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MDM2 SNP309 polymorphism in Turkish population

Türk popülasyonunda *MDM2* SNP309 polimorfizmi

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SUMMARY

Objective: *Murine double minute 2* (*MDM2*) gene has a critical role on regulation of p53 tumor suppressor pathway. MDM2 is a major negative regulator of p53 function. *MDM2* protein regulates p53 function through multiple independent pathways. The present study aims to determine the frequency of MDM2 gene SNP309 (rs2279744) polymorphism in the Turkish population.

Method: This study included a total of 301 healthy Turkish individuals (159 females (53.0%) and 141 males (47.0%) between 2014 and 2016. The frequency of T309G *MDM2* rs2279744 polymorphism was identified using restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR) method.

Results: The mean age of the study population was 49,80±16,4 years (51,97±15,98 years in men and 47,58±16,82 years in women). Genotype frequencies for *MDM2* rs2279744 polymorphism were found to be 17.9% TT, 55.2% TG, and 26.9% GG.

Conclusions: The present study provides information on the allele and genotype frequency distribution of *MDM2* gene rs2279744 polymorphism in the Turkish population, which can be used as a reference parameter for the investigation of susceptibility to various disorders, particularly cancer.

Keywords: *Murine double minute 2, MDM2*, polymorphism, Turkish Population.

ÖZET

Amaç: *Murine double minute 2* (*MDM2*) geni p53 tümör süpressör yolağının düzenlenmesinde kritik bir role sahiptir. MDM2, p53 fonksiyonunda büyük bir negatif regülatördür. MDM2 proteini birbirinden bağımsız birçok yolla p53 fonksiyonunu düzenler. Bu çalışmada bir Türk Populasyonunda *MDM2* geni SNP309 (rs2279744) polimorfizm sıklığının belirlenmesi amaçlanmıştır.

Yöntem: Bu çalışmada, MDM2 rs2279744 polimorfizm sıklığı toplam 301 (kadın: 159, % 53,0 ve erkek: 141, % 47,0) Türk sağlıklı bireyde incelendi. T309G MDM2 rs2279744 polimorfizim sıklığı 301 sağlıklı kontrolde RFLP-PCR metoduyla belirlendi.

Bulgular: Çalışma grubunun yaş ortalaması 49,80±16,4 yıl (erkek, 51,97±15,98; kadın, 47,58±16,82) idi. *MDM2* rs2279744 polimorfizmine ait gözlenen genotip frekansları % 17.9 TT, % 55.1 TG ve %26.9 GG olarak tespit edildi.

Sonuç: Bu çalışma, Türk toplumunda *MDM2* geni rs2279744 polimorfizminin allel ve genotip frekans dağılımları hakkında bilgi vermektedir. Bu allel ve genotip dağılımları kanser başta olmak üzere birçok hastalığa yatkınlığın araştırılmasında referans parametre olacaktır.

Anahtar sözcükler: *Murine double minute 2, MDM2*, polimorfizm, Türk Popülasyonu

INTRODUCTION

Murine double minute 2 (*MDM2*) gene was firstly obtained from the "double minute" (small chromatin pieces without centromeres) chromosomes of the spontaneously transformed mouse cell lines[1]. Human homologous of MDM2, *HDM2* (Human double minute 2), is localized on the 12q13-14 region of the chromosome. MDM2 is a 90 kilodalton (kD) protein which can form a complex with p53 tumor suppressor protein[2]. p53 protein activates the transcription of *MDM2* gene[3]. In case of any damage to the DNA, degradation of p53 protein stops or another tumor suppressor, namely *p14ARF*, which is stimulated by any kind of increased oncogenic activity binds *to MDM2* and contributes to the activation of p53 protein. The product of *P14ARF* gene binds and inhibits MDM2, thereby, playing a role in the activation of p53. Binding of *P14ARF* to MDM2 prevents the interactions between MDM2 and p53, as well as stimulating degradation of MDM2[4]. MDM2 inhibits the activity of p53 protein and ensures degradation of this protein by ubiquitin ligase[5]. The level of MDM2 protein within cell or an organism has a major influence on p53 response and formation of several diseases such as cancer[6]. p53 represents the major pathway of interaction between tumor functions and MDM2 proteins form the autoregulatory feedback cycle. In this cycle, p53 positively regulates MDM2 levels, while MDM2 negatively regulates p53 levels and activity. In addition, MDM2 also contributes to carcinogenesis irrespective of p53 by inhibiting the functions of E2F family transcription factors and Rb (retinablastoma) and transition of normal cells to G_0/G_1-S phase[7]. If a mutation occurs in the region of *MDM2* that affects the p53 gene, p53 gene can be suppressed without any control and the cell cycle of a cell with DNA damage may not be stopped[1].

MDM2 SNP309 is a functional polymorphism that effects *p53* protein levels in a cell. Replacement of G allele by T allele increases the binding affinity of Sp1 transcription activator. Therefore, expression of the *MDM2* gene increases. Over-expression *of MDM2* prevents *p53* functions as well as aiding in the escape of damaged cells from cell cycle checkpoints and becoming carcinogenic[8,9]. In the present study, we aimed to investigate rs2279744 single nucleotide polymorphism which results in T-G replacement in position 309 of MDM2 in 301 healthy individuals and genotype distribution.

MATERIALS AND METHODS

The study protocol was approved by both scientific and ethics committees and written informed consents were obtained from all participants. In the present study, a total of 301 (females: 142, 47,2 %) and males: 159, 52,8 %) Turkish healthy individuals were studied. The mean age of study population was 49,80±16,4 year (males, 51,97±15,98; females, 47,58±16,82). Healthy controls were composed of 301 individuals who visited the outpatient department for physical examination, without tumors. All participants in the study gave informed consent, provided a blood sample, and completed a comprehensive epidemiologic questionnaire. A questionnaire given to each control collected information on demographic factors, such as age and sex.

Two milliliters peripheral blood samples were collected in to sitrat containing tubes from all subjects. DNA was extracted from whole blood by salting out procedure as soon as the samples reached to laboratory[10].

MDM2 SNP309 polymorphism was analyzed using a PCR-RFLP method. This polymorphic side in *MDM2* gene was amplificated on a thermal cycler (Applied Biosystems Gene AmpR PCR system 9700, USA) by using a forward primer (5′-CGC GGG AGT TCA GGG TAA AG-3′) and a reverse primer (5′- CTG AGT CAA CCT GCC CAC TG-3′). The reaction performed in 25 μL of total volume containing 10 mmol/L Tris-HCl (pH 8.3 at 25°C), 50 mmol/L KCl, 1.5 mmol/L $MgCl_2$, 2.5 U of Taq DNA polymerase (Fermentas), 5 nmol of each of four deoxynucleotide triphosphates (dNTPs-Fermentas), 10 pmol of each of the appropriate primers and 100 ng of genomic DNA. PCR conditions were one cycle of 95°C for 5 min; 30 cycles of 94°C for 60 s, 55°C for 60 s, 72°C for 60 s, and one cycle of 72°C for 5 min. After PCR amplification, a fragment with 157 base pair (bp) was obtained. For RFLP analysis, the PCR products were digested with *MspA1I* restriction endonuclease (RE) enzyme (Promega) at 37°C during overnight, according to the manufacturer's instructions. Both PCR and RFLP products were separated on 2% agarose gel stained with GelRed™ Dropper Bottle (Sweden) and imaged on UV transilluminator. Genotypes of the rs2279744 polymorphism were identified according to presence or absence of recognition side of *MspA1I* RE enzyme. The wild type genotype (TT) has no recognition side of the enzyme. However, a recognition region of the RE enzyme occurs with substitution of T-to-G nucleotide in 309 position of *MDM2* gene in polymorphic type genotype (GG). Thus, two fragments (110 and 47 bp) shown in GG genotype[11] (Figure 1).

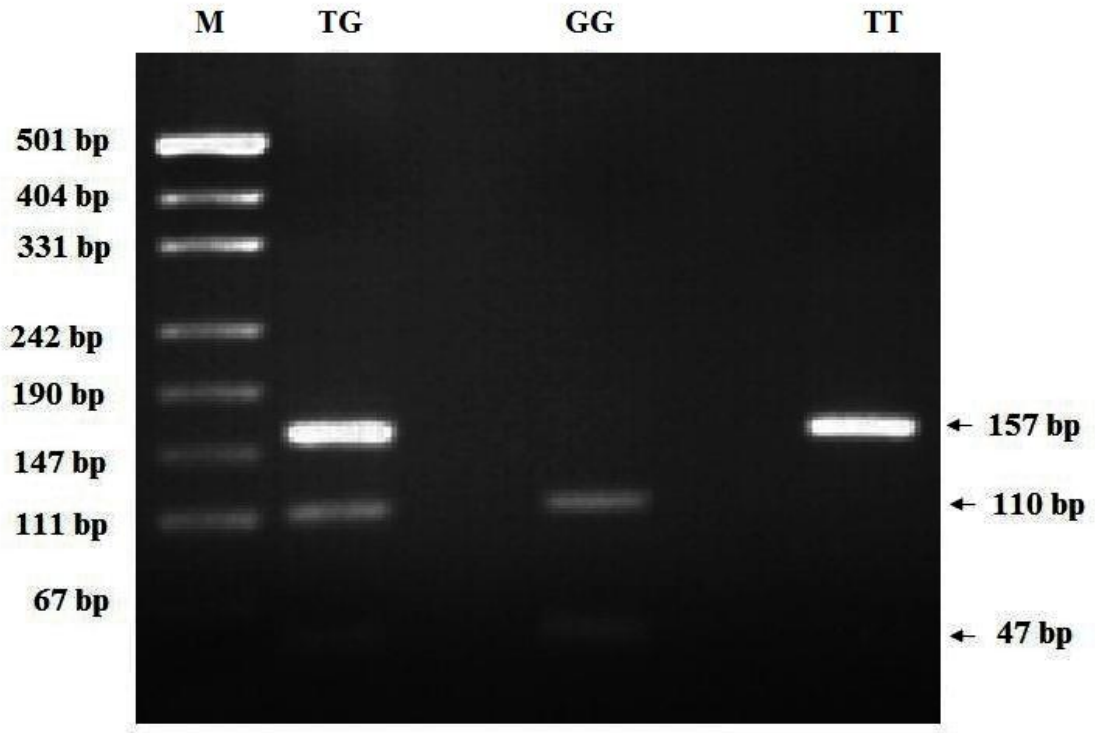


Figure 1. PCR-RFLP patterns of polymorphisms of *MDM2 T309G*. M: pUCI19/Msp I DNA ladder (501, 489, 404, 331, 242, 190, 147, 111, 110bp); MDM2 PCR product, 157 bp, TG (157, 110, 47 bp); GG (110, 47 bp); TT (157 bp)[35]

For all polymorphisms studied, all statistical analyses were performed using the Statistical Package for Social Sciences Program (SPSS, version 15). Genotype-related odds ratios (ORs), their corresponding 95% confidence intervals (CIs), and associated p-values were estimated *via* unconditional logistic regression. The Chi-square ($\chi 2$) was used to compare the gender distribution, test the association between the genotypes and alleles in relation to the controls, and test for deviation of the genotype distribution from Hardy – Weinberg equation (HWE).

RESULTS

MDM2 SNP309 polymorphism was identified using the restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR) method. Table 1 shows the demographic characteristics of the study population. The distribution of sex, age, and ethnic origin of the study population was similar. *MDM2* SNP309 gene polymorphism was identified in 301 healthy individuals. The mean age of the study population was found to be 49,80±16,4 years (51,97±15,98 years in men and 47,58±16,82 years in women) (Table 1). Genotype distribution of the study population was consistent with the Hardy-Weinberg equilibrium (HWE) ($\chi 2$: 3.77, *P*: 0.455). The frequencies of TT, TG, and GG genotypes were 17.9%, 55.2% and 26.9%, respectively. When the frequencies of T and G alleles were investigated, T allele was found to be 0.43 and G allele was 0.57 ($\chi 2$:17.82, *P*: 0.001) (Table 2). Figure 1 shows the results of the analysis of rs2279744 polymorphism of *MDM2* gene localized in the region 12q13-14 of chromosome.

Table 1. Characteristics of the study population

	Healthy individuals
Sample size	301
Gender	
Males	142 (47,0)
Females	159 (53,0)
Age (year)	
Range	15-90
Means±SD	49,80±16,4
Males	51,97±15,98
Females	47,58±16,82

Table 2. Genotype frequencies for *MDM22* rs2279744 polymorphism

Genotype MDM2 rs2279744(309 T>G)	Sample size (n=301)	Percentage (%)	*p*-values	χ^2
Allele Frequence				
T allele	274	45.5	0,001	17,82
G allele	328	54.5		
Genotype Frequence				
TT	54	17,9		
TG	166	55,2	0.0521[a]	3,77
GG	81	26,9		
Dominant				
TT	54	17,9		
TG + GG	247	82,1		
Recessive				
TT + TG	220	73,1		
GG	81	26,9		
Overdominant				
TT + GG	135	44.8		
TG	166	55.2		

Hardy-Weinberg equilibrium;
Hardy Weinberg equilibrium (first degree of freedom $p>0.05$ if $\chi^2<3.84$)

DISCUSSION

Single nucleotide polymorphisms represent the most common type of genetic variations found in human genome. There may be thousands of polymorphic genes in human genome, and the susceptibility of the individuals with these genetic variations to cancer may be affected[12]. In the present study, we aimed to determine the frequency of *MDM2* gene rs2279744 polymorphism in a Turkish population consisting of healthy individuals. Genotype distributions and allele frequencies of this polymorphism in healthy individuals have been investigated. When rs2279744 (T309G) polymorphism was investigated in healthy individuals, 81 (26.9%) were found to have GG, 166 (55.1%) had TG, and 54 (17.9%) had TT genotype. According to the *MDM2* rs2279744 polymorphism, no statistically significant difference was found between the distribution of different genotypes (χ2:3.77, *p*: 0.455). In a previous study performed in the Turkish population, Tuna et al. (2013) reported GG genotype in 23.9%, TG in 56.3%, and TT in 19.7% of healthy individuals[13]. Similarly, in the study of Petenkaya et al. (2006), the genotype distribution among a healthy study population was found as 26.0% GG, 53.0% TG, and 21.0% TT[14] (Table 3). Comparison of the present study to these previous studies shows that the genotype distributions are highly similar. Based on these findings, it appears that there are a high number of individuals with TG genotype in the Turkish population. With a sample size of 301 individuals, the present study was larger from the previous studies in the Turkish population and this is a crucial aspect of epidemiological studies.

Table 3. Distribution of polymorphisms of *MDM2* rs2279744 genotype frequencies in different populations

Country	Year	Sample size	MDM2 (309 T>G) (%)			Ref
			TT	TG	GG	
Japan	2006	438	22,6	55,0	22,4	(21)
Korea	2008	299	20,4	50,8	28,8	(31)
China	2013	574	34,7	51,6	13,7	(23)
Finland	2005	185	31,0	53,0	16,0	(24)
America	2005	118	38,1	44,1	17,8	(32)
Italy	2006	92	43,0	43,0	13,0	(20)
Spain	2007	184	52,7	34,3	13,0	(26)
Austria and Poland	2007	98	40,8	52,0	7,0	(27)
Tunisia	2013	167	38,3	33,5	28,1	(30)
China	2005	1420	29,4	50,1	20,5	(18)
America	2010	454	38,5	43,8	17,6	(25)
China	2011	132	35,6	53,8	10,6	(33)
China	2012	226	22,1	52,2	25,7	(34)
Germany	2010	499	37,1	46,9	16,0	(28)
Germany and Romania	2012	350	40,3	47,1	12,6	(29)
Turkey	2006	103	28,1	55,4	16,5	(19)
Turkey	2010	110	42,7	43,6	13,6	(15)
Turkey	2006	149	21,0	53,0	26,0	(14)
Turkey	2013	75	20,0	49,3	30,7	(13)
Turkey	**2017**	**301**	**17,9**	**55,2**	**26,9**	**This study**

Recently, Akkız, H *et al.* identified a SNP (rs2279744) at position 309 of the promoter region of MDM2 gene which results in T→G nucleotide replacement in patients with hepatocellular carcinoma. The researchers reported a significant relation between G allele of the SNP309 that occurs in promoter of *MDM2* gene and the development of hepatocellular carcinoma[15]. Various studies from other countries reported an association between the aforementioned SNP in position 309 of *MDM2* gene and gastric carcinoma[7] non-small cell lung cancer[16], endometrial cancer[17], squamous-cell carcinoma of the esophagus[18] and bladder cancer[19]. *MDM2* rs2279744 polymorphism is a functional polymorphism that effects intracellular *p53* protein levels. Replacement of G allele by T allele increases the binding affinity of Sp1 transcription activator. Therefore, expression of the *MDM2* gene increases. Over-expression *of MDM2* prevents *p53* functions as well as aiding in the escape of damaged cells from cell cycle checkpoints and becoming carcinogenic[8,9]. The

allele frequencies in the present study were found to be 0.57 for G and 0.43 for T allele. When the allele frequencies were statistically evaluated, the allele frequency of individuals with G allele was found to be significantly increased (χ2:17.82, *P*:0.01) (Table 2). Another study from Turkey previous reported these frequencies as 0.48 for G allele and 0.52 for T allele, which were highly comparable to our findings[14]. Several studies performed in other countries demonstrated an elevated risk of cancer among individuals with G allele[20-22]. Thus, considering available data, *MDM2* rs2279744 polymorphism can increase the susceptibility to cancer in the Turkish population.

When the genotype distribution found in the present study was compared to the data for different ethnic origins as demonstrated in Table 3, GG genotype frequency appeared to be similar to Japanese population[21]. GG genotype frequency in this study was higher than that reported in China[23], Finland[24], America[24,25], Italy[20], Spain[26], Austria and Poland[27], Germany[28], Germany and Romania[29] and lower than in Tunisia[30] and Korea. Moreover, the maximum and minimum GG genotype frequencies recorded in different countries were 30.7% and 7.0%, respectively. GG genotype frequency, as found to be 26.9% in this study, was within this range.

In conclusion, the present study provided essential information on allele and genotype distribution of *MDM2* SNP309 polymorphism in a Turkish population. In addition to the data on *MDM2* gene polymorphism in a Turkish population, the findings of this study provide a framework for future studies that would investigate the role of MDM2 protein on susceptibility to various diseases, particularly cancer.

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