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***APOL1* Renal Risk Variants are Associated with Chronic Kidney Disease in Children and Youth with Perinatal HIV infection**

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Conflicts of Interest

No conflicts of interest were declared by all the authors.

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All authors meet authorship criteria. Brad Karalius and Kunjal Patel had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Abstract

APOL1 renal risk alleles are associated with chronic kidney disease (CKD) in adults, with the strongest effect being for HIV-associated nephropathy. Their role in youth with perinatal HIV infection (PHIV) has not been studied. In a nested case-control study of 451 PHIV participants in the Pediatric HIV/AIDS Cohort Study, we found a 3.5-fold increase odds of CKD in those carrying high-risk *APOL1* genotypes using a recessive model (95% confidence interval [CI]: 1.2-10.0). We report an unadjusted incidence of 1.2 CKD cases/100 person-years (95% CI: 0.5, 2.5) in PHIV youth carrying *APOL1* high-risk genotypes, with important implications for sub-Saharan Africa.

Keywords

Perinatal; HIV; Chronic kidney disease; *APOL1*; African ancestry; Youth

Introduction

Genetic variants of *APOL1*, encoding apolipoprotein L1, are strongly associated with chronic kidney disease (CKD) in individuals with sub-Saharan African ancestry¹. Risk allele frequency is highest in West Africa, with lower prevalence elsewhere in sub-Saharan Africa². Risk alleles are absent from populations outside Africa, unless population admixture has occurred. African Americans have a ~35% prevalence of *APOL1* risk alleles, while 12-14% of individuals have high-risk genotypes comprising two risk alleles, inherited in a homozygous or compound heterozygous state^{3,4}.

Carriage of high-risk *APOL1* genotypes increases CKD risk in adults⁴⁻¹⁰. The strongest association is for HIV-associated nephropathy (HIVAN) with odds ratios (OR) of 29 in the USA⁴ and 89 in South Africa¹⁰. A spectrum of CKD, described in children born with HIV infection, includes HIVAN, nephrotic syndrome, and various forms of immune-complex glomerulonephritis¹¹⁻¹⁶.

The association between *APOL1* variants and CKD in these children has not been investigated. We evaluated this relationship in a large U.S. cohort of youth with perinatal HIV-1 infection (PHIV). As ancestry may confound association between *APOL1* risk variants and CKD, we determined continental ancestry with a genetic panel, and adjusted for African ancestry in our analysis. We also evaluated the association between self-reported race and CKD, and African ancestry and CKD.

Methods

The Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study is an ongoing prospective cohort study of youth with PHIV designed to evaluate the impact of HIV and antiretroviral therapy on long term outcomes¹⁷. Between 2007 and 2009, 451 PHIV participants aged 7 to 16 years with comprehensive medical history since birth were enrolled at 15 sites within the USA and Puerto Rico. Participating sites and the Harvard T.H. Chan School of Public Health obtained Institutional Review Board approvals, and consent/assent

was obtained from parents/legal guardians and participants. This study analyzed data as of January 1, 2014.

DNA was extracted from saliva and buccal cells from participants who consented for genetic testing. Continental ancestry across five super-populations (Africa, Eurasia, East Asia, Americas, and Oceania) was determined using a panel of ancestry informative markers¹⁸⁻²⁰. *APOL1* genotyping was performed for two renal risk alleles: G1 (coding variants rs73885319A>G [p.S342G] and rs60910145G>T [p.I384M]) and G2 (6 base-pair deletion, rs71785313), by Taqman assays (Applied Biosystems, Foster City, CA)⁴. Carriage of two *APOL1* risk alleles (G1/G1, G1/G2, or G2/G2) was defined as high-risk for renal disease; possession of zero or one risk allele (+/+, G1/+ or G2/+) was considered low-risk for renal disease.

We performed a nested case control study. Cases of CKD were defined as a clinical diagnosis established by chart documentation of nephropathy, nephrotic syndrome, chronic renal failure, and/or focal segmental glomerulosclerosis (FSGS), or by clinical tests, either of the following: 1) persistent proteinuria for >6 months established by 2 sequential urine protein/creatinine ratios (UPC) ≥ 0.2 g/g not followed by a UPC <0.2g/g, or alternatively two or more sequential urine dipstick protein 1+ not followed by a urine dipstick protein <1+, or 2) persistent low glomerular filtration rate, for >6 months established by 2 sequential estimated glomerular filtration rates (eGFR) <60 mL/min/1.73 m² not followed by an eGFR above this value. Clinical diagnoses were accepted even without laboratory abnormalities as effective combination antiretroviral therapy can result in subsequent normalization²¹. For children, the bedside Schwartz equation was used to calculate eGFR²². For those ≥ 18 years of age, the CKD-EPI 2009 eGFR was used²³. A control group consisted of AMP participants with no clinical history or chart documentation of kidney disease, all measured UPCs <0.2g/g, all protein dipstick tests <1+ and all eGFRs ≥ 80 mL/min/1.73 m².

Kruskal-Wallis and Fisher Exact tests were used to compare distributions of covariates by case-control status. Area under the curve (AUC) HIV viral load was calculated using the trapezoidal rule and mean case-control difference calculated (supplementary material 1)²⁴. Logistic regression models were used to determine associations between *APOL1* risk status, self-reported race, and African ancestry with CKD.

Results

Of 451 AMP participants, 419 had *APOL1* genotype data available. The combined frequency of G1 and G2 risk alleles was 27%. Self-reported blacks (302 participants) had an allele frequency of 35%, with 13% (40 participants) having two risk alleles, 43% having one risk allele, and 44% having none. This genotype distribution did not deviate from Hardy-Weinberg equilibrium expectations ($p=0.66$). No self-reported white (91 participants) or other race (two Asians, three Native Americans) had two risk alleles. However, 11% of white participants carried one risk allele. Race was not self-reported in 21 participants, none of whom had 2 risk alleles and 3 had one risk allele. As expected, there was a strong positive correlation between *APOL1* risk allele frequency and proportion of African ancestry

($r=0.93$, $p<0.001$). Risk allele frequency ranged from approximately 3% in participants with 0-10% African ancestry to 60% with 90-100% African ancestry.

Among 428 participants with ancestry data, median proportions of African ancestry correlated with self-reported race. Among non-Hispanics, blacks showed much higher proportions of African ancestry (76%, interquartile range [IQR] 69-84%) compared to whites (1%, IQR 1-3%). Similarly, among Hispanics, the median African ancestry proportion was higher in blacks (36%, IQR 21-57%, minimum 1%) than in whites (6%, IQR 2-24%, maximum 85% (supplementary material 2).

There were 27 cases of CKD, all with ancestry data and self-reported race/ethnicity and 207 subjects in the comparison group (196 had genetically-determined ancestry, 193 self-reported race, and 194 *APOL1* genotype data). Among CKD cases, 24/27 (89%) were black, of whom 7 (29%) had high-risk *APOL1* genotypes. Of 26 CKD cases with genotype data, 7 (27%) had high-risk genotypes. Among control participants, 140/193 (73%) were black, of whom 16 (11%) had high-risk genotypes. Of all control participants with genotype data, 8% had high-risk genotypes. Breakdown by diagnosis for the 27 CKD cases is shown in supplementary material 1.

CKD was identified at a median age of 14.3 years (interquartile range: 8-16.3 years). No statistically significant differences between cases and controls were noted in socio-demographic or clinical characteristics (Table 1) including mean AUC HIV viral load (mean difference: $3.55 \log_{10}$ copy-years/mL, 95% confidence interval [CI]: -3.01 to $10.11 \log_{10}$ copy-years/mL). Seven of 40 subjects with two *APOL1* risk alleles had CKD (17.5%). Over 580.2 person-years of follow up, we estimated a crude incidence rate of 1.2 cases per 100 person-years (95% CI: 0.5-2.5) for this high-risk group. The median age of these seven was 8.8 (IQR: 1.1-18.0) years whereas the median age of the 19 CKD cases with 0 or 1 risk allele was 14.3 (IQR: 10.5-16.3) years, $p=0.54$.

Subjects with high-risk genotypes had a 4.1-fold increased odds of CKD compared to those with low-risk genotypes (95% CI: 1.5-11.2) in unadjusted analysis (Table 2). When adjusted for African ancestry, this finding was slightly attenuated, but still significant (adjusted OR 3.5; 95% CI: 1.2-10.0). When analysis was limited to self-reported blacks, the increased risk for CKD associated with high-risk genotype persisted (adjusted OR 3.3; 95% CI: 1.1-9.6).

There was a 3-fold increased odds of CKD in self-reported blacks compared to white/other race (95% CI: 0.9-10.5). We found an 8.8-fold (95% CI: 1.9-41.4) and a 2.8-fold (95% CI: 0.5-14.9) increased odds of CKD among participants with 71-80% and >80% genetically-determined African ancestry, respectively, compared to those with 25% African ancestry (supplementary material 2).

Discussion

We show for the first time that high-risk *APOL1* genotype is associated with increased susceptibility to CKD in youth with PHIV, with a 3.5-fold increased odds ratio compared to low-risk genotypes. We found that 27% of CKD cases in the AMP cohort carried two risk alleles.

While most individuals carrying a high-risk genotype will not develop kidney disease, a recent report estimates the lifetime risk of kidney disease in these individuals to be at least 15%²⁵. In our cohort, 18% of children with PHIV who carried the high-risk genotype developed CKD, which supports the observation in adult studies that HIV infection is a potent environmental factor that interacts with *APOL1* genetic risk. With a median age of 15.3 years for children included in the analysis, there is potential for even higher rates of CKD over their lifetimes. Since our participants were HIV-infected at birth, we were able to estimate the crude incidence of CKD, and report a rate of 1.2 cases per 100 person-years in PHIV children with the *APOL1* high-risk genotype. Unfortunately, lack of data on the incidence of CKD in a similar population of PHIV children with this genotype from other countries, including sub-Saharan Africa, precludes us from making any direct comparisons.

There was no difference between our comparison group and CKD cases in proportions with an undetectable viral load and CD4 counts. Persistent viremia over a sustained period of time, and not viral load at the time of diagnosis, may be more relevant in causing HIV-related renal injury^{24,26,27}. We therefore investigated cumulative HIV burden, and although a mean viral load difference of 3.55 log₁₀ copy-years/ml between cases and controls was observed, it was not statistically significant. While it is possible the small number of cases of CKD may have resulted in a type II error, other as yet unidentified environmental triggers may also play a role in the development of CKD in PHIV children with two risk alleles.

The observed combined allele frequency for *APOL1* G1 and G2 was 35% in participants who self-identified as black, and 13% had two risk alleles, similar to that described in adult African Americans⁴, and strongly supporting sub-Saharan origins of youth in the AMP cohort²⁸. Determining African ancestry further allowed us to examine the relationship between Hispanic ethnicity, race and proportion of African ancestry. Participants who self-identified as black had a wide range in their proportion of African ancestry, as did those identifying as white. Compared to whites and blacks who do not self-report Hispanic ethnicity, self-reported Hispanic ethnicity was associated with higher mean African ancestry proportion in white-Hispanics and lower African ancestry proportion in black-Hispanics, likely the consequence of migration into the United States from the Caribbean region, where these populations underwent admixture²⁹. African admixture also accounts for the presence of a single risk allele in 11% of our white participants. Since children in our cohort had varying proportions of African ancestry, we adjusted for genetic ancestry, rather than self-reported race, when evaluating the association between CKD and the *APOL1* risk alleles. The marginal difference in effect size after adjustment suggests that the increased risk for CKD was associated specifically with high-risk *APOL1* haplotypes, rather than African ancestry per se.

Major strengths of this study include use of ancestry informative markers, allowing us to estimate and adjust for proportion of African ancestry, and availability of *APOL1* genotypes on a large number of children with perinatally-acquired HIV infection drawn from 15 sites across the USA and Puerto Rico. There are limitations worth noting. The strongest association of *APOL1* risk alleles was with HIVAN and FSGS, which can only be definitively diagnosed by biopsy. Some cases of CKD identified may represent other types of kidney disease such as HIV immune-complex glomerulonephritis¹⁶ or antiretroviral drug-

associated renal diseases³⁰ that may not be associated or less strongly associated with *APOL1* risk alleles. HIV viral load measurements were not performed at regular intervals over participants' lifetime, affecting an accurate assessment of the impact of viral burden on renal disease expression.

Our findings may have important implications for youth with PHIV living in sub-Saharan Africa, where HIV prevalence is the highest in the world. Of 3.2 million children living with HIV globally in 2013, 91% are in sub-Saharan Africa³¹. Even with the recent 43% reduction in the number of new pediatric HIV infections in this region, the prevalence of PHIV among children will increase as antiretroviral therapy allows them to survive into adolescence and beyond³². Therefore the burden of HIV-related kidney disease among youth in those regions of sub-Saharan Africa, where *APOL1* high-risk genotypes are prevalent, is likely to be substantial.

In summary, *APOL1* risk alleles are prevalent in black children and youth with PHIV living in the USA. This study provides robust evidence that carriage of high-risk *APOL1* genotypes increases risk for CKD in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and clinical characteristics of CKD cases and the comparison group among children and youth with perinatal HIV infection.

Characteristics	Total (N=234)	CKD (N=27)	Comparison (N=207)	P-Value ^I
Age at CKD diagnosis/last visit (years)				0.005
Median	15.3	14.3	15.6	
Q1, Q3	12.5, 17.6	8.0, 16.3	13.0, 17.8	
Min, Max	0.4, 21.6	0.4, 19.7	7.1, 21.6	
Sex, N (%)				0.68
M	96 (41)	10 (37)	86 (42)	
F	138 (59)	17 (63)	121 (58)	
Race, N (%)				0.19
White	54 (23)	3 (11)	51 (25)	
Black	164 (70)	24 (89)	140 (67)	
Other	2 (1)	0 (0)	2 (1)	
Missing	14 (6)	0 (0)	14 (7)	
Ethnicity				0.17
Not Hispanic	169 (72)	23 (85)	146 (71)	
Hispanic	65 (28)	4 (15)	61 (29)	
Birth weight (grams), N (%)				0.93
<1500	9 (4)	1 (4)	8 (4)	
1500-2500	51 (22)	6 (22)	45 (22)	
>2500	132 (56)	18 (67)	114 (55)	
Missing	42 (18)	2 (7)	40 (19)	
Gestational age (weeks), N (%)				0.51
<32	13 (6)	0 (0)	13 (6)	
32-36	35 (15)	5 (19)	30 (15)	
37	105 (45)	13 (48)	92 (44)	
Missing	81 (35)	9 (33)	72 (35)	
Caregiver education level ² , N (%)				0.88
<High School	44 (19)	5 (19)	39 (19)	
High School or GED	60 (26)	7 (26)	53 (26)	
> High School	78 (33)	11 (41)	67 (32)	
Missing	52 (22)	4 (15)	48 (23)	
Household income ² , N (%)				0.45
<\$10,000	41 (18)	8 (30)	33 (16)	
\$10,001-\$20,000	37 (16)	5 (18)	32 (15)	
\$20,001-\$40,000	49 (21)	4 (15)	45 (22)	
>\$40,001	52 (22)	6 (22)	46 (22)	
Missing	55 (23)	4 (15)	51 (25)	
Passive cigarette smoke exposure ^{2,3} , N (%)				0.48

Characteristics	Total (N=234)	CKD (N=27)	Comparison (N=207)	P-Value ^I
Yes	55 (23)	8 (29)	47 (23)	
No	165 (71)	18 (67)	147 (71)	
Missing	14 (6)	1 (4)	13 (6)	
Active cigarette smoking ⁴ , N (%)				0.30
Yes	21 (9)	4 (15)	17 (8)	
No	168 (72)	19 (70)	149 (72)	
Missing	45 (19)	4 (15)	41 (20)	
Any cigarette smoke exposure, N (%)				0.25
Yes	69 (29)	11 (41)	58 (28)	
No	123 (53)	12 (44)	111 (54)	
Missing	42 (18)	4 (15)	38 (18)	
Ever marijuana use, N (%)				0.82
Yes	62 (27)	8 (30)	54 (26)	
No	127 (54)	15 (55)	112 (54)	
Missing	45 (19)	4 (15)	41 (20)	
Frequent marijuana use ⁵ , N (%)				0.30
Yes	21 (9)	4 (15)	17 (8)	
No	168 (72)	19 (70)	149 (72)	
Missing	45 (19)	4 (15)	41 (20)	
CD4 count at CKD diagnosis/last visit ⁶				0.87
Median	638	647	635	
Q1, Q3	464, 852	468, 786	464, 852	
Min, Max	3, 2822	3, 1846	20, 2822	
Missing, N (%)	7 (3)	1 (4)	6 (3)	
CD4% at CKD diagnosis/last visit ⁶				0.35
Median	34	33	34	
Q1, Q3	25, 38	22, 36	26, 38	
Min, Max	0.4, 58	1, 51	0.4, 58	
Missing, N (%)	8 (3)	1 (4)	7 (3)	
Viral load <400 copies/mL at CKD diagnosis/last visit ⁶				0.36
Yes	138 (62)	12 (52)	126 (64)	
No	83 (38)	11 (48)	72 (36)	
Missing	13 (6)	4 (15)	9 (4)	
Tenofovir disoproxil fumarate				
Ever use, N (%)	107 (46)	11 (41)	96 (46)	
Cumulative duration up to CKD diagnosis/last visit (years)				0.89
0	127 (54)	16 (59)	111 (54)	
>0-3	61 (26)	6 (22)	55 (26)	
>3	46 (20)	5 (19)	41 (20)	

¹P values were determined by Kruskal-Wallis test for continuous variables and Fisher's Exact test for categorical variables. Missing categories excluded in tests.

²Most recent value for these variables were presented relative to date of CKD diagnosis/last visit (i.e. could be after date of CKD diagnoses/last visit).

³Passive smoke exposure defined as caregiver smoking an average of at least once a week. The highest reported level of caregiver smoking as of January 1, 2014 was used to define passive smoke exposure.

⁴Active smoking defined as participant smoking at least once a week. The highest level of participant smoking reported prior to or at date of CKD diagnosis/last visit was use to define active smoking.

⁵Frequent marijuana use defined as use at least once a week in the past 3 months.

⁶CD4 count and viral load determined as the most recent value within 6 months prior to the date of CKD diagnosis or the last visit.

Table 2Association of number of *APOL1* risk alleles, race, and African ancestry with CKD.

Comparison	CKD N=27 ¹	Control N=207 ²	Unadjusted OR (95% CI)	P-value	Adjusted OR for <i>APOLI</i> risk alleles (95% CI)	P-value
	Percent high-risk genotype					
<i>APOLI</i> :						
2 risk alleles vs 0/1 allele All races, n (%)	7 (27%)	16 (8%)	4.1 (1.5, 11.2)	0.01	3.5 (1.2, 10.0)	0.02
<i>APOLI</i> :						
2 risk alleles vs 0/1 allele Self- reported blacks, n (%)	7 (30%)	16 (12%)	3.2 (1.2, 9.0)	0.03	3.3 (1.1, 9.6)	0.03
Percent black						
Self-reported Black vs. White/ Other race, n (%)	24 (89%)	140 (73%)	3.0 (0.9, 10.5)	0.08	--	--
Proportion of ancestry that is African:				0.02		
26%-70% vs. 25%			3.9 (0.8, 19.0)		--	--
71%-80% vs. 25%			8.8 (1.9, 41.4)		--	--
>80% vs. 25%			2.8 (0.5, 14.9)		--	--

The unadjusted ORs were for *APOL1* risk allele status, race and ancestry, individually; the ORs for *APOL1* risk allele status were adjusted for African ancestry.

¹Of 27 CKD cases, 26 with *APOL1* genotype data, all with self-reported race (1/24 black participants with missing genotype)

²Of 207 controls, 194 with *APOL1* genotype data, 193 with self-reported race (6/140 black participants with missing genotype)