End-Stage Renal Disease in African Americans With Lupus Nephritis Is Associated With *APOL1*

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Abstract

Objective—Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE) that exhibits familial aggregation and may progress to end-stage renal disease (ESRD). LN is more prevalent among African Americans than among European Americans. This study was undertaken to investigate the hypothesis that the apolipoprotein L1 gene (*APOL1*) nephropathy risk alleles G1/G2, common in African Americans and rare in European Americans, contribute to the ethnic disparity in risk.

Methods—APOL1 G1 and G2 nephropathy alleles were genotyped in 855 African American SLE patients with LN-ESRD (cases) and 534 African American SLE patients without nephropathy (controls) and tested for association under a recessive genetic model, by logistic regression.

Results—Ninety percent of the SLE patients were female. The mean ± SD age at SLE diagnosis was significantly lower in LN-ESRD cases than in SLE non-nephropathy controls (27.3 ± 10.9 years versus 39.5 ± 12.2 years). The mean ± SD time from SLE diagnosis to development of LN-ESRD in cases was 7.3 ± 7.2 years. The G1/G2 risk alleles were strongly associated with SLE-ESRD, with 25% of cases and 12% of controls having 2 nephropathy alleles (odds ratio [OR] 2.57, recessive model $P = 1.49 \times 10^{-9}$), and after adjustment for age, sex, and ancestry admixture (OR 2.72, $P = 6.23 \times 10^{-6}$). The age-, sex-, and admixture-adjusted population attributable risk for ESRD among patients with G1/G2 polymorphisms was 0.26, compared to 0.003 among European American patients. The mean time from SLE diagnosis to ESRD development was ~2 years earlier among individuals with *APOL1* risk genotypes ($P = 0.01$).

Conclusion—*APOL1* G1/G2 alleles strongly impact the risk of LN-ESRD in African Americans, as well as the time to progression to ESRD. The high frequency of these alleles in African Americans with near absence in European Americans explains an important proportion of the increased risk of LN-ESRD in African Americans.

Systemic lupus erythematosus (SLE) is an auto-immune disorder with a markedly increased prevalence among women and among individuals of African ancestry. Genome-wide association studies (GWAS) have identified multiple susceptibility loci for SLE (1–6), as well as for the presence of anti-RNA binding proteins (7) and anti–double-stranded DNA antibodies (8). Lupus nephritis (LN) is a common and potentially severe complication of SLE, which is initiated by immune complex deposition in the renal microvasculature. As with SLE overall, African Americans have a higher prevalence of LN than European Americans (9–11), with lack of equal access to care having often been suggested as a contributing cause of the ethnic disparity in prevalence (12). Familial clustering of LN and LN-associated end-stage renal disease (LN-ESRD) has been observed (13), suggesting that genetic factors contribute not only to the risk of SLE but also to LN-ESRD. Risk alleles in the Fcγ receptor and other genetic regions have been implicated in LN susceptibility (14–16). A subset of individuals with LN ultimately develop progressive nephropathy or ESRD;

thus, factors associated with progressive renal damage are of critical importance and remain unknown.

Two coding alleles in the apolipoprotein L1 gene (*APOL1*), G1 and G2, are strongly associated with several etiologies of progressive nondiabetic nephropathy in African Americans, including focal segmental glomerulosclerosis (FSGS), human immunodeficiency virus–associated collapsing glomerulopathy (HIVAN), hypertension-attributed ESRD, focal global glomerulosclerosis with interstitial and vascular changes (FGGS), and sickle cell nephropathy; ~12% of African Americans in the general population have 2 risk alleles and are at heightened risk of nephropathy (17–20). These *APOL1* alleles are less strongly associated with mild forms of kidney disease (21–23), including LN without progression to ESRD (24,25).

The role of alleles in *APOL1* and other genes has not yet been studied in a large sample of African Americans with LN-ESRD. Herein we report the results of a study by a national consortium, in which *APOL1*-mediated genetic risk for LN-ESRD was compared in a population-based sample of African American SLE cases who were receiving dialysis or had undergone kidney transplantation versus African American SLE patients without nephropathy (controls).

PATIENTS AND METHODS

Study populations

African American subjects with SLE and LN-ESRD were identified through the rheumatology, nephrology, and kidney transplant services of 18 academic referral centers, the Center for Medicare and Medicaid Services, and via a validated query approach using i2b2 (Informatics for Integrating Biology and the Bedside; based at Partners HealthCare System, Boston, MA). Patients with LN-ESRD (cases) had a clinical diagnosis of SLE and were either receiving dialysis or had undergone kidney transplantation. Additionally, cases were required to have World Health Organization class III, IV, or V disease in the native kidney, documented in a biopsy report (reviewed by one of the authors [BIF]) or 2) nephropathy attributed to SLE by a physician based on clinical grounds or prior kidney biopsy, documented in the medical record without an available pathology report. African American controls were drawn from the PROFILE multicenter national consortium cohort and had SLE without proteinuria, abnormal urinary sediment (casts), or renal biopsy evidence of nephropathy (Systemic Lupus International Collaborating Clinics/American College of Rheumatology criteria for kidney involvement) (26).

Genotyping

Two single-nucleotide polymorphisms (SNPs) in the *APOL1* G1 nephropathy risk allele (rs73885319 and rs60910145) and an indel for the G2 risk allele (rs71785313) were genotyped in all cases and controls using a custom assay designed at the Wake Forest School of Medicine Center of Genomics and Personalized Medicine on the Sequenom platform. The G1 and G2 genotype calls were visually inspected for quality control.

Statistical analysis

The individuals included in this analysis all passed the quality control analysis for an ongoing GWAS for LN-ESRD, assessed using an Illumina chip (27). Admixture estimates were computed using a linkage disequilibrium–pruned ($r^2 < 0.2$) set of high-quality SNPs (i.e., <5% missing genotype data, no differential missingness between cases and controls, no significant deviation from Hardy-Weinberg equilibrium, no excess heterozygosity), and self-reported and genotypic ancestry were consistent for all individuals in the analyses described herein. Demographic characteristics were compared between LN-ESRD cases and SLE controls using either logistic regression, linear regression, or Wilcoxon's signed rank test. Compound G1/G2 homozygotes were defined as individuals who were homozygous for the G1 risk allele, homozygous for the G2 risk allele, or heterozygous for the G1 and G2 risk alleles. To test for association between G1/G2 compound risk and LN-ESRD, a logistic regression model was computed, with adjustment for age at SLE onset, sex, and admixture proportion (computed using the program Admixture) (28). The corresponding GWAS adjusted for these admixture estimates and using the same model as reported herein had an inflation factor of 0.99. Thus, after adjustment for these admixture estimates, there is no evidence of inflation of the tests of association. Because information on age at onset of SLE was missing for a subset of cases, the analysis was repeated with adjustment for admixture only; in this analysis the sample size could be maximized and the estimates of effect could be directly compared. To meet the distributional assumptions of conditional normality and homogeneity of variance for linear regression, age at SLE onset and duration from SLE onset to ESRD onset were square root transformed when analyzed as the response variable.

To estimate the crude (unadjusted) attributable risk, we used the standard formula for case–control designs:

$$\text{Attributable risk} = \frac{n_1 m_0 - m_1 n_0}{m_0 n}$$

where n_0 and n_1 denote the number of cases without and with the G1/G2 compound risk, respectively, and m_0 and m_1 denote the number of controls without and with the G1/G2 compound risk, respectively; here, $n_0 + n_1 = n$. The odds ratio (OR)–based population attributable risk (29), using the rare disease assumption, was computed as follows:

$$\% \text{ population attributable risk} = \frac{b \times (\text{OR} - 1.0)}{b \times (\text{OR} - 1.0) + 1.0}$$

where b is the estimated proportion of individuals with the G1/G2 compound risk genotype.

RESULTS

The study sample comprised 1,389 African Americans with SLE (855 cases with LN-ESRD and 534 non-nephropathy controls). The proportion of women in the sample was slightly higher among controls than among cases (93% versus 88%; $P = 0.0025$) (Table 1), consistent with the reported increased incidence of LN-ESRD in men (30). Eighty-five

percent of the LN-ESRD cases had received cytotoxic therapy and 9% reported having a first-degree relative with ESRD (data unavailable for SLE non-nephropathy controls). The mean ± SD age at onset of SLE was $27.3 ± 10.9$ years and $39.5 ± 12.2$ years in cases and controls, respectively ($P = 4.21 × 10^{-42}$). The mean duration from SLE onset to ESRD onset in cases was $7.3 ± 7.2$ years. Among controls, the mean duration from SLE diagnosis to the most recent encounter was 10.1 years.

More than 95% of the LN-ESRD cases had a diagnosis of hypertension. Diagnosis of LN was based on available kidney biopsy report in 571 (66.8%) of the cases and review of medical records in 284 (33.2%).

APOL1 G1/G2 genotypes varied based on ESRD status, as shown in Table 2. The African admixture proportion was highest in individuals with 2 copies of the risk alleles for either G1 or G2. Dichotomization of the study population into compound homozygotes for the risk alleles versus heterozygotes and homozygotes for the wild-type allele (i.e., recessive genetic model for risk alleles) revealed a significant association with LN-ESRD (Table 3). Without adjustment for age, sex, and admixture proportion, the logistic model yielded an estimated OR of 2.57 (95% confidence interval 1.89–3.50) for *APOL1* association with LN-ESRD (recessive model; $P = 1.49 × 10^{-9}$). Adjustment for these covariates markedly reduced the sample size but still yielded a highly significant association with LN-ESRD. In fact, adjusting only for global measures of European American admixture in these samples increased the magnitude of the effect to an OR of 2.80 and still yielded a highly significant association ($P = 2.21 × 10^{-8}$), despite reducing the sample size by 26%. Comparison of LN-ESRD cases with and those without available kidney biopsy results revealed no statistically significant differences in the *APOL1* association ($P = 0.90$); specifically, the OR was 2.46 for LN-ESRD cases without an available kidney biopsy report and 2.54 in cases with a kidney biopsy report.

From these estimates we could compute crude (unadjusted) and OR-based estimates of attributable risk. In the African Americans, the crude estimate of attributable risk was 0.155. Under the rare disease assumption and without adjustment for covariates, the OR-based population attributable risk was 0.195. After adjustment for age, sex, and population admixture estimates, the OR-based population attributable risk was 0.256. The latter increase in the attributable risk estimate is consistent with the increase in the OR from 2.57 to 2.72 with adjustment for admixture estimates. The frequency of the G1/G2 risk genotype is on the order of 0.002 in samples from European Americans. Assuming the same OR (2.72), the same OR-based calculations suggest a G1/G2 attributable risk for LN-ESRD in European Americans to be on the order of 0.0034. These estimates suggest that the attributable risk is ~75 times greater in African Americans than in European Americans, based purely on allele frequency.

If the G1/G2 alleles in *APOL1* function as a progressor gene for lupus ESRD, one would anticipate that, on average, the time to onset of ESRD would be reduced among individuals with 2 copies of the risk alleles. Our data revealed a 2-year reduction in the time from diagnosis of SLE to the onset of ESRD in this group *(P = 0.01)* (Table 4), representing a 26% shorter mean duration and a 33% shorter median duration compared with patients

having 0 or 1 allele. Specifically, as the number of risk alleles increased, the duration of time from SLE onset to ESRD onset decreased (mean $\pm$ SD 8.8 $\pm$ 7.8 years, 7.2 $\pm$ 6.8 years, and 5.8 $\pm$ 6.6 years among patients with no risk allele, 1 risk allele, and 2 risk alleles, respectively; P for trend = 0.0004). After adjustment for admixture and ESRD status, there was a weak trend toward individuals with 2 G1/G2 risk alleles having a modestly earlier age at SLE diagnosis (P = 0.0840).

DISCUSSION

To our knowledge, this is the first report of an association between *APOL1* nephropathy risk alleles and severe LN with progression to ESRD in the high-risk African American population. Although a large proportion of patients with SLE develop kidney involvement (hematuria, proteinuria, and/or declining kidney function), most do not progress to development of ESRD. There is strong evidence in support of the notion of an inherited contribution to LN, including far higher rates of LN and LN-ESRD in populations with African ancestry relative to European ancestry, and strong familial aggregation. Delineation of genetic factors that lead to ESRD in patients with LN will likely enrich our understanding of the etiology of progressive LN and improve risk prediction, and may ultimately yield therapeutic targets to prevent progression to end-stage disease.

Because renal damage is one of the main predictors of mortality in SLE, the magnitude of the impact of the *APOL1* G1/G2 alleles on LN-ESRD is very important. The OR-based attributable risk of 0.26 is greater than any individual such estimate for an SLE risk allele, including any individual SNP allele in the major histo-compatibility complex. Given the relative allele frequencies of the G1 and G2 risk alleles across various ethnicities, a large proportion of the ethnic disparity in LN-ESRD burden among individuals of African descent can be attributed to these alleles. Other factors contribute to this disparity as well, but genetic factors, and specifically the *APOL1* alleles, need to be taken into consideration in studies that aim to more accurately characterize additional factors that might be targets for intervention.

The findings reported herein are consistent with the hypothesis that the G1/G2 alleles in *APOL1* accelerate progression to ESRD (31). The difference of 2 years in the median time from diagnosis of SLE to development of ESRD represents an important 33% shorter median time from SLE onset to ESRD development in patients with versus those without the risk G1/G2 genotype. Extensions of these data are relevant with regard to kidney transplantation. The likelihood of donating a kidney to a relative with ESRD as opposed to an unrelated individual is higher among African Americans than among European Americans (32). Kidneys from deceased donors harboring 2 *APOL1* nephropathy alleles have been shown to fail more rapidly after transplantation than those from deceased donors with 0 or 1 risk alleles (33).

Our data revealed that membranous, focal proliferative, and diffuse proliferative forms of LN were more likely to progress to ESRD; only a few patients with the LN–collapsing glomerulopathy lesion (34) were identified in our population-based series. In a previous study of a small number of patients at Wake Forest School of Medicine, we detected

association of the *APOL1* gene with LN-ESRD, which we were unable to replicate after including additional cases with milder (non-ESRD) forms of LN (24). The present study and the study by Larsen et al (34) confirm that the association of alleles of the *APOL1* gene with LN is limited to the most aggressive forms that are more likely to progress to ESRD. This is consistent with reports of patients with other nephropathies such as hypertension-attributed disease and in population-based studies of African Americans (20–22).

We elected not to test specific histologic variants or subtypes of LN for an association because renal lesions may change over time, renal biopsies were not interpreted by a single pathologist, and 85% of the LN-ESRD cases had received cytotoxic therapy (treatment may alter the findings on kidney biopsy). The exclusion of cases with physician-reported SLE and ESRD with biopsy evidence of idiopathic FSGS, HIVAN, or other non–SLE-associated kidney diseases from the analysis strengthens the likelihood of a true association. Additionally, the consistent association results in individuals without available kidney biopsy reports support the assumption that LN was the cause of their ESRD. We could not assess the effect of renin–angiotensin–aldosterone system (RAAS) blockade on risk for progression of LN; however, previous studies failed to demonstrate marked improvement in progression of *APOL1*-associated nephropathy to ESRD with intensive blood pressure control or RAAS inhibition (20).

In conclusion, this large population-based study of African American patients with LN provides strong evidence of an association between LN-ESRD and the *APOL1* G1 and G2 nephropathy risk alleles. These findings extend the spectrum of *APOL1*-associated non-diabetic kidney disease by adding progressive LN to the list that already includes FSGS, FGGS (hypertension attributed), HIVAN, and sickle cell nephropathy. Furthermore, our results support the hypothesis that the G1 and G2 alleles of the *APOL1* gene mediate progression of LN, as the association with ESRD was stronger than previously described associations with disease that was nonprogressive as manifested by mildly decreased kidney function or modest albuminuria. Although the precise mechanism by which *APOL1* contributes to development of severe nephropathy remains unknown, inhibition of the effect of these genetic alleles may assist in slowing progressive renal injury in a broad spectrum of nondiabetic kidney diseases, including LN.

Acknowledgments

References

1. Kozyrev SV, Abelson AK, Wojcik J, Zaghlool A, Linga Reddy MV, Sanchez E, et al. Functional variants in the B-cell gene BANK1 are associated with systemic lupus erythematosus. Nat Genet. 2008; 40:211–6. [PubMed: 18204447]

2. Harley JB, Alarcon-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, Moser KL, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet. 2008; 40:204–10. [PubMed: 18204446]

3. Hom G, Graham RR, Modrek B, Taylor KE, Ortmann W, Garnier S, et al. Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX. N Engl J Med. 2008; 358:900–9. [PubMed: 18204098]

4. Graham RR, Cotsapas C, Davies L, Hackett R, Lessard CJ, Leon JM, et al. Genetic variants near TNFAIP3 on 6q23 are associated with systemic lupus erythematosus. Nat Genet. 2008; 40:1059–61. [PubMed: 19165918]

5. Han JW, Zheng HF, Cui Y, Sun LD, Ye DQ, Hu Z, et al. Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. Nat Genet. 2009; 41:1234–7. [PubMed: 19838193]

6. Yang W, Shen N, Ye DQ, Liu Q, Zhang Y, Qian XX, et al. Asian Lupus Genetics Consortium (ALGC). Genome-wide association study in Asian populations identifies variants in ETS1 and WDFY4 associated with systemic lupus erythematosus. PLoS Genet. 2010; 6:e1000841. [PubMed: 20169177]

7. Kariuki SN, Franek BS, Kumar AA, Arrington J, Mikolaitis RA, Utset TO, et al. Trait-stratified genome-wide association study identifies novel and diverse genetic associations with serologic and cytokine phenotypes in systemic lupus erythematosus. Arthritis Res Ther. 2010; 12:R151. [PubMed: 20659327]

8. Chung SA, Taylor KE, Graham RR, Nititham J, Lee AT, Ortmann WA, et al. Differential genetic associations for systemic lupus erythematosus based on anti-dsDNA autoantibody production. PLoS Genet. 2011; 7:e1001323. [PubMed: 21408207]

9. Freedman BI, Wilson CH, Spray BJ, Tuttle AB, Olorenshaw IM, Kammer GM. Familial clustering of end-stage renal disease in blacks with lupus nephritis. Am J Kidney Dis. 1997; 29:729–32. [PubMed: 9159307]

10. National Institute of Diabetes and Digestive and Kidney Diseases. US Renal Data System, USRDS 2012 Annual Data Report. Vol. 1: Atlas of chronic kidney disease and end-stage renal disease in the United States. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases, NIH; 2012.

11. Richman IB, Taylor KE, Chung SA, Trupin L, Petri M, Yelin E, et al. European genetic ancestry is associated with a decreased risk of lupus nephritis. Arthritis Rheum. 2012; 64:3374–82. [PubMed: 23023776]

12. Powe NR. To have and have not: health and health care disparities in chronic kidney disease. Kidney Int. 2003; 64:763–72. [PubMed: 12846781]

13. Ramos PS, Brown EE, Kimberly RP, Langefeld CD. Genetic factors predisposing to systemic lupus erythematosus and lupus nephritis. Semin Nephrol. 2010; 30:164–76. [PubMed: 20347645]

14. Karassa FB, Trikalinos TA, Ioannidis JP. FcγRIIIA-SLE Meta-analysis Investigators. . The FcγRIIIA-F158 allele is a risk factor for the development of lupus nephritis: a meta-analysis. Kidney Int. 2003; 63:1475–82. [PubMed: 12631364]

15. Quintero-Del-Rio AI, Kelly JA, Kilpatrick J, James JA, Harley JB. The genetics of systemic lupus erythematosus stratified by renal disease: linkage at 10q22.3 (SLEN1), 2q34–35 (SLEN2), and 11p15. 6 (SLEN3). Genes Immun. 2002; 3 (Suppl 1):S57–62. [PubMed: 12215904]

16. Quintero-Del-Rio AI, Kelly JA, Garriott CP, Hutchings DC, Frank SG, Aston CE, et al. SLEN2 (2q34–35) and SLEN1 (10q22. 3) replication in systemic lupus erythematosus stratified by nephritis. Am J Hum Genet. 2004; 75:346–8. [PubMed: 15307049]

17. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010; 329:841–5. [PubMed: 20647424]

18. Tzur S, Rosset S, Shemer R, Yudkovsky G, Selig S, Tarekegn A, et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. Hum Genet. 2010; 128:345–50. [PubMed: 20635188]

19. Kopp JB, Nelson GW, Sampath K, Johnson RC, Genovese G, An P, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol. 2011; 22:2129–37. [PubMed: 21997394]

20. Lipkowitz MS, Freedman BI, Langefeld CD, Comeau ME, Bowden DW, Kao WH, et al. the AASK Investigators. Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans. Kidney Int. 2013; 83:114–20. [PubMed: 22832513]

21. Friedman DJ, Kozlitina J, Genovese G, Jog P, Pollak MR. Population-based risk assessment of APOL1 on renal disease. J Am Soc Nephrol. 2011; 22:2098–105. [PubMed: 21997396]

22. Freedman BI, Langefeld CD, Turner J, Nunez M, High KP, Spainhour M, et al. Association of APOL1 variants with mild kidney disease in the first-degree relatives of African American patients with non-diabetic end-stage renal disease. Kidney Int. 2012; 82:805–11. [PubMed: 22695330]

23. Foster MC, Coresh J, Fornage M, Astor BC, Grams M, Franceschini N, et al. APOL1 variants associate with increased risk of CKD among African Americans. J Am Soc Nephrol. 2013; 24:1484–91. [PubMed: 23766536]

24. Freedman BI, Edberg JC, Comeau ME, Murea M, Bowden DW, Divers J, et al. The non-muscle myosin heavy chain 9 gene (MYH9) is not associated with lupus nephritis in African Americans. Am J Nephrol. 2010; 32:66–72. [PubMed: 20523037]

25. Lin CP, Adrianto I, Lessard CJ, Kelly JA, Kaufman KM, Guthridge JM, et al. Role of MYH9 and APOL1 in African and non-African populations with lupus nephritis. Genes Immun. 2012; 13:232–8. [PubMed: 22189356]

26. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012; 64:2677–86. [PubMed: 22553077]

27. Kimberly RP, Freedman BI, Langfeld CD, Absher D, Andringa KK, Birmingham D, et al. Lupus Nephritis-ESRD Consortium. Apolipoprotein L1 risk variants underlie racial disparities in lupus nephritis-induced end-stage renal disease [abstract]. Arthritis Rheum. 2012; 64 (Suppl):S313.

28. Alexander DH, Novembre J, Lange K. Fast model-based estimation of ancestry in unrelated individuals. Genome Res. 2009; 19:1655–64. [PubMed: 19648217]

29. Coughlin SS, Benichou J, Weed DL. Attributable risk estimation in case-control studies. Epidemiol Rev. 1994; 16:51–64. [PubMed: 7925727]

30. Schwartzman-Morris J, Putterman C. Gender differences in the pathogenesis and outcome of lupus and of lupus nephritis. Clin Dev Immunol. 2012; 2012:604892. [PubMed: 22690240]

31. Palmer ND, Freedman BI. APOL1 and progression of nondiabetic nephropathy. J Am Soc Nephrol. 2013; 24:1344–6. [PubMed: 23813212]

32. Reeves-Daniel A, Bailey A, Assimos D, Westcott C, Adams PL, Hartmann EL, et al. Donor–recipient relationships in African American vs. Caucasian live kidney donors. Clin Transplant. 2011; 25:E487–90. [PubMed: 21504475]

33. Reeves-Daniel AM, DePalma JA, Bleyer AJ, Rocco MV, Murea M, Adams PL, et al. The APOL1 gene and allograft survival after kidney transplantation. Am J Transplant. 2011; 11:1025–30. [PubMed: 21486385]

34. Larsen CP, Beggs ML, Saeed M, Walker PD. Apolipoprotein L1 risk variants associate with systemic lupus erythematosus-associated collapsing glomerulopathy. J Am Soc Nephrol. 2013; 24:722–5. [PubMed: 23520206]

Table 1

Characteristics of the SLE patients with ESRD (cases) and the SLE patients without nephropathy (controls)[*]

	LN-ESRD cases (n = 855)[†]	SLE non-nephropathy controls (n = 534)[†]	P[‡]
Female, no. (%)	749 (88)	465 (93)	0.0025
Age at recruitment, years	41.14 ± 11.66 (41)	41.5 ± 11.73 (42.4)	0.54
Age at ESRD development, years	33.82 ± 11.57 (33)	NA	NA
Age at SLE onset, years	27.27 ± 10.90 (25)	39.46 ± 12.21 (40)	4.21×10^{-42}
Time from SLE onset to ESRD, years	7.33 ± 7.19 (5)	NA	NA
African ancestry, proportion	0.83 ± 0.09 (0.85)	0.83 ± 0.09 (0.85)	0.61
No. of ACR SLE criteria (excluding renal criteria) met	4.36 ± 1.74 (4)	4.94 ± 1.07 (5)	1.59×10^{-9}
Hypertension, no. (%)	763 (96)	NA	NA
History of ESRD in first-degree relatives, no. (%)	62 (9)	NA	NA
Cytotoxic therapy, no. (%)	558 (85)	NA	NA

[*] Except where indicated otherwise, values are the mean ± SD (median). SLE = systemic lupus erythematosus; ESRD = end-stage renal disease; LN = lupus nephritis; NA = not applicable or not available; ACR = American College of Rheumatology.

[†] For some variables, n values were slightly lower due to missing data.

[‡] By Wilcoxon's signed rank test (except for percent female [chi-square test]).

Table 2

Estimated African admixture proportion as a function of number of *APOL1* risk alleles [*]

APOL1 allele	LN-ESRD cases			SLE non-nephropathy controls		
	Risk allele frequency, no. (%)	African admixture proportion, mean ± SD (n)	P[†]	Risk allele frequency, no. (%)	African admixture proportion, mean ± SD (n)	P[†]
WT/WT	279 (33)	0.81 ± 0.10 (234)		223 (42)	0.82 ± 0.10 (169)	
G1/WT	238 (28)	0.83 ± 0.10 (195)		160 (30)	0.83 ± 0.07 (122)	
G2/WT	122 (14)	0.84 ± 0.07 (95)		89 (17)	0.83 ± 0.10 (72)	
G1/G1, G2/G2, or G1/G2	216 (25)	0.86 ± 0.07 (175)		62 (12)	0.89 ± 0.06 (44)	
			1.2×10^{-7}			0.0001

[*] WT = wild-type (see Table 1 for other definitions).

[†] Significance (by Wilcoxon's signed rank test) of the variation in median African admixture proportion by *APOL1* G1/G2 genotype.

Table 3

Results of test for association between *APOL1* compound risk and LN-ESRD in patients with SLE[*]

Model (n, cases/controls)	OR (95% CI)	P
Unadjusted (855/534)	2.57 (1.89–3.50)	1.49×10^{-9}
Adjusted for admixture (699/407)	2.80 (1.95–4.02)	2.21×10^{-8}
Adjusted for age, sex, and admixture (494/283)	2.72 (1.76–4.19)	6.23×10^{-6}

[*] Compound risk is coded as a binary variable in which the risk genotypes are as follows: homozygous for the G1 allele, homozygous for the G2 allele, or compound heterozygous for G1/G2 (i.e., 2 copies of any risk allele). The frequency of G1/G2 compound heterozygosity was 0.25 among LN-ESRD cases and 0.12 among SLE non-nephropathy controls. OR = odds ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).

Table 4

Results of tests for association of the *APOL1* G1/G2 risk allele with age at ESRD development, age at SLE onset, and time from SLE onset to ESRD development[*]

	No admixture adjustment			Admixture adjusted		
	0/1 risk alleles	2 risk alleles	P	0/1 risk alleles	2 risk alleles	P
Age at ESRD development, years	33.9 ± 12.1 (33)	33.5 ± 10.1 (33)	0.9152	33.8 ± 12.0 (32.5)	33.4 ± 10.0 (33)	0.8603
Age at SLE onset, years	30.9 ± 12.9 (29)	30.0 ± 11.2 (29)	0.1278	31.3 ± 13.0 (30)	30.4 ± 11.4 (29)	0.0840
Cases	27.0 ± 11.1 (25)	28.1 ± 10.2 (27)	0.1372	27.0 ± 11.1 (25)	28.3 ± 10.3 (27)	0.1554
Controls	39.4 ± 12.4 (41)	40.0 ± 11.0 (39)	0.6925	39.4 ± 12.4 (41)	40.0 ± 11.0 (39)	0.3268
Time from SLE onset to ESRD development, years	7.89 ± 7.30 (6)	5.81 ± 6.64 (4)	0.0003	7.87 ± 7.33 (6)	5.81 ± 6.06 (4)	0.0111

[*] Values are the mean ± SD (median). See Table 1 for definitions.