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ORIGINAL ARTICLE

Association of TNF-α 308 G/A Polymorphism With Type 2 Diabetes: A Case–Control Study in the Iranian Kurdish Ethnic Group

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Abstract
Objectives: Tumor necrosis factor-α (TNF-α) plays roles in the development of obesity, insulin resistance, and possibility of Type 2 diabetes mellitus (T2DM). The objective of the current study was to evaluate the association of TNF-α promoter–308 G/A polymorphism with T2DM.
Methods: In all, 1038 patients with T2DM and 1023 normoglycemic controls were included in this study. All participants were genotyped using the polymerase chain reaction-restriction fragment length polymorphism method. Genotypic and allelic frequencies were then analyzed in each group. Serum lipids, fasting glucose, fasting serum insulin, homeostatic model assessment of insulin resistance, and hemoglogin A1c levels were determined by conventional methods.
Results: The allelic frequency of the A allele was significantly different between case and control participants ($p = 0.006$). Genotypes GA and AA were found to be significantly associated with 2.24- and 3.18-fold increased risk for T2DM, respectively. Similarly, the dominant model of -308 G/A polymorphism was found to have a higher risk for T2DM (odds ratio = 2.34, $p = 0.001$). Individuals with T2DM carrying the GA + AA genotypes of -308 G/A variation had significantly lower fasting plasma insulin than those carrying GG genotype.
Conclusion: Our findings revealed that there is an association between the TNF-α promoter -308 G/A polymorphism and T2DM in this population.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world [1]. Currently, 366 million people have diabetes worldwide, and the number is predicted to reach 552 million by 2030 [2]. T2DM is characterized by peripheral insulin resistance in the liver, skeletal muscle, and adipose tissues, as well as impaired insulin secretion from the pancreatic beta cells [3]. Evidence has been presented that Type 2 diabetes mellitus (T2DM) drives from the coexistence of genetic and environmental factors [4,5]. However, the molecular mechanisms underlying T2DM are poorly understood.

The role of tumor necrosis factor (TNF)-α in the pathogenesis of T2DM has been investigated in several studies. The *TNF-α* gene is located within the HLA III region in chromosome 6p21, and involved in inflammatory responses. This gene encodes a potent cytokine that has been implicated as an important factor in obesity-associated insulin resistance and pathogenesis of T2DM [6−8]. There were studies focused on *TNF-α* -308 G/A polymorphism (rs1800629), which lead to a higher rate of *TNF-α* gene transcription than that of wild-type *in vitro* expression studies [9]. It is reported that -308 G/A polymorphism associates with either increased or decreased insulin resistance in patients with T2DM and patients without diabetes [10−15]. A recent meta-analysis reported no relationship of this polymorphism with risk for T2DM [16]. Because of controversial reports from several populations, there is still no definitive evidence of the association between this variation and risk for T2DM [9]. Hence, further studies in different population are needed to clarify the precise role of *TNF-α* -308 G/A polymorphism in susceptibility to T2DM.

To our knowledge, because the relationship between -308 G/A polymorphism of *TNF-α* and T2DM in the Kurdish ethnic group of Iran have not yet been addressed and because of controversial results from other populations, we aimed to explore the possible association between this polymorphism and T2DM and its metabolic quantitative traits in a sample of the Iranian Kurdish ethnic group. We examined the allele and genotype frequencies of above polymorphism in patients with and without T2DM, and detected their effects on anthropometric, diabetes, and obesity-related parameters.

2. Material and methods

2.1. Participants and protocols

The study population included 1038 Iranian unrelated patients with T2DM (males/females: 502/536; age: 54.98 ± 1.01 years) and 1023 Iranian unrelated healthy controls (males/females: 493/530; age: 53.3 ± 9.7 years). All patients originated from Ilam and Kermanshah provinces situated in the west of Iran, and belonged to the Kurdish ethnic group. Patients with diabetes and healthy controls were distinguished based on their glycemic status, which was defined according to World Health Organization 1997 criteria [17]. The control group only contained individuals with a normal fasting glucose level and negative family history of T2DM among first-degree relatives. The written informed consent was obtained from all participants prior to enrollment in the study.

Screening included standardized questionnaires for personal data and clinical measurements such as age, sex, obesity, drug consumption during the past month, and medical or family history of diabetes [18]. All those who were not taking diabetes medication underwent a 2-hour oral glucose tolerance test (OGTT) after an overnight fast. Criteria for control selection were fasting glucose <6.1 mmol/L and 2 hours plasma glucose <7.8 mmol/L after OGTT. Diabetes was defined as fasting glucose ≥7.0 mmol/L, 2 hours glucose ≥11.1 mmol/L after OGTT, or use of hypoglycemic medication. Systolic and diastolic blood pressure was measured twice in the right arm of the patients who had been resting for at least 10 minutes in a comfortable position. Signed informed consent was obtained from all patients, and the study was approved by the Institutional Ethics Committee Ilam University of Medical Sciences. All participants were interviewed to obtain clinical data and T2DM family histories. Body mass index was estimated by dividing weight in kilograms by the height in meters squared. Insulin resistance was assessed from glucose and insulin concentrations using the homeostasis model assessment of insulin resistance (HOMA-IR) equation [19].

2.2. Sample preparation

Blood samples were collected from patients and controls in the morning, after an overnight (12−14 hour) fasting. Five milliliters of venous blood was withdrawn from the antecubital vein into Vacutainer tubes (Terumo GmbH, Eschborn, Germany) containing EDTA as the anticoagulant. To separate plasma, blood samples were centrifuged at 3000 rpm for 10 minutes. Supernatant was used for biochemical experiments, and the buffy coat and red blood cell pellet were used for DNA extraction.

2.3. Biochemical assays

Serum blood glucose, triglycerides, total cholesterol, and low-density and high-density lipoprotein cholesterol (LDL-C and HDL-C) levels were measured by the standard enzymatic method (Pars Azmon kit, Tehran, Iran), using the auto analyzer system BT3000 (Biotechnica, Rome, Italy). Serum concentrations of insulin were assessed using a specific enzyme-linked immunosorbent assay kit for human insulin according to the manufacturer's instructions (Monobind Inc., Lake Forest, CA, USA).

2.4. Genotyping

Leukocyte genomic DNA was extracted from the blood specimen using the standard procedure involving proteinase K (Qiagen, Hilden, Germany) and phenol/chloroform (Merck, Darmstadt, Germany). The -308 G/A *TNF-α* promoter polymorphism was amplified by the polymerase chain reaction (PCR) method using the primer pair 5′-AGGCAATAGGTTTTGAGGGCCAT-3′ (forward) and 5′-TCCTCCCTGCTCCGATTC CG-3′ (reverse). PCR was performed in a final volume of 25 μL containing 100 ng genomic DNA, 1.5 mmol/L $MgCl^2$, 0.5 mmol/L of each dNTPs, and 0.5 pmol of each primer. After an initial denaturation of 2 minutes at 94°C, the samples were subjected to 35 cycles at 94°C for 1 minute, 58.5°C for 40 seconds, and 72°C for 30 seconds, with a final extension of 10 minutes at 72°C. All PCR materials were purchased from the CinnaGen Company (Tehran, Iran). The 107-bp product was digested with restriction enzyme NcoI (Fermentas, St. Leon-Rot, Germany) for 5 hours at 37°C followed by agarose gel electrophoresis. The digested products were stained with ethidium bromide. A-allele was not cleaved by NcoI and gave a 107-bp band, and G-allele was cleaved into two bands 87- and 20-bp.

2.5. Statistical analysis

All statistical analyses were carried out using the statistical program SPSS (version 19, SPSS Inc., Chicago, IL, USA). Differences in genotype/allele frequencies were compared using the Chi-square test or Fisher's exact test where appropriate. One-way analysis of variance was utilized to compare the clinical features among groups with different genotypes. Odds ratios and 95% confidence interval were calculated by logistic regression analysis using diabetes as a dependent variable and the genotypes as independent variables.

We used the Pearson goodness-of-fit chi-square (χ^2) test to evaluate the deviation from Hardy−Weinberg equilibrium. The Armitage trend test was applied to assess for the presence of association between different groups of genotypes. Other genetic models including dominant, recessive, and multiplicative models were also considered to analyze single nucleotide polymorphism association [20]. The Bonferroni method was used to correct for multiple comparisons where applicable. A p value <0.05, using two-sided tests, was considered statistically significant, whereas a value of corrected $p < 0.0167$ for genotype analysis was considered significant after Bonferroni correction.

Baseline quantitative results were expressed as mean ± standard deviation (SD) and compared with the Student t test; the continuous variables that failed the normality test were logarithmically transformed prior to analysis. The variables transformed were triglyceride, insulin, and HOMA-IR. Statistical differences are based on analyses of log-transformed data, but means of untransformed data are presented in Tables 1 and 3.

3. Results

The clinical, anthropometrical, and biochemical characteristics of the participants are shown in Table 1. Sex distribution was almost the same in T2DM patients and controls. The mean of age in patients with T2DM and the control group was 54.98 ± 11.1 years and 53.3 ± 9.7 years, respectively. All characteristics of the participants differed significantly between T2DM and

Table 1. Anthropometrical and biochemical characteristics of study groups.

	Groups		
Characteristics	T2DM	Control	p
Number of individuals (male/female)	1023 (493/530)	1038 (502/536)	_
Age (y)	54.98 ± 1.11	53.3 ± 9.7	0.18
BMI (kg/m^2)	28.8 ± 4.86	26.9 ± 4.32	<0.001
WHR	0.94 ± 0.07	0.91 ± 0.062	<0.001
FPG (mmol/L)	9.18 ± 2.75	5.29 ± 0.57	<0.001
HbA1c (%)	8.13 ± 1.72	5.02 ± 0.35	<0.001
TG (mmol/L)	2.07 ± 0.47	1.65 ± 0.46	<0.001
TC (mmol/L)	5.13 ± 1.06	4.65 ± 1.1	<0.001
HDL-C (mmol/L)	0.93 ± 0.25	2.99 ± 0.69	<0.001
LDL-C (mmol/L)	3.89 ± 0.94	3.04 ± 0.8	<0.001
SBP (mm Hg)	13.1 ± 1.85	11.86 ± 1.07	<0.001
DBP (mm Hg)	8.46 ± 1.31	8.0 ± 0.95	<0.001
FPI (μIU/mL)	9.9 ± 3.41	7.33 ± 2.08	<0.001
HOMA-IR	3.98 ± 1.77	1.72 ± 0.5	<0.001

Data are presented as mean ± standard deviation. p values <0.05 are considered as significant. BMI = body mass index; DBP = diastolic blood pressure; FPG = fasting plasma glucose; FPI = fasting plasma insulin; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment−insulin resistance; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride; WHR = waist to hip ratio.

normoglycemic control ($p < 0.001$). Patients with T2DM s had significantly higher values for body mass index, triglyceride, hemoglobin A1c, glucose, total cholesterol, waist to hip ratio, LDL-C, HOMA-IR, diastolic and systolic blood pressure and insulin, and lower levels of HDL-C than normoglycemic control participants (all $p < 0.001$).

The genotype distribution and relative allele frequencies of -308 G/A TNF-α promoter polymorphism for the study patients are shown in Table 2. This variant was in Hardy-Weinberg equilibrium in T2DM ($\chi^2 = 1.49$, df = 1, $p = 0.22$) and control patients ($\chi^2 = 2.7$, df = 1, $p = 0.12$). The A-allele frequency of -308 G/A *TNF-α* promoter polymorphism was significantly (0.006) different between case and control groups (16% vs. 8%, respectively). Genotypes GA and AA were found to be significantly associated with 2.24- and 3.18-fold increased risk for T2DM, respectively. In addition, in the dominant model (GG vs. GA + AA), the -308 G/A *TNF-α* polymorphism was found to be significantly associated with T2DM (OR = 2.34, 95% CI = 1.88−2.91, $p = 0.001$), but no significant association was detected for the recessive model (GG + GA vs. AA).

We classified the anthropometric, clinical, and biochemical characteristics of the study patients according to the dominant model for 308 G/A *TNF-α* polymorphism (Table 3). As shown in Table 3, patients with T2DM carrying the GA + AA genotypes of this variation had a significantly lower fasting plasma insulin (GG; 10.13 ± 3.49 vs. GA + AA; 8.66 ± 2.59 μIU/mL, $p = 0.03$) as compared with those carrying GG genotype. No significant difference was found for any of the clinical and biochemical variables in normoglycemic individuals carrying GG genotype in comparison with carriers of GA + AA genotypes.

4. Discussion

The candidate gene approach focuses on the associations between genetic variation within prespecified genes of interest and phenotypes or disease states based on *a priori* knowledge of the gene's biological functional impact on the trait or disease in question [21,22]. Case-control studies are often used to find the differences of allele frequency of a candidate gene between case and control patients [21].

Inflammation has been widely known as an important feature of T2DM, with high levels of proinflammatory cytokines, including IL-1, IL-6, and *TNF-α*. Because *TNF-α* can impair insulin signal pathways and lead to β-cell destruction, increased *TNF-α* is considered to play a central role in the development of T2DM [7]. So far, many studies have focused on the association between -308 G/A *TNF-α* promoter polymorphism and T2DM, but the results were still controversial [6,9,16−18,23−25]. In this study, we examined the association of the mentioned

Table 2. Genotype/allele status and associated risk for Type 2 diabetes mellitus in study groups.

SNP	Genotype/Allele	Groups		OR (95% CI)	*p*
		T2DM	**Control**		
308 TNF-α	G/G	737	871	1	Reference
	G/A	269	142	2.24 (1.78−2.80)	0.005
	A/A	32	10	3.18 (1.84−5.66)	0.001
	G/G vs. G/A + A/A			2.34 (1.88−2.91)	0.001
	G/G + G/A vs. A/A			3.01 (0.86−10.17)	0.06
	G	0.84	0.92		
	A	0.16	0.08	2.19 (1.21−4.55)	0.006

All data adjusted for age, sex, and body mass index. All $p < 0.0167$ are considered significant after Bonferroni corrections. CI = confidence interval; OR = odds ratio; SNP = single nucleotide polymorphism; T2DM = Type 2 diabetes mellitus; TNF-α = tumor necrosis factor-alpha.

Table 3. The characteristics of the study subjects according to the dominant model of -308 G/A polymorphism of tumor necrosis factor-alpha.

	Patients with Type 2 diabetes			Control patients		
Characteristics	GG (737)	GA + AA (301)	*p*	GG (871)	GA + AA (152)	*p*
BMI (kg/m^2)	29.0 ± 5.09	27.68 ± 3.10	0.19	27.06 ± 4.27	24.51 ± 4.41	0.05
WHR	0.94 ± 0.068	0.92 ± 0.06	0.34	0.90 ± 0.06	0.92 ± 0.11	0.36
FPG (mmol/L)	9.16 ± 2.87	9.25 ± 1.92	0.87	5.28 ± 0.56	5.25 ± 0.67	0.83
HbA1c (%)	8.16 ± 1.78	7.95 ± 1.33	0.56	5.02 ± 0.34	4.92 ± 0.42	0.37
TG (mmol/L)	2.07 ± 0.46	2.06 ± 0.51	0.92	1.64 ± 0.46	1.69 ± 0.40	0.71
TC (mmol/L)	5.08 ± 1.02	5.35 ± 1.23	0.22	4.63 ± 1.10	4.83 ± 0.98	0.56
HDL-C (mmol/L)	0.92 ± 0.24	0.97 ± 0.21	0.28	2.98 ± 0.67	3.15 ± 0.88	0.42
LDL-C (mmol/L)	3.45 ± 0.92	3.70 ± 0.97	0.06	2.92 ± 0.80	3.06 ± 0.73	0.21
SBP (mm Hg)	13.04 ± 1.83	13.35 ± 1.94	0.42	11.88 ± 1.08	11.36 ± 0.81	0.09
DBP (mm Hg)	8.41 ± 1.20	8.68 ± 1.75	0.32	7.99 ± 0.95	8.09 ± 0.83	0.74
FPI (μIU/mL)	10.13 ± 3.49	8.66 ± 2.59	0.03*	7.30 ± 2.09	7.76 ± 1.77	0.47
HOMA-IR	4.06 ± 1.83	3.53 ± 1.26	0.14	1.70 ± 0.50	1.79 ± 0.39	0.58

Data are presented as mean ± standard deviation. *p* values <0.05 are considered as significant. BMI = body mass index; DBP = diastolic blood pressure; FPG = fasting plasma glucose; FPI = fasting plasma insulin; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment−insulin resistance; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride; WHR = waist to hip ratio.

polymorphism with T2DM and related metabolic traits using a case−control method. We selected this variation due to their previous association with T2DM [9,10,19,20,26].

In our study, the allelic frequency of the A-allele of this variant was significantly (0.006) different between case and control groups (16% vs. 8%). The frequency of A-allele of this polymorphism differs from 9% in Chinese populations [27], 16% in French and Scandinavian populations [28,29], 18% in Germans [30], to 24% in Australians [10]. There are some points should be concerned for the inconsistent results. Hamann et al [31] did not find any difference in allele frequencies of the -308 G/A *TNF-α* polymorphism among patients with noninsulin-dependent diabetes mellitus and unrelated controls [31]. In another study, there was not any significant difference in the A-allele of this variant between case and control groups [26]. Kubaszek et al [32] reported, in their study among the Finnish population, that the A-allele of the -308 G/A *TNF-α* variation was associated with twofold higher risk for T2DM, and was also a predictor for the conversion from impaired glucose tolerance to T2DM. Also, no significant differences were identified for allele frequencies between control patients and patients with components of the metabolic syndrome [27]. Ethnic differences may attribute to these different results. However, study design or small sample size or some environmental factors may affect the results [9,33,34].

Based on our results, the frequencies of genotype GA show a significant difference between case and control individuals. A study conducted by Elsaid et al [26] showed that there was no significant difference in the genotype frequencies of GA between case and control groups. In another study, the heterozygous genotype of -308 G/A *TNF-α* polymorphism presented with greater frequency in patients with T2DM than in healthy participants and it was statistically significant [35]. In our study, we found a significant difference in the distribution of AA genotype between the study groups. In agreement with our results, Heijmans et al [13] reported that individuals carrying the AA homozygous genotype (TNF hyperproducer) have a 4.6-times greater risk of presenting with T2DM than an individual with the GG homozygous genotype (TNF hypoproducer). However, our results are in contrast with the results from the Taiwanese population [25]. We also found that the dominant model of -308 G/A *TNF-α* polymorphism be significantly associated with T2DM. This result was in accordance with the results from Caucasian and Asian populations [9].

In our study, patients with T2DM carrying the GA + AA genotypes of -308 G/A *TNF-α* variation had significantly lower fasting insulin levels, as compared with the carriers of GG genotype. This result was in contrast to another study, which found that patients homozygous for the A allele had higher fasting insulin levels [10]. Furthermore, no significant differences were identified between patients with the GG genotype and those with the mutant allele (GA and AA) for clinical and biochemical parameters in some previous studies [27,30]. The reason for the apparent discrepancies between the studies, including ours, can be attributed to several factors such as the study design, sample size, population heterogeneity, and gene-environment interactions [33,34].

In conclusion, this is the first study performed in the Kurdish ethnic group from West Iran, in which the significance of -308 G/A *TNF-α* genetic variation were investigated in the pathogenesis of T2DM. The findings

of our study revealed that the -308 G/A polymorphism of *TNF-α* is associated with the risk of T2DM.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. Oman Med J 2012 Jul;27(4):269−73.
2. Shikata K, Ninomiya T, Kiyohara Y. Diabetes mellitus and cancer risk: review of the epidemiological evidence. Cancer Sci 2013 Jan; 104(1):9−14.
3. Meshkani R, Saberi H, Mohammadtaghvaei N, et al. Estrogen receptor alpha gene polymorphisms are associated with type 2 diabetes and fasting glucose in male subjects. Mol Cell Biochem 2012 Jan;359(1−2):225−33.
4. Goldstein BJ. Insulin resistance as the core defect in type 2 diabetes mellitus. Am J Cardiol 2002 Sep;90(5A):3G−10G.
5. Hamman RF. Genetic and environmental determinants of non-insulin-dependent diabetes mellitus (NIDDM). Diabetes Metab Rev 1992 Dec;8(4):287−338.
6. Li H, Groop L, Nilsson A, et al. A combination of human leukocyte antigen DQB1*02 and the tumor necrosis factor alpha promoter G308A polymorphism predisposes to an insulin-deficient phenotype in patients with type 2 diabetes. J Clin Endocrinol Metab 2003 Jun;88(6):2767−74.
7. Nishimura M, Obayashi H, Mizuta I, et al. TNF, TNF receptor type 1, and allograft inflammatory factor-1 gene polymorphisms in Japanese patients with type 1 diabetes. Hum Immunol 2003 Feb; 64(2):302−9.
8. Rasmussen SK, Urhammer SA, Jensen JN, et al. The -238 and -308 G−>A polymorphisms of the tumor necrosis factor alpha gene promoter are not associated with features of the insulin resistance syndrome or altered birth weight in Danish Caucasians. J Clin Endocrinol Metab 2000 Apr;85(4):1731−4.
9. Feng RN, Zhao C, Sun CH, et al. Meta-analysis of TNF 308 G/A polymorphism and type 2 diabetes mellitus. PLoS One 2011 Apr; 6(4):e18480.
10. Dalziel B, Gosby AK, Richman RM, et al. Association of the TNF-alpha -308 G/A promoter polymorphism with insulin resistance in obesity. Obes Res 2002 May;10(5):401−7.
11. Day CP, Grove J, Daly AK, et al. Tumour necrosis factor-alpha gene promoter polymorphism and decreased insulin resistance. Diabetologia 1998 Apr;41(4):430−4.
12. Fernandez-Real JM, Gutierrez C, Ricart W, et al. The TNF-alpha gene Nco I polymorphism influences the relationship among insulin resistance, percent body fat, and increased serum leptin levels. Diabetes 1997 Sep;46(9):1468−72.
13. Heijmans BT, Westendorp RG, Droog S, et al. Association of the tumour necrosis factor alpha -308G/A polymorphism with the risk of diabetes in an elderly population-based cohort. Genes Immun 2002 Jun;3(4):225−8.
14. Romeo S, Sentinelli F, Capici F, et al. The G-308A variant of the Tumor Necrosis Factor-alpha (TNF-alpha) gene is not associated with obesity, insulin resistance and body fat distribution. BMC Med Genet 2001 Sep;2:10.
15. Walston J, Seibert M, Yen CJ, et al. Tumor necrosis factor-alpha-238 and -308 polymorphisms do not associated with traits related to obesity and insulin resistance. Diabetes 1999 Oct;48(10):2096−8.
16. Feng R, Li Y, Zhao D, et al. Lack of association between TNF 238 G/A polymorphism and type 2 diabetes: a meta-analysis. Acta Diabetol 2009 Dec;46(4):339−43.
17. Santos MJL, Patiño GA, Angel BB, et al. Association between tumor necrosis factor-alpha promoter polymorphisms and type 2 diabetes and obesity in Chilean elderly women. Rev Med Chil 2006 Sep;134(9):1099−106.
18. Zeggini E, Groves CJ, Parkinson JR, et al. Large-scale studies of the association between variation at the TNF/LTA locus and susceptibility to type 2 diabetes. Diabetologia 2005 Oct;48(10):2013−7.
19. Bouhaha R, Baroudi T, Ennafaa H, et al. Study of TNFalpha -308G/A and IL6 -174G/C polymorphisms in type 2 diabetes and obesity risk in the Tunisian population. Clin Biochem 2010 Apr; 43(6):549−52.
20. Berhouma R, Kouidhi S, Ammar M, et al. Genetic susceptibility to type 2 diabetes: a global meta-analysis studying the genetic differences in Tunisian populations. Hum Biol 2012 Aug;84(4):423−35.
21. Kwon JM, Goate AM. The candidate gene approach. Alcohol Res Health 2000;24(3):164−8.
22. Zhu M, Zhao S. Candidate gene identification approach: progress and challenges. Int J Biol Sci 2007 Oct;3(7):420−7.
23. Furuta M, Yano Y, Ito K, et al. Relationship of the tumor necrosis factor-alpha -308 A/G promoter polymorphism with insulin sensitivity and abdominal fat distribution in Japanese patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2002 May;56(2): 141−5.
24. Liu HL, Lin YG, Wu J, et al. Impact of genetic polymorphisms of leptin and TNF-alpha on rosiglitazone response in Chinese patients with type 2 diabetes. Eur J Clin Pharmacol 2008 Jul;64(7): 663−71.
25. Shiau MY, Wu CY, Huang CN, et al. TNF-alpha polymorphisms and type 2 diabetes mellitus in Taiwanese patients. Tissue Antigens 2003 May;61(5):393−7.
26. Elsaid A, Helaly MA, Hatata EZ, et al. TNF-α-308 and INF-γ+874 Gene polymorphisms in relation to susceptibility and severity of type 2 diabetes mellitus among Egyptian cases. Eur J Gen Med 2012;9(3):173−7.
27. Lee SC, Pu YB, Thomas GN, et al. Tumor necrosis factor alpha gene G-308A polymorphism in the metabolic syndrome. Metabolism 2000 Aug;49(8):1021−4.
28. Hoffstedt J, Eriksson P, Hellstrom L, et al. Excessive fat accumulation is associated with the TNF alpha-308 G/A promoter polymorphism in women but not in men. Diabetologia 2000 Jan; 43(1):117−20.
29. Herrmann SM, Ricard S, Nicaud V, et al. Polymorphisms of the tumour necrosis factor-alpha gene, coronary heart disease and obesity. Eur J Clin Invest 1998 Jan;28(1):59−66.
30. Brand E, Schorr U, Kunz I, et al. Tumor necrosis factor-alpha-308 G/A polymorphism in obese Caucasians. Int J Obes Relat Metab Disord 2001 Apr;25(4):581−5.
31. Hamann A, Mantzoros C, Vidal-Puig A, et al. Genetic variability in the TNF-alpha promoter is not associated with type II diabetes mellitus (NIDDM). Biochem Biophys Res Commun 1995 Jun; 211(3):833−9.
32. Kubaszek A, Pihlajamaki J, Komarovski V, et al. Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. Diabetes 2003 Jul;52(7):1872−6.
33. Haghani K, Bakhtiyari S. The study on the relationship between IRS-1 Gly972Arg and IRS-2 Gly1057Asp polymorphisms and type 2 diabetes in the Kurdish ethnic group in West Iran. Genet Test Mol Biomarkers 2012 Nov;16(11):1270−6.
34. Saberi H, Mohammadtaghvaei N, Gulkho S, et al. The ENPP1 K121Q polymorphism is not associated with type 2 diabetes and related metabolic traits in an Iranian population. Mol Cell Biochem 2011 Apr;350(1−2):113−8.
35. Garcia-Elorriaga G, Mendoza-Aguilar M, del Rey-Pineda G, et al. Genetic polymorphisms of the tumor necrosis factor and lymphotoxin alpha in type 2 diabetes. Rev Med Inst Mex Seguro Soc 2013 Jan−Feb;51(1):42−9.