Clinical Features and Histology of Apolipoprotein L1-Associated Nephropathy in the FSGS Clinical Trial

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ABSTRACT

Genetic variants in apolipoprotein L1 (APOL1) confer risk for kidney disease. We sought to better define the phenotype of *APOL1*-associated nephropathy. The FSGS Clinical Trial involved 138 children and young adults who were randomized to cyclosporin or mycophenolate mofetil plus pulse oral dexamethasone with a primary outcome of proteinuria remission. DNA was available from 94 subjects who were genotyped for *APOL1* renal risk variants, with two risk alleles comprising the risk genotype. Two *APOL1* risk alleles were present in 27 subjects, of whom four subjects did not self-identify as African American, and 23 of 32 (72%) self-identified African Americans. Individuals with the *APOL1* risk genotype tended to present at an older age and had significantly lower baseline eGFR, more segmental glomerulosclerosis and total glomerulosclerosis, and more tubular atrophy/interstitial fibrosis. There were differences in renal histology, particularly more collapsing variants in those with the risk genotype (P=0.02), although this association was confounded by age. *APOL1* risk genotype did not affect response to either treatment regimen. Individuals with the risk genotype were more likely to progress to ESRD (P<0.01). In conclusion, *APOL1* risk genotypes are common in African-American subjects with primary FSGS and may also be present in individuals who do not self-identify as African American. *APOL1* risk status is associated with lower kidney function, more glomerulosclerosis and interstitial fibrosis, and greater propensity to progress to ESRD. The *APOL1* risk genotype did not influence proteinuria responses to cyclosporin or mycophenolate mofetil/dexamethasone.

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FSGS is the most common pattern of glomerular injury observed in glucocorticoid-resistant nephrotic syndrome, and it commonly progresses to ESRD.[1] Many subjects with primary FSGS do not respond to first-line therapy with glucocorticoids,[2,3] and the optimal second-line therapy has been a matter of some debate. To address this issue, the National Institutes of Health–sponsored FSGS Clinical Trial (FSGS-CT) randomized 138 subjects with steroid-resistant FSGS to treatment with cyclosporin versus mycophenolate combined with pulse oral dexamethasone, and all subjects received low-dose oral prednisone.[4]

Genetic variants in *apolipoprotein L1* (*APOL1*), encoding APOL1, have been shown to be strongly associated with glomerular disease, including FSGS, HIV-associated collapsing glomerulopathy, and hypertension-attributed CKD and end stage kidney disease.[5–7] We wished to learn more about the phenotype of *APOL1*-associated nephropathy, particularly whether subjects with two *APOL1* risk alleles manifest particular histologic variants and whether they tend to be responsive or resistant to cyclosporin

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or mycophenolate mofetil, and we investigated these issues in the context of the FSGS-CT.

RESULTS

As shown in Table 1, the *APOL1* risk genotype (the presence of two risk alleles, defined as G1/G1 homozygotes, G2/G2 homozygotes, and G1/G2 compound heterozygotes) was present in 72% of self-identified African-American patients, which is the same frequency previously observed for sporadic FSGS.[6] Surprisingly, 6% (four of 62) of individuals who identified themselves as non–African American had two *APOL1* risk alleles; these included two of 42 European American non-Hispanics and two of 17 European American Hispanics. Among self-identified Hispanic individuals, *APOL1* risk status was present among those who reported African ancestry and those who did not report African ancestry. There were three subjects who self-identified as having Asian, Native American, and other ancestry, none of whom carried *APOL1* risk alleles. These results suggest that, among Americans, self-identified race or ethnicity is not a reliable criterion to exclude the possibility that individuals carry *APOL1* risk alleles.

Summaries of other demographic, clinical, and histologic data are presented in Table 2 (considering all subjects) and Table 3 (limited to those self-identified as African American). Several observations can be made about findings that reached statistical significance in at least one of these two approaches. FSGS onset occurred at an older age among those with two *APOL1* risk alleles when all subjects were considered; among these individuals, the youngest individual was 2 years old, and the others were 9–37 years old, which resembles the peak onset age brackets of 15–39 years for *APOL1*-associated FSGS as previously reported.[6] This observation must be tempered by the fact that the data are right-censored, because the FSGS-CT excluded subjects >40 years of age. Baseline eGFR was significantly lower, and the number of glomeruli showing segmental glomerulosclerosis, global glomerulosclerosis, and total glomerulosclerosis (segmental plus global glomerulosclerosis) and the extent of tubular atrophy and fibrosis were all greater among those with the *APOL1* risk genotype, which is consistent with the faster progression rate that has been observed in these individuals.[6] Most *APOL1*-associated FSGS was present in subjects entering the study after age 12 years, and this makes age a confounding variable for the interpretation of some results (Supplemental Table 1). Subjects >12 years old tended to have a lower baseline eGFR and more collapsing glomerulopathy, segmental glomerulosclerosis, total glomerulosclerosis, and interstitial fibrosis, and *APOL1* 2 risk allele status was associated with the first four of these variables.

With regard to glomerular histology (FSGS variant), there were differences when the data from all subjects were analyzed, driven particularly by an excess of collapsing variant and fewer tip lesion cases among subjects with two *APOL1* risk alleles. There was no similar trend when self-identified African Americans were analyzed, possibly because of reduced statistical power. There were no differences between genotype groups with respect to mean levels of soluble urokinase-type plasminogen activator receptor (suPAR), which were elevated in both genotype groups, consistent with a proposed role for suPAR in the pathogenesis of primary and recurrent FSGS after kidney transplantation.[8]

Importantly, there were no differences in complete remission (CR) rate or CR plus partial remission (PR) rate between the *APOL1* risk and nonrisk genotype groups, although the numbers are too small to draw firm conclusions. Furthermore, ANOVA analyses looking for an interaction between treatment (cyclosporin versus mycophenolate mofetil) and *APOL1* risk genotype in the outcome, defined as remission score, yielded a nonsignificant *P* value (0.45). This suggests that the *APOL1* risk genotype status did not affect an individual's propensity to respond to these remittive agents (Figure 1). Note that this curve is likely not an entirely accurate reflection of the typical FSGS course, because individuals who progressed to low eGFR early and rapidly would not have been eligible to participate in the FSGS-CT.

In a follow-up analysis to week 78 of the trial, renal survival assessed from the onset of FSGS was significantly shorter among subjects with two *APOL1* risk alleles (Figure 2). We conducted multivariable analysis excluding variables associated with *APOL1* risk genotype, including baseline eGFR and tubular atrophy/interstitial fibrosis, to avoid multiple colinearity. Previous

Table 1. Racial and ethnic background and *APOL1* risk allele status of the study population

Racial and Ethnic Background	Zero or One *APOL1* Risk Alleles	Two *APOL1* Risk Alleles	Subgroup Percentage with Two *APOL1* Risk Alleles
African American, non-Hispanic	8	21	72
African American, Hispanic	1	2	67
European American, non-Hispanic	40	2	7
European American, Hispanic	15	2	12
Amerindian	1	0	0
Asia	1	0	0
Other	1	0	0
Total	67	27	

The distributions of *APOL1* risk alleles are shown by groups defined by self-identified race and ethnicity. DNA was available from 94 subjects.

Table 2. Demographic, clinical, and histologic variables by APOL1 risk status (all subjects)

Variable	Zero or One *APOL1* Risk Alleles	Two *APOL1* Risk Alleles	*P* Value
Number of subjects	67	27	
Onset age (yr)	13 (8, 23)	17 (13, 27)	0.03
Enrollment age (yr)	14 (10, 28)	17 (13, 27)	0.07
Baseline eGFR (ml/min per 1.73 m^2)	130 (83, 195)	94 (68, 109)	0.003
Baseline serum albumin (g/dl)	3.1 (2.3, 3.7)	3.0 (2.1, 3.8)	0.84
Baseline urine protein-to-creatinine ratio	3.6 (2.2, 7.1)	4.7 (2.8, 10.2)	0.28
Baseline serum suPAR (ng/ml)	4297 (3402, 5405)	4020 (3104, 4510)	0.18
Change in suPAR (ng/ml)	−27 (−1062, +764)	+103 (−532, +1541)	0.33
FSGS histologic variant			0.02
Collapsing	3	8	
Tip	10	2	
Cellular	2	0	
Perihilar	7	2	
Not otherwise specified	45	15	
Segmental glomerulosclerosis (%)	20 (9, 31)	25 (19, 34)	0.02
Global glomerulosclerosis (%)	0 (0, 12)	7 (0, 17)	0.43
Total glomerulosclerosis (%)	25 (12, 50)	44 (24, 62)	0.02
Tubular atrophy/fibrosis (%)	10 (5, 25)	20 (5, 60)	<0.01
Arteriosclerosis (score)	0 (0, 1)	0 (0, 1.2)	0.13
CR (remissions coded as one or two)	11	1	0.17
CR or PR sustained at week 52 (remission coded as one, two, or three)	29	7	0.16
Reached end stage kidney disease during the follow-up period	8	10	<0.01

Data are presented as medians (25th, 75th percentiles). Note that the total glomerulosclerosis is not the sum of segmental glomerulosclerosis plus global glomerulosclerosis, because the values are medians.

work in this cohort has suggested that the outcome of end stage kidney disease/death was associated with lower baseline eGFR, severe nephrotic syndrome, public insurance, and more tubular atrophy/interstitial fibrosis (S. Hogan *et al.*, unpublished data). The multivariable model included premature birth, birth weight, body mass index (scored as underweight/healthy weight, overweight, obese, or severely obese to account for different thresholds in children and adults), insurance (scored as none, public, or private), baseline proteinuria, and *APOL1* risk status. In this model, baseline proteinuria (P=0.001) and *APOL1* risk status (P=0.02) were the only variables significantly associated with renal survival.

DISCUSSION

APOL1 kidney risk variants are strongly associated with kidney disease among African Americans,[5] and the association is strongest for HIV-associated nephropathy (odds ratio, 29; 95% confidence interval, 13 to 68) and FSGS (odds ratio, 17; 95% confidence interval, 11 to 26).[6] Previous studies have established that *APOL1*-associated FSGS is characterized by a tendency to present between ages 15–39 years old and rapid progression to end stage kidney disease but similar response to glucocorticoids compared with those lacking two *APOL1* risk alleles.[6] With regard to response to therapy, the only other published data suggest that *APOL1*-associated hypertension-attributed kidney disease is refractory to therapy with angiotensin-converting enzyme inhibitors.[9]

This study offers several new insights into the nature of *APOL1*-associated FSGS. First (most important from a clinical standpoint), although the numbers of subjects are small, the response to cyclosporin and mycophenolate mofetil/dexamethasone was similar in those with and without two *APOL1* risk alleles, suggesting that both approaches could be considered when these individuals have not responded to glucocorticoids or for individuals for whom glucocorticoids are contraindicated. Second, the finding that *APOL1* risk alleles can be present in subjects who do not self-identify as having African ancestry suggests that, when a clinical role for *APOL1* genetic testing has been shown, testing may be indicated in individuals who present with characteristic renal syndromes, regardless of the ancestry that they may report. Third, this is the first systematic analysis of renal histology in *APOL1*-associated FSGS. The finding of more glomerulosclerosis, tubular atrophy, and interstitial fibrosis is consistent with the tendency toward rapid functional loss that is a reflection of these structural alterations. The distribution of FSGS variants differed between *APOL1* risk groups and was driven largely by more collapsing variants in the *APOL1* risk group. The propensity of individuals with *APOL1* risk to collapsing glomerulopathy has been reported before in the setting of HIV-associated nephropathy[10] and lupus nephritis.[11] Fourth, there was no association between *APOL1* risk status and suPAR levels. It is possible that cytokines, such as suPAR, may interact with APOL1 variants; studies to address this possibility will require analysis of patients with FSGS and appropriate healthy volunteers. Fifth, as

Table 3. Demographic, clinical, and histologic variables by *APOL1* risk status (self-identified African Americans only)

Variable	Zero or One *APOL1* Risk Alleles	Two *APOL1* Risk Alleles	*P* Value
Number of subjects	9	23	
Onset age (yr)	10 (4.5, 30)	17 (13, 27)	0.10
Enrollment age (yr)	10 (5, 30)	18 (13, 29)	0.12
Baseline eGFR (ml/min per 1.73 m^2)	130 (63, 178)	94 (79, 109)	0.34
Baseline serum albumin (g/dl)	2.6 (1.6, 3.2)	3.3 (2.1, 3.8)	0.16
Baseline urine protein-to-creatinine ratio	1.6 (0.7, 2.4)	1.5 (1.0, 2.3)	0.87
Baseline serum suPAR	4474 (3180, 5559)	3864 (2826, 4472)	0.25
Change in suPAR (ng/ml)	+580 (+82, +1353)	+60 (−510, +1659)	0.49
FSGS histologic variant			0.23
Collapsing	0	6	
Tip	1	1	
Cellular	0	0	
Perihilar	0	2	
Not otherwise specified	8	14	
Segmental glomerulosclerosis (%)	20 (9, 29)	25 (16, 44)	0.12
Global glomerulosclerosis (%)	0 (0, 0)	7.4 (0. 17)	0.03
Total glomerulosclerosis (%)	20 (9, 35)	36 (20, 62)	<0.05
Tubular atrophy/fibrosis	10 (2.5, 30)	20 (6, 70)	0.31
Arteriosclerosis (score)	0 (0, 1)	0 (0, 1)	0.56
CR (remissions coded as one or two)	0	1	>0.99
CR or PR sustained at week 52 (remission coded as one, two, or three)	2	5	>0.99
Reached end stage kidney disease during the follow-up period	0	8	0.07

Data are presented as medians (25th, 75th percentiles).

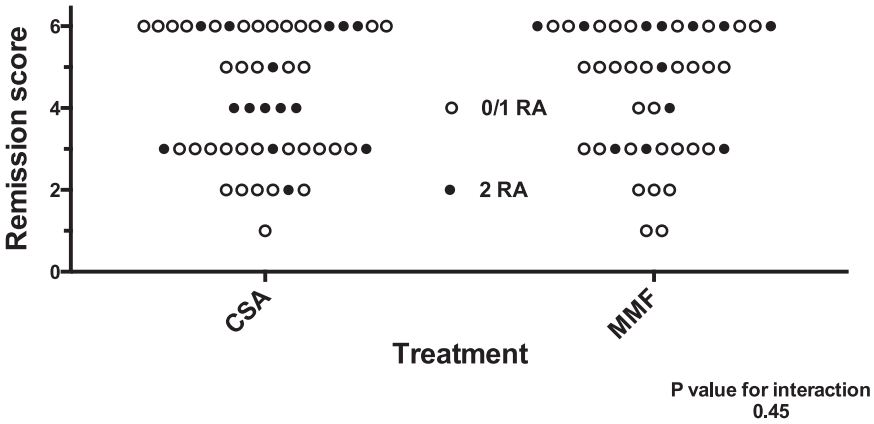

Figure 1. Interaction between *APOL1* genotype and treatment response. Randomized treatment with cyclosporin (CSA) or mycophenolate mofetil combined with oral pulse dexamethasone (MMF) was associated with remissions scored as one to six. Each of 94 (total) subjects is depicted as a circle, with open circles denoting those with zero or one *APOL1* risk alleles (RAs) and closed circles denoting those with two *APOL1* RAs. Analysis for interaction between treatment and genotype using two-way ANOVA yielded a non-significant *P* value (*P*=0.45), suggesting that the presence or absence of the *APOL1* risk genotype was not associated with differential responses to these medications.

previously shown, *APOL1*-associated FSGS has a propensity to progress rapidly to end stage kidney disease, suggesting that early treatment should be aggressive if the clinical setting warrants.

This study has several limitations; 42 of 138 subjects in the FSGS-CT, representing 30% of all subjects, did not provide DNA for analysis, reducing statistical power. We did not characterize ancestry-informative markers, and therefore, we did not determine the fraction of African ancestry in each subject, although we do not believe that this information would change the analyses or interpretation, because the prevalence of two *APOL1* risk alleles in this study was nearly identical to that previously reported.[6] Both therapeutic arms used glucocorticoids, and therefore, the results are not strictly applicable to responses that might be seen with cyclosporin or mycophenolate mofetil used as monotherapy for steroid-resistant FSGS.

In summary, *APOL1*-associated FSGS may occur in individuals with various self-reported ancestries and is associated with more severe kidney fibrosis at diagnosis and more rapid progression to end stage kidney disease, but it has equal propensity to respond to glucocorticoids as well as cyclosporin and mycophenolate as used in this study. The strongest argument for *APOL1* genetic testing in clinical practice might be that individuals carrying two risk alleles should be treated aggressively with remittive agents from the initial diagnosis of FSGS. At present, however, there are no data that would indicate that aggressive treatment with available agents retards progressive kidney function loss in these high-risk individuals.

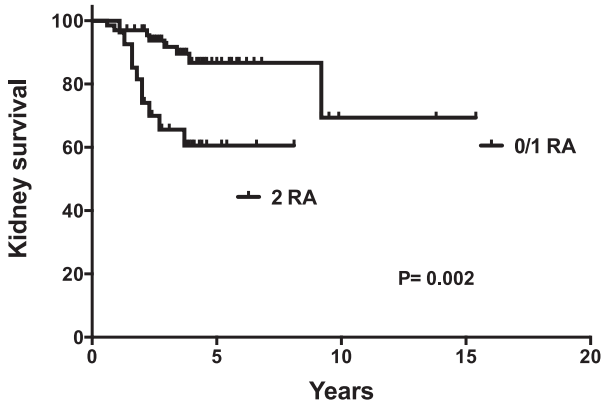

Figure 2. Renal survival analysis. Renal survival, assessed from FSGS onset to dialysis or kidney transplant and censored for death with kidney function, was significantly shorter for individuals with two *APOL1* risk alleles (RAs) compared with others. Analysis includes all 94 subjects.

CONCISE METHODS

Subjects and Treatment

The FSGS-CT enrolled children and adults with primary steroid-resistant, biopsy-proven FSGS who were between the ages of 2 and 40 years, had an eGFR>40 ml/min per 1.73 m^2, and had a urine protein-to-creatinine ratio>1 g/g. Exclusion criteria included secondary FSGS, diabetes mellitus, and chronic infection (including chronic viral infection) as well as the other criteria as previously described.[4] Race and ethnicity (Hispanic ancestry) were determined by self-report of subjects or report by parents; genetic studies for ancestry informative markers were not carried out. Of these subjects, 138 individuals were randomized to receive either cyclosporin or mycophenolate mofetil combined with pulse oral dexamethasone; both groups received low-dose oral prednisone and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. CR was defined as a urine protein-to-creatinine ratio <0.2 g/g, and PR was defined as a 50% reduction, reaching a value of 0.2 to <2.0 g/g. The FSGS-CT defined remission on a six-point ordinal scale, on which one denoted CR during the first 24 weeks that was sustained to week 52, two denoted CR during weeks 27–48, three denoted a PR by week 26 that was sustained to week 78, four and five denoted a transient PR, and six denoted failure to obtain a PR. For the purposes of this study, a CR is equivalent to a score of one or two, and a PR is equivalent to a score of three. Of these subjects, 94 individuals provided DNA for genetic studies.

Clinical and Laboratory Testing

Serum and urine chemistry measurements were made during the treatment period and every 26 weeks after week 78 using standard methods that were performed in a central laboratory (Spectra East Core Laboratory). eGFR was calculated according to the Schwartz equation for subjects <18 years of age and the Cockroft–Gault equation adjusted for body surface area for subjects ≥18 years of age.

Genetic Testing

APOL1 genotyping for 94 subjects from whom DNA was available was performed using a Taqman assay and allele-specific primers[6]; this approach shows 100% concordance with Sanger sequencing (C.A. Winkler, unpublished data). Exon sequencing of 86 subjects with DNA available as of 2010 included the following genes: *NPHS2* sequencing, which identified two subjects with heterozygous mutations (one subject each had R138Q and L139R) and one subject with a heterozygous A242V variant (sequencing carried out independently by L.M.G.-W. and F.H.)[12]; *PLCE1* sequencing, which identified eight novel heterozygous codon variants, of which four variants were missense mutations[13]; *WT1* exons 8 and 9, which identified one Frasier syndrome variant and one novel potential mutation; and *INF2* sequencing, with no mutations identified. In summary, Mendelian genetic variants accounted for one and possibly, two patients with FSGS, both with *WT1* variants.

Pathology

Kidney biopsy tissue was available for all subjects and reviewed by a central pathology committee, which confirmed the diagnosis of FSGS, made an FSGS histologic variant diagnosis according to the Columbia Classification,[14] and carried out quantitative analysis of histologic variables as recently described.[15]

suPAR

Serum suPAR levels were measured in the FSGS-CT as previously described and reported.[16]

Statistical Analyses

Data for subjects with zero or one *APOL1* risk alleles versus those with two risk alleles are summarized as medians (interquartile ranges). Differences between groups were compared by Mann–Whitney *U* tests for nonparametric data using two-tailed tests. Analysis of histology (FSGS variants) was by chi-squared testing, whereas analysis of progression to end stage kidney disease was by Fisher exact testing. Cox survival analysis was performed using the Gehan–Breslow–Wilcoxon test and Prism software (GraphPad Software, La Jolla, CA). A P value <0.05 was considered to be significant.

Human Subjects Research Issues

The FSGS-CT protocol was approved by the institutional review boards at the participating institutions, and all subjects gave informed assent or consent. Genetic analysis for *APOL1* kidney risk variants was approved by the National Institute of Diabetes and Digestive and Kidney Diseases Institutional Review Board.

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DISCLOSURES

None.

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See related editorial, "*Apolipoprotein L1*-Associated Nephropathy and the Future of Renal Diagnostics," on pages 1232–1235.

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