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APOL1 Bi- and Monoallelic Variants and Chronic Kidney Diseases in West Africans

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Abstract

Background: Apolipoprotein L1 gene (*APOL1*) variants are risk factors for chronic kidney disease (CKD) among African Americans (AA). Data are sparse on the genetic epidemiology and clinical association of *APOL1* variants with CKD in West Africans, a major group among the AA population. The Human Health and Heredity in Africa (H3Africa) Kidney Disease Research

Network studied 8,355 participants from Ghana and Nigeria: 4,712 participants with CKD stages 2–5, 866 participants with biopsy proven glomerular diseases, and 2777 controls (eGFR ≥90 ml/min/1.73m^2 without proteinuria). The association of CKD with high-risk carriers (two *APOL1* alleles) and low-risk carriers (<2 *APOL1* alleles) was determined by fitting logistic regression models controlling for covariates, including clinical site, age, and sex.

Results: Monoallelic and biallelic *APOL1* variant prevalence were 43.0% and 29.7%, respectively. Compared with low-risk carriers, the adjusted odds of CKD and focal segmental glomerulosclerosis (FSGS) among high-risk carriers were 1.25 (95%CI: 1.11–1.40) and 1.84 (95%CI 1.30–2.61), respectively. Compared with those with no *APOL1* variant (G0/G0), persons with one *APOL1* variant (G0/G1, G0/G2) had higher odds of CKD (OR 1.18, 95% CI 1.04–1.33) and FSGS (adjusted OR 1.61; 95% CI 1.04–2.48). Covariates did not modify the association of 1–2 *APOL1* variants with CKD or FSGS.

Conclusion: In the present study both monoallelic (G1/G0, G2/G0) and biallelic (G1/G1, G2/G2, G1/G2) risk variants had 18% and 25% higher odds of CKD, and 61% and 84% higher odds of FSGS, respectively.

Chronic kidney disease (CKD) disproportionately affects children and adults with African ancestry.[1–3] African Americans (AAs) have a four-fold increased risk of chronic kidney disease (CKD) compared with Americans of European ancestry.[4] This excess CKD burden is not fully explained by clinical and environmental factors, suggesting an underlying genetic risk. Over a decade ago, variants in the Apolipoprotein L1 (*APOL1)* gene were found to be associated with excess risk of focal and segmental glomerulosclerosis (FSGS) and CKD in AAs.[5–6] *APOL1* risk alleles are found exclusively in Africans and people of recent African descent.[7–8] The risk alleles in *APOL1* are two linked single-nucleotide variants (G1 haplotype) and a deletion (G2 haplotype). Persons who are homozygous or compound heterozygous for the high-risk G1 and G2 haplotypes are at increased risk for CKD attributed to hypertension, kidney disease such as focal segmental glomerulosclerosis (FSGS), and HIV-associated nephropathy.[6,9]

Allele frequencies of the G1 and G2 *APOL1* haplotypes differ across sub-Saharan Africa, with G1 frequencies ranging from 0–45% and G2 from 0–24%.[10] These high-risk *APOL1* variants are hypothesized to have evolved more than 10,000 years ago and rose to a high frequency in Africa because they provided protection against lethal African sleeping sickness due to *Trypanosoma brucei rhodesiense and gambiense* infections. There is a paucity of data from well-characterized African populations in sub-Saharan Africa on associations of *APOL1* with CKD. The few reported studies from Africa are limited in scope, cohort size, and geographical spread across West Africa.[11–13] Furthermore, studies in West Africa would be particularly informative because the ancestry of AAs is primarily derived from West Africa, and such data should be important in explaining differences in genotype-phenotype associations.[14–15]

Thus, we conducted a case-control study in West Africans to determine the association of *APOL1* risk variants and haplotypes with CKD, types of CKD, severity of CKD, and effect modification by clinical factors.

STUDY DESIGN AND METHODS

The Human Health and Heredity in Africa (H3Africa) Kidney Disease Research Network is a member of the H3Africa consortium. Recruitment and data collection were described in detail earlier.[16] For a summary, and the full study protocol and statistical analysis plan, see the Supplementary Appendix at NEJM.org. The study was approved by the Institutional Review Board of all participating Institutions; all participants gave written informed consent. The authors vouch for the accuracy and completeness of the data and the reliability of the study protocol. The contributions of the authors are described in the Supplementary Appendix.

Definition of Case-Control Status

Persons with CKD were aged 1–74 years with CKD-EPI estimated glomerular filtration rate (eGFR) <90ml/min/1.73m^2, and/or urine albumin/creatinine ratio (ACR) ≥3.0 mg/mmol (30 mg/g), and persons with biopsy confirmed glomerular diseases, pregnant women were excluded from the study (Supplementary Appendix). Study controls were participants without CKD defined as having an eGFR ≥90ml/min/1.73m^2 and urine ACR <3.0mg/mmol (<30 mg/g). The study population is representative of the West African population affected by CKD with and without *APOL1* CKD risk variants, and our findings are likely to be generalizable (Supplementary Appendix Table S1).

Genotyping

APOL1 kidney risk variants G1 (rs73885319, p.S342G and rs60910145, p.I384M) and G2 (rs71785313, p.N388_Y389del) were genotyped using custom TaqMan assays (Applied Biosystems; see the Supplementary Appendix).

Kidney Biopsy

Kidney biopsies were performed when the GFR was ≥15 and the ACR was greater than 50 mg/mmol or albuminuria ›500 mg/24 hours, renal biopsy samples were read after staining for light, immunofluorescence and electron microscopy at the University of Michigan and Massachusetts General Hospital, as detailed in theSupplementary Appendix.

Statistical Analyses

APOL1 risk status was defined according to the number of copies of the risk alleles (0, 1, or 2 copies). Our analyses included participants with missing data on age, sex and urine ACR; body mass index (BMI) and mean arterial pressure (MAP) used as covariates in association models. Proportion of missingness for any variable was less than 10% (Table 1). We performed multivariate imputation using the method of fully conditional specifications also known as multivariate imputation by chained equations. Logistic regression model was used for categorical variables, and the predictive mean matching method based on linear regression which imputes a value randomly from a set of observed values was used for imputing continuous variables each with specified predictors. For each imputation variable, 25 imputations were performed. We then fitted recessive genetic models to examine the association between *APOL1* high risk variants and CKD, comparing participants with two copies of *APOL1* risk alleles (high-risk) with participants with one or no copy of *APOL1*

risk allele (low risk). Adjustment covariates in the models include age, sex, clinical site and the baseline BMI, MAP, HIV status, diabetes mellitus status, and history of tobacco use Albuminuria was not treated as a covariate because it is part of the definition of CKD. We used multiple imputation with 25 imputations to replace missing values for BMI and MAP. Effect estimates from the imputed datasets were combined using Rubin's rules.[17] Stratified analyses were performed to evaluate potential effect modification by socio-demographic variables and clinical comorbidities. All statistical analyses were performed by using SAS 9.4 software (Supplementary Appendix).

RESULTS

Among the 8,355 participants with available clinical and genotypic data, 5,578 had CKD (4,712 patients with CKD stages 2–5, and 866 with biopsy-proven glomerular diseases) and 2,777 had no CKD. Table 1 displays baseline characteristics of cases, stratified by CKD stage/biopsy. The study population comprised of 63.3% Nigerians and 36.7% Ghanaians. Participants with CKD had higher blood pressure and were more likely to have hypertension and diabetes mellitus (Table 1). Baseline characteristics of participants with biopsy-proven glomerular diseases are depicted in Table S2, which shows histologic findings among the 866 biopsied patients minimal change disease (MCD; n = 300, 34.6%); focal segmental glomerulosclerosis (FSGS; n= 214, 24.7%); membranous nephropathy (MN; n = 88, 10.2%); lupus nephritis (LN; n = 101, 11.7%) and others (n= 161, 18.6%, Table S3).

Distribution of APOL1 Risk Alleles in West Africans

Overall, 43.0% and 29.7% participants carried 1 and 2 *APOL1* risk variants, respectively (Table S4). The G1 haplotype was more frequent (40.7%) than the G2 haplotype (13.9%). The prevalence of *APOL1* high-risk carriers was higher among persons with CKD compared to those without CKD (31.6% vs. 25.7%). The frequency of G1 or G2 risk haplotypes in Ghana and Nigeria, and in the major ethnic groups in the two countries are shown in Tables S5 and S6, and Figure S1.

Association between *APOL1 Risk Haplotypes* and CKD

Among participants carrying 2 *APOL1 risk alleles*, odds ratio of CKD was 1.25 (95% CI 1.11–1.40) compared to low-risk carriers after adjusting for age, sex, mean arterial pressure, HIV status, diabetes mellitus, clinical sites, tobacco use, and ethnic group (Table 2, Figure 1). Odds of having CKD were 1.37 higher (95% CI 1.16–1.61), 2.05 higher (95% CI 1.35–3.13), 1.34 higher (95% CI 1.12–1.61) for G1/G1, G2/G2, and G1/G2 genotype, respectively. In *APOL1* high-risk carriers, there is a graded increased odds by CKD stage; adjusted OR (95% CI) of 1.20 (1.04–1.38), 1.32 (1.12–1.56), 1.37 (1.18–1.59) for CKD stages 2, 3, and 4/5 respectively (Table 3). There were no differences by sex, age, and hypertension, the number of participants with history of diabetes and individuals positive for HIV were too small for meaningful interpretation of the association between CKD and high risk *APOL1* genotype in these subgroups. (Figure S2). Secondary analysis excluding participants with CKD stage 2 or history of diabetes had minimal impact on the effect size of association between CKD and 2 *APOL1* variants (Tables S7 and S8).

Association between One *APOL1* Risk Variant and CKD

To determine the impact of one *APOL1* variant with disease risk, we compared the odds of CKD in participants with a single disease risk variant (G0/G1, G0/G2) versus those with no risk variant (G0/G0). The odds of having CKD was higher in participants with G0/G1 or G0/G2 compared to those with G0/G0 genotype, (adjusted OR 1.18 (95% CI 1.04–1.33) (Table 2, Figure 1 Panel B). We observed a dose-response relationship between dose of *APOL1* risk variants and odds of CKD.

Association between *APOL1* Risk Haplotype and Biopsy-Proven Glomerulopathy

Four major histologic patterns were identified in 866 participants who had kidney biopsies, MCD (300/866, 34.6%), FSGS (214/866, 24.7%), LN (101/866, 11.7%), and MN (88/866, 10.2%) (Table S2). High-risk *APOL1* carriers had 84% (95% CI 1.30–2.61) higher adjusted odds compared to those with low-risk haplotypes of having FSGS (Table 4, Figure 1 Panel A). The odds for MCD, LN, and MN, were not increased (Table 4, Figure S3). There was increased odds of having FSGS with one risk compared with no variant (adjusted OR 1.61; 95% CI 1.04–2.48; Figure 1 Panel B).

DISCUSSION

The genetic locus containing *APOL1* was initially identified as an important risk factor for CKD among AAs.[6] However, definitive estimates of the genetic risk of *APOL1* on CKD obtained from large studies in West Africa, the ancestral origin of most AAs have been lacking. In the present study, among 8,355 participants from Ghana and Nigeria, 29.7% of the population were identified as high-risk *APOL1* carriers. High-risk *APOL1* carriers in the present study had 25% higher odds of having CKD than low-risk carriers. The association was even stronger in patients with biopsy-proven FSGS who had 84% higher odds of FSGS compared with those with low-risk genotypes. There were also increasing odds of disease with advanced CKD. An important and novel finding is that we observed a strong association of a single risk variant with CKD (18% higher odds) and FSGS (61% higher odds) compared to those with no risk variant. This implies that the dose of *APOL1* genetic risk variants may also be relevant for kidney disease.

We found the frequency of high-risk *APOL1* alleles in Ghana and Nigeria as 29.7%, which is higher than the 11.0–16.5% reported among AAs.[18–20] This is expected given that AAs have an approximately 20% European admixture and derive their origins predominantly from West Africa and also from other parts of Africa. The prevalence of *APOL1* high-risk variants in the present study were also higher than the 7–11% reported in East Africa but similar to prior small single center studies from West Africa.[11–12] Prior to the present study, the largest study of *APOL1* and kidney disease in sub-Saharan Africa included 10,769 participants.[21] However, *APOL1* variants were imputed (not genotyped) in that study, which lacked data on biopsy-proven kidney disease.[21] A recent large study comprising ~2000 participants provided new estimates of *APOL1* risk alleles and associations with CKD in rural South Africa.[22] The addition of our study to growing data may reveal clearer picture of how *APOL1* high-risk variants' geographic distribution, haplotype frequencies, associations and effect sizes vary across Africa as a result of population and migration patterns

over millenia interacting with infections and other selection pressures.[23] We observed a wide variation in high-risk *APOL1* haplotypes among ethnolinguistic groups in our study, suggesting that West African people are not monolithic regarding the distribution of *APOL1* risk variants and that ethnic origin should be considered when evaluating genetic risk factors for CKD in sub-Saharan African persons.

APOL1 risk variants for CKD are a major contributor to the disparity in prevalence of CKD among AAs compared with European Americans. The strength of association of *APOL1* high-risk variants varies depending on the cause of CKD, stage of CKD, or study design, and reported estimates of 1.5 – 10.5 increased risk among AAs.[24–25] In the present study, we observed an association with CKD similar to that already reported among AAs.[24,26] The 27% higher odds of CKD and 84% higher odds of FSGS in the present study represent a substantial public health burden of kidney disease among the millions of West Africans, especially in light of the high and premature mortality associated with CKD in West Africa.[1]

We also found a stronger association with CKD progression, suggesting that not only is *APOL1* high-risk haplotype a risk factor for CKD in this population, it may also be a risk factor for disease progression as previously reported for AAs.[26] The findings are also consistent with recent reports in patients with FSGS and MN.[27–28] *APOL1* variants were first discovered in association with ESKD and advanced FSGS, and subsequently with higher risk of disease progression.[24, 26, 29–30] The evidence to date points to *APOL1* CKD risk variants acting as a genetic risk factor for rapid deterioration in kidney function among West African and African ancestry populations globally regardless of the initial kidney insult.[26, 30]

In the present study, we found an almost two-fold increased odds of developing biopsy-proven FSGS in participants with *APOL1* high-risk genotype. Since FSGS is a primary podocytopathy, this finding is not surprising because podocytes are the major target of cytotoxic activity of *APOL1* high-risk variant protein within the kidney.[31] The odds ratio (OR) of ~2 associated with 2 *APOL1* risk variants in patients with FSGS observed in this study is modest compared with OR of ~10 reported in AA.[6] The reason for this is unclear, but possible explanations include survival bias in the AA population, and the possibility that European admixture in AAs may have changed the genetic background against which the *APOL1* risk variant phenotype is expressed. Further, studies reporting high OR are discovery studies that tend to focus on extreme phenotypes and therefore would be expected to have large effect size compared with population and longitudinal studies. Nonetheless, we would still recommend routine genotyping for *APOL1* in patients with FSGS from Nigeria and Ghana. Adopting this recommendation would, in our opinion, help in design and recruitment of participants for future clinical trials.[32–33] Consistent with other reports, we did not find any association with other biopsy-proven glomerulopathies such as MCD, MN, and LN.[28–30]

We also found modest increased odds of CKD in participants with one *APOL1* risk variant compared with those with no risk. In previous studies, carrying one *APOL1* variant was associated with progression to lupus nephritis in patients with systemic lupus erythematosus (SLE), but not with risk of sickle cell disease nephropathy.[34–35] While there is a need for

large studies to evaluate the role of *APOL1* risk variant dose in CKD of diverse etiology, one might speculate that one *APOL1* risk variant in the presence of genetic or environmental modifiers may predispose to the development or progression of CKD.

In the present study, high-risk genotype was not associated with CKD in those with a history of diabetes, consistent with the findings that the *APOL1* high-risk genotype is not a risk factor for diabetic kidney disease, but may be a risk factor for disease progression.[26] There are likely to be other genetic and environmental factors associated with CKD in Africans, which would need to be tested in large longitudinal studies that account for gene-environment interactions and avoid the limitations of previous underpowered studies.[36–39]

Our study has several strengths. It is a large study of *APOL1*-kidney disease associations on the African continent in which the *APOL1* variants were directly genotyped and has provided much needed estimates of effect sizes of *APOL1* high-risk variants in West Africa. Additionally, we obtained kidney biopsies in >800 study participants. The availability of a tissue diagnosis on a large sample size facilitated tests of association between *APOL1* variants by histological classification. The finding of a monotonal increase in odds of *APOL1*-associated kidney disease has an important clinical implication because it changes the risk classification of carriers of one copy of an *APOL1* high-risk variant.

This study also has certain limitations. The observed moderate association between *APOL1* high-risk variants and CKD may be due to the heterogeneity of CKD. However, in exploratory analyses, using CKD stratifications, and sub-analysis of participants with biopsy-proven FSGS, we detected a stronger association. There is a need for longitudinal studies in Africa to evaluate the association between *APOL1* haplotype and progression of CKD. We were not able to genotype for the recently reported *APOL1* N264K (rs73885316) G2 disease-associated modifier.[39–40] Therefore, the potential impact of this variant on our findings is unclear. Furthermore, we did not screen for monogenic kidney diseases by whole genome sequencing (WGS). Future studies utilizing WGS in CKD patients from Africa will define the impact of the *N264K* variant and other modifiers on risk of CKD in Africans, and also remove the confounder effects of participants with monogenic kidney diseases.[39–40] Study participants were recruited from two West African countries, and our results may not be generalizable for other regions of Africa.

In this large study of the prevalence and association of *APOL1* high-risk variants with CKD in persons in West Africa, a region that contributes substantially to the ancestry of African Americans; almost one-third of those tested carried high-risk variants of *APOL1.*

In conclusion, both monoallelic (G1/G0, G2/G0) and biallelic (G1/G1, G2/G2, G1/G2) risk variants had 18% and 25% higher odds of CKD, and 61% and 84% higher odds of FSGS, respectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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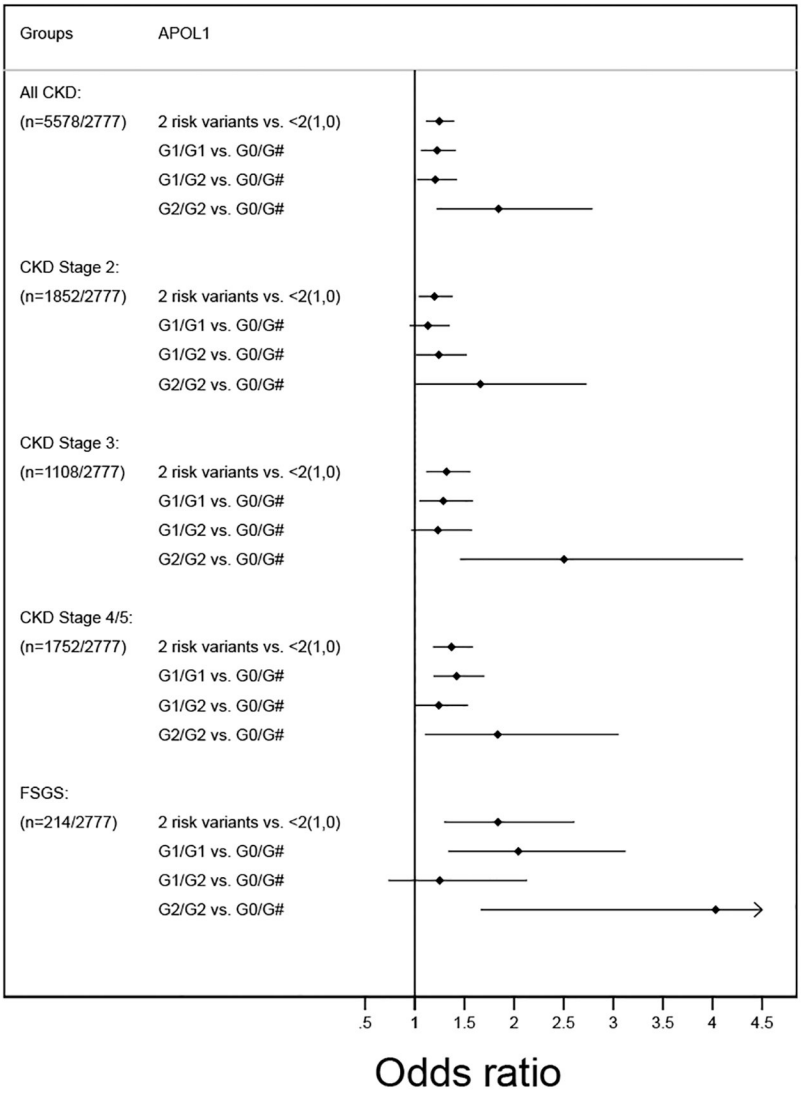

Figure 1Panel A: Association of High-risk *APOL1* Genotype with CKD Among 8,355 West Africans in the Human Heredity and Health in Africa (H3Africa) Kidney Disease Research Network

Note: Forest plot for the association between biallelic *APOL1* high-risk genotype and CKD showed significant odds of CKD among individuals with 2 *APOL1* risk variants compared with those with 1 or 0 risk variant. The adjusted odds of disease increase with worsening CKD stages and the odds was higher in participants with biopsy-proven FSGS. #: G0/G1, G0/G2, G0/G0

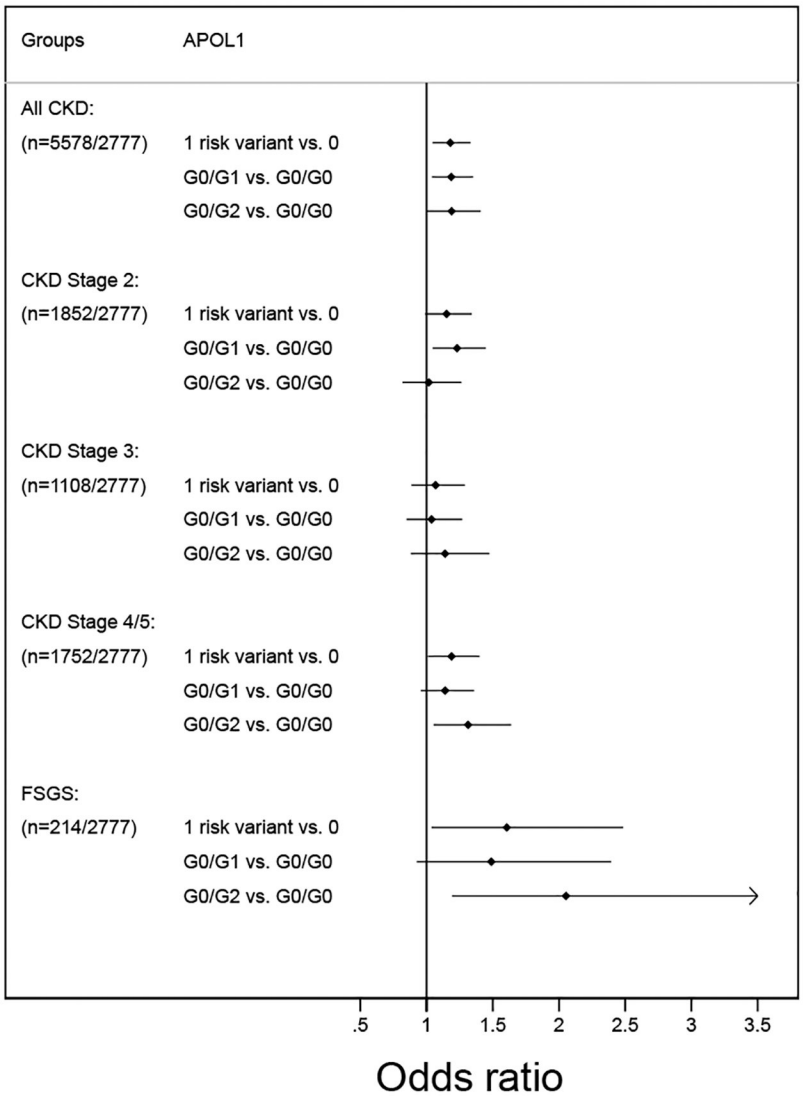

Figure 1 Panel B: Association of One *APOL1* Risk Variant with CKD Among 8,355 West Africans in the Human Heredity and Health in Africa (H3Africa) Kidney Disease Research Network

Note: Forest plot showing higher odds of developing CKD in participants with single disease risk variant (G1/G0, G2/G0) versus those with no risk variant (G0/G0). Similar pattern was observed for participants with biopsy-proven FSGS.

Table 1:

Baseline Characteristics by Chronic Kidney Disease or Glomerular Disease and Controls Among 8355 West Africans in the Human Heredity and Health in Africa (H3Africa) Kidney Disease Research Network

Group	CKD Stage 2 (n=1852)	CKD Stage 3 (n=1108)	CKD Stage 4/5 (n=1752)	Biopsy-Proven Glomerular Diseases (n=866)	Controls (n=2777)	Subjects with Imputed Data†
Mean Age (Years)	50.3±14.6	53.9±14.8	49.7±15.4	29.4±14.2	43.2±14.3	45 (0.5%)
Sex (% Female)	62.0	46.5	44.7	46.0	57.0	28 (0.3%)
Mean BMI (kg/m^2)	27.2±10.1	26.4±7.3	25.9±10.4	23.4±7.7	25.9±8.7	414 (5.0%)
Mean Glomerular Filtration Rate (mL/min)	82.3±17.3	44.7±9.1	15.1±6.5	89.2±46.3	111.9±14.9	290 (3.5%)
Mean Serum Creatinine (mg/dl)	1.0±0.2	1.7±0.4	6.1±3.1	1.7±2.1	0.7±0.2	276 (3.3%)
Median Albumin/Creatinine Ratio mg/g (IQR)	11.6 (67.3)	32.8 (324.3)	86.8 (653.5)	540.9 (1593.5)	9.3 (20.5)	783 (9.4%)
Mean Hemoglobin Concentration (g/dl)	12.7±4.1	12±2.7	11.6±2.9	12.1±6.1	12.6±2.2	567 (6.8%)
Hemoglobin Alleles (SS Count)	26 (1.6%)	18 (1.8%)	21 (1.4%)	8 (1.0%)	43 (2.0%)	N/A
Hemoglobin Alleles (AS Count)	146 (9.1%)	127 (12.8%)	166 (11.0%)	120 (14.7%)	96 (4.5%)	N/A
History of Diabetes Mellitus (% Yes)	20.2	32.3	25.3	2.7	13.5	0 (0.0%)
History of Hypertension (% Yes)	45.2	53.1	56.3	28.9	36.0	0 (0.0%)
Mean Systolic Blood Pressure (mmHg)	132.4±24.1	137.7±26	142.1±29.3	121.1±22.2	128.2±24.5	345 (4.1%)
Mean Diastolic Blood Pressure (mmHg)	78.3±14.9	80.1±16	83.2±18.3	74.9±15.9	76.9±15.2	449 (5.4%)
HIV positive or AIDS (%)	10.1	7.9	7.4	0.2	16.3	0 (0%)
History of Tobacco Use (% Yes)	8.9	14.2	11.9	5.9	6.6	0 (0%)
0 APOL1 Risk Variants Count (%)	487 (26.3)	292 (26.3)	428 (24.5)	225 (26.0)	852 (30.7)	N/A
1 APOL1 Risk Variants Count (%)	808 (43.6)	466 (42.0)	742 (42.4)	365 (42.1)	1212 (43.7)	N/A
2 APOL1 Risk Variants Count (%)	557 (30.1)	351 (31.7)	581 (33.2)	276 (31.9)	713 (25.7)	N/A

†Values represent combined cases and controls. N/A: There were no genotypes imputation for Hemoglobin alleles and APOL1 alleles.

Table 2:

Association of *APOL1* Risk Alleles and Haplotype with Chronic Kidney Disease among 8355 West Africans in the Human Heredity and Health in Africa (H3Africa) Kidney Disease Research Network

***APOL1* risk variants**	**OR (95% CI)**	
	Unadjusted	**Adjusted†**
All CKD cases (N=5578) vs. Controls (N=2777)		
APOL1 Risk Alleles: 2 vs. 1 and 0	1.34 (1.21–1.49)	1.25 (1.11–1.40)
G0/G1 vs G0/G0	1.16 (1.03–1.31)	1.19 (1.04–1.35)
G0/G2 vs G0/G0	1.18 (1.01–1.38)	1.19 (1.00–1.41)
G0/G1 and G0/G2 vs G0/G0	1.17 (1.05–1.30)	1.18 (1.04–1.33)
G1/G1 vs G0/G0	1.46 (1.26–1.69)	1.37 (1.16–1.61)
G1/G2 vs G0/G0	1.40 (1.18–1.65)	1.34 (1.12–1.61)
G2/G2 vs G0/G0	2.25 (1.52–3.34)	2.05 (1.35–3.13)

†Covariates adjusted for: Age, Sex, BMI, Mean Arterial Pressure, HIV status, Diabetes Mellitus status, Clinical Sites, Tobacco use status, Language group (Akan, Ewe, Ga-Adangbe, Hausa/Fulani, Igbo, Others, Yoruba). Confidence interval (CI) widths are not adjusted for multiplicity and may not be used in place of hypothesis testing.

Table 3:

Association of APOL1 Risk Alleles and Haplotype with Chronic Kidney Disease Stratified by CKD Stages in the Human Heredity and Health in Africa (H3Africa) Kidney Disease Research Network

Comparison	CKD Stage 2 (n=1852)	CKD Stage 3 (n=1108)	CKD Stages 4/5 (n=1752)	Biopsy-proven glomerular diseases (n=866)
	Unadjusted Odds ratio (95% CI)			
APOL1 risk alleles: 2 vs. 1 or 0	1.25 (1.09–1.42)	1.34 (1.15–1.56)	1.44 (1.26–1.64)	1.35 (1.15–1.6)
G0/G1 vs G0/G0	1.23 (1.05–1.43)	1.10 (0.91–1.32)	1.17 (1.00–1.37)	1.10 (0.90–1.35)
G0/G2 vs G0/G0	1.02 (0.83–1.25)	1.18 (0.93–1.51)	1.34 (1.09–1.64)	1.23 (0.95–1.60)
G0/G1 and G0/G2 vs G0/G0	1.17 (1.01–1.35)	1.12 (0.94–1.33)	1.22 (1.05–1.41)	1.14 (0.94–1.38)
G1/G1 vs G0/G0	1.30 (1.08–1.57)	1.42 (1.14–1.77)	1.66 (1.38–2.01)	1.46 (1.15–1.85)
G1/G2 vs G0/G0	1.39 (1.13–1.73)	1.33 (1.04–1.72)	1.49 (1.20–1.85)	1.31 (0.99–1.72)
G2/G2 vs G0/G0	1.92 (1.18–3.12)	2.48 (1.47–4.17)	2.18 (1.34–3.55)	2.82 (1.64–4.83)
	Adjusted Odds ratio (95% CI) [†]			
APOL1 risk alleles: 2 vs. 1 or 0	1.20 (1.04–1.38)	1.32 (1.12–1.56)	1.37 (1.18–1.59)	1.13 (0.93–1.39)
G0/G1 vs G0/G0	1.23 (1.05–1.45)	1.04 (0.85–1.27)	1.14 (0.96–1.36)	1.35 (1.06–1.73)
G0/G2 vs G0/G0	1.02 (0.82–1.26)	1.14 (0.88–1.47)	1.31 (1.05–1.64)	1.51 (1.11–2.04)
G0/G1 and G0/G2 vs G0/G0	1.15 (0.99–1.34)	1.07 (0.89–1.29)	1.19 (1.01–1.40)	1.36 (1.08–1.71)
G1/G1 vs G0/G0	1.25 (1.02–1.53)	1.34 (1.05–1.70)	1.59 (1.29–1.96)	1.43 (1.07–1.93)
G1/G2 vs G0/G0	1.37 (1.09–1.72)	1.28 (0.97–1.68)	1.39 (1.09–1.76)	1.25 (0.90–1.74)
G2/G2 vs G0/G0	1.83 (1.10–3.04)	2.61 (1.50–4.54)	2.05 (1.22–3.45)	2.42 (1.28–4.57)

[†]Covariates adjusted for: Age, Sex, BMI, Mean Arterial Pressure, HIV status, Diabetes Mellitus status, Clinical Site, Tobacco use, Language group (Akan, Ewe, Ga-Adangbe, Hausa/Fulani, Igbo, Others, Yoruba). Confidence interval (CI) widths are not adjusted for multiplicity and may not be used in place of hypothesis testing.

Table 4:

Association of APOL1 Risk Alleles and Haplotype with Biopsy-Proven Glomerulopathies in the Human Heredity and Health in Africa (H3Africa) Kidney Disease Research Network

Comparison	MCD (n=300/2777)	FSGS (n=214/2777)	Membranous (n=88/2777)	Lupus (n=101/2777)	Other GN (161/2777)
	Unadjusted Odds ratio (95% CI)				
APOL1 risk alleles: 2 vs. 1 or 0	1.03 (0.79–1.36)	1.87 (1.40–2.49)	1.28 (0.81–2.03)	1.11 (0.71–1.73)	1.54 (1.10–2.16)
G0/G1 vs G0/G0	1.13 (0.83–1.55)	1.06 (0.71–1.60)	0.95 (0.55–1.62)	1.21 (0.71–2.04)	1.12 (0.73–1.73)
G0/G2 vs G0/G0	1.25 (0.85–1.85)	1.68 (1.06–2.68)	0.53 (0.22–1.29)	1.43 (0.75–2.73)	1.03 (0.57–1.83)
G0/G1 and G0/G2 vs G0/G0	1.17 (0.88–1.55)	1.24 (0.86–1.79)	0.83 (0.50–1.38)	1.27 (0.78–2.07)	1.10 (0.73–1.64)
G1/G1 vs G0/G0	1.02 (0.69–1.52)	2.26 (1.49–3.42)	0.83 (0.41–1.69)	1.22 (0.64–2.34)	1.97 (1.24–3.11)
G1/G2 vs G0/G0	1.37 (0.91–2.06)	1.50 (0.89–2.52)	1.42 (0.73–2.79)	0.94 (0.42–2.11)	1.05 (0.56–1.95)
G2/G2 vs G0/G0	0.61 (0.14–2.59)	5.93 (2.82–12.47)	2.71 (0.79–9.39)	4.87 (1.76–13.49)	2.47 (0.84–7.31)
	Adjusted Odds ratio (95% CI) †				
APOL1 risk alleles: 2 vs. 1 or 0	0.92 (0.66–1.29)	1.84 (1.30–2.61)	1.23 (0.73–2.07)	0.96 (0.58–1.61)	1.23 (0.83–1.84)
G0/G1 vs G0/G0	1.37 (0.94–2.00)	1.49 (0.93–2.39)	1.08 (0.59–1.98)	1.18 (0.65–2.14)	1.22 (0.74–2.00)
G0/G2 vs G0/G0	1.52 (0.95–2.43)	2.05 (1.19–3.54)	0.47 (0.18–1.24)	1.43 (0.70–2.93)	1.05 (0.56–1.99)
G0/G1 and G0/G2 vs G0/G0	1.39 (0.98–1.98)	1.61 (1.04–2.48)	0.80 (0.45–1.43)	1.22 (0.70–2.12)	1.13 (0.71–1.81)
G1/G1 vs G0/G0	1.04 (0.63–1.71)	2.85 (1.69–4.81)	0.88 (0.40–1.96)	1.02 (0.48–2.18)	1.79 (1.03–3.11)
G1/G2 vs G0/G0	1.37 (0.82–2.27)	1.73 (0.94–3.19)	1.37 (0.64–2.94)	0.92 (0.38–2.24)	0.79 (0.38–1.63)
G2/G2 vs G0/G0	0.55 (0.12–2.63)	5.62 (2.2–14.34)	2.02 (0.51–7.91)	2.80 (0.82–9.53)	1.62 (0.46–5.70)

†Covariates adjusted for: Age, Sex, BMI, Mean Arterial Pressure, HIV status, Diabetes Mellitus status, Clinical Sites, Tobacco use, Language group (Akan, Ewe, Ga-Adangbe, Hausa/Fulani, Igbo, Others, Yoruba). Confidence interval (CI) widths are not adjusted for multiplicity and may not be used in place of hypothesis testing.