Original Article

Association of Matrix Metalloprotease 1 and 9 Promoter Polymorphisms with Obstructive Sleep Apnea: A Case-Control Study from Turkey

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Received: 05-Nov-2024;
Revision: 23-Sep-2025;
Accepted: 04-Nov-2025;
Published: 29-Dec-2025

ABSTRACT

Background: Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, and genetic factors play a role in its development. Matrix metalloproteinases (MMPs) degrade the extracellular matrix, but the role of *MMP-1* and *MMP-9* promoter polymorphisms in the development of OSA is not yet clear. **Aim:** To investigate the relationship between *MMP1* (rs1799750) -1607 1G/2G and *MMP9* (rs3918242) -1562 C/T changes in OSA. **Methods and Materials:** This study includes 85 OSA patients and 97 healthy controls. Genotyping for *MMP-1* (−1607) G/2G and *MMP-9* (−1562) C/T was performed using Polymerase Chain Reaction Restriction Fragment Length Polymorphism (PCR-RFLP). Statistical significance was defined as *P* values less than 0.05. **Results:** This study examined 85 OSA patients and 97 healthy controls. No significant difference was found between OSA patients (47 males, 38 females, mean age: 43.85 ± 10.09) and the control group (51 males and 46 females, mean age: 43.57 ± 9.61) in terms of age and gender ($P = 0.847$ and $P = 0.767$). However, body mass index (BMI) was significantly higher in OSA patients ($P < 0.001$). A statistically significant difference was detected in association with the *MMP1-1607* G/2G and 2G/2G genotypes and OSA compared to the G/G genotype ($P = 0.013$). *MMP9*-1562 C/T polymorphism showed no significant association with OSA, either at the genotypic level or when the C/T and T/T genotypes were combined ($P > 0.05$) when evaluated individually. **Conclusion:** The *MMP-1*-1607 2G/G and 2G/2G genotypes are significant risk factors for OSA, while the *MMP-9* − 1562 C/T polymorphism is not.

KEYWORDS: *Matrix metalloproteinase, MMP-1, MMP-9, obstructive sleep apnea, promoter, RFLP*

INTRODUCTION

Obstructive sleep apnea (OSA) is an increasingly prevalent sleep-related respiratory disorder. It is commonly considered to be an independent risk factor for a variety of clinical outcomes that involve cardiovascular disease, OSA, stroke, systemic hypertension, and abnormal glucose metabolism.[1] OSA is usually identified with obstruction and the periodic constriction of the pharyngeal airway during sleep.[2] Untreated sleep apnea can lead to severe health and economic problems.[3] It has become clear in recent years that other factors besides pharyngeal anatomy and craniofacial structure play a role in the pathophysiology of OSA. The non-anatomical causes include a low respiratory stimulation threshold, the unbalanced control of respiration, and impaired pharyngeal dilator muscle function.[4] In OSA, airway obstruction occurs only during sleep; thus, anatomical and non-anatomical factors contribute to the development of this common syndrome.[5] During respiration, more than 20 muscles in the upper respiratory tract play an essential role in respiratory stability.[6] Decreased muscle activity during

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Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_761_24

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How to cite this article: Kocak M, Avcikurt AS, Sarioglu N, Erel F, Angin M, Altinisik J. Association of matrix metalloprotease 1 and 9 promoter polymorphisms with obstructive sleep apnea: A case-control study from Turkey. Niger J Clin Pract 2025;28:1364-9.

sleep may cause respiratory obstruction.[7] Therefore, understanding the nerve control and mechanical consequences of the airway muscles is essential for identifying the possible causes of OSA and developing preventive measures.[8]

Matrix metalloproteinases (MMPs) are zinc-bound proteins that degrade the extracellular matrix components and many non-matrix proteins.[9] MMPs support embryonic development, differentiation, migration, and cell proliferation. In addition, they are essential for angiogenesis, tissue repair, cell apoptosis, and immune response.[10] *MMP-1*, or interstitial collagenase, is a subfamily of MMPs that cleave stromal collagens. *MMP-1* specifically degrades the significant component of the extracellular matrix (ECM), type I collagen, and types II, III, V, and IX collagens. These types of collagens are the most abundant ones in the body. Therefore, *MMP-1* is an essential collagenase for modeling the ECM.[11] The *MMP-1* gene is expressed in a wide variety of cells, including macrophages, epithelial and endothelial cells, stromal fibroblasts, and some tumor cells, and is localized on the *11q22* chromosome.[12]

The addition or deletion of guanine plays a role in the effect of the expression level of the gene on the *rs1799750* polymorphism, known as G/2G at the *MMP-1* promoter region −1607. The insertion of guanine at the promoter region −1607 forms a binding region (5′-GGA-3) for a member of the ETS (E26) transcription factor family. It has been reported that the 2G allele binds more significant amounts of ETS-1 transcription factor, resulting in higher transcriptional activity than the 1G allele in melanoma and normal fibroblast cells. The 2G allele increases the expression of *MMP-1*, resulting in an intense degradation of ECM.[13-20]

MMP-9, also described as gelatinase-B, is a type IV collagenase that plays a vital role in many biological processes. Several cytokines, such as TNF-α, IL-6, and hypoxia, are reported to stimulate the production of *MMP-9*. This protease's gene coding is located on chromosome 20q11.2-q13.1.[10,21] The polymorphism known as C/T at the *MMP-9* promoter region position −1562 occurs when the T nucleotide replaces the C nucleotide. The *MMP-9* promoter region C/T polymorphism at position −1562 creates a binding site for a transcriptional suppressor protein. The C/T polymorphism in the *MMP-9* promoter region is essential for transcriptional activity. Regarding the *MMP-9* −1562 C/T polymorphism, the C allele is identified with the Sp1 nuclear protein. In contrast, the T allele is identified with the lack of the Sp1 nuclear protein region, and this causes the increased transcription activity of the T allele.[21,22]

In recent years, many studies have examined the mechanisms behind the pathophysiology of sleep apnea syndrome. However, the causes are not yet fully understood. In addition, many studies have found high expression levels of MMPs in patients' blood samples. This study aims to determine the relationship between OSA and the *MMP-1* −1607 1G/2G and *MMP-9* −1562 C/T changes affecting the gene expression levels.

Methods and Materials

Patient and control groups

Ethical consideration

Approval for the study was obtained from the Balikesir University Faculty of Medicine Regional Ethics Committee (approval number: 2018/187: 21.11.2018). A total of 85 patients who presented to the Sleep Medicine Laboratory of the Chest Diseases Department of Balıkesir University Faculty of Medicine between November 2018 and March 2019 were included in the study. The study was conducted by the principles of the Declaration of Helsinki, and informed consent was obtained from all participants. Individuals with an OSA diagnosis confirmed by polysomnography (PSG) with an AHI ≥5, aged ≥18 years, diagnosed by a pulmonologist, and who provided written informed consent were included in the study. The control group consisted of individuals not taking regular medications, without chronic diseases, and without known neurological, autoimmune, or malignant diseases. Power analysis was performed using G Power version 3.1.9.7.[23] Based on previous studies evaluating associations between MMP gene polymorphisms and sleep-related disorders, a moderate effect size (Cohen's w = 0.3) was assumed for Chi-square tests of independence. Using this estimate, with a significance level of $\alpha = 0.05$ and statistical power $(1-\beta) = 0.80$, a minimum of 143 participants (72 OSA patients and 71 controls) was required to detect significant differences in genotype distributions between the two groups in a 2×3 contingency table design. Genomic DNA was isolated from all patients and controls before the study started.

Genomic DNA isolation

A 250-prep PureLink DNA Mini Kit (Invitrogen) was used to isolate the genomic DNA from the blood. DNA isolation was performed step-by-step following the manufacturer's instructions.

Polymerase chain reaction

PCR was used to amplify the *MMP-1*-1607 G/2G promoter region›s polymorphic region and the *MMP-9*-1562 C/T genes. DNA from OSA patients and

the individuals in the control group was used, and a 50 µl solution was prepared for each sample.

The PCR solutions included 100 ng DNA, 0.5 mM from each primer, 0.2 mM dNTP mix, 1X KCl buffer, 1.25 U Taq DNA polymerase, 2.75 mM for *MMP-1*, and 2 mM MgCl for *MMP-9*. Techne TC-3000x Thermal Cycler (Bibby Scientific Ltd., UK) and Applied Biosystems Veriti® 96-Well Thermal Cycler (Thermo Fisher Scientific, Applied Biosystems, Grand Island, NY).

The PCR program was set to 35 cycles. The annealing temperatures of the *MMP-1* and *MMP-9* primers were 56°C and 52°C, respectively. As a result of the PCR, the *MMP-1* PCR product was amplified using primers to be 216 base pairs (bp), and the *MMP-9* PCR was 451 bp.

Agarose gel electrophoresis was used to examine the amplification results by PCR. The PCR products were visualized by being run on a 1.5% agarose gel.

The restriction enzymes used for *MMP-1*-1607 and *MMP-9-1562* were AlwI and PaeI (Thermo Fisher Scientific, Waltham, MA, USA), respectively. They were restricted by the enzyme protocol. The cut products were imaged on a 3.5% agarose gel. Table 1 shows the forward and reverse primers for analyzing the identified by PCR–RFLP.

The PCR product of the *MMP-1*-1607 G/2G polymorphic region was cut with the AlwI (BspPI) enzyme, and the genotypes were determined. In the agarose gel image of the PCR-RFLP products, the following determinations were made: a GG genotype individual only when the 216 bp band was seen; a G2G genotype individual when the 216, 196, and 20 bp bands were seen; and a 2G2G genotype individual when the 196 and 20 bp bands were seen. Figure 1 shows the PCR-RFLP products in a 3.5% agarose gel with a 100 bp marker.

The PCR product of the *MMP-9*-1562 C/T polymorphic region was cut with the PaeI (SphI) enzyme, and the genotypes were determined. In the agarose gel image of the PCR-RFLP products, the following evaluations were made: a CC genotype with only the 451 bp band was seen; a CT genotype, the 451, 236, and 211 bp bands were seen; and a TT genotype, the 236 and 211 bp bands were seen. The image of the PCR-RFLP products in a 3.5% agarose gel (100 bp marker) [Figure 2].

Statistical analysis

IBM SPSS Statistics for Windows, Version 20.0, software was used for the statistical analysis. The *MMP-1* and *MMP-9* genotype distributions were evaluated via the Hardy–Weinberg equation. The normally distributed variables were analyzed with descriptive statistics. The mean and standard deviation were calculated. The independent samples *t*-test was used to compare the quantitative data, for example, the mean, standard deviation, median, minimum, and maximum values. Pearson's Chi-squared test was used to compare the qualitative data. A binary logistic regression model was used for the association between genotypes, and the odds ratio (OR) and 95% confidence intervals were reported. Statistical significance was defined as *P* values less than 0.05.

Results

This study examined 85 OSA patients (47 males, 38 females) and 97 healthy controls (51 males and 46 females). Participants in the OSA group had a mean age of 43.85 ± 10.09 years and a BMI of 31.69 ± 5.42 kg/m², while those in the control group had a mean age of 43.57 ± 9.61 years and a BMI of 24.86 ± 3.55 kg/m² [Table 2]. There was no significant difference between the mean age of the patient and control groups regarding age and gender ($P = 0.847$, $P = 0.714$) [Table 2]. The BMI was significantly higher in the patient group ($P = 0.001$)

MMP-1 − 1607 genotype distribution in the obstructive sleep apnea group

Genotype and allele frequencies of the *MMP1* gene were compared between patients with OSA and healthy controls. Binary logistic regression was applied using the G/G genotype as the reference group. The G/2G genotype was not significantly associated with OSA (OR = 1.21; 95% CI: 0.55–2.67; $P = 0.62$), and no significant association was observed for the 2G/2G genotype either (OR = 0.51; 95% CI: 0.23–1.17; $P = 0.12$). However, the dominant genetic model (G/2G + 2G/2G vs G/G) showed a significant association with OSA (OR = 1.19; 95% CI: 1.19–4.15; $P = 0.013$).

At the allelic level, comparison of the 2G allele against the G allele (reference) revealed no association with

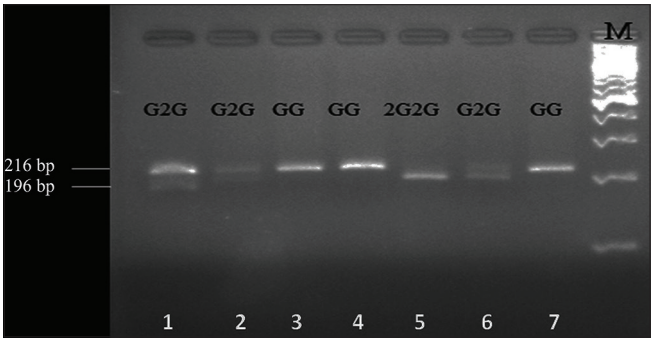

Figure 1: Image of the *MMP-1*-1607 G/2G polymorphic region. The 3rd, 4th, and 7th specimens in the gel have the GG genotype, the 1st, 2nd, and 6th specimens have the G2G genotype, and the 5th specimen has the *2G2G* genotype

Table 1: Primers used in the PCR study

Primers		Primer Sequence (5'->-3')	Base length	Tm
MMP1-1607	Forward	CTATTTTCTTTGTCTGTGCTGGAGTC	26	56°C
	Reverse	TCTTGGATTGATTTGAGATAAGTCAGATC	29	56°C
MMP9-1562	Forward	ATTATCTCCATCTCACAGTCTC	22	52°C
	Reverse	ATATTCACCTTCTTCAAAGCCC	22	52°C

MMP: Matrix metalloproteinase, Tm: Melting temperature

Table 2: Demographic characteristics of the study participants

Demographics	OSA (*n*=85)	Control (*n*=97)	*P*
Age (years)			
Mean±SD	43.85±10.09	43.57±9.61	0.847*
Gender, *n* (%)			
Male	47 (55.3)	51 (52.6)	0.714†
Female	38 (44.7)	46 (47.4)	
BMI (kg/m²)			
Mean±SD	31.69±5.42	24.86±3.55	0.001*

OSA: Obstructive sleep apnea, Min: Minimum, Max: Maximum, SD: Standard deviation, BMI: Body mass index. *Student T Test was used. †Pearson's Chi-Square Test was used

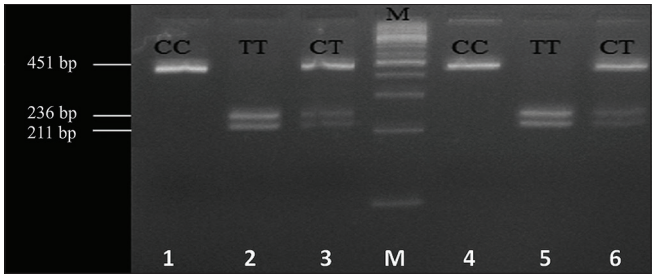

Figure 2: Image of the *MMP-9*-1562 C/T polymorphic region. The 1st and 4th specimens in the gel have the CC genotype, the 3rd and 6th specimens have the CT genotype, and the 2nd and 5th specimens have the TT genotype

OSA (OR = 0.66; 95% CI: 0.43–1.00; *P* = 0.054) [Table 3].

The G/G variant was seen in 43.5% of the patient group and 25.8% of the control group. The G/2G variant was observed in 37.6% of the OSA group and 52.6% of the control group. The 2G/2G variant was observed in 18.8% of the OSA group and 21.6% of the control group at 18.8% and 21.6%, respectively [Table 3].

MMP-9 − 1562 genotype distribution in the obstructive sleep apnea group

Genotype and allele distributions of the *MMP9*-1562 C/T were analyzed in patients with OSA and healthy controls. Using the C/C genotype as the reference group, no statistically significant associations were observed for the C/T (OR = 0.40; 95% CI: 0.07–2.39; *P* = 0.31) or T/T genotypes (OR = 0.63; 95% CI: 0.11–3.54; *P* = 0.60). Additionally, the dominant model comparison (C/T + T/T vs C/C) did not reveal a significant difference (OR = 1.42; 95% CI: 0.74–2.74; *P* = 0.30).

At the allelic level, the comparison of the T allele versus the C allele (reference) also did not yield statistically significant results (OR = 1.22; 95% CI: 0.69–2.17; *P* = 0.55). [Table 4].

In the OSA group's *MMP-9* −1562 genotype distribution, the C/C variant was seen in 69.4% of patients and 76.3% of the control group. The CT variant was observed in 28.2% of the OSA group and 19.6% of the control group. The T/T variant was observed in 2.4% and 4.1% in the OSA and control groups, respectively [Table 4].

Discussion

This study determined the relationship between *MMP-1* and *MMP-9* gene promoter polymorphisms and OSA risk. It was observed that individuals with the G/G genotype at *MMP-1*-1607 had a lower risk of OSA compared to those carrying at least one 2G allele (G/2G +2G/2G); in other words, the risk of OSA increased in individuals carrying the 2G allele. It was demonstrated that the likelihood of developing OSA in individuals with the G/2G or 2G/2G genotype was approximately 1.19 times higher than in those with the G/G genotype.

MMPs are expressed at basic levels under physiological conditions. However, they are expressed differently as a reaction to the growth factors, hormones, and inflammatory cytokines by activating the JNK-, MAPK-, and NF-κB-dependent signaling pathways.[24-26]

Although transcriptional and post-transcriptional mechanisms regulate the gene expression level of the metalloproteinases, the transcriptional mechanisms have the most significant effect. Most MMPs include similar series in the promoter regions that form the binding sites for the transcription factors that will be mentioned. These are the activator protein (AP-1)-1 and AP-2 regions, the polyomavirus enhancer-A (PEA) binding protein-3 region, the SP-1 site, the NF-κB region, and the STAT region.[27,28]

The polymorphism (rs1799750), known as G/2G at the −1607 position of the *MMP-1* promoter region, affects the expression level of the gene depending on the addition or deletion of the guanine (G) nucleotide. The insertion of G at the promoter region −1607 position forms a binding site for E26, a member of the ETS

Table 3: MMP1-1607 genotype distributions in the study participants

Genotype *n* (%)	OSA (*n*=85, Allele=170)	Control (*n*=97, Allele=194)	OR	%95 CI	*P*
G/G	37 (43.5)	25 (25.8)	1 (Ref)		
G/2G	32 (37.7)	51 (52.6)	1.21	0.55-2.67	0.62
2G/2G	16 (18.8)	21 (21.6)	0.51	0.23-1.17	0.12
G/2G+2G/2G	48 (56.5)	72 (74.2)	1.19	1.19 – 4.15	0.013*[a]
G Allele	106 (62.4)	101 (52.0)	1 (Ref)		
2G Allele	64 (37.6)	93 (48.0)	0.66	0.43-1.0	0.054

OSA: Obstructive sleep apnea, MMP: Matrix metalloproteinase. *CI, confidence interval; *Odds ratio, 95% confidence intervals (95% CI). [a]Statistically significant at $P \leq .05$

Table 4: MMP9-1562 genotype distributions in the study participants

Genotype *n* (%)	OSA (*n*=85, Allele=170)	Control (*n*=97, Allele=194)	OR	95% CI	*P*
C/C	59 (69.4)	74 (76.3)	1 (Ref)		
C/T	24 (28.2)	19 (19.6)	0.40	0.07-2.39	0.31
T/T	2 (2.4)	4 (4.1)	0.63	0.11-3.54	0.60
C/T + T/T	26 (30.6)	23 (23.7)	1.42	0.74-2.74	0.30
C Allele	142 (83.5)	167 (86.1)	1 (Ref)		
T Allele	28 (16.5)	27 (13.9)	1.22	0.69 – 2.17	0.55

OSA: Obstructive sleep apnea, MMP: Matrix metalloproteinase. *CI, confidence interval; *Odds ratio, 95% confidence intervals (95% CI)

transcription factor family, and the 2G allele has higher expression than the G allele.[29,30]

A study on the relationship between persistent airway obstruction and *MMP-1*-1607 polymorphism in asthma by Huang *et al*.[31] found that the genotypes containing the G allele (1G2G and GG) were identified with continuous airway obstruction. In addition, the heterozygous 1G/2G genotype was more common in asthma patients with persistent airway obstruction. Liu *et al*.[32] examined the relationship between the *MMP-1*-1607 G/2G polymorphism and the development and progression of lung cancer. The study found that the 2G/2G genotype was significantly associated with the disease progression and development.

The polymorphisms are nucleotide substitutions causing relatively conservative amino acid changes in the proteins. -1562 C>T SNP is in the promoter region of the *MMP-9* gene and does not give rise to an amino acid substitution. It was reported that the T allele, instead of the C allele, formed a 1.5-fold more active promoter. As a result, this sequence variation might cause an increase in *MMP-9* protein levels, which is expected to influence tissue degradation.[33] In one study, the T allele was associated with high levels of *MMP-9* in OSA patients,[33] whereas Demacq *et al*.[34] suggested that levels of *MMP-9* were not affected by this SNP. Cao *et al*.[35] suggested that this SNP was associated with increased risk but not the severity of OSA and increased *MMP-9* expression. Yalcınkaya *et al*.[36] reported no association between this SNP and the disease. Elevated serum levels and higher activity of *MMP-9* in moderate and severe OSA patients were reported by Tazaki *et al*.[37] Similarly, in obese patients with OSA, serum *MMP-9* levels were found to be increased.[37,38] The systematic review and meta-analysis by Fang *et al*.,[39] demonstrated that *MMP9* levels are elevated in individuals with OSA and that this elevation is associated with disease severity. However, current pooled data do not provide sufficient evidence to confirm an association between the MMP9-1562 C>T polymorphism and susceptibility to OSA.

In conclusion, this study demonstrated a significant association between the MMP-1-1607 G/2G and 2G/2G genotypes and increased risk of developing obstructive sleep apnea (OSA). No such association was observed for the MMP-9-1562 C/T polymorphism. Our findings suggest that the MMP-1-1607 G/2G and 2G/2G genotypes may be potential genetic markers for OSA. To better understand the role of these polymorphisms in the onset and progression of OSAS, our findings should be validated in larger cohorts and supported by studies incorporating protein-level biomarkers.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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