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Gene polymorphisms associated with lipid metabolism disorders in young adults with risk of sudden cardiac death

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Abstract

Aim. To study the frequency of polymorphisms in genes associated with lipid metabolism disorders in young people with risk of sudden cardiac death, to identify the relationships between gene polymorphisms and risk factors of sudden cardiac death, and to develop mathematical models to identify the probability of carrying mutations in these genes.
Methods. The study included 436 young people (mean age 19.8±1.6 years). A standard examination and survey by questionnaire specially developed by us were conducted to identify an increased risk of sudden cardiac death. 59 individuals with a risk of sudden cardiac death were selected. The control group was 65 people, which was comparable to the study group. A blood test was performed to determine lipid profile and polymorphisms: *Leu28Pro* (rs 429358) in gene *APOE*, *C3238G* (rs 5128) in gene *APOC3*, *Gln192Arg* (rs 662*)* in gene *PON1, Ser447Ter* (rs 328) in gene *LPL*, *G250A* (rs 1800588) in gene *LIPC*. Statistical analysis was performed using the statistical package SPSS 17.0 and Statistica 6.0. The parametric Kruskal–Wallis test, the Mann–Whitney U-test, the Pearson's chi-squared test, the Spearman rank correlation coefficient, and logistic regression analysis were used.
Results. We revealed a high frequency of *Gln192Arg* (rs 662) polymorphism in the *PON1* gene in the group of individuals at risk of sudden cardiac death and its correlation with the deaths in relatives under age 50 years. Mathematical models for predicting the presence of polymorphisms in genes associated with lipid metabolism disorders have been developed. Among the developed mathematical models, the models for identifying carriers of the minor allele of *Gln192Arg* polymorphism in the *PON1* gene, *Ser447Ter* in the *LPL* gene, and *250 G>A* in the *LIPC* gene had the highest sensitivity, specificity, and accuracy.
Conclusion. In persons at risk for sudden cardiac death, it is advisable to conduct a screening for mutations in genes associated with lipid metabolism disorders, especially in *Gln192Arg* polymorphism in gene *PON1*.
Keywords: genes associated with lipid metabolism disorders, lipid metabolism, prevention, sudden cardiac death, prognosis, single-nucleotide polymorphism.

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Background. The mortality rate of young and middle-aged people in the Russian Federation remains at a rather high level. In 2019, the population in the Russian Federation was 146.781 million people, including 52.383 million young people (20–44 years old) and 29.506 million middle-aged people (45–59 years old); the mortality rate of working age people (16–59 years old) comprised 379,883 cases in 2018, including 114,236 deaths due to cardiovascular disease [1].

Moreover, many of the deceased who died due to circulatory system diseases suffered sudden cardiac death (SCD). Due to the rather high prevalence of cardiovascular disease in general and SCD in particular, special attention has been given to the primary prevention of SCD [2, 3].

The first idea of the epidemiology of SCD in the Russian Federation was provided by the Russian RESONANS study conducted in 2011 with residents of Khanty-Mansiysk, Voronezh, and Ryazan. The RESONANS study included 285,736 people with ischemic heart disease (IHD). According to the primary analysis, the incidence of SCD in IHD patients was 69 per 100 thousand of the male population and 26 cases per 100 thousand of the female population.

Thus, an analysis of medical documentation and a survey of witnesses for the onset of lethal outcomes, relatives, and medical personnel were performed. As a result, the incidence of SCD was 156 cases per 100 thousand in the male population and 72 cases per 100 thousand in the female popula-

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tion. The adjusted indicator of the SCD incidence in IHD patients exceeded the official statistics by 2.3 times in men and by 2.8 times in women. Thus, it was concluded that every second case of SCD in the Russian Federation is not detected among men, and two-thirds of SCD cases are not detected among women [2, 4].

The next major study on the incidence of SCD in Russia was the GERMINA register compiled by R.M. Linchak et al. in 2012 on the Bryansk region territory. That study included 417,740 patients aged 25–64 years, and the medical records of 1,447 patients who died due to cardiovascular disease were analyzed. In total, 106 deaths were compatible with the SCD criteria, which corresponded to an incidence of 25.4 per 100 thousand population. Men predominated among the deceased (85%), and the main causes of SCD were acute (37%) and chronic (43%) forms of IHD and most of the SCD cases occurred extramurally (76%) [3].

The large ZODIAC study was performed from 2017 to 2019 to analyze the incidence and structure of SCD in the city of Chita, Trans-Baikal Territory. That study was based on an investigation of autopsy protocols for individuals whose deaths occurred outside of a medical organization. The prevalence of SCD in people of working age according to the register was 29.6 per 100 thousand of the population per year. The predominant causes of SCD included various forms of IHD (58% acute forms and 21% chronic forms) [5].

It was revealed in this register that the incidence of SCD increased in men aged ≥ 31 years, up to 70 years of age, then decreased, and this indicator among men was significantly higher (by 36%) than among women. In women, the increase in SCD due to acute forms of IHD starts at the age of 51 years with a maximum at the age of > 70 years. The overwhelming majority of other forms of IHD were recorded in a group of men and women patients aged 51–70 years, but the number of men significantly prevailed [5].

Thus, summarizing the data of three major studies on SCD conducted in the Russian Federation, the incidence of SCD is 25.4–29.6 cases per 100 thousand population, and most cases of SCD are caused by acute and chronic forms of IHD. Certainly, IHD is a multifactorial disease, which is based on atherosclerotic lesions of the coronary arteries, the intensity of which is determined by environmental factors and genetic characteristics [2–5].

The development and progression of atherosclerosis are induced by disorders of the qualitative and quantitative composition of lipoproteins, which consist of phospholipids, triglycerides, cholesterol, protein components, and apolipoproteins (APOs). The protein components of lipoproteins (APO) determine the structure of molecules, provide communication with cellular receptors, and are responsible for interactions with enzymes.

Depending on the APOs included in the structure, lipoproteins can be classified as apoB-containing (chylomicrons, intermediate, very low density, and low-density lipoproteins), apoAI-containing (high-density lipoproteins), or apoA-containing (lipoprotein a) lipoproteins [6]. ApoB-containing lipoproteins are considered the most atherogenic, and the severity of atherosclerosis in patients is directly proportional to the total contact time of the vascular wall endothelial layer with these lipoproteins [6].

A significant contribution to the development of dyslipidemia is made by genetic polymorphisms of various genes responsible for lipid metabolism. The most studied genes and polymorphisms include the *Leu28Pro* polymorphism (rs 429358) in the *APOE* gene, the *C3238G* (rs 5128) polymorphism in the *APOC3* gene, the *Gln192Arg* polymorphism (rs 662) in the *PON1* gene, the *Ser447Ter* polymorphism (rs 328) in the *LPL* gene, and the *G250A* (rs 1800588) polymorphism in the *LIPC* gene [7–17].

Apo E is synthesized in the liver and brain and is a chylomicron and low-density lipoprotein that initiates the capture and removal of low-density lipoproteins by interacting with receptors on the surface of hepatocytes. The *APOE* gene is localized on chromosome 19, and mutations change the structure of the APO molecule, which disrupts lipid metabolism. Several polymorphic variants of the *APOE* gene are known, including *Leu28Pro* (rs 429358), which is believed to be related to obesity, in addition to an effect on lipid metabolism through changes in the structure of the Apo E molecule, disruption of the mechanism of lipid metabolism, and potentiation of hyperlipoproteinemia. The carriage of the minor T allele in this polymorphism is the risk variant [7, 8, 18].

Apo C3 plays a key role in triglyceride metabolism. It reduces the clearance of triglyceride-saturated lipoproteins and their remnants by inhibiting lipolysis, affects Apo B and Apo E-mediated uptake of these lipoproteins, and promotes the formation of high-density lipoproteins in the liver [9, 19].

The *APOC3* gene encodes a relatively small protein (79 amino acids) that is located at the same locus as the *APOA5* gene on chromosome 11q23. The polymorphisms of this gene (single nucleotide base substitutions, SNP), including *1100 C>T* (*G34G*, rs 4520), *3238 C>G* (rs 5128), *455 T>C* (rs 2854116), and *482 C>T* (rs 2854117) are the most studied, and changes in them are associated with the development of hypertriglyceridemia, arteri-

al hypertension, and IHD [10, 11]. We studied the *3238 C>G* (rs 5128) polymorphism, and carriage of the minor G allele in this polymorphism is traditionally the risk variant [10, 11].

Serum paraoxonase (PON1) is an enzyme secreted by the liver that binds to high-density lipoproteins and prevents lipoprotein peroxidation. Two polymorphisms in the PON1 gene, *Gln192Arg* (rs 662) and *L55M* (rs 854560) are responsible for the oxidation of low-density lipoproteins, are the most studied [12]. This enzyme hydrolyzes a wide range of organophosphorus compounds and has antioxidant and anti-atherogenic properties [13]. The relationship between the presence of a polymorphism in the alleles of the *PON1* gene and the risk of myocardial infarction in young men has been reported [14]. We studied the *Gln192Arg* polymorphism (rs 662), and carriage of the minor G allele in this polymorphism is traditionally the risk variant [20].

Lipoprotein lipase (LPL) is an enzyme involved in lipoprotein metabolism that serves as a modulator of triglyceride metabolism. The LPL gene is located on chromosome 8p22 and encodes a 448 amino acid protein. Changes in this gene increase the risk of various ischemic events [21]. The main function of LPL is the hydrolysis of triglycerides into very low density lipoproteins and chylomicrons, as well as the transfer of the hydrolyzed products to peripheral tissues [22]. The most common polymorphism is the *Ser447Ter* (*S447X*) variant, a mutation in exon 9, which leads to premature codon termination. The carriage of the minor G allele in this polymorphism is the risk variant [15].

The hepatic lipase gene (*LIPC*) is located on the long arm of chromosome 15 (15q21) and encodes hepatic triglyceride lipase, an extracellular protein synthesized by liver parenchyma cells that are involved in lipoprotein metabolism [23]. *LIPC* catalyzes the hydrolysis of triglycerides and phospholipids from plasma lipoproteins, facilitating the remodeling of very low, low, and high-density lipoprotein remnants. *LIPC* also plays an important role in the absorption of high and low-density lipoprotein remnants by the liver. Low *LIPC* activity is associated with a high concentration of high-density lipoproteins. Polymorphism of the *250G/A* loci in the *LIPC* gene is associated with insulin resistance and dyslipidemia, the development of IHD, and cerebral stroke. The carriage of the minor A allele in this polymorphism is the risk variant [16, 17].

Thus, the issue of stratification of the risk of SCD and identifying new predictors for its development, particularly of various genetic polymorphisms, is extremely relevant.

This study aimed to investigate the frequency of gene polymorphisms associated with lipid metabolic disorders in young people at risk of SCD, to identify the relationships between the gene polymorphisms and SCD risk factors, and to develop mathematical models to identify the probability of carriage of mutations in these genes.

Materials and methods. A total of 436 men were examined when they were conscripted into military service at the age of 18–24 years. A standard examination was performed, which included a general blood test, urine test, lung fluorography, electrocardiography (ECG), and consultations with specialists (therapist, surgeon, neurologist, psychiatrist, ophthalmologist, otorhinolaryngologist, and dentist). In addition to the standard examination, 12-lead electrocardiogram data were recorded using the "Cardiometer-MT" complex. Echocardiography was performed, and a survey was conducted using a questionnaire developed by us, aimed at identifying the increased risk of SCD. A biochemical blood test was performed to determine the lipid profile (cholesterol, triglycerides, low-density lipoproteins, very low-density lipoproteins, and high-density lipoproteins) and gene polymorphisms associated with lipid metabolic disorders.

Parameters, such as the source of the rhythm, heart rate, duration of the main intervals and segments, the duration and amplitude of all main waves in all leads, and the calculations of their digital values were automatically assessed when the ECG data were recorded. The voltage criteria for left ventricular myocardial hypertrophy were determined with subsequent verification of the values obtained by a cardiologist.

According to the questionnaire, complaints of syncopal conditions, shortness of breath or pain in the chest area during exercise, signs of cardiac arrhythmia, and conduction disorders were identified. According to the survey, the presence of SCD in close relatives < 50-years was assessed. The compliance of a lethal outcome in a relative with existing SCD criteria was clarified for those who answered yes.

Based on the presence of the complaints and/or changes according to the ECG data (elongation or shortening of the corrected *QT* interval, shortening of the *PQ* interval), we selected 59 men for the SCD risk group.

A total of 65 people without any of the above complaints and with normal ECG data were randomly selected as the control group.

This study was approved by the Independent Ethics Committee of the S.M. Kirov Military Medical Academy on February 18, 2020 (protocol no. 232).

The gene polymorphisms (SNP) in the subjects from the risk and control groups were determined

Table 1. Clinical characteristics of the patients examined (n = 59).

Parameter	Risk group (n = 59)	Control group (n = 65)	p
Age, years	19.7 ± 1.6	21.5 ± 4.4	$p = 0.52$
BMI, kg/m^2	23.4 ± 3.7	23.3 ± 2.9	$p = 0.73$
Degree 1 obesity, n (%)	5 (8.5)	8 (12.3)	$p = 0.487$ $\chi^2 = 0.484$
History of unexplained episodes of loss of consciousness, n (%)	3 (5.3)	0	$p = 0.066$ $\chi^2 = 3.387$
Severe shortness of breath during exercise, n (%)	26 (45.6)	0	$p = 0.0001$ $\chi^2 = 36.244$
Pain and/or discomfort in the chest during exercise, n (%)	22 (38.6)	0	$p = 0.0001$ $\chi^2 = 29.465$
Complaints about irregularity in the cardiac function, n (%)	9 (15.8)	0	$p = 0.002$ $\chi^2 = 10.691$
Attacks of unexplained palpitations, n (%)	11 (19.3)	0	$p = 0.0005$ $\chi^2 = 13.298$
Cases of sudden cardiac death in relatives, n (%)	16 (28.1)	0	$p = 0.0003$ $\chi^2 = 20.239$
Corrected *QT* interval, ms	405.0 ± 18.4	402.2 ± 17.6	$p = 0.61$
Shortening of the *PQ* interval, n (%)	2 (3.4)	0	$p = 0.135$ $\chi^2 = 2.240$
Shortening of the corrected *QT* interval, n (%)	1 (1.7)	0	$p = 0.292$ $\chi^2 = 1.111$
Elongation of the corrected *QT* interval, n (%)	1 (1.7)	0	$p = 0.292$ $\chi^2 = 1.111$

Note: BMI — body mass index.

using Litekh Co. (Russia) kits for the *Leu28Pro* polymorphism (rs 429358) in the *APOE* gene, the *C3238G* polymorphism (rs 5128) in the *APOC3* gene, the *Gln192Arg* polymorphism (rs 662) in the *PON1* gene, the *Ser447Ter* (rs 328) polymorphism in the *LPL* gene, and the *G250A* (rs 1800588) polymorphism in the *LIPC* gene. DNA was isolated from whole blood samples according to the manufacturer's protocol and the frequency and concentration were tested on a Nanodrop 2000C spectrophotometer. The DNA was amplified using the DT-Prime 5 amplifier (Russia).

The statistical analysis was performed using Statistica 6.0 (https://statistica.software.informer.com/6.0/) and SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software. The Kruskal–Wallis test, the Mann–Whitney *U*-test, Pearson's test, the χ^2 test, and Spearman's rank correlation method were used to analyze the data. A p-value < 0.05 was considered significant. To develop a model for predicting the presence of a polymorphism (hetero- or homozygous) in the genes associated with lipid metabolic disorders, we used logistic regression to identify the main factors, and developed mathematical models. The models were developed based on the SCD risk group. The information capacity of the models obtained (sensitivity, specificity, and accuracy) was determined according to the control group data by calculating accuracy, sensitivity, and specificity.

Results and discussion. The average age of the SCD risk group was 19.7 ± 1.6 years. The patients examined did not have any chronic diseases or abnormalities on standard laboratory tests. Five patients had degree 1 obesity, two patients had a shortening of the *PQ* interval, one patient had a shortening of the corrected *QT* interval, and one patient had an elongated corrected *QT* interval to 472 ms. Echocardiography revealed no significant pathologies. Thus, the thickness of the posterior wall of the left ventricle was 9.4 ± 0.9 mm, the thickness of the interventricular septum was 9.5 ± 0.9 mm, the mass index of the left ventricular myocardium was 72.2 ± 14.5 g/m^2, and the ejection fraction of the left ventricle was 63.5 ± 4.2%.

A biochemical blood test revealed no lipid metabolic disorders. The level of total cholesterol was 4.35 ± 0.59 mmol/L, the triglyceride level was 1.23 ± 0.56 mmol/L, the low-density lipoprotein level was 2.17 ± 0.70 mmol/L, the very low-density lipoprotein level was 0.54 ± 0.26 mmol/L, and the high-density lipoprotein level was 1.57 ± 0.41 mmol/L.

Table 2. Genes associated with lipid metabolic disorders.

Gene, polymorphism	Group	Distribution of patients-carriers of genetic polymorphism, n (%)				p
		With a normal variant	With a heterozygous risk variant	With a homozygous risk variant	Total number of homo- and heterozygous variants	
APOE Leu28Pro (C>T) rs 429358	Control, *n* = 65	57 (87.7)	8 (12.3)	0 (0)	8 (12.3)	*p* = 0.12
	Risk group, *n* = 59	58 (98.3)	1 (1.7)	0 (0)	1 (1.7)	
APOC3 C3238G (C>G) rs 5128	Control, *n* = 65	52 (80.0)	13 (20.0)	0 (0)	13 (20.0)	*p* = 0.13
	Risk group, *n* = 59	42 (70.4)	15 (25.9)	2 (3.7)	17 (29.6)	
PON1 Gln192Arg (A>G) rs 662	Control, *n* = 65	44 (67.7)	21 (32.3)	0 (0)	21 (32.3)	*p* = 0.006*
	Risk group, *n* = 59	26 (44.0)	21 (35.6)	12 (20.4)	33 (56.0)	
LPL Ser447Ter (C>G) rs 328	Control, *n* = 65	55 (84.6)	9 (14)	1 (1.4)	10 (15.4)	*p* = 0.07
	Risk group, *n* = 59	50 (84.5)	6 (10.3)	3 (5.2)	9 (15.5)	
LIPC250 G>A rs 1800588	Control, *n* = 65	38 (58.5)	20 (30.7)	7 (10.8)	27 (41.5)	*p* = 0.89
	Risk group, *n* = 59	36 (61.0)	17 (28.8)	6 (10.2)	23 (39.0)	

Note: *differences between groups are statistically significant.

Table 1 presents the clinical characteristics of the two groups.

Subsequently, in the control group (65 patients) and the SCD risk group (59 patients), a blood test was performed using the Litech kits to determine the gene polymorphisms, which were single nucleotide base-SNP substitutions [23], including the *Leu28Pro* (rs 429358) polymorphism in the *APOE* gene, the *C3238G* (rs 5128) polymorphism in the *APOC3* gene, the *Gln192Arg* (rs 662) polymorphism in the *PON1* gene, the *Ser447Ter* (rs 328) polymorphism in the *LPL* gene, and the *G250A* polymorphism (rs 1800588) in the *LIPC* gene. Table 2 presents the gene polymorphism results.

Significant differences were obtained only for the *PON1* gene ($p = 0.006$) after comparing the results of the genes associated with lipid metabolic disorders in the SCD risk group to those in the control group. Homozygous risk variants were more common in the SCD risk group, and there were fewer people with a normal genetic variant ($p = 0.006$). The total number of individuals with homo- and heterozygous risk variants in this gene exceeded the number of similar patients in the control group by almost two times (56.0% vs. 32.3%, respectively, $p = 0.006$). No significant differences were revealed for the remainder of the genes studied ($p > 0.05$).

A correlation analysis was performed to study the relationships between the risk factors for SCD and the presence of gene polymorphisms associated with lipid metabolic disorders.

A weak inverse correlation was established between the body mass index (BMI) and the *250 G>A* polymorphism in the *LIPC* gene ($R = –0.26$, $p = 0.047$). In subjects with a normal distribution of alleles (GG) in this polymorphism, the BMIs were 23.9 ± 3.6 kg/m^2 and 22.8 ± 4.2 kg/m^2 in individuals with a heterozygous risk variant (GA), and 22.1 ± 1.9 kg/m^2 in individuals with the homozygous risk variant (AA).

A direct moderate correlation was revealed between the complaints of heart palpitations and the polymorphism in the *LPL Ser447Ter* gene ($R = 0.398$, $p = 0.002$). An inverse correlation was observed between the length of the corrected *QT* interval and the *LPL Ser447Ter* gene polymorphism ($R = –0.26$, $p = 0.046$). Seven (14%) subjects with the normal variant of the allele distribution (CC) in this polymorphism had complaints of heart palpitations, and the corrected *QT* interval length was 406 [397; 425] ms. Three (50%) individuals with a heterozygous risk variant (CG) had complaints of palpitations, with a corrected *QT* interval length of 391 [378; 393] ms, and the length of the corrected *QT* interval was 401 [388; 410] ms in one (33.3%) person with a homozygous risk variant (GG) and complaints of palpitations.

The direct correlation between lethal outcomes in close relatives < 50 years by the SCD mechanism according to the survey data and the *Gln192Arg* polymorphism in the *PON1* gene ($R = 0.24$, $p = 0.046$) are of greatest interest. This relationship was weak by definition ($R = 0.24$); however, its presence may indicate the significance of the *Gln192Arg* polymorphism in the *PON1* gene and the genesis of SCD development. Lethal outcomes

of close relatives by the SCD mechanism were registered in seven (26.9%) people with a normal variant in the allele distribution of (AA) this polymorphism, in four (19.0%) people with a heterozygous risk variant (AG), and five (41.7%) individuals with the homozygous risk variant (GG).

Mathematical models were developed by applying logistic regression to identify the probability of carriage of mutations in the genes associated with lipid metabolic disorders. The relationship of the factors in the mathematical models is as follows:

$$P(Y)=1/(1+e^{-(B0+B1*X1+B2*X2+.....+Bn*Xn)}),$$

where P (Y) is the probability of event Y, that is, the probability of assigning the person under study to the group of mutation carriers (hetero- or homozygote) of the studied gene responsible for a lipid metabolic disorder; e is the base of the natural logarithm (~2.72); X1, X2... Xn are the attributes included in the prediction model; B is the coefficient of the regression equation, indicating the effect of the corresponding predictors on the dependent variable.

The following mathematical models were constructed.

1. Mathematical model to identify carriers of the minor allele *C3238G* (rs 5128) polymorphism in the *APOC3* gene (χ^2 = 18.12; df = 3; $p < 0.001$):

$$P(Y)=1/(1+e^{-(-22.191+0.059*X1+10.967*X2-0.208*X3)}),$$

where X1 is the length of the *QT* interval (ms); X2 is the amplitude of the *P* wave in lead V_5 (mm), and X3 is the time of internal deviation in lead V_3 (ms). The sensitivity of the constructed model was 87.5%, the specificity was 51.2%, and the accuracy was 61.4%.

2. The mathematical model to identify carriers of the minor allele *Gln192Arg* (rs 662) polymorphism in the *PON1* gene (χ^2 = 41.605; df = 6; $p = 0.001$) is as follows:

$$P(Y)=1/(1+e^{-(28.862-0.368*X1+0.254*X2+0.322*X3-2.261*X4+2.531*X5-0.408*X6)}),$$

where X1 is the alpha angle of the *P* wave (degrees); X2 is the angle of the alpha *T* wave (degrees); X3 is the *Q* wavelength in lead V_4 (ms); X4 is the amplitude of the *R* wave in lead V_1 (mm); X5 is the *S* wave amplitude in lead aVL (mm); X6 is the time of internal deviation in lead aVF (ms). The sensitivity of this model was 87.5%, the specificity was 80.0%, and the accuracy was 84.2%.

3. The mathematical model to identify carriers of the minor allele *Ser447Ter* (rs 328) polymorphism in the *LPL* gene (χ^2 = 38.59; df = 5; $p < 0.001$) is as follows:

$$P(Y)=1/(1+e^{-(-2063.46+913.445*X1+713.95*X2-6.845*X3-85.943*X4+2.23*X5)}),$$

where X1 is the amplitude of the *P* wave in lead V_3 (mm); X2 is the amplitude of the *Q* wave in standard lead II (mm); X3 is the time of internal deviation in lead V_1 (ms); X4 is the *Q* wavelength in standard lead II (ms); X5 is the value of the minimum *RR* interval (ms). The sensitivity of the model was 88.8%, the specificity was 93.7%, and the accuracy was 92.9%.

4. The mathematical model to identify carriers of the minor allele *250 G>A* (rs 1800588) polymorphism in the *LIPC* gene (χ^2 = 48.591; df = 6; $p < 0.0001$):

$$P(Y)=1/(1+e^{-(-3.109+6.974*X1-10.189*X2-0.782*X3-0.548*X4-2.261*X5+1.548*X6)}),$$

where X1 is the amplitude of the *P* wave in lead V_6 (mm); X2 is the amplitude of the *Q* wave in lead V_6 (mm); X3 is the *Q* wavelength in standard lead I (ms); X4 is the *Q* wavelength in standard lead III (ms); X5 is the *Q* wavelength in lead V_4 (ms), and X6 is the *Q* wavelength in lead V_6 (ms). The sensitivity of the model was 82.6%, the specificity was 85.3%, and the accuracy was 84.2%.

5. The mathematical model to identify carriers of the minor allele *Leu28Pro* (rs 429358) of the polymorphism in the *APOE* gene was not constructed due to the low frequency of hetero- and homozygous risk variants.

Among these mathematical models, the models to identify carriers of the minor allele of the *Gln192Arg* polymorphism in the *PON1* gene, the *Ser447Ter* polymorphism in the *LPL* gene, and the *250 G>A* polymorphism in the *LIPC* gene had the highest information content (sensitivity, specificity, and accuracy).

Several features were revealed during the examination of subjects with an increased risk of SCD. Thus, this category had a high frequency of homozygous risk variants of the *Gln192Arg* (rs 662) polymorphism in the *PON1* gene; that is, polymorphisms responsible for lipid metabolic disorders and causing early development of IHD. A direct weak correlation was revealed between deaths in close relatives < 50-years-of-age and the presence of the *Gln192Arg* polymorphism in the *PON1* gene, suggesting the contribution of this polymorphism to the development of SCD. These data suggest that a study of gene polymorphisms should be conducted in young people with the risk of SCD, and the data can be used to stratify SCD risk. The mathematical model for predicting the risk variant (hetero- or homozygous) of the *Gln192Arg* polymorphism in the *PON1* gene

had high sensitivity (87.5%), specificity (80.0%), and accuracy (84.2%).

CONCLUSIONS

1. Carriers of the minor allele of the *Gln192Arg* (rs 662) polymorphism in the *PON1* gene ($p = 0.06$) were more common in the risk group for SCD. No significant differences in the *Leu28Pro* (rs 429358) polymorphism of the *APOE* gene, the *C3238G* (rs 5128) polymorphism of the *APOC3* gene, the *Ser447Ter* (rs 328) polymorphism of the *LPL* gene, or the *G250A* polymorphism (rs 1800588) in the *LIPC* gene were detected in the SCD risk group compared to the control group.

2. A correlation was revealed between deaths in close relatives < 50-years-old according to the questionnaire with the presence of *Gln192Arg* polymorphisms in the *PON1* gene ($R = 0.24$, $p = 0.046$).

3. The mathematical models developed to identify the carriers of the minor allele of the *Gln192Arg* polymorphism (rs 662) in the *PON1* gene, the *Ser447Ter* (rs 328) polymorphism in the *LPL* gene, and the *G250A* (rs 1800588) polymorphism in the *LIPC* gene were highly informative (sensitivity, specificity, and accuracy).

4. The genetic polymorphisms responsible for lipid metabolic disorders should be detected in young people with a risk of SCD, particularly the *Gln192Arg* polymorphism of the *PON1* gene.

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