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► To cite this version:

Aude Servais, Olivier Gribouval, François Gaillard, Corinne Antignac. APOL1 risk genotype in Europe: Data in patients with focal segmental glomerulosclerosis and after renal transplantation. *Néphrologie & Thérapeutique*, 2019, 15, pp.S85 - S89. 10.1016/j.nephro.2019.02.005 . hal-03484976

HAL Id: hal-03484976

<https://hal.science/hal-03484976>

Submitted on 20 Dec 2021

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***APOL1* risk genotype in Europe: data in patients with focal segmental glomerulosclerosis and after renal transplantation**

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No disclosure of interests to declare

Abstract

Apolipoprotein L1 (*APOL1*) risk variants are strongly associated with sporadic focal segmental glomerulosclerosis in populations with African ancestry. We determined the frequency of G1/G2 variants in patients with steroid-resistant nephrotic syndrome/focal segmental glomerulosclerosis with African or French West Indies origin in France and its relationships with other steroid-resistant nephrotic syndrome genes. In a cohort of 152 patients (139 families), the *APOL1* risk variants were genotyped: the two risk allele (high risk) genotype was found in 43.1% of subjects compared to 18.9% in a control population ($p < 0.0001$). Compared to patients in the low risk group, patients in the high risk group were more likely to originate from French West Indies than from Africa. *APOL1* high risk genotype was more frequent in young adult patients, but it was also found in children and it was associated with a bad renal prognosis. *APOL1* high risk genotype was usually not associated with other causative mutation in known monogenic steroid-resistant nephrotic syndrome genes and families in which multiple individuals have focal segmental glomerulosclerosis may have *APOL1*-associated disease. After renal transplantation, recipients of deceased-donor kidney transplantation from individuals with recent African ancestry possessing two *APOL1* high-risk variants have slightly shorter allograft survival. Effects of *APOL1* are independent of other traditional risk factors. Recently it was shown that black living kidney donors homozygous for *APOL1* high-risk alleles have significantly lower glomerular filtration rate and increased risk of end-stage renal disease after donation. However, *APOL1* genotype may not summarize by itself the totality of this risk. We showed that living kidney donors of African ancestry in France with low-risk *APOL1* genotype have lower post-donation eGFR increase and lower baseline kidney volume compared to Caucasian donors.

Keywords

APOL1, Focal segmental glomerulosclerosis, Steroid-resistant nephrotic syndrome, Kidney transplantation, Living donor

1. Introduction

Apolipoprotein L1 (*APOL1*)-associated nephropathies are a spectrum of related nondiabetic kidney diseases strongly associated with G1 and G2 coding risk variants in populations with African ancestry. It has been observed that African Americans have a fourfold increased risk for end-stage renal disease. Two studies identified a locus on chromosome 22 associated with nondiabetic end-stage renal disease, focal segmental glomerulosclerosis, human immunodeficiency virus (HIV)-associated nephropathy (which is manifested as collapsing glomerulopathy), and this was extended to hypertension-attributed end-stage renal disease [1, 2]. The major source of genetic risk for African American hypertension-attributed end-stage renal disease and focal segmental glomerulosclerosis was then localized to *APOL1*, encoding apolipoprotein L1 (ApoL1) [3]. Focal segmental glomerulosclerosis, HIV-associated nephropathy, hypertension-attributed end-stage renal disease, hypertension-attributed chronic renal failure, non-diabetic end-stage renal disease were associated with two *APOL1* risk alleles: G1, comprising two missense variants (S342G and I384M), and G2, which bears a 6-base-pair in-frame deletion leading to the deletion of two amino acids (N388_Y389del) [3-7]. G1 and G2 are mutually exclusive, never occurring on the same chromosome. In particular, these variants were strongly associated with sporadic focal segmental glomerulosclerosis in either the homozygous or compound heterozygous state with a recessive pattern of inheritance. One risk allele was associated with only a small increase in renal disease risk. Two risk alleles versus zero risk alleles yielded an odd ratio from 10 to 17 for focal segmental glomerulosclerosis [3, 4].

ApoL1 is the trypanolytic factor of human serum that confers resistance to *Trypanosoma brucei brucei*. In vitro studies revealed that only the kidney disease-associated ApoL1 variants lyse *Trypanosoma brucei rhodesiense*, one of the causes of human African sleeping sickness. *APOL1* gene may have undergone natural selective pressure in Western Africa [3].

2. *APOL1* risk genotype in European patients of different African ancestries, with focal segmental glomerulosclerosis

We analysed *APOL1* risk allele genotype frequency in a large cohort of 152 patients with focal segmental glomerulosclerosis, of African ancestry living in Europe [8]. The two risk allele genotype was frequent (high risk group), found in 43% of patients in the whole cohort and in 60% of patients originating from French West Indies, significantly higher than in controls (18.9%, $p < 0.0001$). The frequency of the two risk allele genotype in patients originating from French West Indies in our study is similar to that observed in African American patients with focal segmental glomerulosclerosis: the *APOL1* risk genotype was present in 60% to 72% of self-identified African-American patients with focal segmental glomerulosclerosis in previous studies compared to 12.5 to 13% in controls [3, 4, 9-11].

To analyse the relative roles of *APOL1* and of the genes known to be involved in focal segmental glomerulosclerosis/ steroid-resistant nephrotic syndrome in these patients, we screened for pathogenic mutations with a panel including 35 steroid-resistant nephrotic syndrome genes. Of note, 41.5% of patients had a familial disease in the *APOL1* high risk group, whereas a mutation in steroid-resistant nephrotic syndrome genes was found in only one. Most of the mutations in monogenic steroid-resistant nephrotic syndrome genes were found in young patients in the *APOL1* low risk group. Because of the high frequency of G1 and G2 and the large increased risk of focal segmental glomerulosclerosis associated with these variants, families in which multiple individuals have the disease may have *APOL1*-associated disease rather than one of the rarer Mendelian forms of disease. Accordingly, it has been shown that relatives of African American with non-diabetic end-stage renal disease are enriched for *APOL1* risk variants [12].

Patients in the high risk group were more likely to originate from French West Indies than from Africa. Among patients originating from Africa, most patients originated from West Africa. This is concordant with the prevailing hypothesis that G1 and to a lesser degree G2 renal risk alleles rose to high frequencies in West Africa because of positive selection by *Trypanosoma brucei rhodesiense*, the causal agent of acute human African trypanosomiasis [13]. The variants are found outside Africa at high frequencies in persons of African ancestry. The transatlantic slave trade resulted in the forced diaspora of millions of Africans from the Atlantic coastal regions of Africa to the Caribbean and the Americas [13]. The high allele frequencies of *APOL1* G1 and G2 variants in African Americans and in Caribbean reflect the *APOL1* G1 and G2 frequencies along the Atlantic coast of Africa. The higher frequency observed in patients originating from the French West Indies compared to patients originating from Africa might be due the fact that a high proportion of them originated from West Central Africa, in particular Nigeria, where a very high prevalence of the high risk genotype is observed in the general population compared to other countries of West Africa [14].

We showed that *APOL1*-associated focal segmental glomerulosclerosis in our cohort presented at a broad age range between 0 and 64 years, but in the majority of patients the disease was diagnosed between 6 and 40 years and 54% were adults. Age at onset according to *APOL1* high risk allele or mutation in steroid-resistant nephrotic syndrome genes is presented on Figure 1. In very young children with disease onset before 1 year of age, a mutation in monogenic steroid-resistant nephrotic syndrome genes was more likely to be identified. Together these data support the idea

that focal segmental glomerulosclerosis among *APOL1* high risk individuals is a disease presenting during childhood and early adulthood.

Most patients had normal blood pressure in both groups. It demonstrates that focal segmental glomerulosclerosis associated with *APOL1* high risk genotype are distinct from hypertensive nephropathies associated with *APOL1* high risk genotype. Numerically more patients presented with collapsing focal segmental glomerulosclerosis in the *APOL1* high risk group and more patients with minimal change disease in the low risk group but it was not statistically significant.

Baseline and last follow up estimated glomerular filtration rate were significantly lower among patients with the *APOL1* high risk genotype, which is consistent with the faster progression rate that has been observed in these individuals in two previous studies [4, 5]. In our study, renal survival also tended to be worse in patients with the *APOL1* high risk genotype (Figure 2). Due to its prognostic value, we suggest to add *APOL1* in gene panels used in steroid-resistant nephrotic syndrome.

As *APOL1*-associated focal segmental glomerulosclerosis has a propensity to progress rapidly to end-stage renal disease, the question of treatment is crucial. In a previous study, the frequency of glucocorticoids sensitivity was similar in subjects with two *APOL1* risk alleles (12/42, 29%), and in subjects with zero or one *APOL1* risk allele (5/15, 33%) [4]. Furthermore, *APOL1* risk genotype did not seem to affect response to other immunosuppressive treatment regimen [5]. In the NEPTUNE study, *APOL1* high risk genotype was associated with a 69% reduction in the probability of complete remission at any time, independent of histologic diagnosis [4, 11]. In our study, 94 percent of patients were steroid-resistant, since most samples were addressed because of steroid-resistance for genetic testing. In the high risk group, all patients were steroid-resistant and only very few could be retrospectively considered as immune forms. In a recent study, it has been shown that *APOL1* high-risk variants are not associated with steroid-sensitive nephrotic syndrome but show significant associations with steroid-resistant nephrotic syndrome [15]. This is concordant with the clinical and experimental data showing the role of the intracellular expression of *APOL1* in the podocytes[16].

3. *APOL1* and kidney transplantation

3.1. *APOL1* in deceased-donor kidney transplantation

Contrary to the association seen in native kidney disease, there is no difference in allograft survival at 5 years post-transplant for recipients with high-risk *APOL1* genotypes. *APOL1* recipient genotypes do not increase risk of allograft loss after kidney transplantation [17].

The effect of transplanting kidneys from deceased African American donors with two *APOL1* nephropathy risk variants was also studied. First, *APOL1* risk variants were genotyped in 106 African American deceased organ donors and graft survival assessed in 136 resultant kidney transplants. Twenty-two of 136 transplanted kidneys (16%) were from donors with two *APOL1* high-risk variants. A multivariate model revealed that graft survival was significantly shorter in donor kidneys with two *APOL1* risk variants, but not for overall African ancestry excluding *APOL1* [18]. A second study included an additional 548 patients from 55 centers [19]. The latter report generally confirmed the previous findings: presence of two *APOL1* high-risk variants in donors appeared to translate into heightened risk for earlier allograft failure after deceased-donor kidney transplantation. A third study from the same team replicated and extended the observation in deceased-donor kidney transplantation by assessing the outcomes of 478 additional deceased-donor kidney transplantations from African American donors and performing a combined analysis in 1153 deceased-donor kidney

transplantations [20]. Results strongly supported the initial observations that recipients of deceased-donor kidney transplantation from individuals with recent African ancestry possessing two *APOL1* high-risk variants had shorter allograft survival (effects of two renal risk variants were of stronger significance than possession of a single risk variant). Effects of *APOL1* were independent of other traditional risk factors known to adversely impact renal allograft survival. Novel findings included that donor age did not significantly impact allograft survival based on the number of *APOL1* high-risk variants and recipients of kidneys from these donors had higher serum creatinine concentrations at latest follow-up.

Viral infections, including active cytomegalovirus infection, are possible "second hits" that may lead to glomerular injury and allograft failure in *APOL1* high-risk recipients [21]. Furthermore, de novo post-transplant collapsing focal segmental glomerulosclerosis is associated with potential predisposing factors such as acute rejection, viral infection and acute vaso-occlusion[22]. In these de novo post transplant focal segmental glomerulosclerosis, donor *APOL1* high-risk genotype independently predicts poor outcome.

3.2. *APOL1* in living-donor kidney transplantation

Living kidney donation provides best results for patients and graft survival compared to deceased kidney donors [23]. Overall, living kidney donation is safe and donors have an absolute risk of end-stage renal disease significantly lower than general population [24]. However, it is now recognized that living kidney donation increases the relative risk of end stage renal disease compared to healthy non-donors [24, 25]. The magnitude of end-stage renal disease risk increase varies according to sex, age and race [24, 26]. It has been shown that black donors have an increased risk of hypertension and end-stage renal disease compared with matched black non donors [24, 27]. The risk of end-stage renal disease is also higher among donors biologically related to the recipients [24, 25].

It is possible that the increased risk of renal failure after kidney donation could be explained by *APOL1* high-risk alleles that are shared between the donor and their related recipient. Young blacks with good baseline health-suitable potential donors who did not donate-carrying the *APOL1* high-risk alleles are at higher risk of developing chronic kidney disease in the future [28].

Two case reports mentioned focal segmental glomerulosclerosis and end-stage renal disease occurring within 7 years in donors harboring the *APOL1* G1 or G2 variants [29, 30]. Recently it was shown that black living kidney donors homozygous for *APOL1* high-risk alleles had significantly lower glomerular filtration rate and increased risk of end-stage renal disease after donation [31]. In that study, patients were divided into *APOL1* high-risk (n=19) or low-risk (n=117) genotypes. Donors in the *APOL1* high-risk group had a 10 ml/min predonation lower estimated glomerular filtration rate. At a median of 12 years after donation, donors with the *APOL1* high-risk genotype had a lower estimated glomerular filtration rate (57 ± 18 versus 67 ± 15 ml/min per 1.73m^2 ; $P=0.02$) and a faster decline in estimated glomerular filtration rate after adjusting for predonation estimated glomerular filtration rate (1.19 versus 0.4 ml/min/year). Two donors developed end-stage renal disease; both carried the *APOL1* high-risk genotype. However, decline in estimated glomerular filtration rate between donors and matched non donors grouped by *APOL1* genotype was similar.

The systematic screening of *APOL1* gene variants is still under debate, but the recently published guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) suggest to propose *APOL1* genotyping in black donors at risk [32].

3.3. Post-donation kidney function of low-risk APOL1 genotype living kidney donors of African ancestry

APOL1 high-risk genotype may not summarize the totality of end-stage renal disease risk increase in donors. In France, we analyzed a cohort of 38 donors of African ancestry and determined their *APOL1* status [33]. We showed that 7 (18%) had a *APOL1* high risk genotype. At donation and 1 year after donation, these *APOL1* high risk genotype donors tended to have a 9 ml/min/1.73m² and 5 ml/min/1.73m² lower estimated glomerular filtration rate than low risk patients, respectively, but it did not reach significance, probably because of the limited number of participants and of the short follow up. We then focused on the low risk *APOL1* group of donors. We compared compensatory response of the remaining kidney 1 year after donation between living kidney donors of Caucasian and African origin. We matched 62 Caucasian living kidney donors with 31 donors of African descent with low-risk *APOL1* genotype on age, body mass index, measured glomerular filtration rate and sex. African and Caucasian donors had similar baseline measured glomerular filtration rate, similar baseline estimated glomerular filtration rate, and similar 1-year postdonation estimated glomerular filtration rate. However, African donors had a lower absolute estimated glomerular filtration rate increase after donation compared to Caucasian donors. Relative estimated glomerular filtration rate increase after donation tended to be lower for donors of African ancestry compared to Caucasian donors. It has been previously reported that absolute estimated glomerular filtration rate increase after donation is negatively correlated with the baseline ratio of measured glomerular filtration rate divided by the volume of the remaining kidney (measured glomerular filtration rate/volume) [34]. As absolute estimated glomerular filtration rate increase was different between groups, we compared renal volume and measured glomerular filtration rate/volume ratio. At baseline, African donors had lower remaining-kidney volume compared to Caucasian donors and remaining kidney “measured glomerular filtration rate/volume” ratio was higher in donors of African descent compared to Caucasian donors. For donors of African ancestry, lower kidney volume could reflect reduced nephron number [35]. Since baseline measured glomerular filtration rate is similar in both groups, reduced nephron number in African donors could reflect higher baseline single nephron glomerular filtration rate. The “already high” single nephron glomerular filtration rate in donors of African ancestry could limit postdonation glomerular filtration rate increase. In agreement, donors of African descent had lower postdonation estimated glomerular filtration rate increase. Nephron-number difference between groups could be linked to a lower birth-weight of newborns of African ancestry as observed in African American [36].

4. Conclusion

Our results suggest that even low-risk *APOL1* donors have lower compensatory response of the remaining kidney compared to Caucasian donors. Therefore, *APOL1* genotype may not be sufficient to explain the discrepancy between donors of African descent and Caucasian donors. Better description of living kidney donation outcomes of donors with low-risk *APOL1* genotype is needed.

Funding

The research leading to these results has received funding from the Investments for the Future Program grant ANR-10-IAHY-01 (to C.A.) and from the European Union’s Seventh Framework Programme (FP7/2007–2013) grant 305608 (EURenOmics).

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Figure legends

Figure 1. Percentage of patients with mutation of steroid-resistant nephrotic syndrome genes or *APOL1* variant detected in relation to age of onset of proteinuria. Histograms indicate fraction (in percentage) of patients with mutation detected in n patients per N patients examined per age group (on top of histograms). Reproduced from [8].

Figure 2. Renal survival in the high risk (HR) and low risk (LR) groups by Kaplan Meyer analysis ($p=0.06$). Reproduced from [8].

Age at onset of proteinuria