HHS Public Access

Author manuscript

Neonatology. Author manuscript; available in PMC 2024 April 14.

Published in final edited form as:

Neonatology. 2023 ; 120(4): 532–536. doi:10.1159/000529850.

Fetal High-Risk APOL1 Genotype Increases Risk for Small for Gestational Age in Term Infants Affected by Preeclampsia

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Abstract

Background: Hypertensive disorders of pregnancy cause fetal growth restriction and increased maternal morbidity and mortality, especially in women of African ancestry. Recently, preeclampsia risk was associated with polymorphisms in the Apolipoprotein L1 (*APOL1*) gene in women of African ancestry.

Objectives: We assessed *APOL1* genotype effects on pregnancies with and without preeclampsia.

Method: We conducted an unmatched case-control study of 1,358 mother-infant pairs from two independent cohorts of Black women.

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Author Contributions

TA, LAB, RLD, SMW study conception and design. TA, RD data harmonization and analysis. TA, RD wrote the manuscript and prepared tables and figure. LAB, RLD, SMW, CLS edited the manuscript. All authors contributed to data interpretation. All authors approved the final manuscript.

Statement of Ethics

This is an observational study of the existing de-identified genetic and clinical data; no new data were collected for the purpose of this study. Case Western Reserve University Institutional Review Board has confirmed that no ethical approval is required. Written informed consent was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. LAB has received royalties for APOL1 research tools that are unrelated to the scope of this manuscript.

Results: Term preeclampsia cases with high-risk *APOL1* genotypes were more likely to be small for gestational age compared to *APOL1* low-risk term cases (*OR* 2.8) and *APOL1* high-risk controls (*OR* 5.5). Among preterm pregnancies, fetal *APOL1* genotype was associated with preeclampsia.

Conclusions: Fetal *APOL1* genotype was associated with preeclampsia in preterm infants and with altered fetal growth in term infants. This may indicate *APOL1* genotype impacts a spectrum of pregnancy complications mediated by a common pathophysiological event of placental insufficiency.

Keywords

Small for gestational age; Fetal growth; Preeclampsia; African American; Genetics

Introduction

Preeclampsia (PE) is a progressive, multiorgan disorder of pregnancy defined as new onset hypertension with proteinuria and/or significant end-organ dysfunction after 20 weeks of gestation [1]. Maternal mortality has increased over the past decades in the US, with PE/eclampsia accounting for approximately 8% of all maternal deaths [2]. In addition, PE disproportionately affects women of African ancestry, making it one of the most important causes of perinatal health disparities globally [3]. African American women have significantly higher risk of PE compared to European Americans even after adjustment for maternal co-morbidities and socioeconomic status, with odds ratios (*OR*) varying from 1.3 (*95% CI* 1.28–1.33) to 1.67 (*95% CI* 1.64–1.71) [4,5]. PE is also associated with several short-term (hepatic and kidney failure, pulmonary edema) and long-term maternal complications (cardiovascular disease and chronic kidney disease). In neonates, in addition to accounting for approximately 15% of preterm births, PE is associated with at least a two-fold increase in risk for fetal growth restriction [6,7].

Several recent studies, including our work, reported association of Apolipoprotein L1 (*APOL1*) polymorphisms (known as G1 and G2) with PE risk in Black women. Both G1 (rs73885319, rs60910145) and G2 (rs71785313) encode variants that appear to be gain-of-function mutations providing both a beneficial effect on the immune system but a detrimental effect of kidney disease risk. The G1 and G2 variants are restricted to individuals of recent African ancestry. In prior studies of PE, findings differed on the impact of the maternal *APOL1* genotype [8] and the observed model of inheritance [9,10]. Most recently, a study reported increased PE risk in African Americans associated with a recessive model of the fetal *APOL1* genotype and with maternal-fetal *APOL1* genotype discordance [11]. These inconsistencies in the observed model of inheritance and the role of maternal versus fetal genotype leave several important questions related to the mode of action of the *APOL1* risk alleles on PE unanswered.

The goals of this study were to identify possible effects of *APOL1* risk alleles on fetal growth and to clarify the model of inheritance of the fetal *APOL1*-associated risk for PE in women of African ancestry.

Materials and Methods

Study Design

We utilized a retrospective unmatched case-control study design to analyze growth outcomes of infants born to mothers with and without PE based on the timing of delivery and fetal *APOL1* genotype and inheritance pattern. The study was reviewed by Case Western Reserve University Institutional Review Board and determined to be exempt from ongoing IRB oversight.

Study population

A combined dataset including de-identified genetic and clinical data of self-identified Black mother-infant pairs was compiled from two separate cohorts from the University of Tennessee Health Sciences Center's CANDLE database [9] and the Ohio March of Dimes database [10] that were previously described. This study defined cases as infants born to mothers with hypertension and/or PE during the current pregnancy. Controls were term infants born to mothers with uncomplicated pregnancies. Small for gestational age (SGA) was defined as infants with birth weight below 10^{th} percentile for their corresponding gestational age [12]. Presence of any two *APOL1* G1 and/or G2 alleles comprised a high-risk genotype, consistent with the original studies.

Statistical analysis

Descriptive summary statistics and subsequent analyses were performed using two-tailed Student's t-test or Mann-Whitney test for continuous variables and Fisher's exact test or Chi-square test for categorical variables. Linear regression analysis and one-way analysis of variance with Bonferroni correction for multiple comparisons was used to evaluate relationships between birth weight, gestational age, and other variables. Logistic regression analyses with and without adjustment for co-variates assessed the association between fetal *APOL1* genotype and PE in the entire dataset and following stratification of cases by term or preterm delivery. We used Akaike Information Criterion (AIC) in multivariate analysis to select the best-fitting model. Fetal *APOL1* genotype associations were examined in dominant, recessive, and additive inheritance models. All analyses were performed in R version 2022.02.2+485.

Results

Following merging and harmonization, the combined dataset included 1,358 mother-infant pairs. Cases included 213 preterm (<37 weeks of gestation) and 257 term pregnancies with gestational hypertension and/or PE. Term healthy pregnancies (n=888) were included as controls. There were no significant differences in maternal age, gravidity, and fetal sex between cases and controls (Supplemental Table 1).

Analysis of growth outcomes in term infants showed significantly lower birth weight (BW) in PE cases compared to controls: 3,005±522 g versus 3,228±459 g (p<0.0001). When analyzed by *APOL1* genotype, we observed a significant negative linear trend in BW of term infants based on case status and presence of high-risk *APOL1* genotypes (Table 1). Control

infants, regardless of *APOL1* genotype, and term cases with low-risk *APOL1* genotypes demonstrated expected increases in BW with gestational age (GA) at birth. However, term cases with high-risk *APOL1* genotypes did not show a positive increase in BW with increasing GA indicating altered fetal growth.

Infant growth trajectories differed based on both PE status and fetal *APOL1* genotype. Among term pregnancies with PE, *APOL1* high-risk infants were 2.8 times more likely to be SGA compared to those with low-risk *APOL1* genotype (*OR* 2.8, *95%CI* [1.2, 6.4], p=0.017) (Fig. 1). When considering PE, term infants with low-risk *APOL1* genotype born to mothers with PE were 2.4 times more likely to be SGA compared to infants born to mothers without PE (*OR* 2.4, *95%CI* [1.6, 3.6], p=0.0001), whereas term infants with high-risk *APOL1* genotype were 5.5 times more likely to be SGA when PE was present (*OR* 5.5, *95%CI* [2.1, 14.1], p=0.0006). Preterm infants demonstrated appropriate increase in BW with GA, with similar proportions of SGA preterm cases with low-risk *APOL1* genotypes compared to preterm cases with high-risk *APOL1* genotypes (23.2% versus 27.3%, p=0.65).

APOL1 allele frequencies for the common variant G0 and the two risk alleles G1 and G2 (65.5%, 23.5%, and 11%, respectively) in control infants were similar to reported frequencies in African Americans. Genotype frequencies of 0, 1 and 2 risk alleles (44.1%, 42.7%, and 13.2%, respectively) in controls also did not deviate from reported data [13]. Among cases, 2 risk allele genotypes were enriched in preterm cases (38.5%, 41.3%, and 20.2%) driven by increased allele frequencies of both G1 (26.8%) and G2 (14.1%). Regression analysis for inheritance patterns did not identify association of *APOL1* genotype with PE in any of the inheritance models (dominant, recessive, or additive) when all cases were compared to controls. However, when stratified by prematurity, *APOL1* genotype was associated with PE in preterm cases in both recessive (*OR* 1.71, *95%CI* [1.09, 2.69]) and additive inheritance models (*OR* 1.33, *95%CI* [1.05, 1.69]) when adjusted for maternal age and study location.

Discussion

This is the first study reporting association of fetal *APOL1* genotype with altered fetal growth in African Americans with PE. While PE is a known independent risk factor for fetal growth restriction that increases risk of SGA at least two-fold [7, 8], two previous studies found similar proportions of SGA infants when fetal low- and high-risk *APOL1* genotypes were compared without adjustment for other factors [14,15]. In our larger cohort of infants, we used the same method of identifying SGA infants but were able to stratify our data by gestational age and presence of PE. An increase in odds of being SGA was observed only in term infants born to mothers with PE indicating that *APOL1*-mediated deleterious effects on fetal growth become evident later in gestation in pregnancies complicated by PE. This finding indicates that in pregnancies with mild and/or late-onset forms of PE, progressive placental insufficiency may be further exacerbated during the third trimester in the presence of *APOL1* risk alleles. The mechanism remains unknown, but our findings suggest PE in both perterm and term pregnancies may share a common pathogenetic mechanism of progressive placental insufficiency. When the *APOL1* effects are early and severe, it may

result in preterm delivery, whereas less severe cases, placental insufficiency could manifest as fetal growth restriction.

Overall, our observations were consistent with previous reports that fetal *APOL1* genotype contributes to elevated PE risk [9–11]. We observed an association of fetal *APOL1* risk genotypes with PE in preterm cases in both recessive and additive inheritance models. From these combined reports, it is clear that carriage of any number of *APOL1* risk alleles can be detrimental to fetal outcomes. The lack of clarity on the inheritance pattern may indicate one risk allele has some negative effect. Still, two risk alleles predispose to early and/or more severe forms of PE. In addition, it has not been established if there is a difference in the effect of G1 versus G2 alleles or if there is a triggering environmental exposure as is required for *APOL1* genotype risk and kidney disease.

Limitations of our study include growth outcome data being limited to birth weight and corresponding GA at delivery in most infants, thus making it impossible to distinguish between constitutionally small and growth-restricted infants. Also, we cannot exclude possible population stratification as we could not assess variation in ancestry due to the lack of ancestry informative makers. There was also limited maternal *APOL1* genotype data that precluded studying maternal-fetal genotype discordance and possible parent of origin effects of *APOL1* risk alleles on the outcomes. In addition, there was no tractable control group for prematurity, as all preterm births result from an abnormal maternal or fetal predisposing condition.

Conclusion

Fetal high-risk *APOL1* genotype is associated with altered fetal growth in term infants born to mothers with PE as indicated by increased proportion of SGA infants. In pregnancies complicated by preterm deliveries, fetal high-risk *APOL1* genotype is associated with increased PE risk. These adverse outcomes likely develop secondary to a common deleterious impact of fetal *APOL1* risk alleles on progressive placental insufficiency. Further studies may provide additional information on effects of the maternal versus paternal passage of the *APOL1* high-risk alleles and the discordance between the maternal and fetal *APOL1* genotypes, along with other environmental factors that may alter the *APOL1* genetic risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Sources

LAB is supported by DK127638. SMW and the creation of the Ohio March of Dimes database were supported by the March of Dimes Prematurity Research Center Ohio Collaborative.

Data Availability Statement

No new data sets were generated in the current study. Data used from the CANDLE and March of Dimes consortia can be accessed by contacting the respective parent studies.

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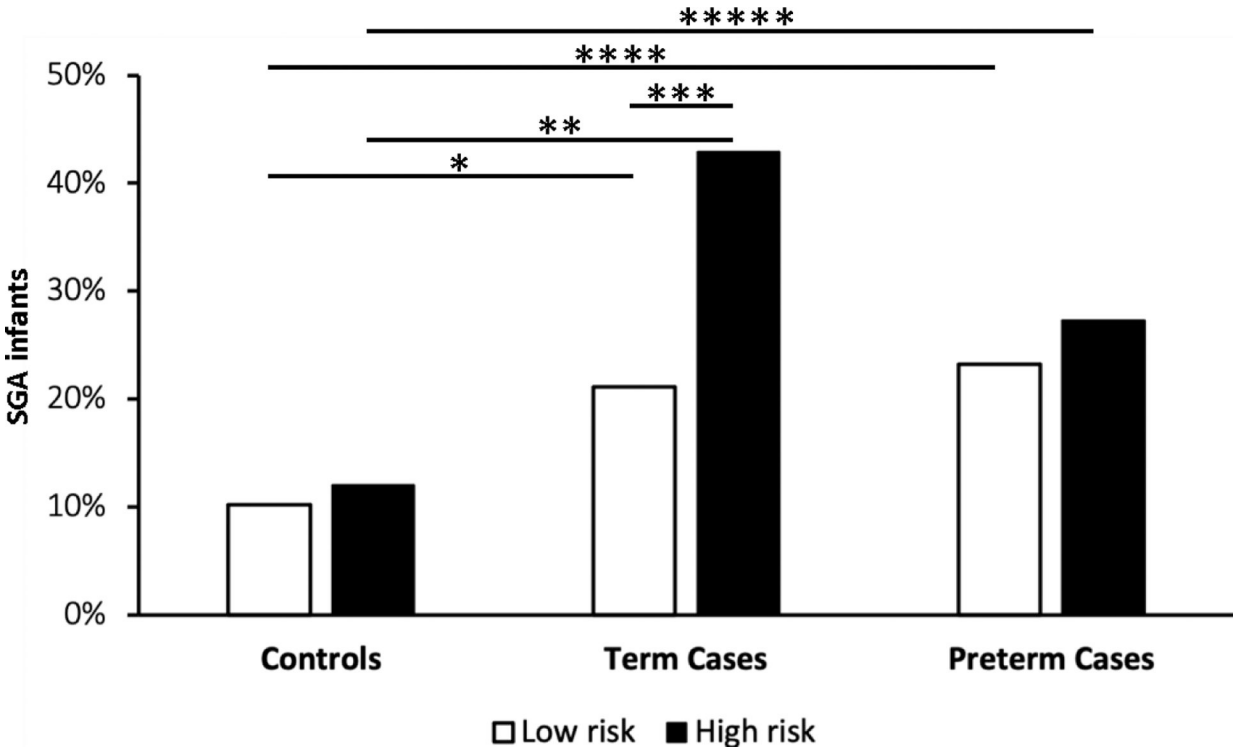

Figure 1. Small for gestational age (SGA) infants based on presence of preeclampsia (PE) and *APOL1* genotype.

High risk indicates an *APOL1* genotype consisting of any combination of G1 and G2 risk alleles (G1/G1, G1/G2 or G2/G2). Low risk indicates an *APOL1* genotype of the non-disease common variant G0 or only one risk allele (G0/G0, G0/G1, G0/G2). Control infants (no PE) had similar percentage of SGA infants with low- and high-risk *APOL1* genotypes. Term cases (PE present) with low-risk *APOL1* genotype were more likely to be SGA compared to low-risk controls (*). Term cases with high-risk *APOL1* genotype were more likely to be SGA compared to corresponding high-risk controls (**). Among term cases, infants with high-risk *APOL1* genotype were significantly more likely to be SGA compared to low-risk term cases (***). Low- and high-risk preterm cases were not different from each other, but preterm cases were significantly different from corresponding controls (**** and *****, respectively) with the increase in SGA similar to low risk term cases. *p=0.0001; **p=0.0006; ***p=0.017; ****p<0.0001; *****p=0.04.

Table 1.

Fetal *APOL1* genotype and growth outcomes in term and preterm infants.

	APOL1	*n*	GA	BW	β^*, g	SD	*p*-value#	SGA
Controls	low-risk	771	39.3±1.1	3,231±460	151.5	14.7	<0.0001	74/728 (10.2%)
	high-risk	117	39.3±1.0	3.210±454	176.5	40.3	<0.0001	13/108 (12.0%)
Cases	***Term***:							
	low-risk	224	38.9±1.2	3,026±506	193.5	27.4	<0.0001	43/204 (21.1%)
	high-risk	33	38.8±1.1	2,849±609	161.5	105.3	0.137	12/28 (42.9%)
	Preterm:							
	low-risk	170	33.6±3.3	1,974±664	182.8	10.8	<0.0001	32/138 (23.2%)
	high-risk	43	34.2±2.7	2,162±584	204.5	24.5	<0.0001	9/33 (27.3%)

*β = β coefficient, representing the mean increase in BW (in grams) per week increase in gestational age. SD, standard deviation. GA, gestational age (in weeks). SGA, small for gestational age.

#*p*-value indicates significance of linear relationship between BW and GA in each group.