Non-diabetic end-stage renal disease in Saudis associated with polymorphism of MYH9 gene but not UMOD gene

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Abstract
The prevalence of risk factors of chronic kidney disease in Saudi Arabia has augmented an already serious public health problem, therefore, determination of genetic variants associated with the risk of the disease presents potential screening tools that help reducing the incidence rates and promote effective disease management.

The aim of the present study is to determine the association of UMOD and MYH9 genetic variants with the risk of non-diabetic end-stage renal disease (ESRD) in the Saudi population.

Two single nucleotide polymorphisms (SNP), rs12917707 in gene UMOD and rs4821480 in gene MYH9 were genotyped in 154 non-diabetic ESRD Saudi patients and 123 age-matched healthy controls using Primers and Polymerase chain reaction conditions (PCR), Sanger sequencing, and TaqMan Pre-designed SNP Genotyping Assay. The association of these genetic variants with the risk of the disease and other renal function determinants was assessed using statistical tools such as logistic regression and One-way Analysis of Variance tests.

The genotypic frequency of the two SNPs showed no deviation from Hardy–Weinberg equilibrium, the minor allele frequency of UMOD SNP was 0.13 and MYH9 SNP was 0.08. rs4821480 in MYH9 was significantly associated with the risk of non-diabetic ESRD (OR=3.86; 95%CI: 1.38–10.82, P value .010), while, rs12917707 showed lack of significant association with the disease, P value .380. and neither of the 2 SNPs showed any association with the renal function determinants, serum albumin, and alkaline phosphatase enzyme.

Abbreviations: ANOVA = Analysis of Variance, C = centigrade, CI = confidence interval, CKD = chronic kidney disease, Cl = Chlorine, df = degree of freedom, ESRD = end stage renal disease, FSGS = focal segmental glomerulosclerosis, GFR = glomerular filtration rate, GWASs = genome wide association studies, Inc. = Incorporation, K = potassium L = Liter, mmol = millimole, n = Number, Na = sodium, NY = New York, OR = odds ratio, SD = standard deviation, SNP = single nucleotide polymorphism, U = Unit.

Keywords: genetic, non-diabetic, polymorphism, renal disease, Saudi

1. Introduction
End-stage renal disease (ESRD) is a major non-communicable global health problem with high morbidity and mortality rates.1–3 The disease is the final stage of chronic kidney disease (CKD), characterized by a significant drop in the glomerular filtration rate (GFR) and irreversible loss of kidney function.4,5 The magnitude of the problem in Saudi Arabia is disconcerting, and aggravated by the 5% annual increase in the incidents related to kidney failure, in addition to the high prevalence of major risk factors for CKD. This has led to Saudi Arabia ranks sixth of the highest countries with renal failure and the disease as the fourth cause of death in the country.6 The disease constitutes serious public health, and economic burden on both patients and society, in terms of lack of effective treatment, life-long exhausting dialysis sessions, scarcity of compatible organ donors, and the risk of life-threatening complications such as cardiovascular diseases, anemia, mineral and bone disorders.6,7 Determination of the disease risk factors that help in early identification of those at risk believed to reduce the disease incidence rates. In the Gulf region as general and Saudi Arabia in particular, three important risk factors for CKD, namely, diabetes, hypertension, and obesity are highly prevalent, along with these manageable factors, genetic factors were reported to have an effect on kidney function-related traits,8–10 disease pathogenesis and progression.11 The genetic influence on kidney function and failure have attracted the attention of many investigators. Recent genome-wide association studies (GWASs) using estimated glomerular filtration rate (eGFR) as the phenotype of interest have identified several loci that may affect renal function.10,11 Number of genes and genetic variants were reported to have association with kidney diseases, ADPRT1, AKR1B1, RAGE, GFPT2, and PAI-1 genes polymorphisms were reported to be associated with chronic renal insufficiency in Asian Indians,12 mutations in CDCA7 tran-
scription factor were shown to be associated with ESRD in white women with type 1 diabetes but not men,\(^{13}\) and several genetic variants in \(MTHFR\) gene were implicated in diabetic kidney disease in Whites, Africans, Asians and Latin Americans. Two of the most important genes studied for potential association with the state of health and disease of the kidney are \(UMOD\) and \(MYH9\).\(^{9,15,16}\)

\(UMOD\) gene codes for Uromodulin protein also known as Tamm-Horsfall protein, the most abundant protein in mammalian urine. The function of this protein yet to be elucidated, but it is believed to act as a constitutive inhibitor of calcium crystallization in renal fluids and it increases membrane expression of the renal outer medullary potassium channel (ROMK2), it also activates the Na-K-2Cl co-transporter in the thick ascending limb in the loop of Henle.\(^{17}\) Excretion of this protein in urine may provide defense against urinary tract infections caused by uropathogenic bacteria. The gene is located on chromosome 16 (16p12.3), with a number of mutations and genetic variations reported to be associated with blood pressure, familial juvenile hyperuricemic nephropathy, medullary cystic kidney disease type 2.\(^{15,18}\) The association of several genetic variants of the \(UMOD\) gene with the deterioration of renal function and consequently CKD was reported in many previously published studies.\(^{6,19}\)

On the other hand, \(MYH9\) gene encodes non-muscle myosin-9, a subunit of myosin II protein. There are three forms of myosin II, namely, myosin IIA, myosin IIB, and myosin IIC. They play key roles in cell motility, maintenance of cell shape, and cytokinesis. The genetic variants of \(MYH9\) were reported to be associated with hypertensive ESRD, and focal segmental glomerulosclerosis (FSGS),\(^{20}\) IgA nephropathy,\(^{21}\) diabetic kidney disease,\(^{22}\) and lupus nephritis.\(^{23}\) The scarcity of genotyping studies addressing the association of these two genes with ESRD in Saudi population makes the present study an initial attempt to explore the potential relationship between the genetic variants, rs12917707 and rs4821480 of the 2 candidate genes, \(UMOD\) and \(MYH9\) respectively, and the risk of non-diabetic ESRD in Saudis.

2. Material and methods

2.1. Subjects

In this retrospective case-control study, the cases group comprised of 154 non-diabetic ESRD patients (52% males and 48% females, mean age 56.28 ± 15.9 years) under hemodialysis for at least 3 months, recruited from the nephrology and dialysis unit in King Abdalla hospital, Bisha, Kingdom of Saudi Arabia. Patients encountered diabetes prior to being diagnosed with kidney disease, with malignancy or infectious co-morbidity were excluded from the study. The control group, on the other hand, comprised of 123 (50.5% males and 49.5% females, mean age 54.2 ± 18.9 years) apparently healthy individuals with normal renal function. All participants gave verbal consent prior sample collection, this study was conducted in compliance with the declaration of Helsinki, and ethically approved by the ethical and technical committee of the deanship of scientific research, University of Bisha.

2.2. DNA extraction and genotyping

DNA was extracted from peripheral blood samples collected from the controls and patients in a non-diagnosis day, using Qiagen QIAamp DNA blood mini kit (Qiagen, Inc. Hilden, Germany). Two single nucleotide polymorphisms (SNPs) were selected for genotyping based on their strong association with kidney diseases as previously reported in number of studies, rs12917707 in \(UMOD\) gene, and rs4821480 in \(MYH9\) gene. The DNA regions that encompass these 2 loci were amplified with Primers and Polymerase chain reaction conditions (PCR) using primer sets and amplification conditions shown in Table 1.

Genotyping of (SNPs) rs12917707 and rs4821480, was performed by Sanger sequencing at Macrogen Inc. South Korea, and with TaqMan Pre-designed SNP Genotyping Assay (Applied Biosystems Inc., Foster City, CA, USA) using the Applied Biosystems 7300 Real Time PCR, following the manufacturer’s instructions for dried-down DNA method. For each SNP, genomic DNA samples of 10 ng were amplified with 2× TaqMan master mix and the corresponding 20× TaqMan SNP genotyping assay mixture, under the following amplification conditions: 2 minutes at 50°C and 10 minutes at 95°C for polymerase activation, and then 40 cycles of 15 seconds at 95°C for denaturation and 1 minute at 60°C for annealing and extension. The SNP variant is determined by the fluorescence of the bound allele specific dye-labelled probe. The Sanger sequence reads were visualized, cleaned and analyzed with 4Peaks Software (Mekentosj, Amsterdam).

The renal function tests, electrolytes, uric acid, alkaline phosphatase, and serum albumin were carried out in the laboratories of King Abdalla Hospital, Bisha, using Cobas 8000 Biochemical analyzer.

2.3. Statistical analysis

Statistical analysis was performed using Statistical Package for Social Science (IBM-SPSS) version 25 (IBM Corporation Armonk, NY). The values of variables with normal distribution are presented as mean±standard deviation, for comparisons between groups Student t test and one-way Analysis of Variance (ANOVA) test were used. The association between categorical variables was assessed using Chi-square test or Fisher exact test. The odds ratio for the 2 SNPs different study parameters was calculated using binary logistic regression. For all test the \(P\) value of <.05 considered statistically significant.

3. Results

Demographic data and clinical characteristics for the study arms are presented in Table 2. The genotypic frequency of the 2 SNPs, rs12917707 and rs4821480 in the control group showed no deviation from Hardy Weinberg equilibrium, with \(x^2=0.1, P\) value =.751and \(x^2=0.25, P\) value=.617, respectively. Results of allelic and genotypic frequencies for both SNPs are shown in Table 1.

| Table 1 | Primers and PCR conditions. |
|---------|----------------------------|
| **UMOD** gene: rs12917707 (G>T) | **Primers** | R: 5’-ATCTAGTCATGCAAGCCGAC-3’<br> F: 5’-GGAGGCGCTTCATACGACGAGG-3’ |
| **PCR conditions** | 94°C – 72°C; 30 cycle |
| **MYH9** gene: rs4821480 (G>T) | **Primers** | R: 5’-GGACGGCTCTGATTACGCTC-3’<br> F: 5’-GAGGGGATGCAATTCTCAG-3’ |
| **PCR conditions** | 94°C – 72°C; 35 cycle |
Table 3 and Figures 1 and 2, the only allele to show association with the disease was the T allele of rs4821480 with $x^2 = 10.7$ and $P$ value $= .001$, and the only genotype to show association with the disease was TT of the same SNP, with $x^2 = 19.59$ and $P$ value $= .000$.

To assess the occurrence of non-diabetic ESRD given the presence of the risk allele, we used binary logistic regression, the results showed no significant association of rs12917707 with the disease; OR $= 1.73; 95\%$CI $0.50 – 5.94$, $P$ value $.38$ for the T allele in the homozygous recessive model and OR $= 1.52; 95\%CI: 0.36 – 6.30$, $P$ value $.56$ for the T allele in the heterozygous model as compared to the homozygous model of the reference G allele, similar results were obtained with regression model adjusted for age and sex, OR $= 1.64; 95\%$CI: $0.48 – 5.61$, $P$ value $.57$ for the

### Table 2
Demographic and clinical characteristics of study arms.

| Clinical parameters | Cases Mean ± SD | Control Mean ± SD | $P$ value |
|---------------------|----------------|------------------|-----------|
| Age/year            | 56.28±18.28    | 53.28±15.9       |           |
| Gender              |                |                  |           |
| Male n (%)          | 80 (52%)       | 62 (50.5%)       |           |
| Female n (%)        | 74 (48%)       | 61 (49.5%)       |           |
| Creatinine (mmol/L) | 0.8±0.3        | 0.7±0.23         | .600      |
| Serum albumin (g/L) | 33.9±7.56      | 29.6±12.8        | .000      |
| Alkaline phosphatase (U/L) | 171.6±22.7 | 45.8±5.2        | .000      |
| Blood urea (mmol/L) | 23.09±9.9      | 10.4±3.21        | .040      |
| Blood sodium (mmol/L) | 132.55±22.29  | 100.59±59.9     | .000      |
| Blood chloride (mmol/L) | 94.95±19.9   | 48.08±12.99     | .000      |

### Table 3
Allelic and genotypic frequency of rs12917707 and rs4821480.

| SNP             | Allele frequency | $x^2$- test | Genotype frequency |
|-----------------|------------------|-------------|--------------------|
|                 | Cases            | Control     | $x^2$- test        | Cases         | Control     | $x^2$- test |
| rs12917707 G>T  | G=0.88           | G=0.87      | df=1               | GG=0.84       | GG=0.87     | df=2       |
|                 | T=0.12           | T=0.13      | $x^2=0.028$        | GT=0.10       | GT=0.10     | $x^2=0.676$ |
|                 |                  |             | $P=.001$           | TT=0.06       | TT=0.03     | $P=.713$   |
| rs4821480 G>T   | G=0.77           | G=0.92      | df=1               | GG=0.67       | GG=0.89     | df=2       |
|                 | T=0.23           | T=0.08      | $x^2=10.7$         | GT=0.21       | GT=0.07     | $x^2=19.59$ |
|                 |                  |             | $P=.001$           | TT=0.12       | TT=0.04     | $P=.000$   |

Figure 1. Chromatogram of rs12917707 showing the position of wildtype variant.

Figure 2. Chromatogram of rs4821480 showing the position of wildtype variant.
Table 4
Logistic regression of the two SNPs and the risk of non-diabetic ESRD.

| MYH9rs12917707rs4821480 | OR 95%CI | P value | OR 95%CI adjusted for age & sex | P value |
|-------------------------|---------|---------|---------------------------------|--------|
| GG                      | 1       |         |                                 |        |
| GT                      | 0.866 (0.24 – 3.06) | .828 | 0.873 (0.22 – 3.02) | .832 |
| TT                      | 3.867 (1.38 – 10.82) | .010 | 3.845 (1.37 – 10.73) | .010 |
| UMOD                    |         |        |                                 |        |
| rs12917707rs12917707    |         |        |                                 |        |
| GG                      | 1       |         |                                 |        |
| GT                      | 1.52 (0.36 – 6.30) | .560 | 1.50 (0.36 – 6.17) | .420 |
| TT                      | 1.73 (0.50 – 5.94) | .380 | 1.64 (0.48 – 5.61) | .570 |

CI = confidence interval, ESRD = end stage renal disease, OR = odds ratio, SNP = single nucleotide polymorphism.

4. Discussion
The multifactorial etiology of ESRD is well documented in the previously published literature.[24,25] In addition to number of environmental factors, several mutations and genetic variants were reported to have an association with kidney diseases.[24–26,8]

In the present study the rs4821480 SNP of the MYH9 gene has a significant association with the risk of developing non-diabetic ESRD, the results indicate that the risk of developing the disease in individuals with the risk allele is four folds compared with those carrying the ancestral allele and attributable fraction of 40%, similar level of association was also obtained when data adjusted for age and sex. This result goes in concordance with the OR ranges between 4 and 8 reported by Winkler et al.[26] in FSGS, and the findings of Oleksyk et al.[27] and the 2.59 odd ratio reported by Freedman et al.[28] in non-diabetic African Americans. The risk demonstrated by our finding is much higher than that reported in the European Americans with OR = 1.89,[29] but not the Hispanic Americans with OR = 3.70.[30] MYH9 is a highly conserved gene encodes non-muscle myosin heavy chain type II isoform A, a cytoskeletal protein expressed in most of the human cells, plays vital cellular functions, such as cytoskeleton reorganization, focal contact formation, and lamellipodial retraction.[31] In the kidneys, this protein is mainly expressed in the podocytes, where it is reported to regulate actin dynamics and maintain normal cellular structure.[29] Podocytes are key players in the kidneys, where they provide a filtration barrier in the glomeruli.[26] In the present study, the rs4821480 of MYH9 is an intronic variant, its risk allele may alter the structure or function of the protein, possibly by affecting the alternative splicing, or altering messenger RNA half-life.[32] or introduce change in a variable portion of the non-helical tailpiece of the protein,[33] resulting in accumulation of a non-functional protein.

Table 5
Comparison of clinical parameters according to rs12917707 genotype.

| rs12917707 | Cases | Control |
|------------|-------|---------|
|            | GG    | GT      | TT      | P value | GG    | GT      | TT | P value |
| Urea       | 22.63 | 27.45   | 22.32   | .840    | 40.47 | 3.48    | 3.22 | .673 |
| Creatinine | 829.72 | 826.86   | 885.2   | .413    | 60.08 | 53.11   | 51.91 | .206 |
| Albumin    | 34.26 | 32.22   | 34.23   | .673    | 21.64 | 33.28   | 21.27 | .302 |
| Alkaline ph.| 181.31 | 152.29   | 126.00 | .698    | 34.37 | 110.44  | 60.25 | .000 |
| Chlore      | 95.27 | 89.18   | 99.01   | .465    | 56.06 | 44.00   | 48.25 | .554 |
| Blood Na    | 153.00 | 125.21   | 136.38 | .403    | 111.67 | 136.11  | 134.5  | .699 |
| Blood K     | 5.24  | 4.88    | 5.00    | .428    | 3.13  | 3.71    | 3.45  | .513 |
in the podocyte, this, in turn, will adversely affect kidney function. The association of this SNP with the risk of non-diabetic ESRD can also be attributed to possible linkage disequilibrium with other MYH9 variants, a possibility not explored in the current paper.

Of all the clinical parameters assessed in this study, serum urea was the only parameter to show significant difference according to rs4821480 genotype in the cases group, however, no significant difference in the level of serum urea in the controls group, which implies the absence of true association between the level of serum urea and the SNP genotype. Whereas in a true association we assume, the significant difference should have occurred in both study arms, and certain degree of consistency in the variation of urea level according to the presence of the recessive or the ancestral allele, in the contrary, the level of urea in heterozygous genotype carriers is higher than both homozygous dominant and recessive in the cases, while homozygous dominant in the control group, showed higher levels than the other 2 genotypes.

The second gene in the present study is UMOD, encodes the most abundant protein in the urine of healthy humans, though its function is yet to be determined, the protein is believed to protect against urinary tract infections, control the amount of water in the urine, and play a key role in tubular injury and interstitial inflammation. The association between the genetic variants of the UMOD gene and the risk of kidney diseases was reported by many studies. In the present study we investigated rs12917707 of UMOD gene, this SNP showed no significant difference according to rs4821480 genotype in the cases group, however, no significant difference in the level of serum urea in the controls group, which implies the absence of true association between the level of serum urea and the SNP genotype. Whereas in a true association we assume, the significant difference should have occurred in both study arms, and certain degree of consistency in the variation of urea level according to the presence of the recessive or the ancestral allele, in the contrary, the level of urea in heterozygous genotype carriers is higher than both homozygous dominant and recessive in the cases, while homozygous dominant in the control group, showed higher levels than the other 2 genotypes.

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