

# The angiotension converting enzyme (ACE) gene I/D polymorphism in different ethnic groups of geriatric age living in the Far North

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## ABSTRACT

The study of ACE gene I/D polymorphism has been carried out in elderly, senile and long-liver patients with coronary heart disease (CHD) taking into account their nationality, age and sex. It has been recorded that with the increase of age there is a decrease in the frequency of the genotype ACE\*\*/I and a tendency of increase in the frequency of the genotype ACE\*D/\*D. A comparative analysis of genotypes ACE\*D/\*D and ACE\*D/\*I has showed sex differences in the frequency of homozygous genotype detection. Left ventricular hypertrophy can be observed significantly more often among carriers of genotype ACE\*\*/I established by Sokolow-Lyon ECG signs. Association analysis of ACE gene I/D polymorphism has registered significant differences in BMI and blood lipid parameters.

## KEYWORDS

CHD; Geriatric Age; Risk Factors; ACE Gene; Non-Indigenous and Yakut Patients

## 1. INTRODUCTION

Republic of Sakha (Yakutia) is the biggest region in the Russian Federation with the territory of over 3 million square kilometers, occupying one fifth part of the country. More than one third of the territory of Republic is situated beyond the Arctic Circle. The population of Yakutia is less than one million. The population density is 0.3 people per 1 square kilometers, which is 28.3 times lower compared to the indicator of the Russian Federa-

tion in the whole. Yakutia differs from the other regions of Russia not only in the magnitude of its territory, but also in the harsh climatic conditions. The main population of the Republic comprises indigenous and non-indigenous people—Yakut (45.67%) and Russian (41.27%).

The frequency of cardiovascular disease (CVD) occurrence increases with the age worldwide and it is 75% of all the deaths among the people aged 65 and older [1]. The process of aging in Russia as a whole, including the Republic of Sakha (Yakutia), is accompanied by an increase in the proportion of older people in the general population [2,3]. To date, mortality caused by cardiovascular diseases in Russia remains the highest in the world [4,5]. In the structure of mortality in Republic of Sakha (Yakutia) the leading place is also taken by circulatory system diseases—46.9% [6].

More attention is paid to the study of genetic predisposition as a risk factor of CHD and candidates are being searched for the role of death genes and human longevity [7].

In recent years, a lot of money is allocated for fundamental research of aging and age-related diseases study [8]. One of the most investigated candidate genes of CHD is angiotensin converting enzyme (ACE), which is localized on the chromosome 17q23, containing 26 exons and 25 introns [9]. There is a close connection between ACE genotype and activity of an enzyme that controls the content of angiotensin II, which plays a key role in the regulation of human hemodynamics. This polymorphism is associated with multifactorial diseases, such as, myocardial infarction, stroke, asthma, insulin dependent diabetes mellitus, ischemic heart disease and the causes of aging and longevity. Revealing high-risk individuals before signs of the disease is essential for the proper medical

genetic counseling. Prevention of diseases, which substantially reduces human life, is one of the approaches to increasing the actual length of the active life [10].

## 2. AIM

To study features of ACE gene I/D polymorphism in the group of patients with CHD of geriatric age living in the Republic of Sakha (Yakutia), according to their nationality, age and gender.

## 3. MATERIALS AND METHODS

Study was carried out under the joint research project of YSC ILC SB RAMS and Institute of Internal Medicine SB RAMS in Novosibirsk "Atherosclerosis: epidemiology, etiopathogenesis and development of prevention, diagnosis and treatment of the inhabitants of the Far North on the example of the population of Yakutia". The present work had been performed from 2004 to 2009 at the Republican Hospital No. 3 of the Ministry of Health of the Republic of Sakha (Yakutia), Geriatric Centre and YSC ILC SB RAMS.

The criteria for inclusion to the study group are people aged 60 years and older with a verified diagnosis of CHD: the Minnesota category code 1.1.1.-1.2.7, 4.1-4.2, 5.1-5.2, 6-1, 7-1, 8-3 (the latter for people over age 40); exertional angina by questionnaire Rose; detection of zone violation of local myocardial contractility by echocardiography, diagnosis of myocardial ischemia during daily ECG monitoring.

Written informed consent for conduction of biomedical research in this paper was obtained from 272 patients—non-indigenous—Russian (n = 111) and Yakut (n = 161), among them 151 were men and 121 women. Average age of patients is  $77.2 \pm 0.5$  years. Experience of living in the North of non-indigenous patients was more than 35 years at the time of the study. According to the classification of age periods (WHO, 1963), the patients were divided into three age groups: 60 - 74 years of (elder, n = 115), 75 - 86 years (senile, n = 113) and 90 years and older (long livers, n = 44). The study was approved by the local Committee on Biomedical Ethics at YSC CMP SB RAMS.

Molecular genetic studies were carried out in the Department of Molecular Genetics SB RAMS YSC ILC. DNA samples were obtained from peripheral blood lymphocytes using the phenol-chloroform extraction. Polymorphism analysis of I/D ACE gene was performed by PCR and RFLP methods. The following Sequence of oligonucleotide primers was used:

ACE F: 5' ctg-gag-acc-act-ccc-atc-ctt-tct 3'; R: 5 "gat-gtg-gcc-atc-aca-ttc-gtc-aga-t 3".

Statistical processing of the results was performed using methods of parametric and nonparametric statistics.

We calculated arithmetical mean (M), the average error of the mean value (m) for signs having a continuous distribution, and also frequency of occurrence signs with discrete values. To estimate intergroup differences in the characteristic values that have continuous distribution, we used the student t-test, and when comparing frequency values— $\chi^2$ -Pearson criterion.

We used Pearson's r-criterion, Spearman's  $r_s$ -criterion and  $\chi^2$  Pearson criterion to make analysis of the dependence between signs. As for statistical processing of material, we used standard package of the program of applied statistical analysis (Statistica for Windows v. 6.0). A critical level of zero statistical hypothesis reliability (no significant differences or factor influences) was taken as 0.05.

## 4. RESULTS AND DISCUSSIONS

In the analysis of I/D polymorphism of ACE gene in 272 patients of geriatric age with CHD, the genotype frequency of *ACE*\*D/\*D has been amounted to 18, 8% (n = 51), *ACE*\*D/\*I—43, 0% (n = 117), *ACE*\*I/\*I—38, 2% (n = 104). No significant differences have been found in the frequency distribution of genotypes of *ACE*\*D/\*D, *ACE*\*D/\*I, *ACE*\*I/\*I according to nationality and age ( $\chi^2 = 4.00$ ;  $p > 0.10$  and  $\chi^2 = 2.23$ ;  $p > 0.10$  respectively). However, we have noted that the frequency of the genotype *ACE*\*I/\*I decreases with age: in the elderly—40, 9% (n = 47), at senile age—38, 1% (n = 43) and 90 years of age and older—31, 8% (n = 14).

As mentioned above, the proportion of genotype *ACE*\*D/\*D in our group of patients was only 18.8% (less than 1/5 of patients). After having analyzed the genotype *ACE*\*D/\*D and *ACE*\*I/\*I frequencies, we found out that with the increase of age there was a corresponding increase in relative number of patients with genotype *ACE*\*D/\*D, and the number of patients with genotype *ACE*\*I/\*I—slightly reduces (t = 1.74; p = 0.085). According to our data, the reduction in the number of carriers of this genotype occurs in the age of over 75.

Similar results were also obtained by other researchers. For example, when studying I/D polymorphism of ACE gene in different age groups of St. Petersburg residents there was revealed a significant decrease in *ACE*\*I allele and genotype of *ACE*\*I/\*I among people over 70 years [10,11]. On examination of europeoid male population of Novosibirsk it was pointed out that with age there was traced a decrease of allele *ACE*\*I frequency and the relevant genotypes, as well as, an increase of allele *ACE*\*D and its homozygous genotype. It was also found out that *ACE*\*D/\*D had the smallest mortality and was higher for genotype allele *ACE*\*I [12]. During a cohort study in Germany it was detected that the prevalence of D allele of ACE gene and homozygotes for this allele was higher among people over 80 years [13]. However, these find-

ings were not confirmed in other large studies of centenarians living in France and Denmark [14]. A frequency increase of the homozygous genotype of the *ACE\*D/\*D* with the age seems rather contradictory, since, according to the literature, it is characterized by increased cardiovascular risk and mortality in the developed countries [15-18].

In V. N. Anisimov's opinion [19], the data on the polymorphism of the genes, associated with a range of serious diseases, does not reveal any association with the longevity or lead to paradoxical conclusions, like in the case of a high frequency of genotype *ACE\*D/\*D* at centenarian residents of France.

We have identified gender discrepancies, when comparing carriers of homo- and heterozygous genotypes of *ACE\* D/\*D*, *ACE\*D/\*I*, *ACE\*I/\*I*. The frequency of genotype *ACE\*D/\*D* is observed somewhat higher among men (n = 35, or 23, 2%) than among women (n = 16, or 13, 2%) ( $\chi^2 = 5, 23; p = 0.072$ ). If we compare men and women, the patients with genotypes *ACE\*D/\*D* and *ACE\*D/\*I*, it can be noted that the carriers of genotype *ACE\*D/\*D* are significantly more common among men (n = 35, or 68.6%) than among women (n = 16, or 31, 4%) ( $\chi^2 = 5, 23; p = 0.021$ ). This can probably be explained by the association of the genotype *ACE\*D/\*D* with the increased risk of CVD, which are more exposed to men than women [20].

Linkage between left ventricular hypertrophy (LVH), and *I/D* polymorphism of the ACE gene, which is one of

the candidate genes contributing to the process of myocardial hypertrophy, is of particular interest. On the basis of series observations, there was formed the view on the role of the genotype *ACE\*D/\*D* as a risk factor for LVH [21-23]. For the diagnosis of LVH—an independent predictor of coronary heart disease—traditional (most commonly used) ECG-LVH criteria (Sokolow-Lyon index, Cornell voltage and Gubner-Ungerleider signs) were used. A result of research detected a slightly higher connection of Sokolow-Lyon index with genotype *ACE\*I/\*I* (n = 25, or 24.0%) than with the genotype of *ACE\*D/\*D* (n = 7, or 13.7%) and *ACE\*D/\*I* (n = 16, or 13.7%) ( $\chi^2 = 4, 73; p = 0.092$ ). In this case there was no association of other studied ECG signs of LVH (Cornell voltage and Gubner-Ungerleider) with homo- and heterozygous genotypes of ACE gene (Table 1).

In the group of Yakut, unlike non-indigenous people, there is a trend toward more frequent detection of genotype *ACE\*I/\*I*, than genotype *ACE\*D/\*I* (Table 2).

If in the total group of patients with genotype *ACE\*I/\*I* only a certain predisposition to the development of LVH (judging on the basis of Sokolow-Lyon) has been traced, then in the group of Yakut carriers of genotype *ACE\*I/\*I* the myocardial remodeling has been observed more frequently. In both groups, LVH is reflected more precisely by the signs of Sokolow-Lyon, than using the other two studied ECG signs of LVH (Table 3).

According to the several authors, who studied *I/D* polymorphism of ACE gene among patients with acute

**Table 1.** The frequency of genotypes *ACE\*D/\*D*, *ACE\*D/\*I*, *ACE\*I/\*I* in patients of geriatric age with CHD and their connection with ECG signs of left ventricular hypertrophy (n = 272).

Signs of LVH	Frequency of genotypes						$\chi^2$	p
	<i>ACE*D/*D</i> (n = 51)		<i>ACE*D/*I</i> (n = 117)		<i>ACE*I/*I</i> (n = 104)			
	abs.	rel.%	abs.	rel.%	abs.	rel.%		
Sokolow-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.** The frequency of detection of genotypes *ACE\*D/\*I* and *ACE\*I/\*I* in Yakut people of geriatric age with CHD (n = 161).

Genotypes	n	Genotypes <i>*D/*I</i> and <i>*I/*I</i>				$\chi^2$	p
		no		yes			
		abs.	rel.%	abs.	rel.%		
<i>ACE*D/*I</i>	117	54	46.2	63	53.8	3.58	=0.056
<i>ACE*I/*I</i>	104	35	33.7	69	66.3		

Note:  $r_s = 0.13; p = 0.056$ .

**Table 3.** Frequency of genotypes *ACE\*D/\*I* and *ACE\*I/\*I* in Yakut patients of geriatric age with CHD and their correlation with ECG-signs of LVH (n = 161).

ECG-signs of LVH	Frequency of genotypes						$\chi^2$	p
	<i>ACE*D/*D</i> (n = 51)		<i>ACE*D/*I</i> (n = 117)		<i>ACE*I/*I</i> (n = 104)			
	abs.	rel.%	abs.	rel.%	abs.	rel.%		
Sokolow-Lyon	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

coronary syndrome, genotypes *ACE\*D/\*I* and *ACE\*I/\*I* are associated with a favorable prognosis even after an episode of acute myocardial ischemia, but only at the age of less than 75 years. In the senile age the risk of mortality among carriers of genotype *\*I/\*I* tends to be doubled compared with carriers of genotype *ACE\* D/\*D* [24]. Based on the study made in Denmark, we can notice the relatively high risk of death in carriers of genotype *ACE\*I/\*I* compared with the carriers of *ACE \*I/\*D* and *ACE \*D/\*D* [25]. The decrease in the number of patients with genotype *ACE\*I/\*I* with the age, detected by us, indirectly confirms the findings of the above mentioned authors.

Association analysis of *I/D* polymorphism ACE gene gave significant differences in body mass index (BMI) and blood lipids. We have revealed a BMI that corresponds to excess body weight ( $p < 0.05$ ) significantly more often among patients with genotype *ACE\*D/\*I* than with *ACE\*D/\*D*. Separate studies results showed an association of *ACE\*D* allele with the presence of abdominal obesity [26] and, conversely, lack of correlation of polymorphism *I/D* ACE gene with the increased body mass [27]. It has been found that the carriers of genotype *ACE\*D/\*I* compared with the carriers of genotype *ACE\*D/\*D* have significantly higher levels of total cholesterol (TC), cholesterol with very low density lipoproteins (VLDL), high density lipoprotein cholesterol (HDL), triglycerides (TG) ( $p < 0.05$ ) (See **Table 4**).

The results of comparison of groups of patients with genotypes *ACE\*D/\*D* and *ACE\*I/\*I* indicate that there have been significant differences in the content blood

total cholesterol, atherogenic factor (SC) ( $p < 0.05$ ) and especially HDL cholesterol ( $p < 0.002$ ) for almost the same values of the patients' age ( $0.05 < p < 0.10$ ) in the two groups (See **Table 5**).

Comparative analysis of lipid composition of the blood in the groups of carriers of genotypes *ACE\*D/\*D*, *ACE\*D/\*I*, *ACE\*I/\*I* have revealed significantly lower levels of HDL-C ( $H = 13, 99; p < 0.001$ ) in the patients with genotype *ACE\*D/\*D*.

The study results are consistent with the data of other authors who have identified the highest level of HDL cholesterol in carriers of genotype *ACE\*D/\*I* in comparison with carriers of genotypes *ACE\*D/\*D* and *ACE\*I/\*I* [28]. Genotype of *ACE\*D/\*D* is interconnected with adverse changes in blood biochemical parameters, namely, low HDL-C [29]. In the survey of Yakut population the genotype *ACE\*D/\*I* of angiotensin-converting enzyme has been associated with increased total cholesterol and LDL cholesterol in myocardial infarction [30]. According to the results of an earlier research among patients of Moscow population with CHD there was found a correlation of D allele of ACE gene converting enzyme with high plasma levels of total cholesterol and LDL-C [31].

No interrelation of homo- and heterozygous genotypes of ACE gene has been identified with systolic and diastolic blood pressure, smoking factor and diabetes mellitus.

The observed tendency to the increase in the frequency of genotype *ACE\*D/\*D* with the age leads to the need for more in-depth analysis with the inclusion into the study probably a larger number of long-livers.

**Table 4.** The revealed differences when comparing the genotypes of *ACE\*D/\*D*, *ACE\*D/\*I* in patients of geriatric age with CHD (n = 168).

Indexes	Genotypes		t	p	U	p
	<i>ACE*D/*D</i> (n = 51)	<i>ACE*D/*I</i> (n = 117)				
BMI (kg/m <sup>2</sup> )	25.19 ± 0.57	26.63 ± 0.36	2.17	=0.032	2361.0	=0.032
TC (mmol/l)	4.61 ± 0.16	5.02 ± 0.12	1.92	=0.056	2340.0	=0.041
VLDL (mmol/L)	0.51 ± 0.27	0.62 ± 0.03	2.58	=0.011	1983.0	=0.005
HDL cholesterol (mmol/l)	0.75 ± 0.04	0.91 ± 0.04	2.13	=0.034	2117.5	=0.013
TG (mmol/L)	1.12 ± 0.06	1.37 ± 0.06	2.59	=0.011	1989.0	=0.005

**Table 5.** Differences identified when comparing groups of carriers of genotypes *ACE\*D/\*D*, *ACE\*I/\*I* in patients of geriatric age with CHD (n = 155).

Indexes	Genotypes		t	p	U	p
	<i>ACE*D/*D</i> (n = 51)	<i>ACE*I/*I</i> (n = 104)				
Age (years)	78.90 ± 1.28	76.36 ± 0.81	1.74	=0.085	2173.5	=0.069
TC (mmol/l)	4.61 ± 0.16	5.02 ± 0.13	2.08	=0.040	2020.0	=0.025
HDL cholesterol (mmol/l)	0.75 ± 0.04	1.04 ± 0.06	3.21	=0.002	1570.0	<0.002
SC (units)	5.90 ± 0.39	4.96 ± 0.30	1.83	=0.069	1921.0	=0.023

## 5. CONCLUSIONS

1) With the increase in age, the number of patients with genotype *ACE*\**I*/*I* decreases and the tendency to increase proportion of patients with genotype *ACE*\**D*/*D* can be observed. The link between genotype *ACE*\**I*/*I* with one of the ECG signs of LVH (Sokolow-Lyon) allows including it to the factors of cardiovascular risk in the group of people older than 75 years.

2) Patients with genotype *ACE*\**D*/*D* are identified significantly more often among men, than among women.

3) There has been established an association of genotype *ACE*\**D*/*I* with blood lipids and BMI.

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## ABBREVIATIONS

- ACE—Angiotension Converting Enzyme
- BMI—Body Mass Index
- CHD—Coronary Heart Disease
- CMP—Complex Medical Problems
- CVD—Cardio Vascular Disease
- DNA—Deoxyribonucleic Acid
- ECG—Electrocardiography
- HDL—High Density Lipoprotein Cholesterol
- HLV—Hypertrophy of Left Ventricular
- LDL—Low-Density Lipoprotein
- PCR—Polymerase Chain Reaction
- RFLP—Restriction Fragment Length Polymorphism
- SB RAMS—Siberia Branch of Russian Academy of Medical Science
- TC—Total Cholesterol
- TG—Triglyceride
- VLDL—Very Low-Density Lipoprotein
- YSC—Yakut Scientific Centre