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Mini Review

APOL1 Genotypes and Renal Transplantation

Carlos Eduardo Duran*, Mayra Estacio, Esteban Echeverri, Daniela Espinosa, Johanna Schweineberg, Juan Guillermo Posada and Liliana Mesa

Department of Microbiology, Valle Del Lili Foundation, Cali, Valle del Cauca, Colombia

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ABSTRACT

APOL1 is an autosomal recessive gene variant observed in the African American (AA) population and has been associated with increased risk of chronic kidney disease includes related forms of Focal Segmental Glomerulo-Sclerosis (FSGS), human immunodeficiency virus–associated nephropathy, severe lupus nephritis, sickle cell nephropathy, and focal global glomerulosclerosis with renal interstitial and vascular changes.

Keywords: Interstitial, Glomerulosclerosis, Allografts, Postransplantation, Nephrologist

INTRODUCTION

There has been a critical need to assess the effects of APOL1 renal risk variants in transplantation because it long had been recognized that renal allografts from deceased AA donors had shorter allograft survival [1]. The presence of two APOL1 renal risk variants in deceased AA donors shortens survival of their renal allografts independent of other traditional risk factors. No prospective study has examined the potential interaction of APOL1 genotype of the donors, deceased or living, and recipients, or fully accounted for other factors that likely reduce survival rates, including rejection, bacterial or viral infections, recurrent disease, and donor specific anti-HLA antibodies. APOL1 genotyping may have applications for organ quality scoring in deceased donor kidney allocation, and for the evaluation and selection of living donor candidates [2].

LITERATURE REVIEW

The problem

The risk of kidney failure in AA is higher than in other populations: 8% *vs.* 2%. This excess in risk is in large part associated with traditional risk factors that disproportionately affect this group such as diabetes, low socioeconomic status, smoking and obesity [3]. Yet, in 2010, Genovese et al. described that the Focal Segmental Glomerulosclerosis (FSGS) and hypertension-attributed End-Stage Renal Disease (ESRD) are associated with two independent sequence variants in the APOL1 among African American individuals. The prevalence of mutations of the APOL1 gene among Afro-descendant patients with chronic kidney disease for the G1 and the G2 variants can be of 20-22% and 13-15%, respectively [4].

This higher incidence of G1 and G2 alleles in populations of African ancestry is explained through positive selection, due to a survival advantage provided by the APOL1 protein against Trypanosoma brucei rhodesiense, which is the cause of African sleeping sickness [5]. The history of APOL1 in kidney transplantation begins with the observation of kidneys donated by Afro-descendant are known to function for shorter periods of time than kidneys donated by European Americans [6]. Several studies in donors deceased and living evaluated whether this difference was due to the presence of mutations in APOL1.

In these studies effects of APOL1 were independent of other traditional risk factors known to adversely impact renal allograft survival [7]. However, the mechanism by which APOL1 causes shorter allograft survival is not fully understood, Chen et al in a study of implant biopsy samples from living and deceased black kidney donors with high-risk and low-risk APOL1 genotypes to identify early differences in morphometric parameters prior to development of clinically evident renal phenotypes. APOL1 high-risk variant kidney donors had a 15% lower podocyte density compared with low-risk donors at baseline and this suggests recipients of these kidneys are at increased risk of allograft dysfunction from accelerated podocyte loss and increased susceptibility to "second hits" [8]. It is uncertain whether there is a role for screening APOL1-nephropathy variants in African Americans who are potential live kidney donors, retrospective studies suggest that transplantation of a kidney from a living donor with two APOL1 risk variants can lead to FSGS with early allograft failure in the recipient, and importantly, subsequent ESKD in a previously healthy donor (Tables 1,2) [9].

*Corresponding author. Carlos Eduardo Duran, E-mail: carlosed36@gmail.com

Table 1. Summary renal outcomes of studies in deceased donors with APOL1 risk variants.

Author	Date of publication	Population	Prevalence APOL1	Outcomes
Amber M. Reeves-Daniel [6].	2011	106 AA deceased kidney donors 136 resultant kidney transplants	16% donors with two APOL1 risk variants	Graft survival in APOL1 risk variants (HR 3.84; p=0.008)
B.T. Lee [10].	2012	119 African American kidney transplant recipients	58 (48.7%) carried two APOL1 kidney disease risk variants	Allograft survival of the high risk 2 APOL1 allele group compared to the low risk 0 or 1 APOL1 allele group (HR 0.96, 95% CI 0.61-1.49, p=0.840)
Barry I. Freedman, [11].	2015	675 AA deceased kidney donors	14.6% donors with two APOL1 risk variants	Graft survival in APOL1 patients with a donor two APOL1-risk variant (HR 2.26; p=0.001)
Barry I. Freedman [12].	2016	478 deceased AA kidney donors	14.8% donors with two APOL1 risk variants	Renal allograft survival in recipients of APOL1-two-renal-risk-variant kidneys (HR 2.00; p=0.03)

Table 2. The outcomes are summary.

Author	Date of publication	Population	Prevalence APOL1	Outcomes
Mona D Doshi [14]	2018	136 black living kidney donors	APOL1 high-risk (two risk alleles; n=19; 14%) or low risk (one or zero risk alleles; n=117; 86%)	Mean follow-up: 12 years
				Donors with 2 *vs*. 0 or 1 APOL1 variants had: lower eGFR 57 ± 18 *vs*. 67 ± 15 ml/min per 1.73 m^2; P=0.02
				The proportion of donors developing microalbuminuria was not different between the two groups P=0.86.
				Compared with matched healthy nondonor controls annual decline of eGFR: 0.5 *vs*. 0.6 ml/min/1.73 m^2; P= 0.39.
François Gaillard [15].	2018	62 Caucasian living kidney donors and 31	31 donors of African descent with low-risk APOL1 genotype (0 or 1 G1 or G2 allele of	Early postdonation GFR 1 year after donation between living kidney donors of
		donors of African descent		Caucasian and African origin

			APOL1)	African donors had lower absolute eGFR increase after donation compared with white donors (+13.2 ± 10.9 mL/min per 1.73 m^2 *vs.* +18.1 ± 11.2 mL/min per 1.73 m^2 P = 0.03).

DISCUSSION

For Francois Gaillard et al the results suggest that even low-risk APOL1 donors have lower compensatory response compared with Caucasian donors [10-13]. Therefore, APOL1 genotype may not be sufficient to explain the discrepancy between donors of African descent and white donors. The number of participants in each group limited the statistical power. A large-scale study is being done to improve outcomes after kidney donation and kidney transplantation. The APOLLO is a national observational study, and the purpose is to test kidney donors (living or deceased) and kidney transplant recipients for variants APOL1 to determine whether they impact outcomes [14]. There is a lot of controversy surrounding the screening for APOL1 in AA live transplant donors populations, its benefit are unclear in some reports, as is the benefit of stratification by genotype in postransplantation renal disease [15]. A 2019 survey conducted in nephrologist and surgeons' members of the American Society of Nephrology, American Society of Transplantation, and American Society of Transplant Surgeons revealed that 87% of members believed that APOL1 testing offers valuable clinical information about AA live donor's eligibility, yet only 4% offer it in routine testing. This highlights the importance of providing a framework that assist in the decision-making process of ordering this test when it is indicated and highlights the lack of clear guidelines and indications for it [16-17]. In 2020 the American Society of Transplantation referred in relation to the universal application of APLO1 genotyping

of dead donors, the consensus was that it was premature to include it in the algorithms for diseased donor kidney allocation, considering there was a lack of nationwide information [18]. Living donors programs have been known to implement this screening in donors of African ancestry, but a lot of controversy exists in regards to the possibility that this may diminish the ability of persons of African ancestry of gaining access to living donor kidney transplantation programs further increasing an already existing disparity. The 2017 KDIGO living donor guideline indicates that the presence of two APOL1 RRV is associated with an increased lifetime risk of kidney failure, but that at this moment it cannot be quantified, or serve as a contraindication for donation [19]. There are ethical issues that must be considered when testing por APOL1 RRV. It is important to explain the context in which the exam is made and the meaning of the outcome both for the donors and the recipients so that the people involved can make informed decision.

CONCLUSION

African ancestry is associated with increased risk of developing ESRD; the variants of APOL1 in deceased donors have increased risk of graft failure maybe in relation to subclinical, prodromal podocyte depletion in donor kidneys trigger initial stress that predisposes recipients to worse kidney outcomes. Although the current literature is not sufficient to support new policies that introduce APOL1 genotyping into the practice of either diseased or living donation.

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