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Lack of association of matrix metalloproteinase-9 promoter gene polymorphism in obstructive sleep apnea syndrome☆

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ABSTRACT

Purpose: Obstructive sleep apnea syndrome (OSAS) is a public health problem. There is an effort to establish the genetic contributions to the development of OSAS. One is matrix metalloproteinases, extracellular matrix degrading enzymes related to systemic inflammation. However, the impact of matrix metalloproteinase−9 (*MMP-9*) genotypes on the development of OSAS is unknown. Our aim was to determine whether *MMP-9* single nucleotide polymorphism (SNP) (*MMP-9* −1562C > T) is related to susceptibility to OSAS.
Material and methods: A total of 106 patients with a history of sleep apnea and 88 controls without a history of sleep apnea were enrolled in this study. Genotypes were determined by restriction fragment length polymorphism analyses after polymerase chain reaction.
Results: Genotypes and allele frequencies of the *MMP-9* −1562C > T SNP was not statistically different between the patient and control groups ($p > 0.05$). There was a statistical association between apnea −hypopnea index (AHI) and body mass index (BMI), and also between AHI and neck circumference ($p < 0.001$). There was no association among the genotypes and AHI, neck circumference, or BMI ($p > 0.05$).
Conclusions: We found no association between *MMP-9* −1562C > T SNP and OSAS. Studies to investigate the role of other polymorphisms and expression of *MMP-9* gene will provide more information.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a common sleep disorder characterized by recurrent episodes of upper airway obstruction. It results in recurrent arousals and episodic oxyhemoglobin desaturations during sleep (Patil et al., 2007). OSAS is accepted as a public health problem with high morbidity in both adults and children (Cao et al., 2015). OSAS causes neurocognitive dysfunction (Adams et al., 2001) cardiovascular disease (Nieto et al., 2000, Shahar et al., 2001), metabolic dysfunction (Ip et al., 2002, Punjabi et al., 2004, Reichmuth et al., 2005), and respiratory failure (Bickelmann et al.,1956). Therefore, for prevention and treatment of OSAS, understanding its pathogenesis is important. However, it is a multifactorial disease, and the exact etiopathogenesis of OSAS is not known. In recent years, there has been an effort to establish the genetic contribution to the development of OSAS (Kent et al., 2010).

One of the explanations for the pathogenesis of OSAS relates to systemic inflammation. Release of inflammatory mediators, increased leukocyte adherence to endothelial cells, reduced nitric oxide availability, and vascular injury are considered as contributing to the pathogenesis of OSAS (Lavie, 2003, Gozal and Kheirandish, 2008, Dyugovskaya et al., 2002). When neutrophils are stimulated, they release enzymes during inflammation. Matrix metalloproteinases (MMPs) are one of these enzymes in the

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systemic inflammation. MMPs are a family of Zn^{2+}-dependent extracellular matrix (ECM)–degrading enzymes (Vu and Werb, 2000). The function of MMPs has been presumed to be remodeling of the ECM, because of their ability to degrade ECM molecules. MMP-9 (92-kDa type IV collagenase, and gelatinase B) is one of the Zn^{2+}- and Cu^{2+}-dependent endopeptidases. It is involved in degradation of collagen type IV (a major component of the basement membrane underlining the endothelium and surrounding each vascular smooth muscle cell), elastin, and fibronectin (Volna et al., 2011, Zhang et al., 1999). MMP-9 has been suggested to be important in the connective tissue remodeling processes (Zhang et al., 1999).

In the last few years, studies of the association betweem MMPs and OSAS has gained interest. In one study, it was shown that monocytes isolated from adults with severe OSAS had higher production of MMP-9 than monocytes from control subjects (Tamaki et al., 2009). Tazaki et al. (Tazaki et al., 2004) found that patients with moderate and severe OSAS had higher serum levels and activity of MMP-9. Similarly, Ye et al. (Ye et al., 2007) and Tazaki et al. (Tazaki et al., 2004) found elevated serum levels of MMP-9 in obese patients with OSAS. In addition, some correlations were found between MMP-9 concentration and Apnea–Hypopnea Index (AHI), body mass index (BMI), inflammatory cytokines, and some polysomnographic parameters (Volna et al., 2011, Tazaki et al., 2004). Hopps et al. (Hopps et al., 2015) also found that MMP-9 levels were correlated with the severity of OSAS. Also it was shown that treatment of sleep apnea with nasal continuous positive airway pressure diminished serum levels of MMP-9 and its production from monocytes (Tamaki et al., 2009, Tazaki et al., 2004). Vuralkan et al. (Vuralkan et al., 2014) found that MMP-9 levels were decreased after uvulopalatal flap surgery. However, no correlation was found between OSAS and MMP-9 in children with OSAS.

However, the impact of MMP-9 genotypes on the development of sleep apnea is unknown. In the recent literature, only one study showed that the *MMP-9* −1562C > T polymorphism was associated with increased risk of OSAS in a Chinese population (Cao et al., 2015) (Table 1). Therefore we designed this study to determine, in a Turkish population, whether the single nucleotide polymorphism (SNP) *MMP-9* −1562C > T was related to susceptibility to OSAS.

2. Material and methods

A prospective, cross-sectional clinical study was designed and conducted at the Departments of Otolaryngology, Medical Genetics, and Pulmonary Medicine, Baskent University, Ankara, Turkey. This study was approved by the Baskent University Institutional Review Board and Ethics Committee (Project No. KA11/242) and supported by Baskent University Research Fund. Written informed consent was obtained from all participating subjects.

The study was performed on 106 consecutive adult patients who were examined using polysomnography (PSG) at Baskent University Faculty of Medicine between December 2009 and April 2013. All patients had complaints of snoring or apnea. Clinical history and physical examination of the patients were performed, and the Epworth Sleepiness Scale was administered to all patients. Patients with malignancies, genetic disorders, or craniofacial anomalies were excluded from study.

All of the patients were assessed with standard overnight, laboratory-based PSG (Astro-Med Grass-Telefactor, RI, USA). This included electroencephalography (C4-M1, C3-M2, O2-M1, and O1-M2), electrooculography, and electromyography (from the mandibular and tibialis anterior muscle). Oronasal air flow was measured with thermistor and nasal canullae, thoracoabdominal movements, and body position. Blood oxygen saturation was measured with pulse oximetry. Electroencephalography electrodes were positioned according to the International 10–20 system. Records were reviewed by technicians, and good-quality records for more than 4 h were accepted as sufficient.

Apnea was defined as a drop $\geq$90% of baseline in airflow that lasted for longer than 10 s. Hypopnea was defined as a $\geq$30% reduction in oronasal flow amplitude of $\geq$10 s, accompanied by $\geq$3% desaturation or arousal. Severity of disease was assessed with AHI. AHI was defined as the mean number of apneas and hypopneas per hour during sleep. AHI $\geq$5 was considered to indicate OSAS. Subjects were classified based on their AHI, with AHI $\leq$15 denoting simple snoring and mild apnea, and AHI >15 denoting moderate to severe apnea. The control group consisted of 88 healthy volunteers without a sleep disorder history or systemic diseases. Polysomnographic, demographic, and anthropometric indexes of the subjects were examined.

Table 1
Summary of the selected studies of the association between obstructive sleep apnea syndrome (OSAS) and *MMP-9* (matrix metalloproteinase–9).

Aim of the study	Results of the study (Related to MMP-9)	Reference
To examine serum levels of MMP-9, TIMP-1 in patients with OSAS	MMP-9 serum levels were higher in men with moderate to severe OSAS than in patients with mild OSAS or in obese controls.	Tazaki et al., 2004
To examine serum levels of MMP-9, CRP in patients with OSAS	MMP-9 serum levels were significantly higher in patients with moderate to severe OSAS than in patients with mild OSAS or obese controls.	Ye et al., 2007
To investigate the effect of hypoxic stress on the production of TNF-α, MCP-1, MMP-9 in patients with OSAS	The production of MMP-9 by monocytes was significantly elevated compared to values before sleep in patients with severe OSAS.	Tamaki et al., 2009
To evaluate the association of severity of OSAS, adiposity, CRP, with MMP-9 plasma levels in Greek children	Children with moderate to severe OSAS were similar to mild OSAS or without OSAS regarding MMP-9 plasma levels.	Kaditis et al., 2010
To evaluate the connection between OSAS and oxidative stress related markers	There was strong positive correlation with levels of MMP-9 and body mass index.	Volna et al., 2011
To evaluate the tissue changes in palatopharyngeal muscle in patients with OSAS	MMP-9 was increased in muscle samples from patients with OSAS.	Molina et al., 2011
To investigate MMP-9 level and gene polymorphism (−1562C > T) in OSAS patients with or without cardiovascular disorders	MMP-9 serum level was higher in OSAS patients with cardiovascular disorders but MMP-9 genotypes was not associated with MMP-9 serum level	Yüksel et al., 2013
To assess the markers of oxidant–antioxidant status in patients with OSAS who underwent uvulopalatopharyngeal surgery	There was significant differences between preoperative and postoperative MMP-9 levels.	Vuralkan et al., 2014
To evaluate plasma levels of MMP-2, MMP-9, and their inhibitors in patients with OSAS	There was significant increase in plasma concentration of MMP-9 correlated with the severity of disease.	Hopps et al., 2015
To investigate functional polymorphisms in the promoter region of MMP-2 and MMP-9 (−1562C > T) in patients with OSAS	MMP-9-1562T allele was associated with increased risk of OSAS.	Cao et al., 2015

CRP, C-reactive protein; MCP-1, monocyte chemoattractant protein–1; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor.