



# The Role of a Single Nucleotide Polymorphism of the Matrix Metalloproteinase-1 Gene Promoter Region in Invasion and Prognosis of Meningiomas

## *Menenjiyomlu Hastalarda Matriks Metalloproteinaz-1 Geni Promotor Bölgesi Tek Nükleotid Polimorfizminin İnvazyon ve Prognozadaki Rolü*

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### ABSTRACT

**AIM:** The matrix metalloproteinase (MMP) enzyme family has been shown to be active in tumorigenesis and tumor progression. In this study, we analyzed the prevalence of a guanine insertion in the MMP-1 gene promoter region in meningiomas and its effect on invasion and prognosis.

**MATERIAL and METHODS:** The study was performed with 33 meningioma patients. We also included 33 healthy patients in the study as a control group. The promoter area was amplified by polymerase chain reaction (PCR) following DNA isolation. The polymorphism was detected by restriction fragment length polymorphism (RFLP).

**RESULTS:** According to the WHO classification of meningiomas, 87.9% of the affected patients were grade 1, and 12.1% were grade 2. In total, 72.7% of the meningioma patients (n=24) had at least one copy of the insertion (2G/1G or 2G/2G genotypes) and 27.3% (n=9) did not (1G/1G). There was no significant difference between the meningioma and control groups according to genotype distribution.

**CONCLUSION:** In this study, the polymorphism in the matrix metalloproteinase-1 gene promoter region did not have an effect on the initiation, growth and progression of meningioma.

**KEYWORDS:** Meningioma, Single nucleotide polymorphism, SNP, MMP-1, Interstitial collagenase, Matrix metalloproteinase

### ÖZ

**AMAÇ:** Matriks metalloproteinaz (MMP) enzim ailesinin tümör oluşumu ve progresyonunda etkili olduğu gösterilmiştir. Bu çalışmada menenjiyomlarda matriks metalloproteinaz-1 geni promotor bölgesine guanin insersiyonunun prevalansı ve bunun invazyona ve prognoza etkisi araştırıldı.

**YÖNTEM ve GEREÇLER:** Çalışma 33 tane menenjiyomlu hasta ile yapıldı. Aynı zamanda 33 tane sağlıklı kişi de çalışmaya kontrol grubu olarak dahil edildi. DNA izolasyonundan sonra promotor bölge polimeraz zincir reaksiyonu ile çoğaltıldı. Polimorfizm, restriksiyon fragman uzunluk polimorfizmi ile tesbit edildi.

**BULGULAR:** Dünya Sağlık Örgütü (DSÖ) sınıflamasına göre hastaların %87,9'unda derece I, %12,1'inde derece II menenjiyoma saptandı. Menenjiyomlu hastaların %72,7'si (n=24) en az bir tane guanin insersiyonuna sahipti (2G/1G or 2G/2G genotipleri), ve %27,3'ü (n=9) sahip değildi (1G/1G). Genotip dağılımına göre menenjiyomlarla kontrol grubu arasında bir fark yoktu.

**SONUÇ:** Bu çalışmada menenjiyomlarda matriks metalloproteinaz-1 geni promotor bölgesindeki polimorfizmin, menenjiyomların başlamasına-büyümesine ve ilerlemesine etki etmediği izlenmiştir.

**ANAHTAR SÖZCÜKLER:** Menenjiyom, Tek nükleotid polimorfizmi, SNP, MMP-1, Matriks metalloproteinaz, İnteristiyel kollajenaz

### INTRODUCTION

Meningiomas are mostly benign, slowly developing, extra axial tumors that arise from arachnoid cap cells and their progression is highly difficult to anticipate (18). Although some subtypes of meningiomas are histopathologically benign, they may still exhibit aggressive behavior.

The matrix metalloproteinase (MMP) enzyme family is active in invasion and progression of many diseases by their degradation of the extracellular matrix (24, 28). Matrix metalloproteinase-1 (MMP-1), also known as collagenase-1, is a zinc-dependent endopeptidase (17, 19, 33) that is responsible for the breakdown of the extracellular matrix. Studies have shown

that the amount of MMP-1 in a tumor is closely related to the tumor grade and invasiveness (13). MMP-1 gene expression is controlled by activator protein-1 (AP-1) bound to regions in the MMP-1 promoter and mitogen-activated kinase through polyomavirus-enhancing activity-3 (PEA-3/ETS) (22, 31). A new ETS-binding site is created by a guanine insertion in the MMP-1 gene promoter region at bp position 1607, thus enhancing the transcriptional activity of the MMP-1 gene. The presence of this guanine insertion is also correlated with the incidence and progression of several cancers (21). Studies of brain tumors suggest that there is a close relationship between the insertion in the MMP-1 promoter region and an increase in tumor grade in astrocytoma, glioblastoma multiforme and pituitary adenoma cases (1, 10, 11, 13, 31).

This aim of this study was to detect a guanine insertion in the MMP-1 gene promoter region in meningiomas and to show the effect of this polymorphism on the frequency and invasion of meningioma tumors.

### MATERIAL and METHODS

This study was conducted under Goztepe Training and Research Hospital's Ethics Committee approval (Decision #: 48/G; June 2008). Thirty-three patients underwent surgery at the Goztepe Training and Research Hospital Neurosurgery Clinic between 2006 and 2008. The pathological and clinical characteristics of the patients were recorded. DNA isolation of tissue biopsy samples was performed at the Yeditepe University Genetics and Bioengineering Department Molecular Diagnostic Laboratory. Isolated DNA samples under UV light are presented in Figure 1. A control group of 33 healthy patients were also included in the study. DNA was isolated from meningioma tissues in the patients, and from blood in the control group.

Isolated DNA samples were amplified by *Polymerase Chain Reaction* (PCR) with primers targeting the MMP-1 gene promoter region. Genotyping was performed by incubation with the Alul restriction enzyme and subsequent agarose gel electrophoresis. The bands were visualized by ethidium bromide under UV light. The Qiagen QIAamp DNA Mini Kit (cat no: 51306) was used for genomic DNA isolation from the biopsy tissue.

### PCR Amplification

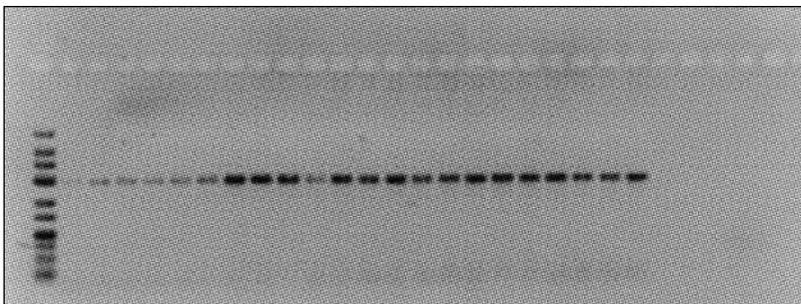
The MMP-1 promoter region of isolated DNA samples was targeted for amplification using a thermal cycling device. The amplification also served as a site-directed mutagenesis step in which a guanine was introduced by the reverse primer. Mutagenesis of the amplicon is required to generate a restriction site that is recognized and cut by the Alul enzyme in subsequent RFLP analysis.

Forward Primer: TCAC TTTTAAACATAGTCTATGTCA (27 bp)

Reverse Primer: TCTTGATTGATTTGAGATAAGTCATAGC (29 bp)

### Restriction Fragment Length Polymorphism (RFLP)

At this stage, PCR products were treated with the Alul restriction enzyme. Amplicons containing the directed mutation are treated with Alul enzyme, and blind cuts are performed as indicated below. Genotyping with the Alul enzyme is dependent on the presence or absence of the guanine base insertion within the amplicons obtained. Amplified fragments containing the guanine insertion do not contain an Alul restriction site and result in a single full-sized product. However, in the case that the insertion is absent, Alul will cut the amplicon into two fragments of 262 bp and 28 bp in length. An agarose gel containing DNA obtained from tissue biopsy samples is presented in Figure 2.



**Figure 1:** Images of isolated DNA samples under UV light after gel electrophoresis for ten minutes in a 2% agarose gel at 100 mA, 150 W.



**Figure 2:** Agarose gel containing DNA from 33 patient tissue biopsy samples. The DNA was isolated from tissue biopsy samples and amplified by PCR after treatment with the Alul restriction enzyme.

**Statistical Analyses**

Statistical analyses were performed with NCSS 2007 and PASS 2008 Statistical Software (Utah, USA). To compare quantitative data, we used a one-way ANOVA test and descriptive statistical methods, including average, standard deviation and frequency. Chi-squared tests (with both a single square and multiple squares) were performed to compare the qualitative data. The results were evaluated by a 95% confidence interval and a significance level of  $p < 0.05$ .

**RESULTS**

The study was performed between 2006 and 2008, with a total of 33 meningioma patients ranging in age from 9 to 83 years. Of these, 20 patients were females (60.6%), and 13 were males (39.4%). The mean age of the patients is  $52.63 \pm 16.23$ . The subtypes encountered included transitional (57.6%), meningothelial (18.2%), atypical (12.1%), fibrous (6.1%) and psammomatous (6.1%) meningiomas. According to the WHO classification of meningiomas, 87.9% of the affected patients were grade 1, and 12.1% were grade 2. Patients presented with headaches (84.8%), imbalance (21.2%), seizures (15.2%), hearing loss (12.1%), vision loss (6.1%) and anosmia (6.1%).

In total, 72.7% of the meningioma patients ( $n=24$ ) had at least one copy of the insertion (2G/1G or 2G/2G genotypes) and 27.3% ( $n=9$ ) did not (1G/1G). There were more meningioma patients with at least one copy of the insertion than patients with no insertion. In meningioma patients, the set of 2G/1G+2G/2G genotypes were significantly higher than the 1G/1G genotype, and this difference was significantly different ( $p < 0.01$ ) (Table I). The expected frequency of the 2G/1G+2G/2G genotypes to the 1G/1G genotype was the same but comparing expected frequencies of genotypes with the frequencies in the meningioma patients showed that there was statistically significant difference between these groups and there were more 2G/1G+2G/2G occurrences in the meningioma group (P value 0.009) (Table II). Comparing the 2G/1G+2G/2G genotype distribution of the meningioma group to the control group showed that the 2G/1G+2G/2G genotype distribution was 72.7% in both the meningioma and control group. Therefore, there was no significant difference between the groups ( $p > 0.05$ ) (Table III). Similarly, there was no significant difference between distributions of age and gender within the genotype groups.

**DISCUSSION**

A total of 26 consecutive members of the MMP family have been identified so far in the relevant literature. These enzymes have been classified by substrate and structural properties. Tumor cells break down important structural components of the extracellular matrix and prepare the environment for neovascularization. In this way, they ensure a path of travel within the affected tissue. The tumor cells are then able to both metastasize and grow further (14, 17, 19). MMPs have an important role at this stage of tumor progression due to their collagen breakdown, which is a fundamental structure within the extracellular matrix (4,5, 7). The matrix metalloproteinase

(MMP) enzyme family is active in invasion and progression of many tumors by their degradation of the extracellular matrix (24, 28). Matrix metalloproteinase-1 (MMP-1) is also known as collagenase-1. MMP-1 is a zinc-dependent endopeptidase (17, 19, 33) that is responsible for the breakdown of many proteins and collagens. MMP-1 was considered to be less active than MMP-2 and MMP-9 in human brain tumors because no collagen is present in brain tissue (6, 20, 29). However, studies have shown that such hypotheses are not accurate and suggest that the amount of MMP-1 in a tumor is closely related with its tumor grade and invasiveness (13).

MMP-1 is included in the interstitial collagenase group and breaks down stromal collagens and is located on chromosome 11 along with MMP-3. MMP-1 stimulates synthesis of other enzymes, such as MMP-3, MMP-1 and MMP-9 (9). Although these two enzymes have been identified in various tumor cells, they are also found in various normal cells, including epithelium cells, endothelium cells and macrophages (32). A single nucleotide polymorphism (SNP) in the promoter region of these enzymes affects their expression levels.

MMP-1 gene expression is controlled by activator protein-1 (AP-1) bound to regions in the MMP-1 promoter and mitogen-

**Table I:** Table Showing the Number of Meningioma Patients with at Least One Copy of the Insertion (2G/1G or 2G/2G Genotypes) and Patients with No Insertion

Genotype	n	%	p
2G/1G + 2G/2G	24	72.7	p<0.01
1G/1G	9	27.3	

*p < 0.01 means that the difference between these groups is statistically significant.*

**Table II:** Table Showing the Number of Meningioma Patients with at Least One Copy of the Insertion (2G/1G or 2G/2G Genotypes) and Patients with no Insertion, and Comparing These Numbers with Expected Frequencies of These Genotypes in the Population

Genotype	Frequency observed	Frequency expected	p
	n (%)	n (%)	
2G/1G + 2G/2G	24 (%72.7)	16.5 (%50,0)	0.009**
1G/1G	9 (%27.3)	16.5 (%50,0)	

*The p value of 0.009\*\* means that the difference between these groups is statistically significant.*

**Table III:** Table Comparing 2G/1G + 2G/2G and 1G/1G Distributions between the Meningioma and Control Groups

Genotype	Meningioma (n: 33)	Control group (n: 33)	p
	n (%)	n (%)	
2G/1G + 2G/2G	24 (% 72.7)	24 (% 72.7)	0.009**
1G/1G	9 (%27.3)	9 (%27.3)	

*There was no statistical difference between the groups ( $p > 0.05$ ).*

activated kinase through polyomavirus-enhancing activity-3 (PEA-3/ETS) (22, 31). A new ETS-binding site is created by a guanine insertion in the MMP-1 gene promoter region at bp position 1607, thus enhancing the transcriptional activity of the MMP-1 gene. The presence of this guanine insertion is also correlated with the incidence and progression of several cancers (21).

The MMP-1 SNP is located at bp position 1607. Insertion of a guanine base at this position creates a binding site for members of the EST transcription factor family, which results in further MMP-1 expression (21, 22). While MMP-1 expression is increased depending on it, degradation of the extracellular matrix gradually increases depending on the level of MMP-1 (31). The polymorphism within the MMP-1 promoter region therefore has an important role in tumor invasion, metastasis and angiogenesis (21, 25). Highly invasive melanoma cells (34) as well as other cancer types such as lung and renal cell carcinoma, have been shown to contain the additional guanine in the MMP-1 promoter region.

PCR-based studies performed on glial tumors of different grades have shown that MMP-1 expression was greater in high-grade glial tumors (26). MMP-1 expression was found to be significantly higher in glioblastoma samples than in normal samples with the 2G/2G genotype (11). Similarly, studies on astrocytomas reveal a significant increase when this region is deleted, as tumor grade is increased. The MMP-1 promoter polymorphism was found to be significant in astrocytoma development (9, 30).

In the single study performed on pituitary adenomas by Altas et al. in 2010, the 1G/2G and 2G/2G distributions were significantly higher in invasive adenomas than in benign pituitary adenomas (1). The deletion in the MMP-1 promoter region was found in both glial tumors and pituitary adenomas, which are high-grade invasive tumors.

Currently, no studies in the literature research the relationship between the single nucleotide polymorphism of the matrix metalloproteinase-1 promoter region and tumor invasion. Microscopic invasion and infiltration of tumor cells have important roles in the recurrence of meningiomas (8, 12, 15). The studies on tumor invasion and recurrence are focused on MMP-2 and MMP-9. MMP-2 expression is particularly observed in grade 2 and 3 meningiomas (16). There is a clear relationship between MMP-2 expression and tumor recurrence in meningiomas. MMP-2 and MMP-9 expression is associated with histologic malignancy. Therefore, the expression of these enzymes in anaplastic and atypical meningiomas is higher, which contributes to the invasive character of grade 2 and 3 meningiomas (30). However, its relation to MMP-9 expression is unclear. MMP-9 expression helps meningioma cells infiltrate the dura (12). Invasion of the normal arachnoid membrane adjacent to benign meningioma cells is highly important for meningioma recurrence. Invasion of the arachnoid membrane is one of the risk factors for recurrence that may then lead to an osseous invasion (3, 12).

In our study on the polymorphism of the MMP-1 promoter region in meningioma patients, 27.3% of patients were 1G/1G, 42.4% were 1G/2G and 30.3% were 2G/2G. In total, the fraction of patients that exhibited at least one insertion was 72.7%, and 27.3% of patients had no insertion. The expected frequency of patients with at least one copy of the insertion (2G/1G or 2G/2G genotypes) and patients with no insertion should be equal. Regarding this similarity, there was a statistically significant larger number of 2G/1G or 2G/2G genotypes in meningioma group. However, comparing 2G/1G + 2G/2G and 1G/1G distributions between the meningioma and control groups showed that there was no statistically significant difference between these groups. This may be due to selection of control group or no effect of copy of insertion on tumorigenesis. The hypothesis was that copy of insertion has an influence on transcription meningioma tumorigenesis. There were significant differences when genotypically comparing recurrence patients. The presence of a guanine insertion was not found to be significantly correlated with recurrence in this study. With respect to progression, several patients had atypical meningioma, and thus it was not possible to establish a significant relationship between tumor progression and the malignancy grade of the tumor. As stated in the literature, high-grade tumors exhibit the greatest frequency of insertion. Similarly, an insertion is expected to be higher in grade 2 and 3 meningiomas. Furthermore, considering the fact that recurrence rate is closely related with tumor grade, a connection can be made between guanine insertion, tumor grade and recurrence rates in tumors with higher malignancy.

There is an insufficient number of studies in the literature that investigate the polymorphism of the MMP-1 gene promoter region in brain tumors. Therefore, additional studies should address the progression to malignancy in meningiomas. The effect of the MMP-1 promoter polymorphism will become clearer through these types of studies, and such studies will help us understand the relationship between the guanine insertion and tumorigenesis and tumor progression.

This study is generally focused on grade 1 (benign) meningioma patients. The fraction of grade 2 (atypical) meningioma patients in our study is only 12%. In the literature, the insertion in the promoter region is reported to be significantly greater in high-grade tumors. To provide further information on meningiomas, there should be more atypical patients and particularly patients with malignant meningiomas. Therefore, atypical patients with malignant meningioma should be included in the study and the genotype determined using our method.

After inclusion of atypical patients with malignant meningioma, long-term follow-up of the patients should be performed and patients with reported recurrence and those that die during follow-up should be assessed. We can thus elucidate the progression and recurrence effects of the polymorphism on the MMP-1 gene promoter region, which is observed especially in metastatic cases and also in high-grade glial tumors and meningioma patients. The meningioma grade and geno-

type of exitus patients can also be compared with the goal of ascertaining the effects of an insertion on prognosis.

### CONCLUSION

We found that a polymorphism on the matrix metalloproteinase-1 gene promoter region does not have an effect on formation, growth and progression of meningioma. To obtain further information on the subject, the number of atypical and malignant cases should be increased, long-term follow-up should be performed and cases that die or develop recurrence should be evaluated separately.

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