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Association between Apolipoprotein L1 genetic variants and risk of preeclampsia and preterm birth among U.S. Black women

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ABSTRACT

Background: Preeclampsia and preterm birth disproportionally affects Black women, but the current understanding of genetic predisposition to preeclampsia and preterm birth is rudimentary. It has been hypothesized that carriers of high-risk genetic variants in the apolipoprotein L1 gene (*APOL1*) may have an increased risk of preeclampsia and preterm birth. These genetic variants are found only among individuals of recent African ancestry. Previous studies have been small and have yielded inconsistent results.
Objective: To examine whether *APOL1* genetic variants are associated with risk of preeclampsia or preterm birth.
Study design: We conducted a retrospective case-control study of 6616 Black women from the Black Women's Health Study, a cohort of self-identified Black women in the U.S. Genotype data on *APOL1* risk alleles for this case control study were obtained through new genotyping and existing genetic data from a prior case control study of breast cancer using the Illumina Infinium Global Diversity Array or Multi Ethnic Genotyping Array. Primary analyses evaluated risk based on a recessive model, comparing women who carried two *APOL1* risk alleles to women who carried zero or one risk allele. We used multivariable logistic regression models to examine associations among 1473 participants with a history of preeclampsia (cases) and 5143 parous women who had not experienced preeclampsia (controls), and among 1296 participants who had a history of preterm birth and 5320 without such history.
Results: The odds ratio (OR) of preeclampsia for two *APOL1* risk alleles vs. zero or one risk allele was 0.99 (95 % confidence interval (CI): 0.74, 1.32) after adjustment for principal components, genotype platform, and age in 1995. For preterm birth, the comparable multivariable OR was 1.04 (95 % CI: 0.86, 1.25).
Conclusions: This large prospective study from a general population of Black women found no evidence of an association of *APOL1* genotype with risk of either preeclampsia or preterm birth.

Abbreviations

BWHS	Black Women's Health Study
BMI	body mass index
OR	Odds ratio
CI	Confidence interval
APOL1	Apolipoprotein L1

1. Introduction

Preeclampsia is a complex multifactorial disease of the mother, fetus, and placenta[1,2], affecting approximately 2–8 % of pregnancies overall[3,4]. The prevalence of preeclampsia/eclampsia among Black women is 60 % higher than that among White women, and the prevalence has been increasing over time[5–9]. Preterm birth rate in the United States was on the rise. Black women have the highest preterm birth rates (14.75 %), in comparison to 9.5 % for Non-Hispanic White women, and 10.23 % for Hispanic women[10]. Our current understanding of genetic predisposition to preeclampsia and preterm birth is rudimentary[11,12], with only a few, relatively small genome-wide association studies (GWAS)[11,13–18], predominantly from White populations[12,19,20]. There is a critical lack of knowledge on genetic factors related to preeclampsia and preterm birth

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in Black women.

Common coding variants in the apolipoprotein L-1 gene (*APOL1*)[21] have been shown to be strongly associated with risk of kidney disease in Black Americans, with odds ratios as high as 29 for severe forms of kidney disease[21,22]. There are two risk alleles in the *APOL1* gene, known as G1 and G2, while the common non-risk alleles are collectively referred to as G0. The G1 allele is a compound missense allele (S342G/I384M) and the G2 allele is an inframe deletion of asparagine-388 and tyrosine-389. These genetic variants, which extend protection against trypanosomiasis, or "sleeping sickness", are present only in individuals with recent African ancestry. Forty to fifty percent of Black Americans carry one risk allele (either G1 or G2), and 10–15 % carry two (G1G1, G2G2, or G1G2)[21,23,24]. Kidney disease risk follows a recessive pattern of inheritance with two risk alleles conferring a high risk relative to 0 or 1 risk allele. In particular, *APOL1* is associated with increased risk of focal segmental glomerulosclerosis and a spectrum of kidney disease[25].

Several studies in both animals and humans support a potential role of *APOL1* genetic variants in the etiology of preeclampsia and the pathophysiology of preterm birth. Transgenic mice with *APOL1* developed preclampsia[26], had more loss of litters, greater fetal and neonatal demise, and reduced litter sizes[26]. Of all human tissues, placenta has been found to have very high levels of *APOL1* mRNA and apolipoprotein L1 expression[12,13]. There have been only a few human studies on *APOL1* genetic variants in relation to risk of preeclampsia and preterm birth; sample sizes have been relatively small and results have been inconsistent.

To address this critical gap, we examined whether *APOL1* variants are associated with increased risk of preeclampsia and/or preterm birth among Black women, a population that disproportionally suffers from both conditions.

2. Materials and methods

2.1. Black Women's Health Study (BWHS)

The BWHS is a long-term prospective cohort of 59,000 Black women (age 21–69 years). Participants were drawn from among subscribers to *Essence* magazine and members of selected Black women's professional organizations, and > 80 % living in CA, GA, IL, IN, LA, MD, MA, MI, NJ, NY, SC, VA, and DC. Approximately 95 % of BWHS participants were born in the United States. Data on pregnancies and births were obtained on biannual questionnaires[27]. Follow up was over 80 % for each questionnaire cycle. The Boston University Medical Campus Institutional Review Board approved the study. Study participants gave informed consent.

3. Outcome

Preeclampsia: On the 2009 questionnaire, participants were asked if they "had ever developed preeclampsia or toxemia during a pregnancy"[27]. In addition, women who gave birth from 1995 through 2003 were asked about details of those pregnancies on the biennial questionnaires, including whether preeclampsia/toxemia was the reason for an early delivery. Information on preeclampsia in BWHS study was self-reported. However, other studies indicate that maternal recall of complications, and birth characteristics is highly accurate (γ=0.76–0.93)[28,29].

Preterm birth: On the 1997 questionnaire, all participants were asked if they had ever delivered a baby early and if so, how many weeks early was the delivery, according to their doctor. Follow-up questionnaires from 1997 through 2003 asked about all births during the previous 2 years, including whether their doctor said the "child was born at least 3 weeks early," and if yes, how many weeks early[30,31]. Due dates and birth dates were also collected for a more precise estimate of gestational age. The proportion of preterm births in our sample (15.2 %) is similar to the proportion in national data for Black babies born < 37 weeks of gestation (15.6 %).

In a prior study of BWHS participants[31], women residing in Massachusetts were linked to their registry data from the Massachusetts Department of Public Health. Among these women, 91.3 % of women who reported a singleton preterm birth during 1995–2003 had ≤ 37 gestation weeks documented by the registry. Eleven out of 12 reports of spontaneous preterm birth were corroborated by registry data.

4. Genotype data

We conducted a retrospective case-control study of 6616 Black women who have provide biospecimen sample, with 1473 participants with a history of preeclampsia (cases) and 5143 parous women who had not experienced preeclampsia. Women who provided biospecimens are similar compared to overall BWHS cohort[32] in terms of their geographic region, education level, body mass index (BMI), medical characteristics, and prevalence of preeclampsia and preterm birth. For this analyses, genotyping data in 4320 participants was obtained from a prior case control study of breast cancer, and new genotyping data in 2296 participants was obtained specifically for this analysis.

Samples were genotyped using the Illumina Multi Ethnic Genotyping Array (MEGA) on the Illumina Infinium Global Diversity Array (GDA), with a custom booster that included the *APOL1* variants. The MEGA and GDA both offered extremely high genomic coverage with similar genomic backbones. The MEGA GWAS data came from women who had served as controls for BWHS research on breast cancer risk[33]; apart from not having breast cancer up to a certain time-point, there were no other inclusion/exclusion criteria for being included in MEGA genotyping. Some of the women whose samples were genotyped on the MEGA had experienced preeclampsia (N = 431, 10 %) and most had not (N = 3889). For this study, we additionally genotyped DNA from all participants with preeclampsia. This led to genotyping of an additional 1042 preeclampsia cases and 1254 controls on the GDA, which by then had replaced the MEGA in the Illumina inventory of genotyping arrays. Thus, for analyses of preeclampsia, there were a total of 1473 cases and 5143 controls with genotyping data available, and for preterm birth analyses, there were 1296 cases and 5320 controls. Variants with call rate < 98 %, minor allele frequency < 0.01, and Hardy Weinberg Equilibrium p < 1e-4 were excluded from all batches.

5. Statistical analyses

The association between *APOL1* genotype and kidney phenotypes generally follows a recessive model in which two *APOL1* risk alleles are necessary to confer increased risk. Our primary analysis used a recessive model, with *APOL1* status defined as a binary variable (carriers of two risk alleles vs. individuals who carry zero or one risk allele). An individual would be classified as carrying two risk alleles if she had two G1 risk alleles, or two G2 risk alleles, or one G1 plus one G2 risk allele. We also examined dominant (one or two risk alleles vs. zero allele) and additive (per variant allele) models.

We used logistic regression and adjusted for top 3 principal components, genotype platform, and age in 1995. Principal components of ancestry were estimated using smartpca in the Eigensoft package and used to control for potential confounding by ancestry[34]. We conducted stratified analyses by parity, age at first birth, history of preterm birth.

BWHS participants had also been asked whether they themselves had been born three or more weeks early. We conducted a separate analysis to examine the association of *APOL1* status with prevalence of having been born preterm. Nulliparous women were included in this analysis.

6. Results

Baseline characteristics were similar between women with and without a history of preeclampsia in terms of their education, age at first

birth, and number of births (Table 1). Compared to women without a history of preeclampsia, women with preeclampsia were more likely to have BMI at age 18 ≥ 25 kg/cm^2, and more likely to have a history of preterm birth.

The odds ratio of preeclampsia for two *APOL1* risk alleles vs. 0 or 1 risk allele was 0.89 (95 % confidence interval (CI): 0.74, 1.06) in an unadjusted model, and 0.99 (95 %CI: 0.74, 1.32) after adjustment for principal components, genotype platform, and age (Table 2). We performed stratified analyses by parity (1 birth, 2 or more births), age at first birth (<25, ≥25 years), participants own birth (born full term, born preterm), and participants' history of preterm birth (yes, no). Associations of *APOL1* genetic variants with risk of preeclampsia were null and consistent across different stratified analyses. Among participants who also have a history of preterm birth, the multivariable OR for preeclampsia was 1.43 (95 %CI: 0.85, 2.39). Under alternative models (dominant, per allele), there was no evidence of an association of *APOL1* genotype with preeclampsia risk (Supplementary Table 1).

For the association of *APOL1* genetic variants with risk of preterm birth, the OR was 1.02 (95 % confidence interval (CI): 0.85, 1.22, Table 3) in unadjusted analyses and 1.04 (95 %CI: 0.86, 1.25) after adjustment for principal components, genotype platform and age in 1995. For participants' own birth, we observed a null association between *APOL1* with risk of being born preterm (Table 4).

7. Discussion

In this case-control study of 6616 U.S. Black women from the prospective BWHS cohort study, we found no evidence of an association of *APOL1* genetic variants with risk of preeclampsia or preterm birth.

Physiologically, the vasculature of the placenta and glomeruli are very similar[35]; they are both complex microvascular filters that require many of the same vascular growth factors (e.g. VEGF) to maintain vascular function. They are also functionally interconnected, with kidney dysfunction increasing risk of pregnancy complications, and vice versa. The *APOL1* gene encodes apolipoprotein L1, an abundant plasma protein, and binds to high density lipoprotein (HDL)[36]. Apolipoprotein L1 is also highly expressed in vascular tissue[37,38], including both placental and glomerular vasculature. As the *APOL1* genetic variants explain much of the racial health disparities in chronic kidney disease, *APOL1* may also be an important contributor to racial disparities in preeclampsia and preterm birth[11]. Some transgenic mouse models of *APOL1* kidney disease developed preclampsia[26]. Of all human tissues, placenta has been found to have very high levels of *APOL1* mRNA and apolipoprotein L1 expression[37,39,40]. *APOL1* is also expressed in vascular endothelium and arterial smooth muscle cells[41]. Additionally, circulating serum apolipoprotein L1 levels are higher in women with preeclampsia than women without[42].

Although evidence from basic science is provocative, epidemiological research on *APOL1* genetic variants with reproductive outcomes is sparse and limited by sample size. There have been few publications on

Table 1
Baseline characteristics of 6616 parous Black Women's Health Study participants with GWAS data.

Characteristics of study participants	Cases of preeclampsia (n = 1473)	Controls (n = 5143)
Age at enrollment in 1995, median (Std Dev)	37 (9.7)	40 (10.5)
Body mass index at age 18, kg/m^2, n (%)		
< 20	490 (33.3)	2223 (43.2)
20–24	681 (46.2)	2321 (45.1)
≥ 25	285 (19.4)	535 (10.4)
missing	17 (1.2)	64 (1.2)
Education, years (%)		
< 12	229 (15.6)	927(18.0)
12–15	603(40.9)	1817(35.3)
≥ 16	640(43.5)	2395(46.6)
Missing	1 (0.07)	4(0.1)
Age at first birth, years (%)		
< 25	841 (57.1)	2944 (57.2)
≥ 25	619 (42.0)	2126 (41.3)
missing	13 (0.9)	73 (1.4)
Parity, n (%)		
1	458 (31.1)	1770 (34.4)
2 or more	1015 (68.9)	3373 (65.6)
Participants born preterm (%)	88 (6.2)	253 (5.1)
Participants with ≥ 1 preterm birth (%)	438 (31.0)	858 (17.3)

Table 2
Apolipoprotein L1 genetic variants in relation to preeclampsia prevalence.

	Preeclampsia Yes, n N = 1473	Preeclampsia No, n N = 5143	Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
***APOL1* status**				
All cases and controls				
Zero or one risk allele	1298	4463	1.00 (reference)	1.00 (reference)
Two risk alleles[a]	175	680	0.89 (0.74, 1.06)	0.99 (0.74, 1.32)
Stratified analyses				
Parity 1 birth				
Zero or one risk allele	403	1550	1.00 (reference)	1.00 (reference)
Two risk alleles[a]	55	220	0.96 (0.70, 1.32)	0.59 (0.29, 1.19)
Parity 2 or more births				
Zero or one risk allele	895	2913	1.00 (reference)	1.00 (reference)
Two risk alleles[a]	120	460	0.85 (0.69, 1.05)	1.08 (0.79, 1.49)
Age at first birth < 25				
Zero or one risk allele	749	2559	1.00 (reference)	1.00 (reference)
Two risk alleles[a]	92	385	0.82 (0.64, 1.04)	1.02 (0.70, 1.48)
Age at first birth ≥ 25				
Zero or one risk allele	536	1845	1.00 (reference)	1.00 (reference)
Two risk alleles[a]	83	281	1.02 (0.78, 1.32)	1.01 (0.64, 1.59)
Participants born preterm				
Zero or one risk allele	77	223	1.00 (reference)	1.00 (reference)
Two risk alleles[a]	11	30	1.06 (0.51, 2.22)	1.35 (0.40, 4.53)
Participants born full term				
Zero or one risk allele	1221	4240	1.00 (reference)	1.00 (reference)
Two risk alleles[a]	164	650	0.88 (0.73, 1.05)	0.98 (0.73, 1.32)
History of preterm birth				
Zero or one risk allele	377	749	1.00 (reference)	1.00 (reference)
Two risk alleles[a]	61	109	1.11 (0.79, 1.56)	1.43 (0.85, 2.39)
No, history of preterm birth				
Zero or one risk allele	921	3714	1.00 (reference)	1.00 (reference)
Two risk alleles[a]	114	571	0.81 (0.65, 1.00)	0.85 (0.60, 1.21)

*Women who carry two risk alleles of apolipoprotein L1 were defined as either carry two risk alleles of G1 (G1G1), carry two risk alleles of G2 (G2G2), or carry one risk allele of G1 and one risk allele of G2.

[a] Adjusted for principal components, genotype platform, age in 1995. CI, confidence interval; OR, odds ratio.

Table 3
Apolipoprotein L1 genetic variants in relation to history of preterm birth.

	History of preterm birth N = 1296 n	No history of preterm birth N = 5320 n	Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
***APOL1* status**				
Zero or one risk allele	1126	4635	1.00 (reference)	1.00 (reference)
Two risk alleles[a]	170	685	1.02 (0.85, 1.22)	1.04 (0.86, 1.25)

*Women who carry two risk alleles of apolipoprotein L1 were defined as either carry two risk alleles of G1 (G1G1), carry two risk alleles of G2 (G2G2), or carry one risk allele of G1 and one risk allele of G2.

[a] Adjusted for principal components, genotype platform, age in 1995. OR, odds ratio; CI, confidence interval.

Table 4
Apolipoprotein L1 genetic variants in relation to history of being born preterm.

	Participant born preterm n	Participant born full-term n	Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
***APOL1* status**				
Zero or one risk allele	394	4020	1.00 (reference)	1.00 (reference)
Two risk alleles*	54	614	0.94 (0.78,1.15)	0.97(0.79, 1.18)

*Adjusted for principal components, genotype platform, age in 1995. OR, odds ratio; CI, confidence interval.
This analysis consists of 5082 women who provided responses to question whether themselves were being born preterm and have *APOL1* information.

the relation of *APOL1* genetic variants to risk of preeclampsia[43–45]. One that included 24 and 93 mothers with preeclampsia from two U.S. datasets[43] reported that maternal *APOL1* genetic variants was not associated with risk of preeclampsia; however, fetal *APOL1* genetic variants was associated with a statistically significant increase in preeclampsia (odds ratios (ORs) 1.84, n = 121 and OR= 1.92, n = 73), under a recessive model. Another U.S. study was unable to assess maternal *APOL1*, but found that fetal *APOL1* genetic variants were associated with preeclampsia, with an OR of 1.41 under a dominant model and no evidence of association in a recessive model (N = 395 preeclampsia cases)[45]. A stronger association was observed when only preterm births among preeclampsia cases were considered (N = 191). A study based on 428 South African pregnant women (N = 244 preeclampsia cases) reported an OR of 2.2 for the association of maternal *APOL1* G1 risk allele with early onset preeclampsia, but no association with carrying a G2 allele[44]. A nested case control study based on 213 Black mother and infant pairs found that fetal *APOL1* kidney risk alleles were associated with a 3.6-fold increased risk for preeclampsia in a recessive mode, and association differ by country of origin (1.7-fold increased risk for preeclampsia in an additive model among African American women, but not among Haitian American women)[46]. This study also suggested that maternal-fetal *APOL1* discordance is associated with 2.6-fold increased risk of preeclampsia[46]. One case control study of 395 cases and 282 controls from a single center in the U.S. also reported a 1.4-fold increased risk of preeclampsia with fetal *APOL1* [45]. In our study based on 1473 preeclampsia cases and 5143 controls, we found no evidence of an association of maternal *APOL1* genotype with risk of preeclampsia.

Others have examined *APOL1* in relation to preterm birth. A 4.6-fold odds of being born preterm associated with fetal *APOL1* among children with glomerular disease was reported in a very small sample (N = 16 preterm birth cases)[47], but there was no association of maternal *APOL1* genetic variants with preterm birth. In our study, we examined this relation among preterm births in a larger number of Black women (N = 1296 preterm birth cases). Consistent with the literature[48], no association of maternal *APOL1* genetic variants with preterm birth was found.

In this large case control study of 6616 Black women, provides convincing evidence against the hypothesis that carriers of APOL1 risk variants are at increased risk of either preeclampsia or preterm birth.

Our findings of null association between maternal APOL1 genetic variants with risk of preeclampsia and preterm birth support prior findings in the literature. However, our study has a large sample size with sufficient statistical power to address this hypothesis. Compared with previous studies, our study was a large study from a general population of Black women in the U.S. with large number of preeclampsia and preterm birth cases. Our study has some limitations. We did not have information on paternal and fetal *APOL1* genetic variants. The literature to date suggests that fetal APOL1 status may play a more important role than maternal status[43,46]. Some preliminary evidence suggests environmental factors, such as country of maternal origin, may potentially interact with *APOL1* genetic variants in the etiology of preeclampsia[46]. In our study, majority of BWHS participants (95 %) were born in the United States, thus prohibiting meaningful analyses stratified on country of origin. This limitation is also a strength, however, since environmental factors, such as maternal folate supplementation, may be more uniform, thus reducing potential confounding. Finally, one prior study from South Africa reported an association with early-onset preeclampsia only[44]. In the BWHS, majority of preeclampsia and preterm birth cases occurred before 1995 enrollment. It was not feasible to validate all self-reports preeclampsia and preterm birth cases through obtaining pregnancy medical records[27]. The misclassification and underreporting of preeclampsia and preterm birth are inevitable and most likely to be non-differential with regards to participants' APOL1 status. We did not have detailed information on each pregnancy, clinical risk factors, the timing and severity of preeclampsia, information on proteinuria, and information on renal function. Therefore, our study could not differentiate between early onset vs. late onset preeclampsia, first vs. recurrent preeclampsia/preterm birth, and whether the preterm birth was spontaneous or indicated. Future studies are needed to investigate this associations with differentiation of early onset vs. late onset preeclampsia.

8. Conclusions

In this large prospective study from a general population of Black women, a population that disproportionally suffers from preeclampsia and preterm birth, we found no evidence of an association of *APOL1* genetic variants with risk of preeclampsia and preterm birth.

Article type

Case control study

Data sharing statement

The data underlying this article cannot be shared publicly to protect the privacy of individuals who participated in the study. The data will be shared on reasonable request to the last author.

Attestation statements

Data regarding any of the subjects in the study has not been previously published. Data will be made available to the editors of the journal pre and/or post publication for review or query upon request. STROBE checklist was used.

The Clinical Trial Registration Date

Not applicable

Capsule (26 words)

A large study from a general population of Black women found no association between apolipoprotein L1 (APOL1) genetic variants with risk of preeclampsia and preterm birth.

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CRediT authorship contribution statement

Julie Palmer: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Gary Zirpoli:** Data curation. **Kathryn Lunetta:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Chunyu Liu:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **David Friedman:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization. **Shanshan Sheehy:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

All authors have no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.eurox.2025.100365.

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