

UDK 575: 616-053.9(57156)

Study of Angiotensin Converting Enzyme (ACE I/D) Gene and Cholesteryl Ester Transfer Protein (CETP D442G) Gene Polymorphism in Elderly Patients with Coronary Heart Disease Living in Yakutia

*Yakut scientific centre on complex medical problems of Russian Academy of Medical Sciences,
Yakutsk*

Arkhipova Natalia Spartakovna – junior research associate YSC CMP RAMS, doctor-
cardiologist, nati8692@mail.ru,

Popova Elena Kapitonovna – candidate of medical sciences, associate professor of
Propaedeutic and Faculty Therapy, North-East Federal University,

Grigoriev Lena Valerevna – candidate of medical sciences, laboratory chief

Ar'ev Alexander Leonidovich – Doctor of Medicine, professor of Gerontology and Geriatrics,
St.Petersburg Medical Academy of Post-graduating Study

The authors have studied I/D polymorphism of ACE gene and CETP D442G gene in group of senior patients with coronary heart disease in regard to nationality, age, sex and coronary heart disease clinical manifestations. Having analyzed ACE I/D gene polymorphism the authors found out the association of genotype II with old myocardial infarction (OMI) (Q-negative), left ventricle hypertrophy (LVH) (with Sokolov-Lyon sign), sick sinus syndrome (SSS) and with a high angina functional class (AFC).

Keywords: coronary heart disease, elderly age, senile age, long-livers, polymorphism, angiotensin converting enzyme gene, cholesteryl ester transfer protein gene.

Introduction

As the population of our planet is getting older, the mode of cardiovascular pathology (in particular coronary heart disease, causing 75 % of death among persons aged 65 and older) is increasing. [2, 7]. Akberov R. F and co-workers [1] assume that genetic predisposition to atherosclerosis occurrence is shown only with aggravating influence of the environment. Coronary heart disease is genetically heterogeneous disease and in most cases is characterized by multifactorial inheritance [5]. To study genetic predisposition to atherosclerosis, in particular coronary heart diseases, the gene analysis is carried out. About 10 genes-candidates of

atherosclerosis and coronary heart disease are known. Among them ACE gene is studied the most. [10]. ACE is a leading factor of renin-angiotensin system. The rates of genotypes and alleles of ACE gene is considerably different in different populations. The lowest rate of D-allele and DD-genotype is in eastern countries such as Japan and China. The higher rate is in Western Europe and the USA [4]. It correlates with mode of atherosclerosis and coronary heart disease among the population in these countries. Thanks to studying CETP gene mutation we know about interrelation between its activity, HDL cholesterol presence and risk of cardiovascular diseases [6]. Mutations of CETP gene, which lead to its synthesis reduction, are well studied in Japanese population [8, 9]. One of CETP gene mutations is determined in the 15th exon. Its consequence is replacement in the 442nd position of amino-acid sequence of D-alanine on glycocoll (D442G).

Considering genetic predisposition to coronary heart disease, it is important to find out genetic associations: polymorphic variants of ACE I/D gene and CETP D442G gene in senior patients with coronary heart disease.

Material and Methods

272 patients with coronary heart disease aged 60 and older have been examined. Among them there were non-indigenous people (n=111) and Yakuts (n=161), men (n=151) and women (n=121). The average age of the patients was $77,2 \pm 0,5$ year. All the patients were examined and treated at the cardiological department of the Geriatric center, Yakutsk. To reveal age differences patients were divided into three age groups: 60–74 years (advanced age, n=115), 75–86 years (senile age, n=113) and 90 years and more (long-livers, n=44). All the patients signed informed consent. The research was approved by local committee on biomedical ethics at Yakut scientific centre on complex medical problems of Russian Academy of Medical Sciences. The coronary heart disease diagnosis was verified on the basis of complaints, anamnesis, examinations, electrocardiograms (ECG) and echocardiography (EchoCG) data, Holter ECG monitoring, and medical documentation study. Samples of DNA were received from peripheral blood lymphocytes using method of Phenolum-chloroformic extraction. The analysis of ACE I/D gene and CETP D442G gene polymorphism were carried out with polymerase chain reaction technique.

Statistical processing of the received results was obtained with use of methods of parametrical and nonparametric statistics. Average number (M), average error (m) – for the signs having continuous distribution; and also mode of occurrence of signs with discrete value were calculated.

Student criterion (t) was applied to estimate inter-group differences of signs having continuous distribution. To compare mode of χ^2 Pearson criterion was applied also. The analysis of signs relations was made by means of r -Pearson criterion, r_s - Spearman criterion and χ^2 Pearson criterion. Statistical processing of the material was carried out with the help of standard software package Statistica for Windows v. 6.0. Critical significance level of null hypothesis (on absence significant differences or factor influences) was considered to be 0,05.

Results and discussion

Analyzing I/D polymorphism of ACE gene, mode DD genotype occurrence was 18,8 % ($n=51$), DI - 43,0 % ($n=117$), II - 38,2 % ($n=104$). We have not revealed authentic differences in mode of distribution of genotypes DD, DI, II among non-indigenous persons ($n=111$) and Yakuts ($n=161$) ($\chi^2=4,00$; $p> 0,10$). Also we haven't detected authentic differences and in mode of distribution of genotypes DD, DI, II on age groups: advanced age ($n=115$), senile age ($n=113$) and long-livers ($n=44$) ($\chi^2=2,23$; $p> 0,10$); elderly, senile age ($n=228$) and long-livers ($n=44$) ($\chi^2=1,66$; $p> 0,10$). However it is noticed that mode of genotype II decreases with the years: at advanced age - 45,2 % ($n=47$), at senile age - 41,3 % ($n=43$) and at the age over 90 years - 13,5 % ($n=14$). Earlier it was stressed [3] that at senile age the risk of a lethality at carriers of a genotype II with an acute coronary syndrome is enlarged twice in comparison with carriers of genotype DD. Considering results of the research of aforementioned authors and ours, it is possible to assume that the genotype of ACE gene II at coronary heart disease patients over 75 years plays a role of the negative factor concerning the forecast of clinical course. Differences between men and women in mode of homozygous genotype comparing the carriers of homo - and heterozygotic genotypes DD, DI, II have been detected. Mode of genotype DD at men ($n=35$, or 23,2 %) is a little above than at women ($n=16$, or 13,2 %) ($\chi^2=5,23$; $p=0,072$). If to compare men and women-carriers of genotypes DD and DI it is possible to notice that there are more carriers among men ($n=35$, or 68,6 %), than among women ($n=16$, or 31,4 %) ($\chi^2=5,23$; $p=0,021$). Possibly, it can be explained by association of genotype DD with raised risk of cardiovascular diseases (CVD). Men are more often subjected to CVD than women [11] are subject. Relations between LVH and ACE gene polymorphism which is one of the genes-candidates promoting the process of myocardium hypertrophy are of particular interest.

We have found out a little stronger relation of Sokolov-Lyon sign with genotype II ($n=25$, or 24,0 %), than with genotype DD ($n=7$, or 13,7 %) and DI ($n=16$, or 13,7 %) ($\chi^2=4,73$; $p=0,092$).

Thus there was no association of other studied ECG-signs of LVH (Cornell-voltage and Huebner-Ungerleider) with homo - and heterozygotic genotypes of ACE gene. (tab. 1).

Statistically significant relation of genotype DD with complete left bundle branch block, genotype II with sick sinus syndrome and FC III is found out (tab. 2).

There is a difference in mode of ACE I/D gene polymorphism according to OMI (Q-negative) presence in anamnesis, FC III stenocardia and exertional angina FC II during examination.

Table 2 shows that genotype II-carriers more often have high FC stenocardia and more frequent mode of OMI (Q-negative) ($\chi^2=3,00$; $p=0,080$), in comparison with group of genotype DD-carriers.

In group of Yakuts unlike non-indigenous persons, there is a tendency to more frequent mode of genotypes II, than DI (tab. 3)

If in the common group of patients-carriers of a genotype II there is only a little predisposition to development LVH (judging by Sokolov-Layon sign), in group of Yakuts (but not in the group of non-indigenous patients) DI-genotype carriers more often have remodeling of myocardium. In both groups LVH was more accurately reflected by means of Sokolov-Layon sign, than using other two ECG-signs of LVH (tab. 4).

We have studied the mode of CETP D442G genotypes polymorphism in 288 (83,4 %) of 354 patients (aged 60 and older) with coronary heart disease. Authentic difference in mode of DG genotype distribution in groups of non-indigenous persons ($n=6$, or 5,2 %) and Yakuts ($n=28$, or 16,3 %) ($\chi^2=8,21$; $p=0,004$) is determined. Statistically significant difference according to mode of DD genotype distribution is not observed (tab. 5).

In 254 of 288 patients (88,2 %) homozygous genotype DD is revealed, the quantity of heterozygotes CETP D442G gene CETP is 11,8 %. Mode of DG genotype carriers among Yakuts is more frequent than in a group of non-indigenous persons (see tab. 5).

Authentic difference in mode of DD and DG genotypes distribution in age groups is not revealed ($\chi^2=1,79$; $p> 0,10$). Authentic differences in mode of DD and DG genotypes distribution in men ($n=159$) and women ($n=129$) ($\chi^2=1,41$; $p> 0,10$) is also unrevealed.

There is no statistically significant relation among D442G genotypes and ECG-signs of LVH: Sokolov-Layon ($\chi^2=0,02$; $p> 0,10$), Cornell-voltage ($\chi^2=0,09$; $p> 0,10$) and Huebner-Ungerleider ($\chi^2=0,01$; $p> 0,10$). In determining the relation between D442G CETP gene and myocardial infarction it is revealed that carriers of genotype DG in comparison with carriers of genotype DD have a tendency to larger predisposition to earlier transferred myocardial infarction

($\chi^2=3,66$; $p=0,053$) – in 2,1 times (12,6 % and 26,5 % accordingly) and to unstable angina ($\chi^2=3,21$; $p=0,070$).

Conclusions

1. The association of a genotype II with the age of the patients, with one of ECG-signs of LVH (Sokolov-Layon) (in group of non-indigenous patients and Yakuts), OMI (Q-negative), SSS and high FC angina is revealed.
2. In group of Yakuts there is a tendency to more frequent revealing of II genotype carriers and association of DI genotype with one of ECG-signs of LVH (Sokolov-Layon sign)
3. DD genotype carriers are revealed more frequently among men than among women.
4. The mode of DG genotype carriers among Yakuts is more frequent than among non-indigenous persons.
5. It is revealed that old myocardial infarction (without pathological Q on ECG) and unstable angina are being developed more often in DG-genotype carriers than in DD-genotype carriers.
6. Relation between D442G genotypes and ECG-signs of LVH is not revealed.

Thus, analysis of ACE I/D gene polymorphism shows that the carriage of genotype II plays an unfavorable role concerning prognosis for HVD in patients with coronary heart disease (senior age groups). To determine the role of CETP DG in prognosis for HVD it is necessary to make additional analysis of association with risk factor of coronary heart disease.

Literature

1. Akberov R. F, Sharafiev A.Z., Mihajlov M. K, others. Progressing multifocal atherosclerosis: etiology, clinical-roentgen diagnostics, modern aspects of treatment. – Kazan.: Idel-press, 2008. – 214p.
2. Vorob'ev P.A., Gorokhova S.G. Coronary heart disease in old people//Clinical gerontology. – 2002. – № 7. – pp. 28–33.
3. Sajgitov R. T, Glezer M. G, Sementsov D.P., Malygina N.A. I/D polymorphism of ACE gene in patients with an acute coronary syndrome//Cardiovascular therapy and preventive measures. – 2006. – № 8. – pp. 34-41.
4. Kuznetsova T, Staessen L.A., Wang J.G., Etc. Polymorphism (presence/absence) a gene angiotensin enzyme and risk of cardiovascular and renal diseases//Cardiology. – 1998. – V. 39, № 7. – pp. 61–75.

5. Malygina N.A., Kostomarova I.V., Melentev A.S., others. Relation of cholesteryl ester transfer protein gene with a genetic predisposition to a myocardial infarction//Clinical medicine. – 2002. – № 8. – pp. 25-29.
6. Barter P.J., Brewer H.B., Chapman M.J. et al. Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis // Arterioscler. Thromb. Vasc. Biol. – 2003. – Vol. 23. – P. 160-167.
7. Bello N., Mosca L. Epidemiology of coronary heart disease in women // Prog. Cardiovasc. Dis. – 2004. – Vol. 46, 4. – P. 287-295.
8. Boekholdt S.M., Thompson J.F. Natural genetic variation as a tool in understanding the role of CETP in lipid levels and disease // J. Lipid Res. – 2003. – Vol. 44. – P. 1080-1023.
9. Curb J.D., Abbott R.D., Rodriquer B.L. et al. A prospective Study of HDL-C and mutations and the risk of coronary heart disease in the elderly // J. Lipid Res. – 2004. – Vol. 45. – P. 948-953.
10. Murray R.K., McKusick V.A. Mendelian Inheritance in Man. Catalogs of Human Genes and Genetic Disorders, 12th ed. – Johns Hopkins Univ. Press, 1998. Online Mendelian Inheritance in Man (OMIM): Center for Medical Genetics, Johns Hopkins ..., 2003. – 693 p.
11. US Department of Health and Human Services. Healthy people 2010: Understanding and improving health. – Washigton, D.C.: U.S. Government Printing Office, 2000.

Table 1

Mode of genotypes DD, I/D and II ACE gene in patients with coronary heart disease (senior age group) (n=272) and their relations with ECG-signs of left ventricle hypertrophy

Signs of left ventricle hypertrophy	Mode of genotypes						χ^2	p
	DD (n=51)		DI (n=117)		II (n=104)			
	abs	rel., %	abs.	rel., %	abs.	rel., %		
Sokolov-Lyon	7	13,7	16	13,7	25	24,0	4,73	=0,092
Cornell-voltage	18	20,5	37	42,0	33	37,5	0,25	>0,10
Huebner-Ungerleider	1	11,1	6	66,7	2	22,2	2,12	>0,10

Table 2

Mode of genotypes DD, I/D and II in patients with coronary heart disease (aged 60 years and older) (n=272) and their relations with complete left bundle branch block (CLBBB), sick sinus syndrome (SSS) and exertional angina FC III (EA FCIII)

Signs	Mode of genotypes						χ^2	p
	<i>DD</i> (n=51)		<i>DI</i> (n=117)		<i>II</i> (n=104)			
	abs.	rel.,%	abs.	rel.,%	abs.	rel.,%		
CLBBB	4	7,8	2	1,7	1	1,0	7,08	=0,029
SSS	0	0	2	1,7	7	6,7	6,49	=0,038
EA FC III	4	7,8	20	17,1	27	26,0	7,74	=0,021

Table 3

Frequency of ACE I/D and II genes revealing in Yakuts (aged 60 and more) with coronary heart disease (n=161)

Genotypes	n	Genotypes and <i>II</i>				χ^2	p
		absent		present			
		abs.	rel.,%	abs.	rel.,%	3,58	=0,056
<i>DI</i>	117	54	46,2	63	53,8		
<i>II</i>	104	35	33,7	69	66,3		

Note: $r_s = 0,13$; $p = 0,056$

Table 4

Mode of genotypes I/D, II and ACE gene in Yakuts (aged 60 and older) (n=161) and their relation with ECG-signs of left ventricle hypertrophy

ECG-signs of LVH	Mode of genotypes						χ^2	p
	<i>DD</i> (n=51)		<i>DI</i> (n=117)		<i>II</i> (n=104)			
	abs.	rel., %	abs.	rel., %	abs.	rel.,%		
Sokolov-Layon	0	0	101	86,3	79	76,0	3,91	=0,046
Cornell-voltage	0	0	37	31,6	33	31,7	0,01	>0,10
Huebner-Ungerleider	0	0	6	5,1	2	1,9	0,83	>0,10

Table 5

Frequency of homo - and heterozygotes CETP D442G gene revealing in Yakuts and non-indigenous patients (aged 60 and older) with coronary heart disease

Genotypes	Patients (n=288)				χ^2	p
	non-indigenous (n=116)		Yakuts (n=172)			
	abs.	rel.,%	abs.	rel.,%		
<i>DD</i>	110	94,8	144	83,7	8,21	=0,004
<i>DG</i>	6	5,2	28	16,3		

Note: $r_s = 0,17$; $p = 0,004$

UDC Subject Classification 616.127-005.8:616-002.4

A.I. Sivtseva, A.V. Pal'shina, A.N. Khorunov, M.E. Sannikova, M.Yu. Chibyeva
Cardiac remodeling in destructive pulmonary tuberculosis concurrent with chronic obstructive bronchitis

State Institution "Research-Practice Center 'Phthisiatry' ",
 Ministry of Health, Sakha Republic (Iakutiia)

The aim of the study was to explore cardiac remodeling in patients with pulmonary tuberculosis (PTB) associated with chronic obstructive bronchitis (COB). 28 patients with various clinical forms of PTB were examined using Doppler echocardiography technique. Anatomical characteristics and velocity rates for right (RV) and left ventricles (LV) were calculated. Our data showed that all patients had right ventricular dilatation (RVEDD; 24.27 ± 0.51 mm), right atrial dilatation (RAEED; 30.39 ± 0.47 mm), increased mean pulmonary artery pressure (mPAP; 25.68 ± 1.21 mmHg), reduced LV systolic function (EF; 54.22 ± 1.33 %), increased myocardial stress (MS; 157.11 ± 5.8 dyn/sm), and pseudonormal filling type (Peak E: 0.79 ± 0.01 m/s; Peak A: 0.41 ± 0.03 m/s.).

Keywords: heart remodelling, pulmonary destructive tuberculosis, Doppler echocardiography.