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ORIGINAL ARTICLE

Analysis of the association between rs12917707 and rs11864909 single nucleotide polymorphisms in the region of the uromoduline gene and chronic kidney disease – a family-based study

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Abstract

Chronic kidney disease (CKD) is an important challange for healthcare systems wordwide because of its high prevalence and serious late complications. The results of recent studies suggest an association between CKD development and genetic variation within the uromodulin gene (UMOD). The aim of this study was to investigate associations between two common single nucleotide polymorphisms – rs12917707 and rs11864909, located in the region of UMOD and chronic renal disease. The study group consisted of 109 patients with chronic kidney disease, caused by chronic renal glomerulonephritis or chronic tubulointerstitial nephritis, and 109 pairs of their biological parents. Genotyping for rs12917707 and rs11864909 was carried out using the TaqMan Pre-designed SNP Genotyping Assay. In the transsmission disequilibrium test, allele C of rs11864909 was preferentialy transmitted from parents to the children with chronic tubulointerstinal nephritis. The rs12917707 was not associated with CKD. Neither of the investigated polymorphisms was associated with the progression of chronic kidney disease. The obtained results suggest an association of rs11864909 with chronic kidney disease secondary to chronic tubulointerstinal nephritis.

Key words

chronic kidney disease, genetic association, family-based study, UMOD polymorphism

INTRODUCTION

Epidemiological data unequivocally proves the importance of chronic kidney disease (CKD) as a public problem worldwide, and based on study population results, its prevalence is estimated at over 10% of the adult population in the USA, Europe and Asia [1,2]. Moreover, contemporary analyses project escalation of the prevalence and incidence of CKD in the future [3]. Both the aging of populations and increasing incidence of metabolic disturbances are the drivers of the increasing burden of CKD [4]. CKD may lead to end stage renal disease that requires renal replacement therapy: dialysis or renal transplantation. As an independent risk factor for cardiovascular disease, chronic kidney disease causes increased morbidity and mortality; therefore, CKD is not only a medical issue but also an economic problem for healthcare wordwide [1]. There is a strong genetic component in CKD [5] chich, apart from genes, demographic and environmental factors (age, gender, socioeconomic conditions, educational background), are important risk factors for CKD [4].

The results of genetic studies show the significant association of many genes and their polymorphisms with CKD development [5, 6], one of which is the uromodulin gene (UMOD). Uromodulin is selectively synthetized by epithelial cells of trick thick ascendenting limb of Henle's loop, and in physological conditions excreted mainly into the urine. Its important role in renal homeostasis has been firmly proved [7]. Uromodulin acts both within the renal tubules as well as renal interstitium. Excreted by the apical tubular cell membrane into the urine, it acts as the local protektor and interacts with microbes, ions, mineral molecules, and others. Uromodulin crossing the basoleteral surface of the tubular cell membrane translocates into the renal interstitium where it contributes to the regulation of inflammation. Although uromodulin urinary excretion and expresion of its gene have been extensively studied in various pathophysiological states, its role is still unclear [8, 9].

The results of a genome-wide association study (GWAS), showed association between UMOD single nucleotide polymorphisms and both renal function as well as susceptibility to chronic kidney disease [6, 10].

OBJECTIVE

The aim of this study was to investigate associations between two common single nucleotide polymorphisms: rs12917707 and rs11864909 (located in UMOD locus) and chronic kidney disease in the Polish population.

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MATERIALS AND METHOD

The study was conducted in the Department of Internal Medicine, Diabetology and Nephrology, at the Medical University of Silesia in Zabrze. The study group was recruited from CKD patients in dialysis units and outpatient nephrology clinics. The protocol of the investigation was approved by the Ethics Committee of the Medical University of Silesia and all participants (or their legal guardians in the cases of patients under the age 16) gave written consent for the study procedures. For the purpose of the study, the family-based model of genetic association was chosen, and CKD patients and their biological parents were invited to provide blood sample for genetic analysis.

The genomic DNA was isolated from peripheral blood leukocytes with a DNA isolation kit (Epicenter Technologies Corp., Madison, Wisconsin, USA) in an own laboratory modification. Genotyping of single nucleotide polymorphisms rs7456421 and rs 2030712 was performed with TaqMan Predesigned SNP Genotyping Assay (Applied Biosystems Inc., Foster City California, USA) using 7300 Real Time PCR of the Applied Biosystems Company.

109 patients with chronic kidney disease and 109 pairs of their biological parents, a total of 109 'family trios' were investigated.

The CKD group consisted of 48 (44%) females and 61 (56%) males; mean age – 15.5 (±6.45) years; body mass index calculated at 19.1 (±3.5) kg/m^2. The results of a prior kidney biopsy was used for classification into two categories: chronic glomerulonephritis – 27.5%, and chronic tubulointerstitial nephritis – 72.5% of cases. Within the CIN group, 62 patients were diagnosed with congenital urinary tract defects. During the study, the mean value of glomerular filtration rate (GFR), estimated for all CKD patients on the basis of MDRD (Modification of Diet in Renal Disease) or Schwartz formulas, was 28.2 ml/min. 46.8% of CKD patients with mean values of serum creatinine 2.77 (±1.0) mg/dl and estimated GFR (eGFR) 36.0 (±15.2) ml/min were conservatively treated. The group undergoing renal replacement therapy consisted of 58 patients: 33 individuals (56.9%) were treated with continuous ambulatory peritoneal dialysis (CAPD), 17 (29.3%) – haemodialysis, and 8 (13.8%) underwent successful renal transplantation. The mean values of serum cretinine and eGFR in these subgroups were, respectively: 6.78 (±2.7) mg/dl and 12.49 (±4.17) ml/min, 7.93 (±2.24) mg/dl and 12.04 (±3.45) ml/min, 1.08 (±0.13) mg/dl and 80.5 (±13.4) ml/min. Each patients' medical history allowed characterisation of the progress of the CKD. The mean observation time for all CKD patients was 7.1 (±5.7) years. Rapid CKD progression was defined as necessity for replacement therapy within a 5-year observation period from stage 2 CKD, and/or with doubled serum creatinine concentration, where the index 1/ serum creatinine concentration was below 0.3. 49. 5% of the patients were counted into this group.

Statistical analysis. Statistical analysis was performed on Microsoft Office Exel 2003, Statistica 7 and SAS software packages.

Depending on distribution, all data were presented as mean values with standard deviations or median values with upper and lower quartile. The Mann-Whitney Test was used for ascertainment of statistical differencies among subgroups with p value <0.05.

Statistical analysis was performed for all those studied in the CKD group, and independently for two subgroups according to CKD ethiology: patients with chronic glomerulonephritis (CGN) and patients with chronic tubulointerstitial nephritis (CIN).

Using the transmission disequilibrium test (TDT), the allele transfer from parents to their affected offspring with CKD was estimated. In the case of both parents being homozygotes, the family was excluded from further analysis as non-informative.

Multiple linear regression analysis was used to identify potential demographic, clinical and genetic predictors of chronic kidney disease progression.

RESULTS

Genotype distribution of investigated polymorphisms are presented in Table 1; Tables 2 and 3 include corresponding TDT results.

Single nucleotide polymorphism rs12917707. The distribution of genotypes in the group of all patients with chronic renal disease was as follow: GT – 28.4%, GG – 70.6%, TT – 0.9%. The T was a minor allele (MAF = 0.15). Genotype distribution was similar in all study subgroups (Tab. 1).

Table 1. Distribution of rs12917707 and rs11864909 genotype in study groups [%]

	rs12917707			rs11864909		
	GG	TT	GT	CC	TT	CT
CKD	70.6	0.9	28.4	54.1	3.7	42.2
CGN	70.9	1.3	27.8	59.5	3.8	36.7
CIN	70.0	0	30.0	40.0	3.3	56.7

CKD – chronic kidney disease
CGN – chronic glomerulonephritis
CIN – chronic tubulointerstitial nephritis
TDT – Transmission Disequilibrium Test

Based on TDT results, no association was fund between rs12917707 and CKD (Tab. 2).

Table 2. Frequency of rs12917707 allele transmission in study groups (TDT results)

	Allele T transmitted observed/ expected		Allele G transmitted observed/ expected		p
Study groups	Yes	No	Yes	No	
CKD	28/33	38/33	38/33	28/33	0,22
CGN	8/11.5	15/11.5	15/11.5	8/11.5	0,14
CIN	20/21.5	23/21.5	23/21.5	20/21.5	0,65

Single nucleotide polymorphism rs11864909. In all CKD patients, the CT genotype was observed in 42.2%, while CC in 54.1% and TT in 3.7%. Allele T has minor frequency of 25% (MAF = 0.25). There were significant differences in genotype distribution of rs11864909 in subgroups with different CKD aetiology (Tab. 1).

The TDT results revealed association between the C allele and CKD in patients with chronic tubulointerstitial nephritis, but not those with chronic glomerulonephritis (Tab. 3). There was bordeline association (p=0.07) between rs11864909 and CKD in the whole study group (Tab. 3).

Table 3. Frequency of rs11864909 allele transmission in study groups (TDT results)

	Allele C transmitted observed/ expected		Allele T transmitted observed/ expected		p
Study groups	Yes	No	Yes	No	
CKD	54/45.5	37/45.5	37/45.5	54/45.5	0,07
CGN	14/22	10/22	10/22	14/22	0,41
CIN	43/34.5	26/34.5	26/34.5	43/34.5	0,04

Results of multiple linear regression analysis. Neither of the investigated polymorphisms was associated with the progression of chronic kidney disease. The chronic glomerulonephritis history (odds ratio 21.2) and the younger age of CKD diagnosis (odds ratio 0.886) were the only factors predisposed to a faster decline in renal function.

DISCUSSION

Single nucleotide polymorphism rs11864909 is located on 16 chromosome (16p12.3) in genomic position 20400839, close to uromodulin gene UMOD within the PDILT gene [11]. The PDILT gene encodes *disulfide isomerase-like of the testis* protein – the enzyme which affects the physiologically important process of disulfide bridge formation that occurs in the endoplasmic reticulum [12]. Disulfide bonds play an important role in the folding and stability of some proteins [13]; however, available data exhibits the expression of PDILT in the testis and suggests that PDILT performs a specialized chaperone function in testicular cells [12]. Proximity of the PDILT gene to the UMOD gene can suggest their 'co-operation' at the regulatory level [14].

The association of rs11864909 polymorphism with renal function was published for the first time in 2012 by Okada et al. and comprised the results of over 71,000 study participants from East Asia [15]. This is the only published study suggesting an association between rs11864909 polymorphism and renal function. Results of the presented study confirmed this data. Moreover, the current observation is the first to prove the correlation between rs11864909 polymorphism and the prevalence of chronic kidney disease, secondary to chronic tubulointerstinal nephritis. This data suggests that the C allele of rs11864909 may act as a risk factor for CKD of this aetiology. However, in the entire study group, there was also marked tendency, with bordeline significance, to a more frequent transmission of rs11864909 C allele from parents to their children with CKD.

CONCLUSIONS

The obtained results suggest the association of rs11864909 single nucleotide polymorphism with chronic kidney dysfunction, related to chronic tubulointerstinal nephritis.

The allele C seems to be a risk factor for chronic kidney disease prevalence in this group of patients.

The limitation of this research was the relatively small study population, restricted mainly by problems with family recruitment. It seems valuable to conduct a broader survey in this area in the future.

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REFERENCES

1. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. BMC Public Health. 2008; 8: 117.
2. Evans PD, Taal MW. Epidemiology and causes of chronic kidney disease. Medicine 2011; 39(7): 402–406.
3. Ayodele OE, Alebiosu CO. Burden of chronic kidney disease: an international perspective. Adv Chronic Kidney Dis. 2010; 17(3): 215–224.
4. McClellan WM, Flanders WD. Risk Factors for Progressive Chronic Kidney Disease. J Am Soc Nephrol. 2003; 14 Suppl. 2: S65–S70.
5. O'Seaghdha CM, Fox CS. Genetics of chronic kidney disease. Nephron Clin Pract. 2011; 118(1): c55–63.
6. Köttgen A, Glazer NL, Dehghan A, Hwang SJ, Katz R, Li M, et al. Multiple loci associated with indices of renal function and chronic kidney disease. Nat Genet. 2009; 41(6): 712–717.
7. Serafini-Cessi F, Malagolini N, Cavallone D. Tamm-Horsfall glycoprotein: biology and clinical relevance. Am J Kidney Dis. 2003; 42(4): 658–676.
8. Lhotta K. Uromodulin and chronic kidney disease. Kidney Blood Press Res. 2010; 33(5): 393–398.
9. El-Achkar TM, Wu XR. Uromodulin in kidney injury: an instigator, bystander, or protector?, Am J Kidney Dis. 2012; 59(3): 452–461.
10. Gudbjartsson DF, Holm H, Indridason OS, Thorleifsson G, Edvardsson V, Sulem P, et al. Association of variants at UMOD with chronic kidney disease and kidney stones-role of age and comorbid diseases. PLoS Genet. 2010; 6, 7,e1001039.
11. http://www.ncbi.nlm.nih.gov/gene/204474 (accessed 14.11.2013)
12. van Lith M, Hartigan N, Hatch J, Benham AM. PDILT, a divergent testis-specific protein disulfide isomerase with a non-classical SXXC motif that engages in disulfide-dependent interactions in the endoplasmic reticulum. J Biol Chem. 2005; 280(2): 1376–1383.
13. Oka OB, Bulleid NJ. Forming disulfides in the endoplasmic reticulum. Biochim Biophys Acta 2013; 1833: 2425–2429.
14. Yilmaz A, Grotewold E. Components and mechanisms of regulation of gene expression. Methods Mol Biol. 2010; 674: 23–32.
15. Okada Y, Sim X, Go MJ, Wu JY, Gu D, Takeuchi F, et al. Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. Nat Genet. 2012; 44(8): 904–909.