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SLC30A8 gene polymorphism (rs13266634 C/T) and type 2 diabetes mellitus in south Iranian population

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Abstract Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder which is characterized by chronic hyperglycemia. T2DM is due to the interplay of genetic susceptibility and environmental factors. Zinc is an important element for insulin storage and secretion. Zinc transporters ensure zinc transportation across the biological membranes and enable the cellular flow of zinc into the extracellular matrix or the intracellular vesicles. Solute carrier family 30 member 8 (*SLC30A8*) gene encodes zinc transporter protein member 8. The rs13266634 C/T polymorphism in *SLC30A8* gene has been reported with higher risk of T2DM in literature. Thus, the present study aimed to investigate the association between rs13266634 polymorphism and T2DM in Fars province, Southern Iran and compare the results with other populations. A total of 306 subjects were collected from the outpatients of Shahid Motahhari clinic affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. These subjects were genotyped using polymerase chain reaction-restriction fragment length polymorphism and validated by direct sequencing. The frequency of CC genotype in diabetic and control groups was 90 (59.6 %) and 89 (57.4 %). The number of CT genotype was 51 (33.8 %) in the case and 49 (31.6 %) in the control group. The TT genotype was 10 (6.6 %) and 17 (11 %) in diabetic and non-diabetic subjects, respectively. No significant difference was found between the normal and T2DM subjects regarding the allelic and genotypic distribution ($p = 0.35$, OR = 1.19, 95 % CI 0.82–1.7) and ($p = 0.94$, OR = 1.7, 95 % CI 0.7–3.9). No significant difference was found between the normal and diabetic subjects regarding the rs13266634 C/T polymorphism in *SLC30A8* gene. In comparison with other ethnic groups, the C allele frequency in our population was very similar to that of the European but higher than that of the Eastern Asian and lower than the African populations.

Keywords SLC30A8 · Type 2 diabetes mellitus · Polymorphism · Iranian population

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Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by chronic hyperglycaemia. Hyperglycaemia occurs because of the defects in insulin secretion and insulin sensitivity [1]. The prevalence of diabetes is increasing alarmingly. WHO has estimated that by 2030, as many as 366 million people worldwide will have developed diabetes mellitus the majority of whom will have T2DM [2]. The factors influencing the prevalence of diabetes are age, gender, place of residence, ethnicity, socioeconomic status, lifestyle, and obesity [3]. The prevalence of T2DM in Iran was reported as 7.7 % [4]. Type 2 diabetes is multifactorial due to the interplay of common variation in multiple genes and environmental factors [5].

There are several evidences indicating the role of the genetic factors in T2DM [6, 7]: (a) Concordance for diabetes is generally higher among the monozygotic twins compared to the dizygotic ones, (b) The familial collection of T2DM, (c) Noticeable differences in the prevalence of T2DM among various populations, (d) The great risk of

developing the disease in the offspring of one parent or two parents with T2DM, and (e) migration studies.

Some of the most replicated T2DM susceptibility genes are Peroxisome proliferator-activated receptor-γ (*PPARG*), K inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*), Glucokinase (*GCK*), Transcription factor 7-like 2 (*TCF7L2*), *CDK5* regulatory subunit associated protein 1-like 1 (*CDKAL1*), Solute carrier family 30 (zinc transporter), member 8 (*SLC30A8*), and Fat mass and obesity-associated protein (*FTO*) [8].

Zinc is an important element for insulin storage and secretion [9]. Two Zn^{2+} ions bound with insulin hexamers to assist correct insulin maturation, storage, and secretion. Binding of zinc to insulin is thought to be important for proper insulin crystallization and, consequently, secretion [10, 11]. The pancreatic beta cells contain the highest zinc content among the other cells in human body [12]. β-cells need particular transporters to amass zinc in secretion vesicles. The two main parts entangled in zinc homeostasis are metallothioneins and zinc transporters. Zinc transporters ensure zinc transportation across the biological membranes and enable the cellular flow of zinc into the extracellular matrix or the intracellular vesicles [13]. Solute carrier family 30 member 8 (SLC30A8) gene (chromosome 8q24.11) encodes zinc transporter protein member 8 (ZnT-8) which includes eight exons and 369 amino acids and is thought to be the β-cell zinc homeostasis regulator. The single nucleotide polymorphism (SNP) (C to T, rs13266634) in the *SLC30A8* gene in the codon of amino acid 325 leads to the formation of two protein variants: Arginine (R) and Tryptophan (W). The C allele (Arginine) of this SNP is associated with increased susceptibility for the progression of type 2 diabetes [14].

The present study aims to investigate the association between the *SLC30A8* gene SNP rs13266634 and T2DM in Fars province, Southern Iran and compare the results with other populations.

Materials and methods

Subjects

The present hospital-based, case–control study was conducted on 151 patients (85 females and 66 males) with T2DM and 155 non-diabetic subjects (76 females and 79 males) at the age of 50 and older who were selected from the same hospital. The controls had no past history of glucose intolerance.

All blood samples were collected from Shahid Motahhari outpatient clinics affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. It should be noted that Shiraz is one of the big cities of Iran with several ethnic groups. Therefore, our study population could represent the southern Iranian population.

Diabetes was defined according to the American Diabetes Association (ADA) criteria. The patients were included in this study if their diabetes was definitely confirmed and they received antidiabetic medications. The inclusion criteria for the control group were having no past history of glucose intolerance, absence of family history of diabetes in the close relatives, and fasting plasma glucose (FPG) less than 100 mg/dL. Fasting cholesterol, FPG, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and plasma glucose were measured by standard enzymatic assays. Plasma insulin levels and HbA1C were determined by means of an enzymatic immunoassay.

Homeostasis model assessment-insulin resistance (HOMA-IR) was computed as fasting plasma insulin × fasting glucose (mg/dL)/405.

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran and informed consents were obtained from all the subjects taking part in the study.

Genotype analysis

For genotype determination, genomic DNA was extracted from a peripheral blood sample using a commercial extraction kit (CinnaPure DNA Extraction Kit, Sinagene Company, Tehran, Iran). To genotype the rs13266634 polymorphism in the *SLC30A8* gene, the polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) was used. The primers used were as follows: Forward, 5′-GGACAGAAAGAGTTCCCATAG CG-3′; Reverse, 5′-ATAGCAGCATGTTTGAAGGTGGC-3′ [15]. PCR amplification conditions were 5 min of initial denaturation at 95 °C followed by 40 cycles of melting at 94 °C for 40 s, annealing at 69 °C for 45 s, and final elongation at 72 °C for 5 min. The PCR products were digested with MspI (Fermentas, German) and visualized on 1.5 % agarose gel. In wild-type genotype of rs13266634 (CC), the RFLP fragments were 234 and 195 bp. In heterozygote genotype (CT), three fragments with 429, 234, and 195 bp were produced. In addition, one fragment with 429 bp was produced in homozygote genotype (TT). Finally, one product from each genotype was sequenced with ABI sequence Genetic Analyzer (Applied Biosystems, Foster City, CA) to confirm the results, increase the accuracy of the utilized methods, and decrease the personal as well as the instrumental errors.

Statistical analyses

All the analyses were performed using the SPSS statistical software, version 15 (SPSS Inc, Chicago, IL, USA). The

results are expressed as mean ± SD. The gene counting method was used to estimate the allele frequencies. Moreover, group findings were compared using the χ^2 test and *t* test. The χ^2 test was used for comparison of number and sex and *t* test was applied for comparison of continues variables such as age and laboratory data. Also, the risk of the disease was assessed by calculating the odds ratios (ORs) and 95 % confidence intervals (CIs). $p < 0.05$ was considered as statistically significant. Furthermore, the Hardy–Weinberg equilibrium was carried out in Arlequin 3.11 software. Power calculation was performed using STATA/SE.10 program.

Results

The comparison of the clinical and biochemical characteristics of the control and diabetic subjects is presented in Table 1. Our results showed no statistically significant differences between the cases and the controls regarding the distribution of number, sex, and age ($p > 0.05$). The FPG, lipid profile, insulin level, HOMA-IR, and HbA1C were significantly different between case and control group ($p < 0.05$).

The frequency of CC genotype in diabetic and control groups was 90 (59.6 %) and 89 (57.4 %), respectively. In addition, the number of CT genotype was 51 (33.8 %) in

Table 1 Demographic characteristic of the subjects

	Case	Control	*p* value
Number	151	155	0.81
Male	66	79	0.28
Female	85	76	0.47
Age (years)	60.2 ± 6.6	60.2 ± 7.7	0.97
Age of diagnosis (years)	52.9 ± 8.7	–	–
Duration of disease (years)	7.2 ± 5.9	–	–
FPG (mg/dL)	142.3 ± 65.8	86.6 ± 7.7	$p < 0.05$
2hpp (mg/dL)	201.8 ± 67.3	–	–
Triglycerides (mg/dL)	136.75 ± 29.41	123 ± 25.31	$p < 0.05$
Cholesterol (mg/dL)	163.04 ± 35.48	100.45 + 27.49	$p < 0.05$
LDL cholesterol (mg/dL)	94.53 ± 27.49	87.2 ± 30.34	$p < 0.05$
HDL cholesterol (mg/dL)	41.33 ± 7.29	37.45 ± 10.12	0.97
Insulin (mmol/L)	9.49 ± 2.78	5.71 ± 3.77	$p < 0.05$
HOMA-IR	3.63 ± 2.02	1.6 ± 0.55	$p < 0.05$
BMI (kg m^{-2})	27.34 ± 4.86	26.44 ± 3.86	0.48
HbA_1C	6.38 ± 1.76	4.1 ± 1.12	$p < 0.05$

FPG fasting plasma glucose, *2hpp* 2-h postprandial blood glucose, HbA_{1c} hemoglobin A_{1c}

Table 2 Comparison of *SLC30A8* genotypes and allele frequencies between T2DM and control groups

	Case ($n = 151$)	Control ($n = 155$)	OR (95 % CI)	*p* value	Study power (%)
SLC30A8 genotype frequency					
CC (RR)	90 (59.6 %)	89 (57.4 %)	1.09 (0.7–1.77)	0.78	5
CT (RW)	51 (33.8 %)	49 (31.6 %)	1.1 (0.7–1.83)	0.77	4
TT (WW)	10 (6.6 %)	17 (11 %)	0.58 (0.24–1.39)	0.25	5
CC+CT (RR+RW)[a]	141 (93.4 %)	138 (89 %)	1.73 (0.76–3.9)	0.85	21
CT+TT (RW+WW)[b]	61 (40.4 %)	66 (42.6 %)	0.91 (0.58–1.44)	0.65	5
SLC30A8 allele frequency					
C (R)	231 (76.5 %)	227 (73.2 %)	1.19 (0.82–1.7)	0.35	17
T (W)	71 (23.5 %)	83 (26.8 %)			

OR odds ratio, *CI* confidence interval from conditional logistic regression, *n* number of sample

[a] Dominant model (CC+CT vs. TT)

[b] Recessive model (CT+TT vs. CC)

Table 3 Positive association between rs13266634 and T2DM in various populations

Population	Genotypes frequency			Allele frequency		OR (95 %CI)	*p* value	References
	CC (%)	CT (%)	TT (%)	C (%)	T (%)			
French	43.5	43.7	12.8	65	35	0.76 (0.59–0.97)[a]	0.03	Cauchi et al. [16]
	38.5	48	13.5	63	37			
Austrian	54.9	38.2	6.9	74	26	0.76 (0.61–0.94)[a]	0.01	Cauchi et al. [16]
	49	41.9	9.2	69.8	30.2			
French & Swiss (Non-obese subjects)	55	38	8	73	27	0.87 (0.76–0.99)[a]	0.04	Cauchi et al. [17]
	49	42	9	70	30			
Norwegian	N/A			N/A		1.20 (1.09–1.33)[b]	0.00039	Hertel et al. [18]
Russian	59.5	39.3	1.2	79.2	20.8	1.22 (1.01–1.49)[b]	0.045	Potapov et al. [19]
	53.3	40.9	5.8	73.7	26.3			
Chinese (shanghai)	N/A			57	43	1.20 (1.09–1.32)[b]	0.0002	Xu et al. [20]
				54	46			
Chinese (hunan)	30.25	47.63	22.12	54.06	45.94	N/A	0.043	Huang et al. [15]
	27.95	40.61	31.44	48.25	51.75			
Chinese (han)	39	46	15	62	38	1.19 (1.04–1.37)[b]	0.009	Han et al. [21]
	33	49	18	57	43			
Korean	35.7	50.5	13.8	60.9	39.1	1.19 (1–1.42)[b]	0.045	Lee et al. [22]
	31	49.5	19.5	55.7	44.3			
Korean	N/A			62.7	37.3	1.18 (1.02–1.38)[b]	0.029	Ng et al. [23]
				58.5	41.5			
Hong kong	N/A			57.2	42.8	1.17 (1.06–1.3)[b]	0.002	Ng et al. [23]
				53.2	46.8			
Japanese	38	44.5	17.5	61	39	1.18 (1.03–1.35)[b]	0.016	Horikoshi et al. [24]
	34	46	20	57	43			
Indian (indo-europen)	N/A			79	21	1.32 (1.13–1.53)[b]	0.0003	Chauhan et al. [25]
				75	25			
Tunisian	N/A			85	15	1.59 (1.14–2.22)[c]	0.0039	Kifagi et al. [26]
				80	20			

OR odds ratio, *CI* confidence interval, Subjects by genotype with type 2 diabetes (top row) and nondiabetic subjects (bottom row), N/A not available

[a] The OR of the T allele

[b] The OR of the C allele

[c] The OR of CC genotype

the case and 49 (31.6 %) in the control group. The number of TT genotype was also 10 (6.6 %) and 17 (11 %) in diabetic and non-diabetic subjects, respectively. In the dominant model, the number of CC and CT genotypes was 141 (93.4 %) in the case and 138 (89 %) in the control group. In the recessive model, on the other hand, the frequency of CT and TT genotypes in the case and the control group was 61 (40.4 %) and 66 (42.6 %), respectively.

The frequency of allele C was 231 (76.5 %) in the diabetic patients and 227 (73.2 %) in the controls. Besides, allele T frequency was 71 (23.5 %) and 83 (26.8 %) in the cases and controls, respectively. No significant association was observed between rs13266634 polymorphism of *SLC30A8* and susceptibility to T2DM (p value = 0.35) (Table 2).

There was no significant correlation of genotypes with blood lipid profiles, insulin level, and HOMA-IR thereby suggesting for an unlikely role of these genetic variants in insulin resistance syndrome. Complete concordance between the result of genotyping and the result of direct sequencing was documented. This SNP was within the Hardy–Weinberg equilibrium (p-value = 0.079). The association between rs13266634 and susceptibility to T2DM has been studied in other ethnic groups with both positive and negative associations, which are mentioned in Tables 3 and 4, respectively.

Table 4 Negative association between rs13266634 and T2DM in various populations

Population	Genotypes frequency			Allele frequency		OR (95 % CI)	*p* value	References
	CC (%)	CT (%)	TT (%)	C (%)	T (%)			
African- American	N/A			91.6	8.4	1.46 (0.43–4.89)[a]	0.86	Lewis et al. [27]
				91.4	8.6			
American (Arizona)	83.7	15.1	1.2	91	9	1.04 (0.84–1.2)[a]	0.71	Rong et al. [28]
	82.3	16.7	1	91	9			
Ashkenazi	58.1	36.1	5.8	76.1	23.9	0.97 (0.8–1.18)[b]	0.76	Cauchi et al. [16]
	56.5	37.2	6.3	75.1	24.9			
Morrocan	69.6	28.1	2.3	83.6	16.4	0.99 (0.77–1.27)[b]	0.95	Cauchi et al. [16]
	69.4	28	2.6	83.4	16.6			
Indian (Sikh community)	54.5	36.6	8.8	73	27	1.21 (0.72–2.04)[c]	0.46	Sanghera et al. [29]
	53.9	38.7	7.4	73	27			
Japanese	37.3	48.6	14.1	61.6	38.4	1.10 (0.9–1.36)[a]	0.35	Furukawa et al. [30]
	35.6	47.3	17.1	59.3	40.7			
Japanese	32.8	52.5	14.7	59.1	40.9	1.10 (0.91–1.33)[a]	0.31	Tabara et al. [31]
	33.2	47	19.8	56.7	43.3			
Iranian (Eastern Azerbaijan)	49.6	50.4	0	74.8	25.2	N/A	0.31	Mohaddes et al. [32]
	42.4	56.8	0.8	70.8	29.2			
Iranian (Fars)	59.6	33.8	6.6	76.5	23.5	1.19 (0.82–1.7)[a]	0.35	Current study
	57.4	31.6	11	73.2	26.8			

OR odds ratio, *CI* confidence interval, subjects by genotype with type 2 diabetes (top row) and nondiabetic subjects (bottom row), *N/A* not available

[a] The OR of the C allele

[b] The OR of the T allele

[c] The OR of CC genotype

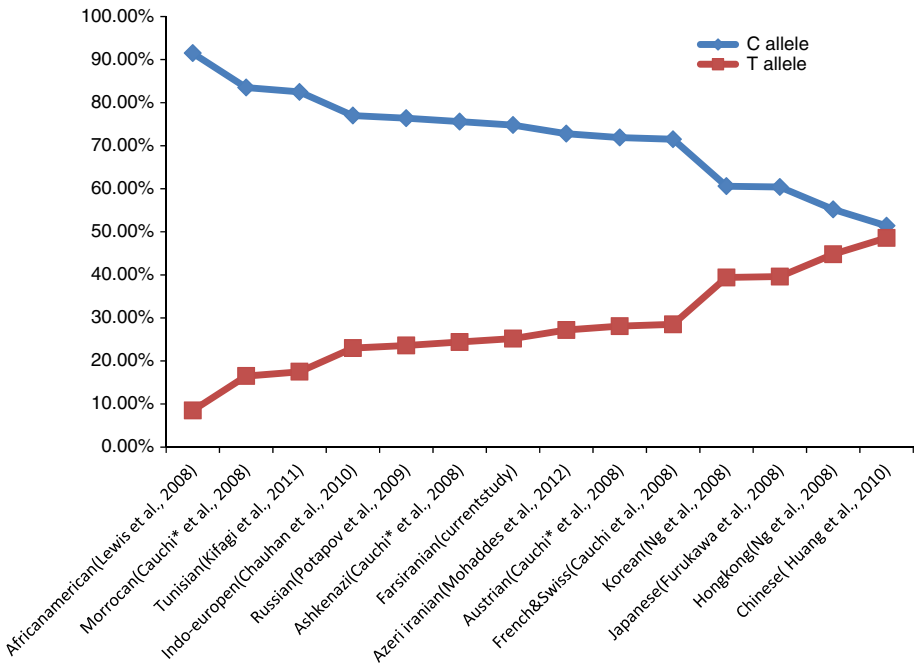

Fig. 1 Frequency of C and T alleles in different populations

Discussion

T2DM is a polygenic disease with unknown number of contributing genes. It is also not clear whether any single gene is shared among all the ethnic groups showing some degree of population specificity. SNP in *SLC30A8* (rs13266634) has been reported to be associated with T2DM in various studies [14, 33].

There are several hypotheses for the role of this polymorphism in T2DM. This DNA variant might be gain-of-function mutation and affects the expression of ZnT8 protein. This polymorphism site is identified at the C-terminal region of the protein structure and may affect the posttranslational modification mechanism in the C-terminus of ZnT-8 as R325W polymorphism disrupts the protein kinase A and protein kinase C recognition motif (R-X-S/T) in the ZnT-8 molecule [9]. On the other hand, Weijers [34] generated models of the wild-type ZnT-8 protein and its Arg325Trp variant and suggested that the rs13266634 polymorphism may be tolerated and results in sufficient zinc transfer to the correct sites in the pancreatic β cells. He also proposed that this polymorphism had a low predictive value for future development of type 2 diabetes. SNP rs13266634 in SLC30A8 have been associated with type 2 diabetes in many populations (Table 3), but in other studies no significant association was found (Table 4). Our study was consistent with the similar study from Eastern Azerbijan Population of Iran with similar genotype frequency.

Several reasons can be considered for these controversial findings:

(a) The small sample size in some of the studies.
(b) Different ethnic groups and population tratification.
(c) Cases and controls were not matched for body mass index (BMI), age, sex, and family history and possibly some young individuals in the control group might develop T2DM in the future.
(d) Difference in the diagnostic criteria for T2DM (World Health Organization or American Diabetes Association).
(e) Different sources of controls (population or hospital).

Among the whole inspected population, both diabetic cases and nondiabetic subjects, the highest frequency of C allele has been reported in African-American community with 91.5 % [27]. The Morrocan with 83.5 % [16] and the Tunisian with 82.5 % [26] have been reported as other populations with high rates of C allele frequency. Therefore these populations are keeping the lowest rates of the T allele frequency. On the other hand, the lowest frequencies of C allele have been found in the Hunan province people of China with 51.4 % [15]; Hong kong and Japanese societies with 55.2 and 57.9 % respectively [23, 31].

The C allele frequency of rs13266634 in our population was higher than that of the Eastern Asian populations. Besides, this allele's frequency in Fars province was very similar to that of the European and neighborhood countries than Asian, Indian. However, the frequency of this allele in our population was lower than the African populations.

In general, the frequency of C allele is the highest in the African populations. Nevertheless, its frequency becomes lower in Europe and the Middle East and the lowest frequency is related to East Asia. A reverse trend can be observed regarding T allele. A summary of the results is presented in Fig. 1.

Conclusion

In summary, the SNP rs13266634 in SLC30A8 was not significantly associated with type 2 diabetes in our study. Considering these results, it is recommended to investigate other SNPs in *SLC30A8* and other T2DM susceptibility genes in South Iranian population.

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