9 (0.2, 3.6)	1.1 (0.2, 7.3)	0.8 (0.5, 1.3)	0.5 (0.2, 1.3)
rs3218020	1.0 (0.8, 1.2)	1.0 (0.7, 1.3)	1.2 (0.9, 1.7)	1.3 (0.8, 2.0)
rs3218009	1.5 (1.1, 2.0)	1.5 (1.0, 2.3)	0.7 (0.3, 2.0)	0.3 (0.0, 2.1)
rs3218002	0.9 (0.6, 1.2)	0.8 (0.5, 1.2)	0.9 (0.6, 1.2)	1.0 (0.6, 1.5)
rs3217999	0.9 (0.2, 3.4)	1.0 (0.1, 6.8)	1.0 (0.6, 1.4)	1.0 (0.6, 1.7)
rs3217992	1.0 (0.8, 1.3)	1.0 (0.8, 1.4)	1.2 (0.8, 1.8)	1.3 (0.8, 2.3)

	European American†		African American†	
Gene/SNP	**Preterm**	**Spontaneous Preterm**	**Preterm**	**Spontaneous Preterm**
rs1063192	**1.1 (0.9, 1.3)**	**1.1 (0.9, 1.4)**	**1.0 (0.6, 1.6)**	**1.1 (0.6, 2.0)**
rs3217989	**0.9 (0.3, 3.4)**		**0.9 (0.7, 1.2)**	**0.7 (0.5, 1.1)**
CNNM2				
rs11191457	**1.0 (0.8, 1.4)**	**1.0 (0.7, 1.5)**	**1.0 (0.7, 1.4)**	**1.0 (0.6, 1.6)**
rs7897654	**1.1 (0.9, 1.4)**	**1.1 (0.8, 1.6)**	**1.2 (0.9, 1.6)**	**1.4 (0.9, 2.0)**
rs2297787	**1.2 (0.8, 1.7)**	**1.3 (0.8, 2.3)**	**1.0 (0.7, 1.3)**	**1.0 (0.7, 1.6)**
rs17787717	**1.1 (0.7, 1.5)**	**0.9 (0.6, 1.5)**	**1.1 (0.6, 2.2)**	**1.1 (0.4, 2.9)**
rs7902220			**2.0 (1.3, 3.0)**	**2.8 (1.7, 4.5)**
rs6584535	**1.0 (0.8, 1.4)**	**1.0 (0.7, 1.5)**	**0.8 (0.5, 1.5)**	**0.6 (0.2, 1.5)**
rs11191512	**1.1 (0.8, 1.4)**	**1.1 (0.7, 1.5)**	**1.2 (0.9, 1.6)**	**1.3 (0.9, 1.9)**
rs7914558	**1.1 (0.9, 1.4)**	**1.1 (0.8, 1.5)**	**1.2 (0.9, 1.5)**	**1.4 (1.0, 2.0)**
rs4917991	**1.1 (0.8, 1.3)**	**1.0 (0.7, 1.4)**	**1.1 (0.8, 1.4)**	**1.3 (0.9, 1.8)**
rs11191527	**1.1 (0.8, 1.5)**	**1.0 (0.7, 1.5)**	**0.9 (0.6, 1.4)**	**0.9 (0.5, 1.6)**
rs12264034			**0.9 (0.7, 1.2)**	**0.9 (0.6, 1.4)**
rs11191537	**0.8 (0.6, 1.1)**	**0.7 (0.5, 1.1)**	**1.0 (0.6, 1.5)**	**0.7 (0.3, 1.3)**
rs7087944	**0.0 (0.0, 0.0)**	**0.0 (0.0, 0.0)**	**0.9 (0.6, 1.3)**	**0.8 (0.5, 1.5)**
rs2296569	**1.1 (0.8, 1.4)**	**1.2 (0.8, 1.7)**	**0.2 (0.0, 0.9)**	**0.4 (0.1, 1.7)**
rs4917995	**1.0 (0.7, 1.4)**	**0.9 (0.6, 1.4)**	**1.0 (0.7, 1.4)**	**1.1 (0.7, 1.8)**
rs11191549	**1.1 (0.8, 1.3)**	**1.0 (0.7, 1.4)**	**1.1 (0.9, 1.5)**	**1.3 (0.9, 1.9)**
CCND1				
rs7106515			**1.0 (0.7, 1.5)**	**1.2 (0.7, 2.1)**
rs1982774	**1.0 (0.8, 1.3)**	**1.1 (0.8, 1.4)**	**0.9 (0.7, 1.3)**	**1.0 (0.6, 1.5)**
rs592483	**1.0 (0.8, 1.2)**	**1.0 (0.8, 1.4)**	**1.0 (0.8, 1.4)**	**1.1 (0.7, 1.6)**
rs611003	**1.1 (0.8, 1.3)**	**1.1 (0.8, 1.4)**	**1.1 (0.8, 1.4)**	**1.0 (0.7, 1.4)**
rs11827026	**0.9 (0.5, 1.6)**	**0.7 (0.3, 1.5)**	**1.1 (0.8, 1.4)**	**0.9 (0.6, 1.4)**
rs655089	**0.9 (0.7, 1.2)**	**0.9 (0.7, 1.2)**	**0.9 (0.7, 1.1)**	**1.0 (0.7, 1.4)**
rs667515	**1.0 (0.8, 1.2)**	**0.9 (0.7, 1.3)**	**0.8 (0.6, 1.1)**	**1.0 (0.7, 1.5)**
rs2450254	**0.9 (0.7, 1.1)**	**0.8 (0.6, 1.1)**	**1.0 (0.8, 1.3)**	**1.2 (0.8, 1.7)**
rs3212860	**3.4 (0.9, 11.9)**	**3.3 (0.5, 22.6)**	**1.0 (0.7, 1.4)**	**0.9 (0.5, 1.6)**
rs1352075	**0.9 (0.7, 1.1)**	**0.9 (0.7, 1.2)**	**1.2 (0.9, 1.6)**	**1.0 (0.7, 1.6)**
rs3862792	**0.7 (0.3, 1.5)**	**0.4 (0.1, 1.6)**	**1.1 (0.8, 1.6)**	**1.0 (0.6, 1.7)**
rs603965	**0.9 (0.8, 1.2)**	**1.0 (0.7, 1.3)**	**1.1 (0.8, 1.6)**	**1.2 (0.7, 1.9)**
rs3918298	**0.6 (0.3, 1.5)**	**0.4 (0.1, 1.5)**	**1.0 (0.7, 1.4)**	**0.8 (0.5, 1.4)**
rs649392	**1.2 (1.0, 1.5)**	**1.3 (1.0, 1.8)**	**0.9 (0.7, 1.2)**	**1.1 (0.8, 1.7)**
rs3212891	**1.2 (1.0, 1.5)**	**1.3 (0.9, 1.7)**	**1.0 (0.8, 1.3)**	**1.0 (0.7, 1.5)**
rs7121246			**0.9 (0.6, 1.2)**	**0.8 (0.5, 1.3)**
rs12281701			**0.8 (0.5, 1.3)**	**0.8 (0.5, 1.5)**
rs1192925	**1.0 (0.8, 1.3)**	**1.1 (0.8, 1.5)**	**1.0 (0.8, 1.4)**	**1.1 (0.7, 1.7)**
MDM2				
rs769412	**1.1 (0.7, 1.6)**	**0.9 (0.5, 1.6)**	**1.0 (0.6, 1.5)**	**0.9 (0.5, 1.6)**

†Stratified by genetic ancestry

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