УДК 577.21
DOI: https://doi.org/10.17816/MAJ630505

MOLECULAR DIAGNOSTICS OF FAMILIAL HYPERCHOLESTEROLEMIA IN RUSSIA: YESTERDAY, TODAY AND TOMORROW

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For citation: Zakharova FM, Mandelshtam MYu, Bogoslovskaya TYu, Vasilyev VB. Molecular diagnostics of familial hypercholesterolemia in Russia: yesterday, today and tomorrow. *Medical Academic Journal.* 2024;24(1):23–36. DOI: https://doi.org/10.17816/MAJ630505

Received: 19.04.2024 Accepted: 06.05.2024 Published online: 27.05.2024

Familial hypercholesterolemia is a severe hereditary disease leading to the development of atherosclerosis and its complications in the form of angina pectoris, myocardial infarction, cerebral stroke, or even leading to sudden death. Since the description of the disease, the concept of it has undergone significant evolution. First, it became clear that the prevalence of this disease was significantly higher than originally thought (1:300 for heterozygous familial hypercholesterolemia and not as 1:500 as estimated earlier). Secondly, it has been established that it is not based on the pathology of the low-density lipoprotein receptor gene alone, but includes at least four monogenic forms (defects of the *APOB, PCSK9, ARH* genes) and may also have a multigenic nature. Thirdly, with the development of DNA analysis methods from the initially available Southern hybridization to next generation DNA sequencing, the exceptional molecular heterogeneity of familial hypercholesterolemia became obvious and, accordingly, the need to establish national spectra of mutations leading to the development of familial hypercholesterolemia was established. Researchers have moved from characterizing individual mutations to creating national registries and databases. Finally, research into the genetics of familial hypercholesterolemia has led to the emergence of new classes of cholesterol-lowering drugs. In Russia, molecular diagnostics of familial hypercholesterolemia has also undergone significant changes since the beginning of the study of familial hypercholesterolemia in 1987 and to the present, consideration of these changes formed the basis of this review.

Keywords: hypercholesterolemia; molecular diagnostics; low density lipoprotein receptor; coronary heart disease.

МОЛЕКУЛЯРНАЯ ДИАГНОСТИКА СЕМЕЙНОЙ ГИПЕРХОЛЕСТЕРИНЕМИИ В РОССИИ: ВЧЕРА, СЕГОДНЯ, ЗАВТРА

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Для цитирования: Захарова Ф.М., Мандельштам М.Ю., Богословская Т.Ю., Васильев В.Б. Молекулярная диагностика семейной гиперхолестеринемии в России: вчера, сегодня, завтра // Медицинский академический журнал. 2024. Т. 24. № 1. С. 23–36. DOI: https://doi.org/10.17816/MAJ630505

Рукопись получена: 19.04.2024 Рукопись одобрена: 06.05.2024 Опубликована online: 27.05.2024

Семейная гиперхолестеринемия — тяжелое наследственное заболевание, ведущее к развитию атеросклероза и его осложнений в виде стенокардии, инфарктов миокарда, мозговых инсультов или даже приводящее к внезапной смерти. С момента описания заболевания представление о нем претерпели существенную эволюцию. Во-первых, стало очевидно, что распространенность этого заболевания заметно выше, чем исходно предполагалось (1 : 300 для гетерозиготной формы, а не 1 : 500, как оценивалось ранее). Во-вторых, установлено, что в его основе лежит не патология одного лишь гена рецептора липопротеинов низкой плотности, оно включает, по крайней мере, четыре моногенные формы (дефекты генов *APOB, PCSK9, ARH*) и также может иметь мультигенную природу. В-третьих, с развитием методов анализа ДНК от доступной исходно гибридизации по Саузерну до методов секвенирования ДНК нового поколения стала очевидна исключительная молекулярная гетерогенность семейной гиперхолестеринемии и, соответственно, определена необходимость установления национальных спектров мутаций, ведущих к ее развитию. От характеристики отдельных мутаций исследователи перешли к созданию национальных регистров и баз данных. Наконец, исследование генетики семейной гиперхолестеринемии привело к появлению новых классов гипохолестеринемических препаратов. В России молекулярная диагностика также претерпела существенные изменения с момента начала изучения семейной гиперхолестеринемии в 1987 г. и по настоящее время; рассмотрение этих изменений легло в основу настоящего обзора.

Ключевые слова: гиперхолестеринемия; молекулярная диагностика; рецептор липопротеинов низкой плотности; заболевания сердечно-сосудистой системы.

List of abbreviations

FH — familial hypercholesterolemia; LDL — low-density lipoproteins.

What is the incidence of familial hypercholesterolemia in Russia?

FH is the most prevalent hereditary disease in humans and typically exhibits an autosomal dominant type of inheritance. The classical form is associated with impaired low-density lipoprotein (LDL) catabolism due to LDL receptor dysfunction or quantitative deficiency [1]. This disease has two variants, heterozygous and homozygous, differing in symptom severity. Previously, the incidence of the heterozygous form of FH in most populations of the world was estimated at 1:500, while that of the homozygous form was estimated to be one case per million of patients examined [1]. However, studies conducted in individual countries using standardized diagnostic criteria have revealed that the incidence of FH in outbred populations is substantially higher: 1:219–300 for the heterozygous form and 1:300,000 for the homozygous form [2–4]. In populations where the founder effect is substantial, the incidence of FH may be even higher, as observed in Johannesburg Jews (1:67) [5], South African Afrikaners (1:76) [6–8], French-speaking Canadians (1:270) [9], and Lebanese Christians (1:90) [10]. The exact incidence of FH in Russia remains unknown. According to various estimates, the number of patients with the heterozygous form of FH in Russia varies from 287,000 [11] to 1,300,000 people [12], while 150–300 people in the country have the homozygous form of FH [11]. The incidence of FH in the Tyumen and Kemerovo regions was evaluated as part of the largest population study in the modern annals of Russia, ESSE-RF (Epidemiology of cardiovascular diseases and their risk factors in the regions of the Russian Federation) [12]. The incidence of reliably established FH (definite FH according to the criteria of the Dutch Lipid Clinic Network, DLCN) [3, 13] (Table 1) was determined in a group of 1630 patients from the Tyumen region and 1622 patients from the Kemerovo region aged 25–64 years, which amounted to 0.24% (1 of 407 examined), and that of probable FH was 0.68% (1 of 148 examined), with the total number of patients with these two diagnoses being 0.92% (1 of 108 examined). In this study, 40% of FH patients had experienced ischemic heart disease because of atherosclerosis, and 23% had received statin therapy. In the combined group of patients diagnosed with probable or definite FH, the odds of developing ischemic heart disease and myocardial infarction were 3.71 (95% CI (confidence interval) 1.58–8.72) ($p = 0.003$) and 4.06 (95% CI 0.89–18.55) ($p = 0.070$), respectively, compared to patients without FH. These results suggest that the FH incidence in Russia may be significantly higher than previously believed and that only a small proportion of FH patients are diagnosed and receive appropriate treatment. Thus, the FH incidence in Russia may be even higher than the average among the white races. The necessity of conducting genetic studies on the molecular nature of FH in Russia is determined by the elevated risk of coronary atherosclerosis among FH patients and the potential for preventive medical intervention.

Molecular nature of familial hypercholesterolemia

In 1938, Muller first characterized FH as an "inborn error of metabolism" that led to high blood cholesterol and early myocardial infarctions in patients. Muller proposed that FH is a monogenic, autosomal dominant disease [14]. Later, in the mid-1960s and early 1970s, it was discovered that FH clinically exists in two forms: a less severe heterozygous form and a more severe homozygous form [15].

M. Brown and J. Goldstein [16] demonstrated that the primary cause of FH is dysfunction of the receptor that extracts LDL from the bloodstream. The LDL receptor gene was cloned [17], the initial mutations in it were identified, and the LDL receptor cell cycle was established. After the cloning of the apolipoprotein B (*APOB*) gene in 1985 [18] and the identification of a variant known as familial defective apolipoprotein B (FDB) in 1989 [19–21], it became evident that FH was not restricted to mutations in the receptor gene but necessitated *APOB* gene analysis. It was subsequently determined that several variants, located in diverse gene locations, contribute to a defective binding of APOB to the receptor [22]. However, 95% of all FDB cases are linked to a single mutation p.(Arg3527Gln), previously cited as R3500Q.

In 2001, the autosomal recessive hypercholesterolemia (*ARH*) gene [23] was identified, which encodes an adapter protein for the LDL receptor that facilitates the internalization of the LDL receptor that has bound lipoproteins. The *PCSK9* gene of the subtilisin-kexin type proprotein convertase [24], which functions as a chaperone in the intracellular transport of the receptor, was cloned in 2003. It was discovered that mutations in this gene can result in both hypercholesterolemia due to increased receptor degradation and hypocholesterolemia as a result of decreased receptor degradation [25, 26]. Fig. 1 illustrates the interaction scheme of proteins that are involved in the removal of LDL from the circulation. In 2013, rare variants of the apolipoprotein E (*APOE*) gene were identified in FH patients.

The LDL receptor, a product of the *LDLR* gene, interacts with a single LDL protein, apolipoprotein B-100 (APOB-100), a product of the *APOB* gene. This interaction leads to lipoprotein-receptor complex uptake, which is facilitated by the accessory protein LDLRAP1, a product of the gene

Table 1 / Таблица 1

Diagnostic criteria of familial hypercholesterolemia according to Dutch Lipid Clinic Network (DLCN) [3, 13]
Диагностические критерии семейной гиперхолестеринемии по голландской сети липидных клиник (Dutch Lipid Clinic Network, DLCN) [3, 13]

Criteria group	Symptoms of hypercholesterolemia	Points
Amnestic	Presence of first-degree relatives with ischemic heart disease up to 55 years of age in men, up to 60 years of age in women, or with LDL cholesterol level above the 95th percentile in the population	1
	Presence of first-degree relatives with tendon xanthomas and/or lipoid corneal arcus, or children under 18 years of age with LDL cholesterol level above the 95th percentile for this population and age	2
Clinical	Early ischemic heart disease in a patient (up to 55 years of age in men, up to 60 years of age in women)	2
	Early cerebral or peripheral vascular disorders in a patient (up to 55 years of age in men, up to 60 years of age in women)	1
Examination data	Presence of tendon xanthomas	6
	Presence of lipoid corneal arcus under age 45	4
Biochemical	LDL cholesterol level ⩾8.5 mmol (328 mg/dL)	8
	LDL cholesterol level 6.5–8.4 mmol (251–327 mg/dL)	5
	LDL cholesterol level 5.0–6.4 mmol (193–250 mg/dL)	3
	LDL cholesterol level 4.0–4.9 mmol (155–192 mg/dL)	1
Genetic	Pathogenic mutation in one of the *LDLR, APOB*, or *PCSK9* genes	8

N o t e: LDL — low-density lipoproteins. The diagnosis of familial hypercholesterolemia is considered definite in case of the score of 8 or more; probable if the score is 6 to 8; possible if the score is 3 to 5; and unlikely if the score is 2 or less. Only one point from each category is used for the calculation. For example, if a patient under 45 years of age has both tendon xanthomas and lipoid corneal arcus, the score for these examinations is taken as 6.

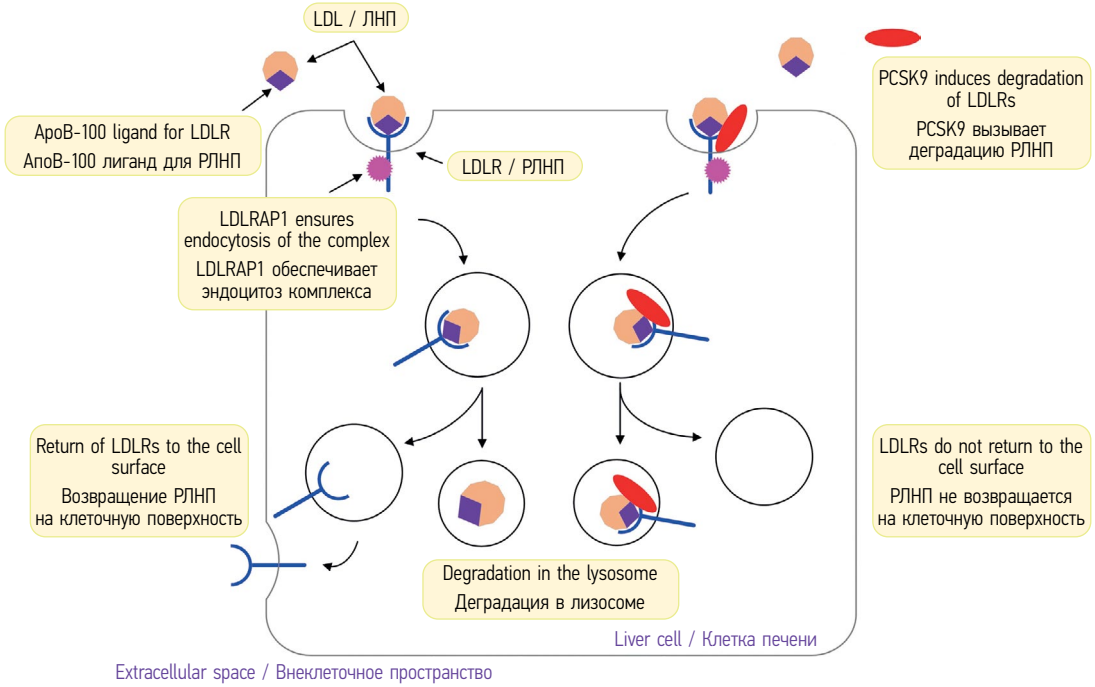

Fig. 1. Interactions of proteins involved in LDL uptake from bloodstream. LDL — low-density lipoprotein; LDLR — low-density lipoprotein receptor

Рис. 1. Взаимодействия белков, участвующих в захвате липопротеинов низкой плотности из кровотока. ЛНП — липопротеины низкой плотности; РЛНП — рецептор липопротеинов низкой плотности

of the same name, also known as *ARH*. The PCSK9 protein serves as a molecular chaperone for this complex. An autosomal dominant form of hypercholesterolemia is caused by receptor dysfunction due to mutations in its gene or impaired binding to the ligand due to mutations in the *APOB* gene. Dominant mutations in the *PCSK9* gene result in an increase in affinity for the receptor, LDL receptor degradation in lysosomes, and prevent its return to the cell surface, leading to the development of FH. Mutations in the *LDLRAP1 (ARH*) gene are linked to the development of an autosomal recessive form of hypercholesterolemia.

The ClinVar database currently contains 4,127 clinically significant variants associated with FH incidence for the *LDLR* gene. Of these, 1,422 variants were classified as pathogenic mutations and 875 variants were classified as likely pathogenic. The remaining variants were considered benign variants or variants of uncertain clinical significance. According to the same database, the *PCSK9* gene contains 25 pathogenic and 10 likely pathogenic variants, while the *LDLRAP1* gene contains 40 pathogenic and 15 conditionally pathogenic variants. The purpose of providing these figures is to illustrate the extremely high level of heterogeneity in FH.

The *APOE* gene variants, which were recently identified in the context of FH research, should be individually discussed. A small number of *APOE* gene variants are associated with FH development. These include the c.500_502delTCC/[p.(Leu167del)] variant, which is associated with FH in a large French family [27], and the [p.(Arg163Cys)] variant, which was found in a homozygous state in a 9-year-old boy and his heterozygous mother in a Canadian family of Italian origin [28] [29]. Another 7 *APOE* variants [p.(Glu21Lys), p.(Leu46Pro), p.(Gln99Lys), p.(Pro102Arg), p.(Arg269Gly), and p.(Leu270Glu)] were identified in probands with FH without changes in other genes associated with FH. However, no reliable evidence of their role in the genesis of the disease was obtained based on functional tests or family analysis [30]. Thus, the *APOE* gene is evidently associated with FH occurrence, but makes only a minor contribution to the diversity of its forms. The *ABCG5/ABCG8* and *LIPA* genes are potential locations for rare mutations in FH [3]. However, it has become clear that most cases of FH, in which mutations in the aforementioned genes are not identified, are linked to polygenic heredity, as they imitate monogenic forms of the disease [31].

This is the process by which the modern understanding of the genetics of FH was established. Typically, FH is considered a monogenic disease that involves the *LDLR, APOB, LDLRAP1,* and *PCSK9* genes, necessitating the analysis of all four of these genes for diagnosis. This has become possible with the introduction of next generation sequencing methods into diagnostic practice in 2010–2012, enabling whole-exome or whole genome sequencing. These methods are also employed to identify numerous intron mutations that can result in splicing disorders and a severe clinical phenotype. Moreover, 80%–85% of FH cases are caused by LDL receptor gene mutations. Mutations in the *APOB* gene are responsible for 5%–10% of FH cases, and the rarest mutations are those in the *PCSK9* gene and in the LDL receptor adaptor protein gene *LDLRAP1*, occurring in no more than 1% of patients with the disease [3]. The utilization of next-generation sequencing methods in Russia was delayed, and FH diagnostics employing them commenced in 2019 [32–35].

The severity of FH is phenotypically and clinically distinct among mutations in the *LDLR, APOB, LDLRAP1,* and *PCSK9* genes. Thus, homozygotes for the p.(Arg3527Gln) mutation in the *APOB* gene exhibit total plasma cholesterol concentrations of 330–420 mg/dL and LDL cholesterol levels of 260–350 mg/dL [36]. Thus, the phenotypic expression is significantly less severe than that in homozygotes for LDL receptor gene mutations with cholesterol levels of 600–1200 mg/dl. Heterozygotes for this *APOB* gene mutation exhibit elevated LDL cholesterol levels by 60–70 mg/dl; however, they are not always diagnosed with FH. Consequently, the risk of cardiovascular diseases is highest in FH caused by the *LDLR* gene pathogenic variants and substantially lower in patients with *APOB* gene defects [37]. Additionally, the LDL cholesterol level in *PCSK9*-associated hypercholesterolemia can be as elevated as in *LDLR*-associated hypercholesterolemia [38].

History of familial hypercholesterolemia studies in Russia

In Russia, research related to FH genetics was initiated in 1987 (Table 2) and included three stages. Initially, FH was diagnosed using only one available method: Southern hybridization for identifying *LDLR* gene deletions and restriction fragment length polymorphism analysis for disease diagnostics, and the molecular heterogeneity of the disease was thus revealed [39]. At this stage, it was established that large-scale LDL receptor gene rearrangements are rare in the Russian population; a deletion was observed in only one of 50 probands in St. Petersburg [40]. A systematic search for deletions in the *LDLR* gene in 42 patients with FH in Novosibirsk was conducted much later [35]. The patients underwent targeted sequencing of lipid metabolism genes, and no functionally significant substitutions were detected in the *LDLR, APOB*, and *PCSK9* genes using the method of multiplex amplification of ligase-linked samples. The search results identified deletions in the *LDLR*

Table 2 / Таблица 2

Primary milestones in the study of familial hypercholesterolemia genetics in Russia
Основные вехи изучения генетики семейной гиперхолестеринемии в России

Year	Event
1987	Start of genetic studies of familial hypercholesterolemia at the Institute of Experimental Medicine
1989	First report of *LDLR* gene deletion in Russia [40]
1998	First point mutations of *LDLR* gene in St. Petersburg [51]
1998	First report of *APOB* mutation in Russia [73]
2001	First report of *LDLR* gene mutations in Moscow [74]
2005	Spectrum of *LDLR* gene mutations in St. Petersburg [41]
2008	Spectrum of *LDLR* gene mutations in a population sample in Novosibirsk [47]
2009	Spectrum of *LDLR* and *APOB* gene mutations in Moscow [45]
2013	Spectrum of *LDLR* gene mutations in Petrozavodsk [42]
2017	Diagnostics and treatment of familial hypercholesterolemia (Russian recommendations) [72]
2017	Launch of next-generation sequencing for diagnosing familial hypercholesterolemia with the study of many genes, including *PCSK9* [75]
2020	Summary of *LDLR* gene variants in Russia [49]
2021	Results of the ESSE-RF study of familial hypercholesterolemia in the regions of Russia [50]

gene in two patients, which is in good agreement with the early estimate of the gene deletion frequency in FH in St. Petersburg at 2%. Globally, in outbred populations, the *LDLR* gene deletions in FH make up about 8%–10% of all variants of this gene [3].

At stage 2, the polymerase chain reaction method and Sanger DNA sequencing were employed following manual or automatic analysis of the conformational polymorphism of single-stranded DNA fragments. An examination of 74 probands diagnosed with FH in St. Petersburg, in whom all exons and the promoter region of the *LDLR* gene were studied, revealed 33 types of mutational changes in the *LDLR* gene in a total of 59% (44 out of 74) of probands. This included 30 mutations that, in our opinion, cause the disease in 55% (41 out of 74) of families with FH. This cohort did not exhibit any mutations in the *APOB* gene [41]. Similar studies were conducted on populations in Petrozavodsk and Moscow. The Petrozavodsk cohort of 52 patients underwent genetic analysis, and 22 probands (42%) were found to have *LDLR* gene mutations. Of these, 14 varieties of mutations were suspected to be responsible for the disease in 14 families (27%) [42, 43]. To date, 18 mutations have been identified in FH patients in Petrozavodsk [44]. In the most extensive study of this period [45], conducted in Moscow, 21 *LDLR* gene mutations were detected in 23 of 50 probands with FH (46%). The same study examined common *APOB* gene mutations, which accounted for a total of 2.6% in a large sample of 730 patients with FH in Moscow [45]. However, among the variants detected, only the p.Arg3527Gln (R3500Q) mutation is definitively associated with hypercholesterolemia and results in a defective variant in binding to the APOB-100 receptor (FDB). It was revealed in 14 (1.9%) patients with FH [45]. A smaller study [46], which included 111 patients with a heterozygous form of FH, revealed that five individuals (4.5%) were carriers of R3500Q mutation. During stage 2, in Novosibirsk, the coding region of the *LDLR* gene was sequenced in 20 patients aged 45–49 years with the highest level of total serum cholesterol in this age group, irrespective of family history of the disease [47]. Consequently, seven previously undescribed mutations and 12 known mutations in the *LDLR* gene were discovered. The spectrum of LDLR gene mutations in a population sample of patients with hypercholesterolemia was significantly different from the spectrum of mutations in FH patients from clinical samples, as demonstrated by this study [47].

Stage 3 involved the utilization of next-generation sequencing techniques. In Western Siberia, 80 individuals (60 probands) with heterozygous FH underwent targeted high-throughput sequencing to investigate the spectrum of rare variants in 43 genes, including *LDLR, APOB, PCSK9*, and *LDLRAP1* [35]. The targeted gene panel included coding regions and adjacent splicing sites of 43 genes, including *LDLR*, *APOB*, *PCSK9*, *LDLRAP1*, *CETP*, *LPL*, *HMGCR*, *NPC1L1*, *PPARA*, *MTTP*, *LMF1*, *SAR1B*, *ABCA1*, *ABCG5*, *ABCG8*, *CYP7A1*, *STAP1*, *LIPA*, *PNPLA5*,

APOA1, *APOA5*, *APOC2*, *APOE*, *LCAT*, *ANGPTL3*, *LIPC*, *APOA4*, *APOC3*, *SREBF1*, *LMNA*, *PPARG*, *PLIN1*, *POLD1*, *LPA*, *SMAD1*, *SMAD2*, *SMAD3*, *SMAD4*, *SMAD5*, *SMAD6*, *SMAD7*, *SMAD9*, *LIPG*. Pathogenetically significant variants in genes associated with FH were identified in 47.5% of the examined individuals. Clinically significant variants in the *LDLR* gene were observed in 19 probands (73.1% of all variants identified in probands); pathogenic variants were detected in the *APOB* gene in three probands (11.5%); in four probands (15.4%), rare clinically significant variants were identified in the *LPL, SREBF1, APOC3*, and *ABCG5* genes. Large-scale studies were conducted in Moscow and included the study of 63 genes in 52 patients [48]; pathogenic variants were revealed in 48% of patients (in 24 cases in the *LDLR* gene and in two cases in the *APOB* gene). In a large cohort of 595 patients, mutations in *LDLR, APOB,* and *PCSK9* were searched using targeted and whole genome sequencing. However, potentially pathogenic variants were not detected in 301 patients out of 595 (50.6%) [34]. In St. Petersburg, a comparable study that included 31 adult patients and 28 children and adolescents with definite or possible FH according to DLCN criteria identified pathogenic variants in these groups in 58% and 89% of cases, respectively [33]. Thus, the disease is linked to polygenic heredity, as even whole genome sequencing in Russia was unable to detect gene mutations in autosomal dominant FH in approximately 50% of adult patients with FH. At stage 3, reports were published summarizing the search results for mutations in the FH genes in Russia [34, 44, 49]. During this stage, the study of FH genetics was further extended geographically in Russia, and individual *LDLR* gene mutations were identified in multiple cities [50, 44].

The success of further research on FH genetics in Russia will be determined by several factors, one of which is the establishment of a comprehensive registry of FH patients in the country. The other is the integration of targeted sequencing into the mainstream practice of laboratories [44].

The spectrum of mutations in the low-density lipoprotein-receptor gene in patients with familial hypercholesterolemia in Russia

Currently, it is evident that the founder effect in Russia is not manifested in FH in relation to *LDLR* gene mutations. Most pathogenic variants (142 out of 203, or 70%) in Russia were identified in single families, while only 61 variants were observed in two or more families [44]. Only five mutations were detected in ten or more families. The variant c.478T > G [p.(Cys160Gly)] (rs879254540), first described in St. Petersburg [51] and subsequently documented in Moscow and Novosibirsk, was identified in a total of ten families. This mutation is specific to Russia and is considered a Slavic mutation. Deletion c.654_656delTGG [p.(Gly219del)] (rs121908027) (14 families) is a variant responsible for up to 30% of FH cases in Ashkenazi Jews in St. Petersburg [52], as well as globally. Variants c.986G > A p.[Cys329Tyr] (rs761954844) (13 families), c.1202T > A [p.(Leu401His)] (rs121908038) (33 families), c.1775G > A p.[Gly592Glu] (rs137929307) (43 families) are widespread among people of the Caucasian race and not exclusively in Russia [44]. It is important to note that the ESSE-RF study only examined the incidence of FH in 11 regions of the Russian Federation. Specifically, mutations in the *LDLR*, *APOB*, and *PCSK9* genes were searched in patients with verified and probable FH. The cities of Krasnoyarsk, Vologda, Ivanovo, St. Petersburg, Orenburg, Tomsk, Omsk, Petrozavodsk, Vladivostok, Tyumen, and Kemerovo were covered [50]. The majority of the LDLR gene variants were detected in St. Petersburg, Moscow, Novosibirsk, and Petrozavodsk, as the studies were

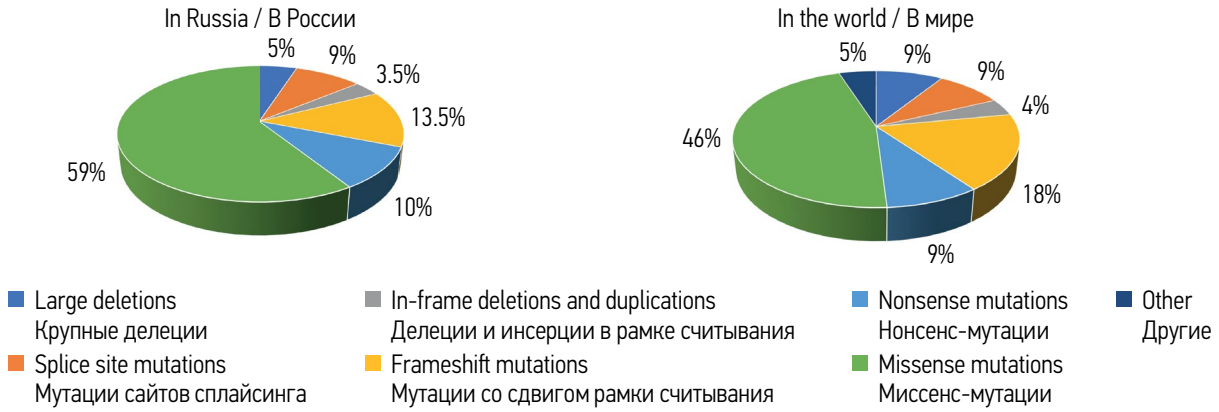

Fig. 2. Comparison of the distribution of mutations in the *LDLR* gene in patients with familial hypercholesterolemia in Russia and worldwide by type

Рис. 2. Сравнение распределения мутаций в гене *LDLR* у пациентов с семейной гиперхолестеринемией в России и в мире по типам

conducted significantly longer and within the context of other programs. Notably, the distribution of LDL receptor gene mutations by type in Russian FH patients is similar to that of the global population (Fig. 2).

The establishment of national databases on genetic variants that cause the disease and on genetic polymorphisms of the *LDLR* gene that are prevalent in Russia is a critical component of the research on the range of *LDLR* gene mutations [53, 54].

New hypocholesterolemic drugs that appeared during the study of the genetics of familial hypercholesterolemia

As the genetics of FH have become more well understood, new classes of hypocholesterolemic medications have emerged in addition to the traditional treatment of statins, ezetimibe, and bile acid sequestrants in the intestine. These drugs predominantly include monoclonal antibodies against PCSK9, including alirocumab and evolocumab [55]. Alirocumab is a human IgG1 antibody that is administered subcutaneously at a dose of 75–150 mg once every two weeks or 300 mg once every four weeks. Evolocumab is a human IgG2 antibody administered subcutaneously at a dose of 140 mg once every two weeks or 420 mg once every four weeks. They decrease LDL cholesterol levels by 40%–64% when used concurrently with statins in heterozygous FH [56] and achieve a reduction in LDL cholesterol by 20%–30% in the presence of a non-null allele of the LDL receptor gene in homozygous FH [56, 57]. Another therapeutic agent is inclisiran, a small interfering RNA that inhibits PCSK9. When administered subcutaneously at a dose of 300 mg once every four months, inclisiran can reduce LDL cholesterol levels in homozygous FH by 12%–37% [58]. Another new hypocholesterolemic drug is bempedoic acid, which inhibits ATP citrate lyase in its activated form. ATP citrate lyase is involved in liver cholesterol biosynthesis at earlier stages than hydroxymethyl-CoA reductase, which is inhibited by statins [59, 60]. In patients with heterozygous FH or as monotherapy, the use of bempedoic acid is recommended in conjunction with dietary measures and the maximum tolerated dose of statins for the treatment of hypercholesterolemia. Novel drugs for FH treatment also include mipomersen, an antisense oligonucleotide to the *APOB* gene mRNA, and lomitapide, an inhibitor of microsomal triglyceride transfer protein, which is involved in the assembly and secretion of very low-density lipoproteins in the liver and chylomicrons in the intestine [30]. Angiopoietin-like protein 3 (ANGPTL3) modulates the metabolism of triglyceride-rich lipoproteins predominantly by inhibiting lipoprotein lipase [61]. The development of familial combined hypolipidemia, which is characterized by a decrease in the level of LDL and high-density lipoproteins, has been demonstrated to be caused by mutations in the *ANGPTL3* gene due to a loss of its function [62]. The human antibody against *ANGPTL3* (evinacumab [63]) has been demonstrated to be efficacious in reducing LDL cholesterol by 23% in individuals with elevated LDL cholesterol. Consequently, it is a promising treatment option for hypercholesterolemia [64, 65]. This entire collection of lipid-lowering drugs can be employed to treat FH, depending on the extent of cholesterol increase associated with mutations in different genes causing the disease [66].

Conclusion

Genetic diagnostics of FH is justified, as physicians possess a substantial arsenal of medications that are effective in treating the condition. Unfortunately, the disease is not consistently diagnosed in Russia, and not all patients receive the necessary treatment, despite understanding the molecular character of the condition [67]. An example is the most recent study [50] conducted within the ESSE-RF program, where the frequency of heterozygous FH was determined among 18,142 participants. The prevalence of definite or probable FH according to DLCN criteria was 0.58% (1 out of 173 patients). Tendon xanthomas were present in only 16.1% of patients, while 36.2% of patients had mutations in one of the three dominant hypercholesterolemia genes. Cardiovascular diseases were present in 45.6% of patients, and 63% of patients received statins. Only one patient received an additional PCSK9 inhibitor, and none of the patients received ezetimibe. Only 3% of patients attained the recommended cholesterol level during treatment.

A significant issue linked to FH is the disease diagnostics among children, which remain at an extremely low level [68, 69]. Based on the prevalence in the population, the estimated number of patients with the heterozygous form of FH in Russia may be more than 840 thousand [37], including about 200 thousand children under the age of 18 [70]. Cascade screening is the most cost-effective and efficient method for diagnosing FH in children. This method involves identifying the disease among the relatives of the index patient [69, 70]. Conducting such screening is significantly facilitated by detecting a genetic defect in the family. Currently, in the all-Russian registry RENESSANS (register of FH patients and patients with very high cardiovascular risk with insufficient efficacy of lipid-lowering therapy) [71], more than 1,700 patients with FH are registered, which is less than 2% of the potential number of patients [70].

The necessity for more comprehensive diagnostics of the disease, as well as early and aggressive

cholesterol-lowering therapy, is underscored by the ineffective treatment of FH in Russia and the poor diagnostics. This appears to be the future of FH research in Russia. Russian guidelines for FH diagnostics and treatment [72] acknowledge the obvious benefits of genetic screening, since identifying a specific gene mutation significantly simplifies the diagnosis of FH and cascade screening. The reduction in the cost of DNA analysis technologies and the advancement of these technologies provide optimism that these methods will be extensively utilized in Russian medical practice for FH diagnostics in the future.

Additional information

Source of financing. The work was carried out within the framework of state tasks of the Ministry of Science and Higher Education of the Russian Federation: NIR No. FGWG-2022-0009 (NIOKTR reg. No. 122020300191-9).

Competing interests. The authors declare no competing of interest.

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Personal contribution of each author: *F.M. Zakharova* — making drawings and diagrams; *M.Yu. Mandelshtam* — preparing the main text and tables; *T.Yu. Bogoslovskaya* — preparing a bibliography; *V.B. Vasilyev* — preparing a section on the treatment of familial hypercholesterolemia and editing the final version of the text.

Дополнительная информация

Источник финансирования. Работа выполнена в рамках государственных заданий Министерства науки и высшего образования РФ: НИР № FGWG-2022-0009 (рег. № НИОКТР 122020300191-9).

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Наибольший вклад распределен следующим образом: *Ф.М. Захарова* — изготовление рисунков и диаграмм; *М.Ю. Мандельштам* — подготовка основного текста и таблиц; *Т.Ю. Богословская* — подготовка библиографии; *В.Б. Васильев* — подготовка раздела о лечении семейной гиперхолестеринемии и редактирование финальной версии текста.

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