Pediatr Nephrol (2015) 30:983–989
DOI 10.1007/s00467-014-3031-0

ORIGINAL ARTICLE

Clinical phenotype of *APOL1* nephropathy in young relatives of patients with end-stage renal disease

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Received: 22 August 2014 / Revised: 26 November 2014 / Accepted: 2 December 2014 / Published online: 23 December 2014

Abstract
Background Two coding variants—G1 and G2—in the apolipoprotein L-1 (*APOL1*) gene are associated with increased incidence of end-stage renal disease (ESRD) in the adult African American population. These variants associate with hypertension-attributed renal disease, focal segmental glomerulosclerosis (FSGS), and HIV-associated nephropathy. We hypothesized that as a genetic disease, *APOL1* nephropathy has a pediatric phenotype.
Methods We investigated the incidence of *APOL1* variants in young African Americans with hypertension or FSGS and a family history of ESRD by conducting a case–control study of 93 pediatric and young adult African Americans with hypertension or FSGS to determine the association with *APOL1* risk variants, G1, and G2 using custom-made TaqMan-based allelic discrimination assays.
Results Forty of the 61 cases (66 %) with a family history of kidney disease had two *APOL1* risk variants, significantly higher than the prevalence in controls and the general African American population ($p<0.001$); 24 of 29 patients with hypertension-attributed kidney disease had two *APOL1* risk variants, while none of nine hypertensive patients without kidney disease had more than one risk allele.
Conclusions Although it was a small study cohort, our findings strongly suggest for the first time that two *APOL1* risk alleles in young hypertensive African Americans with a family history of ESRD are strongly associated with kidney disease.

Keywords Hypertension · Focal segmental glomerulosclerosis · End-stage renal disease · Pediatrics · APOL1 · African Americans

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Introduction

African Americans are four to five times more likely to develop end-stage renal disease (ESRD) compared with European Americans and have a more rapid progression to ESRD than the established age-associated progression in the general population [1, 2]. This increased risk is independent of socioeconomic status. A familial clustering of ESRD in the African American population is well established and can be explained by the recent discovery of variants in the apolipoprotein L-1 (*APOL1*) gene on chromosome 22. The two *APOL1* risk variants consist of a missense variant labeled G1 and a six-base-pair deletion labeled G2. G1 (rs73885319) and G2 (rs71785313) have been extensively studied in the African American population. The presence of 2 risk alleles in any combination (G1/G1, G2/G2, G1/G2) confer an increased risk of nondiabetic nephropathy with faster disease progression and earlier renal replacement therapy (RRT) [3].

Polymorphisms identified in the *APOL1* gene have also been associated with an increased predisposition to focal segmental glomerulosclerosis (FSGS), HIV-associated nephropathy (HIVAN), lupus nephritis, and hypertension-attributed kidney disease in the African American population [4–6]. These variants do not appear to impart the same risk on

immunoglobulin A nephropathy (IgAN) or diabetic nephropathy [7, 8]. African Americans with sickle cell disease who had the *MYH9* or *APOL1* risk allele have an increased risk for renal dysfunction compared with those without those risk alleles, also supporting the role of a genetic variation at a locus close to the *MYH9* gene in renal dysfunction [9, 10].

Variations in the *APOL1* gene are common in the African population and absent in European Americans. The allele frequency of the G1 and G2 variants in the African Yoruba population is ~ 38 % and in European Americans is 4–8 % [11]. The frequency of these variants varies in the African population, with G1 being more common in west Africa and rare in east Africa, while the G2 variant is more uniformly distributed in Africa and is not as prevalent as G1 [12].

These coding variants confered a selective advantage to Africans with one or two copies of the risk variant in regions where sleeping sickness was endemic [12]. Research has shown that *APOL1* risk allele homozygosity and compound heterozygosity (harboring two risk variants) are protective against the *Trypanosoma brucei* parasite, similar to protection from malaria offered by the sickle cell trait [12].

Case–control studies have shown that patients who harbor two *APOL1* risk alleles are at a higher risk for developing ESRD than patients who carry one or zero risk alleles [12, 13]. In a recent study of 407 African Americans with nondiabetic ESRD enrolled in the Accelerated Mortality on Renal Replacement (ArMORR) study, study participants who harbored two *APOL1* risk alleles began dialysis up to 14 years earlier than participants with no *APOL1* risk allele [14]. This trend has been demonstrated in other studies [13, 14].

Further analysis of the *APOL1* genotype in individuals with FSGS and HIVAN revealed a significantly increased risk for disease in patients who carry two risk alleles. The estimated lifetime risk for FSGS was 4 % in patients who had two *APOL1* risk alleles, conferring a 17-fold increased risk of FSGS [4]. These patients developed FSGS earlier and were shown to have faster decline in renal function compared with patients with one or zero *APOL1* risk alleles. Patients with HIV with two *APOL1* risk alleles have a 50 % chance of developing HIVAN and a 29-fold increased risk for HIVAN [4].

The association between the two *APOL1* risk variants and African Americans with nondiabetic ESRD secondary to FSG, hypertension, or HIVAN has been made in adult populations [4, 8, 12, 15, 16]. The presentation of APOL1 nephropathy in the pediatric and young African American population remains unclear. The discovery of the *APOL1* risk variants has shed light on the etiology of ESRD in the African American population and defining a pediatric phenotype might lead to earlier identification of at-risk children and young adults and enable intervention at an earlier point than is currently practiced. We hypothesized that if APOL1 nephropathy is a genetic disease, a pediatric phenotype is likely to exist, so we set out to analyze the frequency of the *APOL1* variants G1 and G2 in a pediatric and young adult African American cohort presenting with clinically diagnosed hypertension and biopsy-proven FSGS who had a positive family history of ESRD in a first- or second-degree relative.

Methods

The institutional review board of the Washington University in St Louis School of Medicine approved this study, and informed consent was obtained from all participants. Recruitment and specimen processing were done in the Washington University Kidney Translational Research Core. The study comprised 117 individuals residing a single geographic region in the United States who enrolled between August 2011 and June 2013 (Fig. 1). Ninety-three participants presented with hypertension or FSGS, of whom 61 had a family history of ESRD in a first- or second-degree relative and 32 who had no family history of ESRD. Controls consisted of 24 healthy adults with no family history of ESRD and thus ensured that they did not have ApoL1 nephropathy during childhood. Renal-biopsy-proven minimal-change-associated nephrotic syndrome was excluded from the analysis. The diagnoses of hypertension and HIVAN were made by a large group of physicians using generally accepted clinical practice and not an individual protocol. None of the hypertension-attributed kidney disease patients had renal biopsies.

Clinical data collected were demographics, physician-reported diagnosis or cause of ESRD, family history of ESRD, biopsy reports where applicable, and age at diagnosis, enrollment, and dialysis initiation or transplant. Peripheral venous blood was collected from each participant for genomic DNA extraction using the QIAamp DNA mini kit (QIAGEN Science, MD, USA). DNA quality was assessed for all samples using the ratio of absorbance at 260 and 280 nm with a Nanodrop spectrophotometer. A ratio >1.7 was considered adequate.

The genotyping of *APOL1* variants (rs73885319 and rs71785313) was performed on an Applied Biosystems 7900HT Fast Real-Time Polymerase Chain Reaction (PCR) system (7900HT Fast System) using custom TaqMan single nucleotide polymorphism (SNP) genotyping assay for each marker with PCR primers and TaqMan FAM and VIC dye-labeled probes, which were designed according to the manufacturer's recommendations. The genotypes were identified using the allelic discrimination plots generated by the Sequence Detection System (SDS) software version 2.3 (Applied Biosystems, Foster City, CA, USA). Allelic discrimination plots for G1 and G2 are included in the supplementary materials.

Quality control measures compared results from TaqMan analysis with targeted exome sequencing results in 15 % of

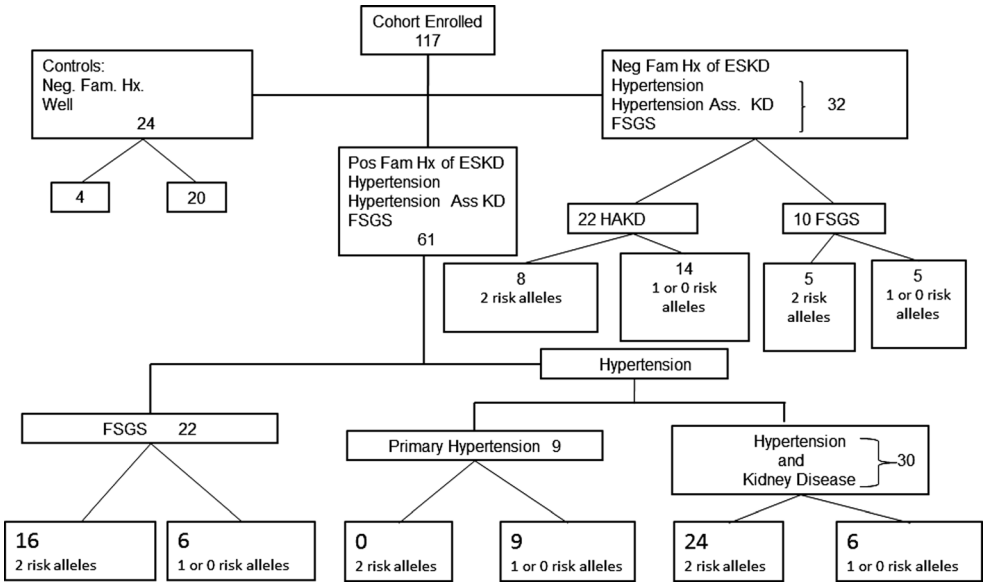

Fig. 1 Study group breakdown of 117 individuals enrolled and the frequency of apolipoprotein L-1 (*APOL1*) risk alleles. *ESKD* end-stage kidney disease, *FSGS* focal segmental glomerulosclerosis

participants including duplicate samples within and between plates for 15 % to confirm assay accuracy and to control for genotyping errors. All genotypes obtained were confirmed.

All statistical analyses were performed with SAS 9.2 statistical software (SAS Institute, Cary, NC, USA). Allele frequency of patients and healthy controls was compared using Fisher's exact test, with statistical significance set at $p<0.05$ for all tests.

Results

Pediatric and young African American patients presenting with either hypertension or FSGS, all with a family history of ESRD, were identified as cases (Fig. 1). Twenty-four healthy African American participants without a family history of ESRD were used as controls (Table 1). They were significantly older than cases in order to eliminate the possibility of younger controls developing significant kidney disease later in life. In addition, we also included 32 control individuals with hypertension or FSGS without a family history of ESRD. Male and female cases and controls were equally represented. Mean [standard deviation (SD)] ages for FSGS and hypertensive cases were 24.3 (7.4) and 23.6 (6.9) years, respectively.

Table 1 Characteristics of cases with a family history of end-stage renal disease (ESRD) and controls

	Cases (61)	Controls (24)
Mean age (years) ± SD	23.1±7.0	45.5±14.9
Sex (% female)	54	50
Hypertension/FSGS	39/22	0
Onset age (*n*)		
<18 years	17	1
18–35 years	44	4
>35 years	0	19
ESRD at enrollment	40	0

SD standard deviation, *FSGS* focal segmental glomerulosclerosis.

As shown in Fig. 1, among 61 cases with a positive family history of ESRD, there were 39 cases of hypertension and 22 cases of FSGS. Forty (66 %) of the 61 cases had two *APOL1* risk alleles (G1/G1, G1/G2, or G2/G2), a significantly higher prevalence than in controls and the general African American population ($p<0.001$). Hypertension with a positive family history of ESRD was significantly associated with the presence of two *APOL1* risk alleles ($p<0.001$) (Table 2). FSGS with a positive family history of ESRD was also strongly associated with the presence of two *APOL1* risk alleles ($p<0.001$) (Table 2). The frequency of two *APOL1* risk alleles in the general African American population is reported to be 10–12 %. The prevalence of two *APOL1* risk alleles in our controls (4/24) was not significantly different from that in the general African American population.

Among the 39 cases presenting with hypertension and a positive family history of ESRD, there were nine cases of hypertension alone and 30 cases of hypertension-attributed kidney disease (Fig. 1). Of those 30, 24 (80 %) had two risk alleles (G1/G1 or G1/G2 or G2/G2), while none of the hypertensive patients who presented without kidney disease [normal glomerular filtration rate (GFR) and no proteinuria] had more than risk alleles. Compared with participants with zero or one risk allele, the presence of two risk alleles was

Table 2 Prevalence of a two apolipoproteinn L-1 (*APOL1*) risk alleles in cases with hypertension or focal segmental glomerulosclerosis (FSGS) and controls

	Cases	Controls	Odds ratio (95 % Cl)	*P* value
Hypertension	39	24	8 (2.29–28)	<0.001
Two risk alleles	24 (61.5 %)	4 (16.7 %)		
FSGS	22	24	13.3 (3.2–55.5)	<0.001
Two risk alleles	16 (72.7 %)	4 (16.7 %)		

significantly associated to the development of ESRD among the hypertensive cohort ($p<0.001$) (Table 3). During the enrollment period, we found most cases of hypertension-attributed kidney disease receiving dialysis for ESRD in Washington University affiliated clinics, while our hypertension-alone group consisted of patients presenting with primary hypertension in our pediatric nephrology clinics. All cases of hypertension-attributed kidney disease had initially presented with kidney disease and hypertension.

In the hypertensive cohort, the presence of two risk alleles was significantly associated with the development of ESRD compared with participants with no or one risk allele ($p<0.001$). No hypertensive participant without kidney disease had two risk alleles. Among hypertensive patients who had reached ESRD, those with two risk alleles developed ESRD 6 years later than those no or with one only risk allele. There was no significant difference for age at ESRD in the FSGS cohort (Table 4).

Among the 22 cases presenting with FSGS, there were 12 with and ten without ESRD (Table 3). Of the 12 cases with ESRD, eight had two risk alleles, and of the ten without, eight had two risk alleles ($p<0.646$). However, compared with controls, FSGS was strongly associated with two risk alleles (Table 3).

There were 32 African American participants with clinically diagnosed hypertension-attributed kidney disease ($n=22$) or biopsy proven FSGS ($n=10$) without a family history of ESRD. Their ages were similar to individuals with a positive family history, and 69 % of them had ESRD. Eight of 22 individuals (36 %) with hypertension-associated kidney disease had two risk alleles, significantly greater than the prevalence in controls, suggesting that even without a family history of ESRD two *APOL1* risk alleles are associated with ESRD.

Discussion

Our findings demonstrate that ApoL1 nephropathy presents in the young not as a silent disease with clinical consequences appearing later in life, nor as primary hypertension. Rather, its presentation is as hypertension-attributed kidney disease or as FSGS. This phenotype is similar to that reported in adult populations [3]. We did not include systemic lupus erythematosus or sickle cell anemia in our cohort, but these diseases also associate with *APOL1* variants when they cause kidney disease in African Americans.

A familial clustering of ESRD has been well established in the African American population, with an increased incidence in family members of patients with kidney disease [17–21]. A genetic role explains these findings and is supported by the recent identification of two variants—G1 and G2—on the last exon of the *APOL1* gene on chromosome 22, which was observed among individuals of recent African ancestry and that associate with increased risk for kidney disease [4, 12, 14]. Homozygosity for the risk alleles (G1/G1, G1/G2, G2/G2) is strongly associated with increased disease risk [13].

The *APOL1* variants have been associated with mild kidney disease, a phenotype that we specifically sought in our cohort. Freedman et al. assessed the risk of mild kidney disease in the cohort of the Natural History of APOL1 Nephropathy [15]. This cohort comprised 826 relatives of patients with ESRD. Seven hundred and eighty-six participants were genotyped, and multivariate analysis revealed associations between the *APOL1* risk variants, proteinuria, chronic kidney disease (CKD), and GFR < 60 ml/min/1.73 m^2 [15]. A trend was found associating quantitative albuminuria and *APOL1* variants [15], but we were unable to find and enroll individuals in our cohort matching the microalbuminuric or

Table 3 Prevalence of two apolipoprotein L-1 (*APOL1*) risk alleles in patients with end-stage renal disease (ESRD) versus no ESRD among hypertensive and focal segmental glomerular sclerosis (FSGS) cases

Comparative data						
Hypertension	ESRD ($n=30$)	No ESRD ($n=9$)	*P* value	Control ($n=24$)	OR (95 % CI)	*P* value
Two vs. one or no risk allele	24 (80 %)	0	<0.001	4 (16.7)	20.0 (4.9–80.9)	< 0.001
FSGS	ESRD ($n=12$)	No ESRD ($n=10$)	*P* value	Control ($n=24$)	OR (95 % CI)	*P* value
Two vs. one or no risk allele	8 (67 %)	8 (80 %)	0.646	4 (16.7)	10.0 (2.0–50.0)	0.007

OR odds ratio, *CI* confidence interval

Table 4 Age at end-stage renal disease (ESRD) between different apolipoprotein L-1 (*APOL1*) genotypes among participants with ESRD

	Participants with ESRD (*n* years ± SD)	Hypertensive participants with ESRD (*n* years ± SD)	FSGS with ESRD (*n* years ± SD)
G1/G1 + G1/G2 + G2/G2	25.5±6.4	26.3±5.8	23.1±7.9
G1/WT + G2/WT + WT/WT	21.4±5.6	19.7±6.2	24.0±3.7
P value G1/G1 + G1/G2 + G2/G2 vs G1/WT + G2/WT + WT/WT	0.076	0.020	0.841

SD standard deviation, *WT* wild type

nonproteinuric CKD participants in the cohort of the Natural History of APOL1 Nephropathy. Thus, our analysis was limited to hypertension with or without kidney disease and proteinuric kidney disease and biopsy-proven FSGS in a young cohort of African American patients from a defined geographic area.

The high prevalence of two *APOL1* risk alleles in our cases compared with controls allowed us to do subset analysis despite the limitations of our small cohort. Hypertension-attributed kidney disease with a positive family history of kidney disease was associated with an 80 % prevalence of two risk alleles, while hypertension without kidney disease was not associated with two risk alleles. Furthermore, in pediatric cases with hypertension and no family history of kidney disease, the prevalence of two *APOL1* risk alleles was 9 % (data not shown), which is not different from the general population. This indicates that *APOL1* risk alleles in pediatric individuals segregate with kidney disease and not just hypertension alone.

Ours is the first study to evaluate the association of the *APOL1* risk variants in a pediatric and young adult population. Findings suggest that *APOL1* nephropathy presents as a kidney disease with hypertension and not isolated hypertension.

We demonstrated a 65 % prevalence of two *APOL1* variants among our 61 cases with a positive family history, hypertension-attributed kidney disease, or biopsy proven FSGS. The significant association between *APOL1* risk variants and hypertension-attributed ESRD in young African American patients compared with controls is consistent with other studies [16]. The presence of these risk variants predicted hypertensive patients who were likely to develop ESRD. The finding of a strong association with ESRD among patients with hypertension-attributed nephropathy and two *APOL1* risk alleles lends itself to the definition of the clinical phenotype of *APOL1* nephropathy and aids in the identification of hypertensive patients who have an increased risk for progressive disease. African Americans who are homozygous for the *APOL1* variants have an increased lifetime risk for FSGS [4]. The presence of two risk alleles was significantly associated with the FSGS group compared with controls in our cohort.

Hypertensive nephrosclerosis (now generally referred to as hypertension-attributed kidney disease in lieu of the discovery of *ApoL1*-associated risk) in African Americans appears to be in the spectrum of *APOL1* nephropathy, along with FSGS and HIVAN, which all present histologically with some extent of glomerulosclerosis [16]. The presence of *APOL1* risk alleles in the African American pediatric population might be indicative of silent kidney disease that may later present as kidney disease or failure, as demonstrated by Freedman et al. [15]. However, we were unable to confirm this possibility in our cohort.

Foster et al. demonstrated that two *APOL1* risk alleles were significantly associated with an increased risk of CKD [13]. In our cohort, no hypertensive participant without ESRD possessed two risk alleles. Also, the high frequency of risk alleles in the hypertensive cohort, and the remarkable finding that the majority of hypertensive participants with two risk alleles developed ESRD, demonstrates that hypertension in African American patients should be viewed seriously. A positive family history of ESRD in a first- or second-degree relative of a hypertensive African American should prompt consideration of *APOL1* nephropathy.

We have not had the opportunity to perform analysis of the recently described G3 haplotype of *APOL1* [22], and future studies should add such analysis to our data set. The G3 haplotype has yet to be associated with CKD, so whether it will add to our findings of *APOL1* nephropathy phenotype in young African American individuals is unknown.

Our discovery will add to current knowledge of *APOL1* nephropathy and will help with earlier identification of at-risk patients. While it is premature to advocate for universal screening of African American children, screening might be an option in the future when interventions are developed to effectively treat patients and prevent progression to ESRD. This might lead to the development of targets for therapy given the significant health and economic burden of *APOL1* nephropathy in the African American population. A longitudinal study to evaluate disease progression is paramount and would go a long way in providing insight and addressing some of the unanswered questions pertaining to *APOL1* nephropathy in the young.

Besides the inherent weakness produced by the small size of the reported cohort, the decision to focus on components of our practice in which we considered risk to be feasible also

introduced a selection bias. However, the finding of no more than the prevalence of *ApoL1* in the general African American population in our patients with primary hypertension limits the importance of this selection bias.

In conclusion, we demonstrated for the first time that kidney disease, not hypertension, is the phenotype of *APOL1* nephropathy in a young adult African American population. We found that two *APOL1* risk alleles in young African Americans with a family history of ESRD are significantly associated with hypertension-attributed kidney disease and FSGS but not primary hypertension in a young African American cohort that included pediatric individuals. Although a small cohort, our findings strongly suggest that *APOL1* nephropathy presents with kidney diseases known to associate with *ApoL1* risk alleles, and not primary hypertension, in patients with a positive family history of ESRD.

Acknowledgments We acknowledge the assistance of Mary Hoffmann, clinical research coordinator, Kidney Translational Research Core (KTRC), Washington University School of Medicine, Masato Hoshi: Senior Scientist, Jain Lab, Washington University School of Medicine, and Jie Zheng Division of Biostatistics, Washington University School of Medicine.

Sources of support This work was supported by a Genzyme (Sanofi) fellowship grant (EA), the National Institutes of Health (NIH) George M. O'Brien Center for Kidney Disease Research (P30-DK079333), and CTSA-ICTS Tissue Procurement and Molecular Phenotyping and Center for Biomedical Informatics Cores (NCRR UL1 RR024992) to Washington University, Children Discovery Institute grants MDII2009177 (S.J.).

Disclosures None.

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