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Analysis of Clinical and Biochemical Characteristics of Patients With Genetically Confirmed Familial Hypercholesterolemia in Russian North Western District Residents

Aim	To compare results of clinical, laboratory, and genetic examination of patients with familial hypercholesterolemia (FHC).
Material and Methods	112 patients aged 40.2±17.9 years (49 men) were examined. The gene of low-density lipoprotein receptor (LDLR) was analyzed and evaluated using the Dutch Lipid Clinic Network (DLCN) criterion of lipid score ≥6. The LDLR gene mutation was searched for using the conformational polymorphism analysis followed by sequencing of the DNA of isolated LDLR gene exons.
Results	Mean variables of the blood lipid profile were total cholesterol (C), 10.12±2.32 mmol/l, LDL–C, 7.72±2.3 mmol/l. Corneal arcus was observed in 15% of patients, tendon xanthomas in 31.8%, and xanthelasma palpebrarum in 5.3%. The types of LDLR gene mutations included missense mutations (42.8%), mutations causing a premature termination of protein synthesis (41.1%), and frameshift mutations (16.1%). In the presence of a mutation in exon 4, patients with IHD compared to patients with no IHD had significantly higher levels of total C (10.88±2.08 mmol/l vs. 8.74±1.57 mmol/l, respectively, p=0.001) and LDL–C (8.60±2.14 mmol/l vs. 6.62±1.79 mmol/l, respectively, p=0.005). Patients with IHD compared to patients with no IHD and a mutation in LDLR gene exon 9 had only a higher LDL–C level (8.96±1.53 mmol/l vs. 6.92±1.59 mmol/l, respectively, p=0.022). A differentiated comparison of IHD patients using a logistic regression depending on the identified type of LDLR gene mutation produced formulas for calculating the odds ratio of IHD and myocardial infarction (MI) with adjustments for the patient's age and baseline LDL.
Conclusion	The detection rate of the LDLR gene mutations was 42.8% for missense mutations, 41.1% for mutations causing a premature termination of protein synthesis, and 16.1% for frameshift mutations. Blood lipid profiles did not differ between patients from different cities and with different types of LDLR gene mutations. Blood lipid profiles were different in IHD patients depending on the mutation type.

Keywords	Familial hypercholesterolemia; ischemic heart disease; mutations; low-density lipoprotein receptor gene
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Introduction

Familial hypercholesterolemia (FH) is an inherited metabolic disorder, more often characterized by autosomal codominant inheritance associated with elevated levels of total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol, high risk of developing cardiovascular diseases (CVDs) of atherosclerotic origin at a young age caused by mutations in the LDL receptor (LDLR) gene, apolipoprotein B-100 gene, proprotein convertase subtilisin/kexin type 9 gene, and less often in other genes causing autosomal dominant or autosomal recessive disease [1–3]. CVDs at a young age are the first manifestations in FH, which is indicative of delayed diagnosis of FH [3].

In the Russian Federation, the total economic cost damage from hypercholesterolemia is 1,295 trillion rubles per year, including direct costs (emergency care, disability allowance) and indirect economic losses (loss of earnings due to temporary disability; loss of gross domestic product

due to permanent disability, premature death in prime working years) [4].

Studies of the FH genetics were regularly conducted in Russia, namely in St. Petersburg, Moscow, Novosibirsk, Petrozavodsk, and with the introduction of full genome sequencing, few mutations of the LDLR gene have been recently found in Ivanovo, Orenburg, Tomsk, Omsk, Tyumen, Vologda, Kemerovo, Vladivostok, and Krasnoyarsk [5].

In this regard, it is necessary to update of the Russian national database and compare clinical and genetic features of the disease in order to improve its diagnosis in Russia.

In Russia, most commonly mutations of various types are found in the LDLR gene in patients with FH [6]: mutations leading to premature termination of protein synthesis on ribosomes (nonsense mutations and frameshift mutations) – type 1 mutations; missense mutations (type 2 mutations); in-frame deletions/insertions (type 3 mutations). This classification allows dividing mutations by the degree of their effects on the functional activity of the receptor.

The identification of mutations helps to determine the further treatment strategy for a patient and his/her immediate relatives, thus, to conduct both secondary and early primary prevention of atherosclerosis complications.

Objective

Compare the results of clinical, laboratory, and genetic examinations of patients with FH residing in different Russian cities.

Material and methods

Clinical data and results of biochemical and genetic examinations of 112 patients (31 patients from Petrozavodsk and 81 patients from St. Petersburg; mean age 40.2±17.9 years, 49 male patients) were analyzed. There were no significant differences in age and sex between patients from St. Petersburg and Petrozavodsk (mean age of Petrozavodsk residents 39.3±17.9 years, 14 male patients; mean age of St. Petersburg residents 41.9±15.6 years, 35 male patients). FH was diagnosed using the Dutch Lipid Clinic Network (DLCN) criteria. The study was carried out following the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and approved by the Committee on Medical Ethics of the Petrozavodsk State University on November 14, 2013.

Blood lipid profile was analyzed: TC, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), and hepatic transaminases (ALT, AST), creatinine, urea, glucose, thyroid hormones, in order to exclude secondary hypercholesterolemia when selecting patients for genetic examination. Genetic analysis was performed in patients with a DLCN score ≥ 6 by single-strand conformational polymorphism analysis (SSCP) followed by sequencing of the LDLR gene. The LDLR exons were amplified by polymerase chain reaction using primers with a 5' – terminal fluorescent label Cy5 cyanine (Syntol) [6, 7]. Amplified samples were analyzed using a DNA single-strand conformational polymorphism analysis [6] performed on ALFExpress-2 automatic sequencer; samples with mobility shifts were sent for sequencing to Eurogen.

The data obtained were processed using Statistica 10.0. Descriptive statistics were used – calculation of absolute and relative (%) rates. The chi-square test and Fisher's exact test were used to assess significance of intergroup differences. Stepwise logistic regression was used to study the informative value of variables and build a prognostic model of CAD and myocardial infarction (MI). The data are expressed as the means and standard deviation (M±SD).

Table 1. Lipid profile in patients with FH

Parameter	Patients from Petrozavodsk (n=31)	Patients from St. Petersburg (n=81)	p
TC, mmol/L	10.12±2.32	10.12±2.29	0.998
LDL cholesterol, mmol/L	7.44±2.23	7.91±2.21	0.331
HDL cholesterol, mmol/L	1.37±0.55	1.15±0.29	0.012
TG, mmol/L	1.67±0.52	1.63±0.70	0.796

Hereinafter: FH, familial hypercholesterolemia.

Results

Arcus cornealis, xanthomas, and xanthelasma are the clinical stigmas of FH. Among patients with clinically and genetically confirmed FH, arcus cornealis was detected in 17 (15%) patients, tendon xanthomas in 36 (31.8%) patients, eyelid xanthelasma in 6 (5.3%) patients. Thus, the absence of these signs does not exclude FH.

All patients had pronounced dyslipidemia with mean TC 10.12±2.32 mmol/L, LDL cholesterol 7.72±2.3 mmol/L, HDL and TG levels within normal limits (1.26±0.36 mmol/L and 1.65±0.68 mmol/L, respectively). There were no significant differences in the levels of TC, LDL cholesterol, and TG between patients from St. Petersburg and Petrozavodsk (Table 1).

Genetic characteristics of patients with FH

Missense mutations in 48 (42.8%) patients and mutations leading to premature termination of protein synthesis in 46 (41.1%) patients were most common in the study group. In-frame deletions/insertions were detected in 18 (16.1%) patients.

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Table 2. Blood lipid profile in patients with FH and different types of LDLR mutations

Parameter	Group 1 – patients with type 1 mutations (n=44)	Group 2 – patients with type 2 mutations (n=46)	Group 3 – patients with type 3 mutations (n=18)	p_{1-2}; p_{1-3}; p_{2-3}
Age, years	38.2±15.5	43.8±17.3	41.8±	0.104; 0.398; 0.662
TC, mmol/L	9.67±1.99	10.59±2.51	9.98±2.26	0.055; 0.599; 0.364
LDL cholesterol, mmol/L	7.37±1.84	8.12±2.5	7.82±2.20	0.131; 0.431; 0.658
HDL cholesterol, mmol/L	1.21±0.35	1.21±0.45	1.23±0.34	0.959; 0.839; 0.834
TG, mmol/L	1,63±0,65	1,62±0,57	1,73±0,81	0,947; 0,600; 0,541

Blood lipid profiles of patients with different types of mutations were compared (Table 2). Patients from St. Petersburg and Petrozavodsk had no differences in blood lipid profiles based on the type of the LDLR mutations. No significant differences were found in patients with the same mutations who lived in different cities. The only exception was higher HDL cholesterol levels in patients with type 1 mutations living in Petrozavodsk (1.50±0.36 mmol/L) than in St. Petersburg residents (1.11±0.30 mmol/L; p=0.003).

The largest number of mutations detected in patients from Petrozavodsk and St. Petersburg were localized in exon 4 (n=38 (33.6%)) and exon 9 (n=27 (23.8%)), which are the longest exons in the gene. No mutations were found in exon 8. Frequency of mutations in other exons: exon 2–3 (2.65%) patients, exon 3–9 (7.96%), exon 5–2 (1.8%), exon 6–9 (7.96%), exon 7–5 (4.4%), exon 10–2 (1.76%), exon 11–2 (1.76%), exon 12–6 (5.3%), exon13–4 (3.5%), exon 14–1 (0.88%), exon 15–3 (2.7%), exon 16–3 (2.6%), exon 17–1 (0.88%) patient.

Table 3. Blood lipid profile in patients with different mutation localizations (exons) depending on the presence of CAD

Parameter	Patients without CAD (n=58)	Patients with CAD (n=39)	p
Exon 4			
Number of patients	20	17	–
TC, mmol/L	8.74±1.57	10.88±2.08	0.001
LDL cholesterol, mmol/L	6.62± 1.79	8.60±2.14	0.005
HDL cholesterol, mmol/L	1.33± 0.32	1.20±0.36	0.255
TG, mmol/L	1.28± 0.47	1.96±0.86	0.005
Exon 9			
Number of patients	16	5	–
TC, mmol/L	9.59±2.58	10.74±1.39	0.358
LDL cholesterol, mmol/L	6.92±1.59	8.96±1.53	0.022
HDL cholesterol, mmol/L	1.23±0.56	1.29±0.39	0.825
TG, mmol/L	1.52±0.47	1.08±0.23	0.065

CAD and LDLR mutations

CAD was diagnosed in 46 patients – 10 (32.3%) patients from Petrozavodsk and 36 (44.4%) patients from St. Petersburg. Twenty six patients had a history if MI – 7 (22.5%) patients from Petrozavodsk and 19 (23.4%) patients from St. Petersburg.

In the presence of the exon 4 mutations, levels of TC (10.88±2.08 mmol/L), LDL (8.60±2.14 mmol/L), and TG (1.96±0.86) were higher than in patients without CAD (TC 8.74±1.57 mmol/L, p=0.001; LDL 6.62±1.79 mmol/L, p=0.005; TG 1.28±0.47 mmol/L, p=0.005). Patients with CAD and LDLR exon 9 mutation had only elevated LDL cholesterol (8.96±1.53 mmol/L); patients without CAD had 6.92±1.59 mmol/L (p=0.022). The results are presented in Table. 3.

Among patients with exon 3 mutation, lower levels of HDL cholesterol were found in the subgroup of patients with CAD (1.10±0.09 mmol/L) compared with those without CAD (1.35±0.12 mmol/L; p=0.027). Statistical processing of differences in the blood lipid profiles is not possible in the case of mutations in exon 2, 5, 7, 8, 10, 11 and 13 due to limited sample size. There were no significant differences in the case of mutations in exons 6 and 12.

When comparing patients with CAD from both cities with the subgroup of patients without CAD (Table 4), it was shown that patients with CAD were older (51.1±10.1 years) than persons without CAD (35.1±16.5 years). Patients with CAD and LDLR mutation had higher, compared to those without CAD, levels of TC (11.01±2.1 and 9.23±2.03 mmol/L, respectively; p=0.000070), LDL cholesterol (8.88±2.18 and 6.97±1.7 mmol/L, respectively; p=0.00003), and TG (1.85±0.78 and 1.51±0.54 mmol/L, respectively; p=0.014). HDL levels did not differ significantly between the subgroups.

Patients with MI with LDLR mutation were older (49.8±11.9 years) than patients without MI (38.4±16.7 years; p=0.002). The data are presented in Table 5.

Table 4. Blood lipid profile in patients with CAD and LDLR mutation

Parameter	Patients with CAD (n=46)	Patients without CAD (n=66)	p
Age, years	51.1 ±10.1	35.1±16.5	0.000001
TC, mmol/L	11.01±2.1	9.23±2.03	0.000070
LDL cholesterol, mmol/L	8.88±2.18	6.97±1.97	0.00003
HDL cholesterol, mmol/L	1.17±0.33	1.26±0.42	0.314
TG, mmol/L	1.85±0.78	1.51±0.54	0.014

Table 5. Blood lipid profile in patients with MI and LDLR mutation

Parameter	Patients with MI (n=26)	Patients without MI (n=87)	p
Age, years	49.8±11.9	38.4±16.7	0.002
TC, mmol/L	10.95±2.5	9.60±2.02	0.008
LDL cholesterol, mmol/L	8.87±2.62	7.35±1.99	0.004
HDL cholesterol, mmol/L	1.09±0.32	1.27±0.40	0.048
TG, mmol/L	1.84±0.67	1.58±65	0.100

Table 6. Blood lipid profile in patients with CAD and different types of LDLR mutations

Parameter	Patients without CAD (n=58)	Patients with CAD (n=39)	p
Type 1 mutations			
Number of patients	22	17	–
Age, years	30.4±13.8	50.1±9.3	0.00001
TC, mmol/L	8.75±1.6	10.75±1.82	0.0008
LDL cholesterol, mmol/L	6.57±1.40	8.55±0.34	0.0006
HDL cholesterol, mmol/L	1.25±0.35	1.20±0.76	0.695
TG, mmol/L	1.47±0.55		0.079
Type 2 mutation			
Number of patients	27	13	–
Age, years	39.2±18.1	53.6±12.6	0.014
TC, mmol/L	9.79±2.35	11.20±2.54	0.093
LDL cholesterol, mmol/L	7.35±2.38	9.35±2.65	0.026
HDL cholesterol, mmol/L	1.23±0.51	1.17±0.32	0.705
TG, mmol/L	1.56±0.58	1.73±0.60	0.425
Type 3 mutations			
Number of patients	9	9	–
Age, years	34.3±16.3	49.2±7.6	0.024
TC, mmol/L	8.75±1.75	11.20±2.1	0.016
LDL cholesterol, mmol/L	6.81±1.78	8.82±2.21	0.050
HDL cholesterol, mmol/L	1.34±0.31	1.12±0.35	0.175
TG, mmol/L	1.46±0.40	2.01±1.04	0.162

Patients with MI had higher levels of TC (10.95±2.5 mmol/L), LDL (8.87±2.62 mmol/L), and TG (1.84±0.67 mmol/L) than patients without a history of MI who had TC 9.60±2.02 mmol/L (p=0.008) and LDL 7.35±1.99 mmol/L (p=0.004). HDL cholesterol levels were lower in patients with MI (1.09±0.32 mmol/L) compared to patients without MI (1.27±0.40 mmol/L; p=0.048).

We also conducted a differentiated comparison of patients with and without CAD depending on the type of mutations (Table 6). Patients with CAD and type 1 mutations were older (50.1±9.3 years) than patients without CAD (30.4±13.8 years; p=0.00001). The subgroup of patients with CAD and type I mutations had higher levels of TC (10.75±1.82 mmol/L) and LDL (8.55±0.34 mmol/L) compared to patients without CAD (TC 8.75±1.6 mmol/L; p=0.0008 and LDL 6.57 ±1.40 mmol/L; p=0.0006). Patients with CAD and type 2 mutations were older (53.6±12.6 years) than patients without CAD (39.2±18.1 years; p=0.014). The subgroup with CAD and type 2 mutations had higher LDL (9.35±2.65 mmol/L, p=0.026). Patients with CAD and type 3 mutations were older (49.2±7.6 years) than patients without CAD (34.3±16.3 years; p=0.024). The subgroup of patients with CAD and type 3 mutations had higher levels of TC (11.20±2.1 mmol/L) and LDL (8.82±2.21 mmol/L) compared to patients without CAD (TC 8.75±1.75 mmol/L; p=0.016 and LDL 6.81 ±1.78 mmol/L; p=0.050).

Based on the logistic regression analysis, formulas were obtained for the estimation of odds ratio (OR) of CAD in patients with mutations of various types, taking into consideration age and baseline levels of LDL:

Type 2 mutation:

- Male patients: OR=exp (-7.33 + 0.08×age + 0.43×LDL)
- Female patients: OR=exp (-8.58 + 0.08×age + 0.43×LDL)

Type 1 or 3 mutation:

- Male patients: OR=exp (-6.03 + 0.08×age + 0.43×LDL)
- Female patients: OR=exp (-7.28 + 0.08×age + 0.43×LDL)

Tables 7–16 for the calculation of the probability of CAD and MI are presented in the Appendix published in the Cardiology journal website at https://lib.ossn.ru/jour. Figure 1 shows the distribution of CAD probability according to the type of mutation and age of patients with LDL of 5 mmol/L. The probability of CAD in 40-year old female patients with LDL of 5 mmol/L and type 2 mutation (missense mutation) was 3.8% (Table 7). The probability of CAD in female patients with type 1 and 3 mutations reached 12.7% (Table 8). Male patients aged 40 with LDL of 5 mmol/L and type 2 mutation had a higher probability of CAD than female patients amounting to 12.1% (Table 9). The probability of CAD in patients with types 1 and 3 mutations was 33.6% (Table 10).

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Figure 1. Likelihood of CAD in female and male patients with different types of LDLR mutations and levels of LDL cholesterol

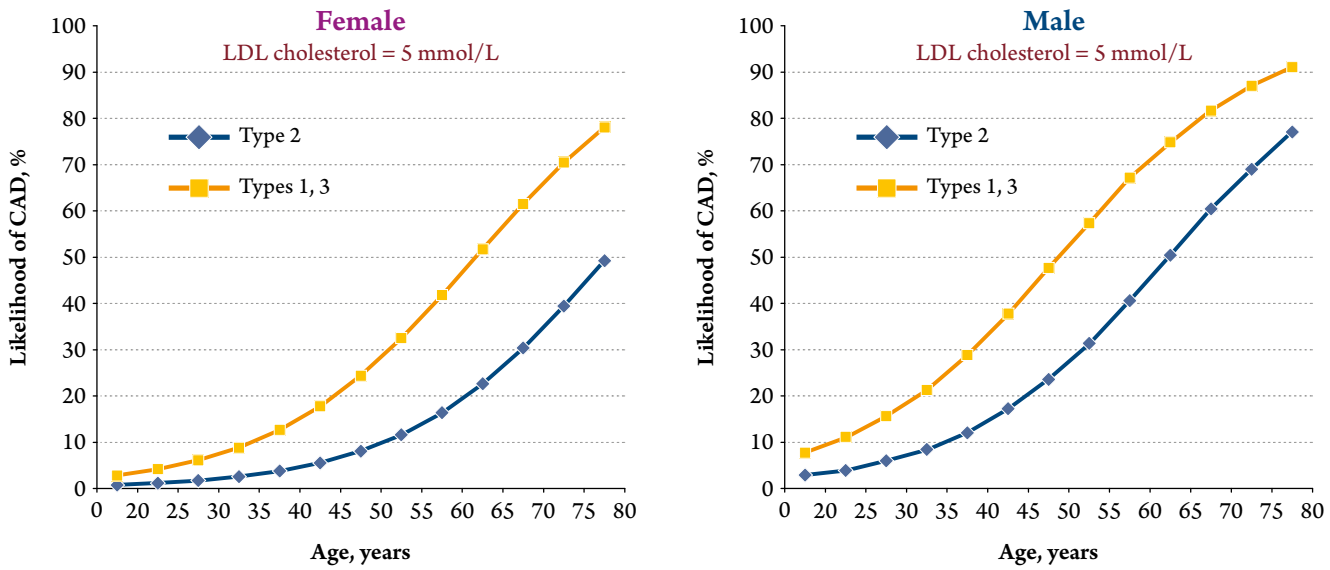


Figure 2. Likelihood of developing MI in 45-year-old male patients depending on the type of LDLR mutations and levels of HDL cholesterol

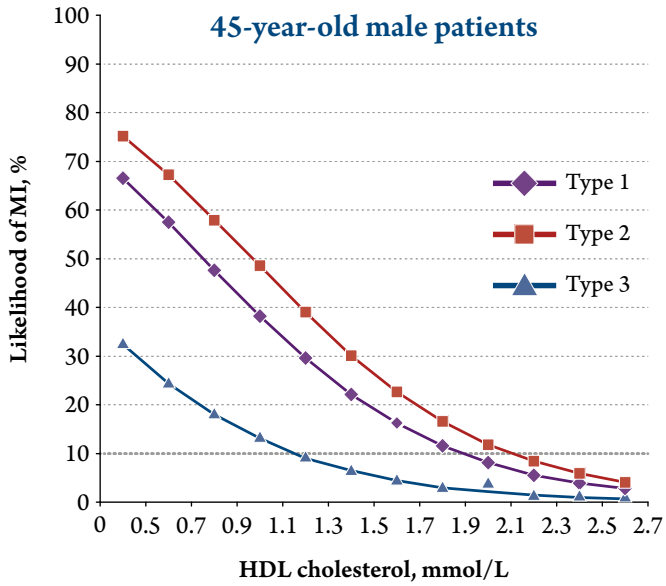
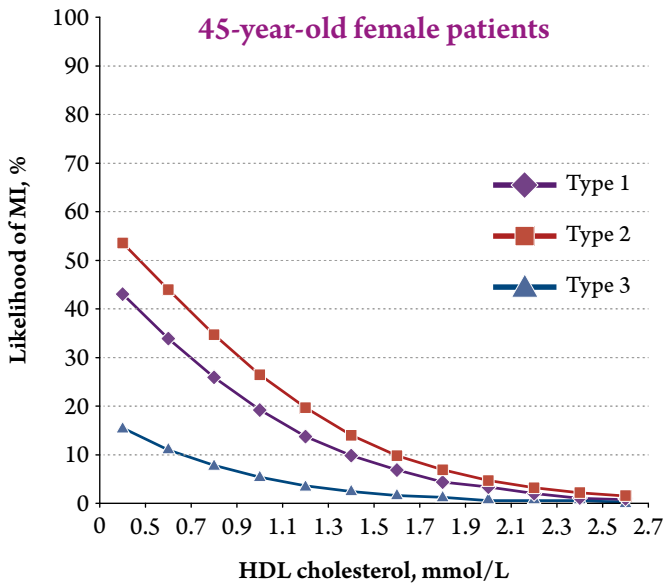


Figure 3. Likelihood of developing MI in 45-year-old female patients depending on the type of LDLR mutations and levels of HDL cholesterol



Odds ratio of MI was primarily associated with a decrease in HDL

Below are the formulas for calculating OR of MI in patients with different types of mutations depending on the levels HDL cholesterol:

Type 1 mutations:

- Male patients: OR=exp (– 0.13 + 0.04×age + 1.95×HDL)
- Female patients: OR=exp (– 1.1 + 0.04×age + 1.95×HDL)

Type 2 mutations:

- Male patients: OR=exp (0.29 + 0.04×age + 1.95×HDL)
- Female patients: OR=exp (– 0.68 + 0.04×age + 1.95×HDL)

Type 3 mutations:

- Male patients: OR=exp (1.56 + 0.04×age + 1.95×HDL)
- Female patients: OR=exp (– 2.53 + 0.04×age + 1.95×HDL)

Figures 2 and 3 provide an example of MI likelihood in 45-year old patients taking into consideration the type of mutation, levels of HDL cholesterol, and patient sex. The likelihood of MI was 58.3% in 45-year old male patients with HDL cholesterol of 0.9 mmol/L and type 2 mutation (Table 15) and 47.8% in type 1 mutations (Table 14), the likelihood of MI reached 18.02% in type 3 (in-frame deletions/insertions) (Table 16). The likelihood of MI was lower in female patients of the same age with HDL cholesterol of 0.9 mmol/L and type 1 mutations than in male patients and amounted to 34.6% (the likelihood of MI was highest in this type of mutations like in male patients

Table 12); it was almost 2 times less in patients with types mutations – 25.8% (Table 11), type 3–7.69% (Table 13), which was 3 times lower than in male patients with similar indicators.

Discussion

FH is a rarely diagnosed disease, and the incidence of this nosology is less than 1% in some countries [1]. In the ESSE-RF trial, the frequency of definite FH according to the modified Dutch criteria, was 1:407 people and that of the probable FH was 1:148 [8]. Estimated number of patients with heterozygous FH can reach 1 million in Russia, and the disease is still not detected in most cases [8].

High mortality in FH is due to the earlier onset of CAD than on average in the population; FH causes 20% of premature cardiovascular death [9–12]. However, despite the high likelihood of CVDs in young patients with monogenic FH, some patients have a normal life expectancy without lipid-lowering therapy [13]. Given the variety of phenotypes of FH, it is possible to perform individual stratification of the risk of developing cardiovascular complications and select timely and adequate treatment.

When examining our patients from Petrozavodsk and St. Petersburg, we found that not all patients had arcus cornealis, xanthomas, xanthelasma, even those with definite FH. Among the examined patients with clinically and genetically confirmed FH, arcus cornealis was detected in 15% of patients, tendon xanthomas in 31.8% of patients, eyelid xanthelasma in 5.3% of patients. According to our findings, the absence of eyelid xantelasma, arcus cornealis, and xanthomas does not exclude FH, which is confirmed in other studies; the prevalence has sex-associated differences, depends on patient age, levels of TC and LDL cholesterol [14]. We have previously compared the genetic traits of FH in patients from Petrozavodsk and St. Petersburg, with only one common mutation c.925-931delCCCATCA, p. (Pro309fs), FH North Karelia [15]. The number of mutations found both in St. Petersburg and Petrozavodsk has increased to four so far, three more mutations are common: c.1202T>A, p. (Leu401His) [16, 17]; c.1775G >A, p. (Gly592Glu) [17–19]; c.2389G >A, p. (Val797Met) [16, 17]. Complete lists of LDLR mutations in Petrozavodsk and St. Petersburg with detailed description are given in Table 17 in the Appendix. However, the frequency of detecting different types of LDLR mutations was similar: missense mutations in 42.5%, mutations leading to premature termination of protein synthesis in 40.7%, in-frame deletions/insertions in 15.9%, the most frequent localization of mutations in hot exons was also similar. At the same time, lipid profiles did not differ in patients from different cities and with different types of mutations. Patients with CAD had higher levels of TC, LDL cholesterol, and TG when mutations were found in exon 4, and higher levels of LDL when mutations were located in exon 9. The data obtained made it possible to calculate the likelihood of CAD and MI depending on the types of mutations, patient age and sex.

Attempts are currently made to stratify the risk of cardiovascular complications in patients with FH; there are several prognostic scores (Montreal score, SAFEHEART register) based on the contribution of classical factors in the risk of CVDs in patients with FH [20, 21]. There are differences in the effect of CVD risk factors between patients with FH and the general population. Elevated homocysteine is less relevant and decreased levels of HDL cholesterol are more important as risk factors for atherosclerosis in patients with FH. Such changes in the contribution of risk factors compared to the general population is associated with the influence of elevated levels of LDL cholesterol [22, 23].

We demonstrated that the likelihood of CAD in patients with FH was more correlated with patient age and levels of LDL cholesterol, and the likelihood of MI was more correlated with HDL cholesterol.

Limitations

Sequencing of the coding region of LDLR was performed, rather than targeted or full exome sequencing, which did not detect mutations of other genes causing FH and intron mutations of LDLR. The relatively small sample size does not allow us to argue with full confidence about the complete characterization of the mutation spectrum. Finally, many new mutations were not functionally characterized, i.e. pathogenicity was established by segregation analysis and analogies with functionally characterized mutations, rather than by direct test of receptor activity in the cultured fibroblasts.

Conclusion

The frequency of detecting different types of mutations of the low-density lipoprotein receptor gene: missense mutations in 42.8%; mutations leading to premature termination of protein synthesis in 41.1%; in-frame deletions/insertions in 16.1%. Lipid profiles did not differ in patients from different cities and with different types of mutations. The likelihood of coronary heart disease and myocardial infarction depending on the types of mutations of the low-density lipoprotein receptor gene, patient age and sex was calculated.

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