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Haplotypes in the *MYH9* Locus Are Associated with Prevalent Chronic Kidney Disease Among South African Patients with Hypertension

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Abstract

Chronic kidney disease (CKD) is a major global health concern, with disproportionately high prevalence in Africa, where hypertension is a leading cause. Variants in the myosin heavy chain 9 (*MYH9*) gene, along with the closely linked apolipoprotein L1 (*APOL1*) gene, are strongly implicated in CKD risk, with some variants appearing more frequently in African populations. Despite the significant burden in African populations, limited genetic data exist on CKD among populations of African ancestry, particularly those with hypertension. This study investigates the association of four *MYH9* (rs3752462T>C, rs4821480G>T, rs2032487C>T, and rs4821481C>T) and three *APOL1* (rs73885319A>G, rs60910145T>G, and rs71785313ATAATTATAA>ATAA) polymorphisms with CKD in South African participants with hypertension. Participants (n = 234) comprising 120 cases (i.e., confirmed CKD) and 114 controls (i.e., without CKD) were selected from the Pharmacogenomics biorepository for hypertension and dyslipidaemia (PRECODE) cohort. Genetic characterisation was performed using polymerase chain reaction–restriction fragment length polymorphism, TaqMan assay and MassArray genotyping, and results were validated using Sanger sequencing. Logistic regression was used to evaluate associations between each single-nucleotide polymorphism (SNP) and prevalent CKD. Linkage disequilibrium (LD) was assessed, and haplotype analysis was carried out to determine combined effects of variants on disease status. Associations were treated as nominal at $p < 0.05$ and significant after Bonferroni correction ($p < 0.0018$) for the 28 SNP tests; $p < 0.01$ for the haplotype analyses. Following adjustment for *APOL1* risk status, only *MYH9* rs2032487T>C remained nominally associated with CKD, with carriers of the C allele having higher odds of CKD than TT genotype carriers (OR = 2.22, 95% CI:1.11–4.42); this did not meet the Bonferroni threshold. LD assessment revealed limited allelic correlation between the *APOL1* and *MYH9* loci. Haplotype analysis identified the *MYH9* E-1 haplotype (T-G-C-C) as significantly associated with higher odds of CKD (OR = 2.36; 95% CI: 1.33–

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4.18). These findings suggest an association between *MYH9* variation and prevalent CKD among South African patients with hypertension. Low frequencies of *APOL1* high-risk genotypes mean that the gene's potential contribution to CKD cannot be fully excluded. However, given these low frequencies in the South African population, *MYH9* variants and haplotypes may warrant further investigation as potential population-specific markers of CKD susceptibility.

Keywords: Africa; Chronic Kidney Disease; genetics; hypertension; *APOL1*; *MYH9*

1. Introduction

Chronic Kidney Disease (CKD) is non-communicable, and characterised by the loss of kidney function over time [1]. The definition of CKD, according to the international guidelines provided by the kidney disease group Improving Global Outcomes (KDIGO), is "an abnormality in kidney structure or function persisting at least three months" [2]. This hinders the kidneys from properly filtering and removing waste products and excess fluids from the body [2]. Consequently, waste and fluids accumulate, leading to severe health complications, including end-stage kidney disease (ESKD) [3].

CKD is categorised into five stages, based on the estimated glomerular filtration rate (eGFR), a measure of how effectively the kidneys filter blood, and albuminuria [4]. Many people do not show symptoms until advanced stages [1]. The delay in early presentation of symptoms is one of the reasons why CKD is often missed, leading to a greater risk of progression to ESKD [5]. Delayed diagnosis of CKD not only impacts patients, but also challenges healthcare systems, emphasising the importance of better screening and early intervention [6].

CKD contributes heavily to the global disease burden and mortality rate, with the World Health Organisation (WHO) ranking it as the ninth leading global cause of death [7]. The estimated worldwide prevalence is reported to be around 10–15%, and CKD-related deaths rose by a staggering 95% between 2000 and 2021 [7]. This increase highlights the growing impact of CKD, and it is anticipated to continue rising, due to aging populations, higher rates of diabetes and hypertension, and better survival rates for those predisposed to CKD [4,8,9]. Despite the global burden, there are notable discrepancies in CKD prevalence among various regions and ethnic groups. African populations have consistently demonstrated a higher prevalence of CKD compared to other regions, with an estimated rate of around 14% in the adult population [6,10].

Along with the variation in prevalence, CKD also displays a high level of heterogeneity, with a vast range of aetiologies. Both communicable and non-communicable diseases pose as risk factors for CKD [8]. Globally, diabetes and hypertension are considered the most common causes [5,11]. Individuals with cardiovascular diseases, glomerulosclerosis, human immunodeficiency virus (HIV) infections, obesity, or systemic lupus erythematosus (SLE) are also predisposed to developing CKD [12–15]. In Africa, hypertension is the leading cause of CKD [16]. Hypertension is generally defined by blood pressure (BP) above 140/90 mmHg (systolic/diastolic) [2]. Hypertension's damaging effects on kidney vasculature and function predispose individuals to kidney injury, leading to CKD [17,18]. The relationship between hypertension and CKD is complex. Hypertension is both a cause and a result of CKD [1,19], making the determination of the exact pathogenesis of the disease difficult [10].

Emerging research has shed light on the role of genetics in CKD susceptibility, with evidence of polygenic risk. The apolipoprotein L1 (*APOL1*), on chromosome 22, has been identified as a candidate gene for increased CKD susceptibility [20,21]. Individuals of

African ancestry possessing any two of the *APOL1* G1 (p.Ser342Gly and p.Ile384Met) or G2 (p.Asn388_Tyr389del) risk alleles are estimated to have twice the risk of developing CKD [21,22]. These variants are almost exclusive to individuals of African ancestry, and are rare in European populations. This is thought to be due to positive selection of the variants due to them conferring protection against the African sleeping sickness *Trypanosoma brucei* parasite infection [23]. The Myosin Heavy Chain 9 (*MYH9)* gene located on chromosome 22q12.3, only 14 kbp upstream from the *APOL1* gene, is also important in CKD risk [24]. *MYH9* encodes the non-muscle myosin heavy chain IIA, a critical motor protein involved in actin cytoskeleton dynamics [25]. This protein plays an essential role in various cellular processes, including cell migration, cell shape maintenance, and cell polarization [24].

In situ hybridisation and immunohistology studies show that *MYH9* mRNA is highly expressed in kidney podocytes [26]. Podocytes are specialised cells found in the glomeruli, and form part of the kidney's filtration barrier. Podocytes are therefore crucial in maintaining normal capillary structure and function, which are vital for the filtration of blood in the kidneys [27]. Mutations in the *MYH9* gene can lead to podocyte dysfunction, contributing to kidney disease. It is hypothesized that *MYH9* mutations result in cytoskeletal rearrangement and increased susceptibility to glomerular injury, leading to kidney disease [13,28].

The role of *MYH9* in CKD first came into prominence in 2008, when mapping by admixture linkage disequilibrium (MALD) identified several single-nucleotide polymorphisms (SNPs) associated with a fourfold increased risk of non-diabetic ESKD [15,29]. These SNPs are now organized into haplotypes such as E-1, S-1, F-1, and L-1, according to their tendency towards linkage disequilibrium (LD), suggesting a complex genetic architecture contributing to CKD risk [12,29,30]. Dense mapping of the *MYH9* region has localised the E-1 haplotype block as the most strongly associated and informative variants [25]. The risk alleles that make up this haplotype are T-G-C-C across the four SNPs (rs3752462T>C, rs4821480G>T, rs2032487C>T, and rs4821481C>T) [13,15,29–31].

The E-1 haplotype frequency is higher in African populations compared to those of European descent [32,33]. European and Middle Eastern populations have higher frequencies of the E-2 haplotype (C-T-T-T), which is indicated as protective [34]. The effects of CKD are often not prevalent until the later stages of the disease, so establishing the associated genetic-risk variants and understanding their interplay with the disease could lead to a better understanding of the disease pathogenesis, as well as help in identifying susceptible patients, and ultimately, the development of novel therapeutic targets and interventions [32,35].

Despite the significant advances in genetic technologies in recent years, however, there are still major gaps in knowledge on genetic susceptibility to CKD. Previous studies have identified *MYH9* as a major susceptibility locus for HIV-associated nephropathy (HIVAN), focal segmental glomerulosclerosis (FSGS), diabetic, and non-diabetic forms of CKD, as well as in lupus nephritis (LN) patients [13]. Although hypertension is one of the leading causes of CKD, there are few studies that focus on CKD risk in hypertensive patients. Furthermore, there is limited data on CKD in Africa. This study aimed to investigate the association between four *MYH9* variants (rs3752462T>C, rs4821480G>T, rs2032487C>T and rs4821481C>T) and CKD susceptibility among South African patients with hypertension. Additionally, three variants in the neighbouring *APOL1* gene (rs73885319A>G, rs60910145T>G, and rs71785313ATAATTATAA>ATAA) were characterised to investigate their potential contribution to CKD susceptibility and explore the relationship between *MYH9* and *APOL1* variation in this population.

2. Results

2.1. Description of the Study Cohort

A total of 234 participants were included in this stud,y and Table 1 shows their demographic and clinical characteristics. Fifty-one percent had CKD (cases, n = 120) and 49% had no CKD (controls, n = 114). Diabetes was more frequent in cases than in controls (32% vs. 18%, $p = 0.04$). Body mass index (BMI) did not differ between the groups ($p = 0.08$).

Table 1. Demographic and clinical characteristics of cases and controls for the CKD genetic association study among South Africans.

Variable	All Participants (n = 234)	Cases (n = 120)	Controls (n = 114)	*p*-Value
Sex, n (%)				
Male	121 (52)	62 (52)	59 (52)	1.00
Female	113 (48)	58 (48)	55 (48)	
Age in years, median (IQR)	66.5 (54.1–77.0)	67.0 (54.1–77.0)	66.2 (54.3–76.9)	0.94
Ethnicity, n (%)				
African	52 (22)	28 (23)	24 (21)	0.79
Mixed	182 (78)	92 (77)	90 (79)	
High BMI (>25 kg/m²), n (%)				
Yes	95 (41)	41 (34)	54 (47)	0.08
No	87 (37)	50 (41)	37 (32)	
Unknown	52 (22)	29 (25)	23 (21)	
High Blood pressure (>130/80 mmHg), n (%)				
Yes	157 (67)	78 (65)	79 (70)	0.37
No	51 (22)	21 (17.5)	30 (26)	
Unknown	26 (11)	21 (17.5)	5 (4)	
Diabetes, n (%)				
Yes	59 (25)	38 (32)	21 (18)	0.04
No	174 (75)	81 (67)	93 (82)	
Unknown	1 (0.5)	1 (1)	0 (0)	
Dyslipidaemia, n (%)				
Yes	32 (14)	20 (17)	12 (11)	0.24
No	201 (86)	99 (82)	102 (89)	
Unknown	1 (0.5)	1 (1)	0 (0)	
Other comorbidities, n (%)				
Yes	79 (34)	40 (33)	39 (34)	1.00
No	155 (66)	80 (67)	75 (66)	
Unknown	0 (0)	0 (0)	0 (0)	
Smoking, n (%)				
Yes	87 (37)	44 (37)	43 (38)	0.97
No	136 (58)	70 (58)	66 (58)	
Unknown	11 (5)	6 (5)	5 (4)	
Alcohol consumption, n (%)				
Yes	58 (25)	31 (26)	27 (24)	0.80
No	164 (70)	82 (68)	82 (72)	
Unknown	12 (5)	7 (6)	5 (4)	
Medications, n (%)				
Yes	159 (68)	80 (66)	79 (60)	0.45
No	72 (31)	39 (33)	33 (29)	
Unknown, n	3 (1)	1 (1)	2 (2)	

Controls were frequency matched to cases for age and sex. Statistics presented: median (interquartile range; IQR) for continuous variables; count (%) for categorical variables. *p*-values calculated using Wilcoxon rank-sum test or chi-squared test; unknown rows show the number of samples for which the data is missing; abbreviations: BMI, body mass index.

2.2. MYH9 and APOL1 Allele Frequencies

Genetic characterisation was successful on four SNPs in the *MYH9* and three SNPs in the *APOL1* gene. We report here the differences in allele relative frequencies between Mixed ancestry and African ancestry populations. Table 2 shows the combined case and control-allele relative frequencies for each variant in African-ancestry participants compared to Mixed-ancestry participants. Allele relative frequencies differed significantly between the two groups for all SNPs ($p \leq 0.003$). Relative frequencies in cases and controls can be found in Supplementary Tables S3 and S4.

Table 2. Comparison of *MYH9* and *APOL1* variant allele relative frequencies (f) between African and Mixed-ancestry participants.

Gene	SNP	Variant Allele	Mixed Ancestry n(f)	African n(f)	*p*-Value
MYH9	rs3752462T>C	T	225 (0.68)	72 (0.79)	0.003
	rs4821480G>T	G	114 (0.34)	58 (0.61)	<0.001
	rs2032487C>T	C	112 (0.32)	43 (0.47)	<0.001
	rs4821481C>T	C	102 (0.30)	54 (0.57)	<0.001
APOL1	rs60910145T>G	G	17 (0.05)	12 (0.13)	<0.001
	rs73885319A>G	G	17 (0.05)	12 (0.13)	<0.001
	rs71785313 Ins>Del	Del	21 (0.07)	14 (0.15)	<0.001

Ins represents the wildtype sequence (ATAATTATAA) for SNP rs71785313, and del represents the sequence after a 6-bp deletion (ATAA).

2.3. MYH9 and APOL1 Genotype Frequency Distributions Between Cases and Controls and Association with CKD

We report here the presence of genetic variation in *MYH9* and *APOL1* genes. Distribution of *MYH9* and *APOL1* genotypes was compared between cases and controls. Table 3 shows genotype count and relative frequencies for each of the seven SNPs, four in *MYH9* (rs3752462, rs4821480, rs2032487, and rs4821481) and three in *APOL1* (rs60910145, rs73885319, and rs71785313) under a dominant genetic model. The codominant, additive and recessive models are also presented in Supplementary Table S5.

Of the seven variants investigated, rs3752462C and rs2032487C showed nominal associations with CKD ($p < 0.05$), but none met the Bonferroni threshold ($p < 0.0018$). For the *MYH9* SNP rs3752462, individuals carrying at least one C allele (T/C or C/C) had lower odds of CKD (OR = 0.57; 95% CI: 0.34–0.97; $p = 0.039$) compared to those with the T/T genotype in the unadjusted analysis, and the estimate was similar after adjusting for age, sex, ethnicity and diabetes (OR = 0.57; 95%CI: 0.34–0.99; $p = 0.047$). For the *MYH9* SNP rs2032487, carriers of at least one C allele had higher odds of CKD than those with the T/T genotype (unadjusted OR = 2.29; 95% CI: 1.21–4.41; $p = 0.012$; adjusted OR = 2.04; 95% CI: 1.06–4.00; $p = 0.035$). This indicates that carriers of the C allele had more than twice the odds of CKD relative to non-carriers. For rs4821480G allele carriers and rs4821481C allele carriers, the associations trended towards higher odds of CKD in both unadjusted analyses (OR = 1.68; 95% CI: 0.94–3.00; $p = 0.062$ and OR = 1.69; 95% CI: 0.99–2.90; $p = 0.054$, respectively) and the adjusted analyses (OR = 1.67; 95% CI: 0.98–3.00; $p = 0.082$ and OR =

1.62; 95% CI: 0.92–2.88; $p = 0.094$, respectively). No differences in *APOL1* genotype frequencies were observed between cases and controls for any of the three variants.

To assess whether the *MYH9* associations were influenced by *APOL1*, the four *MYH9* variants were analysed in dominant logistic regression models that included *APOL1* risk status (as defined in Section 2.4), in addition to age, sex, ethnicity and diabetes. These models include only participants with both *MYH9* and *APOL1* genotyping data available (n = 214), so the sample sizes are smaller than in Table 3. To distinguish the effect of including *APOL1* risk status from the effect of the reduced sample size, corresponding models excluding *APOL1* risk status were fitted using the same participants. Unadjusted estimates were also calculated in this reduced sample, to facilitate comparison. The results are presented in Table 4.

The association between *MYH9* rs2032487C>T and CKD remained nominally significant following covariate adjustment, with and without the inclusion of *APOL1* risk status. Carriers of at least one C allele (C/T or C/C) had higher odds of CKD than T/T homozygotes in the unadjusted analysis (OR = 2.45; 95% CI: 1.26–4.76; $p = 0.008$). This estimate remained similar after adjustment for age, sex, ethnicity and diabetes (OR = 2.28; 95% CI: 1.15–4.53; $p = 0.018$), and following additional adjustment for *APOL1* risk status (OR = 2.22; 95% CI: 1.11–4.42; $p = 0.020$); however, these estimates did not meet the Bonferroni threshold ($p < 0.0018$).

For rs3752462T>C, carriers of the C allele showed a trend towards lower odds of CKD compared to T/T homozygotes in the unadjusted analysis (OR = 0.61; 95% CI: 0.35–1.05; $p = 0.073$).

For rs4821480G>T, carriers of at least one G allele had higher odds of CKD than T/T homozygotes in the unadjusted analysis (OR = 1.68; 95% CI: 0.96–2.94; $p = 0.070$). The estimate remained similar after adjustment for age, sex, ethnicity and diabetes (OR = 1.79; 95% CI: 0.97–3.29; $p = 0.062$), and following additional adjustment for *APOL1* risk status (OR = 1.76; 95% CI: 0.95–3.24; $p = 0.072$). Similarly, carriers of at least one C allele at rs4821481C>T had higher odds of CKD than T/T homozygotes (unadjusted OR = 1.71; 95% CI: 0.98–2.96; $p = 0.058$). This estimate remained largely unchanged after adjustment without *APOL1* (OR = 1.70; 95% CI: 0.94–3.07; $p = 0.081$) and with additional adjustment for *APOL1* risk status (OR = 1.66; 95% CI: 0.91–3.02; $p = 0.092$). Neither variant showed a statistically significant association with CKD.

Table 3. The distribution of *MYH9* and *APOL1* genotypes and *APOL1* G0/G1/G2 diplotype relative frequencies (f) between cases and controls among South African CKD patients, and the unadjusted and covariate-adjusted associations with prevalent CKD under a dominant genetic model.

Genotype	Controls, n(f)	Cases, n(f)	n Unadjusted	Unadjusted OR (95% CI)	Unadjusted *p*-Value	n Adjusted	Covariate-Adjusted OR (95% CI)	Covariate-Adjusted *p*-Value
rs3752462T>C			223			218		
T/T	48 (0.44)	66 (0.58)		1.00 (ref)	-		-	-
T/C + C/C	61 (0.56)	48 (0.42)		0.57 (0.34–0.97)	0.039 *		0.57 (0.34–0.99)	0.047 *
rs4821480G>T			227			222		
T/T	46 (0.42)	35 (0.30)		1.00 (ref)	-		-	-
G/T + G/G	64 (0.58)	82 (0.70)		1.68 (0.94–3.00)	0.062		1.67 (0.98–3.00)	0.082
rs2032487C>T			189			182		
T/T	37 (0.39)	20 (0.22)		1.00 (ref)	-		-	-
C/T + C/C	59 (0.61)	73 (0.78)		2.29 (1.21–4.41)	0.012 *		2.04 (1.06–4.00)	0.035 *
rs4821481C>T			226			221		
T/T	52 (0.48)	41 (0.35)		1.00 (ref)	-		-	-
C/T + C/C	57 (0.52)	76 (0.65)		1.69 (0.99–2.90)	0.054		1.62 (0.92–2.88)	0.094
rs60910145T>G			214			210		
T/T	96 (0.91)	92 (0.85)		1.00 (ref)	-		-	
G/T + G/G	10 (0.09)	16 (0.15)		1.67 (0.73–3.99)	0.232		1.69 (0.72–4.11)	0.236
rs73885319A>G			214			210		
A/A	96 (0.91)	92 (0.85)		1.00 (ref)	-		-	-
A/G + G/G	10 (0.09)	16 (0.15)		1.67 (0.73–3.99)	0.232		1.69 (0.72–4.11)	0.236
rs71785313 ins>del			214			210		
ins/ins	91 (0.86)	89 (0.82)		1.00 (ref)	-		-	-
ins/del-del/del	15 (0.14)	19 (0.18)		1.30 (0.62–2.74)	0.492		1.42 (0.66–3.09)	0.368
APOL1 diplotype								
Low-risk diplotypes								
G0/G0	84 (0.79)	78 (0.72)						
G0/G1	6 (0.06)	9 (0.08)		1.00 (ref)	-		-	-
G0/G2	11 (0.10)	14 (0.13)						
High-risk diplotypes								
G1/G1	1 (0.01)	2 (0.02)		1.40 (0.43–4.56)	0.580		1.37 (0.63–5.29)	0.768

G1/G2	3 (0.03)	5 (0.05)
G2/G2	1 (0.01)	0 (0)

* Nominal associations ($p < 0.05$). Bonferroni correction for multiple testing at $p < 0.0018$. Ins represents the wildtype sequence (ATAATTATAA) for SNP rs71785313, and del represents the sequence after a 6-bp deletion (ATAA). Covariate-adjusted estimates were adjusted for possible confounders (age, sex, ethnicity, diabetes). *p*-values are not multiplied by the number of tests; they are compared with the Bonferroni threshold. n unadjusted is the number of participants included in the unadjusted model for that SNP; n adjusted is the number of participants included in the adjusted model for that SNP.

Table 4. Distribution of *MYH9* genotypes and relative frequencies (f) between cases and controls among South African CKD patients, and the unadjusted and adjusted association of *MYH9* variants with CKD following adjustment for possible confounders and *APOL1* risk status under a dominant genetic model.

Genotype	Controls, n(f)	Cases, n(f)	n Unadjusted	Unadjusted OR (95% CI)	Unadjusted *p*-Value	n Adjusted	Covariate-Adjusted OR (95%CI), Without *APOL1*	Covariate-Adjusted *p*-Value, Without *APOL1*	Covariate-Adjusted OR (95% CI), with *APOL1*	Covariate-Adjusted *p*-Value, with *APOL1*
rs3752462T>C			210			206				
T/T	47 (0.44)	59 (0.57)		1.00 (ref)	-				-	-
T/C + C/C	59 (0.56)	45 (0.43)		0.61 (0.35–1.05)	0.073		0.67 (0.38–1.18)	0.167	0.69 (0.39–1.21)	0.186
rs4821480G>T			214			209				
T/T	44 (0.42)	32 (0.30)		1.00 (ref)	-				-	-
G/T + G/G	62 (0.58)	76 (0.70)		1.68 (0.96–2.94)	0.070		1.79 (0.97–3.29)	0.062	1.76 (0.95–3.24)	0.072
rs2032487C>T			179			172				
T/T	37 (0.39)	18 (0.21)		1.00 (ref)	-				-	-
C/T + C/C	57 (0.61)	68 (0.79)		2.45 (1.26–4.76)	0.008 *		2.28 (1.15–4.53)	0.018 *	2.22 (1.11–4.42)	0.020 *
rs4821481C>T			212			208				
T/T	50 (0.48)	38 (0.35)		1.00 (ref)	-				-	-
C/T + C/C	54 (0.52)	70 (0.65)		1.71 (0.98–2.96)	0.058		1.70 (0.94–3.07)	0.081	1.66 (0.91–3.02)	0.092

* Nominal associations ($p < 0.05$). Bonferroni correction for multiple testing at $p < 0.0018$. Covariate-adjusted estimates were adjusted for possible confounders (age, sex, ethnicity, diabetes). Models including *APOL1* were additionally adjusted for *APOL1* risk status. *p*-values are not multiplied by the number of tests; they are compared with the Bonferroni threshold. n unadjusted is the number of participants with *MYH9* and *APOL1* genotyping data included in the unadjusted model for that SNP; n adjusted is the number of participants with *MYH9* and *APOL1* genotyping data included in the adjusted model for that SNP.

2.4. APOL1 Risk Haplotypes and Diplotypes

The three SNPs in *APOL1*—rs60910145, rs73885319 and rs71785313—when evaluated together, define the *APOL1* haplotypes G0, G1 and G2, which are associated with altered risk of CKD. The G1 risk haplotype is defined by the rs73885319-rs60910145 haplotype (G-G), while the G2 risk haplotype is defined by a 6-bp deletion at rs71785313. *APOL1* diplotypes (combinations of two haplotypes, for example, G0/G1 or G1/G2) were inferred from observed genotype combinations. Individuals carrying two *APOL1* risk haplotypes (G1/G1, G1/G2, or G2/G2) were classified as having a high-risk *APOL1* diplotype, while individuals carrying zero or one risk haplotype were classified as low risk (G0/G0, G0/G1, or G0/G2). This classification was used as *APOL1* risk status in the genetic models (Table 3). Table 3 shows the distribution of each of these diplotypes. The frequencies of the high-risk *APOL1* diplotypes were relatively low, with 3% in the controls and 5% in the cases.

2.5. Linkage Disequilibrium Analysis

Pairwise LD was assessed across the four genotyped *MYH9* SNPs and three *APOL1* SNPs in the combined study cohort (Figure 1). The results revealed varying degrees of LD among the investigated variants. Several SNP pairs exhibited relatively high D′ values (81–100%), including comparisons between *MYH9* and *APOL1* variants. However, the corresponding r^2 values were generally lower, particularly for cross-gene comparisons, indicating limited allelic correlation, despite high D′ values. Notably, the pair rs60910145–rs73885319 exhibited a D′ and r^2 value of 100%, indicating complete normalised LD and perfect allelic correlation. rs4821480, rs2032487 and rs4821481 also exhibited moderate-to-high levels of overall LD, with D′ values ranging from 81–91% and corresponding r^2 values ranging from 50–71%. The remaining SNP pairs showed much more moderate levels of LD.

2.6. Haplotype Frequency Distributions Between Cases and Controls and Associations of Possible Haplotypes with CKD

The relative frequencies of haplotypes constructed from the four *MYH9* loci rs3752462, rs4821480, rs2032487, and rs4821481, and their associations with CKD are presented in Table 5. Six haplotypes were observed at frequencies sufficient for analysis (>0.03). Relative to the reference T-T-T-T haplotype, the T-G-C-C haplotype (the E-1 haplotype) occurred more frequently among cases (35.5%) than controls (21.4%), and was associated with higher odds of CKD (OR = 2.36; 95% CI = 1.33–4.18; $p = 0.004$). Five haplotypes were compared with the reference, so the Bonferroni threshold for this analysis was $p < 0.01$ (0.05/5), and the E-1 result was below it. The SNP and haplotype analyses were treated as separate families of tests. None of the remaining haplotypes was associated with CKD at $p < 0.05$.

Table 5. Relative frequencies (f) of *MYH9* haplotypes (rs3752462, rs4821480, rs2032487, and rs4821481), among controls and cases, respectively, and associations with CKD.

Haplotype (n = 229)	Controls, f	Cases, f	OR (95% CI)	*p*-Value
T-T-T-T	0.350	0.269	1.00 (ref)	-
T-G-C-C	0.214	0.355	2.36 (1.33–4.18)	0.004 *†
C-T-T-T	0.237	0.179	1.13 (0.59–2.16)	0.710
C-G-C-C	0.035	0.030	0.60 (0.19–1.88)	0.390
T-T-C-T	0.040	0.035	1.45 (0.39–5.44)	0.580
T-G-C-T	0.059	0.021	0.48 (0.14–1.68)	0.250

* Nominal association ($p < 0.05$); † below the Bonferroni threshold ($p < 0.01$, five comparisons with the reference haplotype). Odds ratio (OR), confidence interval (CI) and *p*-value are adjusted for age, sex, ethnicity and diabetes. n is the number of participants included in the haplotype analysis.

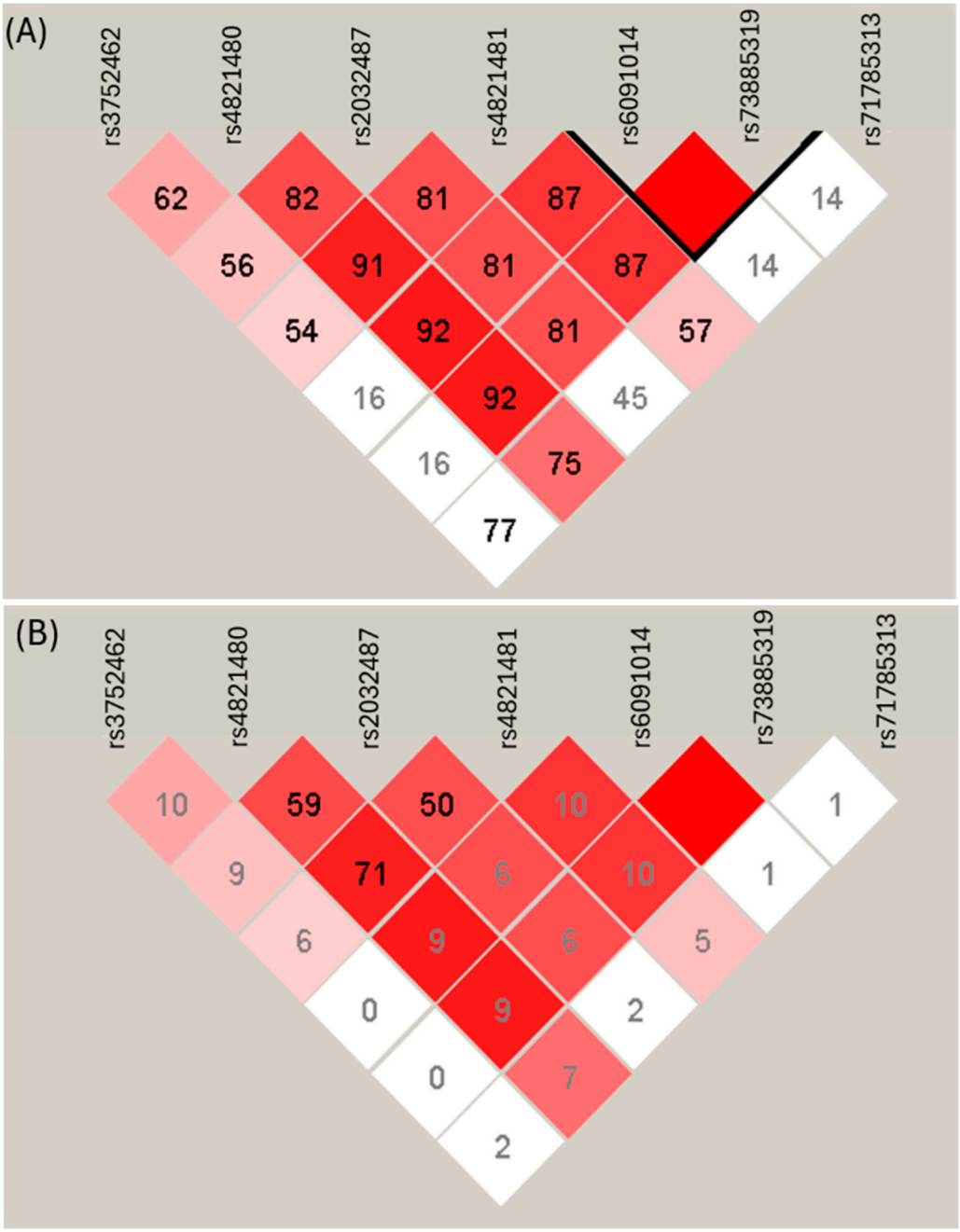


Figure 1. Linkage disequilibrium analyses of the studied *MYH9* SNPs (rs3752462, rs4821480, rs2032487, and rs4821481) and *APOL1* SNPs (rs60910145, rs73885319, and rs71785313). Panel (**A**) shows D′ values and Panel (**B**) shows r^2 values. Each diamond represents the pairwise LD between two SNPs, with the numerical values indicating the corresponding LD statistics (expressed as percentages). Darker red shading represents higher D′ or r^2 values and white represents lower D′ or r^2. The black outline highlights the SNP pair rs60910145–rs73885319, for which D′ = 100%.

Relative frequencies of the haplotypes constructed from the three *APOL1* SNPs of interest, rs60910145, rs73885319, and rs71785313, alone, did not show any differences between CKD cases and controls. These results are shown in Supplementary Table S6.

To assess whether *APOL1* variation affected the *MYH9* haplotype associations, the three *APOL1* SNPs of interest were included in an additional haplotype analysis with the

MYH9 SNPs, where 'ins' represents the wildtype sequence (ATAATTATAA) for SNP rs71785313, and 'del' represents the sequence after a 6-bp deletion (ATAA). These results can be seen in Table 6. Here, the *APOL1* SNPs are part of the haplotypes, which is different from adjusting for participant-level *APOL1* risk status (Table 4). With the T-T-T-T-T-A-ins haplotype as the reference, haplotypes T-G-C-C-T-A-ins (OR = 1.87; 95% CI: 0.97–3.62; p = 0.062) and T-G-C-C-G-G-ins (OR = 3.75; 95% CI: 0.94–14.96; p = 0.062) had higher odds of CKD, but neither reached $p < 0.05$ or the Bonferroni threshold for the analysis ($p < 0.01$). None of the remaining haplotypes was associated with CKD.

Table 6. Relative frequencies (f) of haplotypes (rs3752462, rs4821480, rs2032487, rs4821481, rs60910145, rs73885319, and rs71785313) after inclusion of *APOL1* SNPs, among cases and controls respectively, and associations with CKD.

Haplotype (n = 210)	Controls, f	Cases, f	OR (95% CI)	*p*-Value
T-T-T-T-T-A-ins	0.333	0.270	1.00 (ref)	-
C-T-T-T-T-A-ins	0.237	0.173	0.97 (0.50–1.87)	0.920
T-G-C-C-T-A-ins	0.186	0.238	1.87 (0.97–3.62)	0.062
T-G-C-C-T-A-del	0.024	0.058	1.97 (0.68–5.70)	0.210
T-G-C-C-G-G-ins	0.001	0.060	3.75 (0.94–14.96)	0.062
T-T-C-T-T-A-ins	0.040	0.034	1.37 (0.37–5.02)	0.640

No haplotype reached $p < 0.05$. Bonferroni threshold ($p < 0.01$, five comparisons with the reference haplotype). Odds ratio (OR), confidence interval (CI) and p-value are adjusted for age, sex, ethnicity and diabetes. n is the number of participants included in the haplotype analysis.

3. Discussion

This study investigated the association between four *MYH9* and three *APOL1* SNPs, and prevalent CKD, in South African patients with hypertension. To the best of our knowledge, no previous studies have investigated this association in hypertensive patients within a South African population. Our findings add to the genetic data on CKD in hypertensive individuals and highlight the relevance of population-specific genetic studies. Previous studies have employed similar designs looking at different aetiologies of CKD, such as HIV, FSGS, diabetes and LN, or looking at hypertension-attributed CKD in different populations, especially African Americans [12,29,34].

With respect to, sex, age and ethnicity, we report no significant association with CKD, contrary to reports among Europeans, Asians, and other African populations [6,10]. The higher frequency of diabetes in cases is consistent with existing literature across multiple ancestries, including European, Asian, African American and continental African populations, which report diabetes as one of the leading risk factors for CKD [36–38]. This highlights the importance of comprehensive phenotyping studies to better characterise factors that influence CKD in diverse populations. Due to previous reports of association with CKD, each of these factors were selected as confounders in downstream analyses.

Variability in both the distribution of *MYH9* polymorphisms and CKD manifestation has been reported in studies on different populations. These differences suggest that *MYH9* may have diverse roles in CKD aetiology, depending on the population and specific environmental factors [33,39]. Despite this, previous studies in African ancestry populations have consistently reported that homozygotes for the rs3752462T, rs4821480G, rs2032487C and rs4821481C alleles have a 2–3 times increased risk for developing CKD [12,15,29]. Our findings support these results: individuals who possess at least one of these alleles at rs4821480, rs2032487 and rs4821481 had up to 2.3 times increased odds of CKD than individuals who are homozygous for the T allele, although only rs2032487 reached nominal significance, and none met the Bonferroni threshold. Individuals who possess at

least one C allele at rs3752462 had lower odds of CKD, again at nominal significance only. This suggests that the rs4821480G, rs2032487C and rs4821481C alleles may be associated with higher odds of prevalent CKD, and that rs3752462C may be associated with lower odds compared to the 3752462T allele, but cohorts of larger sample sizes are needed to confirm this. These risk alleles are, in general, more prevalent in African populations [40], which may provide an explanation for the ethnic disparities seen in the global burden of CKD.

While the associations between the *MYH9* rs3752462T, rs4821480G, rs2032487C and rs4821481C variants and CKD are well-established, the mechanisms by which they disrupt kidney function are less well understood. The functional significance of these variants is hypothesised to involve the regulation of *MYH9* gene expression in kidney cells, particularly in podocytes, which are essential for maintaining the glomerular filtration barrier. Each of the *MYH9* SNPs described within this study is an intronic variant, and may play regulatory roles, or disrupt splicing signals, causing incorrect exon inclusion or exclusion. This can result in abnormal or truncated proteins that may lose their normal function. Disruption of the filtration barrier due to altered *MYH9* expression may accelerate kidney damage in hypertensive individuals, ultimately leading to CKD [24,25].

The four *MYH9* SNPs considered in this study tend to be found in strong LD [15], with SNPs rs4821480, rs2032487 and rs4821481 having been reported to be highly correlated to the extent of perfect LD [29,39]. Overall, moderate-to-high D′ values were observed across most SNP pairs in our study (D′ = 0.81–0.92), which is in line with reports by Freedman et al. [12]. While limited significant associations for altered disease risk were seen at the individual SNP level after adjustment for confounders, subsequent haplotype analysis revealed that the magnitude of effect observed for each haplotype was much stronger, reinforcing the notion that combined inheritance of variants may have a cumulative effect on CKD susceptibility. As such, they may provide more information on o the association between *MYH9* and CKD, since LD within the region makes elucidating a single causal SNP difficult [12].

We found that the *MYH9* haplotype with the strongest risk association was made up of alleles T-G-C-C at rs3752462, rs4821480, rs2032487, and rs4821481, respectively. This combination of SNPs and alleles gives rise to the E-1 risk haplotype which is reported to be more strongly associated with, and more informative about, CKD risk than any single SNP [25]. This finding has been consistently corroborated [29,30,38], including by Kopp et al., who report that the E-1 risk alleles may lead to 5-times increased odds of developing CKD [15]. In our data, the E-1 haplotype was associated with about 2.4 times higher odds of CKD, which is more modest than these reports, but in the same direction.

Oleksyk et al. investigated the worldwide distribution of *MYH9* haplotypes, and reported that the E-1 haplotype is most prevalent within African populations, with frequencies ranging from 50–80%. Much lower frequencies were observed in Middle Eastern and European populations, while the haplotype was rare in Asian, American, and Oceanic populations. In contrast, the E-2 protective haplotype (C-T-T-T) is more frequent in non-African populations [33]. In the present study, the E-2 haplotype was identified at frequencies consistent with those generally reported in African populations [15]. Interestingly, the frequency of the E-1 risk haplotype observed in this cohort was lower than previously reported for African ancestry populations, occurring at a level of approximately 35% among cases. In contrast, the E-3 haplotype (T-T-T-T), which is generally regarded as a neutral haplotype and is reported to have much lower frequencies in African populations, was observed at relatively high frequencies, comparable to those observed for the E-1 haplotype. These contrasting findings suggest that the frequencies of *MYH9* haplotypes within this population may be influenced by population-specific LD patterns, genetic diversity, or evolutionary pressures. These results highlight the importance of

considering not only single nucleotides, but also haplotype structures in genetic studies of CKD. African populations exhibit the greatest level of haplotype diversity and, as such, different patterns of LD and allele combinations may exist in different populations [33].

Given the previously reported strong LD between *MYH9* and *APOL1* in African ancestry populations [20], additional analyses incorporating *APOL1* risk variants were performed to determine whether the observed *MYH9* associations could be reflecting underlying *APOL1* risk variation. Interestingly, *APOL1* allele and genotype frequencies did not differ significantly between cases and controls in the present cohort, suggesting that *APOL1* risk variation alone did not account for the observed differences between cases and controls.

Notably, adjustment for age, sex, ethnicity and diabetes, with and without the inclusion of *APOL1* risk status resulted in only modest changes in the effect estimates for the four *MYH9* variants investigated. Comparison of these models showed that the additional adjustment for *APOL1* risk status did not substantially alter the estimates for any of the four variants. In particular, the association between rs2032487C>T and CKD remained nominally significant following covariate adjustment, both with and without inclusion of *APOL1*, while rs4821480G>T and rs4821481C>T retained comparable effect estimates across both adjusted models, although neither reached $p < 0.05$. In contrast, the estimate for rs3752462T>C was moderately attenuated following covariate adjustment, with little additional change after inclusion of *APOL1* risk status. Taken together, these findings suggest that accounting for *APOL1* risk status does not significantly alter the observed associations between *MYH9* variant and CKD, and some of the observed *MYH9* associations may persist after accounting for *APOL1* risk variation.

These findings should also be considered in the context of previous studies which have reported strong associations between individuals carrying any two of the risk alleles and CKD in non-diabetic CKD [20,21,42,43]. The absence of a significant difference in *APOL1* allele and genotype frequencies between cases and controls in our cohort contrasts with these established findings.

Furthermore, the LD analysis revealed variable patterns of LD between *MYH9* and *APOL1* SNPs in the present cohort. Although some cross-gene SNP pairs exhibited relatively high D′ values, their corresponding r^2 values were generally lower, indicating limited allelic correlation, despite evidence of historical linkage. These findings suggest that the relationship between the two loci in this cohort may differ from the strong LD patterns previously reported in populations of African ancestry. These results may suggest a distinct genetic architecture or population-specific linkage pattern within this cohort.

The G1 and G2 alleles are most frequent in populations of West African ancestry, with G1 reportedly occurring at frequencies greater than 40%, while G2 frequencies range between 6 and 24%. In contrast, South African populations are reported to have much lower frequencies, with G1 and G2 frequencies closer to 5%, and the proportion of individuals carrying two risk alleles estimated at only 1% [44,45]. This is consistent with the low frequencies observed in our admixed South African cohort (Tables 2 and 3). The lower prevalence of these risk alleles may influence the detectable contribution of *APOL1* to CKD susceptibility in this population, especially given the limited number of participants carrying two risk alleles. Although some *MYH9* associations persisted following adjustment for *APOL1* risk status, particularly the nominal association with rs2032487C>T, these findings do not establish an independent contribution of *MYH9* to CKD susceptibility. Nevertheless, given the relatively low frequencies of *APOL1* risk alleles reported in South African populations, investigating *MYH9* variants and haplotypes as additional potential candidate markers of CKD susceptibility may be particularly relevant in this population.

The identification of *MYH9* polymorphisms associated with prevalent CKD in hypertensive South Africans adds to the genetic data available for South African populations

and contributes to the understanding of the genetic contribution to CKD susceptibility in this population. Because this was a case-control study of prevalent CKD with limited sample size, the findings do not show that these variants predict who will develop CKD or whose CKD will progress, and they cannot support clinical screening or prevention. Such uses would need validation in larger, independent and prospective studies. These findings provide a basis for further investigation into the potential utility of *MYH9* variants as genetic markers for identifying individuals who may be at increased risk of CKD. In the longer term, improved understanding of genetic susceptibility could contribute to the development of population-specific genetic risk-assessment strategies, potentially allowing for earlier intervention and more personalised treatment strategies [46,47]. For hypertensive patients who carry high-risk *MYH9* variants, this could include closer monitoring of kidney function and timely optimization of blood pressure management to prevent CKD progression.

While much of the genetic research on CKD has focused on African American populations, this study suggests that similar genetic risk factors may exist in African populations, though the prevalence and impact of these factors may vary, due to the extensive diversity exhibited by African populations [48,49]. This highlights the importance of conducting population-specific research, especially in African populations, to ensure that findings are relevant and applicable to diverse ethnic groups.

This study provides data on the associations of *MYH9* polymorphisms with prevalent CKD in hypertensive patients; however, there are some limitations that should be acknowledged. Firstly, the relatively small sample size and admixed nature of the study population may have influenced the observed genetic associations and limit the generalisability of our findings to the broader South African population. To account for potential population stratification, self-reported ethnicity was included as a covariate in the adjusted logistic regression models. However, given the limited sample size, ancestry-stratified analyses were not performed, and self-reported ethnicity may not fully capture the underlying genetic diversity within this population. Consequently, residual population stratification cannot be fully excluded. Additionally, as mentioned, the relatively small number of individuals carrying *APOL1* high-risk genotypes limited statistical power in distinguishing independent effects of *MYH9* and *APOL1* variation. Therefore, residual confounding effects of *APOL1* cannot be completely excluded [20,21]. Furthermore, the available data did not allow us to establish the temporal relationship between CKD and hypertension, the severity of CKD, or to account fully for the potential influence of other comorbidities, such as diabetes. We were also unable to independently validate the recorded diagnoses, including the recorded absence of CKD in controls, provided by clinicians. These limitations may have contributed to phenotype misclassification or residual confounding, and should be considered when interpreting the observed genetic associations.

Further studies involving larger and independently recruited South African cohorts, with adequate representation of different ancestry groups are required, to validate these findings and establish whether the observed associations reflect independent contributions of *MYH9* or underlying interactions with *APOL1*.

4. Materials and Methods

4.1. Study Design and Sample Selection

This study implemented a case-control design, utilising existing DNA samples and clinical classification data from South African hypertensive participants derived from the Pharmacogenomics of Cardiovascular Diseases: Focusing on Dyslipidaemia and Hypertension (PRECODE) cohort. Participants were classified into CKD cases and controls according to the Kidney Disease: Improving Global Outcomes Guidelines. Cases comprised

hypertensive individuals with a clinical diagnosis of CKD verified and recorded by the PRECODE study clinicians (B.D., E.S.W.J), defined as an eGFR less than 60 mL/min/1.73 m^2 or evidence of kidney damage persisting for at least three months, or by evidence of kidney damage, regardless of eGFR. Controls were hypertensive individuals classified as having no CKD based on clinical assessment and kidney function measurements reported by the treating clinicians. Individual kidney function measurements, CKD stage and proteinuria data were not available, and could not be independently verified. Controls were frequency-matched to cases based on overall sex and age distributions. Matching was not done in pairs, so the analyses were unmatched.

The approximate sample size to achieve sufficient statistical power was determined using the Epitools case-control sample size calculator (https://epitools.ausvet.com.au/casecontrolss, last accessed: 26 August 2024). The estimated required sample size was 132 participants per group. However, the total sample size in the case and control groups were 120 and 114, respectively.

Ethical approval was granted by the University of Cape Town Human Research Ethics Committee (HREC; REF: 694/2020). All participants were adults (≥18 years) and provided written informed consent in accordance with the Declaration of Helsinki.

4.2. Clinical Data Collection

Demographic and clinical data were extracted from the Pharmacogenomics and Drug Metabolism Group Biorepository. Variables retained for analysis included age in years, sex (male or female), self-reported ethnicity (African ancestry or Mixed ancestry), body mass index, CKD status, blood pressure measurements, comorbidities such as diabetes or dyslipidaemia, smoking and alcohol use, and medication history. The South African Mixed ancestry individuals are defined as an admixed population of African descent resulting from intermarriages between Black African, European, San or Asian populations.

4.3. SNP Selection and Primer Design

The four SNPs in *MYH9* (rs4821480, rs2032487, rs4821481, and rs3752462) and three *APOL1* SNPs (rs73885319, rs60910145, and rs71785313) were selected based on prior associations with CKD in African ancestry populations. The primer set covering rs4821480 and rs2032487 was adapted from Alqaysi et al. (2020), and for rs3752462 from Liu et al. (2016). Primers for the remaining SNPs were designed using PrimerQuest (Integrated DNA Technologies, Coralville, IA, USA) and assessed for specificity using Primer-BLAST (https://www.ncbi.nlm.nih.gov/tools/primer-blast/, last accessed: 16 November 2024) and OligoAnalyzer (https://www.idtdna.com/calc/analyzer, last accessed: 16 November 2024). Primer sequences and expected amplicon sizes are summarised in Supplementary Table S1. Primer pairs were synthesised by Inqaba Biotechnical Industries (Pretoria, South Africa).

4.4. Molecular Analysis

Genomic DNA was previously extracted using the salting-out method as part of the larger PRECODE study. DNA concentration and purity were measured using a NanoDrop® ND-1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). Integrity was assessed by agarose gel electrophoresis with UV visualisation. Samples with concentrations ≥25 ng/µL, A260/280 ratios ~1.8, A260/230 ratios between 2.0–2.2, and intact molecular weight bands were considered suitable for downstream analyses.

All loci were amplified using standard PCR conditions following optimisation. The rs3752462T>C variant was genotyped using PCR-RFLP. Amplified products were digested with FastDigest *Rsa*I (New England Biolabs®, Ipswich, MA, USA), according to the

manufacturer's instructions. SNPs rs4821480G>T, rs2032487C>T, and rs4821481C>T were genotyped using TaqMan® allelic discrimination assays (Thermo Fisher Scientific, USA). DNA concentration was normalised to 25 ng/µL. Reactions were performed on a QuantStudio™ 3 Real-Time PCR System (Thermo Fisher Scientific, USA), according to the manufacturer's instructions. Genotypes were automatically assigned using instrument software with manual review of ambiguous calls. For each *MYH9* SNP, representative samples encompassing the observed genotype categories (up to 10% of samples per SNP) were selected for validation by Sanger sequencing, on an ABI 3130xl Genetic Analyzer (Applied Biosystems™, Waltham, MA, USA). Chromatograms were analysed using Chromas v2.6.6, and compared with PCR-RFLP and TaqMan Assay genotyping results. Sequencing confirmed representative samples from each genotype group with a 100% concordance rate. Samples which initially had discordant genotype calls were re-genotyped. If discrepancies persisted, genotypes were excluded from downstream analyses, to maintain high genotyping accuracy.

In addition to the *MYH9* variants, genotyping of the *APOL1* G1 and G2 risk variants was performed on 214 remaining participants with available DNA, using MassArray Genotyping (Inqaba Biotech, Pretoria, South Africa) to determine whether observed *MYH9* associations were influenced by LD between the *MYH9* and *APOL1* loci. The G1 risk haplotype was defined by the presence of the rs73885319A>G (p.S342G) and rs60910145T>G (p.I384M) risk alleles, while the G2 risk haplotype was defined by the rs71785313 (p.Y389del) 6-bp deletion (delTTATAA). *APOL1* diplotypes were inferred from observed genotype combinations. Individuals carrying two *APOL1* risk haplotypes (G1/G1, G1/G2, or G2/G2) were classified as having a high-risk *APOL1* diplotype, while individuals carrying zero or one-risk haplotype were classified as low risk This classification was used to define *APOL1* risk status in the adjusted regression models. The *APOL1* SNP MassArray genotyping results were not independently validated in-house.

4.5. Statistical Analyses

Using R software (version 4.0.2), genotype and allele frequencies were calculated and stratified by ethnicity, prior to analysis. As part of the quality control steps, Hardy–Weinberg equilibrium (HWE) assessment was performed for each SNP of interest in the overall cohort, with the analysis stratified by ancestry. HWE *p*-values above 0.05 were deemed sufficient for downstream analyses. Genotype call rates were calculated for each SNP, and the corresponding results are provided in Supplementary Table S2. Missing genotype data were not imputed; therefore, the sample size varied between SNP-specific analyses, according to genotype availability. Participants with missing data for a particular SNP or covariate were excluded only from analyses involving that SNP or covariate and the number of participants in each model is reported with the results. Allelic and genotypic associations with CKD were evaluated under codominant, dominant, recessive, and additive models. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated, to indicate the effect size of each variant. For the descriptive comparisons in Table 1, $p < 0.05$ was considered statistically significant. For the genetic-association analyses, $p < 0.05$ was considered nominal association, and statistical significance was defined after Bonferroni correction. The dominant model is reported in the main results. For the SNP analyses, the Bonferroni correction was applied for the 7 SNPs under 4 genetic models (number of tests, n = 28), giving a significance threshold of $p < 0.0018$ (0.05/28), although the use of this correction is contested. This threshold was applied to the *p*-values from logistic regression models, including the covariate-adjusted models. The haplotype analyses were treated as a separate family of tests. In each haplotype analysis, a Bonferroni threshold was applied; for example, five haplotypes compared with the reference haplotype use a Bonferroni threshold of $p < 0.01$ (0.05/5).

Baseline and clinical characteristics were summarised using the mean with a standard deviation (SD) or median with an interquartile range (IQR) for continuous variables and counts with proportions or counts with relative frequencies for categorical variables. Continuous variables were tested for normality using the Shapiro–Wilk test and compared using Student's t-test or Wilcoxon rank-sum test, as appropriate. Categorical variables were analysed using chi-square or Fisher's exact tests, where appropriate. Multivariable logistic regression was performed to evaluate associations between *MYH9* variants and CKD, after adjustment for potential confounders. Age, sex and comorbid diabetes were selected as confounders, based on the possibility that they may be associated with CKD, as indicated by previous literature. Self-reported ethnicity (African or Mixed ancestry) was retained as a covariate, to minimise confounding due to population stratification. Using SNPStats (https://www.snpstats.net/start.htm, last accessed: 25 May 2026), and Haploview (version 4.1), LD between SNPs was assessed using a pair-loci analysis and reported as D′ and r^2 statistics. Haplotype analysis was also carried out. A haplotype frequency cutoff of 0.03 was applied. The covariates (age, sex, ethnicity and diabetes) were included directly in the SNPStats software.

To assess the independence of the *MYH9* associations, SNPs models were adjusted for *APOL1* risk status (coded as in Section 2.4) and compared with models without *APOL1* risk status in the same participants. The *MYH9* haplotype models were adjusted for age, sex, ethnicity and diabetes. In a combined *MYH9-APOL1* haplotype analysis, the *APOL1* SNPs were included in the haplotypes themselves, with the same four covariates. Changes in the magnitude and statistical significance of *MYH9* associations following inclusion of *APOL1* variants were assessed, to determine potential confounding effects attributable to LD between the two loci.

5. Conclusions

This study provides evidence of associations between selected *MYH9* and prevalent CKD among South African patients with hypertension, while also characterising *APOL1* risk variation in this population. The persistence of the nominal *MYH9* associations following adjustment for *APOL1* risk status suggests that these variants may warrant further investigation as potential markers of CKD susceptibility in South African populations, especially given the limited number of individuals carrying the *APOL1* high-risk genotype.

Historically, African populations have been under-represented in global biomedical research, contributing to substantial gaps in our understanding of the genetic factors underlying disease susceptibility across the continent. This under-representation may limit the applicability of findings from other populations and hinder the development of appropriate population-specific healthcare strategies [52–54]. The present findings highlight the relevance of genetic studies in African populations and underscore the importance of considering population-specific genetic risk factors in the study of CKD. Further studies involving larger, independent South African cohorts are needed to validate the observed associations and clarify the respective contributions of *MYH9* and *APOL1* to CKD susceptibility. Ultimately, such research may contribute to the development of population-specific genetic risk-assessment approaches and inform future personalised strategies for CKD prevention and management.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms272310750/s1.

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Data Availability Statement: The datasets used and analysed during the current study have been uploaded and are available from the Zenodo research data repository (DOI: 10.5281/zenodo.23344783, last accessed 13 October 2026).

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Abbreviations

The following abbreviations are used in this manuscript:

UACR	Albumin-to-creatinine ratio
APOL1	Apolipoprotein L1
BP	Blood pressure
BMI	Body mass index
CKD	Chronic Kidney Disease
CIs	Confidence intervals
ESKD	End-stage kidney disease
EGFR	Estimated glomerular filtration rate
FSGS	Focal segmental glomerulosclerosis
HWE	Hardy–Weinburg Equilibrium
HIVAN	HIV-associated nephropathy
HIV	Human immunodeficiency virus
KDIGO	Kidney disease: Improving Global Outcomes group
LD	Linkage disequilibrium
LN	Lupus nephritis
MYH9	Myosin Heavy Chain 9
OR	Odds ratio
PRECODE	Pharmacogenomics of Cardiovascular Diseases in South Africa: Focusing on Dyslipidaemia and Hypertension
PCR-RFLP	Polymerase chain reaction–restriction fragment length polymorphism
SNP	Single-nucleotide polymorphism
SLE	Systemic lupus erythematosus

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