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Transcription Factor 7-Like 2 (*TCF7L2*) Polymorphism and Context-Specific Risk of Type 2 Diabetes in Tunisian Adults in a Comparison to African American and Caucasian Adults

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Keywords

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- Polymorphism
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Abstract

Background: The purpose of this study was to investigate the effects of TCF7L2 on T2D in a Tunisian population, in a comparison with African Americans and Caucasians, studied before by Yan *et al*.

Methods: We investigated the association between the TCF7L2 rs7903146 polymorphism and T2D in 464 Tunisian participants without diabetes who were inducted into the Atherosclerosis Risk and followed for 5 years.

Results: Compared with homozygous CC individuals, heterozygous CT and homozygous TT individuals had higher cumulative incidence of type 2 diabetes over 5 years of follow-up: 8.68% (95% CI 7.46–9.59) vs. 10.60% (9.29–11.38) and 12.49 (10.48–15.38) in Tunisians, respectively, and 11.3% (95% CI 10.2–12.4) vs. 21.1% (20.8 –21.4) and 27.9% (19.3–36.5) in African Americans, respectively, and 9.7% (8.8–10.6) vs. 11.3% (10.2–12.4) and 13.6% (11.1–16.1), respectively, in Caucasians. Individuals with the risk allele had the highest hazards of diabetes if they were obese and had low HDL cholesterol, followed by individuals with any one and none of the traits.

Conclusions: Our results describe the first significant evidence of association between the TCF7L2 rs7903146 polymorphism and type 2 diabetes risk in a Tunisian population, in a comparison with a comparative study between African Americans and Caucasians. We concluded that the diabetes risk carried by the rs7903146 risk allele is greatly increased in the context of some metabolic risk factors for type 2 diabetes. We also found that in that study, our findings on the Tunisian population are very close to the findings on the Caucasians.

ABBREVIATIONS

CAD: Coronary Artery Disease; DNA: Deoxyribonucleic Acid; HbA1c: Glycosylated Hemoglobin A1c; HDL-C: HDL Cholesterol; LDL-C: LDL Cholesterol; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; PCR: Polymerase Chain Reaction; SNP: Single Nucleotide Polymorphism; TCF7L2: Transcription Factor 7-like 2; T2D: Type 2 Diabetes.

BACKGROUND

Diabetes mellitus, the most frequent metabolic disorder, is characterized by chronic hyperglycemia due to defect in insulin secretion by beta cells of Langerhans islets or resistance against insulin action [1–3]. In 2013 it was reported that in Middle East region about 35 million people suffered from diabetes. The prevalence of diabetes has been estimated as 382 million people throughout the world while nearly 176 million of them seem to be still undiagnosed. It is predicted that this prevalence reaches to 592 million by 2035 [4]. 10 years ago, transcription factor 7-like 2 (TCF7L2), located on chromosome 10q25.3, has been identified as a major T2D susceptibility gene [5]. Single nucleotide polymorphisms (SNPs) of TCF7L2 have been frequently

associated with T2D in populations of different ethnic descent, which makes TCF7L2 one of the most important locus known today to put a risk for T2D [6–8]. Among the most studied SNPs, variant rs7903146 was found to be most significantly associated with T2D risk [7,8]. The T-allele of this SNP has been described as either the causal risk variant or the closest correlate to an unidentified functional variant [9], possibly impairing glucagon-like peptide-1–induced insulin secretion [10], but the exact mechanism still unclear. In addition, potential links between genetic variants of the TCF7L2 locus and CAD are uncertain. The purpose of our study was to investigate whether the rs7903146 SNP of the TCF7L2 gene is associated with type 2 diabetes in a cohort of Tunisian middle-aged adults compared to African American and Caucasian participants of the Atherosclerosis Risk in Communities (ARIC) study [11]. Our second purpose was to evaluate whether the risk of type 2 diabetes was associated with the rs7903146 SNP in the context of metabolic impairments.

METHODS

Patients

A total of 464 Tunisian participants aged 45–64 years, without diabetes who were inducted into the Atherosclerosis risk in Fattouma Bourguiba Hospital in 2011–2015 and followed for 5 years, were diagnosed by angiography. Subjects were defined with cardiovascular disease when presenting a stenosis >50% in at least one major coronary artery. Subjects were defined without coronary artery disease when presenting a stenosis <50 in at least one major coronary artery. Hypertension was diagnosed as a blood pressure of higher than 140/90 mmHg, which was measured according to guidelines [12] and/or the current use of anti-hypertensive drugs. Diabetic subjects were defined by a fasting plasma glucose >7.0 mmol/L, or by the use of anti-diabetic drugs [13]. Obese subjects were defined by a BMI >30.0 Kg/m2. Elevated waist circumference was defined as waist circumference Š102 cm in men or Š88 cm in women [14]. Data on age, sex, smoking, and smoking history were collected from the participants' medical records or by direct interviews. Plasma total cholesterol levels, HDL cholesterol, and triglyceride levels were measured by enzymatic methods, and LDL cholesterol was calculated [15]. Low HDL was defined as <40 mg/dl in men and <50 mg/dl in women. High LDL was defined as >160 mg/dl, and high triglyceride levels were defined as >200 mg/dl [16]. Insulin was measured by radioimmunoassay (125 Insulin Kit; Cambridge Medical Diagnostics, Billerica, MA). Physical activity was quantified using a slightly modified version of the Baecke physical activity questionnaire [17] that classified work, sport, and leisure activities into categories ranging from one (low) to five (high). Impaired fasting glucose was defined by a fasting glucose level between 100 and 125 mg/dl [18]. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: fasting serum insulin (μU/ml) × fasting glucose (mmol/l)/22.5 [19]. Predicted diabetes risk was defined as the probability of developing diabetes over the 5-year follow-up period, which is predicted by a model that includes age at baseline, race, and parental history of diabetes, fasting glucose, systolic blood pressure, waist circumference, height, HDL cholesterol, and triglycerides [20]. This study was approved by our hospital ethical committee chaired by Pr Fekri Abroug, the reported investigations have been carried out in accordance with the principles of the Declaration of Helsinki as revised in 2008. All participants were of Tunisian origin and gave their informed consent for this study.

SNP genotyping

TCF7L2 polymorphism rs7903146 was genotyped using Taqman assays (Applied Biosystems, Foster City, CA). Laboratory-designed probes were obtained from Applied Biosystems and primers from Integrated DNA Technologies (Coralville, IA). All PCR reactions took place in optical 384-well reaction plates (Applied Biosystems).

Statistical analysis

All analyses were stratified by race to crudely account for population stratification as previously described by Yan *et al* [11].

RESULTS

Selected baseline characteristics of are presented by race and genotype status in Table 1. A total of 393 (15.30%), 485 (17.8%) and 923 (9.9%) incident type 2 diabetes cases were identified among Tunisian, African American and Caucasian ARIC participants, respectively (Table 2). The rs7903146 T-allele was observed with similar frequency in Tunisian, African American and Caucasian individuals but was more common among incident type 2 diabetes cases than non-cases in the three races (Table 2). The risk of type 2 diabetes was highest among TT individuals, followed by CT individuals, and lowest among CC individuals in all studied races (Table 2). The risk of type 2 diabetes was higher in African Americans than in Tunisians and Caucasians with the same genotype.

We identified obesity and low HDL as important effect-measure modifiers, although 95% CIs of some individual ICRs were wide (Table 3). Individuals with one or two T-alleles had the highest HRs of developing type 2 diabetes if they were obese and had low HDL, followed by individuals with any one of these two risk factors and lowest among those with none of the traits (Table 4). Homozygous individuals (TT) with two metabolic risk factors had the highest HR of type 2 diabetes 10.01 [95% CI 9.26–13.03] in Tunisians, (6.04 [95% CI 3.70 –9.87] in African Americans and 9.35 [6.72–13.00] in Caucasians) compared with CC individuals with none of these three races. A similar trend was observed for risk differences and risks of type 2 diabetes.

When each effect measure modifier was studied separately, a larger ICR for obesity (P=0.01; P= 0.02) in Tunisians and Caucasians respectively, and a larger ICR for low HDL cholesterol (P = 0.004) in African Americans were observed (Table 3), but testing by bootstrapping [21] did not support significant racial differences.

DISCUSSION

In the current study, we investigate whether the rs7903146 SNP of the TCF7L2 gene is associated with type 2 diabetes in a cohort of Tunisian middle-aged adults compared to African American and Caucasian participants of the Atherosclerosis Risk in Communities (ARIC) study [20]. We also evaluated whether

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Table 1: Selected characteristics of the Tunisian population compared to the ARIC study participants at baseline, presented by race and genotype status:

	African American: ref. Yan *et al*, 2009 [11]				Caucasian : ref. Yan *et al*, 2009 [11]				Tunisian population			
	CC	C	TT	p	CC	CT	TT	p	CC	CT	TT	p
n	1,381	1,133	213	-	4,725	3,783	794	-	236	189	39	-
Age (years)	53 ± 5.83	53 ± 5.60	54 ± 5.83	0.12	54 ± 5.66	54 ± 5.69	54 ± 5.75	0.25	52± 5.55	53± 5.05	53± 5.46	0.15
Sex (male)	500 (36.21)	447 (39.45)	81 (38.03)	0.25	2,188 (46.31)	1,746 (46.15)	379 (47.73)	0.71	119 (50.53)	96 (51.02)	21 (53.62)	0.56
Family diabetes history	318 (23.03)	295 (26.04)	57 (26.76)	0.16	1,006 (21.29)	846 (22.36)	178 (22.42)	0.45	44 (18.78)	38 (20.34)	8 (21.24)	0.38
Predicted diabetes risk*	0.23 ± 0.20	0.20 ± 0.19	0.25 ± 0.22	0.01	0.15 ± 0.15	0.16 ± 0.16	0.17 ± 0.15	0.27	0.15± 0.14	0.15± 0.13	0.16± 0.15	0.25
Ever smoked	715 (51.77)	610 (53.89)	117 (54.93)	0.47	2,793 (59.14)	2,241 (59.27)	475 (59.82)	0.94	132 (55.96)	107 (56.84)	21 (55.38)	0.75
Leisure-time physical activity	2.08 ± 0.58	2.12 ± 0.59	2.05 ± 0.56	0.22	2.48 ± 0.53	2.48 ± 0.53	2.46 ± 0.53	0.62	2.36± 0.55	2.34± 0.53	2.37± 0.55	0.59
Obese	522 (37.80)	393 (34.75)	72 (33.80)	0.22	998 (21.12)	724 (19.16)	141 (17.76)	0.02	60 (25.67)	38 (20.35)	7 (17.59)	0.01
BMI (kg/m2)	29.34 ± 6.11	28.86 ± 5.81	28.55 ± 5.28	0.05	26.73 ± 4.58	26.52 ± 4.60	26.54 ± 4.58	0.09	28.67± 4.64	28.83± 4.82	28.20± 5.01	0.06
Waist circumference (cm)	97.97 ± 15.09	96.74 ± 14.38	96.25 ± 13.28	0.06	95.37 ± 12.93	94.74 ± 12.66	94.96 ± 12.67	0.08	96.94± 13.56	95.38± 13.57	95.35± 13.27	0.08
Hypertension	700 (51.02)	572 (50.66)	103 (48.58)	0.80	1,154 (24.57)	923 (24.51)	174 (22.03)	0.29	75 (31.67)	57 (30.56)	12 (30.10)	0.23
SBP (mmHg)	131.07 ± 21.93	132.19 ± 22.43	129.08 ± 22.07	0.42	119.83 ± 16.48	119.97 ± 17.18	121.17 ± 16.69	0.36	120.56± 15.98	119.34± 15.46	120.45± 15.36	0.41
DBP (mmHg)	77.43 ± 10.34	77.44 ± 11.33	76.14 ± 11.05	0.53	70.97 ± 9.17	70.91 ± 9.10	71.37 ± 9.30	0.67	73.57± 8.49	73.78± 8.56	73.73± 8.49	0.56
IFG	594 (44.30)	461 (42.25)	87 (41.83)	0.55	1,868 (40.20)	1,560 (41.97)	371 (47.63)	<0.01	98 (41.67)	82 (43.71)	19 (50.45)	<0.01
Glucose (mmol/l)	5.47 ± 0.56	5.46 ± 0.54	5.47 ± 0.57	0.95	5.45 ± 0.49	5.48 ± 0.50	5.52 ± 0.52	<0.01	5.45± 0.57	5.53± 0.51	5.56± 0.56	<0.01
Insulin (µU/ml)	13.82 ± 10.67	12.79 ± 8.78	12.62 ± 8.68	0.02	10.24 ± 7.60	9.83 ± 7.27	9.88 ± 8.10	0.04	12.67± 8.45	11.89± 8.48	11.23± 8.34	0.03
HOMA-IR†	3.45 ± 2.90	3.18 ± 2.37	3.15 ± 2.33	0.03	2.54 ± 2.05	2.45 ± 1.97	2.47 ± 2.18	0.12	2.65± 1.88	2.59± 2.01	2.60± 2.09	0.24
Triglycerides (mg/dl)	104.06 ± 62.50	105.63 ± 78.38	104.88 ± 58.04	0.86	130.33 ± 76.91	128.73 ± 76.80	130.75 ± 83.63	0.59	129.97± 76.34	130.72± 75.39	130.63± 78.20	0.73
Low HDL	400 (29.59)	321 (28.92)	59 (28.37)	0.90	1,799 (38.13)	1,436 (38)	306 (38.59)	0.95	80 (35.19)	69 (36.56)	15 (38.21)	0.89
HDL (mg/dl)	56.51 ± 17.77	56.45 ± 17.96	55.48 ± 17.23	0.74	51.41 ± 16.78	51.75 ± 16.95	51.10 ± 16.50	0.49	52.89± 16.56	51.97± 16.47	52.68± 16.56	0.56
LDL (mg/dl)	136.84 ± 42.65	135.78 ± 41.54	136.33 ± 47.07	0.83	137.60 ± 37.46	136.7 ± 37.54	137.49 ± 37.70	0.54	136.67± 39.45	135.67± 39.78	135.34± 38.35	0.56
One metabolic risk factor‡	526 (38.56)	436 (39.03)	83 (39.71)	0.93	1,719 (36.43)	1,300 (34.42)	295 (37.20)	0.10	84 (35.56)	69 (36.89)	14 (36.93)	0.24

Data are means ± SE or *n* (%) unless otherwise indicated. *Probability of developing diabetes over the 9-year follow-up period was predicted by a model including age at baseline, race, parental history of diabetes, fasting glucose, systolic blood pressure, waist circumference, height, HDL cholesterol, and triglycerides [31]. †Calculated as fasting serum insulin (µU/ml) × fasting plasma glucose (mmol/l)/22.5 [20]. ‡Metabolic risk factors refer to obesity or low HDL cholesterol. DBP: Diastolic blood pressure; IFG: Impaired fasting glucose; SBP: Systolic blood pressure.

Table 2: Genotypic frequency of *TCF7L2* rs7903146 presented by race and incident type 2 diabetes status, cumulative incidence of type 2 diabetes by race and genotype over 9 years of follow-up, and estimated HRs of rs7903146 on type 2 diabetes by race: the ARIC study*:

Genotype	African American: ref. Yan *et al*, 2009 [11]				Caucasian: ref. Yan *et al*, 2009 [11]				Tunisian popoulation			
	Controls/ cases	Cumulative incidence (%) (95% CI)	HR (95% CI)†	*P*‡	Controls/ cases	Cumulative incidence (%) (95% CI)	HR (95% CI)†	*P*‡	Controls/ cases	Cumulative incidence (%) (95% CI)	HR (95% CI)†	*P*‡
N	2,242/485	20.6 (18.7–22.5)			8379/923	10.7 (10.0–11.4)			393/71	9.98(9.37–10.35)		<0.01
CC	1,156 (52)/225 (46)	11.3 (10.2–12.4)	1.00		4,295 (51)/430 (47)	9.7 (8.8–10.6)	1.00		192 (49)/32 (42)	8.68(7.46–9.59)	1.00	
CT	921 (41)/212 (44)	21.1 (20.8–21.4)	1.17 (1.02–1.34)	0.03	693 (8)/101(11)	11.3 (10.2–12.4)	1.18 (1.07–1.30)	<0.01	39 (10)/11 (13)	10.60(9.29–11.38)	1.18(1.11–1.28)	
TT	165 (7)/48 (10)	27.9 (19.3–36.5)	1.36 (1.03–1.79)		3,391 (40)/392 (42)	13.6 (11.1–16.1)	1.38 (1.14–1.68)		162 (36)/28 (36)	12.49(10.48–15.38)	1.39(1.15–1.71)	
T-allele (%)	28/32				29/32				25/30			

*The Genotypic distributions were in agreement with Hardy-Weinberg equilibrium in African Americans, Caucasians and Tunisians. †Adjusted for age at baseline, study center, and sex. ‡*P* value for HR from additive models.

Table 3: Association of *TCF7L2* rs7903146 with type 2 diabetes modified by obesity and low HDL cholesterol over 9 years of follow-up in ARIC*

Characteristics	HR (95% CI) †				
	CC genotype	CT genotype	TT genotype	ICR (95% CI)	*P*‡
African-American: ref. Yan *et al*, 2009 [11] Obesity					
No	1	1.32 (1.08–1.61)	1.74 (1.16–2.61)	—0.05 (—0.66 to 0.57)	0.88
Yes	2.91 (2.25–3.76)	3.18 (2.49–4.07)	3.48 (2.44–4.95)		
Low HDL					
No	1	1.05 (0.87–1.26)	1.10 (0.77–1.58)	0.57 (0.18–0.96)	0.004
Yes	1.45 (1.12–1.88)	2.07 (1.66–2.58)	2.96 (2.08–4.20)		
Caucasian: ref. Yan *et al,* 2009 [11] Obesity					
No	1	1.21 (1.06–1.37)	1.45 (1.12–1.88)	0.69 (0.10–1.27)	0.02
Yes	3.55 (2.96–4.25)	4.44 (3.76–5.25)	5.56 (4.30–7.19)		
Low HDL					
No	1	1.20 (1.03–1.40)	1.44 (1.06–1.96)	0.27 (—0.11 to 0.66)	0.16
Yes	2.67 (2.21–3.21)	3.14 (2.64–3.74)	3.69 (2.91–4.69)		
Tunisian Population Obesity					
No	1	1.18 (1.01–1.37)	1.41 (1.09–1.86)	0.71 (0.12–1.32)	0.01
Yes	3.26 (2.57–4.28)	4.53 (3.27–6.01)	3.74 (3.01–4.59)		
Low HDL					
No	1	1.19 (1.12–1.39)	1.39 (1.14–1.93)	0.28 (—0.13 to 0.71)	0.09
Yes	2.54 (2.21–3.48)	3.27 (2.17–3.89)	3.79 (2.98–4.78)		

†Adjusted for age at baseline, study center, and sex. ‡*P* value for ICR.

Table 4: Association of *TCF7L2* rs7903146 with type 2 diabetes* modifted by the number of metabolic risk factors (obesity and low HDL cholesterol):

No. of abnormal metabolic traits†	African American: ref. Yan *et al*, 2009 [11]			Caucasian: ref. Yan *et al*, 2009 [11]			Tunisian population		
	CC genotype	CT genotype	TT genotype	CC genotype	CT genotype	TT genotype	CC genotype	CT genotype	TT genotype
None	1	1.14 (0.88–1.48)	1.30 (0.77–2.20)	1	1.19 (0.98–1.44)	1.42 (0.97–2.09)	1	1.20 (0.97–1.45)	1.41 (0.89–2.11)
One	2.31 (1.71–3.12)	2.70 (2.04–3.58)	3.16 (2.15–4.65)	2.46 (1.96–3.08)	3.09 (2.50–3.82)	3.88 (2.93–5.16)	3.13 (2.01–3.12)	4.10 (3.04–5.23)	4.78 (3.87–5.84)
Two	3.49 (2.46–4.95)	4.59 (3.33–6.33)	6.04 (3.70–9.87)	6.77 (5.33–8.62)	7.96 (6.34–9.98)	9.35 (6.72–13.00)	7.16 (6.35–8.45)	8.35 (7.28–9.47)	10.01 (9.26–13.03)

Data are HR (95% CI). *Adjusted for age at baseline, study center, and sex. †Abnormal metabolic traits included obesity, low HDL cholesterol.

the risk of type 2 diabetes was associated with the rs7903146 SNP in the context of metabolic impairments. We found that the rs7903146 polymorphism was significantly associated with type 2 diabetes risk in our Tunisian Population, as is the case for African Americans and Caucasians according to Yan *et al* [11]. Our findings are in agreement with a recent study of Muendlein *et al*, they investigate three SNPs (rs7903146, rs12255372, and rs11196205) of TCF7L2 and conclude that the three variants are significantly associated with angiographically diagnosed CAD and that this association is significantly modulated by the presence of T2DM [21]. The rs7903146 polymorphism was studied by other teams on African-ancestry, they found a significant association of this variant with type 2 diabetes [22-24], but none of these two studies were population based.

The larger part of actual literature proposes that TCF7L2 is associated with impaired insulin secretion but not with increased insulin resistance [25,26]. We found, for our Tunisian population, a slightly lower fasting insulin and HOMA-IR concentration among individuals with the T-(risk) allele, suggestive of impaired insulin secretion. It's the same for the African Americans and the Caucasians [11]. Interestingly, precedent studies have found that frequencies of the T allele are lowest in North-America and Europe (with a gradient of increasing frequency from North to South), moderate in Asia, and highest in Africa [24,27,28].

Our findings illustrated in Table (2) tell that the risk of type 2 diabetes was greatly increased among rs7903146 T-allele carriers with obesity and low HDL cholesterol in comparison with those CC individuals with HDL in the normal range who were lean. There is powerful proof that abnormal metabolic traits including obesity and dyslipidemia aggregate in T2D and their relatives (29,30).

CONCLUSIONS

Our results describe the first significant evidence of association between the TCF7L2 rs7903146 polymorphism and type 2 diabetes risks in a Tunisian population, in a comparison with a comparative study between African Americans and Caucasians. We concluded that the diabetes risk carried by the rs7903146 risk allele is greatly increased in the context of some metabolic risk factors for type 2 diabetes. We also found that in that study, our findings on the Tunisian population are very close to the findings on the Caucasians. Furthermore, our study findings need to be reproduced in other large, population-based studies.

ETHICS

All patients were Tunisian and gave their informed consent to participate in the study and their consent to publish. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinky and was approved by the Fattouma Bourguiba Monastir ethical committee chaired by Pr Fekri Abroug.

AUTHOR'S CONTRIBUTIONS

AK and MD carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. AK carried out the immunoassays. TT and TI participated in the sequence alignment. AK participated in the design of the study and performed the statistical analysis. MMA, NS and KA conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2004; 27: 5-10.
2. World Health Organization (WHO). Diabetes Mellitus, Report of a WHO Expert Committee, WHO Technical Report Series no. 310. World Health Organization, Geneva, Switzerland, 1965.
3. World Health Organization (WHO). WHO expert committee on diabetes mellitus," WHO Technical Report Series No. 646. World Health Organization (WHO), Geneva, Switzerland, 1980.
4. IDF Diabetes Atlas. New Estimates for 2012 of Diabetes Prevalence, Mortality, and Healthcare Expenditures. 5th edition. 2012.
5. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006; 38: 320-323.
6. Cauchi S, E Achhab Y, Choquet H, Dina C, Krempler F, Weitgasser R, Nejjari C. TCF7L2 is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis. J Mol Med (Berl). 2007; 85: 777-782.
7. Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PI, Shuldiner AR, et al. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med. 2006; 355: 241-250.

8. Saxena R, Gianniny L, Burtt NP, Lyssenko V, Giuducci C, Sjögren M, et al. Common single nucleotide polymorphisms in TCF7L2 are reproducibly associated with type 2 diabetes and reduce the insulin response to glucose in nondiabetic individuals. Diabetes. 2006; 55: 2890-2895.

9. Helgason A, Palsson S, Thorleifsson G, Grant SFA, Emilsson V, Gunnarsdottir S, et al. Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution. Nat Genet. 2007; 39: 218-225.

10. Cauchi S, Froguel P. TCF7L2 genetic defect and type 2 diabetes. Curr Diab Rep. 2008; 8: 149-155.

11. Yan Y, North KE, Ballantyne CM, Brancati FL, Chambless LE, Franceschini N, et al. Transcription factor 7-like 2 (TCF7L2) polymorphism and context-specific risk of type 2 diabetes in African American and Caucasian adults: the Atherosclerosis Risk in Communities study. Diabetes. 2009; 58: 285-289.

12. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2007; 25: 1105-1187.

13. Wang JG, Staessen JA, Franklin SS, Fagard R, Gueyffier F. Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. Hypertension. 2005; 45: 907-913.

14. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: executive summary. Cardiol Rev. 2005; 13: 322–327.

15. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18: 499-502.

16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001; 285: 2486-2497.

17. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr. 1982; 36: 936-942.

18. American Diabetes Association: diagnosis and classification of diabetes mellitus (Position Statement). Diabetes Care. 2005; 28: 37-42.

19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28: 412-419.

20. Schmidt MI, Duncan BB, Bang H, Pankow JS, Ballantyne CM, Golden SH, et al. Identifying individuals at high risk for diabetes: The Atherosclerosis Risk in Communities study. Diabetes Care. 2005; 28: 2013-2018.

21. Carpenter J, Bithell J: Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. Stat Med. 2000; 19: 1141-1164.

22. Muendlein A, Saely CH, Geller-Rhomberg S, Sonderegger G, Rein P, Winder T, et al. Single nucleotide polymorphisms of TCF7L2 are linked to diabetic coronary atherosclerosis. PLoS One. 2011; 6: 17978.

23. Cauchi S, E Achhab Y, Choquet H, Dina C, Krempler F, Weitgasser R, et al. TCF7L2 is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis. J Mol Med (Berl). 2007; 85: 777-782.

24. Helgason A, Palsson S, Thorleifsson G, Grant SFA, Emilsson V, Gunnarsdottir S, et al. Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution. Nat Genet. 2007; 39: 218 –225.

25. Lyssenko V, Lupi R, Marchetti P, Del Guerra S, Orho-Melander M, Almgren P, et al. Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. J Clin Invest. 2007; 117: 2155-2163.

26. Loos RJ, Franks PW, Francis RW, Barroso I, Gribble FM, Savage DB, et al. TCF7L2 polymorphisms modulate proinsulin levels and beta-cell function in a British Europid population. Diabetes. 2007; 56: 1943-1947.

27. Saxena R, Elbers CC, Guo Y, Peter I, Gaunt TR, Mega JL, et al. Large-scale gene-centric meta-analysis across 39 studies identifies type 2 diabetes loci. Am J Hum Genet. 2012; 90: 410-425.

28. Guinan KJ. Worldwide distribution of type II diabetes-associated TCF7L2 SNPs: evidence for stratification in Europe. Biochem Genet. 2012; 50: 159-179.

29. Li JK, Ng MC, So WY, Chiu CK, Ozaki R, Tong PC, et al. Phenotypic and genetic clustering of diabetes and metabolic syndrome in Chinese families with type 2 diabetes mellitus. Diabete Metab Res Rev. 2006; 22: 46-52.

30. Shaw JT, Purdie DM, Neil HA, Levy JC, Turner RC. The relative risks of hyperglycaemia, obesity and dyslipidaemia in the relatives of patients with type II diabetes mellitus. Diabetologia. 1999; 42: 24-27.

31. Pencina MJ, Larson MG, D'Agostino RB. Choice of time scale and its effect on significance of predictors in longitudinal studies. Stat Med. 2007; 26: 1343-1359.

32. https://books.google.co.in/books?id=Uv-ri4rpswUC&pg=PA61&lpg=PA61&dq=Diabetes+Mellitus,+Report+of+a+WHO+Expert+Committee,+WHO+Technical+Report+Series+no.+310,World+Health+Organization,+Geneva,+Switzerland,+1965.&source=bl&ots=KkUYmNkrPM&sig=SMTsnNbw7lRPO79wo_GuN8KjshM&hl=en&sa=X&ved=0ahUKEwiH2ZSS56bNAhUhH6YKHVSuC4MQ6AEIPDAE#v=onepage&q=Diabetes%20Mellitus%2C%20Report%20of%20a%20WHO%20Expert%20Committee%2C%20WHO%20Technical%20Report%20Series%20no.%20310%2CWorld%20Health%20Organization%2C%20Geneva%2C%20Switzerland%2C%201965.&f=false

33. http://apps.who.int/iris/bitstream/10665/41399/1/WHO_TRS_646.pdf http://www.indiaenvironmentportal.org.in/files/file/diabetes%20atlas%202012.pdf

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