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TCF7L2 rs7903146 polymorphism and diabetic nephropathy association is not independent of type 2 diabetes — a study in a south Indian population and meta-analysis

Związek między polimorfizmem rs7903146 genu *TCF7L2* a nefropatią cukrzycową nie jest niezależny od cukrzycy typu 2 — badanie populacji Indii Południowych i metaanaliza

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Abstract

Diabetic nephropathy (DN) is a chronic microangiopathic complication of both type 1 (T1DM) and type 2 diabetes mellitus (T2DM). The *TCF7L2* gene has been reported to be associated with type 2 diabetes risk. We aimed to investigate the impact of *TCF7L2* gene on the susceptibility of T2DM and DN in a south Indian population. Plus to evaluate the association of rs7903146 in the *TCF7L2* gene with T2DM in the Indian population. The subjects recruited for this included 55 diabetic cases with diabetic nephropathy, 68 diabetic cases without nephropathy, and 82 non-diabetic healthy controls. Genomic DNA was isolated from blood and genotyping of *TCF7L2* rs7903146 was performed by PCR-RFLP analysis. A literature survey was carried out into the effect of rs7903146 on genetic susceptibility to T2DM in Indian populations and we then performed a meta-analysis in order to evaluate its association with T2DM. Analysis of *TCF7L2* rs7903146 in normal controls and diabetics with or without nephropathy demonstrated that the 'T' allele is associated with both diabetes ($p = 0.049$) and DN ($p = 0.024$), but this association is not independent of T2DM. Meta-analysis showed that the mutant allele and genotypes are associated with T2DM in Indian populations. In summary, a significant association exists between the 'T' allele and DN, but this association is not independent of T2DM. Pooled meta-analysis of studies on rs7903146 and T2DM confirmed that rs7903146 is significantly associated with susceptibility to T2DM in Indian populations. **(Endokrynol Pol 2014; 65 (4): 298–305)**

Key words: *TCF7L2 gene; SNP; diabetic nephropathy*

Streszczenie

Nefropatia cukrzycowa (DN, *diabetic nephropathy*) jest przewlekłym powikłaniem o charakterze mikroangiopatii występującym zarówno w cukrzycy typu 1 (T1DM, *type 1 diabetes mellitus*), jak i typu 2 (T2DM, *type 2 diabetes mellitus*). Gen *TCF7L2* jest związany z ryzykiem cukrzycy typu 2. Badanie przeprowadzono w celu dokonania oceny wpływu genu *TCF7L2* na podatność na zachorowanie na T2DM i DN w populacji Indii Południowych oraz oceny związku między występowaniem polimorfizmu rs7903146 genu *TCF7L2* i T2DM w populacji południowej części Indii. Do badania włączono 55 przypadków chorych na cukrzycę z nefropatią cukrzycową, 68 przypadków cukrzycy bez nefropatii i 82 osoby niechorujące na cukrzycę jako grupę kontrolną. Genomowe DNA izolowano z krwi i przeprowadzono genotypowanie polimorfizmu rs7903146 genu *TCF7L2* metodą analizy PCR-RFLP. Przeprowadzono również przegląd literatury pod kątem danych dotyczących wpływu występowania polimorfizmu rs7903146 na genetyczną podatność na T2DM w populacji hinduskiej, a następnie przeprowadzono metaanalizę w celu oceny jego związku z T2DM. Analiza polimorfizmu rs7903146 genu *TCF7L2* u zdrowych osób z grupy kontrolnej oraz u chorych na cukrzycę z nefropatią i bez nefropatii wykazała, że allel T jest związany zarówno z cukrzycą ($p = 0{,}049$), jak i DN ($p = 0{,}024$), jednak ten związek nie jest niezależny od T2DM. Metaanaliza wykazała, że zmutowane allele i genotypy są związane z T2DM w populacji hinduskiej.
Podsumowując, istnieje istotny związek między allelem T i DN, jednak związek ten nie jest niezależny od T2DM. Metaanaliza danych z badań dotyczących polimorfizmu rs7903146 i T2DM potwierdziła, że obecność polimorfizmu rs7903146 jest istotnie związana z podatnością na zachorowanie na T2DM w populacji hinduskiej. **(Endokrynol Pol 2014; 65 (4): 298–305)**

Słowa kluczowe: *gen TCF7L2; SNP; nefropatia cukrzycowa*

Introduction

Diabetic nephropathy (DN) is a chronic microangiopathic complication of both type 1 (T1DM) and type 2 diabetes mellitus (T2DM) and is the primary cause of end stage renal disease (ESRD) [1]. Diabetes is characterised by hyperglycaemia resulting from the impairment of insulin secretion, insulin sensitivity, or both. Type 2

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diabetes is the most common form of diabetes, affecting 90% of all people with diabetes. The prevalence of type 2 diabetes continues to rise, with an increasing number of patients at risk of serious diabetes-related microvascular and macrovascular complications [2]. Both longitudinal and cross-sectional studies have demonstrated that type 2 diabetes is influenced by several behavioural as well as lifestyle factors [3]. Multiple lines of evidence indicate that type 2 diabetes is a highly inherited trait and different approaches such as candidate gene and linkage studies have been made to identify type 2 diabetes genes [4-6]. Genome wide association studies (GWAS) have paved the way for researchers to identify more genes that have a relatively low effect on type 2 diabetes susceptibility [7, 8].

Transcription factor 7-like 2 is the key transcriptional factor regulating glucose metabolism through the Wnt signalling pathway. Wnt signalling has also been reported to be critical for the development of the pancreas and islets during embryonic growth. Furthermore, regulation of Wnt signalling's timing and stimulus is crucial for the development of the pancreas [9]. The gene *TCF7L2* located on chromosome 10q25.3 which encodes the transcription factor-4 (TCF-4) has been identified as a major T2DM susceptibility gene. *TCF7L2* rs7903146 SNP is associated with type 2 diabetes and may operate via impaired glucagon-like peptide 1 (GLP1) secretion, which is stimulated more by fat than by carbohydrate ingestion. Moreover, the association between *TCF7L2* variants and T2DM is supported by several prospective mechanisms such as decreased β-cell mass, liver insulin resistance and altered chromatin state in 'T' allele carriers [10, 11]. However, causative links between polymorphisms in or near the *TCF7L2* gene and overt type 2 diabetes are uncertain, because of the fact that the polymorphisms have not yet been proven to correlate with the risk for type 2 diabetes in prospective follow-up studies.

Thus, the objective of this study was to investigate the association of the *TCF7L2* SNPs with SNP rs7903146 with well characterised DN. In particular, we investigated whether the association between *TCF7L2* polymorphisms and DN is independent or dependent of diabetes. Further, we analysed the studies conducted so far on *TCF7L2* gene rs7903146 in diverse populations of India, using meta-analysis to assess the possible heterogeneity in the allele frequency and the nature as well as the magnitude of its association with T2DM.

Material and methods

Subjects and methods

One hundred and twenty three unrelated individuals visiting outpatient clinics at Sri Ramachandra University Hospital, Chennai were diagnosed as type 2 diabetes according to the World Health Organisation criteria [12]. All participants underwent detailed clinical evaluation followed by biochemical investigations such as serum creatinine, fasting and postprandial blood glucose and 24-h urinary albumin excretion. Among them, 55 patients had overt nephropathy, as indicated by persistent urine albuminuria (> 300 mg/L) in two consecutive measurements. Sixty eight individuals with normoalbuminuria indicated by urinary albumin excretion rate of < 20 μg/min even after ten years of diabetes were considered as controls. Eighty two age- and sex-matched healthy subjects were selected as controls. Individuals with hypertension, congestive heart defects and chronic renal disease were excluded from the study. This study was approved by the institutional ethics committee of Sri Ramachandra University. Informed written consent was obtained from all the study participants prior to the commencement of the study. Three ml of blood sample was collected from each participant, genomic DNA was isolated from lymphocytes by standard techniques, and we used a published protocol to genotype the *TCF7L2* rs7903146 SNP [13]. Briefly, the rs7903146 was genotyped by amplifying 188 bp intron region of *TCF7L2* gene by using forward primer 5′ ACA ATT AGA GAG CTA AGC ACT TTT TAG GTA 3′ and reverse primer 5′ GTG AAG TGC CCA AGC TTC TC 3′ followed by the digestion of PCR product with *Rsa*I enzyme. The rs7903146 'T' allele was characterised by the presence of a 188 bp fragment, which was digested further to 159 and 29 bp fragments in rs7903146 'C' allele carriers.

A comprehensive search of the electronic databases: PubMed, Embase, and ISI Web of Science was done using the terms: 'transcription factor 7-like 2/*TCF7L2*', 'rs7903146' and 'type 2 diabetes mellitus/T2D/T2DM'. Papers pertaining to Indian populations with sufficient data retrieved up to April 2013 were considered for estimating an odds ratio (OR) and 95% confidence interval (CI) in the meta-analysis. All the studies included in the meta-analysis are listed in Table I. The data collected from the eligible studies included the study reference, total number of cases and controls, and numbers of genotypes in both cases and controls.

Statistical analysis

TCF7L2 rs7903146 allele frequencies of the present study and ten eligible case control studies were determined by direct gene counting. The genotype distribution of this SNP in all studies was evaluated for Hardy-Weinberg equilibrium by using a *HWSIM* program [14]. The strength of the association between *TCF7L2* variant alleles and their interaction in causing diabetic nephropathy and T2DM was calculated using chi square

Table I. *Main characteristics of the studies included in the meta-analysis*
Tabela I. *Charakterystyka badań włączonych do metaanalizy*

Study reference	Total samples	Control			Case		
		CC	TC	TT	CC	TC	TT
Humphries et al., 2006 [43]	1,137	163	111	26	366	375	96
Chandak et al., 2007 [32]	1,354	205	160	34	391	423	141
Bodhini et al., 2007 [35]	2,069	555	391	92	462	455	114
Mahurkar et al., 2008 (Dravidian) [44]	592	130	104	25	175	126	32
Mahurkar et al., 2008 (Indo-European) [44]	547	207	160	35	78	53	14
Sanghera et al., 2008 [34]	1,081	236	224	77	191	261	92
Rees et al., 2008 [45]	1,260	222	166	44	352	360	116
Gupta et al., 2010 [46]	356	62	78	21	55	96	44
Mukhopadhyaya et al., 2010 [47]	80	5	19	16	17	21	2
Uma Jyothi et al., 2013 [36]	1,379	393	194	34	344	328	86
Present study	150	43	35	4	25	36	7

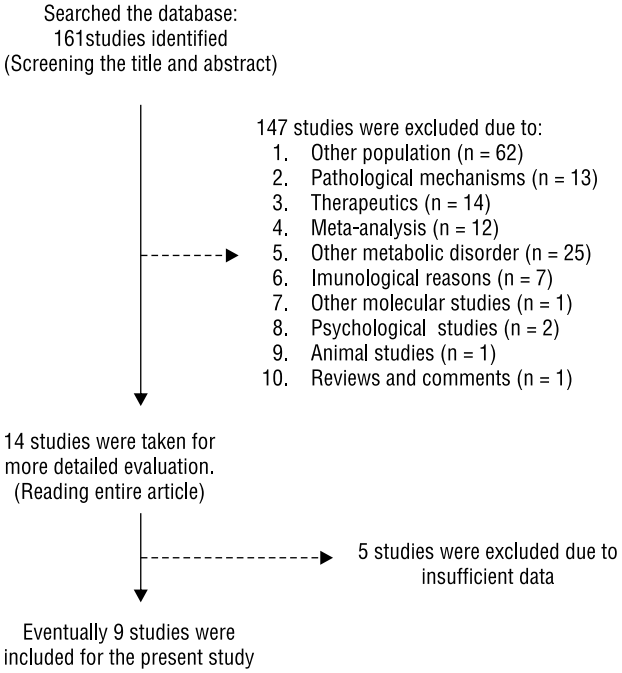

Figure 1. *Schematic representation of the article selection process*
Rycina 1. *Schemat przedstawiający proces selekcji artykułów*

analysis. The OR and corresponding 95% CI limits were also calculated. For *TCF7L2* rs7903146, the meta-analysis examined the association between the carriers of the rare T allele and T2DM risk compared to that for CC genotype (CC *vs.* TC+TT). The pooled OR estimate of each study was calculated by the fixed-effects model [15]. The odds ratio and confidence interval was graphically presented as a forest plot. An estimate of potential publication bias was carried out by the funnel plot. Funnel plot asymmetry was assessed by the method of Egger's linear regression test [16]. The data was analysed using comprehensive meta-analysis software. For a worldwide comparison in a wider context, we have also extracted 20kb up and downstream SNPs around rs7903146 from the HapMap data (The International HapMap Consortium) [17].

Results

Association study

The distribution of *TCF7L2* rs7903146 genotypes among DN, diabetic control and normal controls is documented in Table II. The genotype frequency distribution in all three groups followed Hardy Weinberg equilibrium (Table II). The frequency of 'T' allele was 31.9%, 36.8% and 26.2% in diabetic nephropathy, diabetic control, and normal control respectively. The results of association between different groups are also documented in Table II. The frequency of TT genotype was slightly higher in DN cases than the controls and increased the risk of nephropathy ($p = 0.021$, OR 4.30, 95% CI 1.00–21.44). The 'T' allele is associated with both diabetes ($p = 0.049$, OR 1.64, 95% CI 0.97–2.76) and diabetic nephropathy ($p = 0.024$, OR 1.81, 95% CI 1.04–3.13). The distribution of both allele and genotypes did not show significant differences between diabetes and diabetic nephropathy (Table II).

Meta-analysis

Meta-analysis of 11 studies showed that the mutant allele is associated with T2DM in both fixed effect ($P < 0.001$, OR = 1.336, 95% CI = 1.255–1.422) and random effect ($P = 0.004$, OR = 1.254, 95% CI = 1.075-1.463) (Fig. 2). Similar to the allelic meta-analysis, the pooled odds ratio for mutant genotypes (dominant model) showed a statistically significant association with T2DM adopting both fixed effect ($P < 0.001$, OR = 1.451, 95%

Table II. *Genotype frequencies and association statistics for the rs7903146 in diabetic nephropathy, T2DM control and normal control*

Tabela II. *Częstość występowania poszczególnych genotypów i powiązane statystyki dotyczące polimorfizmu rs7903146 u osób z nefropatią cukrzycową, w grupie chorych na T2DM i grupie kontrolnej obejmującej zdrowe osoby*

	Control	Diabetic without nephropathy	Diabetic nephropathy	p value*	p value**	p value***
CC	43 (52.44)	25 (36.76)	20 (30.36)	Reference		
CT	35 (42.63)	36 (52.94)	27 (49.09)	0.097	0.173	0.869
TT	4 (4.88)	7 (10.29)	8 (14.55)	0.092	0.021	0.550
CT+TT	39 (47.51)	14 (63.23)	14 (63.64)	0.226	0.529	0.643
C	121 (73.8)	86 (63.2)	67 (60.9)	Reference		
T	43 (26.2)	50 (36.8)	43 (39.1)	0.049	0.024	0.708
HWE p-value	0.350	0.253	0.818	–	–	–

*Control *vs.* diabetic without nephropathy, **Control *vs.* diabetic nephropathy, ***Diabetic without nephropathy *vs.* diabetic nephropathy

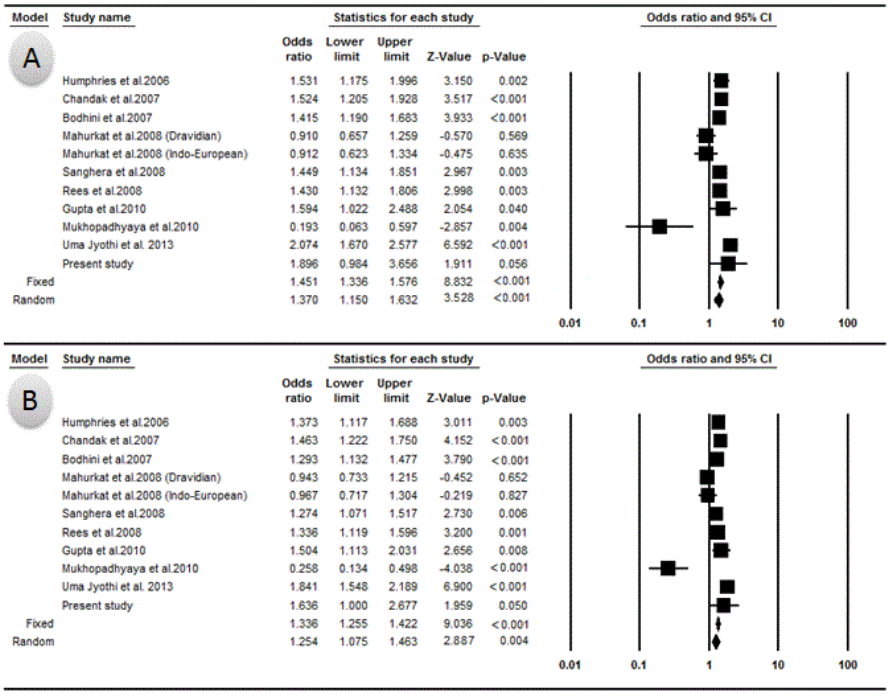

Figure 2. *Forest plot of the fixed and random-effects meta-analysis of 11 studies of rs7903146 for T2DM (***A.** *dominant model,* **B.** *allelic model). Point estimates, 95% confidence intervals (CI), and study weights are provided for each study*

Rycina 2. *Wykres typu forest plot efektów stałych i losowych w metaanalizie 11 badań polimorfizmu rs7903146 u osób z T2DM (***A.** *model dominujący,* **B.** *model alleliczny). Dla wszystkich badań przedstawiono estymacje punktowe, 95% przedziały ufności i wagi*

CI = 1.336–1.576) and random effect (P < 0.001, OR = 1.370, 95% CI = 1.150–1.832) (Fig. 2). The heterogeneity test and sensitivity analysis showed a true heterogeneity between studies for 'T' allele in the allelic model ($P_{heterogeneity} < 0.001$, $\chi^2 = 35.36$, df = 10, I-squared = 74.5%) and dominant model ($P_{heterogeneity} = 0.003$, $\chi^2 = 25.43$, df = 10, I-squared = 64.6%). The comparison of heterogeneity between studies demonstrated that both allelic and dominant model show variations in study outcomes between studies.

The funnel plots generated using standard error and precision values for both allelic and dominant models using both fixed and random effect models are depicted in Figure 3. The shape of the funnel plots was symmetrical, suggesting that there was no evidence for publication bias for rs7903146 polymorphism. The other measures used for assessing the publication bias in allelic and dominant models showed absence of publication bias (Table III). The classic fail-safe 'N' value

Table III. *Measures of publication bias in allelic and dominant models*

Tabela III. *Pomiar stronniczości publikacji w modelach allelicznym i dominującym*

Publication bias test	Allelic model	Dominant model
Classic fail-safe 'N'		
Observed studies p value	P < 0.001	P < 0.001
Observed studies Z value	Z = 1.96	Z = 1.96
Number of missing studies to bring p > alpha	136	130
Orwin's fail-safe 'N'		
OR	1.34	1.45
Number of null studies required	15	23
Begg and Mazumdar rank correlation test:		
Kendall' tau	–0.145	–0.11
One-tailed	0.267	0.32
Two-tailed	0.533	0.64
Egger's regression test:		
Intercept value	–2.99	–2.45
't' value	1.72	1.75
One-tailed	0.059	0.057
Two-tailed	0.119	0. 119
df	9	9

of 136 (P < 0.001, Z = 1.96) for allelic model and 130 (P < 0.001, Z = 1.96) for dominant model, indicated that 136 and 130 null studies (for allelic and dominant models respectively) would be required to convert the combined 'P' value as a non-significant P > 0.05. The Orwin's fail-safe 'N' value to bring observed Odds Ratio of 1.34 to 1.11 is 15 for allelic model, indicating a minimum of 15 null studies would be needed to bring the effect size to null. Similarly, Orwin's fail-safe 'N' value to bring the observed Odds Ratio of 1.45 to 1.11 is 23 for dominant model, indicating a minimum of 23 null studies would be needed to bring the effect size to null. Furthermore, the Duval and Tweedie's 'trim and fill' procedure also failed to show publication bias.

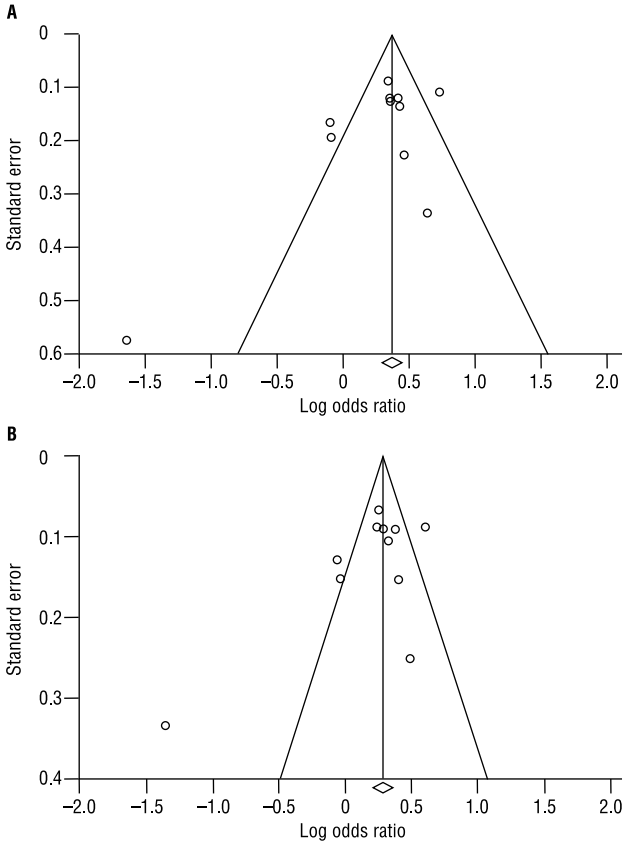

Figure 3. *Egger's funnel plot as a test for publication bias for rs7903146 (***A.** *dominant model,* **B.** *allelic model). The precision of each study (standard error of the log odds ratio [OR]) is plotted against each study's effect estimate (OR)*

Rycina 3. *Wykres lejkowy Eggera w ocenie stronniczości publikacji dotyczących polimorfizmu rs7903146 (***A.** *model dominujący;* **B.** *model alleliczny). Przedstawiono dokładność poszczególnych badań (błąd standardowy logarytmu ilorazu szans w zależności od ich oszacowanego efektu (OR)*

Discussion

Analysis of *TCF7L2* rs7903146 in normal controls and diabetics with or without nephropathy demonstrated that the 'T' allele is associated with both diabetes and DN, but this association is not independent of T2DM. The meta-analysis conducted using the 11 studies also showed a significant association between the mutant allele and T2DM in Indian populations. Furthermore, comparison on heterogeneity between studies confirmed that both the allelic and dominant models exhibited heterogeneity. No evidence or publication bias was observed. Although the role of *TCF7L2* in the regulation of microvascular complications such as DN is not fully known, there have been several studies reporting the association of this gene with DN [18, 19]. Another study showed that the *TCF7L2* gene was associated only with lower estimated glomerular filtration rate (eGFR) but not with albuminuria, indicating a shared genetic risk for T2DM and DN [20]. In contrast to this, no influence of this gene in the pathogenesis of diabetes-induced microvascular complications such as neuropathy, nephropathy and retinopathy has been observed [21].

The first report on a strong genetic association between variants of the *TCF7L2* gene and risk of type 2 diabetes was found in Icelandic individuals, a Danish cohort, and a cohort of the US population [22]. The subsequent genome-wide association analysis on T2DM showed a strong signal for *TCF7L2* in the

French population [23]. This prompted inclusion of *TCF7L2* gene variants in a large number of association studies in various populations world-wide [24–29]. Furthermore, a number of meta-analyses supported this robust finding [30, 31]. The replication studies of *TCF7L2* gene variants among Indian populations also showed a strong association of *TCF7L2* with T2DM [32–36].

Investigations on transcriptional regulation by applying chromatin immunoprecipitation and sequencing techniques in a colorectal cancer cell line revealed overexpression of *TCF7L2*. This provided the first evidence for its central node for T2DM susceptibility [37]. Later, several studies using pancreatic cells and a rat insulin-producing cell line (Ins-1) have indicated a potential role of *TCF7L2* in human T2DM [38–40]. A recent study demonstrated that the liver-specific TCF4 overexpression increases hepatic glucose production, indicating *TCF7L2* directly activates metabolic genes [41]. To date, most studies with *TCF7L2* have genotyped either the one or two most associated SNPs reported in the original study [22], and ignored the remaining polymorphisms of the *TCF7L2* gene. The rs7903146 also showed variations among the world populations with the highest 'T' allele frequency in HapMap populations of African (YRI, MKK, ASW and LWK) and European (CEU and TSI) followed by Mexican (MEX) ancestry and south Asian populations (GIH). East Asian populations (CHB, CHD and JPT) exhibited slightly fewer 'T' allele frequencies than the rest of the world populations (Table SI).

Analysis of 20kb up and downstream SNPs around rs7903146 from the HapMap data demonstrated that the European (CEU and TSI) and Mexican (MEX) populations formed a single large LD block. Unlike in Caucasians, the African populations exhibited weak LD and formed two small LD blocks. In East Asian populations (CHB, CHD and JPT) and south Asian populations (GIH), the LD is fragmented (Fig. S1). Although the functional role of this intronic SNP (rs7903146) is still unknown, the variant risk allele is associated with impaired insulin secretion, reduction of total islet numbers, and quantitative as well as qualitative morphological changes in human islets [42]. Furthermore, carriers of risk variants at *TCF7L2* are more likely to fail sulfonulyurea therapy than metformin and more likely to be on insulin therapy rather than diet alone. Thus, the screening of the entire gene leads to a complete understanding of the variants of exons and the surrounding region with a stronger effect on the risk of disease.

Table SI. ***Genotype, allele frequencies and Hardy-Weinberg equilibrium for TCF7L2 rs7903146 in HapMap populations***

Tabela SI. ***Genotypy, częstość występowania alleli i prawo Hardy'ego-Weinberga dla polimorfizmu rs7903146 genu TCF7L2 w populacji HapMap***

	C/C	C/T	T/T	T allele	HWp
ASW	23 (41.1)	28 (50.0)	5 (8.9)	38 (33.9)	0.339
CEU	62 (54.9)	39 (34.5)	12 (10.6)	63 (27.9)	0.132
CHB	130 (94.9)	7 (5.1)	0 (0.0)	7 (2.6)	0.759
CHD	101 (92.7)	8 (7.3)	0 (0.0)	8 (3.7)	0.691
GIH	52 (51.5)	42 (41.6)	7 (6.9)	56 (27.7)	0.705
JPT	106 (93.8)	6 (5.3)	1 (0.9)	8 (3.5)	0.018
LWK	58 (52.7)	43 (39.1)	9 (8.2)	61 (27.7)	0.796
MEX	32 (55.2)	22 (37.9)	4 (6.9)	30 (25.9)	0.934
MKK	77 (49.4)	63 (40.4)	16 (10.3)	95 (30.4)	0.561
TSI	44 (43.1)	42 (41.2)	16 (15.7)	74 (36.3)	0.269
YRI	76 (51.7)	63 (42.9)	8 (5.4)	79 (26.9)	0.273

In conclusion, we suggest that *TCF7L2* is a potent gene in not just causing T2DM, but also DN. This study could be extended to a larger number of diabetes-induced nephropathic individuals to gain more evidence. Thus it may prove to be a strong predictive classifier to provide an index of 'at risk' status, including probability estimates to T2DM likelihood and nephropathic complications thereafter. These studies can further aid in translational research, as categorising diabetic individuals based on their genetic makeup will help personalise medication and improve treatment options.

Author's contribution

All authors contributed equally to the article.

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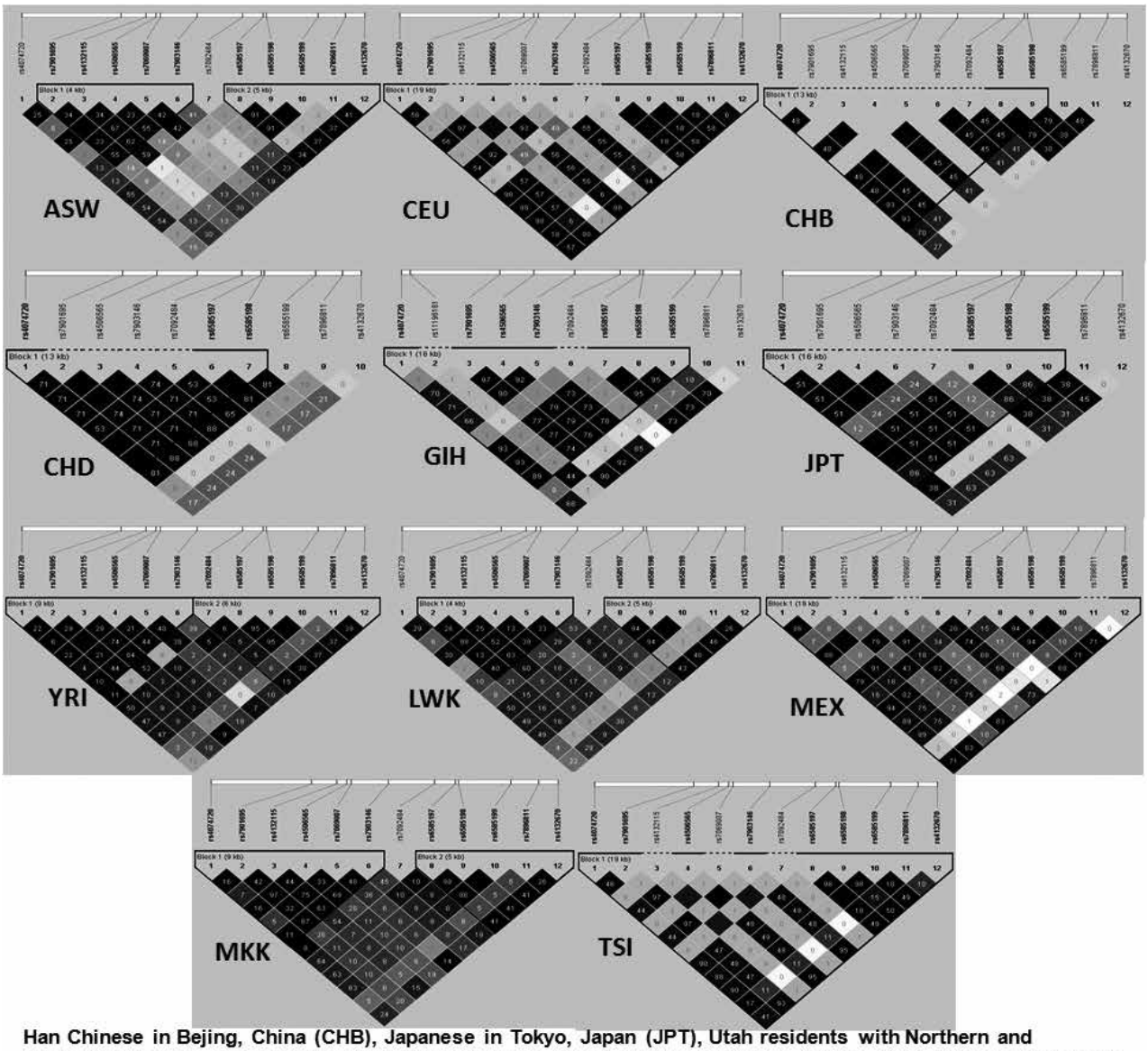

Han Chinese in Bejing, China (CHB), Japanese in Tokyo, Japan (JPT), Utah residents with Northern and Western European ancestry from the CEPH collection (CEU), Yoruba in Ibadan, Nigeria (YRI), African ancestry in Southwest USA (ASW), Chinese in Metropolitan Denver, Colorado (CHD), Gujarati Indians in Houston, Texas (GIH), Luhya in Webuye, Kenya (LWK), Mexican ancestry in Los Angeles, California (MEX), Maasai in Kinyawa, Kenya (MKK), and Toscans in Italy (TSI).

Figure S1. *Linkage disequilibrium profiles in different populations studied in International HapMap Project. Colour coding represents the D'/LOD values and the values in cells are r2 multiplied by 100*

Rycina S1. *Nierównowaga sprzężeń w różnych populacjach badanych w ramach projektu HapMap. Kolorami oznaczono wartości D'/LOD, a liczby w komórkach odpowiadają współczynnikom r2 pomnożonym przez 100*

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