APOL1 renal risk variants: Fertile soil for HIV-associated nephropathy

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Abstract

Apolipoprotein L1 (*APOL1*) genetic variants are potent risk factors for glomerular disease, but one or more additional factors are required for expression of glomerular disease. Uncontrolled or poorly controlled HIV infection is the most potent susceptibility factor for APOL1 nephropathy that has been identified to date. *APOL1* variants are associated with HIV-associated nephropathy (HIVAN), a podocyte disease, but not with HIV-immune complex disease, primarily a disease of the mesangium. The mechanism by which HIV brings out the latent glomerular disease risk remains to be defined. There are at least two classes of candidate mechanisms to explain the potent interaction between HIV-1 and APOL1. First, APOL1 variant proteins and HIV accessory proteins implicated in HIVAN may target the same or related intracellular pathways in podocytes. Recent data suggests roles for interleukin 1b and transcription factor EB (TFEB). Second, features of uncontrolled HIV-infection, including elevated circulating factors such as interferon, may drive *APOL1* gene transcription or act upon podocytes in other ways. Deeper probing of APOL1-HIV interactions may yield insights that will aid understanding HIVAN, APOL1 nephropathy, and podocyte biology.

Keywords

Chronic kidney disease; interferon; Vpr; Nef

Introduction

APOL1 renal risk variants are strongly associated with kidney disease, and the strongest association that has been identified to date is with HIV-associated nephropathy. *APOL1* risk variants are common, representing ~50% of alleles in West African populations and ~35% of alleles in African Americans; thus ~12% of African Americans have two risk alleles but only a small fraction, perhaps 15% or more will develop kidney disease during their lifetimes (Dummer et al. 2015). The strong association between HIV-1 infection and APOL1

nephropathy is important clinically wherever peoples of sub-Saharan descent live, and is important mechanistically in understand the pathophysiological mechanisms by which APOL1 variants damage the kidney.

APOL1 and hypertension-attributed chronic kidney disease, non-HIV FSGS and HIVAN

In 1984, early in the HIV epidemic, and years prior to widespread dissemination of combined anti-retroviral therapy (cART), the syndrome of HIVAN was noted to predominantly affect individuals of sub-Saharan Africa descent (Rao et al. 1984). A major advance was identification of two *APOL1* genetic variants that explain much of this predilection (Genovese et al. 2010). These variants are termed G1 (a haplotype comprising two missense variants, S342G and I3484M) and G2 comprising a two amino acid deletion, 388NY.

Among the three common kidney diseases most strongly associated with *APOL1* genetic variants, there is a hierarchy of increasing odds ratios (OR) for carriage of two variants (G1/G1, G1/G2 or G2/G2), with hypertension attributed chronic kidney disease (HA-CKD) < focal segmental glomerulosclerosis (FSGS) < HIVAN. In the AASK study, Lipkowitz and colleagues showed that for HA-CKD, which often correlates with arterionephrosclerosis on kidney biopsy (although kidney biopsies were not performed), the OR of having two risk alleles among was 2.6 (confidence interval 1.8, 3.6) for HA-CKD subjects compared to control subjects, and 19% of subjects had two risk alleles (Lipkowitz et al. 2013). Among the 35% of subject who had progressed to having a serum creatinine >3 mg/dL compared to control subjects, the OR was 4. This finding indicates that *APOL1* risk variants are particularly associated with progressive kidney disease, a theme that recurs throughout the literature on APOL1 associations with chronic kidney disease.

The results of studies examining association of APOL1 and kidney disease in the setting of HIV infection are summarized in Table 1. In study from the USA, the odds ratio (OR) for non-HIV associated FSGS was 17 (95% confidence interval (CI): 11, 26) (Kopp et al. 2011); 72% of 217 subjects with FSGS had two risk alleles, compared to ~13% of individuals of the general population African American control subjects. Among 54 individuals with biopsy-proven HIVAN in the USA, the OR for carriage of two risk variants was 29 (95%CI: 13, 68) with 72% of HIVAN cases having two risk alleles and 8% of the hypernormal comparator group (subjects with HIV infection for >8 years, with normal serum creatinine and lacking proteinuria) having two risk *APOL1* variants. While the absolute values for the OR differ between FSGS and HIVAN, the confidence intervals overlap. Further, for HIVAN, the comparator group has a lower allele frequency, as the authors were able to define a group with the exposure and without disease, in a way that was not possible to do for idiopathic FSGS (where the provocative factor is unknown) and this would tend to arithmetically increase the OR, as the HIV control group was predicted to be (and was) depleted in subjects with two *APOL1* risk alleles. Thus, with regard to *APOL1* genetic variants, the OR for FSGS and HIVAN are statistically similar in the USA. Atta and colleagues showed that among individuals with HIVAN, the presence of two risk alleles was not associated with

differences in renal pathology or in renal survival, with median renal survival <12 months for those with and without 2 *APOL1* risk alleles (Atta et al. 2012).

In a study from South Africa, comparing 38 individuals with HIVAN to 108 HIV-positive subjects with normal renal function, the OR for carrying two *APOL1* risk alleles was 89 (95% CI: 18, 912) (Kasembeli et al. 2015). Due to the small sample size, the confidence intervals overlapped with those for HIVAN in the USA. The authors noted that this may be the highest OR yet reported for a genetic variant associated with a complex disease (i.e., one in which genetic and environmental factors combine to induce a phenotype). An important insight from this study is that a single copy *APOL*1 G1 risk allele (i.e., when present in a heterogyzous state with the G0 allele) is sufficient to increase the risk for HIVAN (Figure 1). This probably represents an effect of the G1 allele that is present in other populations, but that can only be demonstrated to reach statistical significance when the OR for the association of *APOL1* variants with HIVAN is very high in a population, as is the case in South Africa.

Purswani and colleagues reported that for HIV+ youth, *APOL1* high-risk status conferred an odd ratio for CKD of 4.4 (1.5, 11.2), but without kidney biopsy, it is not known how many of the subjects had HIVAN (Purswani et al. 2016).

The conclusion to be drawn from these studies is while there is a trend for the OR for carriage of two *APOL1* risk variants to be higher in HIVAN than with FSGS, numerical differences have not been conclusively demonstrated due to modest sample sizes and features of study design particularly with regard to the characteristics of the control groups. Nevertheless, HIV is clearly a potent interactor with *APOL1* risk alleles to induce glomerular injury.

APOL1 and other HIV-associated kidney diseases

APOL1 risk variants are also associated with FSGS that presents in the setting of HIV infection; contrasting factors associated with different renal disease are summarized in Table 2. Atta and colleagues showed that compared with HIV+ control subjects lacking both HIVAN and FSGS, the odds ratio for FSGS was 3.0 (95% CI 1.5, 5.8) (Atta et al. 2016). The distinction between collapsing FSGS (or collapsing glomerulopathy) and idiopathic FSGS is readily apparent in some cases and can be subtle in other cases. The former manifests podocyte hyperplasia, with an increase in cell number along the basement membrane, and/or the appearance of cells within Bowman space. These cells were previously believed to be dysregulated visceral epithelial cells (podocytes) (Barisoni et al. 1999). More recently have been proposed to be dysregulated parietal epithelial cells, possibly having progressed part of the way along the differentiation pathway to podocytes; evidence using fate-mapping mice support this theory (Shankland et al. 2014). Other characteristic features of HIVAN include microcystic tubular dilatation and an interstitial mononuclear cell infiltrate.

By contrast, HIV-associated FSGS lacks prominent abnormalities in the podocyte, while manifesting segmental glomerular scars, and lacks microcystic tubular dilatation. The pathogenesis of HV-associated FSGS remains unclear. It has become more common

following the widespread adoption of combined anti-retroviral therapy, which has been associated with HIV-positive individuals living longer and being at increased risk for obesity, metabolic syndrome, and metabolic diseases, including diabetes and atherosclerosis (Table 3). These individuals have systemic immune activation and a pro-coagulant state, both which may contribute to this suite of diseases and to premature aging. It is plausible that these processes predispose to FSGS, although the mechanistic pathway is largely unknown. In particular, they may predispose to adaptive FSGS, where the pathophysiology includes glomerular enlargement, likely on a hemodynamic basis, due to increased body size. It is also plausible that microvascular damage in the kidney, associated with metabolic disease and atherosclerosis, contributes to glomerular injury. The role of *APOL1* variants in arterionephrosclerosis occurring in the setting of HIV infection deserves further investigation.

HIV-associated immune complex kidney disease (HIVICK) may present with multiple immunoglobulin deposits in the glomerulus, or with IgA alone, and has lower predilection to progress to end-stage kidney disease (Foy et al. 2013). HIVICK is not associated with the *APOL1* renal risk alleles (Fine et al. 2012; Kasembeli et al. 2015). Fine et al. noted that among 25 HIV+ subjects who underwent kidney biopsy and had zero APOL1 risk alleles, only 3 (12%) had FSGS while over 40% had HIVICK; the remainder had diabetic nephropathy or arterionephrosclerosis (Fine et al. 2012).

Mechanisms of APOL1 interaction with HIV: possible role of interferon

In a study of 333 African American men with HIV infection in the longitudinal Multicenter AIDS Cohort Study (MACS), Estrella and colleagues reported the rate of eGFR decline was faster in high-risk individuals (those with two *APOL1* risk alleles) compared to low risk individuals, but only when viral load was not suppressed by anti-retroviral therapy (<400 copies/mL) (Estrella et al. 2015). Assuming that eGFR decline rate is a reasonable proxy for glomerular injury (proteinuria might be more sensitive), active viral replication may promote, or may even be essential for APOL1-mediated renal injury, or at least for collapsing glomerulopathy (HIVAN).

Plausibly, the link between viral replication, *APOL1* genotype, and glomerular injury could be explained by either viral gene product(s) or by the host immune response to viral infection. There are no clinical studies that address interactions between viral gene products and APOL1, although there are basic science studies that explore this relationship, as discussed below; this would be fruitful area for future investigation.

There are several links between HIV infection and immune activation that may have relevance for understanding the role of APOL1. As an innate immune protein, *APOL1* gene expression is driven by interferon, with potency $\gamma > \beta > \alpha$ interferon (Nichols et al. 2014). Interferon signaling activates STAT3, which occupies binding sites located within the *APOL1* promoter. Acute and chronic HIV-1 infection is characterized by an intense pro-inflammatory state, including elevated levels of interferons in plasma and tissue (Doyle, Goujon, and Malim 2015). Among HIV+ African-American subjects, plasma levels of inflammatory markers interleukin-6, soluble tumor necrosis factor (TNF) receptors 1 and 2,

chemokine (CC) motif ligand 2 (CC2), and beta2-microglobulin are higher among those with eGFR <60 ml/min/1.73m^2 compared to those with higher eGFR. Among nephrotic subjects compared to others, plasma levels of CCL5 and interferon-α were also higher compared to those without kidney disease (Bruggeman et al. 2014). While kidney biopsies were not available in this study, these data do associate systemic markers of inflammation with kidney disease. There were no differences in cytokine levels among subjects with risk and non-risk *APOL1* genotypes. Further, plasma APOL1 levels in HIV-positive subjects did not correlate with APOL1 genotype, CKD status, or plasma level of proinflammatory cytokines. It is remains possible that either brief or intermittent stimulation of interferon production predisposes to APOL1-induced glomerular injury (which would be difficult to detect even with a longitudinal study) and/or that plasma levels of APOL1 do not correlate closely with glomerular expression of APOL1.

Role of TLR4 signaling

There is emerging evidence that APOL1 renal risk variants enhance signaling downstream from toll-like receptor (TLR) 4 (Wakashin H and Kopp 2015). HIV infection is also associated with TLR4 signaling, suggesting synergy with APOL1 risk variants in promoting innate immune responses. HIV infection is associated with increased expression of TLR2 (but not TLR4) on freshly isolated monocytes and exposure to the HIV envelope protein gp120 further increased expression (Heggelund et al. 2004). A subsequent study confirmed these findings, and found that both TLR2 and TLR4 expression are increased in plasmacytoid dendritic cells obtained from HIV-positive subjects (Hernandez et al. 2012). Contrary findings, namely reduced TLR4 expression, have been reported for alveolar macrophages from HIV-positive subjects and in HIV-infected U1 monocytoid cells (Nicol et al. 2008), and thus the interplay between HIV infection and the TLR pathway is likely context dependent. The HIV regulatory protein Tat stimulates cytokine production in macrophages in a TLR4 dependent fashion (Ben Haij et al. 2015); whether it acts similarly in podocytes remains to be determined.

APOL1 as an HIV restriction factor

As noted above, APOL1 is an innate immune factor, known to target parasites, specifically *Trypanosoma brucei*. An intriguing recent observation by Popik and colleagues suggests that, in addition to its anti-parasite functions, that APOL1 acts as a viral restriction factor (Taylor, Khatua, and Popik 2014). In 293T human macrophages infected with HIV-1, overexpression of APOL1 reduced Gag p55 protein (core structural protein) and p24 protein (a capsid protein) by 90%. In human 937 monocytic cells stimulated by interferon-γ over-expression of APOL1 reduced production of infectious virus by 60–90%, depending on the particular HIV strain used.

APOL1 may exert these effects via two pathways, as shown by Popik and colleagues (Taylor, Khatua, and Popik 2014). First, APOL1 promotes nuclear translocation of transcription factor EB (TFEB), although the mechanism has not been defined. TFEB increases lysosomal biogenesis by increasing expression of genes encoding the lysosomal proteins LAMP1, LAMP2, and CD63, and thus increased endosomal activity. APOL1-

mediated alterations in endolysosomal activity may be responsible for its anti-viral activity, as blockade of endolysosomal function suppressed the antiviral activity. Second, APOL1 reduced accumulation of the regulatory and accessory HIV proteins Nef, Vif, and Vpu (Tat and Vpr were not studied); these effects would be expected to disrupt the viral life cycle. In particular, Vif levels within APOL1-over-expessing cells were depleted by degradation in lysosomes and secretion from the cells in microvesicles, possibly exosomes. Finally, Popik and colleagues made a prediction that APOL1 might suppress mTOR activity, a hypothesis that is worth testing (Taylor, Khatua, and Popik 2014).

More recently, Mclaren and colleagues confirmed the anti-retroviral properties of APOL1 (McLaren et al. 2015). They started with a bioinformatics approach, seeking genes that are shared among at least some of 9 primate species and that showed evidence for evolutionary selection, i.e. an excess of synonymous over non-synonymous changing mutations. The underlying assumption of this analysis is that genes that have demonstrate more altered codons in a way that alters the encoded amino acid are likely undergoing these changes in response to selective pressure, rather than a result of a random process. The authors found that 841 (3.9%) of 21,389 primate genes showed strong evidence positive selection. They next identified 30 genes of this set that were up-regulated during HIV infection of (human) HEK393T cells or were known from previous work to interact with HIV proteins. They selected 27 genes not previously known to interact with HIV proteins, and found that following transient transfection, 16 gene products reduced HIV infection. Four of these gene products reduced retroviral infection by >50%: APOL1, APOL3, APOL6 and TNFRS10D. These data suggest that the APOL family members, in addition to having evolved to play an anti-parasite role, also have anti-viral roles and provide an important new perspective on this gene family. Interestingly, like *APOL1*, *TNFRS10D* expression is induced by interferon, as are *APOL3* (or by the interferon-mimic poly-inosine-cytosine) (Uzureau et al. 2016) and *APOL6* (Zhaorigetu et al. 2011).

APOL1 and the molecular and cellular mechanisms of HIVAN

Mclaren and colleagues also tested the ability of the HIV gene products to reduce HIV infection with a proviral construct that lacked a combination of three HIV proteins, the regulatory protein Nef and accessory proteins, viral protein R (Vpr) and viral protein U (Vpu). In the absence of these proteins, the inhibitory effect of 8 restriction factors including APOL1 and APOL6, was increased. The authors cautioned that since the restriction factors could efficiently inhibit even wild-type HIV constructs containing the full retroviral genome, the infection-enhancing of removing these HIV genes was modest. Nevertheless, these finding do suggest that there may be a functional interaction (not necessarily a molecular interaction) between APOL1 and one more of these HIV proteins. This finding is quite interesting, as data from transgenic mouse models have implicated two of these HIV gene products (from among the six HIV regulatory and accessory genes) as a cause of HIVAN: Nef (Simard et al. 2002) (Rahim et al. 2009; Zuo et al. 2006) and Vpr (Hiramatsu et al. 2007) (Zuo et al. 2006).

Singhal and colleagues have performed a series of informative experiments that illustrate how APOL1 variants exert toxicity, or enhanced toxicity, in cultured cells and provide

insight into the pathogenesis of HIVAN. Previously they showed that an HIV construct lacking the *gag* and *pol* but encoding the six regulatory and accessory genes induces lysosomal injury in cultured human podocytes, with release of cathepsin L into the cytoplasm (Chandel et al. 2013). Recently, they studied human podocytes subjected to lentiviral infection to induce over-expression of each *APOL1* genotype (Lan et al. 2014). They found that the risk variants increased lysosomal permeability in response to various injurious stimuli, the most potent was lentiviral delivery of the same HIV construct.

Most recently, Mikulak and colleagues studied the effect of APOL1 transfection on HIV infection of cultured podocytes (Mikulak et al. 2016). The APOL1 G0 variant reduced viral accumulation, while APOL1 risk variants increased viral accumulation. They found that IL-1b increased expression of the HIV receptor dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) in podocytes, and that HIV infection itself further increased Il-1 β expression, creating a positive-feedback loop enhancing infection. In APOL1-over-expressing cells, there was increased production of Il-1β, although there were no data on whether the cells with risk variants had further increased IL1- β production. They next examined the mechanisms of HIV accumulation within the cell. They found that the APOL1 risk variants, but not the common variant, increases mRNA levels of transcription factor EB (TFEB), the master regulator of lysosomal synthesis. They concluded APOL1 risk variants promote intracellular accumulation of HIV-1 through interfering with the endolysosomal function.

Conclusions

While HIVAN is becoming less frequent as cART has become widely available globally, other glomerular diseases associated with APOL1 are becoming more common in the HIV population. There are important lessons for glomerular disease to be learned from interactions among HIV proteins, the inflammatory consequences of HIV infection, and *APOL1* variant driven gene expression.

Acknowledgments

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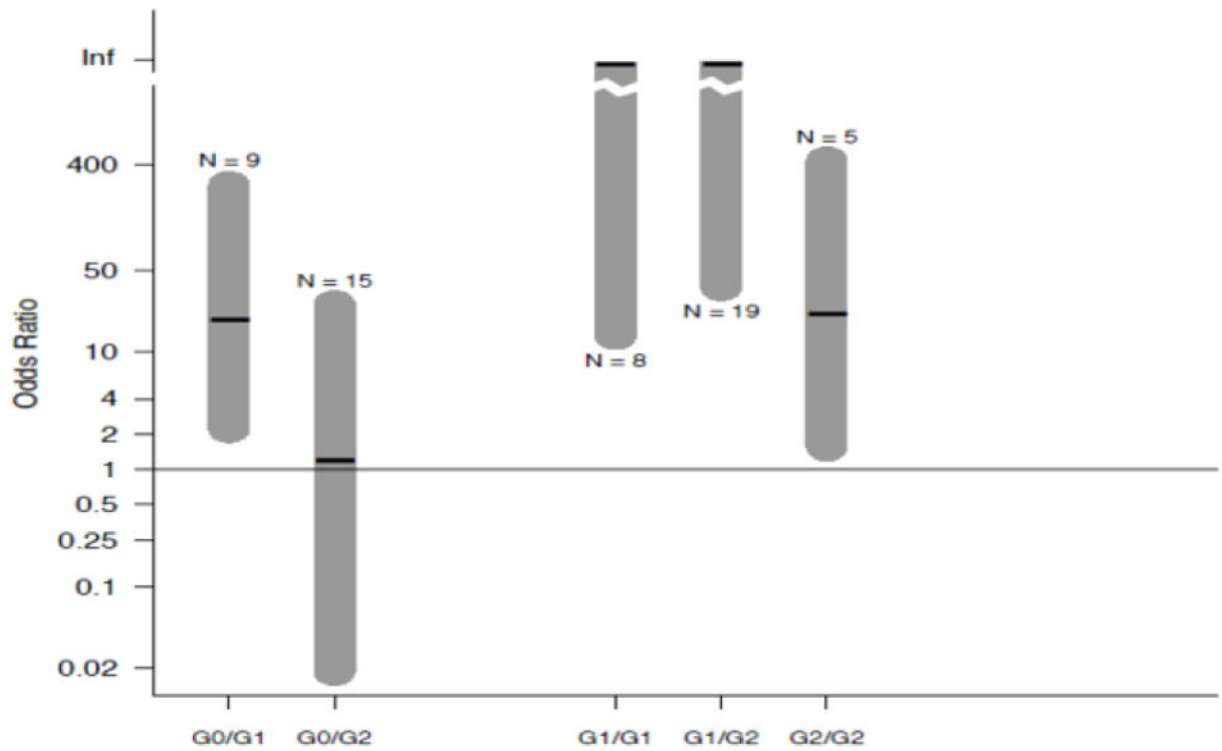
Figure 1. Effect of APOL1 in NIH and South African cohorts
Shown are the odds ratios for APOL1 and HIVAN in South Africa. On the right are the associations with two APOL1 risk alleles. On the left are the associations with one risk APOL1 risk allele. Even with small sample size, an effect can be seen for a single copy of the G1 allele but not for the G2 allele, even though sample sizes were similar. Used with permission (Kasembeli et al. 2015).

Table 1

Prevalence of APOL1 risk alleles among HIV renal histologies.

Disease	Country	N cases	*APOL1* 2 RA prevalence in reference population (HIV status)	*APOL1* 2 RA prevalence in disease	Odds ratio (CI) for kidney disease, when 2 *APOL1* risk alleles are present	Reference
HIVAN	USA	54	8% (HIV+)	72%	29 (14, 68)	(Kopp et al. 2011)
	USA	60	ND	62%	ND	(Atta et al. 2012)
	South Africa	38	3.7% (HIV+)	79%	89 (18, 912)	(Kasembeli et al. 2015)
HIVICK	USA	31	ND	3%	ND	(Fine et al. 2012)
	South Africa	49	3.7% (HIV+)	9%	2.6 (NS)	(Kasembeli et al. 2015)
HIV+ FSGS	USA	35	8% (HIV+)	63%	20 (8, 45)	(Fine et al. 2012)
	USA	203-X	ND	X	3 (1.5, 6)	(Atta et al. 2016)
	South Africa	22	3.7% (HIV+)	8%	2.1 (NS)	(Kasembeli et al. 2015)
HIV-negative FSGS	USA	217	13% (HIV-)	72%	17 (11,26)	(Kopp et al. 2011)

Shown are the results of studies that have examined the prevalence of APOL1 high-risk individuals (those carrying two *APOL1* risk alleles) among HIV+ individuals with particular renal histologies. The rates of *APOL1* two risk allele carriage for the control population are 13% in the general US African American population in the Kopp et al study, 4% in the general South African population in the Kasembeli et al study, and 8% among HIV+ African Americans lacking kidney disease in Kopp et al study. Odds ratio was calculated from data in Fine et al, using data from the HIV+ African American population, lacking kidney disease, taken from the Kopp et al study.

HIVAN, HIV nephropathy. HIVICK, HIV-associated immune complex kidney disease. ND, not determined. NS, not significant.

Table 2

Demographic and clinical associations with HIVAN and HIVICK.

	HIVAN	**HIVICK**
Black race	10.3 (1.3, 80)	NS
HIV RNA >400	11.7 (1.2, 5.2)	2.5 (1.2, 5.2)
Diabetes	NS	2.8 (1.1, 6.8)
Hypertension	NS	2.3 (1.2, 4.5)

As demonstrated by Foy and colleagues, HIV-associated nephropathy (HIVAN) and HIV-associated immune complex disease (HIVICK) have distinct patterns of association with race and with the presence of other diseases (Foy et al. 2013).

Table 3

HIV histopathologies

Without cART	With cART
HIVAN	Drug toxicities (tenofovir)
HIVICK	FSGS
	Diabetic nephropathy
	Arterionephrosclerosis

As shown, the most common renal histolopathologic findings have shifted as combined anti-retroviral therapies (cART) have come into wide-spread use.