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ABSTRACT

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ASSOCIATION OF MMP-9 GENETIC POLYMORPHISM AND MMP-9 CONCENTRATION WITH ECHOCARDIOGRAPHIC PARAMETERS IN UKRAINIAN PATIENTS WITH CORONARY ARTERY DISEASE

Introduction. Cardiovascular diseases are the main cause of reduced life expectancy, workability, and death among the people of Eastern Europe. Matrix metalloproteinase-9 (MMP-9) is known as one of the leading factors involved in the development and progression of atherosclerosis and heart remodeling. The increasing sizes of the heart's chambers lead to changes in the electrophysiological properties of the myocardium and to the subsequent occurrence of arrhythmias and conduction disorders.

Materials and methods. The study included 25 patients with intact coronary arteries (CA), 40 patients with acute coronary syndrome (ACS) and 63 patients with chronic coronary syndrome (CCS) to investigate the effect of MMP-9 polymorphism and its serum concentration on changes in echocardiographic parameters. Real-time PCR was carried out for genotyping on the rs17567-polymorphic locus and ELISA study was performed to measure the MMP-9 plasma concentration.

Results. Statistically significant differences were found in the thickness of the posterior wall of the heart among carriers of the G-allele and AA-homozygotes for the MMP-9 rs17576-single nucleotide polymorphism but only in patients with ACS. The size of the left ventricle posterior wall can be predicted for carriers of these genotypes.

Conclusions. The study revealed no statistically significant relationship between MMP-9 concentration and echocardiographic parameters in patients with ACS and CCS. However, there were statistically significant differences in the left atrium diameter and thickness of the posterior wall of the left ventricle depending on the genotype for MMP-9 rs17576-single nucleotide polymorphism only in patients with ACS. The size of the posterior wall of the left ventricle can be predicted for carriers of AG and GG genotypes.

Keywords: MMP-9; genetic polymorphism; coronary artery disease; echocardiography.

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АСОЦІАЦІЯ ГЕНЕТИЧНОГО ПОЛІМОРФІЗМУ MMP-9 ТА КОНЦЕНТРАЦІЇ MMP-9 З ЕХОКАРДІОГРАФІЧНИМИ ПАРАМЕТРАМИ В УКРАЇНЦІВ, ХВОРИХ НА ІШЕМІЧНУ ХВОРОБУ СЕРЦЯ

Вступ. Серцево-судинні захворювання є основною причиною скорочення тривалості життя, працездатності та смертності жителів Східної Європи. Матриксна металопротеїназа-9 (ММР-9) відома як один з провідних факторів, що беруть участь у розвитку та прогресуванні атеросклерозу, а також ремоделюванні серцевого м'язу. Збільшення розмірів камер серця призводить до зміни електрофізіологічних властивостей міокарда, призводить до подальшого виникнення аритмій і порушення провідності.

Матеріали та методи. До дослідження впливу поліморфізму ММР-9 і її концентрації в сироватці крові на зміни ехокардіографічних параметрів ми залучили 25 пацієнтів з інтактними коронарними артеріями (КА), 40 пацієнтів з гострим коронарним синдромом (ГКС) та 63 пацієнтів з хронічним коронарним синдромом (ХКС). Для генотипування поліморфного локусу rs17567 була проведена ПЛР у режимі реального часу, а для вимірювання концентрації ММР-9 у плазмі було проведено дослідження ІФА.

Результати. Виявлено статистично значущі відмінності в товщині задньої стінки серця серед носіїв G-алелі та основних гомозигот АА поліморфізму ММР-9 rs17576 лише у хворих на ГКС. Для носіїв цих генотипів можна спрогнозувати розміри задньої стінки лівого шлуночка.

Висновки. Дослідження не виявило статистично значущого зв'язку між концентрацією ММР-9 та ехокардіографічними параметрами у пацієнтів з ГКС та ХКС. Проте у пацієнтів з ГКС спостерігалися статистично значущі відмінності в діаметрі лівого передсердя та товщині задньої стінки лівого шлуночка в залежності від генотипу однонуклеотидного поліморфізму ММР-9 rs17576. Для носіїв генотипів AG і GG можна прогнозувати розміри задньої стінки лівого шлуночка.

Ключові слова: ММП-9; генетичний поліморфізм; ішемічна хвороба серця; ехокардіографія.

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INTRODUCTION / ВСТУП

Coronary artery disease (CAD) is a global medical problem that is the leading cause of death in both developing and developed countries, especially in older people [1–3]. MMPs play a vital role at all stages of atherosclerosis through vascular inflammation, endothelial dysfunction, smooth muscle cell migration, vascular calcification, extracellular matrix degradation, plaque activation, and destabilization [4–6]. Several studies reported that the levels of MMPs and their matrix-degrading activity increased in exposed areas of atherosclerotic plaques or following acute coronary syndrome [7–8]. As a result, it is expected that genetic defects resulting in the overexpression of activated MMPs play a crucial role in the pathogenesis of CAD and remodeling of the heart. MMPs are zinc-containing enzymes that belong to a natural protease family. Among the MMP family, MMP-9 is the most critical enzyme produced by the endothelial cells and vascular smooth muscle cells in the vascular wall, neutrophils, and monocytes [6]. Nowadays, it is accepted that genetic component has a significant role in the development of CAD. The human MMP-9 gene, which is located on chromosome 20q12.2–13.1, contains 13 exons and 12 introns. Few gene polymorphisms of MMP-9 have been investigated in relation to CAD. One of them, R279Q (rs17576) of the MMP-9 gene, located in exon 6, is A to G substitution that results in a change in amino acid arginine (R) to glutamine (Q) which lowers the catalytic domain activity of the enzyme [9]. We analyzed seven case-control studies with 5525 cases and 2497 controls concerning MMP-9 (R279Q) polymorphism and risk of CAD [10–16]. Of those, four studies were performed in Asians and three studies were in Europeans. They showed different, sometimes contradictory results in different populations [3].

Our previous study found an association between serum MMP-9 concentrations and the risk of developing ACS in Ukrainian patients [28]. It is known that MMP-9 affects the remodeling of the heart chambers. The increasing size of the heart's chambers leads to changes in the electrophysiological properties of the myocardium and to subsequent arrhythmias and conduction disorders. Therefore, our study aimed to study the association of MMP-9 concentration and rs 17576 polymorphism of the MMP-9 gene with the size of the heart chambers (echocardiographic parameters) in patients with CAD in the Ukrainian population.

Materials and Methods

1. Subjects

128 patients of Sumy Regional Cardiological Clinic (Sumy, Ukraine) were involved in our study. All participants were divided into three groups: 25 patients with angiographically normal (intact) coronary arteries (CA); 40 patients with ACS and 63 patients with CCS, which included class 2–3 stable angina or myocardial infarction (MI) in the past. This study was conducted in accordance with the Declaration of Helsinki (1964). The study protocol was approved by the Ethics Committee of the Medical Institute of Sumy State University, and each participant was required to provide written informed consent. We recorded clinical data, including age, gender, height, weight, smoking status, the presence of arterial hypertension (defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg and/or in case subjects were receiving antihypertensive medication). Body mass index (BMI) was also calculated. All patients were examined using electrocardiography (ECG), coronary angiography, echocardiography. We used Vivid-5 (General Electrics, USA) to estimate echocardiographic parameters. Left atrium diameter (LAD), posterior wall thickness (PWT), interventricular septum thickness (IWST), left ventricular end-diastolic diameter (LVEDD) we measured in parasternal long axis view in B-mode. Ejection fraction (EF) was detected by Simpson in apical view. After coronary angiography, patients with intact CA were assigned to a separate group. A troponin test was conducted for patients with ACS immediately after admission to the hospital. Overnight fasting venous blood samples were collected from each subject for total cholesterol (TC), low-density lipoprotein (LDL – cholesterol), high-density lipoprotein (HDL – cholesterol), triglyceride (TG), AST, ALT, glucose, fibrinogen, erythrocytes, hemoglobin, leucocytes. The glomerular filtration rate was calculated with QxMD Calculator (https://qxmd.com/calculate). Blood for detecting MMP-9 and rs 17567 MMP-9 polymorphism was drawn under standardized conditions before coronary angiography. Blood samples for measuring MMP9 levels were taken and centrifugated immediately after admission to the hospital. Then serum was stored at – 80° C. The drugs for the treatment of each group

corresponded to the current protocols for managing patients with the corresponding disease. ACS patients received double antiplatelet therapy, anticoagulant, beta-blocker, ACE inhibitor, statin. Patients with CCS – antiplatelet drug (aspirin or clopidogrel), beta-blocker, ACE inhibitor, statin. Regardless of nosology, patients with EF below 35% received an aldosterone antagonist (eplerenone).

2. ELISA study

The extracted serum was stored at -80°C before MMP-9 concentration detection. The total serum MMP-9 levels were measured using commercial ELISA immunoassay following the manufacturer's instruction (Platinum ELISA, Affymetrix eBioscience, BMS2016/2 MMP-9, Bender MedSystems GmbH) in all patients.

3. Genotyping

DNA extraction was carried out using whole venous blood by means of "GeneJET Genomic DNA Purification Kit" (Thermo Fisher Scientific, Lithuania). The genotyping for MMP-9 rs17567-single nucleotide polymorphism was performed by Real-time PCR using 7500 Fast Real-time PCR System (Applied Biosystems, Foster City, USA) and Taq-Man Assays (TaqMan®SNP Assay C_11655953_10). PCR conditions were as follows: denaturation at 95°C for 45 seconds, treatment at 95°C for 15 seconds, and 60°C for 30 seconds (45 cycles). The data obtained were processed with 7500 Fast Real-time PCR Software.

4. Statistical analysis

All statistical calculations were done using Statistical Package for the Social Sciences software (SPSS, version 22.0, Chicago, IL, USA). The distribution normality of continuous variables was proved using the Kholmogorov–Smirnov test. Categorical variables were presented as absolute and percentage values. Continuous parameters were presented as mean ± standard deviation (SD) or median with interquartile range. Normally distributed continuous parameters were compared with the help of a two-tailed Student's t-test. The Mann–Whitney test was used to compare the continuous data with other types of distribution. All categorical variables, genotype and allele frequencies were compared using a chi-squared (χ^2) test. The allele distribution compliance with the Hardy–Weinberg equilibrium was determined by the Calculator of Hardy–Weinberg equilibrium (https://wpcalc.com/en/equilibrium-hardy-weinberg/) for each group. The association analysis between MMP-9 rs17567-polymorphism as well as MMP-9 serum concentration and echocardiographic parameters in ACS and CCS patients was performed using correlation analysis and linear regression. Kruskal–Wallis test was used to compare echocardiographic parameters of CAD patients depending on the genotype. The value $P < 0.05$ was accepted as significant.

Results

When we compared the characteristics of patients with CAD and patients with intact coronary vessels, it was found that the comparison groups were not statistically different in the presence of BMI, hypertension, smoking, CX, LDL, HDL, TG, GFR, hemoglobin, erythrocytes (Table 1). However, a statistically significant difference was found in the group of patients with ACS concerning the following: glucose – 5.35 mmol/L ($P = 0.001$), fibrinogen – 2.2 g/L ($P = 0.003$), ALT – 99.05 U/L ($P < 0.001$), AST – 45.2 U/L ($P = 0.003$), MMP-9 – 449.4 ng/ml ($P = 0.002$). The group of patients with CCS was statistically significantly different with age 60.35 ± 7.95, glucose content – 4.7 mmol/L ($P = 0.01$), fibrinogen – 3.7 g/L ($P = 0.038$), MMP-9 – 354.35 ng/ml ($P = 0.004$). The highest MMP-9 concentration had patients with ACS, the lowest – patients with intact coronary arteries and patients with CCS had a middle range of MMP-9 (Table 1).

Using correlation analysis, we did not reveal a statistically significant relationship between MMP-9 concentration and echocardiographic parameters in patients with ACS and CCS (Table 2).

We found statistically significant differences between echocardiographic parameters (PWT and LAD) and the MMP-9 rs17576-polymorphic variant only in patients with ACS (Table 3). After the Bonferroni correction, there were no statistically significant differences in LAD between genotypes for both groups. In contrast, the differences persisted for PWT in the ACS group ($P^a = 0.033$).

The association of echocardiographic parameters and MMP-9 rs17576-single nucleotide polymorphism was investigated using simple linear regression (Table 4).

There were statistically significant differences in the thickness of the posterior wall of the heart between carriers of the G-allele and the main homozygotes of AA in a group of patients who had ACS (Table 4). Thus the thickness (L) of the posterior wall of the heart can be predicted using the obtained linear regression equation.

Table 1 – Baseline characteristic of subjects

Index	ACS n = 40	CCS n = 63	Intact n = 25	P_1	P_2
Age, years[2]	58.35 ± 9.17	60.35 ± 7.95	55.4 ± 9.03	0.209[b]	0.013[b]
Gender, men/women	35/5	55/8	20/5	0.415	0.384
BMI, kg/m^2 [2]	28.69 ± 4.08	30.24 ± 4.97	31.18 ± 5.99	0.051[b]	0.452[b]
AH, n (%)	29 (72.5)	51 (81)	19 (76)	0.755	0.603
Smoker, n (%)	17 (42.5)	11 (17.5)	5 (20)	0.062	0.781
Cholesterol, mmol/L[2]	4.43 ± 1.15	4.44 ± 1.18	4.76 ± 1.67	0.365[b]	0.324[b]
Triglyceride, mmol/L	1.44 ± 0.75[1]	1 (0.84-1.29) [2]	1.24 ± 0.58[1]	0.295[b]	0.369[a]
HDL, mmol/L[2]	1.02 (0.89-1.14) [2]	1.09 ± 0.31[1]	1.07 (0.91-1.44) [2]	0.279[a]	0.439[b]
LDL, mmol/L	2.61 (2.2-3.38)	2.73 (2.07-3.44)	2.8 (1.99-3.36)	0.805[a]	0.628[a]
Glucose, mmol/L[1]	5.35 (4.6-6.9)	4.7 (4.2-5.78)	3.89 (3.53-4.58)	0.001[a]	0.01[a]
Fibrinogen, g/L[1]	2.2 (2-2.8)	3.7 (2.4-27.1)	3 (2.55-3.2)	0.003[a]	0.038[a]
GFR (EPI), ml/min[2]	70.89 ± 21.87	74.41 ± 18.83	79.91 ± 27.8	0.242[b]	0.395[b]
ALT, U/L[1]	99.05 (52.98-212.88)	26.35 (19.18-36.08)	25.35 (19.3-33.28)	< 0.001[a]	0.811[a]
AST, U/L[1]	45.2 (26.78-66.58)	28 (22.6-35.9)	22.25 (19.88-27.73)	0.003[a]	0.168[a]
MMP-9[1]	449.4 (151.15-624.5)	354.35 (149.98-575.58)	67.97 (34.88-303.6)	0.002[a]	0.004[a]
Erythrocytes, $\times 10^{12}$/L[2]	4.52 ± 0.54	4.41 ± 0.51	4.46 ± 0.7	0.749[b]	0.733[b]
Hemoglobin, g/L[2]	148.34 ± 16.79	145.4 ± 14.84	147.11 ± 16.85	0.799[b]	0.679[b]

ACS: acute coronary syndrome; CCS: chronic coronary syndrome; Intact: patients with intact coronary arteries; n: number of cases; BMI: body mass index; AH: arterial hypertension; HDL: high-density lipoprotein; LDL: low-density lipoprotein; GFR (EPI): glomerular filtration rate (according to the Chronic Kidney Disease Epidemiology Collaboration); ALT: alanine aminotransferase; AST: aspartate aminotransferase.

[1]Data are given in the form of median and interquartile range;

[2]Data are given as mean and standard deviation;

[a]Comparison was performed using the Mann-Whitney criterion;

[b]Comparison was performed using Student's t-criterion. P_1: P-value for ACS and Intact group comparison;

P_2: P-value for CCS and Intact group comparison

Table 2 – Analysis of the correlation between echocardiographic parameters of patients with ACS and CCS and the concentration of MMP-9

Index	R^1	P^1	R^2	P^2
LAD, mm	-0.131	0.582	-0.265	0.124
LVEDD, mm	-0.36	0.119	0.183	0.294
IVST, mm	0.066	0.781	0.153	0.394
PWT, mm	-0.016	0.946	-0.052	0.773
EF, %	0.25	0.288	0.101	0.557

LAD: left atrium diameter LAD; LVEDD: left ventricular end diastolic diameter; IVST: interventricular septum thickness; PWT: posterior wall thickness, EF: ejection fraction;

r – Pearson correlation coefficient; R1, p1 – for patient with ACS, R2, p2 – for patients with CCS

Table 3 – Echocardiographic parameters of patients with ACS and CCS depending on the MMP-9 rs17576-polymorphic variant

Index	Genotype						P_1	P_2
	AA (n = 20)		**AG (n = 23)**		**GG (n = 5)**			
	ACS	**CCS**	**ACS**	**CCS**	**ACS**	**CCS**		
LAD, mm	42 (40.5-44)	43 (42-45.75)	40 (38-41)	43 (41-47)	42.5 (39.75-50.5)	43 (37.5-46.5)	0.046 0.138[a]	0.914
LVEDD, mm	52 (50-56.5)	53 (50-55)	50 (49-54)	54 (50-57)	51 (47.75-52.75)	54 (52.5-56.5)	0.424	0.592
IVST, mm	13 (12-15)	12 (11-13)	12 (12-13)	14 (12-14)	12 (12-14.25)	13.5 (12.25-15.5)	0.135	0.172
PWT, mm	12 (11-12)	11 (10-11)	11 (10.5-11.5)	11.5 (11-13)	10.5 (10-11)	10.5 (9.25-11.75)	0.011 0.033[a]	0.149
EF, %	47 (42-54)	49 (45-62.25)	55 (47.5-55)	58 (47.75-62)	53.5 (49-60.25)	56 (51.5-59)	0.172	0.467

LAD: left atrium diameter LAD; LVEDD: left ventricular end diastolic diameter; IVST: interventricular septum thickness; PWT: posterior wall thickness, EF: ejection fraction.

Note. For each genotype, the values of cardiac parameters in the form of median and interquartile range are given. P_1 – for patient with ACS P_2 – for patient with CCS. P^a – P-value after Bonferroni correction

Table 4 – Analysis of the association between MMP-9 rs17576-single nucleotide polymorphism and echocardiographic parameters in patients with ACS and CCS

Analysis of the relationship between MMP-9 polymorphism and LAD

	ACS			**CCS**		
Regression model	**P**	**B**	**r^2**	**P**	**B**	**r^2**
AG vs AA	0.078	-3.59	0.149	0.753	-0.46	0.014
GG vs AA	0.588	1.437		0.382	-2.21	
Constant	<0.001	42.81		<0.001	44.41	

Analysis of the relationship between MMP-9 polymorphism and LVEDD

	ACS			**CCS**		
Regression model	**P**	**B**	**r^2**	**P**	**B**	**r^2**
AG vs AA	0.29	-1.812	0.063	0.689	0.642	0.007
GG vs AA	0.314	-2.312		0.564	1.607	
Constant	<0.001	52.81		<0.001	52.79	

Analysis of the relationship between MMP-9 polymorphism and IVST

	ACS			**CCS**		
Regression model	**P**	**B**	**r^2**	**P**	**B**	**r^2**
AG vs AA	0.074	-1.278	0.121	0.669	0.231	0.012
GG vs AA	0.422	-0.75		0.445	0.786	
Constant	<0.001	13.5		<0.001	12.96	

Analysis of the relationship between MMP-9 polymorphism and PWT

	ACS			**CCS**		
Regression model	**P**	**B**	**r^2**	**P**	**B**	**r^2**
AG vs AA	0.045	-0.764	0.277	0.743	0.188	0.007
GG vs AA	0.009	-1.375		0.669	-0.464	
Constant	<0.001	11.88		<0.001	11.88	

Analysis of the link between MMP-9 polymorphism and EF

	ACS			**CCS**		
Regression model	**P**	**B**	**r^2**	**P**	**B**	**r^2**
AG vs AA	0.28	3.444	0.078	0.239	3.56	0.029
GG vs AA	0.221	5.25		0.435	4.124	
Constant	<0.001	49		<0.001	51.28	

LAD: left atrium diameter LAD; LVEDD: left ventricular end diastolic diameter; IVST: interventricular septum thickness; PWT: posterior wall thickness, EF: ejection fraction

Discussion

Our study demonstrated that patients with ACS had the highest level of MMP-9 concentrations compared to the CCS and the group with intact coronary arteries. Few previous studies demonstrated that MMP-9 could serve as a biomarker of vulnerable plaques and should be a risk marker for plaque rupture [17, 18, 19]. Also, MMP-9 levels elevated earlier than high-sensitive troponin T and had a higher diagnostic value for the early stage of ACS [20].

An association of the MMP-9 serum concentration with the echocardiographic parameters was not found in patients with ACS nor in patients with CCS. Studies by Sundström et al. (2004) enrolling 699 patients with no history of heart failure and myocardial infarction found that only in men detectable plasma MMP-9 was associated with an almost three times higher chance of increased LVEDD and with 2.5 times higher chances of increasing Left ventricular wall thickness. In men, a positive association was determined between the detectable plasma MMP-9 with LV mass and left ventricular wall thickness. In neither men nor women, LVEDD was associated with the detected MMP-9 [21]. Sundström et al. (2004), after summarizing the results, suggested that the increased plasma MMP-9 levels observed in the phenotypes of left ventricle remodeling in men could indicate increased activity of one or both of the processes of vascular and cardiac remodeling. Plasma MMP-9 levels were associated with several aspects of LV remodeling, and also that MMP-9 was associated with LV scores after adjusting for risk factors may contribute to the notion that plasma MMP-9 is a marker of cardiac ECM remodeling [21]. Kelly D. et al. (2007) also supported information that different concentrations of MMP-9 affected the remodeling of the heart in patients in different ways in specific periods after acute myocardial infarction [22]. Elevated MMP-9 levels, especially in concentric hypertrophy, were shown by Franz M, 2009 [23]. Saglam et al. demonstrated higher levels of MMP-3 and MMP-9 concentrations in hypertensive subjects with ventricular hypertrophy and a statistical correlation of these MMPs with left ventricular PWT and Doppler indices of diastolic dysfunction [24]. Similarly, Ahmed et al. (2006) found an increased MMP-9 and TIMP-1 concentration in subjects with left ventricular hypertrophy and higher levels of TIMP-1 in those with chronic heart failure [25]. Pauline B. C. et al. (2020) demonstrated that the MMP-9 level was associated with a smaller LA volume index, independent of CVD risk factors [26].

Only a few studies were found about the association of the MMP-9 genotype with the size of the heart chambers. In patients with acute myocardial infarction, the presence of the G allele of the rs17576 polymorphism MMP-9 gene and other factors increased the likelihood of hypertrophic left ventricular remodeling [27]. Also, the presence of the minor allele G of the rs17576 polymorphism of the MMP-9 gene and the C allele of the MMP-20 rs2245803 gene (CK = -2.228) enhanced its association with hypertrophic changes in left ventricle geometry [27]. Opstad T.B. et al. (2012) revealed that a variant allele of the exon 6 R279Q A/G polymorphism associated with hypertension and the GG genotype this polymorphism gene induced lower MMP-9 gelatinolytic activity ($p = 0.01$) in patients with angiographically verified stable CAD [16].

The results of our study showed association with echocardiographic parameters (LAD and PWT) only in the group of patients with ACS. In addition, in patients with ACS, statistically significant differences in PWT were revealed between carriers of the G-allele and the main homozygotes of AA.

CONCLUSIONS / ВИСНОВКИ

In the present research, we analyzed the link of MMP-9 serum concentration and MMP-9 rs17567-polymorphic variant with echocardiographic parameters among Ukrainians with CAD.

We did not reveal a statistically significant relationship between MMP-9 concentration and echocardiographic parameters in patients with ACS and CCS. However, there was a statistically significant difference in the left atrium diameter and thickness of the posterior wall of the left ventricle depending on the genotype for MMP-9 rs17576-single nucleotide polymorphism in patients with ACS. The size of the posterior wall of the left ventricle can be predicted for carriers of AG and GG genotypes.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Some limitations of the present study should also be noted. Further studies with expanded comparison groups are needed to confirm the obtained results. It will also be interesting to explore the expression of MMP-9 in cases and controls depending on the 17576-polymorphism.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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