JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN

Шолу Мақала / Обзорная Статья / Review Article *DOI: 10.23950/1812-2892-JCMK-00778*

Matrix metalloproteinases genes polymorphism in the development of new cardiovascular events

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Received: 2020-05-15
Accepted: 2020-07-13
UDC: 616.1

J Clin Med Kaz 2020; 4(58):19-22

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ABSTRACT

OThe review article presents a study of the literature on the relationship of gene polymorphism of matrix metalloproteinases (MMP 2 (−1575 G>A), MMP3 (−1171 5A/6A), MMP 9 (−1562 C/T) with the risk of developing new cardiovascular events after percutaneous coronary intervention. To achieve this goal, a systematic search and subsequent analysis of publications and online resources was carried out. All publications are indexed in Scopus, Web of Knowledge and e-library.

Key words: coronary heart disease, percutaneous coronary intervention, (MMP 2 (−1575 G>A), MMP3 (−1171 5A/6A), MMP 9 (−1562 C/T), new cardiovascular events, stenting

ЖАҢА КАРДИОВАСКУЛЯРЛЫҚ ОҚИҒАЛАРДЫҢ ДАМУ ҚАУПІНДЕ МАТРИКСТІК МЕТАЛЛОПРОТЕИНАЗАЛАР ГЕНІНІҢ ПОЛИМОРФИЗМІ

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ТҰЖЫРЫМДАМА

Шолу мақаласында матрикстік металлопротеиназалардың гендік полиморфизмінің (MMP 2 (−1575 G>A), MMP3 (−1171 5A/6A), MMP 9 (−1562 C/T) терiшлік тәждік араласудан кейінгі жаңа жүрек-қан тамырлары оқиғаларының пайда болу қаупімен байланысы туралы әдебиеттер ұсынылған. Осы мақсатқа жету үшін жарияланымдар мен интернет-ресурстарды жүйелі іздеу және кейінгі талдау жүргізілді. Барлық басылымдар Scopus, Web of Knowledge және e-library индекстеледі.

Негізгі сөздер: жүректің ишемиялық ауруы, терiшілік тәждік араласу, (MMP 2 (−1575 G>A), MMP3 (−1171 5A/6A), MMP 9 (−1562 C/T)), жаңа жүрек-қан тамырларының оқиғалары, стенттеу

ПОЛИМОРФИЗМ ГЕНОВ МАТРИКСНЫХ МЕТАЛЛОПРОТЕИНАЗ В РИСКЕ РАЗВИТИЯ НОВЫХ СЕРДЕЧНО-СОСУДИСТЫХ СОБЫТИЙ

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РЕЗЮМЕ

В настоящей статье представлен обзор литературы о взаимосвязи полиморфизма генов матриксных металлопротеиназ (MMP 2 (-1575 G>A), MMP3 (-1171 5A/6A), MMP 9 (-1562 C/T) в риске развития новых сердечно-сосудистых событий после чрескожного коронарного вмешательства. Для достижения этой цели был проведен систематический поиск и последующий анализ публикаций и онлайн-ресурсов. Все публикации индексируются в Scopus, Web of Knowledge и e-library.

Ключевые слова: ишемическая болезнь сердца, чрескожное коронарное вмешательство, (MMP 2 (−1575 G>A), MMP3 (−1171 5A/6A), MMP 9 (−1562 C/T), новые сердечно-сосудистые события, стентирование

Introduction

Despite the progress and widespread use of percutaneous coronary intervention, the development of new cardiovascular events are decisive factors that limit its long-term effectiveness.

Today, there are a number of diagnostic concepts aimed at studying the factors affecting the development of new cardiovascular events after percutaneous coronary intervention. The structure of the developed cardiac complication depends on the nature of the intracoronary intervention procedure, the age of the patient, the presence of concomitant diseases, the degree and extent of the lesion, the length of the lesion, the diameter of the vessel lumen after implantation, and other factors.

One recent area of interest is the study of the role of gene polymorphism of matrix metalloproteinases (MMPs) in the development of new cardiovascular events.

Matrix metalloproteinases are classified according to their substrate specificity and structural similarity and are mainly divided into five classes: collagenases (MMP-1, -8 and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10 and -11), metalloelastases, membrane-type MMP (MT-MMP, MMP-14, -15, -16, -17, -24 and -25) and others (MMP-7, -11, -12, -19 , -20 and -23) [1]. In the MMP genes, polymorphic regions, nucleotide variants that are associated with the level of expression of these genes were found [1-3].

Coronary heart disease (CHD) is a polygenic disease, and hundreds of genes contribute to its predisposition. A large number of sequence variations have been identified in the MMP genes. MMP function can be modeled by certain pharmacological agents that can be used to diagnose and treat new cardiovascular events.

In a number of studies [2,3], associations of CHD with polymorphic variants of the genes MMP 2 (−1575 G>A), MMP3 (−1171 5A/6A), and MMP 9 (−1562 C/T) were revealed (Table 1).

Table 1

Gene		MMP 3
SNP		rs3025058, 5A / 6A
Geno	**Mag**	**Summary**
(-;-)		5A/5A; higher MI risk?
(-;T)		5A/6A
(T;T)		6A/6A; higher CAD risk

Gene		MMP 3
SNP		rs3918242, C1562T
Geno	**Mag**	**Summary**
(C;C)		normal risk
(C;T)		1.14x increased risk for MI; also check haplotype
(T;T)		1.33x increased risk for MI; also check haplotype

Considering that single nucleotide polymorphisms (SNPs), initially determining the genetic background of patients, it is possible to predispose to the development of cardiovascular events through changes in MMP activity. SNP analysis allows in the early period to personify an assessment of the cause-effect relationships of the development of the disease and to predict the risk of developing cardiovascular complication [4].

According to experts [5], excessive arterial stiffness, determined by the pulse wave propagation velocity (PWV), belongs to the category of subclinical lesions of target organs associated with an increase in the incidence of cardiovascular catastrophes. It is noteworthy that the requirements for markers of vascular elasticity are increasing. So, the vascular stiffness indicator instead of the previous recommendations with a PWV value of ≥12 m/s decreased to a PWR of > 10m/s. Based on the knowledge of arterial stiffness indicators, it is possible to predict with a high degree of probability an unfavorable scenario for the development and course of arterial hypertension (AH) in young and middle-aged people. It should be noted that the pathogenesis of the occurrence of excessive arterial stiffness can be associated with the dysfunction of matrix metalloproteinases (MMP), zinc-containing enzymes that have proteolytic activity against connective tissue proteins and are able to play one of the leading roles in vascular remodeling. Control over the activities of MMP is multi-level in which the genetic level occupies an important place.

There is evidence that one of the causes of excessive arterial stiffness in hypertension and coronary heart disease is the destruction of the intercellular matrix, as a result of the effect of cytosine replacement on the thymine of the MMP 9 (-1564) C/T polymorphism. The presence of the T allele is directly related to the high values of PWV [6]. A number of studies in recent years have shown striking gender differences in the presence of the T allele and high PWV. It was found that Chinese women with the T-allele are significantly higher than PWV, and, especially often, this relationship was observed in the group of patients during the menopause [6-7]. Moreover, not only TT homozygotes, but also CT heterozygotes have a higher PWV than CC homozygotes. As a result of this study, a dose-dependent effect of this mutation was suggested [8-10]. Other researchers [11] found that in individuals with signs of a metabolic syndrome, this polymorphism is functionally more active (OR=3.7) and is associated with the development of acute coronary events. The role of MMP2 (-1306 C/T) in left ventricular hypertrophy in hypertension has been confirmed [12], but the effect on PWV has not been studied.

In the modern period, studies on polymorphisms of MMP genes are open and are of interest, which is revealed by the existing various research designs to find the relationship of MMP with the risk of developing cardiovascular diseases.

In vivo studies have shown that genetic polymorphism has an effect on the differential expression of MMP [13]. Moreover, MMP gene polymorphisms are associated with atherosclerosis and the development of acute myocardial infarction.

One of the significant research designs is case-control. There are a number of case-control studies that have identified the potential link between matrix polymorphism of matrix metalloproteinases and cardiovascular events. Although the available results are still inconsistent, the main meta-analyzes [14–16] indicate that polymorphisms of the MMP-3 Glu45Lys and MMP9 1562 C/T genes were associated with the risk of coronary artery disease.

Data on the relationship between the development of vascular aneurysms and the polymorphism of MMP genes are of scientific interest. Thus, a number of genetic and morphological studies indicate that the development of aneurysm with a bicuspid valve is a consequence of the disturbed structure and expression of a number of genes of the aortic wall itself: a decrease in the amount of fibrillin, fragmentation of elastin, a change in the activity of matrix metalloproteinases (MMP), especially an increase in the activity of MMP 2 and enzyme TIMP1 (tissue inhibitor of collagenase), and a decrease in the activity of MMP 1 [17,18,19]. There are indications that such changes can be caused by gene mutations; therefore, it is of interest to study the polymorphism of genes encoding these proteins and their activity regulators [20]. Interestingly, the TIMP1 gene encoding an inhibitor of MMP1 activity is located on the X chromosome [21], and its genetic variability may partly explain the observed predominance among males compared with females (3:1).

According to other studies [22.23], in patients with a more active genotype (5A5A or 5A6A), MMP-3 also shows a predominance of MMP-3 expression in serum and tissues. At the same time, atherosclerotic plaques with a small amount of connective tissue and a thin fibrous cap, which is more often prone to rupture, which also determines clinical instability, are found in this category of patients. The results of other studies confirm that the MMP-3 5A5A genotype is important for the development of AMI [24-26], especially in the Asian population. However, the value of the 5A allele in the prevalence of AMI in the European population is quite contradictory [27-29]. These studies were conducted by Germans and Italians, who did not reveal any connection between the 5M/3A MMP-3 polymorphism and coronary heart disease.

Blankenberg et al. (2003) showed that the concentration of MMP 9 was higher in patients with coronary artery disease, which would recommend it as a new predictor of cardiovascular disease. The level of activity of MMP enzymes is influenced by many factors, such as genetic MMP polymorphism, drugs, and other components [30].

Lacchini et al. (2010) found that there are interethnic differences in the genetic polymorphisms of MMPs. Thus, the distribution of the T allele is much higher in patients with coronary heart disease in East Asia than in residents of the West of Asia. The relationship between the MMP genotype and the concentration of MMPs also differ in different ethnic groups. In addition, there is no close relationship between the genetic polymorphism of MMP 9 and the activity of the enzyme MMP 9 in a healthy population of Europeans [31]. Although in another study (Metzger et al., 2012), a positive relationship was confirmed in African Americans [32].

In a review study by Juan et al. (2015) showed that the presence of the C-1562T T-allele of the MMP-9 gene polymorphism can be susceptible to patients with myocardial infarction only in Europeans than in Asians [33]. In contrast, in another review by Wang et al. (2014) MMP-9 C-1562T was significantly associated with an increased risk of developing myocardial infarction in the Asian population, but was not confirmed in Europeans [34].

The results of the studies can differ for a number of reasons, including demographic and ethnic differences, problems in the design and implementation of the study in terms of inclusion and exclusion criteria, the size of the sample that affects the power of the study and the analysis taking into account mixed factors.

Conclusion

Thus, the existing scientific discussions on the importance of polymorphism of matrix metalloproteinases genes in the development of heart disease, a series of confirmation of the risk of developing cardiovascular complications after interventions, the data on correlations of gene polymorphisms depending on ethnicity undoubtedly arouse interest in further scientific research on assessment of the characteristics of genetic predictors for personification and prediction of the risk of cardiovascular events.

Disclosures: There is no conflict of interest for all authors.

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How to cite this article: Dana Taizhanova, Akerke Kalimbetova, Ainur Akilzhanova. Matrix metalloproteinases genes polymorphism in the development of new cardiovascular events. J Clin Med Kaz. 2020; 4(58):19-22