Is there a relation between *Murine double minute 2* T309G polymorphism and lung cancer risk in the Turkish population? Türk populasyonunda *Murine double minute 2* polimorfizmi ve akciğer kanseri riski arasında bir ilişki var mı?

Abstract

Introduction: Association between *Murine double minute 2* T309G polymorphism and lung cancer risk has been investigated in several populations, but results of these studies are inconsistent. We aimed to investigate the effect of *Murine double minute 2* T309G polymorphism on development of lung cancer in a Turkish population.

Methods: Total 200 subjects including 100 patients and 100 controls were analyzed and used polymerase chain reaction and restriction fragment length polymorphism methods for genotyping analysis of the polymorphism.

Results: We found that smokers compared with non-smokers have approximately eight fold higher lung cancer risk \[p = 0.0001, \text{OR} = 8.27 (4.02–16.9)\]. Frequency of GG genotype was higher in patients than in controls, but this ratio was not significant \[\chi^2 = 3.5, p = 0.17\]. Genotype distribution of the polymorphism was not different neither patients with non-small cell lung cancer nor patients with small cell lung cancer \[\chi^2 = 2.89, p = 0.57\]. We analyzed together with demographic feature (except smoking habit), clinicopathological findings and genotype frequencies of this polymorphism, and any association with lung cancer risk was not obtained.

Conclusion: No correlation between *Murine double minute 2* T309G polymorphism and lung cancer risk was detected in this Turkish population.

Keywords: Lung cancer; *Murine double minute 2* (MDM2) gene; Polymorphism.

Özet

Giriş: Çeşitli popülasyonlarda akciğer kanseri riski ile *Murine double minute 2* T309G polimorfizminin birlikteliği incelenmiş, fakat bu çalışmaların sonuçları arasında tutarsızlık olduğu görülmüştür. Bu çalışmada, bir Türk populasyonunda akciğer kanserinin gelişimi üzerine *Murine double minute 2* polimorfizminin etkisini araştırmayı amaçlanmıştır.

Yöntemler: Bu çalışmada, 100 hasta 100 kontrolden oluşan toplam 200 örnek incelenmiş ve bu polimorfizmin genotip analizi için polimeraz zinkir reaksiyonu ve restrikşiyon fragment uzunluk polimorfizmi yöntemleri kullanılmıştır.

Bulgular: Çalışmada sigara içmeyenlerle karşılaştırıldığında sigara içenlerin yaklaşıklık olarak sekiz kat daha fazla akciğer kanseri gelişme riskine sahip.oldukları bulunmuştur \[p = 0.0001, \text{OR} = 8.27 (4.02–16.9)\]. GG genotipi kontrollere oranla hastalar arasında daha yüksek oranda bulunmuştur fakat bu oran anlamlı değildir \[\chi^2 = 3.5, p = 0.17\]. Bu polimorfizmin genotip dağılımı ne küçük hücreli akciğer kanseri olan hastalarda ne de küçük hücreli olmayan akciğer kanseri olan hastalarda farklılık göstermediği bulunmuştur \[\chi^2 = 2.89, p = 0.57\]. Polimorfizmin genotip siklikları, klinikopatolojik bulgular ve...
demografik özellikler (sigara alışkanlığı hariç) birlikte değerlendirilmiş ve bu bulgular arasında akciğer kanseri riski ile herhangi bir ilişki elde edilemiştir.

**Sonuç:** Bu Türk populasyonunda akciğer kanseri riski ve *Murine double minute* 2 T309G polimorfizmi arasında bir korelasyon belirlenememiştir.

**Anahtar kelimeler:** Akciğer kanseri; *Murine double minute* 2 geni; polimorfizm.

**Introduction**

Lung cancer (LC) is the most common and lethal cancer worldwide. LC account for approximately 13% of all new cancer cases and about 19.4% of all cancer related death in America and worldwide [1]. According to data obtained from Turkey’s Lung Cancer Map Project, the number of annual expected new cases in Turkey is about 30,000 [2].

The molecular mechanism of lung tumorigenesis has not been clearly understood, yet. However, it has been known that, multiple signal pathways and key regulator genes in the pathways such as p53 and *Murine double minute* 2 (*MDM2*) play role in development of LC and often interconnected with cross-talk between pathways involved in carcinogenesis. The detailed examination of these pathways and regulators in LC pathogenesis will provide opportunities for detecting of target molecules and developing of new treatment strategies [3].

p53 is a tumor suppressor gene localized on short arm of chromosome 17. During DNA damage response, p53 is a key protein for preventing of cell proliferation via some mechanisms including apoptosis and cell cycle arrest. However, excessively expression of p53 in absence of stress causes to destroy of normal cells. Therefore, several genes play role for attenuation of the negative mechanism of p53, as a means to maintain homeostasis. *MDM2* is principal regulator of p53 and an oncogene located on the long arm of chromosome 12. Both proteins are intricately dependent on each other for normal cell proliferation and growth [4]. Overexpression of MDM2 inhibits the function of p53. Thus, it enables damaged cells to escape the cell cycle checkpoint and become carcinogenic in a variety of human cancers. Recently, two SNPs altering the MDM2 expression in *MDM2* promoter region have been identified. One of them is *MDM2* (rs2279744). The SNP at nucleotide 309 characterized as a change of thymine (T) to guanine (G). T-to-G SNP in the promoter region of *MDM2* (rs2279744) leads to increased MDM2 expression by binding of the transcriptional activator to promoter of *MDM2*. [5, 6]. This polymorphism has been associated with several cancers such as gastric, bladder, breast and lung cancer [5–8]. The majority of previous studies explaining the association between LC risk and the rs2279744 polymorphism have shown discrepant results. Until now, there is not any study regarding to LC risk and *MDM2* T309G polymorphism in Turkish population from Central Anatolia.

In brief, effect of this polymorphism on LC risk for Turkish population is unknown. Therefore, in this study, we aimed to investigate whether there is a relationship between the rs2279744 polymorphism and LC in a Turkish population.

**Materials and methods**

**Study group**

For this study, as patient group, 100 individuals with LC who have been admitted by Department of Medical Oncology, Cumhuriyet University in Central Anatolia (Sivas) and as control group, 100 healthy, voluntary individuals who were matched in age, gender with patients, were analysed. The definitive diagnosis of patients with LC was performed in the medical oncology clinic in the year of 2012 and 2013. In addition, histological classifications and clinicopathological staging of cancer were performed according to criteria of the Union for International Cancer Control (UICC) Tumor-Node-Metastasis classification of malignant tumors (TNM), seventh edition, 2010 (for lung cancer ICD-O C18-C20). Ethics Committee of Cumhuriyet University in Sivas confirmed this study (The Decision Number: 2014-04/37). All individuals were informed about the study. They agreed to participate via signing a written informed consent form. Both groups filled the form consisted of questions about smoking habits, alcohol consumption, familial history of cancer.

**Samples collection and genotype analysis**

Four milliliter of whole blood samples from both patients and controls were collected in EDTA containing tube. DNA extraction was performed using “salting out procedure” [9].

For detection of *MDM2* T309G polymorphism, methods including polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were used. This polymorphic side in *MDM2* gene was amplified on a thermal cycler (Applied Biosystems Gene AmpR PCR system 9700, USA) by using a forward primer (5’-CGG AGGTGCA 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 MgCl₂, 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 MspAI 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 MspAII 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.

Statistical analysis

Statistical Package for Social Sciences Program-version 15.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Frequencies of demographic features and allele-genotype for this polymorphism between both groups were calculated by using χ² test. Independent t-test was used to evaluate of mean age in groups. In addition, a χ² test was used to detect whether there is a deviation from Hardy-Weinberg equilibrium for the genotype distribution crude odds ratios (ORs) and 95% confidence interval (CI) were also calculated using Fisher’s exact test (two-sided). The demographic features of both groups including smoking habit, familial history of cancer, were compared to distribution of genotypes/alleles using binary logistic regression analysis and obtained adjusted OR values. p Values of <0.0001 were considered statistically significant.

Results

Demographic features of the study group were shown on Table 1. Frequencies of characteristics including mean age, gender, alcohol consumption, familial history of cancer were not different in patient and control groups. We observed that subjects with smoking habit as an independent risk factor for LC had 8.27 fold higher risk of cancer than non-smokers (p = 0.0001) in this population (Table 1). Besides, the frequencies of smokers were significantly higher in the patients compared to the controls. In addition, smoking habit was more frequently in patients with squamous carcinoma than patients with adenocarcinoma (χ² = 6.19, p > 0.04), when smoker ratio was evaluated according to LC subtypes. Other than this, there was no difference between frequencies of characteristics and histological types of LC consisting of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), yet.

In this study, genotype frequencies of both groups were not deviate from Hardy-Weinberg equilibrium. In addition, there was no difference between both groups for genotype distributions (χ² = 3.50, p > 0.17) (Table 2).

| Table 1: Demographic features of subjects. |
|-------------------------------------------|
| **Patients n (%)** | **Control n (%)** | **p Value** | **OR (95% CI)** |
| Age ± SD (year range) | 60.43 ± 9.19 | 59.77 ± 9.85 | 0.20 | 1.49 (0.85–2.60) |
| Mean agea | (35–80) | (39–85) | 0.91 | 1.91 (0.90–4.02) |
| Gender | 46/54 (46/54) | 56/44 (56/44) | 0.20 | 1.49 (0.85–2.60) |
| Smoking habit | 91/9 (91/9) | 91/9 (91/9) | 0.81 | 1.19 (0.63–2.24) |
| Alcohol consumption | 12/88 (12/88) | 47/53 (47/53) | 0.0001b | 8.27 (4.02–16.9) |
| Familial history | 15/85 (15/85) | 10/90 (10/90) | 0.39 | 1.58 (0.67–3.72) |
| Tobacco smoking | 22/78 (22/78) | 17/83 (17/83) | 0.47 | 1.37 (0.68–2.78) |

*pMean age was evaluated older and younger than 60 years. **p<0.001, statistically significant; OR, odds ratio; CI, confidence interval; SD, standard derivation. Significant values were shown as bold values.
Besides, genotype distributions of the rs2279744 polymorphism did not differ among individuals with SCLC-NSCLC and adenocarcinoma-squamous carcinoma-others (χ² = 0.09, p > 0.95; χ² = 2.89, p > 0.57, respectively) (Table 2).

When demographic features, clinicopathological findings and genotype frequencies of this polymorphism together were evaluated, we did not find any association with risk of LC except smoking habit (Table 3).

### Discussion

In this study, we did not observe any positive or negative effects of MDM2 T309G polymorphism on LC risk for our population. As consistent with our study, the similar result for LC risk has been found in Han Chinese of southeast China [10], African-Americans and Caucasians [11]. On the contrary, significant association between this polymorphism and LC risk was detected in Han Chinese of north China [12], Korean [13], Norwegian [14], and non-Hispanic white populations [15]. It is considerable that there was were discrepancies into among themselves of the studies. Namely, G allele was related to significantly increased risk for LC in three studies [12–14], even though the allele has a significantly decreased risk for LC in another study [15]. It has been suggested that reason of the discrepancy might be ethnic group differences.

However, different results from each other have been found in two meta-analyses investigated same Asian, European and African populations [16, 17]. In subgroup analysis based on ethnicity, the results under three models including dominant, recessive and co-dominant models have been shown that G allele of MDM2 SNP309 has been evaluated as a low-penetrant risk factor for developing of LC in Asians in spite of this result was found neither in Europeans nor in Africans [16]. In another meta-analysis, results under the recessive model as the most suitable genetic model have been investigated and, statistically significant risk has not been defined in both Asians and Europeans [16]. It has been reported that the principal
difference among these two studies was the genetic model selection [18]. The other difference was that smoking status and histological type of LC has been analysed in subgroup analysis in addition to ethnicities. Bai et al. obtained a stronger relationship between a higher risk of LC (particularly for NSCLC) and GG genotype in never smokers [17]. The high risk for NSCLC in never smoker has also been found by Liu et al. [19]. On the contrary, the increased risk for NSCLC inclusive adenocarcinoma-AC and/or squamous cell carcinoma-SCC has been found in ever smokers in several studies [11, 14, 15, 19, 20]. In our study, we found no significant association between this polymorphism and LC or subtypes of LC, when the each of the three genetic models and similar subgroup analysis were used.

After these inconsistent results, we think that effects of the other risk factors on LC development such as age and gender should be also evaluated. We did not obtain any correlation among GG genotype and the two factors (age and gender) for LC risk in present study. As consistent with findings of our study, some researchers did not find any association among the rs2279744 polymorphism and age [12, 16, 21] and gender [10, 19, 22] for LC risk. In contrast to this data, it has been reported that age [12–14] or gender [18, 23] together with the MDM2 polymorphism may an effect on the LC risk. However, there were also remarkable discrepancies among these studies. At LC diagnosis, although, risk factor accompanied with GG genotype, was older age in a study [18], but was younger age in another study [13, 14, 17]. Conversely, younger age in smoker man compared to women has been shown protective effect for LC risk in non-Hispanic Whites [15]. On the other hand, in two meta-analyses, women with GG genotype for MDM2 SNP309 had increased LC susceptibility [18, 21]. The reason of this discrepancy may be estrogen-signaling pathway that Bond et al. shown that there was a gender-specific association with MDM2 SNP309 GG genotype and an active estrogen-signalling pathway, either directly or indirectly, allows for the G-allele of SNP309 to accelerate tumor formation in women [24]. Furthermore, increased LC risk has been detected in never-smoker Chinese females and in non-Hispanic White males for MDM2 SNP309. The risk factor in these studies was TT genotype instead of GG genotype [15, 21]. In addition, Chien et al. [22] and Dong

| Features                          | Genotype n (%)       |
|----------------------------------|----------------------|
|                                  | TT       | TG       | GG       |
| Mean age (year)                  | 10/13    | 23/25    | 13/16    |
| <60/>60 (n=46/54)                | (21.7/24.1)| (50.0/46.3)| (28.3/29.6)| (78.3/75.9|
| p Value                          | –        | 0.80     | 1        |
| OR (95% CI)                      | Reference | 1.19 (0.44–3.25)| 1.05 (0.35–3.18)| 0.83 (0.31–2.18) |
| Male/Female (n=81/9)             | 20/3     | 45/3     | 26/3     |
| p Value                          | –        | 0.38     | 1        |
| OR (95% CI)                      | Reference | 2.25 (0.41–12.13)| 1.30 (0.23–7.13)| 0.28 (0.07–1.18) |
| Smoking habit (n=12/88)          | 5/18     | 6/42     | 1/28     |
| Non-smoker/Smoker                | (41.7/20.5)| (50.0/47.7)| (8.3/31.8) | (58.3/79.5) |
| p Value                          | 0.31     | 0.07     |
| OR (95% CI)                      | Reference | 0.51 (0.13–1.90)| 0.12 (0.01–1.19) |
| Recurrence of cancer             | 1/22     | 3/65     | 4/25     |
| Present/Absent (n=8/92)          | (12.5/23.9)| (37.5/48.9)| (50/27.2)| (87.5/76.1) |
| p Value                          | –        | 1        | 0.36     |
| OR (95% CI)                      | Reference | 0.68 (0.06–6.93)| 0.28 (0.02–2.73) | 2.20 (0.25–18.87) |
| Metastases                       | 16/7     | 28/20    | 20/9     |
| Present/Absent (n=64/36)         | (25/19.4)| (43.8/55.6)| (31.2/25) | (75/80.6) |
| p Value                          | –        | 0.43     | 1        |
| OR (95% CI)                      | Reference | 1.63 (0.56–4.70)| 1.02 (0.31–3.36)| 0.72 (0.26–1.97) |
| Pathological stage               | 5/18     | 9/39     | 7/22     |
| T1-T2/T3-T4 (n=21/79)            | (23.8/22.8)| (42.9/49.4)| (33.3/27.8)| (76.2/77.2) |
| p Value                          | –        | 0.75     | 1        |
| OR (95% CI)                      | Reference | 0.83 (0.24–2.83)| 1.14 (0.31–4.22)| 1.05 (0.34–3.29) |

p < 0.001 confirmed as significant.
et al. [25] found an association between TT genotype and increased death risk in NSCLC survival. According to the experimental study; the higher risk of cancer is predicted from G allele compared to T allele. It has been declared by Liu et al. [19] that the data about function of the G allele may be achieved with experimental researches; however epidemiologic studies may resolve more complicated interactions among all variants in MDM2 gene or other candidate genes regarding to carcinogenesis. Therefore, it might not be possible to make a clear inference in human from the in vivo allele function based on experimental data, was suggested by Li and colleagues [15]. As different from these findings, when effect of SNP309 TT genotype on LC risk was analysed, any association was not found in our study (the data not shown).

All conflict results show us that different genetic background of cases and various risk factors may effect to the relationship between MDM2 T309G polymorphism and LC risk in different populations. Besides, same factors consisting of limited sample size, non-random sampling and the pitfalls arising from unknown confounders also need to be considered.

Conclusion

We did not find any association between MDM2 polymorphism and LC risk in our Turkish population. In addition, we did not detect that any effect of the polymorphism on clinicohistopathological parameters of LC. We suggested that MDM2 T309G polymorphism may not be a suitable indicator of LC for the Turkish population from Central Anatolia. It is first study performed with Turkish population despite some limitation factors. In addition, it is a considerable study due to it will be a baseline study for other Turkish population studies. Besides, our results will offer an opportunity to compare to results of other studies which will be made in future.

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