

MATRIX METALLOPROTEINASE-2 GENE POLYMORPHISM AND SUSCEPTIBILITY TO MYOCARDIAL INFARCTION

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ABSTRACT

Background: Myocardial infarction (MI) is a major cause of death in Pakistan. In pathogenesis of MI, Matrix Metalloproteinases-2 (MMP-2) acts as a major contributor by causing extracellular matrix degradation and atherosclerotic plaque rupture. MMP-2 -1306 C/T polymorphism (rs243865) is a variation in MMP-2 gene that increase the risk of MI.

Objectives: The objective of this study was to find out the association of the MMP-2 -1306 C/T polymorphism with development of MI in the Pakistani population.

Methods: It was a case-control study with 36 acute MI patients and 36 matched healthy controls. MMP-2 gene was augmented by Polymerase Chain Reaction and genotype was found out by Restriction Fragment Length Polymorphism (PCR-RFLP). SPSS 26.0 was used to perform statistical analysis.

Results: The heterozygous CT genotype was significantly higher in MI cases (27.8%) than in controls (5.6%; $p = 0.01$), with an odds ratio of 6.53 (95% CI 1.3–32.4). The T allele was also significantly linked with MI ($p = 0.016$). No significantly substantial association was determined between this polymorphism and traditional clinical risk factors, serum MMP-2 levels, or cardiac biomarkers ($p > 0.05$).

Conclusion: The CT genotype and T allele of the MMP-2 -1306 C/T polymorphism are significantly associated with development of MI. This polymorphism may act as an independent genetic risk marker in the Pakistani population.

Key Words: Myocardial infarction; Matrix Metalloproteinase 2; Polymerase chain reaction; Polymorphism, Restriction Fragment Length

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INTRODUCTION

Myocardial infarction (MI), commonly known as a heart attack, is a leading cause of death in our population. It is defined as the death of myocardium due to ischemia. MI is typically diagnosed by rise or fall in cardiac troponins combined with symptoms, like chest pain and ischemic

changes in ECG (Electrocardiogram).¹ In Pakistan, the incidence of myocardial infarction is 188.1 per 100,000 and it accounts for 262.4 deaths per 100,000 people.^{2,3} The pathogenesis of MI involves the rupture of unstable atherosclerotic plaques, which exposes extracellular matrix proteins and causes thrombus formation.⁴ These plaques are usually heavily infiltrated by macrophages, which secrete enzymes called matrix metalloproteinases (MMPs). MMPs are a group of endopeptidases that are zinc-dependent and involved in the destruction of the extracellular matrix and the local fibrous cap, thereby weakening the plaque and increase disease progression.⁵ Although MMPs are involved in normal physiological processes, their increased activity in atherosclerotic plaques plays a role in plaque instability. Among these MMPs, MMP-2, a 72 kDa gelatinase, acts as a major

contributor in the pathogenesis of myocardial infarction and could increase the risk of acute MI.⁶

The MMP-2 gene is located on chromosome 16q13 and contains several transcription factor binding sites in its promoter region.⁷ Genetic variations in these sites can change promoter activity and as a result, can affect MMP-2 enzyme expression. One of these transcription factor-binding sites is the Sp-1 binding site, which has a polymorphism located in its CCACC box in the promoter region, that is -1306 C/T (rs243865) polymorphism.⁸ This polymorphism results in a cytidine (C) to thymidine (T) transition, destroying vital Sp1 transcription factor binding site, significantly decreasing promoter activity and reducing gene expression. This polymorphism has been studied in recent years in association with cardiovascular diseases including myocardial infarction. Studies conducted in various parts of world, including India and Iran, revealed a strong link of MMP-2 -1306C/T polymorphism with myocardial infarction.⁹ A study in Vietnam, has found association of this polymorphism with decrease ejection fraction and carotid artery stenosis.¹⁰ However, international results aren't always consistent, and some studies have found no link at all. Most importantly, we currently have no data on how this genetic susceptibility affects the Pakistani population.

This study aims to determine the frequency and association of the MMP-2 -1306C/T polymorphism with myocardial infarction. By identifying at risk individuals earlier than traditional risk factors allow, we can take preventive steps to reduce the heavy toll this disease takes on lives. Ultimately, this research aims to establish this polymorphism as an independent risk factor for MI.

METHODS

Study Population and Sampling: It was a case-control study which uses a non-probability convenient sampling technique for subject selection. The study population consists of two groups. The first group has 36 diagnosed patients of acute myocardial infarction (cases) recruited

from the Cardiology unit of Hospital, and the second group has 36 age and gender-matched healthy controls from the same population. The recruited patients were unrelated adults (age > 35 years), including both males and females, diagnosed based on the criteria established by the European Society of Cardiology. Individuals with a past history of myocardial infarction were exempted from the study, while controls were selected based on having no present or past history of any cardiac disease.

Data and Sample Collection: The study protocol was approved by the Institutional Review Board of University, and all laboratory work was performed in the Advanced Research Centre for Biomedical Sciences. Written consents were obtained and demographic and clinical data were collected using a proforma, from all subjects. For genetic analysis, 2 ml of venous whole blood was collected into EDTA tube and stored at -20°C for DNA extraction.

DNA Extraction: Whole blood was used to extract the genomic DNA by GeneJET Genomic DNA Purification Mini Kit. This method utilizes silica-based membrane technology in a spin column format. The procedure involved digesting the samples with Proteinase K in a lysis solution, then adding ethanol to facilitate DNA binding to the silica membrane. Impurities were removed by using specific wash buffers, and the purified genomic DNA was stored for later analysis.

Determination of -1306 C/T MMP-2 Genotype by PCR-RFLP: For PCR (Polymerase Chain Reaction), a 50 µl reaction mixture was prepared using 20 µl of nuclease-free water, 25 µl of Dream Taq Green PCR master mix, 1 µl of each primer and 3 µl of extracted DNA. The presence of the 188bp PCR product was confirmed by 1% agarose gel electrophoresis. After this, the product was digested by restriction enzyme and final digested samples were run on a 2.5% agarose gel at 70 volts for 60 minutes to determine the genotypes. All details for the PCR and RFLP (Restriction Fragment Length Polymorphism) are shown in Table 1.^{11,12}

Table 1: PCR-RFLP protocol for MMP-2 -1306 C/T (rs243865) polymorphism

PROCESS	PRIMERS / ENZYME	CONDITIONS	RESULTS
PCR	Forward: 5'-CTT CCT AGG CTG GTC CTT ACT-3' Reverse: 5'-CTG AGA CCT GAA GAG CTA AAG AG-3'	- Initial denaturation at 94°C for 2 min; 31 cycles of 94°C/1 min 62°C/1 min 72°C/2 min; - final extension at 72°C for 2 min	Product Size: 188 bp
RFLP	<i>FspBI</i> (<i>BfaI</i>)	Digestion at 37°C for 2–4 hours	CC: 188 bp CT: 188, 162, 26 bp TT: 162, 26 bp

Statistical Analysis: Data analysis was performed using SPSS 26.0. Mean and Standard deviation were calculated for continuous variables like age while frequencies and percentages were calculated for categorical variables like genotype and allele distribution. Continuous variables (such as age) were analyzed using the Independent-samples t-test or Mann-Whitney U test depending on

data distribution, while categorical variables were analyzed using the Pearson Chi-square test. Hardy-Weinberg Equilibrium (HWE) in the healthy control group was evaluated using the Chi-square goodness-of-fit test. The association of the MMP-2 polymorphism with myocardial infarction was calculated by applying

odds ratio (OR). A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics: Among the 36 Myocardial Infarction patients, 27 (75%) were male and 9 (25%) were female. For cases, 56 years was the median age. Controls were age and gender matched (p-value >0.05).

-1306 C/T Genotype and Polymorphism: Genotype of -1306 C/T MMP-2 was identified by PCR-RFLP in MI patients and controls. The distribution of these genotypes is summarized in Table 2. In both groups, the wild-type homozygous CC genotype was the most common, while the homozygous TT genotype was not found in any subject. Statistical analysis showed a significant association between the CT genotype and MI (p = 0.010), with patients having 6.53 times higher odds of carrying CT genotype than healthy controls.

Table 2: Frequency and Comparison of -1306 C/T MMP-2 Polymorphism between Patients & Controls

Parameter	Sub-group	Category	Patients n (%)	Controls n (%)	p-value	Odds Ratio (95% C.I.)
Genotype	Total Subjects	CC	26 (72.2%)	34 (94.4%)	0.01*	6.53 (1.3–32.4)
		CT	10 (27.8%)	2 (5.6%)		
		TT	0 (0%)	0 (0%)		
	Male Subjects	CC	19 (70.4%)	27 (93.1%)	0.026*	5.68 (1.08–29.8)
		CT	8 (29.6%)	2 (6.9%)		
		TT	0 (0%)	0 (0%)		
	Female Subjects	CC	7 (77.8%)	7 (100%)	0.182	N/A
		CT	2 (22.2%)	0 (0%)		
		TT	0 (0%)	0 (0%)		

*Significant difference (p < 0.05).

To confirm whether the MMP-2 -1306 C/T polymorphism acts as an independent risk factor for myocardial infarction, **a multivariate binary logistic regression analysis** was executed. After adjusting for potential baseline confounders, including age and gender, the heterozygous CT genotype remained a significant, independent predictor of MI (**p = 0.025, Adjusted Odds Ratio [AOR] = 6.54, 95% CI: 1.26–33.87**).

Allele frequency was calculated and compared between patients and control (Table 3). The polymorphic T allele was more prevalent in the MI group compared to the healthy cohort, with patients having 5.64 times higher odds of carrying T allele than healthy controls. These results indicate a substantial correlation between the polymorphic T allele and the risk of MI.

Table 3: Allele Frequency of -1306 C/T MMP-2 Polymorphism

Parameter	Sub-group	Category	Patients n (%)	Controls n (%)	p-value	Odds Ratio (95% C.I.)
Allele	Total Subjects	C	62 (86.1%)	70 (97.2%)	0.016*	5.64 (1.19–26.7)
		T	10 (13.9%)	2 (2.8%)		
	Male Subjects	C	46 (85.2%)	56 (96.6%)	0.03*	4.87 (1.0–24.0)
		T	8 (14.8%)	2 (3.4%)		
	Female Subjects	C	16 (88.9%)	14 (100%)	0.19	N/A
		T	2 (11.1%)	0 (0%)		

*Significant difference (p < 0.05).

The observed genotype frequency of the MMP-2 -1306 C/T polymorphism within healthy control cohort was analyzed for **Hardy-Weinberg Equilibrium**. Because the homozygous mutant TT genotype was entirely absent in the control subjects, the equilibrium was calculated across the remaining categories. The distribution was found to be in strict agreement with the expected frequencies ($\chi^2 = 0.00$, $df = 1$, **p = 0.982**), confirming that the control group is a good reflection of the general population and free from errors in selection or genetic testing.

When compared separately in males and females, as shown in Table 2 and 3, the results in males were similar to the total study population. However, in females, no

significant statistical difference in distribution of CC and CT genotypes and/or C and T alleles between patients and controls was found (p-value = 0.182 & 0.19 respectively). Despite this lack of statistical significance, it was observed that the CT genotype & T allele was present in female patients but was entirely absent in female controls.

Association of Polymorphism with Clinical and Biochemical Factors:

The -1306 C/T MMP-2 genotype was compared between male and female genders by using Chi-square test. A p-value of 0.612 implied that there was no association between gender of subject and MMP-2 genotype.

Then MMP-2 -1306 C/T genotypes were compared with MI risk factors (Table 4). Chi square test was employed to compare CC and CT genotype (as TT genotype had 0 value) in both groups; that is subjects in whom risk factors are present and those in whom risk factors are absent. A p-value >0.05 in all variables implied no

association was found between any MI risk factor and -1306 C/T MMP-2 genotypes. Similarly, these genotypes were compared with cardiac markers in MI patients (Table 4). Statistical analysis indicated that this genotype doesn't appear to have any effect on any cardiac marker in MI patients.

Table 4: Association of -1306C/T MMP-2 genotype with MI risk factors and cardiac markers

Risk Factors/ Cardiac Marker		CC n (%)	CT n (%)	CC vs CT
Hypertension	Present (n= 35)	28 (80)	7 (20)	χ^2 -value= 0.545
	Absent (n= 37)	32 (86.5)	5 (13.5)	p-value =0.46
Diabetes	Present (n= 26)	19 (76)	6 (24)	χ^2 -value= 1.483
	Absent (n= 47)	41 (87.2)	6 (12.8)	p-value =0.223
Family history of MI	Present (n= 28)	24 (85.7)	4 (14.3)	χ^2 -value= 0.187
	Absent (n= 44)	36 (81.8)	8 (18.2)	p-value =0.665
Smoking History	Present (n= 35)	30 (85.7)	5 (14.3)	χ^2 -value= 0.278
	Absent (n= 37)	30 (81.1)	7 (18.9)	p-value =0.598
CK-MB level	Normal (n = 28)	21 (75)	7 (25)	χ^2 -value= 0.485
	High (n = 8)	5 (62.5)	3 (37.5)	p-value =0.486
LDH level	Normal (n = 3)	1(33.3)	2 (66.7)	χ^2 -value= 2.467
	High (n = 33)	25(75.8)	8 (24.2)	p-value =0.116

These findings suggest that the genotype acts as an independent factor in MI susceptibility and is not influenced by traditional risk factors or circulating enzyme levels.

DISCUSSION

The main objective of this research was to determine the association of the -1306 C/T MMP-2 polymorphism with Myocardial Infarction (MI). Our findings suggest that CT genotype & T allele of this polymorphism showed a strong association with MI susceptibility.

The relationship between the -1306 C/T MMP-2 polymorphism and cardiovascular diseases including myocardial infarction has been studied globally with varying results. Several studies align with our findings by showing a positive link between this polymorphism and MI risk. For instance, researches in Malaysia, India and Mexico reported that this MMP-2 genotype acts as a risk factor in development of atherosclerotic plaque and thus results in MI.¹³ In a review article, Bräuninger *et al.* explained the role of MMP-2 polymorphism in development of MI.¹⁴ Similarly, a study in Iran and a separate review by Samah *et al.* confirmed a significant association, while a Turkish study mirrored our results by showing that both the CT genotype and the T allele were more frequent in patients than in healthy cohort.^{9,15} In Vietnam population this polymorphism was linked with drop in ejection fraction and development of cardiac stenosis.¹⁰ While, in Chinese and Russian population -1306 C/T MMP-2 polymorphism was tied to elevated risk of CVD and cardiomyopathy.^{16,17}

Notably, when looking closely at gender, the association was not significant statistically in female subjects (p = 0.182). This difference can be due to two main reasons. First, there is a statistical issue. When we divide our small sample size into subgroups, the statistical power decreases. This makes it much harder for the software to detect a true difference.¹⁸ Second, there is a strong biological reason. Estrogen naturally blocks the activity of MMP genes in women. This hormone changes how MMP-2 behaves during a heart attack.¹⁹ Therefore, the role MMP-2 polymorphism in females might be different

than in males. So, the finding in our study are likely a combined effect of a small sample size and protective female hormones. This trend should be tested in a larger study with more female patients.

When comparing the -1306C/T MMP-2 polymorphism with conventional risk factors, no association was found with hypertension, diabetes, smoking, or family history. This suggests that the genotype may act as an independent risk factor for MI in our population. Our findings regarding risk factors are similar to a previous research article that found no link between the -1306C/T MMP-2 polymorphism and the risk factors of acute MI.²⁰ However, other studies have shown different results. In Vietnam, a positive association was found with this polymorphism and hypertension.¹⁰ Similarly, this polymorphism was positively linked with diabetes, however, these studies were not conducted on MI patients.²¹

As about relation of gene polymorphism and circulating MMP-2 levels in serum, no statistically substantial association was determined between the two variables (p = 0.755). This lack of association may be due to the fact that the activation and release of MMP-2 involves a complicated mechanism driven by post-transcriptional modification and chromatin remodeling and is not influenced by the presence of a polymorphism. This finding is supported by a Polish study which showed no statistically substantial association among plasma MMP-2 levels and the -1306 C/T polymorphism.²²

Similarly, no link was observed between the genotype and cardiac markers like CK-MB and LDH. This may be due to the fact that enzymes like CK-MB and LDH are released through separate biological pathways that are not controlled by MMP-2 genotypes.

In summary, our study demonstrates that the MMP-2 -1306 C/T polymorphism is strongly associated with an increased susceptibility to acute myocardial infarction in the local population. It acts as an independent genetic risk factor.

However, this polymorphism has no association with clinical risk factors and cardiac enzyme levels. Although, due to small female sample size and protective effects of female hormones, results in female population were different than overall population. However, overall results show that this genetic variant can function as a helpful indicator to identify at-risk individuals.

LIMITATIONS

The sample size was relatively small and taken from a single tertiary care center. Follow up of MI patients were not done and data about their outcome was not available. Future studies with larger sample sizes which were conducted in multiple centers are needed to confirm these findings.

CONCLUSION

The study concludes that the CT genotype and T allele of -1306C/T MMP-2 polymorphism are significantly associated with MI. Therefore this polymorphism can be considered as an independent risk factors for MI in the local population. It is recommended to perform larger studies to confirm these results. Using these genetic markers for early screening could help reduce the disease's morbidity, mortality and decrease the burden on the healthcare system.

ETHICAL APPROVAL

Ethical approval of article was granted by the Institutional Review Board of King Edward Medical University, Lahore, vide reference No. 1026/RC/KEMU, Dated: 26.11.2019.

AUTHOR'S CONTRIBUTIONS

IA: Conceptualization of project, data collection, research work

SN: Data collection, manuscript writing, laboratory work

NC: Supervision of project, manuscript writing

NUAW: Literature search, conceptualization of project

AH: Statistical analysis, literature search

MR: Data collection, research work

AJG: Drafting, co-supervision of project

NY: Revision of manuscript

All Authors: Approval of the final version of the manuscript to be published

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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