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Matrix Metalloproteinase Gene Variations and Expression Levels in Breast Cancer Development

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ÖZET

Meme kanseri heterojen bir hastalıktır ve kadınlarda tüm kanserlerin yaklaşık %30'unu temsil etmektedir. Bu kanser türü kansere bağlı ölümlerin ana nedenlerinden biridir ve transforme hücrelerin proliferasyonu, metastazı ile karakterizedir. Ekstrasellüler matriks meme kanseri hücrelerinin büyümesinde, progresyonunda, prognozunda, invazyonunda ve metastazında önemli rol oynamaktadır. İnvaziv ve metastatik meme kanserlerinde matriks metalloproteinazlar (MMP'ler) tarafından ekstrasellüler matriks degradasyonu gerçekleşmektedir. MMP'ler önemli proteolitik enzimlerdir ve tümör büyümesi, invazyonu ve metastazında etkilidirler. MMP genlerinde çeşitli genetik varyasyonlar tanımlanmıştır ve bu genetik varyasyonlar MMP enzim aktivitelerinde, promotör aktivitede, hücre proliferasyonunda ve transkripsiyonel regülasyonda değişikliklerle ilişkilendirilmişlerdir. Bu yüzden meme kanserinde hücre proliferasyonu ve tümör migrasyonu etkilenebilmektedir. MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 ve MMP-12 gibi tek nükleotid gen varyasyonları meme kanseri gibi çeşitli kanser türlerine yatkınlık ile ilişkilendirilmişlerdir. Bu derlemenin amacı, meme kanseri patogenezi hakkında genel bilgi verilmesinin yanısıra, meme kanseri gelişiminde MMP gen varyasyonlarının ve ekspresyon düzeylerinin rollerini incelemektir.

Anahtar Kelimeler: Meme Kanseri, Matriks Metalloproteinaz, MMP Geni, Genetik Varyasyonlar, PZR-RFLP

ABSTRACT

Breast cancer is a heterogeneous disease and represents approximately 30% of all cancers in women. This type of cancer is one of the main causes of cancer-related deaths and is characterized by proliferation and metastasis of transformed cells. Extracellular matrix plays an important role in the growth, progression, prognosis, invasion and metastasis of breast cancer cells. Extracellular matrix degradation occurs by matrix metalloproteinases (MMPs) in invasive and metastatic breast cancers. MMPs are important proteolytic enzymes and are effective in tumor growth, invasion and metastasis. Various genetic variations have been identified in MMP genes and these genetic variations have been associated with changes in MMP enzyme activities, promoter activity, cell proliferation, and transcriptional regulation. Therefore, cell proliferation and tumor migration can be affected in breast cancer. Single nucleotide gene variations such as MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-12 have been associated with susceptibility to various cancer types such as breast cancer. The aim of this review is to provide general information about the pathogenesis of breast cancer as well as to examine the roles of MMP gene variations and expression levels in the development of breast cancer.

Keywords: Breast Cancer, Matrix Metalloproteinase, MMP Gene, Genetic Variations, PCR-RFLP

INTRODUCTION

Cancer is characterized by spread in metastatic tumor cells. Proliferation in the distant region plays an important role in cancer metastasis and invasion. The basement membrane is effective in metastasis and invasion processes (Yoon et al., 2003; Curran et al., 2000). Breast cancer is one of the leading causes of cancer-related death, especially in womenBreast cancer is characterized by malignant cells in the epithelial tissues of the mammary glands (Miller et al., 1998). It represents approximately 11.9% of all cancers and has been associated with risk factors such as smoking, alcohol, hormone treatments, and radiation exposure. (Ferlay et al., 2015; Lukong, 2017). Extracellular matrix plays an important role in preventing the growth and migration of cancer cells (Chiranjeevi et al., 2014). Degradation of the extracellular matrix by MMPs has been associated with invasive and metastatic breast cancer. Tumor cells can be separated and passed through tissue boundaries. Thus, invasion of tumor cells into tissue compartments can be facilitated (Decock et al., 2008). MMPs are an important endopaptidase family and play an important role in cancer

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development and progression (Amălinei et al., 2010). The human MMP gene family consists of approximately 28 members (Jabłońska-Trypuć et al; 2016; Ranjbaran et al., 2016). MMPs are important in physiological processes such as remodeling of the extracellular matrix and embryonic development (Malemud, 2006; Lemaitre et al., 2006). In addition, MMPs are effective in pathological processes such as tumor growth, metastasis and invasion (Hughes et al., 2007). MMPs are classified according to their substrate and structure properties as collagenases, gelatinases, stromelysin, matrilysin, membrane-type MMPs and other MMPs (Visse et al. 2003). MMP-1 and MMP-3 are important members of the MMP family and these genes are localized on chromosome 11q22.2. These genes are effective in the development and metastasis of cancer. MMP-1 degrades Type I, II, III collagen. MMP-3 is an endopeptidase produced by connective tissue and plays an important role in the activation of other MMPs. It is also effective in the degradation of various extracellular substrates (Sternlicht et al., 2000). MMP-2 is another important member of the endopeptidase family and hydrolyzes the structural components of the basement membrane (Jabłońska-Trypuć et al; 2016). It also plays a role in the degradation of the structures of various bioactive molecules. Overexpression of MMP-2 has been reported in head and neck squamous cell carcinoma tissues (O-Charoenrat et al., 2006). MMP-7 is the smallest member of the MMP family and has broad substrate specificity. Overexpression of MMP-7 has been reported in various types of cancer (Liu et al., 2012). MMP-9 degrades important components of the basement membrane such as gelatin and Type IV collagen (Jabłońska-Trypuć et al; 2016). MMP-9 upregulation has been reported in several types of cancer, such as esophageal cancer, breast cancer, and gastric cancer (Liu et al., 2012). MMP-12 can inhibit angiogenesis by degrading plasminogen and collagen. It is also responsible for cell migration in tumor invasion and angiogenesis processes. Positive prognosis of various cancer types has been associated with increased MMP-12 expression (Shin et al., 2005). Various genetic variations have been identified in MMP genes, and enzyme activities and transcriptional arrangements may change as a result of these genetic variations. Therefore, promoter activity, rate of extracellular degradation and cancer proliferation may be affected. (Manshadi et al., 2018). Overexpression of MMPs has been associated with extracellular matrix degradation, tumor cell migration, and thus cancer progression (Hughes et al., 2007).

BREAST CANCER

Breast cancer is one of the most common types of cancer and the mortality rate due to the disease is quite high (de Oliveira Santos, 2018; Zhou et al., 2013). Breast cancer has been associated with high mortality and morbidity (Yari et al., 2015). Breast cancer patients often have a family history, but genetic mutations in various genes are also effective in the development of the disease (Newman et al., 1988). Approximately 30% of patients with breast cancer have a specific genetic predisposition (Rahimi et al., 2015). Therefore, genetic factors such as family history, genetic variations and environmental factors play a role in the pathogenesis of the disease (Dunning et al., 1999). Çeşitli epidemiyolojik çalışmalarda meme kanseri patogenezinde etkili olabilecek genetik varyasyonlar Genetic variations that may be effective in the pathogenesis of breast cancer have been identified in various epidemiological studies (Felizi et al., 2018). The effects of low-penetration genetic variations on the risk of developing breast cancer have been associated with polygenic forms (Rahimi et al., 2015).

MATRIX METALLOPROTEINASES

MMPs consist of approximately 28 endopeptidases with various substrate specificities (Saeed et al., 2013) (Figure 1). MMPs are proteolytic enzymes. They are effective in normal processes such as tissue modeling and in pathological processes such as tumor invasion and metastasis (Saarialho-Kere et al., 1995). MMP'ler güçlü proteolitik aktivitelere sahiptirler. The balance between MMPs and their specific tissue inhibitors is very important in maintaining these proteolytic activities (Chakraborti et al., 2003). MMPs can affect cell adhesion and alter genomic instability. Thus, the cellular microenvironment that facilitates tumor formation may change. Therefore, MMPs have been associated with tumor formation and development (Zhu et al., 2001). MMPs are family of endopeptidases important in the degradation of basement membrane barriers (Felizi et al., 2018). Extracellular matrix degradation and basement membrane degradation have been associated with cell proliferation, tumorigenesis, invasion and metastasis (Howlett et al., 1993; Rahimi et al., 2015). MMPs are also effective in immune system regulation (Vu et al., 2000, Egeblad et al., 2002; Felizi et al., 2018). MMP gene expression is regulated at the transcriptional level. mRNA stability can be modulated in response to growth factors and cytokines (Johnsen et al., 1998). Overexpression of MMP has been associated with degenerative diseases, various types of cancer, and inflammatory diseases (Munhoz et al., 2010). The significant relationship has also been reported between MMP expression, activity, and advanced tumor stage (Egeblad et al., 2002; Ye, 2000). Upregulated MMP expressions are associated with benign cancer cells acquiring malignant features, while downregulated MMP expressions are associated with less aggressive transformation of malignant cells (Egeblad et al., 2002).

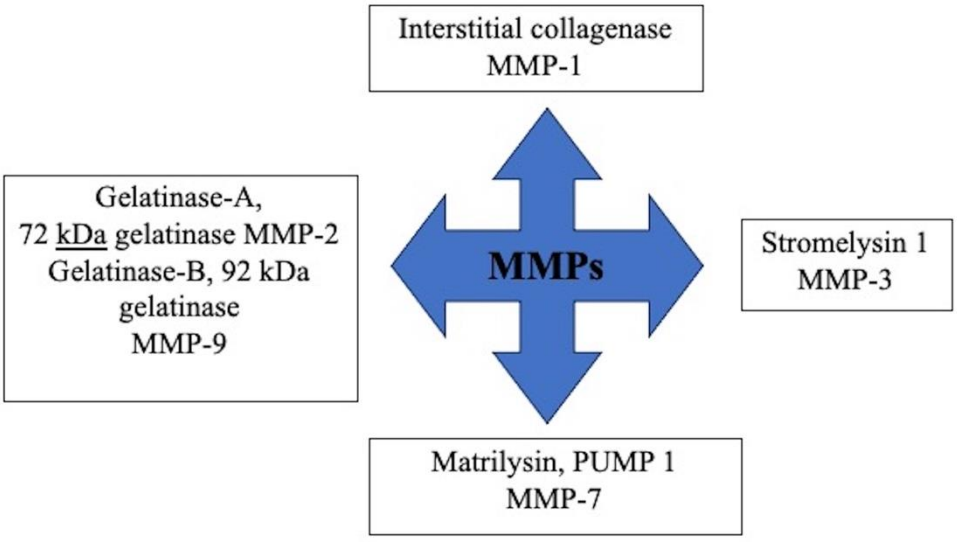
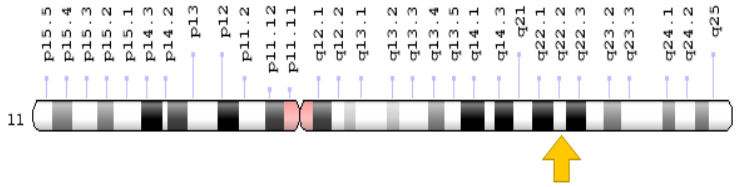
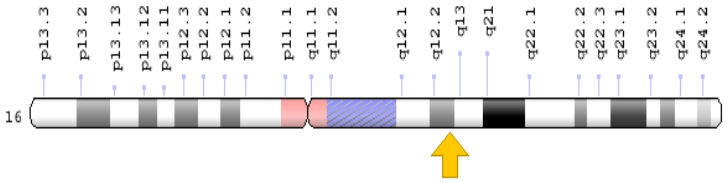
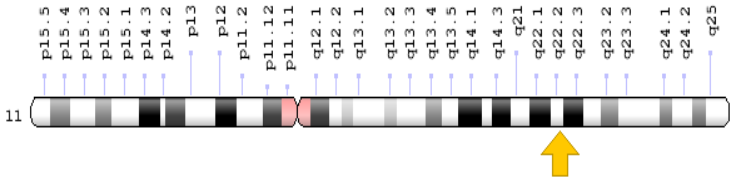
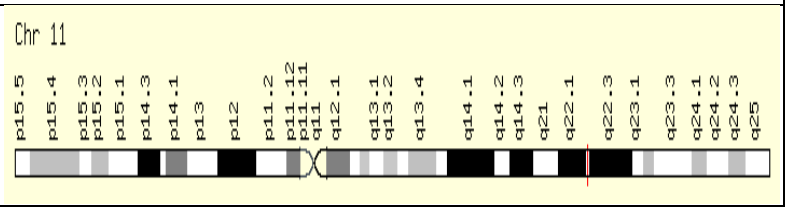
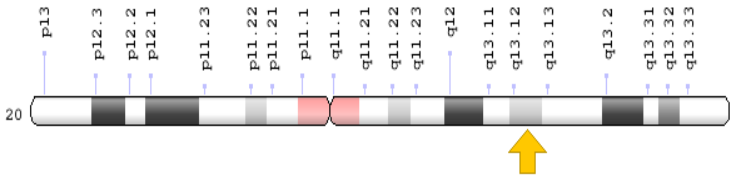
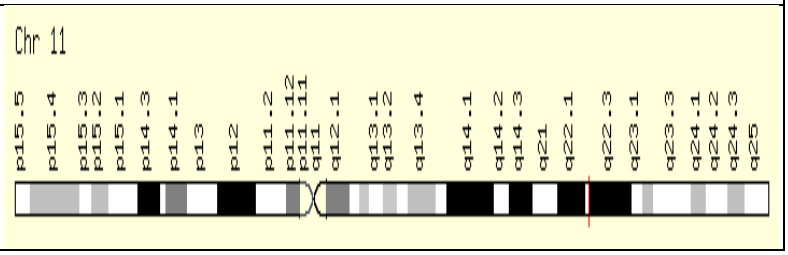


Figure 1. Classifications of MMPs based on structure and substrate specificities

MATRIX METALLOPROTEINASE-1 GENE VARIATION

MMP-1 is an interstitial collagenase and can be expressed ubiquitously. MMP-1 degrades interstitial collagen types I, II, II (Zhou et al., 2018; Zhou et al., 2011). MMP-1 is localized on chromosome 11q22.2. (Genetics Home Reference) (Table 1). MMP-1 expression is regulated by the MMP-1 promoter. MMP-1 (-1607 1G/2G) (rs 1799750) gene variation has been identified in the promoter region of the MMP-1 gene and this genetic variation has been associated with susceptibility to various cancer types, tumor formation and progression. MMP-1 transcription increases as a result of MMP-1 (-1607 1G/2G) (rs 1799750) gene variation (Zhou et al., 2018). The guanine insertion at position -1607 of the MMP-1 promoter region creates a binding site (5'-GGAT-3') for the transcription factor (Zhou et al., 2011). The 2G allele of this gene variation has been associated with greater increased transcriptional activity compared to the 1G allele. In addition, homozygous 2G/2G genotype of MMP-1 (-1607 1G/2G) (rs 1799750) gene variation shows a stronger effect than heterozygous 1G/2G genotype. Therefore, the 2G/2G homozygous genotype of this gene variation has been associated with a higher risk of metastasis than the 1G/2G heterozygous genotype (Liu et al., 2012).

Table 1: Locations and Structures of MMP Genes

Gene	Cytogenetic Location	Gene Structure
MMP-1 Gene	11q22.2, which is the long (q) arm of chromosome 11 at position 22.2	
MMP-2 Gene	16q12.2, which is the long (q) arm of chromosome 16 at position 12.2	
MMP-3 Gene	11q22.2, which is the long (q) arm of chromosome 11 at position 22.2	
MMP-7 Gene	Chromosome 11 (11q21-q22)	
MMP-9 Gene	20q13.12, which is the long (q) arm of chromosome 20 at position 13.12	
MMP-12 Gene	Chromosome 11q22.2	

In some meta-analysis studies, the relationships between MMP-1 (-1607 1G/2G) (rs 1799750) gene variation and various cancer types has been investigated. In a study performed with the Asian population, the 2G/2G homozygous genotype and 2G allele of the MMP-1 (-1607 1G/2G) (rs 1799750) gene variation were identified as genetic risk factors for the development of cancer (Zhou et al., 2018). In a meta-analysis study, relationships have been reported MMP-1 (-1607 1G/2G) (rs 1799750) gene variation and with various cancer types such as lung cancer, colorectal cancer, kidney cancer, bladder cancer, nasopharyngeal cancer, endometrial carcinoma, oral squamous cell carcinoma (Zhou et al., 2018; Zhou et al., 2011). The MMP-1 (-1607 1G/2G) (rs 1799750) gene variation has been associated with early detection and prognosis of breast cancer. MMP-1 mRNA overexpression has been associated with a high recurrence frequency in various cancer types. In another study, a significant relationship has been reported between MMP-1 (-1607 1G/2G) (rs 1799750) gene variation and lymph node metastasis in breast cancer. The 2G allele of this gene variation was determined significantly higher in breast cancer patients with lymph node metastases compared

to those without. Therefore, the MMP-1 (-1607 1G/2G) (rs 1799750) gene variation is accepted as a prognostic marker for breast cancer development (Zhou et al., 2011). In studies with Taiwanese and Polish populations, the MMP-1 (-1607 1G/2G) (rs 1799750) gene variation has been identified as a genetic risk factor for the development of breast cancer (Hsiao et al., 2018). Primer sequences for MMP-1 (–1607 1G/2G) (rs1799750) gene variations is presented in Table 2. Genotypes, PCR product lengths, restriction enzymes, RFLP fragments for MMP-1 (–1607 1G/2G) (rs1799750) gene variations is presented in Table 3.

Table 2. Primer sequences for MMP gene variations

Gene Variations	Primer	Primer Sequences
MMP-1 (–1607 1G/2G) (rs1799750)	F	5′-TCG TGA GAA TGT CTT CCC ATT-3′
	R	5′-TCT TGG ATT GAT TTG AGA TAA GTG AAA TC-3′
MMP-2 (-1306C/T) (rs243865)	F	5'-CTT CCT AGG CTG GTC CTT ACT GA-3'
	R	5'-CTG AGA CCT GAA GAG CTA AAG AGG T-3'
MMP-3 (-1171 5A/6A) (rs3025058)	F	5’-GGA ATT CAC ATC ACT GCC ACC ACT-3’
	R	5’-AGT GCT AGG ATT ACA GAC ATG GGT CA-3’
MMP-7 (-181A/G) (rs11568818)	F	5’-TGG TAC CAT AAT GTC CTG AAT G-3’
	R	5’-TCG TTA TTG GCA GGA AGC ACA CAA TGA ATT-3’
MMP-9 (-1562C/T) (rs3918242)	F	5′-GCC TGG CAC ATA GTA GGC CC-3′
	R	5′- CTT CCT AGC CAG CCG GCA TC -3′
MMP-12 (A-82G) (rs2276109)	F	5′-GAG ATA GTC AAG GGA TGA TAT CAG C-3′
	R	5′-AAG AGC TCC AGA AGC AGT GG-3′
MMP-12 (A1082G)	F	5′-GGG ATA ATT TGG CTC TGG TCT TCA A-3′
	R	5′-CCA TGG GAA CCA TAG AAA AGA-3′

F: Forward**; R:** Reverse

Table 3. Genotypes, PCR product lengths, restriction enzymes, RFLP fragments for MMP gene variations

Gene Variations	Genotypes	Restriction enzymes	PCR product lengths (bp)	RFLP Fragments (bp)
MMP-1 (–1607 1G/2G) (rs1799750)	1G/1G	*XmnI*	118	89 and 29
	1G/2G			118, 89 and 29
	2G/2G			118
MMP-2 (-1306C/T) (rs243865)	CC	*XspI*	193	193
	CT			193, 188 and 5
	TT			188 and 5
MMP-3 (-1171 5A/6A) (rs3025058)	5A/5A	*Tth111I (PsyI)*	129	97 and 32
	5A/6A			129, 97 and 32
	6A/6A			129
MMP-7 (-181A/G) (rs11568818)	AA	*EcoRI*	150	150
	AG			150, 120 and 30
	GG			120 and 30
MMP-9 (-1562C/T) (rs3918242)	CC	*SphI*	435	435
	CT			435, 247 and 88
	TT			247 and 88
MMP-12 (A-82G) (rs2276109)	AA	*PvuII*	199	199
	AG			199, 175 and 24
	GG			175 and 24

PCR: Polymerase Chain Reaction; **RFLP:** Restriction Fragment Length Polymorphism

MATRIX METALLOPROTEINASE-2 GENE VARIATION

MMP-2 is known as gelatinase A and is expressed by connective tissue cells such as endothelial cells, osteoblasts, fibroblasts, and myoblasts. It has proteolytic activity against type IV collagen and is effective in various pathological processes such as cancerMMP-2 plays an important role in tumor invasiveness and metastasis regulation. The significant relationship has been reported between MMP-2 expression levels and tumor grade. Breast cancer has high invasiveness and metastasis potential. Tumor growth, invasion and metastasis are multistage process. This process is facilitated by proteolytic degradation of extracellular matrix and basement membrane. MMP-2 is an important

marker for tumor progression and prognosis. The MMP-2 promoter contains transcription factor that is effective in regulating various genes. The CCACC box in several genes is required for Sp-1 binding and promoter function. Sp-1 is a multifactorial protein and interacts directly with the transcription complex. This protein acts as a transcription factor and is effective in regulating tissue-specific expression. The MMP-2 gene is localized on chromosome 16q13-q21 and contains 13 exons (Genetics Home Reference) (Table 1). The MMP-2 (-1306 C/T) (rs243865) gene variation has been identified in the promoter region of the MMP-2 gene (Saeed et al., 2013). The Sp-1 promoter region (CCACC) is disrupted and MMP-2 expression and activity are affected as a result of this gene variation. In addition, MMP-2 (2735 C/T) (rs 2285053), MMP-2 (-790 G/A) (rs243864), MMP-2 (-1575 G/A) (rs 243866) gene in the promoter region of MMP-2 gene variations have been described (Habel et al., 2019). MMP-2 gene variations are effective in the regulation of MMP-2 gene transcription and have been associated with the development and progression of various cancer types such as breast cancer, colorectal cancer, prostate cancer (Saeed et al., 2013). MMP-2 is an estrogenically sensitive gene and this gene variation has been identified at estrogen receptor binding sites. Thus, the transcriptional response decrease to estrogen. ER-negative tumors have been associated with lower MMP-2 expression levels and thus lower transcriptional response compared to ER-positive tumors (Habel et al., 2019).

In a previous study, the T allele of the MMP-2 (-1306 C/T) (rs243865) gene variation has been associated with low promoter activity. In a study conducted with the population of Saudi Arabia, the significant association has been determined between MMP-1 (-1607 1G/2G) (rs 1799750) gene variation and increased breast cancer. In another study performed with the Chinese population, the CC genotype of the MMP-2 (-1306 C/T) (rs243865) gene variation was determined as genetic risk factor for the development of breast cancer. (Saeed et al., 2013). In a Swedish population study, a significant association has been reported between the MMP-2 (-1306 C/T) (rs243865) gene variation and breast cancer development. In a study performed with the Australian population, the TT homozygous genotype of the MMP-2 (-1306 C/T) (rs243865) gene variation has been associated with lower promoter activity. In a meta-analysis study, the MMP-2 (2735 C/T) (rs 2285053) gene variation has been associated with an increased risk of metastasis (Manshadi et al., 2018In a study performed with the Tunisian population, the significant relationship was reported between MMP-2 (-1306 C/T) (rs243865) gene variation and breast cancer development, progression (Habel et al., 2019). In a study performed with the Iranian population, the MMP-2 (-1306 C/T) (rs243865) gene variation was determined as genetic risk factor for the development of breast cancer (Manshadi et al., 2018). In a study carried out with the Chinese population, MMP-2 (-1306 C/T) (rs243865) gene variation was determined as a protective factor for development of breast cancer (Habel et al., 2019). In a study with Chinese, Australian and Brazilian populations, the significant association was not determined between MMP-2 (-1306 C/T) (rs243865) gene variation and lymph node metastasis (Manshadi et al., 2018). Primer sequences for MMP-2 (-1306C/T) (rs243865) gene variations is presented in Table 2. Genotypes, PCR product lengths, restriction enzymes, RFLP fragments for MMP-2 (-1306C/T) (rs243865) gene variations is presented in Table 3.

MATRIX METALLOPROTEINASE-3 GENE VARIATION

MMP-3 has broad substrate specificity and plays an important role in the connective tissue remodeling process. MMP-3 is known as stromelysin-1 and degrades extracellular matrix components. MMP-3 also activates some other MMPs. MMP-3 is produced by various cell types such as fibroblasts, smooth muscle cells, macrophages, synovial cells and chondrocytes. MMP-3 consists of domains with different functions and these domains include translocation and signal peptide, propeptide, catalytic domain, hemopex domain. There is an interaction between MMP-3 and connective tissue growth factor. As a result of this interaction, angiogenesis supporting factors are released. MMP-3 exerts a tumor inhibitory effect through angiogenesis-inhibiting factors such as angiostatin and endostatin (Munhoz et al., 2010). MMP-3 has been associated with structural changes in the vessel wall via extracellular matrix degradation. Therefore, it is effective in arterial wall remodeling, local invasiveness and metastasis. MMP-3 is overexpressed by some tumor types, and overexpression of MMP-3 has been associated with tumor angiogenesis, invasion and metastasis. The MMP-3 gene is localized on chromosome 11q22.2 (Genetics Home Reference) (Table 1). MMP-3 gene expression is induced by environmental factors and regulated by genetic factors such as DNA variations (Munhoz et al., 2010; Suhaimi et al., 2020). Various genetic variations have been identified in the MMP-3 gene. The MMP-3 (-1171 5A/6A) (rs3025058) gene variation identified in the promoter region of the MMP-3 gene has been associated with a change in transcription factor binding and influencing the promoter activity. The 5A allele of the MMP-3 (-1171 5A/6A) (rs3025058) gene variation has been associated with higher promoter activity, while the 6A allele has been associated with lower promoter activity (Munhoz et al., 2010). In vitro functional assays, promoter activity of the 5A allele of the MMP-3 (-1171 5A/6A) (rs3025058) gene variation was determined significantly higher than 6A allele in transiently transfected fibroblasts (Suhaimi et al., 2020). In DNA-protein interaction analyses, the MMP-3 (-1171 5A/6A) (rs3025058) gene variant of the nuclear protein binds more strongly to the 6A sequence. The 5A allele of this gene variation has been associated with diseases related to increased extracellular matrix degradation, such as acute coronary events, abdominal aorta, intracranial aneurysms, and peripheral arterial occlusive disease (Munhoz et al., 2010). In addition, the 5A/6A heterozygous genotype of this gene variation has been associated with a higher risk of metastasis compared to the 6A/6A homozygous genotype (Liu et al., 2012).

The significant association between MMP-3 (-1171 5A/6A) (rs3025058) gene variation and breast cancer susceptibility has been reported. The 5A/5A homozygous genotype of this gene variation has been associated with worse prognosis. In a study, the MMP-3 (-1171 5A/6A) (rs3025058) gene variation promotes tumor progression and increased MMP-3 expression levels were identified in women with breast cancer (Munhoz et al., 2010). In a study performed with Italian-Caucasian population, the 5A allele of the MMP-3 (-1171 5A/6A) (rs3025058) gene variation has been associated with breast cancer susceptibility. In a study performed with the Iranian population, the significant association was reported between the 5A allele of the MMP-3 (-1171 5A/6A) (rs3025058) gene variation and breast cancer metastasis. However, in another study performed with a South Indian population, the 6A allele of MMP-3 (-1171 5A/6A) (rs3025058) gene variation plays a more active role in the development of breast cancer compared to the 5A allele (Suhaimi et al., 2020). Primer sequences for MMP-3 (-1171 5A/6A) (rs3025058) gene variations is presented in Table 2. Genotypes, PCR product lengths, restriction enzymes, RFLP fragments for MMP-3 (-1171 5A/6A) (rs3025058) gene variations is presented in Table 3.

MATRIX METALLOPROTEINASE-7 GENE VARIATION

MMP-7 is known as Matrixilin-1 or PUMP-1 and is a minimal domain member of MMP family. MMP-7 has broad substrate specificity and MMP-7 expression has been associated with tumor invasion, metastasis in various cancer types. Overexpression of MMP-7 has been detected in various cancer types such as esophageal cancer, stomach cancer, colorectal cancer, kidney cancer, and breast cancer. In addition, MMP-7 expression has been identified as an important risk factor for metastasis and progression in some cancer types. The MMP-7 gene contains 13 exons and is localized on chromosome 11 (11q21-q22) (Yari et al., 2015; Gene Cards The Human Gene Database) (Table 1). Two genetic variations have been identified in the promoter region of the MMP-7 gene as MMP-7 (-181 A/G) (rs 11568818) and MMP-7 (-153 C/T) (rs 11568819As a result of these genetic variations, the binding of nuclear proteins is affected and gene transcription can be modulated. Thus, MMP-7 gene variations have been associated with prognosis in various cancer typesIn a study, an inverse relationship was reported between MMP-7 expression and tumor grade. Increased MMP-7 expression levels have been associated with high-grade tumors, advanced disease stage, and decreased survival. In another study, MMP-7 expression levels were determined significantly higher in patients with breast cancer who developed bone metastases compared to patients with breast cancer without metastases (Beeghly-Fadiel et al., 2009).

The G allele of the MMP-7 (-181A/G) (rs11568818) gene variation has been associated with higher promoter activity (Yari et al., 2015). In a study, the GG homozygous genotype of the MMP-7 (-181A/G) (rs11568818) gene variation has been associated with metastasis and lymph node involvement in patients with colorectal cancerIn a group of patients with gastric cancer, AG heterozygous and GG homozygous genotypes of the MMP-7 (-181A/G) (rs11568818) gene variation have been associated with an increased risk of death. In another study performed with Caucasian population, GG homozygous genotype of MMP-7 (-181A/G) (rs11568818) gene variation has been associated with lymph node metastasis (Beeghly-Fadiel et al., 2009). On the other hand, this gene variation was not determined as a genetic risk factor for the development of breast cancer in the study performed in Western Iranian and Chinese populations (Yari et al., 2015). Primer sequences for MMP-7 (-181A/G) (rs11568818) gene variations was presented in Table 2. Genotypes, PCR product lengths, restriction enzymes, RFLP fragments for MMP-7 (-181A/G) (rs11568818) gene variations were presented in Table 3.

MATRIX METALLOPROTEINASE-9 GENE VARIATION

MMP-9 is an effective collagenase in extracellular matrix degradation and plays an important role in tumor cell invasion and metastasis. MMP-9 gene is localized on chromosome 20q11.2-q13.1(Genetics Home Reference) (Table 1). As a result of genetic variations in the MMP-9 gene, changes in MMP-9 expression have been detected and therefore these changes have been associated with cancer susceptibility. Changes in MMP-9 expression determine the degree of differentiation in breast cancer cells. Overexpression of MMP-9 has been associated with aggressive breast cancer subtypes. Several single nucleotide gene variations have been identified in the MMP-9 gene and the most common genetic variation is the MMP-9 (-1562 C/T) (rs3918242) gene variation. The MMP-9 (-1562 C/T) (rs3918242) gene variation is characterized by a cytosine / thymine base substitution at the -1562 position of the MMP-9 gene. In a study, MMP-9 has been identified as an important diagnostic biomarker and drug target in breast cancer development. In a study performed with Indian population, the T allele of the MMP-9 (-1562 C/T) (rs3918242) gene variation has been associated with increased risk of breast cancer. In a study performed with Iranian population, the MMP-9 (-1562 C/T) (rs3918242) gene variation has been identified as a genetic risk factor for the development of breast cancer. In a meta-analysis study, the significant association was reported between TT homozygous genotype of this gene variation and increased risk of breast cancer. In another meta-analysis study, the TT homozygous genotype of the MMP-9 (-1562 C/T) (rs3918242) gene variation has been associated with increased risk of metastasis (Liu et al., 2012). In another study carried out with Brazilian population, the TT homozygous genotype and T allele of MMP-9 (-1562 C/T) (rs3918242) gene variation were not determined as a genetic risk factor for the development of breast cancer (Felizi et al., 2018). Primer sequences for MMP-9 (-1562 C/T) (rs3918242) gene variations is presented in Table 2. Genotypes, PCR product lengths, restriction enzymes, RFLP

fragments for MMP-9 (-1562 C/T) (rs3918242) gene variations is presented in Table 3.

MATRIX METALLOPROTEINASE-12 GENE VARIATION

MMP-12 substrates consist of extracellular matrix proteins and extracellular non-matrix proteins. MMP-12 plays an important role in inhibiting angiogenesis. It may also regulate angiogenesis by degrading extracellular matrix components. MMP-12 is a proteolytic enzyme and plays a role in the degradation of plasminogen to angiotensin by showing angiostatic effect. MMP-12 is expressed in breast tissue and exerts a protective effect through the degradation of plasminogen to angiostatin and collagen XVIII to endostatin. It has also been associated with cleavage of the D1 domain of the MMP-12 urokinase-type plasminogen activator cellular receptor. This domain is responsible for tumor invasion and cell migration during angiogenesis. The significant association has been reported between increased MMP-12 expression and positive prognosis in various cancer types. The MMP-12 gene is localized on chromosome 20 (20q11.2-q13.1) (Gene Cards The Human Gene Database) (Table 1). Two common genetic variations have been identified in the promoter region of the MMP-12 gene as MMP-12 (A-82G) (rs 2276109) and MMP-12 (A1082G) gene variations. MMP-12 (A-82G) (rs2276109) gene variation has been identified in the promoter region that binds to transcription factor activator protein 1 (AP-1). The A allele of the MMP-12 (A-82G) (rs2276109) gene variation has been associated with high binding affinity for AP-1In in vitro studies, higher binding affinity for AP-1 has been associated with higher MMP-12 promoter activity. The MMP-12 (A1082G) gene variation has been identified in the coding region of the hemopexin domain. This gene variation is responsible for the activity of hemopexin MMP-12. In this genetic variation, MMP-12 enzyme activity is affected by a hydrocsilic amino acid / acidic amino acid exchange.

In previous studies, overexpression of MMP-12 in tumors has been associated with reduced neovascularization in colorectal cancer patients. In a study a significant association was determined between MMP-12 expressed in macrophages and differentiated cancer cells at the tumor site. In a study performed with the Chinese population, AG heterozygous and GG homozygous genotypes of the MMP-12 (A1082G) gene variation have been associated with poor prognosis of breast cancer (Shin et al., 2005; Chehaibi et al., 2014). Primer sequences for MMP-12 (A-82G) (rs2276109) gene variations is presented in Table 2. Genotypes, PCR product lengths, restriction enzymes, RFLP fragments for MMP-12 (A-82G) (rs2276109) gene variations is presented in Table 3.

CONCLUSION

Breast cancer is one of the most common cancer types in the world and various studies have been carried out in different races and populations to determine the etiology of breast cancer. The pathogenesis of breast cancer has not been fully elucidated, but genetic and environmental factors play a role together in the pathogenesis of breast cancer. Single nucleotide gene variations such as MMP gene variations play an important role in the development and progression of breast cancer. MMP gene variations are effective in pathological processes such as tumor invasion and metastasis in breast cancer. In addition, irregularities in MMP expression have been associated with tissue destruction in various cancer types such as breast cancer. As a result of MMP gene variations, changes occur in enzyme activities, transcriptional regulation and promoter activities. Different results have been obtained in studies carried out to investigate the relationships between breast cancer development and MMP gene variations. It is thought that the different results in these studies may be stem from different selection criteria for the patient and control groups, and the fact that the studies were performed with populations of different sizes. Investigation of single nucleotide gene variations such as MMP gene variations in breast cancer pathophysiology is clinically important in terms of early diagnosis and prognosis of breast cancer in order to better understand the pathogenesis of breast cancer and to determine prognostic and therapeutic targets for the disease. Determination of mutant genotypes as important biomarkers for MMP gene variations will ensure that necessary precautions may be taken before invasion and metastasis develop in breast cancer. Thus, it will be possible to develop the new drugs and treatment strategies that can prevent the development of breast cancer.

Declaratıons of interest

We report that there is no declarations of interest in our study.

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