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ASSOCIATION OF THE POLYMORPHISM RS3918242 OF THE MATRIX METALLOPROTEINASE-9 GENE WITH CORONARY ARTERY DISEASE IN A YOUNGER POPULATION

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ABSTRACT

Coronary artery disease (CAD) is a complex disease resulting from the interaction of numerous so-called traditional risk factors and comorbid conditions on the one side (such as dyslipidemia, smoking, obesity, diabetes, hypertension) and genetic factors on the other. The evidence of a genetic contribution to the development of CAD, especially in the last 2 decades is consistent. It is important that a number of established gene polymorphisms in the younger CAD population are in the genes involved in the inflammatory response and tissue maintenance and remodeling processes.

The aim of this study is to investigate the association of the rs3918242 polymorphism of the matrix metalloproteinase 9 (MMP9) gene with the coronary artery disease in the younger population.

In this observational genetic-association study of cases and controls, the demographic, clinical, laboratory and genetic data of the younger population in a group of selected 70 CAD patients aged up to 45 years were analyzed, of which 35 patients have negative and 35 have positive coronary angiography finding, and 43 are men and 27 are women.

The analysis of the genotypic and allelic frequency determined an association of the polymorphism and the occurrence of the positive coronary angiographic findings in the population of patients under the age of 45. The carriers of the heterozygous genotype CT have almost 5 times higher probability of having a positive coronary angiography finding compared to the carriers of the reference homozygous genotype CC (p=0.012). Thus, this parameter could be used for clinical risk assessment for the development of CAD.

Keywords: coronary artery disease, polymorphisms gene, MMP9

INTRODUCTION

Coronary artery disease (CAD) is one of the main causes of morbidity and mortality worldwide despite the significant progress in diagnosis and therapeutic modalities [1–5]. The incidence of CAD in younger population is relatively low and accounts for 2-10% [1, 6, 7, 8]. When it comes to CAD and "young" or "younger population" there are certain discrepancies in the literature, but most

authors believe that these terms should cover the population up to 45 years of age [2, 5, 6]. Hence, in our research, the previously mentioned terms will refer to persons up to 45 years of age.

CAD is a complex disease resulting from the interaction of numerous, so-called traditional risk factors and comorbid conditions, on one side (such as dyslipidemia, cigarette smoking, obesity, diabetes, arterial hypertension) and genetic factors on the other. Some authors define CAD as a complex genetic disease due to the multiple genetic variants (polygenetic disease) that combined with environmental and lifestyle factors promote this disease [9]. According to the data obtained from family and twin studies, the heritability of CAD is estimated to be between 40% and 60% [10–14].

Despite the obvious and proven importance of environmental factors, lifestyle and individual risk factors and comorbidities, the evidence of genetic contribution to the development of CAD, especially in the last 2 decades is strong and consistent [9]. Enlightening of the genetic determinants of CAD remains problematic and difficult, partly due to the involvement of multiple genes, but, also, due to the fact that each individual gene has only a minor effect on the phenotype [15].

The most common type of mutation that contributes to genomic uniqueness is the substitution of one base with another, which is denoted by the term single nucleotide polymorphism (SNP). In the last decade, large number of multicenter and long-term clinical and genetic-association studies including genome-wide association studies (GWAS, Genome-Wide Association Study) have been completed. With this technique, complete scan of the genome is performed enabling precise genotyping of a huge number of SNPs (up to over 1 million SNPs) [16, 17].

However, there are contradictory results among the researches; in some studies no significant association of a certain gene polymorphism has been identified for which there is data for connection with a certain group of patients, usually from some ethnic or geographic population.

Of particular importance is that a large number of established gene polymorphisms in younger CAD population are found in close proximity or are located in genes that are not related to lipid metabolism and coagulation mechanisms, but to the inflammatory response, tissue maintenance and remodeling processes. Matrix metalloproteinases (MMPs) represent a large family of zinc-dependent endopeptidases that are responsible for the processes of tissue maintenance, remodeling and degradation of the extracellular matrix [18, 19]. They can be classified into several groups, namely: collagenases, gelatinases, stromelysins, matrilysins and membrane type MMP. The MMP activity is complex and regulated at several levels – gene transcription, endopeptidase secretion, activation or inhibition [18]. Their inhibition is controlled by the family of the so-called tissue inhibitors of MMP which are known as TIMP (Tissue Inhibitors of MMP). The increased expression of MMP has been determined in numerous pathological processes such as inflammation, carcinogenesis and metastasis, arthritis, vascular neointimal hyperplasia, plaque rupture, etc. [18, 20].

Of the many gene polymorphisms involved in the etiopathogenesis of CAD and the risk of occurrence in a younger population, in this study we decided to include the rs3918242 polymorphism of matrix metalloproteinase MMP-9, which is involved in the processes of tissue maintenance and remodeling. It is a genetic polymorphism consisting of substitution of cytosine (C) by thymine (T) at position 1562 in the promoter region of the gene for MMP-9 located on chromosome 16q13 that can affect the expression levels of MMP-9 [18, 21]. However, there are numerous case-control studies as well as reviews concerning this polymorphism and CAD, but the conclusions are inconsistent. In this study we examine the genotypic and allelic frequencies of this polymorphism in the Macedonian population in terms of possible association with CAD.

The aim of this study is to determine association of the rs3918242 polymorphism of the MMP9 gene with CAD in a younger population in the absence of the known traditional risk factors.

MATERIAL AND METHODS

In this monocentric, observational, genetic-association study of cases and controls, the genetic data of a total of 70 patients with coronary angiography were analyzed with 35 of them having negative coronary angiography finding (normal or without significant lesions), and 35 are with positive coronary angiography findings (presence of at least one significant lesion). The patients were selected according to the inclusion and exclusion criteria. Gender distribution showed 47 men and 23 women, while in terms of age distribution, all of them are under the age of 45.

All routine demographic, clinical and laboratory data, as well as samples of 3 ml venous blood with anticoagulant (disodium salt of ethylenediaminetetraacetate – Na-EDTA) were taken from patients treated at the University Clinic for Cardiology. The study has been approved by the Ethical Committee at the Faculty of Medicine in Skopje. Also, a signed Informed Consent was provided from each patient prior to the inclusion in the study. All patient data is kept confidential and in accordance to the Law on Personal Data Protection.

The molecular analyses were performed in the Laboratory of Molecular Biology at the Institute of Biology, Faculty of Natural Sciences in Skopje. Genotypic and allelic frequencies of the gene polymorphism rs3918242 in the promoter region of the MMP-9 gene were determined in all participants. The extraction of genomic DNA was by sodium chloride/chloroform method (Gemmell and Akiyama, 1996). Genotyping was performed by the allelic discrimination method, using TaqMan-fluorescent probes with a nucleotide sequence that is specific for the amplified region of the corresponding gene, labeled at the 5'-end with the fluorescent FAM or VIC, while at the 3'-end with the quencher NFQ. The amplification was performed with the StepOne RT-PCR System instrument (Applied Biosystems), and the results were processed with the StepOne software, which is an integral part of the system. The design of the oligonucleotide primers for PCR amplification and TaqMan fluorescent probes for genotyping of polymorphisms was done with PrimerExpress v5.0 software (Applied Biosystems).

For statistical analysis, a comparison was made of the frequencies of genotypes and alleles of the rs3918242 polymorphism of the MMP9 gene, with the relevant demographic, clinical and laboratory parameters in patients with negative and positive coronary angiography findings.

Genotype and allele frequencies of the gene polymorphism were analyzed with the non-parametric Fisher's exact test using the genotypic, allelic, dominant, recessive, heterozygous and superdominant models. The allelic frequencies were analyzed with the allelic and additive model, using the Cochran–Armitage trend test. According to these data, the probability index for chances is calculated – odds ratio (OD) with a confidence interval CI (confidence interval) of 95%. Values of $p<0.05$ are considered statistically significant, while those with $p<0.01$ are considered highly significant.

The statistical calculations were performed with XLSTAT 2016, GenAlEx 6.5 and Microsoft Excel 2016 software.

RESULTS

In terms of gender distribution, data showed that from the total number of participants, 43 or 61.43% are male, and 27 or 38.57% are female. In addition, 60% of the participants from the group with positive coronary angiography finding, as well as around 63% of the participants from the group with negative finding are men (Table 1).

Given that the differences in gender and age distribution between the studied groups are not statistically significant ($p>0.05$), the selection of patients is well balanced and allows genetic-association analysis (Table 2).

The distribution of genotypes of the gene polymorphism rs3918242 of MMP9 in patients with positive and negative coronary angiography findings are shown in Table 3, as well as Diagram 1.

Furthermore, Diagram 2 shows allelic distribution of the gene polymorphism rs3918242 of MMP9 in patients with positive and negative coronary angiography findings.

Statistical analyses were made to assess the probability of association of the examined gene polymorphism rs3918242 of MMP9 with CAD. The comparative analysis of genotypic and allelic frequencies was done with several genetic mod-

Table 1. *Distribution of participants by gender*

Coronary angiography findings (n=70)	In all patients		Group with positive finding		Group with negative finding		Fisher's exact test *
Sex	N	%	n	%	N	%	1.000
Male	43	61.43	21	60.00	22	62.86	
Female	27	38.57	14	40.00	13	37.14	
Total	70	100.00	35	100.00	35	100.00	

*comparison is between the group with positive and negative finding

Table 2. *Distribution of participants by age*

Age	In all patients	Group with positive finding	Group with negative finding	Mann-Whitney-test **
N	70	35	35	0.209
Average	34.27	33.23	35.31	
SD	6.61	6.16	6.96	
Min. age	24	24	24	
Max. age	45	44	45	

*comparison is between the group with a positive and regular finding

**two-sided

Table 3. *Genotypic distribution of the gene polymorphism rs3918242 of MMP9 in patients with positive and negative coronary angiography findings*

Coronary angiography findings	MMP9 rs3918242	N	%
Positive finding	**CC**	16	45.71
	CT	17	48.57
	TT	2	5.71
Total		**35**	**100.00**
Negative finding	**CC**	28	80.00
	CT	6	17.14
	TT	1	2.86
Total		**35**	**100.00**

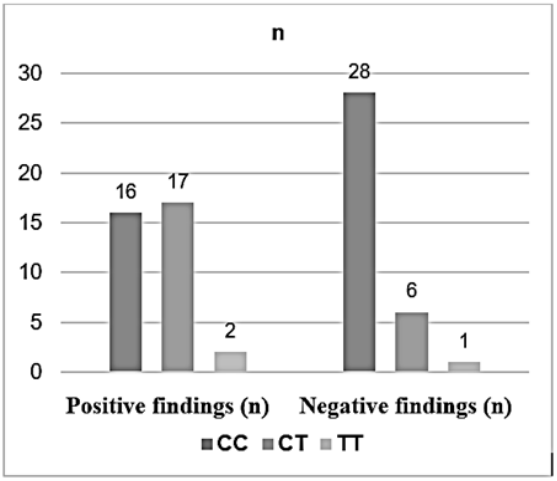


Diagram 1. *Genotypic distribution (CC, CT and TT) of the gene polymorphism rs3918242 of MMP9 in patients with positive and negative coronary angiography findings*

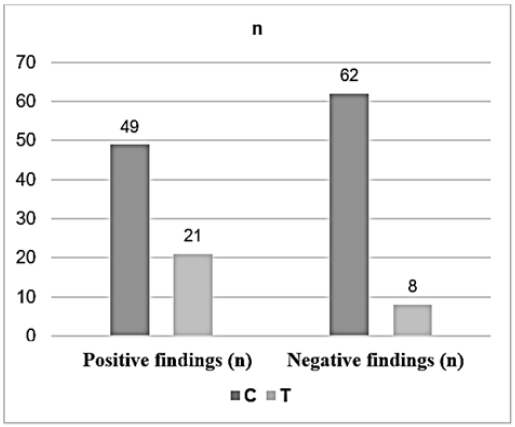


Diagram 2. *Allelic distribution (C, T) of the gene polymorphism rs3918242 of MMP9 in patients with positive and negative coronary angiography findings*

els and the results are presented in Table 4. The comparatively shown results of genotypic combinations, i.e. the frequencies of CC, CT and TT genotype carriers suggest existence of a statistically significant difference between the two studied groups (the group with positive and negative findings).

By using several genetic models, an association was detected between the presence of the rs3918242 polymorphism of the MMP9 gene and the occurrence of a positive coronary angiography finding in the population of patients under the age of 45. Carriers of the heterozygous genotype CT have almost 5 times higher probability of having a positive coronary angiography finding compared to carriers of the reference homozygous genotype CC (p=0.012).

DISCUSSION

Based on the presented results of this study, gene polymorphism rs3918242 of MMP9 is associated with the occurrence of CAD in the younger population. Moreover, the indicated genetic association is statistically significant ($p<0.05$) and has been confirmed using several genetic models.

MMP9 may be particularly important in the process of matrix degradation and subsequent rupture of the atherosclerotic plaque because it has high substrate specificity [21] and high expression in vulnerable regions of the atherosclerotic plaque [20, 22, 23, 24]. For this reason, the genetic analysis of this gene's polymorphisms is extremely important for determining the association with CAD.

Table 4. *Presentation of genotypic and allelic frequencies of the gene polymorphism rs3918242 of MMP9 between the group with positive and negative coronary angiography findings*

Genetic model	MMP9 rs3918242 genotype/allele	Group with positive finding		Group with negative finding		$\chi 2$	*p*	*OR* (95% CI)
Genotypic ǂ	CC	16	45.71	28	80.00	8.867	0.012	Ref.
	CT	17	48.57	6	17.14			4.958 (1.626 - 15.123)
	TT	2	5.71	1	2.86			3.500 (0.294 – 41.704)
	Total	35	100.00	35	100.00			
Dominant	CT + TT	19	54.29	7	20.00	8.811	0.003	4.750 (1.642 – 13.741)
	CC	16	45.71	28	80.00			
	Total	35	100.00	35	100.00			
Recessive	TT	2	5.71	1	2.86	0.348	0.555	2.061 (0.178 - 23.827)
	CC + CT	33	94.29	34	97.14			
	Total	35	100.00	35	100.00			
Heterozygous	CT	17	51.52	6	17.65	8.521	0.004	4.958 (1.626 - 15.123)
	CC	16	48.48	28	82.35			
	Total	33	100.00	34	100.00			
Superdominant	CT	17	48.57	6	17.14	7.835	0.005	4.565 (1.518 - 13.727)
	CC + TT	18	51.43	29	82.86			
	Total	35	100.00	35	100.00			
Allelic	T	21	30.00	8	11.43	7.350	0.007	3.321 (1.355 – 8.140)
	C	49	70.00	62	88.57			
	Total	70	100.00	70	100.00			
Additive #	0 C	16	45.71	28	80.00	2.629	0.007	/
	1 C	17	48.57	6	17.14			
	2 C	2	5.71	1	2.86			
	Total	35	100.00	35	100.00			

ǂ two-sided $\chi 2$ test

two-sided Cochran-Armitage ordinal test

Several studies have shown that gene polymorphisms of the MMP9 family may be associated with CAD risk. However, the results are inconsistent. Rodriguez-Perez et al. showed that the gene polymorphism rs3918242 of MMP9 as well as the CT genotype are associated with the risk of developing myocardial infarction in the Mexican population [25]. Mahmoodi et al. conducted a case-control study to investigate the existence of an association between this gene polymorphism and CAD susceptibility, but the genotypic and allelic frequencies of this polymorphism were similar between CAD patients and controls [26].

Furthermore, a meta-analysis by Zhang et al. from 2014 on 26 studies with 12,776 cases and 6,371 controls found that the gene polymorphism rs3918242 of MMP9 was not associated with CAD risk in overall outcomes [27].

A 2016 published meta-analysis by Li Y-Y et al. of 5,468 subjects from 10 separate studies showed that the gene polymorphism rs3918242 of MMP9 in the Chinese Han population increases the risk for CAD [28].

In a systematic review and meta-analysis by Hassanzadeh-Makoui R. et al. from 2020 of over 40 studies, a total of 11,792 cases and 8,280 controls were included in a quantitative synthesis of association between the rs3918242 gene polymorphism of MMP9 and susceptibility to CAD. The results of this meta-analysis, contrary to the meta-analysis of Zhang et al., suggest that there is a strong positive association between the MMP9 rs3918242 polymorphism and CAD, singling out this single nucleotide polymorphism (SNP) as a risk factor for CAD. The results of the subgroup analysis by ethnicity showed that this gene polymorphism especially increases the susceptibility to CAD in Asians, while no statistically significant association was determined in Europeans. Regarding the type of CAD, however, the results showed a statistically significant association between the MMR9 rs3918242 polymorphism and susceptibility to stable angina across all genotypic models, while only in some genotypic models (dominant and allelic, but not recessive) when it comes to acute coronary syndrome [14].

The gene polymorphism rs3918242 of MMP9 was also examined in the Irish population, in 498 patients with diabetes within the STOP-HF follow-up program. The results of this study showed that the CT/TT genotype was associated with a doubled risk of myocardial infarction (17.9% vs. 8.4%). The conclusion was in favor of an increased risk of myocardial infarction in the population with the minor T-allele of the rs3918242 polymorphism [29].

In a more recent study by Iqbal R. et al. published in 2022, the association of two MMP9 polymorphisms (rs17576 and rs3918242) with myocardial infarction in 5 families and a total of 39 individuals aged 5-75 years in Pakistan was examined. Statistical analysis of genotypic frequencies in the study showed the presence of TT and CT mutations for the rs3918242 polymorphism of MMP9, while all healthy family members were carriers of the wild-type (homozygous) CC genotype for the same polymorphism. Regarding the allelic frequencies, the statistical analysis showed that the T-allele is a risk allele that contributes to a significant association ($p<0.05$) of the rs3918242 polymorphism with myocardial infarction (higher allelic frequency in patients versus controls). What can be concluded from this study is that both mentioned polymorphisms of the MMP9 gene have a significant role in the development of myocardial infarction, whereas the TT and CT genotypes of rs3918242 indicate that the person is a carrier and may later develop myocardial infarction [30].

Another meta-analysis by Feng B. and Li H. was published in 2022 presenting association between rs3918242 polymorphism of MMP9 and susceptibility to myocardial infarction. It included 10 studies published in the period 2005-2017 with a total of 3,087 patients with myocardial infarction and 5,019 healthy controls. It was presented that in patients with myocardial infarction the frequency of mutation of the T-base of the MMP9 polymorphism is higher than in healthy controls, i.e., higher susceptibility to myocardial infarction exists in carriers of the T-allele of MMP9 (CT+CC) compared to carriers of the CC-genotype. Despite several limitations, however, the conclusion of this meta-analysis is that the rs3918242 polymorphism of MMP9 "had potential relevance with susceptibility to myocardial infarction" [31]. Based on the above, it can be concluded that the results obtained from various studies and meta-analyses partially show a positive association of the gene polymorphism rs3918242 of MMP9 with CAD, i.e. with the development of acute myocardial infarction, but to a certain extent they are also contradictory. Therefore, further and focused research is needed taking into account other risk factors as well as other gene variations of MMP9.

CONCLUSION

Our study confirmed association of the gene polymorphism rs3918242 of MMP9 and the occurrence of positive coronary angiography finding in the population of patients under 45 years of age. Carriers of the heterozygous genotype CT are almost 5 times more likely to have positive coronary angiography finding than carriers of the reference homozygous genotype CC.

The obtained results seen in perspective can have application in the clinical practice in the so-called personalized approach, i.e. during the individual clinical assessment of risk for further development of CAD in younger patients.

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Резиме

ПОВРЗАНОСТА НА ПОЛИМОРФИЗМОТ RS3918242 НА ГЕНОТ ЗА МАТРИКС МЕТАЛОПРОТЕИНАЗА-9 СО КОРОНАРНАТА АРТЕРИСКА БОЛЕСТ КАЈ ПОМЛАДАТА ПОПУЛАЦИЈА

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Коронарната артериска болест (КАБ) претставува комплексно заболување, кое со должи на меѓусебна интеракција на бројни, таканаречени традиционални ризик-фактори и коморбидни состојби, од една страна (какви што се дислипидемијата, пушењето цигари, дебелината, дијабетесот, артериската хипертензија) и генетските фактори, од друга страна. Доказите за генетскиот придонес кон развојот на КАБ, особено последниве 2 децении, се силни и конзистентни. Од особено значење е што голем број утврдени генски полиморфизми кај помладата популација со КАБ се наоѓаат во непосредна близина или се лоцирани во самите гени поврзани со инфламаторниот одговор и процесите на ткивно одржување и ремоделирање.

Целта на оваа студија е да се испита асоцираноста на полиморфизмот rs3918242 на генот за матрикс металопротеиназа 9 (MMP9) со коронарната артериска болест кај помладата популација.

Во оваа опсервациска, генетско-асоцијативна студија на случаи и контроли се анализираат демографските, клиничките, лабораториските и генетските податоци за помладата популација, во група од селектирани 70 пациенти со КАБ на возраст до 45 години. Од нив 35 пациенти се со негативен, а 35 со позитивен коронарографски наод и 43 се мажи, а 27 се жени.

Со анализата на генотипската и алелната фреквенција на полиморфизмот rs3918242 на генот за MMP-9, утврдена е асоцираност на полиморфизмот и појавата на позитивен коронарографски наод кај пациенти на возраст до 45 години. Носителите на хетерозиготниот генотип CT имаат речиси петпати повисока веројатност да имаат позитивен коронарографски наод во однос на носителите на референтниот хомозиготен генотип CC (p=0,012). Со тоа, овој параметар би можел да биде применет за клиничка процена на ризикот за развој на КАБ.

Клучни зборови: коронарна артериска болест, генски полиморфизми, MMP9