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Genetic Basis of Thyroid Cancer: The Role of MMP2 and MMP9 Polymorphisms

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ABSTRACT

Background: Matrix metalloproteinases (MMPs) play a critical role in tumor invasion and metastasis in papillary thyroid carcinoma (PTC). This study investigates the association of MMP2 (rs7201) and MMP9 (rs17576) polymorphisms with PTC risk and clinical characteristics, aiming to inform personalized medicine approaches. Methods: A case-control study was conducted with 210 PTC patients and 210 controls. Genotype frequencies were analyzed using Chi-Square tests, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Associations with clinical characteristics (T Status, N Status, Stage) were assessed in PTC patients.
Results: The MMP2 rs7201 CC genotype was significantly associated with increased PTC risk (OR = 3.524, 95% CI = 1.809–6.867, p = 0.001) and advanced T Status (T3: 48.6%, p = 0.029), but not with N Status (p = 0.509) or Stage (p = 0.461). The C allele was more frequent in cases (44%) than controls (32%) (OR = 1.590, p = 0.001). Conversely, MMP9 rs17576 showed no association with PTC risk (GG: OR = 0.727, p = 0.277) or clinical characteristics (p > 0.05). Both polymorphisms were in Hardy-Weinberg equilibrium in controls.
Conclusion: The MMP2 rs7201 CC genotype and C allele are associated with increased PTC risk and tumor progression, highlighting their potential as biomarkers for personalized risk stratification. These findings support genotype-based screening to identify high-risk PTC patients, enabling tailored surveillance

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INTRODUCTION

Thyroid cancer (TC), particularly papillary thyroid carcinoma (PTC), is a significant health concern due to its increasing incidence and potential for metastasis and recurrence (1). TC is a genetically simple disease, characterized by a relatively low somatic mutation burden in each tumor. Driver mutations, which confer a selective growth advantage and promote cancer development, have been identified in over 90% of TC cases (2). In the last 30 years, the availability of the genome sequence has greatly contributed to the understanding of the molecular mechanisms underlying TC (2).

The matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that play a pivotal role in extracellular matrix (ECM) remodeling (3). This family includes over 20 enzymes, each with distinct substrate specificities and tissue distributions. MMPs are involved in normal physiological processes such as wound healing, angiogenesis, and tissue repair.

However, their dysregulation is strongly implicated in pathological conditions, including cancer (3, 4).

In cancer, MMPs contribute to tumor progression by degrading ECM components, facilitating tumor invasion, metastasis, and angiogenesis. Among the MMP family, MMP-2 and MMP-9 are particularly significant due to their ability to degrade type IV collagen, a major component of the basement membrane. This activity is critical for cancer cells to invade surrounding tissues and establish metastases (5). Additionally, MMP-2 and MMP-9 are involved in modulating the tumor microenvironment, influencing cell-cell and cell-ECM interactions, and promoting angiogenesis (6, 7). Serum levels of MMP-2 and MMP-9 play critical roles in the progression and prognosis of thyroid cancer, particularly papillary thyroid carcinoma (PTC). Elevated preoperative serum MMP-2 levels have been identified as a potential biomarker for diagnosing PTC, distinguishing it from benign thyroid nodules (BTNs) with high sensitivity and specificity (8). MMP-2 levels are significantly correlated with tumor burden, lymph node metastasis (LNM), and structurally persistent or recurrent disease (SPRD) (8, 9). Similarly, serum MMP-9 levels are elevated in thyroid cancer patients and are linked to tumor aggressiveness, invasion, and metastasis (10).

The rs7201 polymorphism in MMP-2 and the rs17576 polymorphism in MMP-9 are associated with altered gene expression and serum levels (11, 12). This paper aims to unravel the genetic basis of thyroid cancer by exploring the roles of MMP-2 and MMP-9 polymorphisms, thereby contributing to the identification of potential biomarkers for diagnosis and prognosis. The exploration of genetic variations in thyroid cancer is crucial, as it may lead to personalized treatment strategies and improved patient outcomes. Understanding the interplay between these polymorphisms and thyroid cancer progression could pave the way for novel therapeutic interventions.

MATERIALS AND METHODS

The study population consisted of 420 subjects, including both men and women (210 patients with papillary thyroid carcinoma and 210 controls as the reference group), matched for age (± 5 years) and sex. The study was conducted using a case-control design. Patient samples were collected from Namazi Hospital in Shiraz, and control subjects were selected from the general population after confirmation of their health status by a specialist physician. Ethical approvals for recruitment were obtained from the local Ethics Committee of Arsanjan University (IR.IAU.KAU.REC.1403.049) and informed consent was obtained from all individuals.

Following the collection of peripheral blood samples from all study participants, DNA extraction was performed using the salting-out method, as previously described (13). Genotyping for MMP2 (rs7201) and MMP9 (rs17576) polymorphisms was conducted using the Tetra-primer Amplification Refractory Mutation System Polymerase Chain Reaction (Tetra-ARMS PCR). Genomic sequences of the MMP2 and MMP9 genes, including the flanking regions of the target polymorphisms, were retrieved from the NCBI database. Primers were designed using Primer1 software (14), which facilitates the creation of two outer (forward outer, FO; reverse outer, RO) and two inner (forward inner, FI; reverse inner, RI) primers specific to each allele (Table 1). The FI and RI primers amplify the C and A alleles for rs7201, and the G and

Table 1. Sequences and annealing temperatures of primers used for Tetra-ARMS PCR genotyping of MMP2 (rs7201) and MMP9 (rs17576) polymorphisms

Polymorphism	Primers	Sequence(5'to3')	Annealing Temperatures
MMP-9	FI(G allele):	CGCCCCAGGACTCTACACACG	
rs17567	RI(A allele):	GTTTCCCATCAGCATTGCCGTACT	**66° C**
	FO	CTTCTGCCCCAGCGAGAGTGAG	
	RO	TGGGAGGGAAGAGCCGCGTTTTG	
MMP-2	FI(C allele):	CAGAGCCACCCCTAAAGAGGTC	
rs7201	RI(A allele):	GGCTGCGTTGAAAATATCAAGGT	**62° C**
	FO	GCCTATTACCTGAAGCTGGAGAAC	
	RO	TAAGGCAGCCAGCAGTGAAAAG	

FI: forward inner primer; RI: reverse inner primer; FO: forward outer primer; RO: reverse outer primer. The FI and RI primers are allele-specific, amplifying the C/A alleles for rs7201 and G/A alleles for rs17576.

A alleles for rs17576, respectively, producing distinct band sizes for each genotype (Figure 1). A schematic of the Tetra-ARMS PCR mechanism is provided in Figure 1 to illustrate allele-specific amplification.

The Tetra-ARMS PCR reaction was performed in a 12.5 µL volume, containing 10 pmol of FI and RI primers and 3 pmol of FO and RO primers. PCR products were electrophoresed on a 2% agarose gel, stained with DNA Safe Stain, and visualized to determine genotypes based on band patterns (Figure 2).

The association between various risk factors and susceptibility to thyroid cancer was investigated using statistical analysis, logistic regression, and the calculation of odds ratios (OR) with 95% confidence intervals. Additionally, mean comparisons were performed using a T-test via SPSS 20 software.

RESULTS

Study Population Characteristics

This case-control study included 420 participants (210 cases with confirmed papillary thyroid carcinoma and 210 healthy controls) recruited from Namazi Hospital, Shiraz, Iran, between October 2015 and January 2017. The case and control groups were matched for age (±5 years) and sex. The overall study population comprised 354 females (84.3%) and 66 males (15.7%). The mean age of the control group was 40.54 ± 12.88 years, and that of the case group was 40.31 ± 13.94 years, with no statistically significant difference between the groups (p = 0.864).

The clinical features of the 210 patients with papillary thyroid carcinoma are summarized in Table 2. Tumor size was classified as T1 in 81 patients (41%), T2 in 63 patients (31.8%), T3 in 52 patients (26.3%), and T4 in 2 patients (1%). Regarding lymph node involvement, 23 patients (12.2%) were classified as N0 (no regional lymph node metastasis), 112 (59.6%) as Nx (lymph nodes not assessable), 27 (14.4%) as N1 (regional lymph node metastasis), 16 (8.5%) as N1a, and 10 (5.3%) as N1b. Distant metastasis status was Mx (not assessable) in 196 patients (99.5%) and M1 (distant metastasis) in 1 patient (0.5%). Disease staging revealed that 107 patients (75.9%) were in Stage I, 11 (7.8%) in Stage II, 20 (14.2%) in Stage III, and 3 (2.1%)

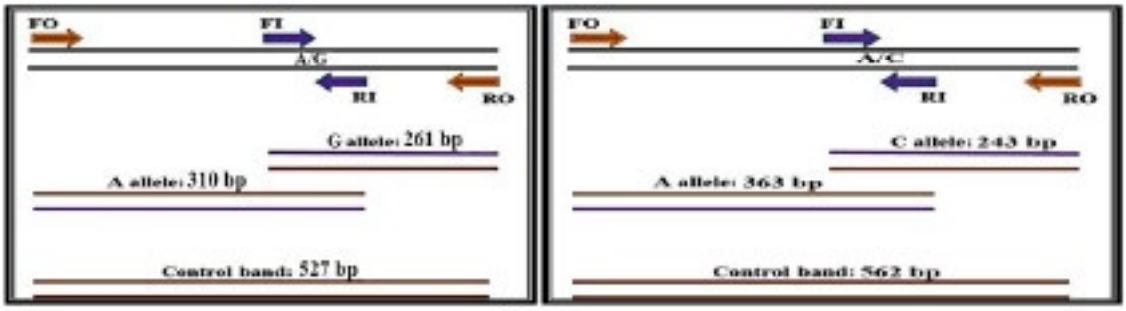

Fig.1 Mechanism of Tetra-ARMS PCR primers for detecting MMP9 (rs17576) (A) and MMP2 (rs7201) (B) polymorphisms. The schematic illustrates the binding of forward outer (FO), reverse outer (RO), forward inner (FI), and reverse inner (RI) primers to the target genomic DNA, producing allele-specific amplicons for each polymorphism.

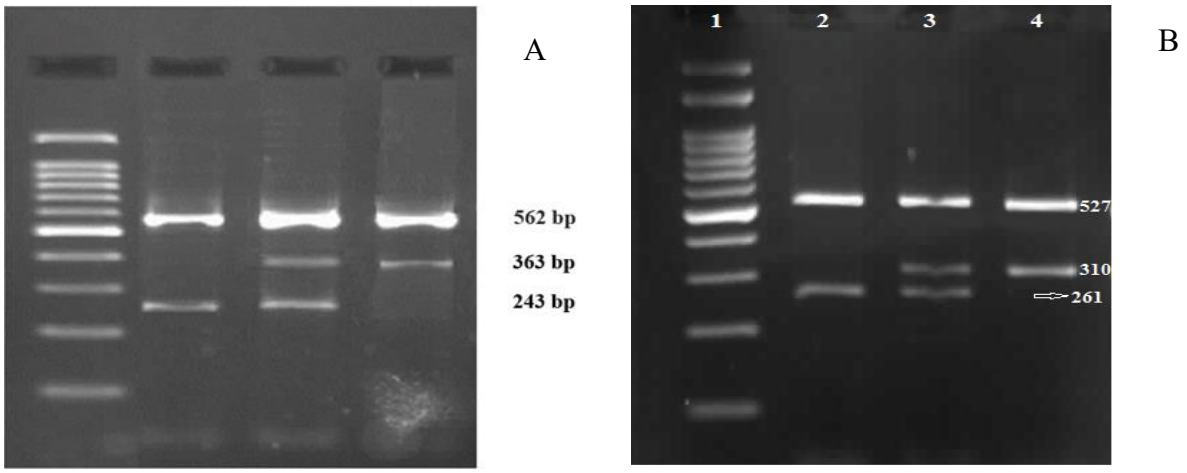

Fig.2 Representative agarose gel electrophoresis showing banding patterns for MMP2-A (rs7201) and MMP9- B (rs17576) genotypes. Distinct band sizes indicate AA, AC, and CC genotypes for rs7201, and AA, AG, and GG genotypes for rs17576, confirming successful amplification and genotyping.

Table 2. Clinical characteristics of patients with papillary thyroid carcinoma (PTC)

Characteristic	Case (n=210)
Mean age at diagnosis, years (Mean ± SD)	43.69 ± 7.622
T Status, n (%)	
T1	81 (41%)
T2	63 (31.8%)
T3	52 (26.3%)
T4	2 (1%)
N Status, n (%)	
N0	23 (12.2%)
Nx	112 (59.6%)
N1	27 (14.4%)
N1a	16 (8.5%)
N1b	10 (5.3%)
M Status, n (%)	
Mx	196 (99.5%)
M1	1 (0.5%)
Stage, n (%)	
I	107 (75.9%)
II	11 (7.8%)
III	20 (14.2%)
IV	3 (2.1%)

in Stage IV. The mean age at diagnosis was 43.69 ± 7.622 years.

Association of MMP2 rs7201 Genotypes with Thyroid Cancer Risk

The distribution of MMP2 rs7201 genotypes and their association with papillary thyroid carcinoma are presented in Table 3. The control group was in Hardy-Weinberg equilibrium for the rs7201 polymorphism (χ^2 = 2.915, df = 1, p = 0.088). A significant difference in distribution of AA, AC, and CC genotypes was observed between the case and control groups. The AC genotype was associated with an increased risk of thyroid cancer (OR = 1.600, 95% CI = 1.052–2.435, p = 0.028). Similarly, the CC genotype showed a stronger association with disease risk (OR = 3.524, 95% CI = 1.809–6.867, p = 0.001). Allelic analysis revealed that the C allele was significantly more frequent in the case group compared to the control group (OR = 1.590, 95% CI = 1.198–2.110, p = 0.001), indicating that individuals carrying the C allele had an approximately 1.6-fold higher risk of developing thyroid cancer compared to those with the A allele.

Association of MMP9 rs17576 Genotypes with Thyroid Cancer Risk

The distribution of MMP9 rs17576 genotypes and their association with papillary thyroid carcinoma are detailed in Table 4. The control group conformed to Hardy-Weinberg equilibrium for the rs17576 polymorphism (χ^2 = 2.410, df = 1, p = 0.120). No statistically significant differences in genotype frequencies were observed between the case and control groups. Allelic analysis indicated that the G allele frequency was similar in cases (38%) and controls (40%) (OR = 0.905, 95% CI = 0.685–1.194, p = 0.479), suggesting no link between the G allele and thyroid cancer susceptibility.

Association of MMP2 and MMP9 Genotypes with Clinical Characteristics

Table 3. Association of MMP2 rs7201 Genotypes and Alleles with Thyroid Cancer

MMP2 Polymorphism	Control, n (%)	Case, n (%)	OR (95% CI)	P-value
Genotype				
AA	92 (43.8%)	62 (29.5%)	1 (Reference)	-
AC	102 (48.6%)	110 (52.4%)	1.600 (1.052–2.435)	0.028
CC	16 (7.6%)	38 (18.1%)	3.524 (1.809–6.867)	0.001
Allele				
A	268 (64%)	234 (56%)	1 (Reference)	-
C	134 (32%)	186 (44%)	1.590 (1.198–2.110)	0.001

Table 4. Association of MMP9 rs17576 Genotypes and Alleles with Thyroid Cancer

MMP9 Polymorphism	Control, n (%)	Case, n (%)	OR (95% CI)	P-value
Genotype				
AA	81 (38.6%)	80 (38.1%)	1 (Reference)	-
AG	90 (42.9%)	102 (48.6%)	1.148 (0.755–1.745)	0.520
GG	39 (18.6%)	28 (13.3%)	0.727 (0.409–1.292)	0.277
Allele				
A	252 (60%)	262 (62%)	1 (Reference)	-
G	168 (40%)	158 (38%)	0.905 (0.685–1.194)	0.479

Table 5. Distribution and Association of MMP2 (rs7201) and MMP9 (rs17576) Genotypes with Clinical Characteristics in Papillary Thyroid Carcinoma

Genotype	T Status, n (%)	N Status, n (%)	Stage, n (%)
MMP2 rs7201	T1 (n=81) / T2 (n=63) / T3 (n=54)	N0/Nx (n=135) / N1 (n=53)	Stage I (n=107) / Stage II-IV (n=34)
AA	27 (45.8%) / 18 (30.5%) / 14 (23.7%)	42 (77.8%) / 12 (22.2%)	30 (71.4%) / 12 (28.6%)
AC	46 (44.2%) / 35 (33.7%) / 23 (22.1%)	69 (69.7%) / 30 (30.3%)	55 (75.3%) / 18 (24.7%)
CC	8 (22.9%) / 10 (28.6%) / 17 (48.6%)	24 (68.6%) / 11 (31.4%)	22 (84.6%) / 4 (15.4%)
p-value	**0.029**	0.509	0.461
MMP9 rs17576			
AA	32 (43.2%) / 24 (32.4%) / 18 (24.3%)	48 (69.6%) / 21 (30.4%)	45 (78.9%) / 12 (21.1%)
AG	38 (39.6%) / 28 (29.2%) / 30 (31.3%)	67 (72.8%) / 25 (27.2%)	43 (69.4%) / 19 (30.6%)
GG	11 (39.3%) / 11 (39.3%) / 6 (21.4%)	20 (74.1%) / 7 (25.9%)	19 (86.4%) / 3 (13.6%)
p-value	0.733	0.866	0.217

The distribution and association of MMP2 (rs7201) and MMP9 (rs17576) genotypes with clinical characteristics in patients with papillary thyroid carcinoma are presented in Table 3-6. For MMP2 rs7201, a significant association was observed with T Status ($\chi^2 = 10.774$, df = 4, p = 0.029). Notably, the CC genotype was more prevalent in T3 (48.6%) compared to T1 (22.9%), suggesting a potential role

in tumor progression. In contrast, no significant associations were found for rs7201 with N Status (χ^2 = 1.350, df = 2, p = 0.509) or Stage (χ^2 = 1.551, df = 2, p = 0.461). For MMP9 rs17576, no significant associations were observed with T Status (χ^2 = 2.013, df = 4, p = 0.733), N Status (χ^2 = 0.287, df = 2, p = 0.866), or Stage (χ^2 = 3.057, df = 2, p = 0.217), indicating that rs17576 genotypes are unlikely to influence these clinical characteristics in this cohort.

DISCUSSION

In this study, we investigated the association of MMP2 rs7201 and MMP9 rs17576 polymorphisms with the susceptibility and clinical characteristics of papillary thyroid carcinoma (PTC). Our findings revealed a significant association between the MMP2 rs7201 polymorphism and thyroid cancer risk, particularly among individuals carrying the AC and CC genotypes. The C allele was significantly more frequent among cases, suggesting it may play a role in increasing susceptibility to thyroid malignancy. Conversely, the MMP9 rs17576 polymorphism did not show any statistically significant association with thyroid cancer risk or clinical staging.

The association between MMP2 polymorphisms and cancer risk has been previously documented in various malignancies. MMP2 encodes for a type IV collagenase that plays a critical role in extracellular matrix degradation, thereby facilitating tumor invasion and metastasis. The rs7201 polymorphism is located in the 3′ untranslated region (3′UTR) of the gene and may influence mRNA stability and gene expression levels (11). Our results are consistent with studies reporting increased cancer susceptibility linked to the C allele of rs7201 in other cancers, such as Head and Neck Squamous Cell Carcinoma (15) and lung carcinoma (16).

The significant association of the CC genotype with advanced tumor stage (T3) observed in our study supports the hypothesis that MMP2 rs7201 variants may contribute not only to the initiation but also to the progression of PTC. Although the association between rs7201 and lymph node metastasis or clinical stage was not statistically significant, a trend toward higher frequency of the CC genotype in more aggressive tumor types was observed. This may warrant further investigation in larger patient cohorts.

On the other hand, our findings do not support a role for the MMP9 rs17576 polymorphism in thyroid cancer susceptibility. This is in agreement with some previous studies that failed to find associations between rs17576 and cancer risk (17, 18), although others have reported significant correlations in esophageal squamous cell carcinoma (19), gastric (20), or prostate cancers (21). It is possible that the functional effect of rs17576 is tissue-specific or modulated by other genetic or environmental factors not assessed in our study.

It is noteworthy that the Hardy-Weinberg equilibrium was maintained in both control groups for the two polymorphisms, indicating the reliability of our genotyping data. The allelic analysis further confirmed the association of the MMP2 rs7201 C allele with PTC risk, while no allelic differences were found in MMP9 rs17576.

The significant association observed between the MMP2 rs7201 C allele and increased risk of papillary thyroid carcinoma highlights the potential utility of this genetic marker in the context of personalized medicine. In light of the current shift toward precision oncology, such genetic variations may serve as valuable tools for individualized risk assessment, early detection strategies, and potentially for tailoring follow-up and therapeutic interventions based on a patient's molecular profile. As noted by Ashley (2015), the integration of genomic data into clinical decision-making represents a transformative step in modern medicine, enabling more effective and targeted management of complex diseases like cancer (22).

Our study has several strengths, including a well-characterized patient population and analysis of clinical-pathological parameters. However, it also has limitations. First, the sample size, particularly for certain clinical subgroups such as N1 (n=53) and Stage II-IV (n=34), was relatively small, which may have limited the statistical power to detect associations with N Status and Stage. Second, the control group was selected from the general population without screening for potential confounders such as family history of thyroid disease, exposure to environmental risk factors (e.g., radiation), or other genetic predispositions, which could influence the observed associations. Third, the study focused on two polymorphisms, and other genetic variants in MMP2, MMP9, or related pathways (e.g., BRAF, TERT) may interact to influence PTC risk and progression. Fourth, the retrospective nature of the study may introduce selection bias, and prospective studies are needed to validate our findings. Finally, functional studies are required to elucidate the mechanistic effects of the rs7201 and rs17576 polymorphisms on MMP2 and MMP9 expression and activity in PTC.

In conclusion, our findings suggest that the MMP2 rs7201 C allele, particularly in the homozygous CC genotype, may be a genetic risk factor for papillary thyroid cancer. This polymorphism could serve as a potential biomarker for early detection or disease progression, pending validation in larger, multi-center studies. In contrast, MMP9 rs17576 does not appear to play a significant role in PTC susceptibility in our population.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Author contributions

Leila Kohan Supervision, Methodology, Reviewing and Editing, Yasam Taabodi and Elahe Kohan Sample collection, Investigations, Statistical analysis, Original draft preparation and Data collection

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