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# Is *TCF7L2* variant associated with non-diabetic chronic kidney disease progression? Results of a family-based study

Czy polimorfizm genu *TCF7L2* jest związany z progresją przewlekłej choroby nerek o niecukrzycowej etiologii?  
Wyniki badania rodzin

## Authors' Contribution:

-  Study Design
-  Data Collection
-  Statistical Analysis
-  Data Interpretation
-  Manuscript Preparation
-  Literature Search
-  Funds Collection

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## Summary

### Introduction:

It is assumed that genetic factors may play a significant role in CKD development. The aim of the study was to investigate the role of rs7903146 polymorphism in the *TCF7L2* gene in development and progression of non-diabetic chronic kidney disease (CKD).

### Material/Methods:

109 children and young adults with CKD caused by primary glomerulopathy and tubulointerstitial nephropathy, stages 3-5, and their 218 biological parents with no renal dysfunction were included in the study. We tested the transmission of alleles of rs7903146 polymorphism in the *TCF7L2* gene from heterozygous parents to offspring affected with CKD using the transmission/disequilibrium test. We also analysed whether rs7903146 polymorphism had any impact on the loss of glomerular filtration rate.

### Results:

The rs7903146 polymorphism in *TCF7L2* allele transmission from heterozygous parents to their affected children was not different from a random proportion expected for no association, in the whole group of subjects, and in the subgroups, depending on CKD aetiology. Lack of association between the analysed polymorphism and the loss of glomerular filtration rate was found in the total group of patients as well as in the subgroups, regarding the cause of CKD.

### Conclusions:

This study found no association between rs7903146 polymorphism in the *TCF7L2* gene and the increased risk for development of CKD caused by primary glomerulopathy and analysed tubulointerstitial nephropathy. The progression rate of CKD of non-diabetic aetiology does not depend on this polymorphism.

### Keywords:

*CF7L2* variant • non-diabetic chronic kidney disease • family-based study • transmission/disequilibrium test

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**Abbreviations:** **CKD** – chronic kidney disease, **eGFR** – estimated glomerular filtration rate, **GN** – glomerulonephritis, **IN** – chronic tubulointerstitial nephropathy, **T2DM** – type 2 diabetes mellitus, **TCF7L2 gene** – the transcription factor-7 like 2 gene, **TDT** – the transmission/disequilibrium test.

## INTRODUCTION

Chronic kidney disease (CKD) has a complex phenotype, which is the consequence of the deleterious influence of underlying kidney disease and superimposing inherited and environmental factors. It is assumed that genetic factors may play a significant role in CKD development [7,14]. However, the specific genes responsible for the onset and progression of CKD have not been determined, yet.

In recent years, variants in the transcription factor-7 like 2 gene (*TCF7L2*) have been documented to be associated with type 2 diabetes (T2DM) in multiple ethnic groups [3,10,11,15,16]. The human *TCF7L2* gene is located on chromosome 10q25.3 and consists of 14 exons and 13 introns [24]. Most published studies have focused on four polymorphic markers: a C-to-T substitution at single-nucleotide polymorphism (SNP) rs7903146 of intron 3, a T-to-C substitution at SNP rs7901695 of intron 3, a G-to-T substitution at SNP rs12255372 and a G-to-C substitution at SNP rs11196205 of intron 4. The *TCF7L2* gene product is a high-mobility box containing a transcription factor that plays a role in activating many genes downstream of the Wnt signalling pathway [24]. The mechanisms through which *TCF7L2* mediates the susceptibility to T2DM remain to be elucidated [13].

Diabetes is a major risk factor for CKD. It is credible that variants of the *TCF7L2* gene might be important both for the development of T2DM and renal disease. The Wnt signalling pathway is essential in the developing kidney, because it plays a role in regulation of cell proliferation and differentiation [6]. Mutations in components of this pathway have been identified as the cause of inherited kidney diseases [1,23]. The genetic variants of the *TCF7L2* gene may be associated with insulin secretion and insulin sensitivity, impaired glucose metabolism, lipid pro-

file and metabolic syndrome features, factors that are also connected with renal alteration phenotype [4,5,22]. However, the overall impact of *TCF7L2* variants on renal function, and in patients with diabetes, is unclear.

Therefore, we investigated, for the first time, whether rs7903146 polymorphism in the *TCF7L2* gene is associated with the development and progression of non-diabetic chronic kidney disease.

We applied two different approaches in our work. Firstly, a family based study was carried out in families in which children were diagnosed with CKD. The family study included the transmission/disequilibrium test (TDT), which evaluates the transmission frequency of specific alleles of a given polymorphism from heterozygous parents to offspring affected with the investigated phenotype [8,9]. Secondly, we performed a case-control orientated study to determine whether polymorphism in the *TCF7L2* gene influences the progression of renal impairment.

## MATERIALS AND METHODS

### Patients

One hundred and nine children and young adults with CKD, stages 3-5 (according to K/DOQI guidelines [19]), due to primary renal disease and their 218 biological parents with no renal dysfunction (in total, 327 people) were included in the study. We included family trios with probands with CKD caused by non-diabetic nephropathy. We excluded family trios with probands with CKD attributed to polycystic kidney disease or other heritable conditions (for example, Alport's syndrome), traumatic or drug-induced kidney injury, and unknown aetiologies. Finally, the causes of CKD were chronic primary glomerulonephritis (n=30) and tubulointerstitial nephritis (n=79).

Chronic primary glomerulonephritis was diagnosed on the basis of clinical criteria and the renal biopsy in all cases. The histopathological findings in renal biopsy were: minimal change disease in 3 cases, focal and segmental glomerulosclerosis in 9, mesangial proliferative glomerulonephritis in 11, mesangiocapillary glomerulonephritis in 5 and extracapillary glomerulonephritis in 2 cases. The number of cases of particular histopathological types of glomerulopathy was different from typical epidemiological data. It is probably due to the fact that only patients with clinical diagnostic doubts were qualified for kidney biopsy.

Of the 79 patients with tubulointerstitial nephritis, 16 had reflux nephropathy, 26 obstructive nephropathy, 20 chronic pyelonephritis with other urinary system abnormalities, and 17 chronic pyelonephritis without urinary tract anomalies. The CKD patients were treated conservatively (n=51) or required renal replacement therapy (haemodialysis, n=17; peritoneal dialysis, n=33; transplantation, n=8). The demographic data of the patients were as follows: 48 females, 61 males, current age 15.42 ± 6.4 (range 0.7-25) years, age at the diagnosis of CKD (minimum stage 2) 7.82 ± 6.72 (0.01-22) years, CKD duration 8.93 ± 5.59 (0.01-21) years.

The data concerning the history of kidney disease were collected from all patients. Many features were taken into consideration. To enumerate them: 24-hour pro-

teinuria, serum cholesterol levels, and the presence of hypertension at two time points, i.e. at the time of CKD diagnosis (minimum stage 2 according to K/DOQI) and at the time of the study. We also analysed serum creatinine concentrations and their changes during the course of the disease and loss of glomerular filtration rate (GFR) from the initial diagnosis of CKD (minimum stage 2) to the time of the study or the development of CKD stage 5, requiring dialysis or transplantation. GFR was estimated using the Schwartz formula in children and the Cockcroft-Gault formula in young adults. Finally, the patients with CKD were divided on the basis of their renal function into two groups: (I) patients with rapid progression of CKD (n=54), defined as starting renal replacement therapy during the 5-year follow-up period from the diagnosis of CKD stage 2 and/or with a doubling of creatinine level during the follow-up period, and (II) patients with slow progression of CKD (n=55), i.e. those who had stable renal function. Characteristics of the study groups are shown in table 1.

Parents of CKD patients. The mean age of the mothers and fathers was 42.33 ± 7.73 and 45.24 ± 7.81 years, respectively. None of the parents presented a documented renal dysfunction, diabetes or impaired fasting glucose, while hypertension (defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg documented in the medical records on at least two separate occasions, or antihypertensive treatment)

**Table 1.** Characteristics of the CKD patients

	Rapid progression of CKD (n=54)	Slow progression of CKD (n=55)	P value
Age on examination (years)	14.55 ± 7.53 (0.7 - 24)	16.48 ± 5.05 (7.3 - 25)	0.18
Age at CKD diagnosis (years)	9.85 ± 6.76 (0.01 - 22)	5.61 ± 6.14 (0.1 - 20)	0.001
<b>Aetiology of CKD:</b>			
--- chronic primary glomerulonephritis	24	6	
--- chronic tubulointerstitial nephropathy	30	49	
CKD duration (years)	2.56 ± 1.59 (0.01 - 6)	11.31 ± 4.76 (3 - 22.5)	0.0001
Proteinuria/CKD (g/24h)	2.66 ± 4.32 (0 - 25)	0.59 ± 1.53 (0 - 11)	0.00001
Proteinuria/E (g/24 h)	1.23 ± 2.16 (0 - 10)	0.59 ± 0.99 (0 - 6.2)	0.32
Serum cholesterol/CKD (mmol/l)	5.55 ± 2.14 (2.1 - 11.96)	4.39 ± 0.95 (2.99 - 8.5)	0.0015
Serum cholesterol /E (mmol/l)	4.88 ± 1.8 (2.94 - 11.4)	4.88 ± 0.92 (3.12 - 6.92)	0.22
Presence of hypertension/CKD n (%)	27 (50)	15 (27.27)	0.01
Presence of hypertension /E n (%)	27 (50)	15 (27.27)	0.01

Data are show as mean ± SD (range) unless specified otherwise.

Parameters were evaluated: at the time of CKD diagnosis, minimum stage 2 by KDOQI (CKD) and at the time of examination (E).

was present in 3.6% (n=4) and 9.8% (n=11) of the examined mothers and fathers, respectively.

The parents and children over the age of 16 gave their written informed consent. The study protocol adhered to the Declaration of Helsinki of 1975 as revised in 1997, and was approved by the Ethics Committee of Wrocław Medical University.

**Methods**

Rs7903146 polymorphism in the *TCF7L2* gene was genotyped in family-based trio members: patients affected with CKD and both their parents. Venous blood was collected into EDTA-containing tubes. Genomic DNA was isolated from peripheral blood white blood cells using a standard salting-out process (Epicentre Technologies, USA). The rs7903146 polymorphism in the *TCF7L2* gene was genotyped using the PCR-based RFLP method. The region was amplified with the following primers: F: 5'-GAG AGC TAA GCA CTT TTT AGg TA -3' R: 5'-CTG ACA TTG ACT AAG TTA CTT GC - 3'. The 113 base pair PCR product was digested with *RsaI* restriction enzyme (New England Biolabs, USA). The C allele creates a restriction site and gives two fragments of 91 and 22 base pairs after digestion with the restriction enzyme.

We tested the transmission of alleles of rs7903146 polymorphism in the *TCF7L2* gene from heterozygous parents to offspring affected with CKD using TDT. We also analysed whether rs7903146 polymorphism in the *TCF7L2* gene had any impact on the loss of glomerular filtration rate (rapid vs slow CKD progression). Additionally, we evaluated the role of selected factors (proteinuria, lipid

disorders and hypertension) in CKD progression in relation to the studied polymorphism.

**Statistical analysis**

Basic characteristics for qualitative parameters are shown as absolute numbers and percentages. Quantitative data are expressed as the mean ± standard deviation (SD) from the mean. The normality of the distribution of the continuous variables was checked by the Shapiro-Wilk test. In the statistical analysis, Freeman-Halton test, Mann-Whitney U test, and chi-squared test were used.

The TDT was used in the family-based study. The observed transmission was compared with the transmission expected for no association (i.e. random transmission, 50:50%), using McNemar's test (Ewens and Spielman, 1995, 2005). Alleles transmitted significantly greater than 50% of the time to affected offspring provide evidence of disease association. P<0.05 was considered significant. All calculations were performed using Statistica 7.1.

**RESULTS**

The results are shown in tables 2-4. The differences in genotype frequency between patients with chronic primary glomerulonephritis (GN group) and chronic interstitial nephropathies (IN group) were not significant (chi-square test; p=0.82) [table 2].

The rs7903146 polymorphism in the *TCF7L2* gene alleles transmission from heterozygous parents to their

**Table 2.** The frequency of genotypes and allele of rs7903146 polymorphism in the *TCF7L2* in the groups of the CKD patients and their parents

	All CKD patients (n=109)	GN (n=30)	IN (n=79)
<b>GENOTYPE n (%):</b>			
CC	54 (49.5)	15 (50)	39 (49.4)
CT	49 (45.0)	14 (46.7)	35 (44.3)
TT	6 (5.5)	1 (3.3)	5 (6.3)
<b>ALLELE n (%)</b>			
C	157 (72.02)	44 (73.3)	113 (71.5)
T	61 (27.98)	16 (26.7)	45 (28.5)
<b>Parents of all children (n=218)</b>			
<b>Parents of GN children (n=60)</b>			
<b>Parents of IN children (n=158)</b>			
<b>GENOTYPE n (%)</b>			
CC	115 (52.75)	31 (51.67)	84 (53.16)
CT	86 (39.45)	22 (36.67)	64 (40.51)
TT	17 (7.8)	7 (11.66)	10 (6.33)
<b>ALLELE n (%)</b>			
C	316 (71.48)	84 (70)	232 (73.42)
T	120 (27.52)	36 (30)	84 (26.58)

GN - chronic primary glomerulonephritis. IN - chronic tubulointerstitial nephropathy.

affected children was not different from a random proportion expected for no association, in the whole group of subjects and in the subgroups, depending on CKD aetiology (chronic primary glomerulonephritis, chronic interstitial nephropathy) [table 3].

Moreover, lack of association between the analysed polymorphism and the loss of glomerular filtration rate (rapid vs slow progression of the disease) was found in the total group of patients as well as in the subgroups, in regard to the cause of CKD [table 4].

The values of 24-hour proteinuria, serum cholesterol concentration and hypertension were not different between subgroups of CKD patients, regarding the analysed polymorphism genotypes CC, CT, TT (data not shown).

**DISCUSSION**

The association between the rs7903146 *TCF7L2* gene polymorphism and T2DM has been confirmed in numerous populations, including Polish [13,17,24]. It is widely known that diabetes is the most frequent cause of CKD in the adult population, but in contrast, non-diabetic nephropathies are more prevalent in children and young adolescents.

In the present study for the first time we have analysed the potential association of rs7903146 polymorphism in the *TCF7L2* gene with CKD in a young population affected

with non-diabetic nephropathies. Our results indicate that the *TCF7L2* variant is not involved in the development and progression of CKD in the examined cohort. We observed that transmission of C and T alleles from heterozygous healthy parents to affected offspring was not different from the transmission expected for no association. Genotype distribution in the group of CKD patients (CC: 49.5%, CT: 45%, TT: 5%) was similar to those described in healthy populations. Buraczyńska et al. in a group of 924 healthy Poles documented the following frequencies of rs7903146 genotypes: CC 53%, CT 39%, and TT 8% [2]. Similarly, Cauchi et al. in a population of 2499 healthy French people observed the following distribution of genotypes: CC 48.3%, CT 42.4%, TT 9.3% [3]. Also Munoz et al. [18] among Americans of Caucasian origin (n=138) found the frequencies: CC 45%, CT 42% and TT 11%.

The data concerning the rs7903146 variant impact on kidney injury are limited. Melzer et al. investigated, as a secondary outcome, the association of rs7903146 variant with renal function among elderly T2DM patients [16]. They found that T allele carriers (n=32) had significantly worse renal function, measured by 24-hour creatinine clearance. However, the small number of patients with renal complications limited that study. Buraczyńska et al. in a large group of Polish patients with T2DM found an association between SNP and diabetic nephropathy (diagnosed as persistent albuminuria ≥300 mg/24 h), especially in patients with an early onset of diabetes [2]. Results of 3 large population-based trials - ARIC,

**Table 3.** The transmission of alleles of rs7903146 polymorphism in *TCF7L2* gene from heterozygous parents to offspring with CKD (transmission/disequilibrium test)

	All patients	GN	IN
<b>The number of total transmitted alleles</b>	90	22	64
<b>C transmitted</b>	44	11	29
<b>T transmitted</b>	46	11	35
<b>p</b>	0.83	1	0.45

GN - chronic primary glomerulonephritis, IN - chronic tubulointerstitial nephropathy.

**Table 4.** Comparisons of allelic and genotypic frequencies between subgroups of the CKD patients

Genotype	Slow progression of CKD (n=55) n (%)	Rapid progression of CKD (n=54) n (%)	GN (n=30)		IN (n=79)	
			Slow progression of CKD (n=6) n (%)	Rapid progression of CKD (n=24) n (%)	Slow progression of CKD (n=49) n (%)	Rapid progression of CKD (n=30) n (%)
CC	29 (52.73)	25 (46.3)	4 (66.67)	11 (45.83)	25 (51.02)	15 (50)
CT	22 (40)	27 (50)	2 (33.33)	12 (50)	20 (40.82)	14 (46.67)
TT	4 (7.27)	2 (3.7)	0 (0)	1 (4.17)	4 (8.16)	1 (3.33)
			p=0.48		p=0.87	
Allele	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
C	80 (72.7)	77 (71.3)	10 (83.3)	34 (70.8)	70 (71.4)	44 (73.33)
T	30 (27.3)	31 (28.7)	2 (16.7)	14 (29.2)	28 (28.6)	16 (26.67)
			p=0.81		p=0.97	

GN - chronic primary glomerulonephritis, IN - chronic tubulointerstitial nephropathy.



FHS and HAPI – suggest that some variants in the *TCF7L2* gene are associated with reduced kidney function and CKD progression overall and among subjects without diabetes [13]. The T allele of rs7903146 polymorphism was significantly associated with lower estimated GFR (in FHS and HAPI studies) and higher serum cystatin C level (FHS study). The data mentioned above, although highly significant for the description of *TCF7L2* gene variant frequency in kidney diseases, could not be compared with our results due to different study designs (population-based case-control study vs family-based study), race variability of examined populations, renal function evaluation by different formulas, estimation of CKD progression and finally diverse clinical phenotypes of the disease.

We applied a family-based study to avoid the potential bias of case-control studies. The TDT is a powerful statistical test to detect linkage between the marker allele and susceptibility to the disease. The group we examined was ethnically homogeneous. Moreover, the members of families enrolled in the study had normal carbohydrate metabolism and all the children suffered from a non-diabetic nephropathy.

The results of our investigation did not show a relationship between the rs7903146 polymorphism and the rate of glomerular filtration decline. There was also no difference in the values of 24-hour proteinuria, serum cholesterol level and presence of hypertension, known risk factors of CKD progression, between the subjects with different genotypes TT, CT and CC. Similarly, in the population-based ARIC study an association of this gene polymorphism with eGFR was not found. Both ARIC and FHS studies did not show any relationship between rs7903146 polymorphism and the degree of albuminuria [13]. The association between rs7903146 polymorphism and CKD progression among individuals without diabetes, found in population-based cohorts, may be the result of the influence of previously undetected diabetes and impaired glucose metabolism. It is therefore plausible that a mutation could mediate reduced kidney function only via its effects on hyperglycaemia. Assuming further that the *TCF7L2* variant increases the risk for CKD through other renal specific mechanisms, the results of the presented studies are ambiguous. It was confirmed that rs7903146 polymorphism of the *TCF7L2* gene may influence insulin secretion and modify the effects of its

action, including damage and endothelial dysfunction [16,22]. Körner et al., who investigated different variants of the *TCF7L2* gene in a cohort of obese children, noted the significant association with glucose metabolism alterations in T allele carriers, which was unrelated to body mass index, age and gender [12]. On the other hand, Melzer et al. found that T allele is connected with the protective lipid profile (higher serum concentration of HDL cholesterol, and lower level of triglycerides) in the overall population of Italian elderly people [16]. The association was not linked to carbohydrate metabolism parameter values. These authors also documented that T allele carriers had lower incidence of metabolic syndrome, defined as hypertension, abdominal obesity, high concentrations of serum triglycerides and low levels of HDL cholesterol. The various factors, specified above, associated with the variant of the *TCF7L2* gene, are simultaneously well-known features that modify the course of CKD [20,21]

Our study has several limitations. By using the transmission/disequilibrium test, the impact of population stratification was excluded, but other forms of selection bias, e.g. associated with patients' survival, could have been introduced. The number of examined families was relatively small, which is due to low prevalence of childhood CKD as compared to adult CKD. There are evident difficulties in obtaining consent and getting samples from patients and both their parents. Finally, although in every child the cause of CKD was of non-diabetic origin, the spectrum of diseases was not homogeneous, including glomerulopathies and tubulointerstitial nephropathies.

In conclusion, rs7903146 polymorphism of the *TCF7L2* gene does not have an impact on the development of CKD caused by primary glomerulopathy and analysed tubulointerstitial nephropathy, which is confirmed by the lack of a significant difference in the transmission of these polymorphism alleles in examined family-based trios. The lack of association between rs7903146 polymorphism and the rate of renal function loss in the investigated patients suggests that the CKD progress rate does not depend on this polymorphism. The question whether rs7903146 polymorphism in the *TCF7L2* gene is involved in progression of non-diabetic CKD still remains an open issue.

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