



# APOL1 Gene — Implications for Systemic Lupus Erythematosus

It is well recognized that African Americans of sub-Saharan African ancestry have nearly a 4-fold increased prevalence of endstage kidney disease (ESKD) over European Americans<sup>1,2,3,4</sup>. In 2008, two coding alleles in the apolipoprotein L1 gene (*APOL1*), G1 and G2, were discovered to account for the majority of excess risk in progressive nondiabetic kidney disease in African Americans<sup>1,2,3,5</sup>. The several forms of *APOL1*-associated kidney disease include focal segmental glomerulosclerosis (FSGS), human immunodeficiency virus-associated nephropathy (HIVAN), hypertension-attributed ESKD, and sickle cell nephropathy<sup>5,6,7,8</sup>. There is a strong biallelic effect observed such that a high-risk genotype defined as the presence of 2 *APOL1* risk alleles confers the strongest risk for HIVAN in the United States<sup>7</sup> with an OR of 29 (95% CI 13–68), and an OR of 89 (95% CI 18–912) in South Africa<sup>9</sup>. This observation of stronger adverse kidney outcomes associated with *APOL1* risk alleles was the rationale for a report by Vajgel, *et al*<sup>10</sup> that appears in this issue of *The Journal*.

Their study involved genotyping *APOL1* G1 and G2 risk alleles in 201 nonwhite Brazilian patients with lupus nephritis (LN) and 222 healthy blood donors. Because of the low *APOL1* biallelic frequency in LN cases (2%), the authors had limited power to test biallelic effects and instead examined monoallelic *APOL1* risk allele effect on LN outcomes. The authors observed a higher prevalence of LN patients with lower estimated glomerular filtration rates (eGFR; chronic kidney disease stages 4 and 5) of persistent duration (> 6 mos) in those with 1 *APOL1* risk allele compared to those with none<sup>10</sup>.

The Vajgel, *et al* findings are consistent with prior studies of *APOL1* risk allele effects on LN renal functional outcomes. In a study of 855 African American systemic lupus erythematosus (SLE) patients with LN-ESKD and 534 African American SLE patients without nephritis, *APOL1* high-risk genotype was associated with progression to ESKD, with an OR 2.72 (95% CI 1.76–4.19,  $p = 6.23 \times 10^{-6}$ )<sup>3</sup>. That study also reported a shorter time from SLE onset

to ESKD among those with an *APOL1* high-risk genotype ( $5.5 \pm 6.1$  yrs) compared to those with 1 or no risk alleles ( $7.9 \pm 7.3$  yrs,  $p = 0.01$ )<sup>3</sup>. Yet Vajgel, *et al*'s study<sup>10</sup>, and other studies, observed no association between *APOL1* risk alleles and LN risk itself, assuming sufficient power to detect an effect on LN risk similar to that on ESKD<sup>11,12</sup>.

In African Americans, the *APOL1* risk allele frequency is about 36% and the prevalence of the high-risk *APOL1* genotype is 13%<sup>6,13</sup>. In the Brazilian nonwhite population studied by Vajgel, *et al*, the *APOL1* risk allele frequency was 9% among patients with LN, and 8% among non-SLE controls ( $p = 0.44$ ). This high frequency of alleles with large effects suggests that natural selection for the beneficial *APOL1* effects is at play. Circulating *APOL1* likely kills the trypanosome by lysis<sup>14</sup>. This includes the parasite *Trypanosoma brucei rhodesiense* causing trypanosomiasis (African sleeping sickness), which evolved to develop a virulence factor, serum-resistant activity (SRA). SRA binds to and inactivates *APOL1*, enabling the parasite to escape the human, host defenses and survive. High-risk *APOL1* genetic variants result in an encoded *APOL1* protein, protected from SRA binding, providing a selective advantage<sup>4,13</sup>.

The high frequency of *APOL1* G1 and G2 alleles is also in part due to incomplete penetrance of their deleterious renal effects. Most people carrying the high-risk genotype never develop significant kidney disease<sup>4,7</sup>. This observation along with the recognition that *APOL1* progressive CKD spans different systemic diseases suggests the possibility of a “2-hit” pathogenic process<sup>4</sup>. A potential second hit interacting with *APOL1* risk genotype may be systemic disease such as HIV or SLE<sup>15</sup>.

Both HIV infections and SLE are diseases characterized by elevated type I interferon (IFN). HIV is a potent inducer of IFN and other innate antiviral immune responses. SLE is a type I IFN-driven autoimmune disease. There have also been reports of FSGS patients with a high-risk *APOL1* genotype, treated with IFN, who developed collapsing glomerulopathy<sup>15</sup>. In 2019 there was a case report of an

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African American boy with SAVI (stimulator of IFN genes–associated vasculopathy with onset in infancy) — a disease of endogenous overproduction of type I IFN, *APOLI* high-risk genotype, and collapsing glomerulopathy. These reports all implicate IFN as the common, key link between *APOLI* and collapsing glomerulopathy<sup>16</sup>.

The most extreme histologic manifestation of *APOLI*-associated nephropathy is collapsing glomerulopathy. First described in HIVAN, this aggressive lesion is characterized by segmental or global collapse and sclerosis of the glomerular tufts, with clinical manifestations of nephrotic syndrome, renal insufficiency, and rapid progression to ESKD<sup>13</sup>. There are an increasing number of reports of collapsing glomerulopathy in LN, in the absence of infection<sup>17</sup>. Some of these reports make the link between *APOLI* high-risk genotype and collapsing glomerulopathy in SLE<sup>18,19</sup>. One study identified 26 cases of collapsing glomerulopathy among 546 renal biopsies from African American patients with SLE. They observed an OR 5.4 (95% CI 2.4–12.1) for developing collapsing glomerulopathy for the *APOLI* high-risk genotype ( $p < 0.001$ ) compared to 1 or no risk alleles<sup>18</sup>. In the Vajgel, *et al* paper, the small number of patients with collapsing glomerulopathy precluded examination of the *APOLI* association in their Brazilian cohort<sup>10</sup>.

Prior studies have investigated the associations between chronic kidney disease, cardiovascular disease (CVD), and *APOLI* risk haplotypes, with differing results. In a single-center cohort study of 113 African American patients with SLE, the *APOLI* risk allele frequency was 40%, and the frequency of the high-risk genotype was 13%<sup>20</sup>. Using chart review to assess and create composite indices for CVD endpoints, they observed that atherosclerotic CVD (defined as abdominal aortic aneurysm, angina, carotid artery disease, myocardial infarction, coronary artery disease, peripheral vascular disease, stroke, or vascular calcifications on imaging) was present in 30% of the cohort. The study reported more prevalent atherosclerotic CVD in those with 1 or more *APOLI* risk alleles, compared to those with none (OR 7.1, 95% CI 2.1–24.0,  $p = 0.002$ ). Their models adjusted for smoking status, ESKD, body mass index, and hypertension. ESKD was present in 20% of those with a high-risk genotype, compared with 2–8% of those with 0 or 1 *APOLI* risk alleles. In contrast, a large metaanalysis of 21,305 participants of African American ancestry, from 8 cohorts, did not find an association between *APOLI* high-risk genotype (prevalence 13%) and incident CVD or all-cause mortality<sup>21</sup>. This was after accounting for multiple risk factors for CVD and death, including kidney function (eGFR). Overall, there is limited evidence for a direct effect of *APOLI* risk alleles on CVD outcomes independent of kidney function.

In recent years, we have learned a great deal about the relationship between *APOLI*, SLE, and kidney disease. Future research focused on how this knowledge affects

prevention, prognosis, and therapy offers hope for improved care and outcomes for people with SLE at high risk of *APOLI*-associated disease.

**LINDA T. HIRAKI**, MD, FRCPS, ScD,

Assistant Professor,  
Pediatrics and Epidemiology,  
Dalla Lana School of Public Health,  
University of Toronto, and  
Clinician Scientist,  
Division of Rheumatology,  
and Scientist, Child Health Evaluative Sciences  
and Genetics and Genome Biology,  
Research Institute,  
The Hospital for Sick Children,  
Toronto, Ontario, Canada.

Address correspondence to Dr. L.T. Hiraki, PGCR, 686 Bay St., Toronto, Ontario M5G 0A4, Canada. E-mail: Linda.hiraki@sickkids.ca. Dr. Hiraki is supported by research grants from the Canadian Institute of Health Research and The Arthritis Society.

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