The rs12255372(G/T) and rs7903146(C/T) polymorphisms of the *TCF7L2* gene are associated with type 2 diabetes mellitus in Asian Indians

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Abstract

One thousand thirty-eight normal glucose-tolerant and 1031 type 2 diabetic subjects selected from the Chennai Urban Rural Epidemiology Study were genotyped using polymerase chain reaction-restriction fragment length polymorphism assay to investigate the association of rs12255372(G/T) and rs7903146(C/T) polymorphisms of the transcription factor 7–like 2 (*TCF7L2*) gene with type 2 diabetes mellitus in Asian Indians. The frequency of the "T" allele of both rs12255372(G/T) and rs7903146(C/T) polymorphisms was significantly higher in diabetic subjects (23% and 33%) compared to that in normal glucose-tolerant subjects (19% and 28%; $P = .001$ and $P = .0001$, respectively). Logistic regression analysis of the rs12255372(G/T) polymorphism showed that the odds ratio (adjusted for age, sex, and body mass index) was 1.56 (95% confidence interval [CI], 1.03-2.37; $P = .034$) for the TT genotype and 1.29 (95% CI, 1.06-1.58; $P = .011$) for the TG genotype when compared with the GG genotype. Adjusted odds ratios for the TT and TC genotypes of the rs7903146(C/T) polymorphism were found to be 1.50 (95% CI, 1.08-2.08; $P = .013$) and 1.44 (95% CI, 1.18-1.76; $P = .0003$), respectively, compared with the CC genotype. Normal glucose-tolerant subjects with the TT genotype of rs12255372(G/T) had significantly higher 2-hour plasma glucose levels (mean ± SD, 6.1 ± 1.4 mmol/L) than those with the GG genotype (5.6 ± 1.0 mmol/L, $P = .011$). Normal glucose-tolerant subjects with the TT genotype of rs7903146(C/T) polymorphism had significantly higher 2-hour plasma glucose levels (mean ± SD, 6.0 ± 1.3 mmol/L) than those with the CC genotype (5.6 ± 1.0 mmol/L, $P = .004$). In conclusion, the T allele of the rs12255372(G/T) and rs7903146(C/T) polymorphisms of *TCF7L2* gene confer susceptibility to type 2 diabetes mellitus in Asian Indians.
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1. Introduction

Although type 2 diabetes mellitus has a strong genetic basis, until recently, most candidate genes for type 2 diabetes mellitus have shown only modest effects and the associations have been inconsistent [1,2]. Reproducible associations have been documented for the Pro12Ala polymorphism in the peroxisome proliferator–activated receptor (*PPARG*) gene and the E23K polymorphism in the *KCNJ11* gene [3,4]. Recently, Grant et al [5] reported that the transcription factor 7–like 2 (*TCF7L2*) gene was strongly associated with type 2 diabetes mellitus in Icelandic subjects. *TCF7L2* encodes a transcription factor that plays a role in the Wnt signaling pathway, a key cell developmental and growth regulatory mechanism. Florez et al [6] reported that polymorphisms rs12255372 and rs7903146 in the *TCF7L2* gene were associated with an increased risk of developing type 2 diabetes mellitus. Subsequent studies confirmed association of these polymorphisms with type 2 diabetes mellitus in British [7], US [8], Finnish [9], Amish [10], Scandinavian, Polish [11], French [12], Dutch Breda [13], European whites, migrant Asian Indian, Afro-Caribbean [14], northern Swedish [15], and German [16] populations. The rs7903146 polymorphism alone was found to be associated with type 2 diabetes mellitus in Japanese population [17]. India has the largest number of people with diabetes mellitus in the world [18]. Although the association of variants of the *TCF7L2* gene

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and type 2 diabetes mellitus has been investigated in several studies among white populations, there is only one study from the western part of India [19]. Hence, we examined the association of the 2 most strongly associated single nucleotide polymorphisms (SNPs) of the *TCF7L2* gene in almost all populations reported so far, the rs12255372 and rs7903146 polymorphisms, with type 2 diabetes mellitus in an Asian Indian population in southern India.

2. Methods

2.1. Study subjects

A total of 2069 subjects, 1031 type 2 diabetic subjects and 1038 normal glucose tolerant (NGT) subjects, were selected from phase 2 and phase 3 of the Chennai Urban Rural Epidemiology Study (CURES), respectively. The methodology of the study has been published elsewhere [20]. Briefly, 26 001 adult subjects (>20 years of age) were recruited in phase 1 of the CURES using a systematic random sampling method covering the whole Chennai city. This included 1529 "self-reported" diabetic subjects. In phase 2 of the CURES, all self-reported diabetic subjects were invited to our center for detailed studies, of whom 1382 responded (response rate, 90.4%). From the latter group, 1031 individuals with diabetes, in whom the diagnosis was made by a physician, who were on drug treatment for diabetes, who had fasting plasma glucose of 7 mmol/L or higher (126 mg/dL), and in whom genotyping could be performed were included in this study. The control group of NGT subjects were chosen from phase 3 of the CURES where every tenth subject from phase 1, excluding those with self-reported diabetes, underwent an oral glucose tolerance test to rule out diabetes. From the latter group, 1038 randomly selected subjects with NGT defined as fasting plasma glucose of less than 5.6 mmol/L (100 mg/dL) and 2-hour plasma glucose value of 7.8 mmol/L or less (140 mg/dL) [21] were included in this study.

Anthropometric measurements including weight, height, and waist were obtained using standardized techniques. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Biochemical analyses were done on a Hitachi-912 Auto-analyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany). Fasting plasma glucose (glucose oxidase−peroxidase [GOD-POD] method), serum cholesterol (cholesterol oxidase−phenol4-amino antipyrene peroxidase [CHOD-PAP] method), serum triglycerides (glycerol phosphatase oxidase−phenol4-amino antipyrene peroxidase [GPO-PAP] method), and high-density lipoprotein cholesterol (direct method–polyethylene glycol-pretreated enzymes) were measured. Low-density lipoprotein cholesterol was calculated using the Friedewald formula [22]. Glycated hemoglobin was estimated by high-performance liquid chromatography using the Variant machine (Bio-Rad, Hercules, CA).

2.2. Genotyping of rs12255372(G/T) and rs7903146(C/T) polymorphisms

DNA was isolated from whole blood using the phenol-chloroform method. The rs12255372 and rs7903146 polymorphisms were genotyped using the following primers: forward, 5′-CTG GAA ACT AAG GCG TGA GG-3′, reverse 5′-GGG TCG ATG TTG TTG AGC TT-3′ and forward 5′-AAG AGA AGA TTC CTT TTT AAA TGG TG-3′, reverse 5′-CCT CAT ACG GCA ATT AAA TTA TAC A-3′ (Sigma, Bangalore, India), respectively. A final reaction volume of 15 μL of polymerase chain reaction contained 100 ng genomic DNA, 5 pmol of each primer, polymerase chain reaction buffer with 1 mmol/L of MgCl$_2$, 100 μmol/L of each deoxynucleotide triphospate (dNTP), and 0.5 U of *Taq* polymerase (Gibco, Life Technologies, New York, NY). Polymerase chain reaction was carried out on a Peltier Thermal Cycler (PTC-200, MJ Research, Waltham, MA) under the following conditions: 95°C for 5 minutes, followed by 34 cycles of 95°C for 30 seconds, 54°C (for rs12255372)/58°C (for rs7903146) for 30 seconds, 72°C for 30 seconds, and a final extension of 72°C for 9 minutes. Restriction fragment length polymorphism was carried out using *Tsp*509I enzyme for the rs12255372(G/T) polymorphism and *Hpy*-CH4III enzyme for the rs7903146(C/T) polymorphism. The resulting products were electrophoresed on a 3% agarose gel. To ensure that the genotyping was of adequate quality, we performed random duplicates in 20% of the samples. The assays were performed by a technician who was masked to the phenotype, and there was 99% concordance in the genotyping. Furthermore, a few variants were confirmed by direct sequencing with an ABI 310 genetic analyzer (Applied Biosystems, Foster City, CA). Informed consent was obtained from all the subjects who participated in this study, and the study was approved by the institutional ethical committee.

2.3. Statistical analysis

SPSS Windows, version 10.0 (SPSS, Chicago, IL), was used for statistical analysis. χ^2 test was used to compare the proportions of genotypes or alleles. One-way analysis of variance was used to compare genotype class for continuous variables. Data for continuous variables were expressed as mean ± SD. Regression analysis of the quantitative traits and the genotype class was adjusted for age and sex. Logistic regression analysis with and without adjustment for age, sex, and BMI was performed using diabetes as the dependent variable and the genotypes as the independent variables. *P* values of less than .05 were considered statistically significant.

3. Results

3.1. Clinical and biochemical characteristics of the study subjects

Table 1 shows the clinical and biochemical characteristics of the study subjects. The diabetic subjects were older

Table 1
Clinical and biochemical characteristics of the study subjects

	NGT subjects	Type 2 diabetic subjects	P
n (males/females)	1038 (426/612)	1031 (474/557)	–
Age (y)	41 ± 11	49 ± 10	<.0001
BMI (kg/m^2)	23.6 ± 4.6	25.1 ± 4.3	<.0001 [a]
Waist circumference (cm)	83.7 ± 11.6	90.4 ± 10.0	<.0001 [a]
Fasting plasma glucose (mmol/L)	4.6. ± 0.4	9.2 ± 4.0	<.0001 [a]
2-h postload plasma glucose (mmol/L)	5.6 ± 1.1	–	–
Total cholesterol (mmol/L)	4.66 ± 0.90	5.15 ± 1.06	<.0001 [a]
HDL cholesterol (mmol/L)	1.11 ± 0.23	1.08 ± 0.23	.004 [a]
LDL cholesterol (mmol/L)	2.90 ± 0.77	3.34 ± 1.01	.001 [a]
Log-transformed serum triglycerides (mmol/L)	1.18 ± 0.01	1.72 ± 0.01	<.0001 [a]

Data are presented as mean ± SD. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

[a] P value adjusted for age and sex.

compared with the NGT subjects (49 ± 10 and 41 ± 11 years, respectively; $P < .0001$). A comparison between diabetic subjects and NGT subjects showed that the age- and sex-adjusted mean ± SD of BMI ($P < .0001$), waist circumference ($P < .0001$), total cholesterol ($P < .0001$), serum triglycerides ($P < .0001$), and low-density lipoprotein cholesterol ($P = .001$) were significantly higher in the diabetic subjects. All the quantitative traits except for serum triglycerides had a normal distribution; the latter values were therefore log transformed before analysis.

3.2. Association of rs12255372(G/T) and rs7903146(C/T) polymorphisms with type 2 diabetes mellitus

The genotypic distribution in both the NGT and the type 2 diabetic groups was in Hardy-Weinberg equilibrium. Table 2 shows the genotype and allele frequencies of the rs12255372 (G/T) and rs7903146(C/T) polymorphisms in the study subjects. The frequency of the "T" allele of rs12255372(G/T) was significantly higher in diabetic subjects (23%) compared with that in the NGT subjects (19%) with the allelic odds ratio being 1.30 (95% confidence interval [CI], 1.11-1.51; $P = .001$). The frequency of the T allele of rs7903146(C/T) polymorphism was significantly higher in diabetic subjects (33%) compared with that in the NGT subjects (28%) and the allelic odds ratio was found to be 1.29 (95% CI, 1.13-1.48;

$P = .0001$). Logistic regression analysis of the rs12255372 (G/T) polymorphism showed that the odds ratio for diabetes was 1.59 (95% CI, 1.08-2.36; $P = .019$) for the TT genotype and 1.27 (95% CI, 1.05-1.53; $P = .013$) for the TG genotype when compared with the GG genotype. Odds ratios adjusted for potential confounders such as age, sex, and BMI also showed that the TT (odds ratio [OR], 1.56; 95% CI, 1.03-2.37; $P = .034$) and TG (OR, 1.29; 95% CI, 1.06-1.58; $P = .011$) genotypes were associated with type 2 diabetes mellitus. The unadjusted odds ratio for the TT and TC genotypes of the rs7903146(C/T) polymorphism was found to be 1.48 (95% CI, 1.10-2.01; $P = .010$) and 1.39 (95% CI, 1.16-1.67; $P < .0001$) when compared with the CC genotype. Even after adjusting for age, sex, and BMI, subjects with the TT and TC genotypes were more prone to diabetes (OR, 1.50; 95% CI, 1.08-2.08; $P = .013$ and 1.44; 95% CI, 1.18-1.76; $P = .0003$, respectively).

3.3. Clinical and biochemical characteristics of the NGT subjects stratified based on rs12255372(G/T) and rs7903146(C/T) genotypes

Table 3 shows the comparison of the clinical and biochemical characteristics of the NGT subjects stratified based on rs12255372(G/T) and rs7903146(C/T) genotypes. Normal glucose-tolerant subjects carrying the TT genotype

Table 2
Frequency of the rs12255372(G/T) and rs7903146(C/T) polymorphisms of *TCF7L2* gene in the study subjects

Genotype	NGT subjects (n = 1038)	Type 2 diabetic subjects (n = 1031)	Unadjusted OR (95% CI), P	OR adjusted for age, sex, and BMI (95% CI), P
rs12255372(G/T)				
TT	46 (5%)	66 (6%)	1.59 (1.08-2.36), .019	1.56 (1.03-2.37), .034
TG	305 (29%)	348 (34%)	1.27 (1.05-1.53), .013	1.29 (1.06-1.58), .011
GG	687 (66%)	617 (60%)	Reference	Reference
Frequency of T allele	19%	23%	1.30 (1.11-1.51), .001	–
rs7903146(C/T)				
TT	92 (9%)	114 (11%)	1.48 (1.10-2.01), .010	1.50 (1.08-2.08), .013
TC	391 (38%)	455 (44%)	1.39 (1.16-1.67), <.0001	1.44 (1.18-1.76), .0003
CC	555 (53%)	462 (45%)	Reference	Reference
Frequency of T allele	28%	33%	1.29 (1.13-1.48), .0001	–

Table 3
Clinical and biochemical characteristics of the NGT subjects stratified based on rs12255372(G/T) and rs7903146(C/T) genotypes

Genotype	rs12255372(G/T)			rs7903146(C/T)		
	TT (n = 46)	TG (n = 305)	GG (n = 687)	TT (n = 92)	TC (n = 391)	CC (n = 555)
BMI (kg/m^2)	24.2 ± 4.8	23.7 ± 4.2	23.5 ± 4.7	24.3 ± 5.1	23.2 ± 4.4	23.7 ± 4.6
Waist circumference (cm)	84.6 ± 10	84.0 ± 10.9	83.6 ± 12	85.2 ± 10.9	82.9 ± 11.4	83.8 ± 11.8
Fasting plasma glucose (mmol/L)	4.7 ± 0.4	4.6 ± 0.3	4.6 ± 0.4	4.7 ± 0.5	4.7 ± 0.4	4.6 ± 0.4
2-h postload plasma glucose (mmol/L)	6.1 ± 1.4 *	5.6 ± 1.1	5.6 ± 1.0	6.0 ± 1.3 **	5.7 ± 1.1	5.6 ± 1.0
Glycated hemoglobin (%)	5.7 ± 0.5	5.6 ± 0.4	5.5 ± 0.4	5.7 ± 0.5	5.6 ± 0.4	5.5 ± 0.4
Total cholesterol (mmol/L)	4.58 ± 0.77	4.63 ± 0.98	4.66 ± 0.88	4.54 ± 0.95	4.65 ± 0.89	4.67 ± 0.91
HDL cholesterol (mmol/L)	1.11 ± 0.25	1.11 ± 0.25	1.11 ± 0.23	1.08 ± 0.24	1.12 ± 0.26	1.12 ± 0.24
LDL cholesterol (mmol/L)	2.87 ± 0.62	2.87 ± 0.85	2.92 ± 0.75	2.85 ± 0.79	2.90 ± 0.78	2.94 ± 0.70
Log-transformed serum triglycerides (mmol/L)	1.13 ± 0.02	1.20 ± 0.01	1.17 ± 0.01	1.32 ± 0.02	1.19 ± 0.02	1.17 ± 0.01

Data are presented as mean ± SD.
* P = .011 compared to GG (adjusted for age and sex).
** P = .004 compared to CC (adjusted for age and sex).

of rs12255372(G/T) polymorphism had significantly higher 2-hour plasma glucose levels (mean ± SD, 6.1 ± 1.4 mmol/L) compared with the GG carriers (5.6 ± 1.0 mmol/L, P = .011 after adjusting for age and sex). The TT carriers of rs7903146 (C/T) polymorphism also had significantly higher 2-hour plasma glucose levels (mean ± SD, 6.0 ± 1.3 mmol/L) compared with the CC carriers (5.6 ± 1.0 mmol/L, P = .004 after adjusting for age and sex). Although the same trend was observed with respect to fasting plasma glucose and glycated hemoglobin values in both the polymorphisms, statistical significance was not achieved. None of the other biochemical parameters including serum lipids showed any significant differences among the 3 genotypes in either the NGT or the diabetic subjects.

4. Discussion

The important finding of this study is that the rs12255372 and rs7903146 SNPs are associated with type 2 diabetes mellitus in this Asian Indian population studied in southern India. The SNPs rs12255372 and rs7903146 showed the strongest association with type 2 diabetes mellitus in an Icelandic sample, and this association was confirmed in white samples from Denmark and the United States in the study by Grant et al [5]. All subsequent studies conducted on various other populations [7-17,19] have replicated the findings of Grant et al. Hence, we selected these 2 SNPs for our study. Replication of this association in Asian Indians who are highly prone to diabetes [18] is of importance.

We observed a significant association between the T allele of the rs12255372(G/T) and rs7903146(C/T) SNPs and type 2 diabetes mellitus in our study population. The frequency of the T allele of rs12255372(G/T) was similar to the Finnish [9] and substantially lower than the Icelandic [5] population. Although the frequency of the T allele of rs7903146(C/T) polymorphism in the NGT subjects was similar to the frequency reported by Chandak et al [19], the T allele frequency was lower in the type 2 diabetic subjects when

compared with that reported by Chandak et al [19] in their diabetic population from the western part of India.

The significantly higher values in the 2-hour plasma glucose levels in the TT homozygotes of both polymorphisms among NGT subjects (even after adjusting for the effect for age and sex) further strengthen our finding that the T allele of these variants is a risk allele for type 2 diabetes mellitus. This is consistent with the studies by Chandak et al [19] and Lehman et al [23] who have also reported rs12255372 and rs7903146 variants to be associated with increased 2-hour plasma glucose levels.

One of the limitations of the present study is that it has not answered the functional consequences of these genetic variants. The consistency of association evidenced by various replication studies suggests that *TCF7L2* gene represents an important locus for genetic susceptibility to type 2 diabetes mellitus, but the biological mechanism for the association between the *TCF7L2* gene and type 2 diabetes mellitus risk is still unclear. From the available information, it can be speculated that the *TCF7L2* gene has a role in insulin secretion [24] and possibly adipose tissue development. Furthermore, the genetic variants that have been studied are present in the introns rather than in the coding regions. However, this may still lead to functional consequences in terms of protein stability and/or expression of alternatively spliced variants. In conclusion, our study confirms the association of the rs12255372 and rs7903146 polymorphisms of the *TCF7L2* gene with type 2 diabetes mellitus in this Asian Indian population in southern India.

Acknowledgments

References

[1] Florez JC, Hirschhorn J, Altshuler D. The inherited basis of diabetes mellitus: implications for the genetic analysis of complex traits (review). Annu Rev Genomics Hum Genet 2003;4:257-91.

[2] Malecki MT, Klupa T. Type 2 diabetes mellitus: from genes to disease. Pharmacol Rep 2005;57(Suppl):20-32.

[3] Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, et al. The common PPAR gamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. Nat Genet 2000; 26:76-80.

[4] Gloyn AL, Weedon MN, Owen KR, Turner MJ, Knight BA, Hitman GA, et al. Large-scale association studies of variants in genes encoding the pancreatic beta cell KATP channel subunits Kir6.2 (*KCNJ11*) and SUR1 (*ABCC8*) confirm that the *KCNJ11* E23K variant is associated with type 2 diabetes. Diabetes 2003;2:568-72.

[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;38:320-3.

[6] 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; 355:241-50.

[7] Groves CJ, Zeggini E, Minton J, Frayling TM, Weedon MN, Rayner NW, et al. Association analysis of 6,736 U.K. subjects provides replication and confirms TCF7L2 as a type 2 diabetes susceptibility gene with a substantial effect on individual risk. Diabetes 2006; 55:2640-4.

[8] Zhang C, Qi L, Hunter DJ, Meigs JB, Manson JE, van Dam RM, et al. Variant of transcription factor 7–like 2 (TCF7L2) gene and the risk of type 2 diabetes in large cohorts of U.S. women and men. Diabetes 2006;55:2645-8.

[9] Scott LJ, Bonnycastle LL, Willer CJ, Sprau AG, Jackson AU, Narisu N. Association of transcription factor 7–like 2 (TCF7L2) variants with type 2 diabetes in a Finnish sample. Diabetes 2006;55:2649-53.

[10] Damcott CM, Pollin TI, Reinhart LJ, Ott SH, Shen H, Silver KD, et al. Polymorphisms in the transcription factor 7–like 2 (TCF7L2) gene are associated with type 2 diabetes in the Amish: replication and evidence for a role in both insulin secretion and insulin resistance. Diabetes 2006;55:2654-9.

[11] Saxena R, Gianniny L, Burtt NP, Lyssenko V, Giuducci C, Sjogren 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; 55:2890-5.

[12] Cauchi S, Meyre D, Dina C, Choquet H, Samson C, Gallina S, et al. Transcription factor TCF7L2 genetic study in the French population:

[13] Ostaptchouk JV, Sverdlov RS, Zhernakova A, Strengman E, Haften TW, Hoftker MH, et al. Association of variants of transcription factor 7–like 2 (TCF7L2) with susceptibility to type 2 diabetes in the Dutch Breda cohort. Diabetologia 2007;50:59-62.

[14] Humphries SE, Gable D, Cooper JA, Ireland H, Stephens JW, Hurel SJ, et al. Common variants in the TCF7L2 gene and predisposition to type 2 diabetes in UK European Whites, Indian Asians and Afro-Caribbean men and women. J Mol Med 2006;84:1-10.

[15] Mayans S, Lackovic K, Lindgren P, Ruikka K, Agren A, Eliasson H, et al. TCF7L2 polymorphisms are associated with type 2 diabetes in northern Sweden. Eur J Hum Genet 2007;15:342-6.

[16] Marzi C, Huth C, Kolz M, Grallert H, Meisinger C, Wichmann HE, et al. Variants of the transcription factor 7–like 2 gene (TCF7L2) are strongly associated with type 2 diabetes but not with the metabolic syndrome in the MONICA/KORA surveys. Horm Metab Res 2007;39:46-52.

[17] Horikoshi M, Hara K, Ito C, Nagai R, Froguel P, Kadowaki T. A genetic variation of the transcription factor 7–like 2 gene is associated with risk of type 2 diabetes in the Japanese population. Diabetologia 2007;50:747-51.

[18] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.

[19] Chandak GR, Janipalli CS, Bhaskar S, Kulkarni SR, Mohankrishna P, Hattersley AT, et al. Common variants in the TCF7L2 gene are strongly associated with type 2 diabetes mellitus in the Indian population. Diabetologia 2007;50:63-7.

[20] Mohan V, Deepa M, Deepa R, Shanthirani CS, Farooq S, Ganesan A, et al. Secular trends in the prevalence of diabetes and impaired glucose tolerance in urban South India—the Chennai Urban Rural Epidemiology Study (CURES-17). Diabetologia 2006;49:1175-8.

[21] Alberti KG, Zimmet PZ. Definition diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus, provisional report of a WHO Consultation. Diabet Med 1998;15:539-53.

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

[23] Lehman DM, Hunt KJ, Leach RJ, Hamlington J, Arya R, Abboud HE, et al. Haplotypes of transcription factor 7–like 2 (TCF7L2) gene and its upstream region are associated with type 2 diabetes and age of onset in Mexican Americans. Diabetes 2007;56:389-93.

[24] Munoz J, Lok KH, Gower BA, Fernandez JR, Hunter GR, Castro CL, et al. Polymorphism in the transcription factor 7–like 2 (TCF7L2) gene is associated with reduced insulin secretion in non diabetic woman. Diabetes 2006;55:3630-4.

expression in human {beta}-cells and adipose tissue and strong association with type 2 diabetes. Diabetes 2006;55:2903-8.