Apolipoprotein G1 and G2 Variants May Partially Explain a Higher Prevalence of Lupus-Nephritis ESRD in African Americans

Written by Rita Buckley

African Americans suffer from lupus-related kidney failure at higher rates compared with individuals without recent African ancestry [Byrne C et al. *Am J Kidney Dis* 1994; Satko SG et al. *Kidney Int Suppl* 2005]. Robert P. Kimberly, MD, University of Alabama at Birmingham, Birmingham, Alabama, USA, presented findings from A National Consortium to Explore the Genotypic Basis for End-Stage Renal Disease (ESRD) in Lupus [1RC2-AR058951; P01-AR049084; P01-AI083194].

To untangle biological and socioeconomic factors, the researchers took a genetic approach, comparing people of African American ancestry with lupus/ESRD to those with lupus and no nephritis.

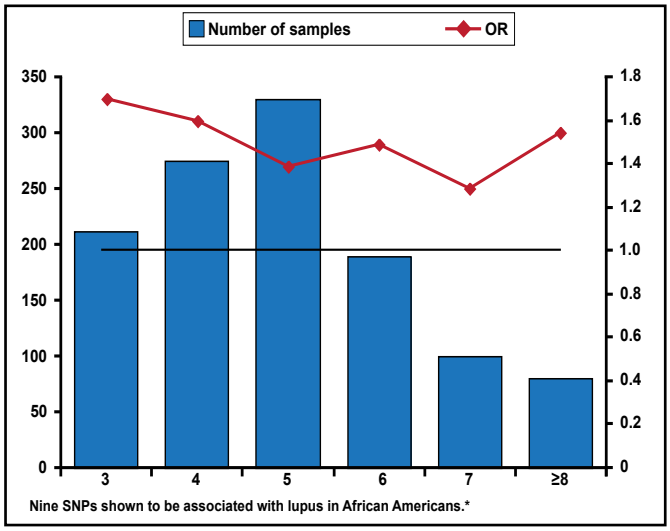
The G1 and G2 coding variants in the apolipoprotein L1 gene (*APOL1*) are strongly and reproducibly associated with focal segmental glomerulosclerosis, HIV-associated collapsing glomerulopathy, and hypertension-attributed ESRD in African Americans [Genovese G et al. *Science* 2010; Tzur S et al. *Hum Genet* 2010]. To explore the role of *APOL1* in lupus nephritis (LN)-related ESRD, the Consortium tested for associations between *APOL1* risk variants and LN-ESRD in a national sample of unrelated African Americans with systemic lupus erythematosus (SLE).

The sample included 668 African American subjects with LN-ESRD (456 with kidney biopsy documentation, 212 physician-reported) and 697 African American subjects with longstanding SLE lacking LN (mean duration of disease was 10.1 years). In cases with LN-ESRD, 87.1% were female, 89% received cytotoxic therapy, mean ± SD age at SLE onset was 26.6±0.4 years and duration of SLE diagnosis to ESRD was 7.2±0.3 years with the median at 5 years. In non-nephritis SLE subjects, 93.5% were female with SLE onset at 35.2±0.8 years of age.

Contrasting all cases with and without ESRD, *APOL1* risk variants were significantly associated with LN-ESRD (OR, 2.35; 95% CI, 1.77 to 3.3; $p=4.25E^{-9}$); significant differences in association were not observed when comparing cases with or without kidney biopsy documentation to SLE subjects without LN. The duration of SLE onset to ESRD for those with the G1/G2 variants was 5.49±0.54 years (median=4). For those without the variants, it was 7.78±0.37 years (median=6; $p<0.05$).

The study demonstrates strong association between both *APOL1* G1 and G2 variants and LN-associated ESRD in African Americans. It appears likely that *APOL1* G1 and G2 coding variants, which are rare in European populations, contribute to nephropathy progression in LN-ESRD, as well as other nondiabetic etiologies of ESRD. These variants and their higher prevalence in those with African ancestry may explain, in part (Figure 1), a higher prevalence of severe LN in African Americans.

Figure 1. The Genetic Load Associated with Lupus in African Americans.



*Source: Vaughn SE et al. *J Leukoc Biol* 2012. SNP=single-nucleotide polymorphism. Reproduced with permission from RP Kimberly, MD.

Genetic Variations Do Not Account for Variable Response to Mycophenolate Mofetil in Lupus Nephritis

Written by Wayne Kuznar

Genetic testing for variants of inosine monophosphate dehydrogenase (IMPDH) isoforms will not predict clinical response to mycophenolate mofetil (MMF) in the treatment of lupus nephritis.

The Study of Mycophenolate Mofetil in Management of Patients with Lupus Nephritis [ALMS] demonstrated the efficacy of MMF for induction and maintenance of response in lupus nephritis, but response was not uniform, leading to a search for predictors of efficacy. The work was supported by a National Institutes of Health grant (5R01AR55088 to Robert Clancy).

Noa Schwartz, MD, New York University, New York, New York, USA, described MMF as a prodrug of mycophenolic