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Original Article

Two copies of *APOL1* variants is associated with an increased risk of ESKD in African Americans based on a meta-analysis

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Abstract: Purpose: The present study aimed to evaluate the association between Apolipoprotein L1 (*APOL1*) polymorphisms and kidney diseases including end-stage kidney disease (ESKD) and chronic kidney disease (CKD). Methods: A systematic literature search in PubMed was performed to extract articles published prior to June 2014 on *APOL1* polymorphisms and kidney diseases. The dichotomous variable data were presented as odds ratio (OR) with 95% CI. In addition, the effect size (ES) with 95% CI was used for the data of HR/OR in the included studies. Results: Nine eligible studies were included in this meta-analysis. Individuals with two copies of the *APOL1* gene exhibited significantly higher risk of developing renal diseases than people with 0/1 copy of *APOL1* (Cohort studies: OR = 2.642, 95% CI 1.451-4.808, P = 0.001; Case-control studies: OR = 3.056, 95% CI 1.520-6.144, P = 0.002). Compared to people with 0/1 copy of *APOL1*, individuals with two copies of *APOL1* had significantly higher risk of developing ESKD (Cohort studies: OR = 2.607, 95% CI 1.363-4.988, P = 0.004; Case-control studies: OR = 3.705, 95% CI 1.915-7.167, P < 0.001). Similar results (Cohort studies: ES = 0.553, 95% CI 0.355-0.751, P < 0.001; Case-control studies: ES = 0.985, 95% CI 0.654-1.316, P < 0.001) were obtained by analyzing the HR/OR. Conclusions: The presence of two copies of *APOL1* variants is associated with an increased risk of developing ESKD.

Keywords: *APOL1* gene, haplotype, meta-analysis, kidney

Introduction

With a significant increase of incidence between 1990 and 2010, chronic kidney failure has been identified as one of the three major causes of death by the WHO Global Burden of Disease [1]. End-stage kidney disease (ESKD) is the last stage of chronic kidney diseases (CKD) such as diabetes, hypertension-attributed kidney disease, glomerulonephritis, and lupus nephritis (LN) [2].

Apolipoprotein L1, a minor apoprotein component of high-density lipoprotein, is encoded by the *APOL1* gene on chromosome 22 [3]. It has been reported that polymorphisms in the exons of *APOL1* rs73885319, rs60910145, and rs71785313 are strongly associated with kidney disease [4, 5]. Previous studies have identified the association between *APOL1* gene polymorphisms and a high risk of ESKD caused by diabetes, hypertension, or LN. However, patients suffering from HIV-associated nephropathy, either with or without *APOL1* polymorphisms, exhibited similar clinical and pathological characteristics, suggesting that *APOL1* may not be involved in the pathogenesis of HIV-associated nephropathy [6]. The majority of these studies have been conducted in African-American populations.

In the present study, we conducted a meta-analysis to evaluate comprehensively the association of *APOL1* gene polymorphisms with a number of kidney diseases including ESKD and CKD. The meta-analysis is based on two types of data, which are the number of patients and

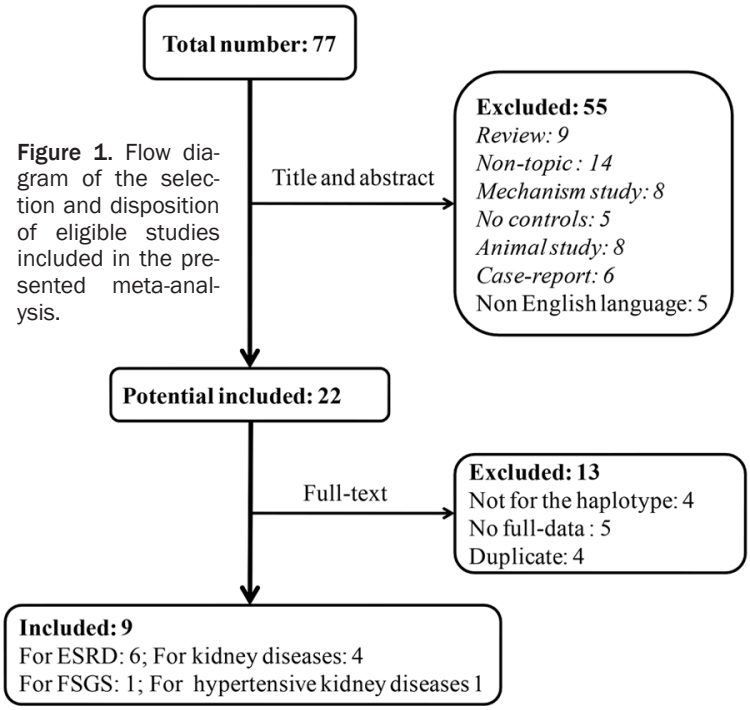

Figure 1. Flow diagram of the selection and disposition of eligible studies included in the presented meta-analysis.

controls and the hazard ratio/odds ratio (HR/OR).

Methods

Literature search

A literature search of the NCBI PubMed database was independently conducted by two investigators to identify relative articles published up to June 2014. Keywords used for the literature search include (APOL1 OR apolipoprotein L1) AND (kidney OR renal) AND (gene OR polymorphism OR SNP). Discrepancies in data interpretation were resolved by discussion, review of the studies, and consultation from two experts on kidney disease genetics when necessary.

Inclusion and exclusion criteria

Inclusion criteria were as follows: i) studies on *APOL1* genotyping in patients with kidney diseases; ii) studies on haplotype of *APOL1* (G1: rs73885319 and rs60910145, G2: rs7178-5313); iii) with the data of 0, 1 and 2 copies of *APOL1* variants or of odds rate (OR) or hazard rate (HR) and 95% confidence interval (95% CI). Studies without *APOL1* haplotype were excluded from this meta-analysis. When two or more studies reported the same subjects, we chose the study with the larger population.

Quality assessments of published studies

The quality of the selected studies was independently assessed by two reviewers based on the Newcastle-Ottawa Scale (NOS). The NOS uses different tools for the evaluation of the quality of case-control and cohort studies and consists of three parameters: selection, comparability, and exposure/outcome assessments. Briefly, the NOS assigns a maximum of four points to selection, two points to comparability, and three points to exposure or outcome. In the present study, NOS scores of 1-3, 4-6, and 7-9 were classified as low, intermediate, and high-quality, respectively. Any discrepancies in the quality assessment of the published studies were resolved by discussion and review of the original studies.

Data extraction

For each eligible study, the following information was extracted: i) the first author's name and the year of publication; ii) study design (case-control and cohort); iii) the types of kidney diseases (ESKD and CKD, *etc.*); iv) the studied population; v) the number of kidney diseases and control of the *APOL1* haplotype. In addition, the HR/OR with 95% CI was extracted and analyzed.

Statistical analysis

The prevalence of the *APOL1* haplotype was compared by calculating an OR (case-control study) with a 95% CI and effect size (ES) with 95% CI based on a fixed-effect model or a random-effect model. Heterogeneity between studies was assessed using both the Chi-square test with a P value ≤ 0.10 and the inconsistency index (I^2) with a cut-off of 50%. Potential publication bias was comprehensively assessed based on Begg's funnel plot and Egger's rank correlation test of asymmetry. Publication bias was determined with a P value ≤ 0.05 based on Egger's and Begg's tests. All statistical analyses were performed using the

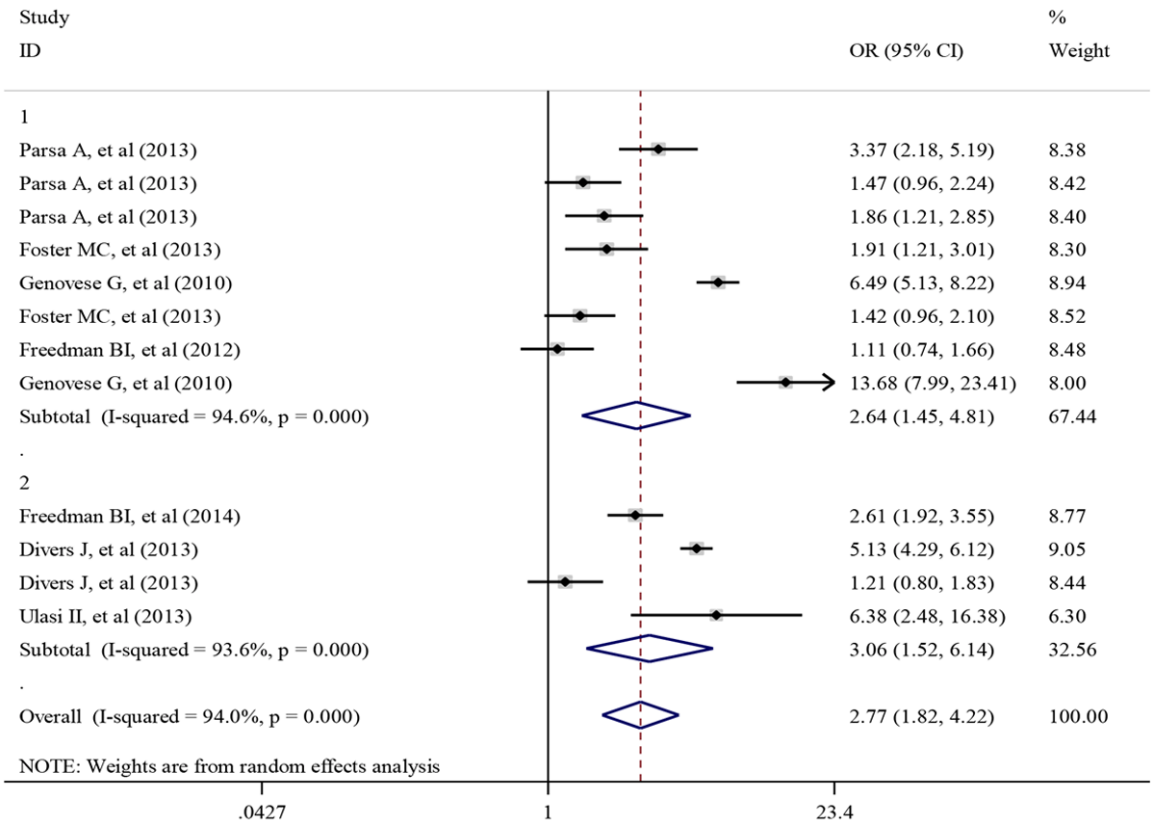

Figure 2. Comparison of the forest plots of APOL1 risk variants between renal diseases and controls (1: Cohort study, 2: Case-control study).

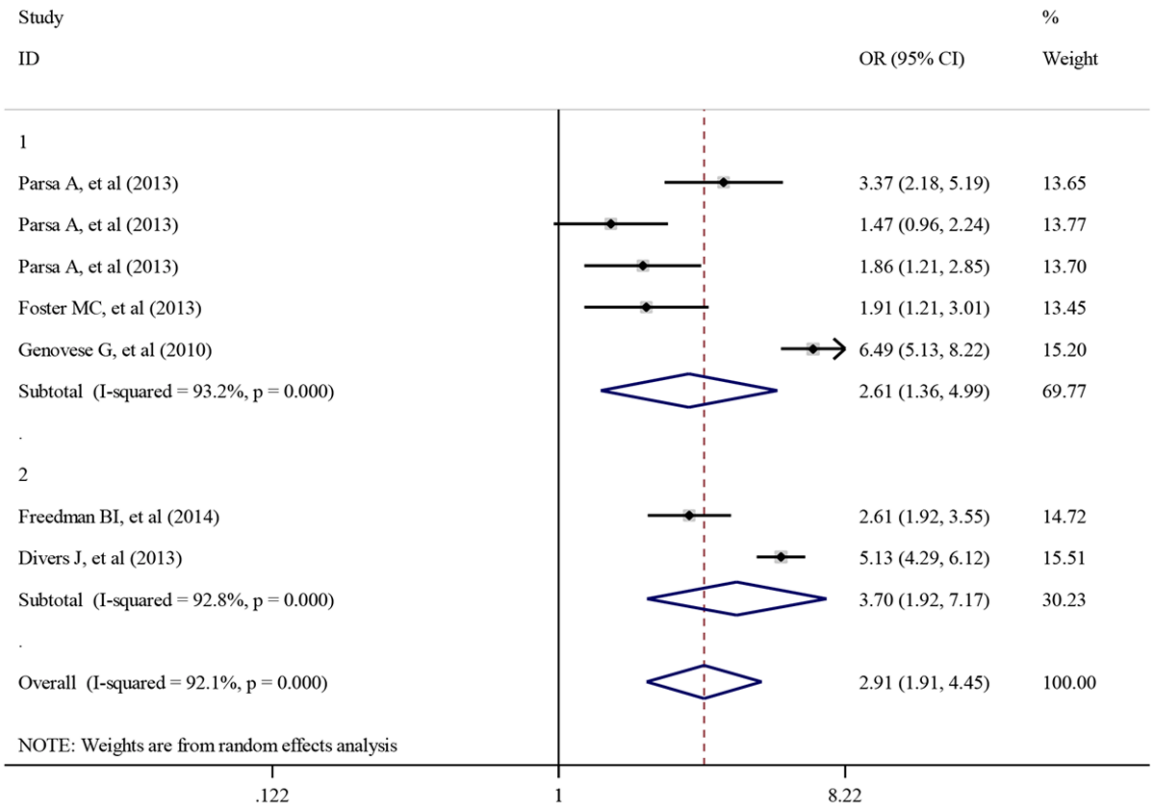

Figure 3. Comparison of the forest plots of APOL1 risk variants between ESKD and controls (1: Cohort study, 2: Case-control study).

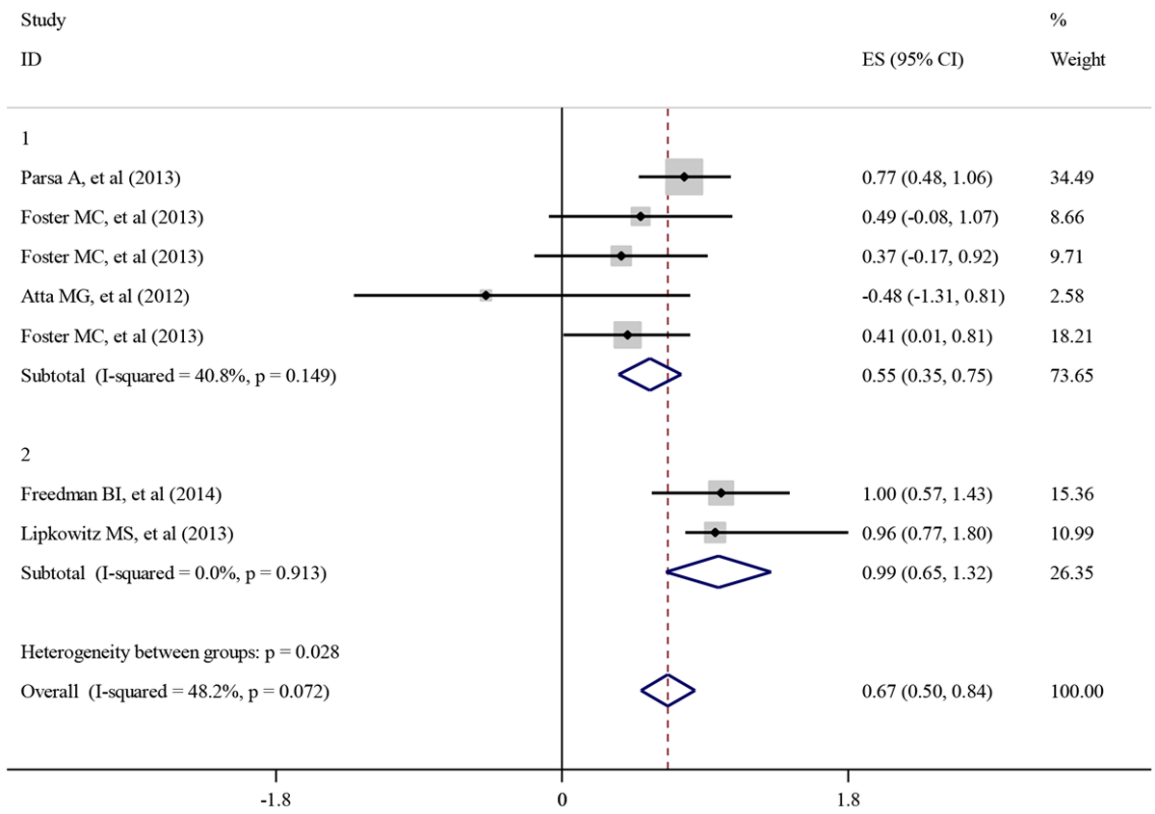

Figure 4. Comparison of the forest plots of APOL1 risk variants between renal diseases and controls, based on the analysis of HR/OR (1: HR, 2: OR).

STATA version 11.0 (STATA Corporation, College Station, TX, USA).

Results

Characteristics and quality of selected studies

Nine eligible studies were identified and included in this meta-analysis based on the PubMed literature search. The studies consisted of five cohort and four case-control studies. Among them, six, four, one, and one studies focused on ESKD, kidney diseases (defined as an MDRD GFR < 60 ml/min per 1.73 m^2 and/or urine ACR > 430 mg/g), focal segmental glomerulosclerosis (FSGS), and hypertensive kidney diseases, respectively. Eight studies were comprised of African American (AA) and one of African subjects. Based on the NOS scores, five, three, and one studies were of intermediate, high, and low quality, respectively. The characteristics of the nine studies are shown in **Figure 1**.

APOL1 haplotype in renal diseases based on analyzed number

Overall, 1, 781 patients with different renal diseases (ESKD, CKD, FSGS, kidney diseases, and hypertensive kidney diseases) harbored two copies of *APOL1* risk variants (G1 homozygote, G2 homozygote and G1/G2 heterozygote) and 2, 752 had 0/1 copy of *APOL1* risk variants. In the control group, 852 patients with renal diseases had two copies of *APOL1* risk variants and 1, 251 had 0/1 copy of *APOL1* risk variants. As heterogeneities were identified in the cohort studies (I^2 = 94.6%, P < 0.001) and case-control studies (I^2 = 93.6%, P < 0.001), the random-effect model was used in this meta-analysis. Compared with patients with 0/1 copy of *APOL1* risk variants, patients with 2 copies of *APOL1* risk variants exhibited a significantly higher risk of developing kidney diseases (Cohort studies: OR = 2.642, 95% CI

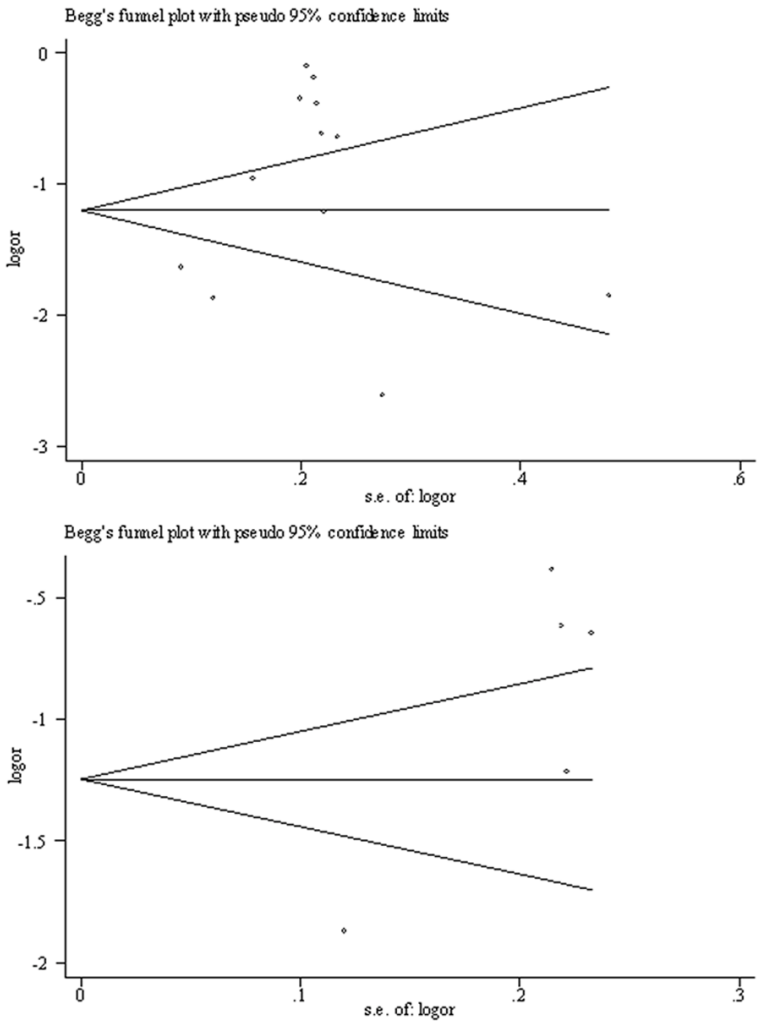

Figure 5. No significant publication bias was found basd on the Begg's funnel plots.

1.451-4.808, P = 0.001; Case-control studies: OR = 3.056, 95% CI 1.520-6.144, P = 0.002) (**Figure 2**).

Among the ESKD diseases, 1, 509 patients harbored two copies of *APOL1* risk variants and 1, 719 contained 0/1 copy of *APOL1* risk variants. In the control group, 652 patients without ESKD contained two copies of *APOL1* risk variants and 900 patients had 0/1 copy of *APOL1* risk variants. As the heterogeneities were identified in the cohort studies (I^2 = 93.2%, P < 0.001) and case-control studies (I^2 = 92.8%, P < 0.001), the random-effect model was used in this meta-analysis. Compared with patients with 0/1 copy of *APOL1* risk variants, patients with two copies exhibited a significantly higher risk of developing ESKD (Cohort studies: OR = 2.607, 95% CI 1.363-4.988, P = 0.004; Case-control studies: OR = 3.705, 95% CI 1.915-7.167, P < 0.001) (**Figure 3**).

APOL1 haplotype in renal diseases based on the HR/OR and 95% CI

As heterogeneities were not identified in the cohort studies (I^2 = 40.8%, P = 0.149) or the case-control studies (I^2 = 0%, P = 0.913), the fixed-effect model was used in this meta-analysis. Compared with patients with 0/1 copy of *APOL1* risk variants, people with two copies of *APOL1* risk variants demonstrated a significantly higher risk of developing kidney diseases (Cohort studies: ES = 0.553, 95% CI 0.355-0.751, P < 0.001; Case-control studies: ES = 0.985, 95% CI 0.654-1.316, P < 0.001) (**Figure 4**).

Sensitivity analysis and publication bias

For overall analysis and ESKD diseases, the results of OR were not changed by sensitivity analysis. No publication bias was identified for the overall analysis (Begg's test: P = 0.903 and Egger's test: P = 0.061). However, publication bias was identified in the ESKD analysis (Begg's test: P = 0.368 and Egger's test: P = 0.017) (**Figure 5**).

Discussion

The two genetic variants (G1 and G2) of *APOL1* are common in populations of recent African descent, but they are rare or absent in most other populations. These variants are believed to explain the differing incidence of ESKD between black and white patients [7, 8]. The present meta-analysis extracted and evaluated published studies to evaluate the role of *APOL1* variants in the pathogenesis of different kidney diseases.

Our results showed that the presence of two copies of *APOL1* variants was associated with

a significantly higher risk of developing kidney diseases, especially ESKD, than 0/1 copy of *APOL1* variants. The association between *APOL1* variants and the pathogenesis of kidney diseases might be attributed to two aspects: variant-specific changes in protein expression and distribution, and variant-specific changes in protein function. It has been reported that increased serum levels of APOL1 were identified in individuals with hyperlipidemia [9] and patients with type 2 diabetes in which the APOL1 level correlated with the triglyceride level. The prevalence of ESKD is increasing due to effective therapy against CKD, which significantly extends the survival and improves the quality of life of CKD patients. The majority of CKD patients who finally develop ESKD have diabetes and hypertension, although others have glomerulonephritis, familial kidney diseases, and malignancies affecting the function of kidney [10]. The mortality due to cardiovascular complications in kidney disease patients receiving dialysis is approximately 30 times higher than that of the general population [11]. *APOL1* variants are involved in the development of kidney diseases through affecting lipid metabolism. Hyperlipidemia may accelerate the progression of CKD, further increasing the morbidity and mortality of patients with kidney disease [12]. In addition, a negative association between total HDL cholesterol and estimated glomerular filtration rate (eGFR) has been reported in Africans [13]. Specifically, lower total HDL cholesterol was associated with higher eGFR, which was more evident in patients with two copies of *APOL1* risk variants than patients with 0/1 risk variant [14]. Therefore, lipid metabolism disorders, such as low HDL cholesterol and/or high triglycerides, contribute to the development of CKD. Additionally, high triglycerides and low HDL cholesterol may be predictors of further loss of renal function [15].

Expression of the *APOL1* protein is localized to specific cell types in normal human kidney tissues [16]. In FSGS and HIV-associated nephropathy kidney disease, reduced expression of *APOL1* in the podocytes and proximal tubules and *de novo* expression of APOL1 in small arterial vessels of the kidney have been observed [16]. However, no significant difference in the pattern of APOL1 expression and distribution was identified between individuals with and without *APOL1* risk variants, suggesting that APOL1 distribution changes are more likely responses to kidney damage. Though our meta-analysis has some limitations, we demonstrate that the *APOL1* gene is associated with the pathogenesis of kidney diseases in the African American population.

In conclusion, our meta-analysis, based on nine published studies, suggests that the *APOL1* gene is associated with the pathogenesis of kidney diseases in the African American population. Specifically, the presence of 2 copies of *APOL1* variants correlates with an increased risk of developing ESKD compared to having 0/1 copy of *APOL1* variants. However, studies with larger sample sizes and randomized studies including more diverse populations should be conducted to further understand the relationship between *APOL1* polymorphisms and different kidney diseases.

Disclosure of conflict of interest

None.

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