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APOL1 nephropathies: 2017 in review

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Abstract

Purpose of review.—To review publications relating to APOL1 renal risk variants published 2017.

Recent findings.—The study of APOL1 variants continues to be highly active; 24 papers published in 2017 were selected to highlight. These include clinical studies of kidney disease, kidney transplantation, hypertension, cardiovascular disease, and genetic diversity. Laboratory studies included APOL1 association with VAMP and with suPAR, mitochondrial dysfunction, endolysosomal dysfunction and inflammasome activation.

Summary.—Our understanding of the role of *APOL1* genetic variants and the mechanisms for renal toxicity continues to deepen. It is not yet clear which pathways are most relevant to human disease and so the most relevant drug targets remain to be defined.

Keywords

arterionephrosclerosis; kidney transplantation; suPAR; mitochondria; endolysosomal trafficking; inflammasome

Introduction

The identification in 2010 of genetic variants in apolipoprotein L1 (APOL1) that associate with kidney disease in peoples with sub-Saharan African heritage began a new and important chapter in the understanding of an important health disparity. This review will summarize clinical and basic aspects of this story that appeared in 2017, as we approach the eighth anniversary of the discovery of the role these variants play in kidney disease. Several reviews have appeared in the past year that summarize recent progress [1]. In all, 91 papers appeared in 2017 with the key word “APOL1”, of which 74 also had the key word “kidney” and only a fraction can be reviewed here. A number of useful reviews have appeared this year, some of which are referenced below and others review the evolution of the *APOL1* gene [1], *APOL1* role in HIV-associated nephropathy [2], role of *APOL1* genetic testing in clinical medicine [3], effects on APOL1 on transmembrane ion flux [4] and possible therapeutic avenues[5].

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Conflicts of interest. None

Arterionephrosclerosis

The African American Study of Kidney Disease and Hypertension (AASK) recruited between 1995 and 2001 African Americans with reduced eGFR and modest levels of proteinuria, using enrollment criteria that earlier had been shown in limited number of renal biopsy cases to correlate with global glomerulosclerosis and arteriosclerosis, which together comprise the clinic-pathologic diagnosis of arterionephrosclerosis. In 2012, Lipkowitz and colleagues showed, using 675 AASK cases and 600 controls, that *APOL1* renal risk variants were associated with kidney disease (OR 2.57) and during follow up, with having kidney disease progression, defined as urine protein/creatinine ratio > 0.6 g/g (OR > 6.3) and serum creatinine > 3 mg/dL (OR 4.6) [6]

Recently Chen and colleagues found that study participants carrying two *APOL1* risk alleles (high risk, HR), representing 17% of the cohort, were 1.7-fold more likely to develop incident proteinuria (defined as doubling of urine protein/creatinine ratio to a value > 0.2 g/g) compare to those with zero or one *APOL1* risk allele (low risk, LR) [**7]. Further, when proteinuria appeared, it heralded faster eGFR decline during the succeeding years. Overall eGFR decline slope was faster for those with *APOL1* HR genotypes (1.6 vs 1.1 ml/min/yr). These data fit the general picture typical of *APOL1* high risk genotypes across multiple proteinuric disorders: more proteinuria, more likely to lose GFR, and more likely to lose GFR faster.

Pediatric kidney disease

A recurring theme in the literature of *APOL1* nephropathy has been that across many distinct forms of CKD, *APOL1* HR African Americans compared to *APOL1* LR African Americans have lower eGFR at study entry, more proteinuria, and faster progression. Ng and colleagues reviewed findings from children with CKD in two longitudinal cohorts, Chronic Kidney Disease in Children (cKID) and Nephrotic Syndrome Study Network (NEPTUNE) [**8]. In cKID, there were 28 LR and 28 HR individuals and in NEPTUNE, there were 27 LR and 21 HR individuals. Focal segmental glomerulosclerosis (FSGS) (rather than minimal change disease) was present in 89% of HR children and 29% of LR children, among whom the next most common conditions were hemolytic-uremic syndrome and Alport syndrome. *APOL1* HR children had a lower eGFR at study entry and had a faster eGFR decline during follow up. Thus, clinical features of *APOL1* glomerular disease are very similar to those previously reported for adults.

Hypertension

Two papers have examined whether *APOL1* risk alleles are associated with higher blood pressure in general adult population: Nadkarni and colleagues, using a cross-sectional design, examined African American participants in the BioMe Biobank at the Icahn School of Medicine, including 5204 African American subjects in the discovery cohort and 1623 subjects in the validation cohort [**9]. Further validation was performed in 2300 subjects at other institutions within the EMERGE consortium. *APOL1* HR subjects had higher systolic and diastolic blood pressures, beginning in the 20 to 29-year-old group. The HR subjects

demonstrated a propensity to lower eGFR, starting in the 30 to 39-year-old group. *APOL1* 2-risk allele frequency was 14 to 16% across the samples, which is slightly higher than the expected 12 to 13% in the general population and may suggest that some subjects might have *APOL1* associated disease that brought them into the health care system. Whether the effect of *APOL1* variants to elevate blood pressure is due to early kidney disease, perhaps undetected by standard testing, or alternatively, is due to an effect on the systemic microvasculature, or by other mechanisms, remains to be determined.

Chen and colleagues used a longitudinal design, with data from the prospective CARDIA study of healthy adults recruited at a median age in the mid-20s [10]. The study included 1154 LR African Americans and 176 *APOL1* HR African Americans, the latter representing 13% of the total. Over twenty-five years of follow up, there were no differences in blood pressure between the groups. Why do these findings from these two studies differ? One possibility is that the BioMe study was much larger and was therefore able to detect a small effect of *APOL1* variants on blood pressure. Another possibility is that there was selective non-recruitment or drop-out of subjects with kidney disease in the CARDIA study.

In the setting of *APOL1* genetic risk, what is the relationship between hypertension and CKD? Nadkarni and Cocoa propose three possible, and not mutually exclusive, relationships: that *APOL1* variants lead to CKD which in turn leads to hypertension; that *APOL1* variants contribute to hypertension, and a second hit leads to CKD; and that *APOL1* variants lead to both hypertension and CKD, and that the latter is impacted both by hypertension and by a second hit [11]. It will take carefully designed, longitudinal cohort studies to develop evidence to support or refute these possible pathways to disease.

Kidney transplantation

The role of *APOL1* variants in adverse kidney transplant outcomes for kidney transplant donors and for recipients is one of intense interest, are reviewed recently [12]. In response, NIDDK, NIH has launched the *APOL1* Long Term Kidney Transplantation Outcomes (APOLLO) study. The funded projects are in progress now. Two papers performed analysis to project possible outcomes for donors and recipients: Julian et al. replaced donor race, African American, with *APOL1* genotypes in the Kidney Donor Risk Index to refine estimates of allograft survival [13]. Locke and colleagues projected the likelihood of CKD in a cohort of young adults aged 18–30, meeting criteria to be kidney donors (e.g., using 3435 subjects enrolled in the CARDIA study, of whom were 48% African American) [14]. After a median follow up of 25 years, the estimated CKD risk was 1.5% for African American women and 2.5% for African American men with two *APOL1* risk variants, compared to 0.5% and 0.9% for African women and men, respectively, who lack two *APOL1* variants. For those with a baseline clinical abnormality or a first-degree relative with diabetes or hypertension the risk for CKD was estimated as 2.5% to 6% for 18-year-old women and 4 to 11% for 18-year-old men. These estimates are useful for selecting and counseling potential kidney donors, and also for estimates of CKD risk in the general population.

Cardiovascular disease and mortality

The data addressing the relationship between *APOL1* renal risk variants and cardiovascular disease have been complex and somewhat contradictory, as summarized in two recent comprehensive and thoughtful reviews [15,16]. As suggested by the first review, differences in study design, study populations, and the handling of confounding by CKD (which is itself a powerful risk factor for cardiovascular disease) may account for discrepant conclusions. Both reviews raised the issue of survival bias, whereby enrolling prevalent patients with CKD necessarily excludes some patients who die early from cardiovascular disease and are not enrolled or counted; if these early deaths occur disproportionately in one genotype, it could lead to bias. Two studies in the past year concluded there is no role for *APOL1* risk variants in cardiovascular disease. In the CARDIA study population, coronary artery calcification (incidence, prevalence, and progression) and carotid artery intimal thickness and left ventricular hypertrophy did not differ according to *APOL1* genotype [*17]. In the SPRINT study, there were no differences by *APOL1* genotype in the composite outcome or in any of its components, which included myocardial infarction, non-myocardial infarction acute coronary syndrome, heart failure, or cardiovascular disease death [*18].

CKD in Africa

Previous studies of the role of *APOL1* in CKD in Africa have been reported from western, central and southern Africa, where *APOL1* risk variant frequencies may reach 20–40%. Stanifer and colleagues carried out a population-based study of CKD in northern Tanzania, an area endemic for *Trypanosoma brucei rhodesiense* [19]. CKD was defined, according to Kidney Disease Improving Global Outcomes, as the presence of albuminuria or $\text{eGFR} < 60 \text{ ml/min/1.73m}^2$. The population was of Bantu origin. *APOL1* risk allele frequencies (G1, 9% and 11% for each SNP, G2, 7%) were quite similar to those of the general population in the area, which had been sampled previously. This similarity in allele frequencies is puzzling in a CKD population; it may be that the GFR estimating equation used was not valid for this population, or alternatively that the kind of kidney disease(s) present were not related to *APOL1* variants.

Genetic diversity in the *APOL1* region

The *APOL* region in chromosome 22 encodes six *APOL* family members, and these have naturally attracted attention as possibly contributing to renal disease. The *APOL* genetic region is highly polymorphic, consistent with it being under recent selection pressure. Skorecki and colleagues had previously reported a null variant in *APOL3* (Q58X), located in the first exon and provisionally associated with kidney disease [20], although this was not confirmed [21]. Recently, this issue was addressed again in four cohorts (the FIND study, a Wake Forest cohort, and two New York cohorts, including both African Americans and Hispanic Americans with primary glomerular disease and controls). The *APOL3* null allele interacted with *APOL1* risk alleles, having an additive effect in the presence of one *APOL1* risk allele but not two *APOL1* risk alleles [*22]. Further, they showed that *APOL1* bound *APOL3*. Sustained exposure to interferon increased expression of *APOL1* to a greater extent than *APOL2* or *APOL3*.

Peng and colleagues examined *APOL1* sequences from the 1000 Genomes project and identified 613 SNPs, 99 of which had minor allele frequencies >1% [23]. Diversity was greatest among Africans, suggesting a role for balancing selection in this population. The density of variants was greatest in exon 7, where the renal risk variants are located, suggesting that this portion of the protein may be particularly under selection pressure.

Copy number variation

There is copy number variation at the *APOL1* locus. A recent paper reported preliminary data from a case (FSGS)/control study and showed that among individuals with the G0/G1 genotype, cases were more likely to carry a *APOL1* gene duplication when compared to controls lacking kidney disease [24]. Peng and colleagues, studying a Chinese population, found no differences in *APOL1* copy number between FSGS cases and controls; *APOL1* sequences were not reported but it is likely that all subjects carried the G0/G0 genotype [25]. Thus, it appears that copy number variation per se is not pathogenic but an increased copy number of the renal risk alleles (G1 or G2) may promote renal disease, as shown for heterozygotes and plausibly for those with two *APOL1* risk alleles. This fits with the finding that interferon increases *APOL1* gene expression in vivo and interferon, administered as therapy for other diseases, is associated with FSGS in patients [26].

APOL1 structure and association with VAMP8

Sharma and colleagues studied the molecular dynamics of the C-terminal domain of APOL1, and showed that in solution, the APOL1 risk variants have increased flexibility compared to G0 [27]. Sedor and colleagues had previously observed that APOL1 interacts with vesicle associated membrane SNARE protein 8 (VAMP8). These authors carried out molecular simulations to show that the APOL1 risk variants have a less flexible C-terminal domain and this reduces affinity for VAMP8. They concluded that this may alter VAMP-positive vesicle trafficking [** 28].

Molecular association of APOL1 with suPAR and integrin: a toxic ménage à trois?

Soluble urokinase-type plasminogen activator receptor (suPAR) is a form of uPAR, which is the plasma membrane receptor for the urine plasminogen activator (urokinase). Circulating suPAR level is a marker for systemic inflammation and immune activation, and has been associated with kidney disease progression. It has been shown that suPAR binds $\alpha\text{v}\beta 3$ integrin on various cells, including podocytes. Hayek and colleagues showed, using purified proteins, that in the presence of Mn^{++} , all three APOL1 variants bind $\alpha\text{v}\beta 3$ integrin, with G2 variant having the highest affinity [**29]. When suPAR was added to the system at levels comparable to that found in plasma of healthy individuals, it did not activate the $\beta 3$ integrin. By contrast, APOL1 G1 and G2 protein were able to activate $\beta 3$ integrin in cultured podocytes. Finally, in wild-type mice, the administration of cDNA encoding APOL1 G1 and G2, but not G0, induced proteinuria; this effect was not seen in mice lacking *Plaur*, the gene encoding both uPAR and suPAR.

Mitochondrial dysfunction and energy crisis

In a landmark paper, Ma, Freedman and colleagues studied HEK cells stably over expressing each of the *APOL1* full-length variants, and found that the G1 and G2 risk alleles, compared with G0, impaired mitochondrial function (with reduced maximal respiration rate, respiratory capacity and membrane potential) [**30]. In the face of an energy shortage, it is not surprising that cellular potassium levels increase, via reduced transcellular Na/K exchange, as this process is dependent on abundant cellular energy stores. Further, among the genes most down-regulated by the risk alleles was nicotinate phosphoribosyltransferase (NPRT), which is a key gene regulating synthesis of nicotinamide adenine dinucleotide. This is a key coenzyme that exists as NAD⁺ and NADH and is essential as an electron donor and acceptor for reduction/oxidation reactions.

Granado and colleagues carried out studies of APOL1 isoforms which lack the signal peptide and thus remain intracellular. They reported similar findings and also noted phosphorylation of stress-induced kinases (JNK/SAPK and p38 MAPK) and of AMP activated kinases [**31]. Podocytes appear to be particularly sensitive to reduced energy availability, although the reasons are not entirely clear, and mutations in various genes related to bioenergetics result in podocytopathy [32]. *APOL1* can now be added to that list of genes.

O'Toole and colleagues studied *APOL1* variant over-expression in HEK293 cells. At high expression levels, cell toxicity was evident with all three isoforms (G0, G1 and G2) and mechanistically was explained by insertion of the proteins into the plasma membrane, acting as ion channels and collapsing the Na⁺/K⁺ gradient [**33]. At lower expression levels, toxicity was not seen. The authors concluded that the acute toxicity seen at high expression levels do not correspond to changes in vivo and so are unlikely to be the mechanism for variant-induced injury in human patients.

Mechanisms: endolysosomal dysfunction, inflammasome activation and *APOL1* gene expression level

In another landmark paper, Beckerman, Susztak and colleagues showed in transgenic mice that the *APOL1* risk alleles induce glomerular disease when expressed in the podocytes under the control of a tetracycline-inducible promoter [**34]. Several points are noteworthy. First, these mice developed segmental glomerulosclerosis and global solidified glomerulosclerosis, the histologic lesions characteristic of human APOL1 nephropathies. Second, the podocytes from the risk allele transgenic mice manifested impaired endolysosomal trafficking and autophagic flux, possibly due to acidification of the endosomal compartment, and this associated with accumulation of autophagosomes. Third, these intracellular processes were accompanied by inflammasome activation, with generation of interleukin 1 β , indicative of pyroptosis. The structural and the functional abnormalities were more severe in mice expressing the G1 and the G2 alleles compared to the G0 allele. Fourth, the induction of glomerular injury was dependent on passing a threshold of gene expression and was likely reversible when gene expression was reduced. The authors extended this finding with a unique resource of 286 human kidneys, obtained

but not used for kidney transplantation, and showed that *APOL1* gene expression (of all genotypes) was higher in CKD kidneys defined as those with eGFR < 60 ml/min/1.73m², compared to controls. This fits well with a model that the *APOL1* risk alleles induce glomerular injury chiefly when they are over-expressed, as would occur for example, in the setting of interferon stimulation.

Conclusions

In the eight years since the identification of *APOL1* as the gene harboring variants responsible much of the predilection for chronic kidney disease among African Americans, much progress has been made in identifying molecular and cellular pathways of injury. Still much remains to be done, particularly to define the role of these pathways in human disease, and in particular APOL1 disease syndromes in particular patients. Have we reached a point where there is broad consensus that we can call the condition(s) APOL1 nephropathy, implying that a causative role has been established for the APOL1 variants, and rather than using the term APOL1-associated nephropathy? We believe this to be the case. To fulfill the promise of precision medicine as it relates to patients with APOL1 nephropathies, we need clinical-pathologic tools to identify, in the patients we see every day in clinic, which molecular and cellular pathways are relevant for the disease (and perhaps for a particular patient) and to devise effective therapies to slow or halt progression of kidney disease.

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Key points

- The most characteristic kidney lesions associated with APOL1 variants are focal segmental glomerulosclerosis and arterionephrosclerosis.
- APOL1 may be associated with elevated blood pressure, starting in the third decade of life.
- APOL1 interactions with VAMP8 and with suPAR may contribute to podocyte injury.
- APOL1 renal risk variants induce mitochondrial dysfunction and inflammasome activation, as well as impairment of endolysosomal trafficking.