The American Journal of Human Genetics, Volume *103*

Supplemental Data

Fetal—Not Maternal—*APOL1* Genotype Associated with Risk for Preeclampsia in Those with African Ancestry

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Supplementary Data:

Table S1: Descriptive Data of Mothers in the UTHSC Case-Control Study by Maternal *APOL1* Genotype.[a]

Maternal *APOL1* Genotype	All (n = 921)	*APOL1* LR (n = 821)	*APOL1* LR (n = 100)
Maternal age (years, at time of delivery)			
15-19	151 (16%)	134 (16%)	17 (17%)
20-24	346 (38%)	310 (38%)	36 (36%)
25-29	246 (27%)	223 (27%)	23 (23%)
30-34	133 (14%)	114 (14%)	19 (19%)
≥ 35	45 (5%)	40 (5%)	5 (5%)
Household income			
$0-$24,999	493 (54%)	436 (53%)	57 (57%)
$25,000-$44,999	164 (18%)	145 (18%)	19 (19%)
$45,000-$74,999	107 (12%)	94 (11%)	13 (13%)
$75,000 or over	50 (5%)	46 (6%)	4 (4%)
Unknown	107 (12%)	100 (12%)	7 (7%)
Smoking			
Yes	78 (9%)	67 (8%)	11 (11%)
No	842 (91%)	753 (92%)	89 (89%)
Unknown	1(0%)	1 (0%)	0 (0%)

a. RA refers to APOL1 risk allele, either G1 (S342G mutation) or G2 (a 6 bp deletion N388del;Y389del). The HR genotype consists of 2 RA. The LR genotype consists of 0 or 1 RA. Results reported as number of patients and percent of patients in parenthesis.

Table S2: Pregnancy Characteristics of UTHSC Case-Control Study Population by *APOL1* Genotype.[a]						
Maternal or Fetal	**Maternal Genotype**			**Fetal Genotype**		
APOL1 Genotype	**All** (n = 921)	***APOL1* LR** (n = 821)	***APOL1* HR** (n = 100)	**All** n = 747)	***APOL1* LR** (n = 644)	***APOL1* HR** (n = 103)
Pregnancy Weight Gain						
0-18 kg	592 (64%)	526 (64%)	66 (66%)	494 (66%)	437 (68%)	57 (55%)
18.1-36.7 kg	199 (22%)	178 (22%)	21 (21%)	178 (24%)	152 (24%)	26 (25%)
36.8-55 kg	5 (5%)	4 (0%)	1 (1%)	3 (0%)	2 (0%)	1 (1%)
Unknown or weight loss	125 (14%)	113 (14%)	12 (12%)	72 (10%)	53 (8%)	19 (18%)
Gestational age						
<36 weeks	81 (9%)	75 (9%)	6 (6%)	63 (8%)	55 (9%)	8 (8%)
37-38 weeks	115 (12%)	103 (13%)	12 (12%)	97 (13%)	86 (13%)	11 (11%)
38-41 weeks	698 (76%)	620 (76%)	78 (78%)	582 (78%)	499 (77%)	83 (81%)
> 42 weeks	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	27 (3%)	23 (3%)	4 (4%)	5 (1%)	4 (1%)	1 (1%)
Birth weight						
<1500 g	15 (2%)	15 (2%)	0 (0%)	9 (1%)	9 (1%)	0 (0%)
1501-2500 g	68 (7%)	62 (8%)	6 (6%)	59 (8%)	48 (7%)	11 (11%)
2501-4000 g	768 (83%)	683 (83%)	85 (85%)	638 (85%)	553 (86%)	85 (82%)
> 4000 g	40 (4%)	35 (4%)	5 (5%)	35 (5%)	29 (5%)	6 (6%)
Unknown	30 (3%)	26 (3%)	4 (4%)	6 (1%)	5 (1%)	1 (1%)
Delivery Type						
Vaginal	562 (61%)	503 (61%)	59 (59%)	463 (62%)	406 (63%)	57 (55%)
Cesarean section	332 (36%)	295 (36%)	37 (37%)	279 (37%)	234 (36%)	45 (44%)
Unknown	27 (3%)	23 (3%)	4 (4%)	5 (1%)	4 (1%)	1 (1%)
Pre-eclampsia						
Yes	93 (10%)	87 (11%)	6 (6%)	73 (10%)	57 (9%)	16 (16%)
No	793 (86%)	703 (86%)	90 (90%)	666 (89%)	581 (90%)	85 (83%)
Unknown	35 (4%)	31 (4%)	4 (4%)	8 (1%)	6 (1%)	2 (2%)
Previa/Abruption						
Yes	5 (1%)	5 (1%)	0 (0%)	3 (0%)	1 (0%)	2 (2%)
No	327 (36%)	290 (35%)	37 (37%)	276 (37%)	233 (36%)	43 (42%)
Missing	589 (64%)	526 (64%)	63 (63%)	468 (63%)	410 (64%)	58 (56%)

a. RA refers to APOL1 risk allele, either G1 (S342G mutation) or G2 (a 6 bp deletion N388del;Y389del). The HR genotype consists of 2 RA. The LR genotype consists of 0 or 1 RA. Results reported as number of patients and percent of patients in parenthesis.

Table S3. Characteristics of Preeclamptic Births in EMC Case Only Study Population, by Maternal *APOL1* Genotype. [a]

APOL1 Genotype	All (n = 24)	*APOL1* LR (n = 22)	*APOL1* HR (n = 22)
Maternal Risk Factors for Preeclampsia			
Maternal Age – y (IQR)	32 (9.5)	32 (9.75)	33 (4)
Nulliparity - n (%)	5 (21%)	5 (23%)	0 (0%)
Obesity - n (%)	6 (25%)	6 (27%)	0 (0%)
History of Hypertension - n (%)	6 (25%)	6 (27%)	0 (0%)
History of Diabetes - n (%)	0 (0%)	0 (0%)	0 (0%)
History of Prior Preeclampsia - n (%)	3 (13%)	2 (9%)	1 (50%)
History of Spontaneous Abortion - n (%)	4 (17%)	4 (18%)	0 (0%)
Perinatal Outcomes			
Cesarean Delivery - n (%)	14 (58%)	12 (55%)	2 (100%)
Gestational Age - weeks (IQR)	36.4 (7.3)	36.8 (6.5)	32.3 (2.7)
Birth Weight - g (IQR)	2,333 (1,311)	2,333 (1,104)	2,058 (938)
Apgar Score, 1 min (IQR)	8 (4.3)	8 (4.0)	8.5 (0.5)
Apgar Score ± 5 min (IQR)	9 (1.0)	9 (1.0)	8.5 (0.5)

a. RA refers to *APOL1* risk allele, either G1 (S342G mutation) or G2 (a 6 bp deletion N388del;Y389del). The HR genotype consists of 2 RA. The LR genotype consists of 0 or 1 RA. Continuous variables are reported as median and interquartile range in parenthesis.

Table S4. Presence of Pathology Changes Consistent with Preeclampsia in EMC Case Only Study Population, by Fetal *APOL1* Genotype.[a]			
Fetal *APOL1* Genotype	**All** (n = 36)	***APOL1* LR** (n = 19)	***APOL1* HR** (n = 17)
Overall Decidual Vasculopathy			
Mild	6 (17%)	3 (16%)	3 (18%)
Moderate	15 (42%)	7 (37%)	8 (47%)
Severe	11 (31%)	8 (42%)	3 (18%)
Presence of Decidual Vasculopathy			
Fetal Membranes	25 (69%)	12 (63%)	13 (76%)
Basal plate	23 (64%)	12 (63%)	11 (65%)
Other Histopathological Findings			
Thrombosis	9 (25%)	6 (32%)	3 (18%)
Hypertrophic Changes	28 (78%)	14 (74%)	14 (82%)
Atherosis	17 (47%)	10 (53%)	7 (41%)
Fibrinoid Necrosis	13 (36%)	8 (42%)	5 (29%)
Retroplacental Hemorrhage/Hematoma	4 (11%)	3 (16%)	1 (6%)
Chronic Villitis	3 (8%)	1 (5%)	2 (12%)
Infarct	6 (17%)	4 (21%)	2 (12%)
Intervillious Thrombus	9 (25%)	3 (16%)	6 (35%)
Distal Villous Hypoplasia	22 (61%)	14 (74%)	8 (47%)
Intervillious fibrin	3 (8%)	1 (5%)	2 (12%)
Increase in Syncytial Knots / Rapid Maturation	22 61%)	14 (74%)	8 (47%)
Villous Edema/Dysmaturity	1 (3%)	0 (0%)	1 (6%)
a. RA refers to APOL1 risk allele, either G1 (S342G mutation) or G2 (a 6 bp deletion N388del;Y389del). The HR genotype consists of 2 RA. The LR genotype consists of 0 or 1 RA. Results reported as number of patients and percent of patients in parenthesis.			

Table S5. Characteristics of Severe Preeclampsia in EMC Case Only Study Population, by Fetal *APOL1* Risk Genotype.[a]

APOL Genotype	All (n = 121)	*APOL1* LR (n = 98)	*APOL1* HR (n = 24)	p-value
Presence of Severe Preeclampsia - n (%)	119 (98%)	95 (98%)	24 (100%)	1.00
Blood pressure ≥ 160/110 - n (%)	111 (92%)	87 (90%)	24 (100%)	0.21
Thrombocytopenia - n (%)	15 (12%)	11 (11%)	4 (17%)	0.49
Renal Insufficiency - n (%)	28 (23%)	22 (23%)	6 (25%)	0.79
Impaired Liver function - n (%)	29 (24%)	22 (23%)	7 (29%)	0.59
Pulmonary Edema - n (%)	5 (4%)	5 (5%)	0 (0%)	0.58
Cerebral or Visual Dysfunction - n (%)	51 (42%)	36 (37%)	15 (63%)	**0.04**[b]
HELLP Syndrome - n (%)	12 (10%)	8 (8%)	4 (17%)	0.25

a. RA refers to *APOL1* risk allele, either G1 (S342G mutation) or G2 (a 6 bp deletion N388del;Y389del). The HR genotype consists of 2 RA. The LR genotype consists of 0 or 1 RA. Those with the high-risk genotype were compared to those with the low-risk genotype with significance testing via a two-tailed Fisher's exact test.

b. p-value ≤ 0.05

Table S6. Characteristics of Severe Preeclampsia in EMC Case Only Study Population, by Maternal *APOL1* Risk Genotype.[a]

APOL Genotype	**All** (n = 24)	***APOL1* LR** (n = 22)	***APOL1* HR** (n = 2)
Presence of Severe Preeclampsia (n, %)	22 (92%)	20 (91%)	2 (100%)
Blood pressure ≥ 160/110 (n, %)	20 (83%)	18 (82%)	2 (100%)
Thrombocytopenia (n, %)	4 (17%)	3 (14%)	1 (50%)
Renal Insufficiency (n, %)	5 (21%)	4 (18%)	1 (50%)
Impaired Liver function (n, %)	5 (21%)	4 (18%)	1 (50%)
Pulmonary Edema (n, %)	0 (0%)	0 (0%)	0 (0%)
Cerebral or Visual Dysfunction (n, %)	5 (21%)	4 (18%)	1 (50%)
HELLP Syndrome (n, %)	3 (13%)	2 (9%)	1 (50%)

a. RA refers to APOL1 risk allele, either G1 (S342G mutation) or G2 (a 6 bp deletion N388del;Y389del). The HR genotype consists of 2 RA. The LR genotype consists of 0 or 1 RA. Reported as number of patients and percent of patients in parenthesis.

Table S7. APOL1 Genotype Distributions in both the EMC Case Only and UTHSC Case Control Populations.[a]

Gene	Variant	Genotype (n(%))			Total (n)	HWE p-value
		wt/wt	wt/m	m/m		
EMC Fetal Genotypes	G1	64 (53%)	50 (41%)	7 (5.8%)	121	p = 0.64
	G2	91 (75%)	21 (17%)	9 (7.4%)	121	**p < 0.0001**
EMC Maternal Genotypes	G1	16 (67%)	8 (33%)	0 (0%)	24	p = 1.00
	G2	19 (79%)	3 (13%)	2 (8.3%)	24	**p = 0.05**
UTHSC Fetal Genotypes	G1	50(63%)	24(30%)	6(8%)	80	p=0.21
	G2	50(68%)	19(26%)	5(7%)	74	p=0.13
UTHSC Maternal Genotypes	G1	57(61%)	35(38%)	1(1%)	93	p<0.11
	G2	71(76%)	20(22%)	2(2%)	93	P=0.64

a. *APOL1* G1 allele comprises two missense variants rs73885319 (G1g) and rs60910145 (G1m); however, the presence of only the G1g variant is sufficient to define the G1 risk allele. *APOL1* G2 allele consists of a 6 base-pair (bp) in-frame deletion, rs717185313. Deviation from Hardy Weinberg Equilibrium calculated using an exact test with selome p-value.

Table S8. Independent Effects of the Fetal *APOL1* G1 and G2 Risk Alleles on the Risk for Preeclampsia in the UTHSC Case Control Study Population

Risk Allele	Stratum	Number Case/Control n/n	1 vs 0 Risk Allele OR (CI)	1 vs 0 Risk Allele p-value	2 vs. 0 Risk Alleles OR (CI)	2 vs. 0 Risk Alleles p-value	2 vs. 1 Risk Alleles OR (CI)	2 vs. 1 Risk Alleles p-value
G1	No G2	583	0.74 (0.36, 1.46)	0.42	1.38 (0.39, 3.92)	0.57	1.87 (0.50, 5.84)	0.33
G2	No G1	464	1.42 (0.65, 2.96)	0.35	2.82 (0.64, 9.81)	0.09	1.99 (0.41, 7.74)	0.28
G1/G2	G1/G2	677	NA	NA	1.80 (0.57, 4.87)	0.25	NA	NA
G1 or G2	All	802	0.95 (0.53, 1.70)	0.89	1.79 (0.85, 3.65)	0.09*	1.89 (0.89, 3.86)	0.98

The *APOL1* risk alleles are as follows; G1 (S342G mutation) or G2 (a 6 bp deletion N388del;Y389del). Stratum refers to analysis that analyzed a subset of genotypes (ex. Subgroup of cases and controls that lacked the G1 allele). G1/G2 compound heterozygotes were compared to subjects lacking both G1 and G2. NA is short for not applicable

* Of note G1 or G2, under the 2 versus 0 allele model, does not reach statistical significance because of the reduced power as compared to the recessive model of inheritance seen in Table 1 (2 versus 0 OR 1 model).

Table S9. *APOL1* Genotype Frequencies in the EMC Study Healthy Controls.

Genotype	*Controls Bethesda*		*Controls Southeast*	
	n=176	*%*	*n=923*	*%*
+/+	*77*	*0.44*	*409*	*0.44*
G1/+	*41*	*0.23*	*250*	*0.27*
G1/G1	*9*	*0.05*	*41*	*0.04*
G1/G2	*8*	*0.05*	*50*	*0.05*
G2/+	*36*	*0.20*	*155*	*0.17*
G2/G2	*5*	*0.03*	*18*	*0.02*