PPARG2 PRO12ALA, OGG1 SER326CYS and ACE I/D Gene Polymorphisms in Healthy Offsprings of Type 2 Diabetic Patients

Tip 2 Diyabetik Hastaların Sağlıklı Evlatlarında PPARG2 PRO12ALA, OGG1 SER326CYS ve ACE I/D Gen Polimorfizmleri

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ABSTRACT Objective: The purpose of this study was to compare genotype distributions of peroxisome proliferator-activated receptor gamma (PPARG) Pro12Ala, 8-oxoguanine glycosylase (OGG1) Ser326Cys, angiotensin-converting enzyme (ACE) I/D polymorphisms between healthy offspring of type 2 diabetic patients and control subjects without family history of type 2 diabetes mellitus (T2DM). **Material and Methods:** We examined 104 non-obese, non-diabetic offspring of type 2 diabetics and 91 control subjects. All participants were evaluated through anthropometric and biochemical measurements, and oral glucose tolerance test (OGTT). The polymorphisms were analyzed by polymerase chain reaction and restriction fragment length polymorphism. **Results:** Several differences were observed in phenotypic traits according to gender and family history. Both female and male offspring had meaningfully higher body mass index when compared to control subjects (p=0.020). Males in offspring group had significantly higher area under the curve (AUC)-glucose than males among control subjects (p=0.001). But this difference was not observed between females in each group (p=0.984). Genotype distributions of each polymorphism between two groups were not different (p=0.324, p=0.882, p=0.370). In all participants, no possible interaction between these genetic variants and phenotypic traits was found (p>0.05). **Conclusion:** Non-determination of any differences in genotype distributions may be linked with ethnic traits. But, further large scale studies are required for the determination of candidate genes for T2DM in Turkish population.

Key Words: Diabetes mellitus, type 2; adult children; polymorphism, genetic; PPAR gamma

ÖZET Amaç: Bu çalışmanın amacı tip 2 diyabetik hastaların sağlıklı evlatları ve tip 2 diabetes mellitus (T2DM) aile öyküsü olmayan kişiler arasında peroksizom proliferatör-aktive reseptör gen gama (PPARG) Pro12Ala, 8-okzoguanin glikozilaz (OGG1) Ser326Cys, anjiyotensin-dönüştürücü enzim (ACE) I/D polimorfizmlerinin genotip dağılımlarını kıyaslamaktı. **Gereç ve Yöntemler:** Tip 2 diyabetiklerin evlatlarından obez olmayan, diyabetik olmayan 104 ve kontrol olarak 91 kişiyi inceledik. Katılımcıların tümü antropometrik ve biyokimyasal ölçümler ve oral glukoz tolerans test (OGTT) ile değerlendirildi. Polimorfizmler polimeraz zincir reaksiyon ve restrüksiyon enzim kesimi yöntemleri ile analiz edildi. **Bulgular:** Cinsiyet ve aile öyküsüne göre fenotipik özelliklerde çeşitli farklar gözlendi. Kontroller ile kıyaslandığında çalışma grubunda, hem kadın hem de erkekler anlamlı bir şekilde daha yüksek beden kitle indeksine sahipti (p=0,020). Araştırma grubundaki erkekler kontrol grubundakilerden anlamlı şekilde daha yüksek eğri altı alan (AUC)-glukoz değerlerine sahipti (p=0,001). Fakat bu fark, her bir grupta kadınlar arasında gözlenmedi (p=0,984). Her bir polimorfizmin genotip dağılımları iki grup arasında farklı değildi (p=0,324, p=0,882, p=0,370). Tüm katılımcılarda, bu genetik varyantlar ve fenotipik özellikler arasında olası bir etkileşim bulunmadı (p>0,05). **Sonuç:** Genotip dağılımlarında herhangi bir fark saptanmaması etnik özelliklerle ilişkili olabilir. Fakat Türk toplumunda T2DM için aday genlerin belirlenmesi için büyük ölçekli başka çalışmalara gereksinim vardır.

Anahtar Kelimeler: Diabetes mellitus, tip 2; yetişkin çocuklar; polimorfizm, genetik; PPAR gama

With the exception of rare monogenic disorders, most of type 2 diabetes mellitus (T2DM) is a complex metabolic disease of heterogeneous etiology as a consequence of an interaction between genetic variation at multiple different chromosomal sites and environmental exposures experienced throughout the lifespan.[1,2] It is very difficult to show the effect of only one gene due to complex genetic structure of susceptible and protective alleles in polygenic diabetes mellitus. Two main abnormalities in the pathogenesis of T2DM are defective insulin secretion in pancreatic β-cells in response to glucose and insulin resistance. Therefore, genome studies are focused on identifying candidate genes associated with glucose transport, beta-cell function, and insulin resistance. Variants in peroxisome proliferator-activated receptor gene (PPARG) have been extensively examined in the epidemiologic studies related to T2DM.[3] PPARG is a prototypical member of the nuclear receptor super-family of transcription factors and integrates control of energy, lipid and glucose homeostasis.[4] Actions of PPARG are mediated by two isoforms, widely expressed PPARG1 and adipose tissue restricted PPARG2. These isoforms are produced from a single gene by alternative splicing, and differ only by an additional 30 amino acids in N terminus of PPARG2. Single nucleotide polymorphism (SNP) in PPARG2 exon 2 results in a proline to alanine substitution at codon 12, found to be modulating the transcriptional activity of the gene.[5] Pro12 Ala polymorphism was the first genetic variant to be definitively implicated in common form of T2DM.[2]

Recently, it has been emphasized that oxidative stress may play role in the pathogenesis of T2DM.[6,7] Several authors have indicated the association of Ser326Cys polymorphism in human 8-oxoguanine glycosylase (OGG1) gene with insulin sensitivity and T2DM.[8-11] OGG1 gene codes for DNA repair enzyme responsible for excising 8-hydroxydeoxyguanine (8-OHdG) from damaged DNA. 8-OHdG is a major form of oxidative DNA damage produced by mutagenic or carcinogenic reactive free radicals resulting in G:C to T:A transversions.[12-14] We have previously detected increased level of serum 8-OHdG in lean normoglycemic offspring of Type 2 diabetic patients.[15] Several SNPs and somatic mutations have been determined in a human OGG1 gene and investigated extensively as a candidate gene for many types of tumors. Among these, many authors have focused on common SNP Ser326Cys. Results indicated that Cys326 has a lower ability to prevent mutagenesis by 8-OHdG than Ser326 in vivo in human cells.[16] There have been only limited numbers of reports examining the association of OGG1 Ser326Cys polymorphism with diabetes; and different results have been found in these studies.

Gene encoding angiotensin-converting enzyme (ACE) has been listed as one of recently evaluated candidates in association with the risk of T2DM.[17] Angiotensin-converting enzyme (ACE) plays an important role in blood pressure regulation and electrolyte balance by hydrolyzing angiotensin I into angiotensin II. There are some evidences supporting the relationship between renin-angiotensin system and insulin resistance or glucose metabolism.[18-20] A polymorphism called as I/D resulting from insertion/deletion of a 287 bp Alu sequence in intron 16 of ACE gene attracts special attention because it accounts for approximately half of the variance in serum ACE levels.[21] Many studies have attempted to link ACE I/D polymorphism with T2DM, but results were often not reproducible with published studies showing not only positive and null but also negative associations.[17] Recently, two meta-analyses have been indicated that a variant of ACE I/D had a positive association with T2DM.[17,22]

Identification of subjects at high risk for T2DM may aid disease prevention. Therefore, we aimed at investigating the distributions of PPARG2 Pro12Ala, OGG1 Ser326Cys, and ACE genotypes in normoglycemic non-obese offspring of Type 2 diabetic subjects. In addition, existence of any possible interaction between these SNPs and phenotypic traits was examined.

MATERIAL AND METHODS

SUBJECTS AND PHENOTYPES

We included 104 non-obese (BMI between 18.5 and 27 kg/m^2), non-diabetic offspring of type 2 diabetics, and 91 control subjects without family history (FH) of T2DM, having similar age and body mass index (BMI). Participants were recruited from hospital staff, medical students, and offspring of patients with T2DM admitted to Outpatient Clinic of Endocrinology and Metabolism at Ege University Hospital. Family history of diabetes was assessed by a questionnaire. Relatives of type 2 diabetics were included in the study if T2DM existed in both of the parents or one parent and one first-or-second-degree relative. All participants were aged between 18 and 35 years, free from acute or chronic infections, known ischemic heart disease, peripheral vascular disease, hypertension, dyslipidemia, and any other serious medical problems. Study protocol was approved by Ethical Committee of Ege University Hospital, and all subjects gave their written informed consent for participating in the study.

All participants were assessed by physical examination, anthropometric measurements, and appropriate laboratory tests. Their body weights were measured on a two-point bioelectrical impedance apparatus (Tanita TBF 300, TANITA Corp. Tokyo, Japan) validated for adults; and their heights by a wall-mounted stadiometer. BMI was calculated as body weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference was measured according to a standard procedure described earlier.[23] Blood pressure (BP) was recorded as the last of two measurements with subjects seated using a sphygmomanometer. Blood samples were taken from antecubital vein for appropriate laboratory tests after a 12-h fast. Subjects who had metabolic impairment and thyroid dysfunction were excluded.

Before OGTT, 250 g of carbohydrate containing diet was advised for all subjects for 3 days. OGTT was performed between 08:00 and 10:00 hours after an overnight fast. Both insulin and glucose levels were measured at baseline, 1 and 2 hours after 75 g glucose ingestion. Plasma glucose was immediately measured by glucose oxidase method using a glucose analyzer (photometer 5010). Serum insulin level was measured through enzyme-labeled chemiluminescent immunometric assay (Immulite 2000, UK). Individuals with normal glucose metabolism according to ADA criteria[24] were allowed to stay in the study. Those with normal glucose metabolism according to ADA criteria continued to participate in the study. Glucose and insulin responses during OGTT were analyzed by calculating the area under the curve (AUC) by using trapezoidal method.

GENOTYPING

Peripheral venous blood samples for genomic DNA were drawn from an antecubital vein into tubes containing EDTA, and stored at -80ºC until analyses were performed. Total genomic DNA was extracted from whole blood by using Magna Pure LC DNA isolation kit (Roche Applied Science, Germany) in accordance with the protocol provided by manufacturer. PPARG2 exon 2 Pro12Ala and ACE (I/D) polymorphisms were genotyped as described earlier.[25,26]

For OGG1 exon-7 (C9072G) Ser326Cys polymorphism, a real-time PCR method was optimized by using LightCycler v:2.0 instrument (Roche Applied Science). For this purpose, 0.5 µM specific primers and 0.2 µM simple probe (Tib Molbiol, Germany) were used in combination with Light-Cycler FastStart DNA Master Hybridization Probes kit (Roche Applied Science). 1.5 mM MgCl$_2$, 2.5 U GC-rich PCR buffer (*Roche Applied Science*) and 50 nmol genomic DNA were added to 10 µl reaction mix (Forward primer: 5'-CCCAACACTGT-CACTAGTCTCA-3', reverse primer: 5'-TTGGGGAA TTTCTTTGTCCA-3', simple probe: 5'- CGCCAATCCCGCCAXITGCTCAG-PH). Following a denaturation step at 94°C for 10 min, DNA was amplified in 45 PCR cycles (94°C for 5s; 51°C for 8s; 72°C for 15s). Melting analysis was set at 95°C for 20s, 40°C for 20s and 85°C 0s with a ramp rate of 0,2 in continuous acquisition mode following a cooling step at 40°C for 30 s. While wild type genotype was identified by a melting amplicon at 62.5°C, heterozygote genotype was

determined at 62.5 and 55.5°C, whereas homozygote polymorphic genotype was at 55.5°C.

STATISTICAL ANALYSIS

Statistical analysis was performed by using SPSS 18.0. Continuous variable was shown as means±SD. Differences in anthropometric, clinical and biochemical data between compared groups were tested by unpaired t test or by ANOVA. Since sex distribution between two groups was not similar, p value calculated by considering sex interaction. Analyses of variables with observed sex influence were performed separately for each sex. Chi-square test was used for assessing the deviation from Hardy-Weinberg equilibrium of genotypic frequencies. Fisher's exact test was applied for comparing allelic frequencies between both groups. Possible interactions between genotype and variables were tested by ANOVA. Spearman's correlation coefficients were performed for correlations. The level of significance was accepted as p<0.05.

RESULTS

Baseline characteristics of two groups were given in Table 1. Besides, the offspring were well matched with the control subjects according to age, and gender distribution of the study population was not similar in both groups (p=0.002). There were 77 females and 27 males in offspring group, 48 females and 43 males in control group. Therefore, p value for parameters affected by gender was calculated separately in each sex. No significant differences were found between offspring and controls with respect to waist circumference, blood pressure, lipid profile, HOMA-IR, and AUC-insulin. Both female and male offspring had meaningfully higher BMI when compared to control subjects (p=0.020). Males in offspring group had significantly higher AUC-glucose than males among control subjects (p=0.001). But this difference was not observed between females in each group (p>0.984).

In females among study population, BMI was significantly and positively correlated with systolic BP (r=0.349, p<0.001), diastolic BP (r=0.354, p=<0.001), waist circumference (r=0.753, p<0.001), triglycerides

TABLE 1: Baseline characteristics of the offsprings of type 2 diabetics and control group.

	Offspring n: 104	Control group n: 91	p value
Gender (Female/ Male)	77/27	48/43	0.002
Age (years)	24.8±4.1	23.3±3.2	0.351
BMI (kg/m²)[a]			0.020
Female	22.2±2.3	21.2±2.0	
Male	23.4±2.4	23.1±2.1	
Waist circumference (cm)[a]			0.196
Female	74.0±7.0	71.8±6.4	
Male	85.2±7.3	85.0±7.4	
Systolic BP (mmHg)	108±11	112±12	0.061
Diastolic BP (mmHg)	71±7	73±8	0.084
Total cholesterol (mg/dL)	167±29	165±26	0.657
Triglycerides (mg/dL)[a]			0.474
Female	73.3±26.6	67.3±24.6	
Male	94.6±32.3	96.1±36.9	
HDL-cholesterol (mg/dL)[a]			0.263
Female	62.0±12.8	65.3±11.1	
Male	50.2±9.0	49.4±9.7	
LDL-cholesterol (mg/dL)	92.2±26.0	90.8±24.2	0.459
HOMA-IR	1.33±0.78	1.17±0.74	0.436
AUC-glucose[a]			
Female	185±33	184±39	0.984
Male	231±44	198±36	0.001
AUC-insulin[a]			0.319
Female	76.7±34.5	70.3±33.6	
Male	98.3±51.0	86.7±53.6	

Data were expressed as means±SD, p value was calculated by considering gender effect, [a]the variable affected by gender.

(r=0.234, p=0.001) and HOMA-IR (r=0.291, p=0.001), and AUC-glucose was positively correlated with AUC-insulin (r=0.369, p<0.001). In males, BMI was positively correlated with systolic BP (r=0.437, p<0.001), diastolic BP (r=0.297, p<0.014), waist circumference (r=0.868, p<0.001), triglyceride (r=0.434, p<0.001), HOMA-IR (r=0.493, p<0.01) and AUC-insulin (r=0.345, p=0.005), and AUC-glucose was positively correlated with AUC-insulin (r=0.369, p=0.002).

Genotypes distributions and allele frequencies of PPARG2 Pro12Ala, OGG1 Ser326Cys and ACE I/D polymorphisms for two groups were shown in Table 2. One subject in offspring group could not be examined for Pro12Ala polymorphism. Distributions of genotypes were in Hardy-Weinberg equilibrium. There were no differences in genotype

TABLE 2: Genotypes distributions and alleles frequencies of PPARG2 Pro12Ala, OGG1 Ser326Cys, ACE I/D polymorphisms between the offspring of type 2 diabetics and control group.

Genotype Haplotype	Offspring n (%)	Control group n (%)	p value
PPARG2, Pro12Ala			0,324
Pro12Pro	88 (85.4)	82 (90.1)	
Pro12Ala	15 (14.6)	9 (9.9)	
Ala12Ala	0 (0)	0 (0)	
Pro	191 (92.7)	173 (95.1)	
Ala	15 (7.3)	9 (4.9)	
OGG1			0,882
Ser/Ser	45 (43.2)	41 (45.1)	
Ser/Cys	48 (46.2)	39 (42.9)	
Cys/Cys	11 (10.6)	11 (12.0)	
Ser	138 (66.3)	121 (66.5)	
Cys	70 (33.7)	61 (33.5)	
ACE			0,370
DD	29 (27.9)	33 (36.3)	
DI	58 (55.8)	42 (46.1)	
II	17 (16.3)	16 (17.6%)	
D	116 (55.8)	108 (59.3%)	
I	92 (44.2)	74 (40.7%)	

and allelic frequencies between offspring of type 2 diabetics and controls. In the study population, we did not observe any relationships between genotype distributions and anthropometric, clinical and metabolic parameters as shown in Table 3, 4 and 5 respectively.

DISCUSSION

Insulin resistance and various components of metabolic syndrome have been demonstrated even in young, non-obese offspring of the patients with T2DM.[27-29] It has been observed that the offspring of diabetic parents displayed excess body fatness beginning in childhood, and accelerated progression of adverse risk profile characteristics of insulin resistance syndrome from childhood to young adulthood.[30] In our study, the offspring of type 2 diabetics have higher BMI than subjects without family history of T2DM; and BMI was positively correlated with components of metabolic syndrome. In concordance with previous studies, these results may suggest that the offspring of diabetic patients are ge-

netically programmed to have higher BMI and metabolic defect. Although HOMA-IR, AUC-insulin were greater in offspring group than controls, the difference was not statistically significant. The reason for the fact that we could not determine a difference between two groups in terms of insulin resistance may be related to the method used for measuring insulin resistance. The gold standard for measuring insulin resistance is hyperinsulinemic clamp technique.[31] Since this method requires considerable experience and extensive equipments, homeostasis model assessment of insulin resistance (HOMA-IR), an easier method for estimating insulin resistance, is used in present study. But this index has lower sensitivity and specificity for detecting insulin resistance in non-diabetic individuals.[32,33] Kowalska and colleagues showed that glucose and insulin concentrations during OGTT in lean non-diabetic offspring of type 2 diabetics were not different from those of controls; however, insulin sensitivity index determined by clamp method was meaningfully low in these individuals.[34]

In present study, males with family history had higher AUC-glucose than controls. But this difference was not observed between the females of each group. In normal subjects, sex-related difference in peripheral glucose metabolism has been reported. After ingestion of 75 g glucose load, normal women have showed greater glucose uptake per unit muscle mass than normal men. It has been suggested that

TABLE 3: Anthropometric, clinical, and biochemical parameters of subjects according to PPARG2 Pro12Ala polymorphism.

	Pro12Pro	Pro12Ala	p value
BMI (kg/ m²)[a]	22.2±2.3	23.0±2.4	0.096
Waist circumference (cm)[a]	77.3±9.1	77.6±8.4	0.936
Systolic BP (mmHg)	110±12	114±11	0.119
Diastolic BP (mmHg)	72±8	74±8	0.408
Total cholesterol (mg/dL)	167±29	163±22	0.534
Triglyceride (mg/dL)[a]	79.8±32.0	77.1±29.6	0.703
HDL cholesterol (mg/dL)[a]	58.6±12.9	58.2±14.3	0.991
HOMA-IR	1.23±0.76	1.31±0.81	0.878
AUC-glucose[a]	194±38	201±51	0.362
AUC-insulin[a]	78.7±40.9	94.9±59.9	0.096

Data were expressed as means±SD, [a]p value was calculated by considering gender effect.

TABLE 4: Anthropometric, clinical, and biochemical parameters of subjects according to OGG1 Ser326Cys genotypes.

	Ser326Ser	Ser326Cys	Cys326Cys	p value
BMI (kg/m²)[a]	22.2±2.4	22.4±2.3	21.9±2.4	0.593
Waist circumference (cm)[a]	77.0±9.0	78.2±9.2	75.8±9.0	0.065
Systolic BP (mmHg)	110±12	110±12	112±13	0.727
Diastolic BP (mmHg)	71.5±8.2	73.6±7.7	72.6±8.0	0.236
Total cholesterol (mg/dL)	162±28	172±28	164±20	0.058
Triglyceride (mg/dL)[a]	75.6±31.0	85.6±32.7	71.5±25.1	0.056
HDL cholesterol (mg/dL)[a]	59.1±14.7	57.1±10.8	62.2±13.2	0.100
HOMA-IR	1.29±0.77	1.50±0.85	1.17±1.01	0.704
AUC-glucose[a]	193±39	196±43	194±34	0.911
AUC-insulin[a]	80.9±40.2	80.7±45.2	82.5±55.5	0.984

Data were expressed as means±SD, [a]p value was calculated by considering gender effect.

TABLE 5: Anthropometric, clinical and biochemical parameters of subjects according to ACE I/D polymorphism.

	DD	ID	II	p value
BMI (kg/m²)[a]	22.5±2.6	22.4±2.4	21.5±2.1	0.201
Waist circumference (cm)[a]	78.0±8.8	77.9±9.4	74.0±8.2	0.586
Systolic BP (mmHg)	112±12	111±12	107±13	0.191
Diastolic BP (mmHg)	73±8	73±8	71±8	0.273
Total cholesterol (mg/dL)	168±33	165±26	165±22	0.798
Triglyceride (mg/dL)[a]	81.6±34.2	76.8±29.6	84.1±32.6	0.080
HDL cholesterol (mg/dL)[a]	60.1±13.1	57.5±13.1	58.9±12.6	0.162
HOMA-IR	1.3±0.7	1.5±0.7	1.1±0.9	0.649
AUC-glucose[a]	200±41	190±37	195±47	0.313
AUC-insulin[a]	85.1±43.9	80.1±44.9	75.7±41.6	0.753

Data were expressed as means±SD, [a]p value was calculated by considering gender effect.

muscle insulin sensitivity is greater in normal women.[34] There is a gender difference in metabolic flexibility defined as transition ability between fat oxidation and glucose oxidation. It has been emphasized that healthy young women are metabolically more flexible than men. There may be an important role of adipose tissue characteristics in sexual dimorphism of metabolic flexibility. As compared with men, women have greater capacity for insulin suppression of non-esterified fatty acids and insulin stimulated glucose oxidation, and higher circulating adiponectin level.[35,36] In contrast to these evidences, 2-hour plasma glucose levels after oral glucose load in women have been found higher than men among non-diabetic subjects. It has been concluded that this difference was not sex specific but partly a result of the smaller skeletal muscle mass.[36,37] Our findings may support that male offspring of type 2 diabetic subjects have a greater risk for developing glucose intolerance in Turkish population.

In this study, frequencies of PPARG2 Pro12Ala, OGG1 Ser326Cys and ACE I/D polymorphisms in subjects genetically predisposed to T2DM and possible association between these SNPs and phenotypic traits were examined. Frequency of each polymorphism was similar in both offspring and control subjects. Furthermore, any possible interactions between these polymorphisms and phenotypic traits could not be showed.

PPARG2 Pro12Ala polymorphism is a genetic variant whose effect is probably modulated by environmental and other genetic factors, and generally associated with increased protection against the development of T2DM and insulin resistance in humans.[38] Several meta-analyses indicate that

PPARG2 12Ala polymorphism is associated with a reduction in the risk of type 2 diabetes.[3,39,40] Allelic frequency is different according to ethnic background. The prevalence of Ala12 allele varies from approximately 4% in Asian populations to approximately 28% in Caucasians.[37] It was calculated 6.2% in all participants of present study.

Association of the polymorphism with BMI is complex and controversial.[4,41,42] This association has been examined in a meta-analysis using data from 30 independent studies.[43] It has been revealed that Ala12 allele carriers had significantly higher BMI than non-carriers in the samples with a mean BMI value as >27. This difference has not been detected in the samples with a mean BMI as <27. Another meta-analysis[44] of 57 studies including data of cohorts with normal or impaired glucose tolerance revealed no significant effect of Pro12Ala polymorphism on diabetes-related traits across all studies. Only in selected subgroups consisting of Caucasians and obese individuals, an association of Ala allele with greater BMI and insulin sensitivity has been observed. The fact that we could not determine any relations between Pro12Ala polymorphism and phenotypic characteristics in non-obese, non-diabetic offspring of type 2 diabetics is partly consistent with these meta-analysis results. Large population based studies exploring the frequency of Pro12Ala polymorphism in Turkish healthy population are not found in the literature. There are several papers from Turkey which examine the relationship of the polymorphism with various disorders such as gestational diabetes mellitus,[45] and polycystic ovary syndrome.[46,47] Consistently with these studies, homozygous carrier for Pro12Ala polymorphism was not detected in our study. But, it has been reported that the percent of carrier for Ala12Ala in the patients with major depression was 2.56%.[48]

OGG1 Ser326Cys polymorphism is one of the candidate genetic variants for T2DM recently attracting the attention of researchers. It has been showed that hOGG1 gene Cys/Cys variant was associated with a significant decrease in insulin sensitivity in normal glucose tolerant subjects.[8] An association between hOGG1 Ser326Cys polymorphism and T2DM has been evaluated in a limited number of studies. No association has been re-vealed in Polish type 2 diabetic population.[10] Ser326Cys polymorphism of OGG1 gene has been found to be associated with diabetes of type 2 in a relatively large population-based Japanese sample.[9] Authors have emphasized that the increase in insulin secretion to compensate for insulin resistance seemed to be impaired in subjects with genotypes under risk. The results of this study have suggested a functional involvement of the OGG1 in the pathophysiology of diabetes. It has been also reported that the Ser(326)Cys exhibited significant association with T2DM in Mexican Americans.[11] A report from China has revealed that variants c.-23A>G and Ser326Cys in OGG1 gene had a joint effect on the risk of T2DM.[49] These evidences may support that OGG1 is a candidate gene for T2DM. But they should be validated with large scale-studies in different populations.

Like OGG1, ACE I/D polymorphism is another genetic variant whose association with T2DM has been examined in recent years. Papers from Turkey have revealed different results in type 2 diabetic subjects and obese patients.[50-53] A meta-analysis[22] of 24 studies showed that variant D is associated with an increased T2DM risk of 14% relative to variant I. In subgroup analysis, a strong association was found in Caucasian and East Asian groups but no association was found in Turkish groups. A similar meta-analysis[17] has reported that the association of allele D with the risk of T2DM is more prominent for population-based studies and among Africans and Caucasians.

In our study, PPARG2 Pro12Ala, OGG1 Ser326Cys and ACE I/D genotypes in offspring of Turkish type 2 diabetics were not found to be different from the subjects without T2DM family history. Non-determination of any differences in genotype distributions may be linked with ethnicity. Furthermore, larger population-based studies are required to determine candidate genes for T2DM in Turkish population.

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