



Original Article

Association of the genetic markers for myocardial infarction with sudden cardiac death



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ABSTRACT

Objective: Investigate the association of rs17465637 gene *MIAF3* (1q41), rs1376251 gene *TAS2R50* (12p13), rs4804611 gene *ZNF627* (19p13), rs619203 gene *ROS1* (6q22), rs1333049 (9p21), rs10757278 (9p21), rs2549513 (16q23), rs499818 (6p24) associated with myocardial infarction available from the international genome-wide studies with sudden cardiac death (SCD) in a case-control study.

Methods: A sample of SCD cases ($n = 285$) was formed using the WHO criteria; the control sample ($n = 421$) was selected according to sex and age. DNA was isolated by phenol-chloroform extraction from the myocardial tissue of SCD cases and blood of control cases. The groups were genotyped for the selected SNPs by real-time PCR using TaqMan probes (Applied Biosystems, United States).

Results: No statistically significant differences in the genotype and allelic frequencies of studied single nucleotide polymorphisms between sudden cardiac death cases and control were detectable in general group. By separating the groups of sex and age differences in the genotype frequencies of rs1333049, rs10757278 and rs499818 are statistical significance. Genotypes CC of rs1333049 and GG of rs10757278 are associated with an increased sudden cardiac death risk in men ($p = 0.019$, OR = 1.7, 95% CI 1.1–2.8; $p = 0.011$, OR = 1.8, 95% CI 1.2–2.8, respectively). Genotype AG of rs499818 is associated with an increased sudden cardiac death risk in the women over 50 years old ($p = 0.009$, OR = 2.4, 95% CI 1.3–4.6).

Conclusion: Polymorphisms rs1333049 and rs10757278 are associated with SCD in men and rs499818 in the women aged over 50 years.

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1. Introduction

Cardiovascular diseases are still leading causes of population mortality in many countries of the world. According to the WHO data as of 2010, 56.8% of all fatal cases in the Russian Federation are caused by cardiovascular diseases, with ischemic heart disease (IHD) accounting for 29.5%.¹ Sudden cardiac death (SCD) is one of the IHD forms in the WHO classification (International Classification of Diseases 10th revision); it can develop on the background of a current cardiovascular disease or be a solitary disease manifestation. SCD is a multifactorial state, contributors to which are both genetic and environmental factors. Development of the

predictive component in modern medicine, on the one hand, and the absence of reliable and affordable tools for diagnosing predisposition for SCD development, on the other, encourage the research into genetic factors underlying development of this IHD form. Numerous current genome-wide association and case-control studies deal with the genetic predisposition for IHD and myocardial infarction (MI).^{2–5} However, the studies on the associations of gene polymorphisms and mutations with SCD are still rather few and almost absent in the Russia. Recent genome-wide studies have detected the association of some single nucleotide polymorphisms (SNPs) with an increased risk of IHD and, in particular, myocardial infarction.^{2,6} According to ICD-10, SCD does not include the death of myocardial infarction; however, the clinical picture and the mechanism of fatal outcome development in SCD and myocardial infarction are rather similar. We assumed that the SNPs associated with the development of myocardial infarction might also contribute to SCD development.

So the aim of this study is investigate the association of rs17465637 gene *MIAF3*, rs1376251 gene *TAS2R50*, rs4804611

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gene *ZNF627*, rs619203 gene *ROS1*, rs1333049, rs10757278, rs2549513, rs499818 associated with myocardial infarction available from the international genome-wide studies with sudden cardiac death.

The associations of rs619203 gene *ROS1*, rs1376251 gene *TAS2R50*, and rs4804611 gene *ZNF627* with MI were first detected in a multistage study involving 11,053 SNPs.⁷ Rs499818 and rs2549513 were detected in the genome-wide Framingham Heart Study as most likely associated with widespread IHD outcomes, namely, MI, stroke, and fatal IHD outcome. The fatal IHD outcome was regarded as the death caused by IHD after exclusion of the remaining causes. Also, in Framingham Heart Study a 13-Kb locus of chromosome 9 (9p21) displayed the association of MI, stroke, and fatal IHD outcome; this locus contains several SNPs, including rs1333049 and rs10757278.⁶ In the list of SNPs associated with MI, IHD was included rs17465637, which is based on the results of joint research analysis with a probability greater than 80% is associated with coronary artery disease (OR 1.20).⁸

2. Methods

The design of study is a case–control. The bank of SCD cases for 1999–2012 ($n = 285$; mean age, 53.2 ± 8.8 years; men, 69.9%; and women, 30.1%) was formed. The group included people who died suddenly in Oktyabr'skii district, Novosibirsk, Russia subject to forensic examination which was conducted according to standard protocol by a qualified medical examiner. Standard protocol includes examination of the corpse, an autopsy and examination of body cavities, extracting organocomplexes, the study of organs and tissues, taking material for histological studies. Taking into account a limited volume of information on the time of fatal event development, the formed group contains the fatal cases that developed during 1 h or no more than 24 h in the absence of witnesses and estimated as a death of cardiac genesis according to autopsy. The main postmortem diagnosis is acute coronary insufficiency and acute circulatory failure. The presence of morphological changes in the cardiac tissue typical for myocardial infarction or cardiomyopathies was the exclusion criteria. The persons in a state of alcoholic and drug intoxication identified during the chemical research were excluded from the group. According to the protocols of a forensic study 56.4% of SCD persons have signs of atherosclerosis (75.7% of them – signs of aortic atherosclerosis, 95.7% – signs of coronary atherosclerosis).

The control group was selected statistically comparable in sex and age of the group SCD at a ratio of 3 control individuals to 2 SCD case from the DNA bank of Health, Alcohol and Psychosocial factors In Eastern Europe (HAPIEE) international project that covered the same district of Novosibirsk ($n = 421$; mean age, 59.3 ± 6.5 years; men, 64.1%; and women, 35.9%). HAPIEE is a prospective cohort study to examine the effects of traditional and nontraditional risk factors, social and psychosocial factors in the development of cardiovascular and other noncommunicable diseases in Eastern Europe. Protocol of study included a questionnaire of social and economic life's conditions, history of chronic disease, the state of physical activity and health. The examination included the measurement of growth, body weight, blood pressure, heart rate, circumferences of chest, waist and hips. Also respiratory and cognitive functions were investigated. The control group included individuals without coronary artery disease and myocardial infarction in anamnesis. The individuals from control group did not have criteria of angina pectoris in the questionnaire of G.A. Rose. The ECG also showed no signs of myocardial ischemia, cicatricial changes of the myocardium.

DNA was isolated by phenol–chloroform extraction from the myocardial tissue of SCD cases and blood of control cases.⁹

The groups were genotyped for the selected SNPs rs17465637, rs2549513, rs1376251, rs499818, rs4804611, rs619203, rs1333049,

rs10757278 by real-time PCR in an ABI 7900HT device using TaqMan probes (Applied Biosystems, United States).

The data were statistically processed with the help of SPSS 16.0 software package; the genotype and allelic frequencies of the studied SNPs were determined in the SCD and control groups. The cohorts were compared according to the genotype and allelic frequencies with the help of contingency tables using χ^2 test according to Pearson. In the case of fourfold tables, two-sided Fisher's exact test with Yates' correction for continuity was used. A relative SCD risk for particular allele or genotype was calculated as the ratio of changes using two-sided Fisher's exact test and Pearson's χ^2 test. The examination of linkage disequilibrium was performed using pair-wise r^2 and D' statistics in CubeX.

The study was approved by ethics committee of Federal State Budgetary of Scientific Institution "Institution of Internal and Preventive Medicine".

3. Results

Eight SNPs regarded as the markers associated with MI and IHD according to the data of international genome-wide studies have been tested for their potential association with SCD, namely, SNPs rs17465637, rs2549513, rs1376251, rs499818, rs4804611, rs619203, rs1333049, and rs10757278 (Table 1).

The frequencies of genotypes of rs17465637, rs2549513, rs1376251, rs499818, rs619203, in the control group are in Hardy–Weinberg equilibrium. The genotype frequencies of rs1333049, rs10757278, rs4804611 in the control group deviated from Hardy–Weinberg equilibrium ($\chi^2 = 5.22$, $p = 0.022$; $\chi^2 = 4.66$, $p = 0.031$; $\chi^2 = 3.91$, $p = 0.048$, respectively). Genotyping errors were excluded using PCR and subsequent restriction fragment length polymorphism (RFLP) analysis by original techniques. The results of real-time PCR are identical to the results of PCR–RFLP. In the age group under 50 years genotype frequencies of rs1333049, rs10757278 are in Hardy–Weinberg equilibrium, and in the group older than 50 years there are deviations from it. This may indicate a loss to some genotypes in a population with age, with a corresponding increase in the share of other genotypes in it.

No statistically significant differences were detectable when comparing the SCD and control cohorts according to the genotype and allelic frequencies of rs17465637, rs2549513, rs1376251, rs4804611, rs619203.

Found statistically significant differences in allele frequencies of rs1333049 in the SCD group and control group ($p = 0.024$). In the group of SCD homozygous genotype CC of rs1333049 and homozygous genotype GG of rs10757278 increase compared with the control group, but the difference did not statistical significance ($p = 0.052$ and $p = 0.059$, respectively). By separating the groups of sex these differences are statistical significance. The odd ratio found in the group of men who died SCD carrier GG genotype rs10757278 (26.4%) is 1.8 times higher than in the control group of men (17.2%) (95% CI 1.2–2.8, $p = 0.011$), and genotype CC rs1333049 (26.2%) 1.7 times higher in group of men who died suddenly than in the control group of men (16.9%) (95% CI 1.1–2.8, $p = 0.019$).

The group of women over 50 years old displayed statistically significant differences in the genotype frequencies of SNP rs499818. The share of carriers of AG genotype is 2.4-fold higher in SCD group of women over 50 years old (55.6%) as compared with the control group of women over 50 years old (34.1%) at 95% CI of 1.3–4.6 and $p = 0.009$.

In addition we examined the correlation among rs1333049 and rs10757278 (based on the literature) using pair-wise r^2 and D' statistics for linkage disequilibrium. In control group D' was -0.978 and r^2 was 0.9511.

Table 1
Genotype frequencies in groups.

SNP	Genotype	SCD		Control group		<i>p</i> ^a
		N (total number)	%	N (total number)	%	
rs17465637	AA	13	4.6	30	7.4	0.338
	AC	121	43.2	167	41.0	
	CC	146	51.2	210	51.6	
rs2549513	AA	195	69.4	288	69.2	0.436
	AC	82	29.2	116	27.9	
	CC	4	1.4	12	2.9	
rs1376251	CC	122	46.2	214	51.6	0.281
	CT	110	41.7	163	39.3	
	TT	32	12.1	38	9.2	
rs499818	AA	18	6.3	32	7.6	0.265
	AG	117	40.9	147	35.0	
	GG	151	52.8	241	57.4	
rs4804611	AA	167	58.6	226	54.1	0.370
	AG	103	36.1	173	41.4	
	GG	15	5.3	19	4.5	
rs619203	CC	20	7.2	26	6.5	0.520
	CG	133	47.7	174	43.8	
	GG	126	45.1	197	49.6	
rs1333049	CC	68	24.7	75	18.0	0.052
	CG	149	54.2	230	55.2	
	GG	58	21.1	112	26.9	
rs10757278	AA	66	23.5	111	26.6	0.059
	AG	142	50.5	229	54.9	
	GG	73	26.0	77	18.5	

^a *p*-Value – χ^2 test according to Pearson.

4. Discussion

All of the studied single nucleotide polymorphisms did not show the association with sudden cardiac death in general groups. By separating the groups of sex and age differences in the genotype and allelic frequencies of rs1333049, rs10757278 and rs499818 are statistical significance. Rs17465637, rs2549513, rs1376251, rs4804611, rs619203 did not show the association with sudden cardiac death in our study even in the separation groups by age and sex.

Rs17465637 has been several times tested for its association with cardiovascular diseases. The first study, performed in the United Kingdom, succeeded in finding a correlation between this polymorphism and IHD.¹⁰ Later, the association with IHD was not confirmed by the PAGE study.¹¹ The association of this polymorphism with MI was not also confirmed in Russia.¹² However, studies with United States and Japanese populations detected the association of rs17465637 with MI development.^{3,13} Association of rs17465637 with cardiovascular death, non-fatal myocardial infarction and non-fatal stroke was not confirmed in Controlled ROsuvastatin multiNAtional Trial in Heart Failure (CORONA) trial.¹⁴ In addition, this SNP is likely to be associated with atherosclerosis; in one study, it showed an association with atherosclerosis, however, multifactorial analysis demonstrated that this association was statistically insignificant.¹⁵

The association rs2549513 with MI has been confirmed by the PAGE study with a US population; however, Russian study has not demonstrated any statistically significant distinctions in the genotype frequencies between the MI group and control.^{11,12}

The association of rs1376251 with MI was tested in the studies performed in Germany and Russia.^{12,16}

According to the data on the association of rs4804611 with MI in Japan, the G allele of associated with an increased risk for MI.¹⁷ A statistically significant effect of this SNP on development of IHD in American Caucasians has been also demonstrated in a PAGE study.¹¹ The association of this SNP with MI has not been

confirmed in case–control studies in Germany and Russia.^{12,16} The association of GG genotype rs4804611 was showed in recent meta-analysis involved five eligible studies, 11,639 subjects (6299 patients and 5340 healthy controls).¹⁸

Association of rs619203 with MI was confirmed in a study conducted by Zee et al.¹⁹ Analysis of a Siberian population has succeeded in detecting statistically significant differences between the MI group and the control.¹² The association with MI has not been validated in Germany and with IHD, in a case–control study in Greece.^{16,18}

Polymorphisms rs17465637, rs2549513, rs1376251, rs4804611, rs619203 studied for association with sudden cardiac death the first in the world. And so we cannot conclude that these polymorphisms do not play role in development of sudden cardiac death. Absence of association may be due to the genetic characteristics of our population or small size of group in our study.

Our results do not contradict the results of worldwide research to find the association of rs1333049 and rs10757278 with cardiovascular diseases. In Framingham Heart Study a 13-Kb locus of chromosome 9 (9p21) displayed the association of MI, stroke, and fatal IHD outcome; this locus contains several SNPs, including rs1333049 and rs10757278.⁶ Rs1333049 was in the list of SNPs associated with MI, IHD based on the results obtained in a genome-wide study WNCCE, German MI Family study.⁸ The association with IHD has been earlier shown for rs1333049 in the studies conducted in the United States, Portugal, China, Turkey, Iran.^{2,20–23,27} The C allele of this SNP is also associated with an earlier onset of angina pectoris, MI, and early need in cardiovascular therapy, as has been shown by the study of IHD (Coronary Disease Cohort Study) and MI (Post-Myocardial Infarction) cohorts.²⁴ Also homozygous carriers CC genotype of the rs1333049 showed a reduced risk of 1 year recurrent myocardial infarction, although the C allele had conferred susceptibility to their first acute myocardial infarction in Japan.²⁵ Homozygous CC of the rs1333049 was at a higher risk of suffering myocardial infarction in Austrian cohort.²⁶ In addition, rs1333049 and rs10757278 associated with atherosclerosis. Rs10757278 is

associated with severity and degree of atherosclerosis progress.^{15,28}

The C allele of rs1333049 polymorphism is associated with an increased risk for atherosclerotic plaque development as well as earlier MI onset and severe course.^{4,5,15} The carriers of CC genotype displayed an elevated level of triglycerides and cholesterol in the blood.²⁴ In 2011, polymorphisms rs1333049 and rs10757278 were for the first time tested in a PAGE study for their correlation according to linkage disequilibrium in two population groups; the correlation coefficient amounted to 0.85 and higher; correspondingly, only one SNP of this region was involved in the further study. The results demonstrated that the association with IHD was more pronounced in the individuals before 55 years old and in women.¹¹ Recent large-scale meta-analysis suggests that rs10757278 (or its proxy rs1333049) polymorphism is significantly associated with MI again.²⁹ According to the results of our study male carriers of the genotype GG rs10757278 and CC genotype rs1333049 have an increased risk of SCD. These results completely match the earlier study with a Siberian population on the association of SNPs with MI.¹⁶ In addition we showed that rs1333049 and rs10757278 is in linkage disequilibrium, that completely match the foreign study.

Rs499818 was identified by genome-wide results of the Framingham Heart Study as the most likely outcomes associated with advanced coronary artery disease: MI, stroke, and fatal IHD outcome.⁶ Association of this SNP with MI was confirmed by the Population Architecture using Genomics and Epidemiology (PAGE) study of multiethnic sample of individuals from four prospective American studies and a Siberian population.^{11,12} According to the latter, the share of genotype AA carriers in the MI group was lower as compared with the control group (OR = 0.4; 95% CI, 0.2–0.9; $p = 0.03$).¹² On the group SCD confirm this pattern was not possible, despite the pathophysiological proximity of MI and SCD. Studies confirming the results of Framingham Heart Study on association rs499818 with death from coronary heart disease in the world have been undertaken. According to our results in the group of women over 50 years old AG genotype rs499818 is associated with increased risk of SCD.

5. Study limitations

The limitations of this study included a small sample size. The results may not translate to patients of other ethnicities without special verification because study included only Russian.

6. Conclusion

The association of polymorphisms rs17465637, rs2549513, rs1376251, rs499818, rs4804611, rs619203, rs1333049, and rs10757278 with sudden cardiac death in a Russian population was studied for the first time. Polymorphisms rs1333049 and rs10757278 are associated with SCD in men and rs499818 in the women aged over 50 years.

Conflicts of interest

The authors have none to declare.

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