DISCLOSURE
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JC viruria and kidney disease in APOL1 risk genotype individuals: is this a clue to a gene×environment interaction?

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APOL1 **nephropathy occurs in a minority of genetically at-risk individuals, suggesting that other factors, such as other genes or environmental factors, contribute. Divers and colleagues report that among individuals with two *APOL1* risk alleles, those with JC viruria are less likely to manifest kidney disease compared with those lacking JC viruria. These data might suggest that JC virus infection confers protection against glomerular injury, perhaps by altering cell function or generating immunity against a related polyomavirus.**

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The identification of two coding-region variants in *APOL1*, encoding apolipoprotein L1 was a major advance in understanding why African-Americans experience more glomerular disease.[1,2] In all the kidney diseases examined to date, the effect is strongly recessive, with two copies of the variant alleles (G1/G1, G2/G2, or G1/G2) increasing risk; there is a small effect of a single risk variant that has not reached statistical significance in any single study. Risk is increased for several kidney diseases, including HIV-associated nephropathy (odds ratio (OR) 29),[3] focal segmental glomerulosclerosis (OR 17),[3] and hypertension-attributed kidney disease, which is perhaps better termed arterionephrosclerosis (the OR ranges from 2.5 for AASK (African-American Study of Kidney Disease and Hypertension) study participants[4] to 7.3 for end-stage kidney disease[1]); allograft loss following deceased donor transplant (OR 3.8);[5] sickle nephropathy (OR 3.4);[6] and most recently, collapsing glomerulopathy in lupus nephritis (OR 5.4).[7] Among population studies, risk allele frequency is highest among the Yoruba people of West Africa, reaching 60%. This high frequency is explained by the protection afforded by the risk alleles against *Trypansoma brucei rhodesiense*. We have only very approximate estimates of the risk of glomerular disease among individuals with two *APOL1* risk variants; in individuals with HIV-1 infection, in the absence of anti-viral therapy, the lifetime risk is estimated as 50%; in focal segmental glomerulosclerosis, the lifetime risk is estimated at 4%;[3] and the risk for clinically manifest arterionephrosclerosis is probably several fold higher.

These powerful genetic associations raise many important research questions. What are the cellular mechanisms by which the *APOL1* variants induce kidney disease? Within kidney, ApoL1 expression has been localized to the podocyte, arteriolar endothelium and with glomerular disease, to the arterial and arteriolar media;[8] how does this localization relate to glomerular injury? We have no insight into the cell biology of *APOL1*-associated glomerular injury. As only a minority of individuals with two *APOL1* risk alleles develop glomerular disease, what are the contributing factors that interact with the risk genotype? Diseases with a genetic

component and with low penetrance are considered complex genetic diseases, in which a second factor (genetic or environmental) interacts with the disease-associated gene variants. As pointed out by Freedman *et al.*[9] many years ago, some African-American kindreds have multiple affected members with kidney disease and manifest inheritance pattern suggests a complex genetic disease—and we now understand that many and probably most of these families have *APOL1* risk variants causing the kidney disease. Among gene×gene interactions, Freedman *et al.* carried out a genome-wide association study in African-Americans with non-diabetic nephropathy and reported several interacting single-nucleotide polymorphisms; the strongest associations were in or near *NPHS2*, encoding podocin (OR 0.72, $P=0.004$), *SUCLA2* (OR 0.27, $P=0.0002$), *PRKCE* (OR 2.22, $P=0.0005$), and *ENOX1* (OR 0.31, $P=0.0005$).[10] The same group found an interaction between *FRMD3* and *MYH9* (the gene lying immediately centromeric to *APOL1*, encoding non-muscle myosin heavy chain 9 and initially identified as the source of the chromosome 22 association with African-American kidney disease susceptibility; there were weaker interactions between *FRMD3* and *APOL1*.

In the current issue of *Kidney International*, Divers *et al.*[11] have addressed the hypothesis that among African-Americans with non-diabetic nephropathy, there might be a relationship between JC viruria and kidney disease among those with a genetic risk for kidney disease, two *APOL1* nephropathy risk alleles. Specifically, they have hypothesized that the presence of the *APOL1* risk genotype might predispose to JC viruria, and this might be an environmental cofactor that would interact with the genetic risk locus to further increase the risk for kidney disease. The authors were perhaps surprised to learn that while there was an association, it was the inverse of the hypothesis—*APOL1* two-risk allele subjects who had detectable JC viruria were *less likely* to manifest kidney disease than those who lacked JC viruria. The authors propose two possible explanations. First, the presence of JC virus in the kidney might protect against other viruses that cause nephropathy, perhaps via shared antigenic epitopes. Second, JC virus might alter cellular function in such a way that reduces glomerular injury from other sources, either viral or toxic. If the other virus is a polyomavirus, what might that virus be?

Polyomaviruses are small viruses containing a circular, double-stranded DNA genome ranging in size from 4.5 to 5.4 kb; the family name derived from the finding that they caused multiple tumors in rodents. The first human polyomaviruses were reported in the same issue of the journal *Lancet* in 1971, BK virus isolated from the urine of a renal transplant patient[12] and JC virus from the brain of a patient with multifocal leukoencephalopathy[13]. Infections with the polyomaviruses BK virus and JC virus are generally acquired in childhood.

BK virus establishes latency in the kidney at the time of primary infection, which occurs in childhood and may be asymptomatic or associated with mild upper respiratory tract infection. Under conditions of immunosuppression, replicating virus is most likely to be present within the distal tubular epithelium, causing interstitial nephritis. Two case reports suggest that BK virus can also (rarely) infect glomerular parietal epithelial cells; cytopathic changes were seen in parietal cells in 17% of kidney transplants with BK interstitial nephritis[14] and a case report suggested an association with crescentic glomerulonephritis.[15] Like BK, JC virus infection is common in childhood; the virus establishes latency in brain oligodendrocytes and renal tubular cells and, to a lesser extent, in B lymphocytes. JC virus is shed from the urine of healthy individuals, and interestingly, the rates are higher than for BK virus.[16] Nevertheless, compared with BK virus, JCV is much less commonly associated with kidney disease, for reasons that are not well understood. With immunosuppression, JC virus has been rarely associated with interstitial nephritis, and in a single case report JC virus was associated with infection of parietal epithelial cells and perhaps podocytes, although overt glomerular pathology was not described.[17]

After a lag of 25 years, the past 6 years have seen the discovery of nine new human polyomaviruses, as PCR-based techniques have been applied to samples obtained from diverse populations and clinical settings. These include KI virus (named after the Karolinska Institute),[18] WU virus (named after the Washington University),[19] Merkel cell virus (MC virus),[20] HPy6 and HPy7,[21] Trichodysplasia-associated Py (HPy8),[22] HPy9,[23,24] Malawi polyomavirus,[25] and St Louis polyomavirus.[26]

As shown in Table 1, the source of the new polyomaviruses has been most commonly respiratory tract, skin, or stool. Their role in human disease remains speculative. The strongest case for a pathogenic role can be made for the MC virus, as the tumors show clonal integration of the virus (i.e. the cells from a particular tumor have virus integrated at single genomic location) and the MC tumors are associated with immunodeficiency (suggesting a predisposing factor). The seroprevalence rates for human polyomaviruses tend to be $>50\%$, as summarized in Table 1 (data from the review by Decaprio and Garcea[27]). Thus, human polyomavirus infections are common infections and individuals with normal immune systems are able to suppress viral replication, to a large extent but not always completely. By contrast, individuals with compromised immune systems are at risk for polyomavirus-associated disease, typically due to reactivation of latent infection, particularly with BK virus, JC virus, and MC polyomavirus.

Four polyomaviruses are known to be present in urine, including BK virus, JC virus, MC virus, and HPyV9 (and HPvY7 in urine from a child following organ transplantion[28]), although the absence of data from the more recently discovered viruses does not preclude that they could infect the kidney. As noted above, BK virus and JC virus are well-recognized causes of interstitial nephritis. Husseiny *et al.*[29] reported that low levels of MC virus