therapeutic advantage and no significant advantage in AEs or SAEs compared to MMF-based standard treatment regimens. Renal function post-transplantation was comparable in both arms and FTY720-treated patients and FTY720 was associated with lower infection rates than MMF-treated patients.

Supplementary data
Supplementary table 1 is available online at http://ndt.oxfordjournals.org.

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References

Preliminary Communication
Apolipoprotein L1 nephropathy risk variants associate with HDL subfraction concentration in African Americans

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Abstract
Background. Coding variants in the apolipoprotein L1 gene (APOL1) are strongly associated with non-diabetic nephropathy in African Americans. ApoL1 proteins associate with high-density lipoprotein (HDL) particles in the circulation. Plasma HDL particle subclass concentrations were compared in 73 African Americans based on APOL1 genotypes to detect differences potentially contributing to renal disease.

Methods. HDL subclass concentrations were measured using nuclear magnetic resonance spectroscopy in African American first-degree relatives of patients with non-diabetic end-stage renal disease. Participants had estimated glomerular filtration rates (GFRs) >
80 mL/min and lacked albuminuria. Additive effects of the number of \textit{APOL1} risk variants on natural logarithm-transformed HDL subclass concentrations were computed.

**Results.** Participants were 58.9\% female with mean ± SD age 47.2 ± 13.3 years and GFR 92.4 ± 18.8 mL/min. The numbers with 2, 1 and 0 \textit{APOL1} nephropathy risk variants, respectively, were 36, 17 and 20. Mean ± SD medium-sized HDL concentrations were significantly lower for each additional \textit{APOL1} risk variant (2 versus 1 versus 0 risk variants: 9.0 ± 5.6 versus 10.1 ± 5.5 versus 13.1 ± 8.2 µmol/L, respectively; \(P = 0.0222\) unadjusted; \(P = 0.0162\) triglyceride- and ancestry adjusted).

**Conclusions.** Lower medium-sized HDL subclass concentrations are present in African Americans based on increasing numbers of \textit{APOL1} nephropathy risk variants. Potential mechanistic roles of altered medium HDL concentrations on \textit{APOL1}-associated renal microvascular diseases should be evaluated.

**Keywords:** \textit{APOL1}; arteriolar nephrosclerosis; FSGS; HDL cholesterol; kidney

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**Introduction**

The African American Study of Kidney Disease and Hypertension (AASK) Trial and Cohort studies revealed that strict blood pressure control, including use of angiotensin-converting enzyme (ACE) inhibitors, failed to halt progression of the kidney disease attributed to essential hypertension in African Americans [1, 2]. Coding variants in the apolipoprotein L1 gene (\textit{APOL1}) and the E1 (extended 1) haplotype in the adjacent non-muscle myosin heavy chain 9 gene (\textit{MYH9}) in linkage disequilibrium with \textit{APOL1} nephropathy risk variants are strongly associated with hypertension-attributed end-stage renal disease (HA-ESRD), focal segmental glomerulosclerosis (FSGS) and HIV-associated collapsing glomerulopathy in African Americans [3–8], as well as with initiation and progression of the kidney disease labeled hypertensive nephrosclerosis (HN) in AASK participants [9, 10]. Hence, this region of chromosome 22q is associated with a spectrum of severe non-diabetic kidney diseases [11–15]. \textit{APOL1} nephropathy risk variants appear to have risen to high frequency in Africa due to the protection they afford from \textit{trypanosoma brucei rhodesiense}, the parasite causing African sleeping sickness [6, 8]. Two coding variants in \textit{APOL1}, termed G1 [342G:384M; identified by two single-nucleotide polymorphisms (SNPs) in perfect linkage disequilibrium: rs73885319 and rs60910145] and G2 (a 6-bp deletion identified by rs71785313) are strongly associated with non-diabetic kidney disease.

Renal histologic findings in AASK participants included focal global glomerulosclerosis (FGGS), arteriolar nephrosclerosis and interstitial fibrosis, while other patients with clinically diagnosed HN have non-nephrotic FSGS [16–18]. Racial differences in the histologic lesions of non-diabetic nephropathy have been reported [16]. African Americans have more extensive solidified glomerulosclerosis with segmental sclerosis relative to European Americans, supporting different disease mechanisms between groups with different population ancestry. Importantly, the renal vascular lesion that is typically attributed to hypertension in African Americans, arteriolar nephrosclerosis, does not correlate with systemic blood pressures [16, 17]. Although non-diabetic and hypertensive African Americans with chronic kidney disease (CKD) and proteinuria above the microalbuminuric range benefit slightly from lower blood pressures and use of ACE inhibitors, many of these patients inexorably progress to ESRD [1, 2]. Results from the AASK trial demonstrated that these treatment measures are of little benefit on renal end points in non-diabetic African Americans with hypertension and CKD without significant proteinuria [2]. These studies suggest that factors beyond essential hypertension can initiate renal microvascular disease in African Americans.

The \textit{APOL1} gene encodes ApoL1 protein. This protein associates with high-density lipoprotein (HDL) particles in the circulation. HDL is the smallest of the lipoprotein classes and its concentration is inversely associated with coronary heart disease risk, obesity and insulin resistance [19]. HDL is comprised of particle subclasses of varying size that differ in lipid and protein content and also potentially in function [20]. With identification of the strong \textit{APOL1} association with non-diabetic kidney disease in African Americans as well as the frequent presence of arteriolar nephrosclerosis in African Americans with idiopathic FSGS and collapsing FSGS, we measured serum HDL subclass concentrations in African Americans based on \textit{APOL1} G1 and G2 nephropathy risk genotypes. These analyses were done in an attempt to determine whether differences potentially contributing to development of renal microvascular disease and non-diabetic nephropathy were present.

**Materials and methods**

**Study subjects**

The ‘Natural History of \textit{APOL1/MYH9}-associated Nephropathy’ study is recruiting the siblings and children of self-described African Americans with non-diabetic forms of ESRD, including nephropathy attributed to HA-ESRD, FSGS and HIV-associated collapsing glomerulopathy. Relatives are genotyped for \textit{APOL1} and \textit{MYH9} nephropathy risk variants, fasting serum, ethylenediaminetetraacetic acid plasma, urine, buffy coat and DNA samples are collected and participants are phenotyped for subclinical kidney disease [serum creatinine and cystatin C concentrations, estimated glomerular filtration rate (GFR) and albuminuria] and associated risk factors [e.g. blood pressure, fasting blood sugar, body mass index (BMI)]. Participants will be evaluated longitudinally to detect triggers for \textit{APOL1}-associated nephropathy.

Seventy-three study participants from 72 families, all with a GFR > 80 mL/min and morning spot urine albumin:creatinine ratio (ACR) < 5.09 mg/mmol (45 mg/g) were selected for measurement of HDL subclass concentrations. Subjects included individuals without \textit{APOL1} nephropathy risk variants (lacking both the G1 non-synonymous coding variant 342G:384M and G2 6 bp deletion; \(N = 20\)), with one \textit{APOL1} G1 or G2 risk variant (\(N = 17\)) or two copies of \textit{APOL1} risk variants (either G1/G1, G1/G2 or G2/G2; \(N = 36\)). The initial 40 study subjects recruited with either zero (\(N = 20\)) or two (\(N = 20\)) \textit{APOL1} G1 variants were evaluated (significant differences in medium HDL concentration were seen); with subsequent inclusion of 33 additional subjects homozygous for G2 risk variants or heterozygous for either G1 or G2. Frequencies of risk variants were not chosen to mimic the distribution in the general African American population. The study protocol was approved by the Wake Forest Institutional
Review Board and all subjects provided written informed consent. This project was performed in accordance with the Declaration of Helsinki.

Genotype analysis
DNA extraction from whole blood was performed using the PureGene system (Genta Systems, Minneapolis, MN). Two SNPs in the APOL1 G1 nephropathy risk variant (rs73885319; rs60910145) and an indel for the G2 risk variant (rs71785313) were genotyped on the Sequenom (San Diego, CA). In addition, 70 di-allelic ancestry informative markers were genotyped to determine whether population substructure biased our results [31]. Samples included 44 Yoruba (YRI), 39 European American controls and the 73 African American study participants using Illumina Inc. Custom Genotyping Services (San Diego, CA) or the Sequenom Mass Array (San Diego, CA).

Laboratory evaluation
Serum creatinine concentrations were measured using creatinase enzymatic spectrophotometry, blood urea nitrogen using the urease enzymatic assay and urine ACR by microalbumin immunoturbidimetric methods at Laboratory Corporation of America (LabCorp, Burlington, NC; www.labcorp.com). Estimated GFR was computed using the four-variable MDRD equation [22].

Lipoprotein particle analysis
Plasma lipoprotein particle profiles were measured by nuclear magnetic resonance (NMR) spectroscopy using the LipopProfile-3 algorithm at Liposcience, Inc. (Raleigh, NC). Plasma samples from participants remained frozen at −80°C until the assays were performed. An HDL particle subclasses (μmol/L) and very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) subclasses (μmol/L) were quantified from the amplitudes of their spectroscopically distinct methyl group NMR signals; weighted-average VLDL, LDL and HDL particle sizes (nm diameter) were derived from the sum of the diameter of each subclass multiplied by its relative mass percentage based on the amplitude of its methyl NMR signal [20, 23]. Diameter range estimates for the subclasses were: large VLDL 29–42 nm, intermediate-density lipoprotein 23–29 nm, large LDL 20.5–23 nm, small LDL 18–20.5 nm, large HDL 9.4–14 nm, medium HDL 8.2–9.4 nm, small HDL 7.3–8.2 nm. Inter-assay reproducibility (coefficient of variation), determined from replicate analyses of 8 plasma pools over 20 days, was 3% for total HDL particles and 13, 15 and 7% for large, medium and small HDL subclasses, respectively. NMR-derived concentrations of triglycerides (TGs) and HDL cholesterol (mg/dL) were also obtained.

Statistical analysis
Demographic characteristics of the study group contrasting those with 0, 1 or 2 APOL1 risk variants was performed using Fisher’s exact test for gender and presence of diabetes mellitus and the Wilcoxon ranked sums test for continuous traits (Table 1). The primary inference of the study was a comparison of HDL subclass concentrations with the number of APOL1 risk alleles (Table 2). Analysis of covariance was employed to compare HDL subclasses with numbers of risk alleles. To best approximate distributions assumptions of analysis of co-variance (i.e. conditional normality and homogeneity of variance), HDL and each HDL subclass concentration was natural log transformed. Given the highly skewed nature of plasma TG concentrations, TG was also natural log transformed to minimize overly influential observations. Analyses were repeated without the transformations and yielded comparable inferences. For completeness, the apolipoprotein B particle concentrations and lipoprotein particle size summaries by the number of APOL1 risk alleles are reported in Table 3; however, these were not primary analyses as these subfractions were not expected to differ based on APOL1 genotype.

Results
Demographic characteristics of study subjects, based upon APOL1 genotype are shown in Table 1. No significant differences were observed in age, sex, presence of diabetes mellitus, BMI, GFR or urine ACR between groups. The group with one APOL1 risk variant consisted of eight subjects with G1/normal and nine subjects with G2/normal genotypes. Among those with two APOL1 risk variants, 20 were G1/G1 and 6 were G2/G2 homozygotes, while 10 were G1/G2 compound heterozygotes.

Among participants, 12.3% (9/73) were taking lipid-lowering medications; although these medications are not felt to impact HDL subclass concentration [24]. Three of 20 subjects (15%) in the group without APOL1 risk variants were taking a statin (one with ezetimibe and flax seed oil); 3 of 36 subjects (8.3%) in the group with two APOL1 risk variants were taking lipid-lowering medications [2 on a statin (one with fenofibrate and prescription omega-3 acid ethyl esters), another over the counter omega-3 fish oil supplements] and 3 of 17 subjects (17.6%) in the group with one APOL1 risk variant were taking statins. No participant was prescribed alpha adrenergic blocking agents.

Results of the apriori HDL subclass concentration analysis based on APOL1 nephropathy risk genotypes are depicted in Table 2. The mean ± SD concentration of medium-sized HDL was significantly lower in those with two APOL1 risk variants (defined as either G1 homozygotes, G2 homozygotes or G1/G2 compound heterozygotes) 9.0 ± 5.6 μmol/L, relative to one risk variant (G1 or G2 heterozygotes) 10.1 ± 5.5 μmol/L, relative to those lacking risk variants (homozygous for normal variants) 13.1 ± 8.2 μmol/L (P = 0.0222), remaining significantly different after adjusting for log (plasma TG concentration) and ancestry (adjusted P = 0.0162). Significant differences between groups were not seen for the concentrations of either the small or large HDL subclasses; although slightly higher large and small HDL particle concentrations were present in risk homozygotes, compared to non-risk homozygotes (Table 2). The study group was composed of unrelated participants except for a single full sibling pair. The analyses were repeated after dropping one sibling, then the other sibling, in order to evaluate all unrelated subjects. P-values for log (plasma TG concentration)-adjusted medium-sized HDL concentrations were P = 0.0189 and P = 0.0186, respectively; dropping both siblings yielded P = 0.0185. Thus, the two related individuals did not influence overall study results.

Table 3 lists lipoprotein subclass particle concentrations of VLDL and LDL, mean particle sizes of VLDL, LDL and HDL and NMR-derived plasma TG and HDL cholesterol values by APOL1 nephropathy risk variants; however, they were not part of the primary analysis since they were not hypothesized to differ based on APOL1 genotypes. As anticipated, similar values for these measurements were observed in subjects with and without APOL1 risk variants.

Discussion
We observed that APOL1 nephropathy risk variant genotypes are associated with decreasing medium-sized HDL subclass concentrations; an effect that persists after
adjustment for serum TGs and African ancestry. Although Miljkovic-Gacic et al. [25] reported that the distribution of lipoprotein subclasses and particle sizes appear to differ in African Americans and Afro-Caribbeans, relative to European Americans, large multi-center trials performed at LipoScience, Inc. reveal similar medium-size HDL particle concentrations in African Americans and European Americans [J. D. Otvos (personal communication)]. Although this analysis did not attempt to demonstrate mechanistic roles for altered HDL subclasses in the

Table 1. Demographic characteristics [% or mean ± SD (median)]

<table>
<thead>
<tr>
<th>Variable</th>
<th>No APOL1 risk variants, N = 20</th>
<th>One APOL1 risk variant, N = 17</th>
<th>Two APOL1 risk variants, N = 36</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>45.0</td>
<td>64.7</td>
<td>63.9</td>
<td>0.33</td>
</tr>
<tr>
<td>African ancestry (%)</td>
<td>77 ± 8</td>
<td>77 ± 12</td>
<td>78 ± 9</td>
<td>0.11</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>21.0</td>
<td>20.0</td>
<td>8.8</td>
<td>0.39</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.2 ± 14.0 (48.0)</td>
<td>52.2 ± 10.6 (51.1)</td>
<td>44.9 ± 13.7 (46.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.4 ± 10.5 (35.3)</td>
<td>32.1 ± 5.9 (33.0)</td>
<td>31.3 ± 8.5 (29.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>130.0 ± 13.1 (130.5)</td>
<td>135.5 ± 25.6 (123.0)</td>
<td>128.5 ± 18.8 (126.0)</td>
<td>0.89</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>86.7 ± 10.6 (84.5)</td>
<td>87.5 ± 15.0 (86.5)</td>
<td>89.6 ± 13.3 (89.8)</td>
<td>0.63</td>
</tr>
<tr>
<td>Estimated GFR (ml/min)</td>
<td>90.6 ± 16.7 (88.2)</td>
<td>90.8 ± 24.6 (91.7)</td>
<td>94.2 ± 17.2 (94.1)</td>
<td>0.60</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>4.93 ± 0.527 (3.30)</td>
<td>6.91 ± 7.64 (3.80)</td>
<td>7.58 ± 9.13 (4.40)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

aBP, blood pressure; urine ACR (normal range 0–3.39 mg/mmol or 0–30 mg/g).

Table 2. Mean (SD) plasma HDL subclass concentrations (µmol/L)

<table>
<thead>
<tr>
<th>HDL subclass</th>
<th>No APOL1 risk variants</th>
<th>One APOL1 risk variant</th>
<th>Two APOL1 risk variants</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total HDL particles</td>
<td>N = 20</td>
<td>N = 17</td>
<td>N = 36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36.8 ± 7.6 (34.6)</td>
<td>33.1 ± 7.7 (32.1)</td>
<td>35.6 ± 7.5 (34.3)</td>
<td>0.6600</td>
</tr>
<tr>
<td>Large HDL particles (9.4–14.0 nm)</td>
<td>5.7 ± 4.1 (4.9)</td>
<td>5.2 ± 2.9 (4.4)</td>
<td>7.0 ± 5.2 (6.3)</td>
<td>0.2418</td>
</tr>
<tr>
<td>Medium HDL particles (8.2–9.4 nm)</td>
<td>13.1 ± 8.2 (10.7)</td>
<td>10.1 ± 5.5 (8.5)</td>
<td>9.0 ± 5.6 (7.9)</td>
<td>0.0222</td>
</tr>
<tr>
<td>Small HDL particles (7.3–8.2 nm)</td>
<td>18.1 ± 6.1 (18.5)</td>
<td>17.8 ± 6.6 (17.4)</td>
<td>19.6 ± 6.8 (20.1)</td>
<td>0.3564</td>
</tr>
</tbody>
</table>

aHDL natural logarithm transformed in unadjusted and adjusted analysis; adjusted analysis accounts for the natural logarithm of plasma TG concentrations and ancestry.

*P-value for additive effect based on the number of APOL1 risk variants.

Table 3. Mean (SD) plasma apoB lipoprotein concentrations and average lipoprotein sizes

<table>
<thead>
<tr>
<th>Number of risk variants</th>
<th>Total VLDL</th>
<th>Large VLDL</th>
<th>Medium VLDL</th>
<th>Small VLDL</th>
<th>Total LDL</th>
<th>Large LDL</th>
<th>Small LDL</th>
<th>VLDL</th>
<th>LDL</th>
<th>HDL</th>
<th>Total TG</th>
<th>HDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero (N = 20)</td>
<td>49.3</td>
<td>3.2</td>
<td>17.5</td>
<td>28.6</td>
<td>1254.5</td>
<td>104.6</td>
<td>461.2</td>
<td>688.7</td>
<td>47.4</td>
<td>20.6</td>
<td>9.1</td>
<td>109.2</td>
</tr>
<tr>
<td>Mean</td>
<td>26.6</td>
<td>3.0</td>
<td>16.4</td>
<td>12.6</td>
<td>318.8</td>
<td>68.9</td>
<td>194.1</td>
<td>346.0</td>
<td>7.4</td>
<td>0.5</td>
<td>0.4</td>
<td>45.9</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>44.3</td>
<td>2.7</td>
<td>12.4</td>
<td>26.6</td>
<td>1190.0</td>
<td>90.0</td>
<td>448.0</td>
<td>633.5</td>
<td>45.5</td>
<td>20.6</td>
<td>9.1</td>
<td>94.5</td>
</tr>
<tr>
<td>Median</td>
<td>52.7</td>
<td>2.7</td>
<td>19.4</td>
<td>30.5</td>
<td>1194.4</td>
<td>79.0</td>
<td>479.3</td>
<td>636.2</td>
<td>47.0</td>
<td>20.7</td>
<td>9.1</td>
<td>105.9</td>
</tr>
<tr>
<td>One (N = 17)</td>
<td>29.0</td>
<td>2.5</td>
<td>15.5</td>
<td>16.5</td>
<td>414.3</td>
<td>58.9</td>
<td>299.1</td>
<td>484.1</td>
<td>9.4</td>
<td>0.5</td>
<td>0.5</td>
<td>39.3</td>
</tr>
<tr>
<td>Mean</td>
<td>52.1</td>
<td>2.0</td>
<td>14.9</td>
<td>29.6</td>
<td>1244.0</td>
<td>83.0</td>
<td>468.0</td>
<td>714.0</td>
<td>43.8</td>
<td>20.8</td>
<td>8.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Two (N = 36)</td>
<td>54.7</td>
<td>3.4</td>
<td>21.4</td>
<td>29.9</td>
<td>1167.1</td>
<td>82.0</td>
<td>530.4</td>
<td>554.7</td>
<td>47.2</td>
<td>20.7</td>
<td>9.2</td>
<td>115.2</td>
</tr>
<tr>
<td>Mean</td>
<td>40.2</td>
<td>4.5</td>
<td>22.3</td>
<td>18.6</td>
<td>427.3</td>
<td>53.0</td>
<td>304.0</td>
<td>434.0</td>
<td>6.5</td>
<td>0.4</td>
<td>0.6</td>
<td>64.3</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>41.7</td>
<td>1.9</td>
<td>13.6</td>
<td>26.7</td>
<td>1072.5</td>
<td>74.5</td>
<td>489.5</td>
<td>540.0</td>
<td>46.9</td>
<td>20.8</td>
<td>9.2</td>
<td>94.0</td>
</tr>
<tr>
<td>Median</td>
<td>0.92</td>
<td>0.81</td>
<td>0.91</td>
<td>0.79</td>
<td>0.59</td>
<td>0.46</td>
<td>0.80</td>
<td>0.45</td>
<td>0.66</td>
<td>0.74</td>
<td>0.66</td>
<td>1.00</td>
</tr>
</tbody>
</table>

aIDL, intermediate-density lipoprotein.

*P-value comparing APOL1 non-risk versus APOL1 risk groups.
development of renal microvascular disease, this should be an important avenue for future research in non-diabetic nephropathy.

Molecular genetic breakthroughs, coupled with clinical and histologic analyses in African Americans with presumed HN suggest that mild to moderate essential hypertension may not routinely initiate arteriolar nephrosclerosis, FSGS and/or interstitial fibrosis [16, 26, 27]. As such, novel pathways underlying the development of these non-diabetic nephropathies and new treatments urgently need to be developed to cure this spectrum of kidney diseases. The association of APOL1 with arteriolar nephrosclerosis, FSGS and interstitial fibrosis in African Americans as well as with FSGS, HIV-associated collapsing glomerulopathy and HA-ESRD may provide these breakthroughs. We proposed three potential mechanisms whereby variation in APOL1 could contribute to nephropathy risk in non-diabetic African Americans [8]. Firstly, altered concentrations of HDL subclasses, due to genetic variation in APOL1, might result in cellular and blood vessel injury [28]. Alternatively, circulating ApoL1 variant proteins (either HDL bound or free in the circulation) may be filtered by the kidney, resulting in renal cell damage and non-diabetic renal disease. Finally, altered APOL1 gene expression in various renal cells could lead to nephropathy, potentially via apoptotic or autophagic pathways. While these and other mechanisms are being intensely studied, this report provides initial evidence in support of a potential role for altered medium-sized HDL subclass concentrations on renal injury.

Although ApoL1 proteins bind to plasma HDL particles, whether APOL1 risk variants significantly altered circulating HDL subclass concentrations was unknown. ApoL1 concentration in human plasma is low (~6 μg/mL) [29]; therefore <1% of HDL particles would have bound ApoL1. This observation suggests that the HDL-bound ApoL1 variant protein is not directly altering the metabolism of medium-sized HDL. Rather, APOL1 G1 and G2 risk variants likely function to decrease production of medium-sized HDL. The liver is the major site of HDL particle assembly and HDL apoA-I catabolism [30]. ApoL1 is expressed in the liver [29] and may play a role in modifying production of nascent HDL particles that are destined to become the medium-sized HDL subclass upon maturation. In support of this hypothesis, apoM, another HDL apolipoprotein in low concentration in the plasma [31] was shown to alter the size distribution of nascent HDL subclasses [32]. In addition, ApoL1 may modulate the catalytic activity of plasma proteins, such as phospholipid transfer protein, hepatic lipase and/or cholesteryl ester transfer protein, that remodel HDL subclasses in plasma [33]. For instance, phospholipid transfer protein remodels medium-sized HDL into the larger and smaller HDL subclasses [34], a trend that fits the HDL subclass distribution differences between non-risk and risk variant subjects in our study (Table 2). Further studies will be necessary to test these hypotheses and determine the interrelationships of risk variant ApoL1 proteins, HDL subclass distribution and renal disease.

It appears that variation in APOL1 may account for the shorter renal allograft survival seen in kidneys donated by African Americans [35]. This effect appears to be driven by the genotype of the kidney donor; subclinical nephropathy is likely present prior to organ harvesting and transplantation with progression of renal disease due to the effects of cold ischemia and nephrotoxic calcineurin inhibitors [36]. Current evidence does not support that the APOL1 genotype of recipients (or related alterations in recipient HDL particle concentration) impacts kidney transplant survival.

Identification of the APOL1 kidney disease association in African Americans may lead to novel mechanisms underlying non-diabetic forms of nephropathy. We suspect that different mechanisms are likely present in diabetes (non-APOL1 associated nephropathy) [37]. This advance holds great promise for developing a cure for this devastating spectrum of kidney diseases. Analysis of the role of reduced medium-sized HDL subclass concentrations on risk of renal microvascular disease appears warranted.

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Conflict of interest statement. None declared.

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