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Analysis of the low density lipoprotein receptor gene (*LDLR*) mutation spectrum in Russian familial hypercholesterolemia

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Abstract. Familial hypercholesterolemia (FH) is a very common human hereditary disease in Russia and in the whole world with most of mutations localized in the gene coding for the low density lipoprotein receptor (*LDLR*). The object of this review is to systematize the knowledge about *LDLR* mutations in Russia. With this aim we analyzed all available literature on the subject and tabulated the data. More than 1/3 (80 out of 203, i. e. 39.4 %) of all mutations reported from Russia were not described in other populations. To date, most *LDLR* gene mutations have been characterized in large cities: Moscow (130 entries), Saint Petersburg (50 entries), Novosibirsk (34 mutations) and Petrozavodsk (19 mutations). Other regions are poorly studied. The majority of pathogenic mutations (142 out of 203 reported here or 70 %) were revealed in single pedigrees; 61 variants of mutations were described in two or more genealogies; only 5 mutations were found in 10 or more families. As everywhere, missense mutations prevail among all types of nucleotide substitutions in *LDLR*, but the highest national specificity is imparted by frameshift mutations: out of 27 variants reported, 19 (or 70 %) are specific for Russia. The most abundant in mutations are exons 4 and 9 of the gene due to their largest size and higher occurrence of mutations in them. Poland, the Czech Republic, Italy and the Netherlands share the highest number of mutations with the Russian population. Target sequencing significantly accelerates the characterization of mutation spectra in FH, but due to the absence of systematic investigations in the regions, one may suggest that most of *LDLR* mutations in the Russian population have not been described yet.

Key words: familial hypercholesterolemia; low density lipoprotein receptor gene; mutations.

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Анализ спектра мутаций гена рецептора низкой плотности (*LDLR*) при семейной гиперхолестеринемии в России

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Аннотация. Семейная гиперхолестеринемия – распространенное во всем мире наследственное заболевание человека, при котором чаще всего дефекты обнаруживаются в гене рецептора липопротеинов низкой плотности (*LDLR*). Цель работы – систематизировать знания о мутациях гена *LDLR* в России. Проведен анализ литературы по предмету исследования, составлены сводные таблицы, показывающие встречаемость мутаций в отдельных регионах, и определены часто встречающиеся мутации. Более трети (80 из 203, т. е. 39.4 %) патогенных или вероятно патогенных мутаций представлены вариантами, специфичными для России и не встречающимися в других странах. Наибольшее количество вариантов охарактеризовано в крупных городах: Москве (130 патогенных мутаций), Санкт-Петербурге (50), Новосибирске (34) и Петрозаводске (19), тогда как регионы охарактеризованы гораздо хуже. Подавляющее число патогенных мутаций (142 из 203, или 70 %) найдено в единичных семьях, и только 61 вид мутаций встречался в двух или в нескольких родословных. Лишь 5 видов мутаций были найдены не менее чем в 10 семьях. Как и везде в мире, в России в гене *LDLR* преобладают миссенс-мутации, но особенным национальным своеобразием характеризуются мутации типа сдвига рамки считывания: из 27 найденных вариантов 19 (70 %) специфичны для России. Наивысшее число мутаций в гене *LDLR* в российской популяции обнаружено в четвертом и девятом экзонах. Это определяется тем, что четвертый и девятый экзоны являются самыми протяженными в гене и кодируют функционально важные участки белка, что обуславливает повышенную плотность патогенных мутаций в расчете на один нуклеотид длины именно в этих экзонах. Российская популяция имеет наибольшее число совпадающих му-

таций с популяциями Польши, Чешской Республики, Нидерландов и Италии. Внедрение методов таргетного секвенирования существенно ускорило характеристику мутационного спектра при семейной гиперхолестеринемии, но из-за отсутствия систематических исследований в регионах большинство видов мутаций в России, вероятнее всего, еще не описано.

Ключевые слова: семейная гиперхолестеринемия; рецептор липопротеинов низкой плотности; мутации.

Introduction

The term ‘familial hypercholesterolemia’ (FH) is generally used to refer to monogenic diseases caused by mutations in the low-density lipoprotein (LDL) receptor (*LDLR*) gene (OMIM 606945), in the apolipoprotein B (*APOB*) gene (OMIM 107730), in the *PCSK9* gene (OMIM 607786), in the adapter protein gene for the LDL receptor *LDLRAP1* (OMIM 605747) and some minor genes, such as *STAP1*, *APOE*, *LIPA*, or in the sterol transporter genes, sterolins *ABCG5/ABCG8* (Defesche et al., 2017; Berberich, Hegele, 2019). At the same time, 80–85 % of FH cases are caused by mutations in the LDL receptor gene. Mutations in the apolipoprotein B gene are responsible for 5–10 % of FH cases. Mutations in the *PCSK9* gene and in the LDL receptor adapter protein gene are the rarest, occurring in no more than 1 % of patients with FH.

It was previously believed that heterozygous FH occurs in 1 out of 500 people examined in the population, but the current data allow us to conclude that it is much more frequent. A study of 69,106 patients in Denmark who were diagnosed with FH based on the recommendations of the Dutch Lipid Clinic Network (DLCN) demonstrated that the prevalence of the disease is 1:219 (Benn et al., 2012). It may be even higher in Russia, i. e. 1:148 (Ershova et al., 2017). However, in this instance, cases of not only definite, but also probable FH were taken into account. Such frequency allows attributing FH to the most common monogenic human diseases.

Already in 2018, the ClinVar database (Landrum et al., 2016) included 4973 variants of the *LDLR* gene (Iacocca et al., 2018) associated with FH, of which 2351 variants were classified as pathogenic, and 1525 as probably pathogenic, the rest considered as benign variants or variants of uncertain clinical significance. The history of FH research in Russia has recently been reviewed (Vasilyev et al., 2020; Meshkov et al., 2021a). Most of the mutations leading to FH, as expected, were found in the *LDLR* gene, 187 pathogenic or likely pathogenic variants of which were identified in Russia (Meshkov et al., 2021a); 67 out of 187 were not described in other populations of the world. An important article on the genetics of FH in St. Petersburg was later published based on targeted sequencing of genes involved in the origin of the disease (Miroshnikova et al., 2021). As a result, 23 variants of the *LDLR* gene sequence were found in the St. Petersburg population, most of which had not been described in that area (Mandelshtam et al., 1993; Tatishcheva et al., 2001; Zakharova et al., 2005, 2007; Vasilyev et al., 2020). The results of studying mutations in the regions of Russia appeared only recently (Meshkov et al., 2021b). Continuously replenished data on the subject indicate the necessity for regular revisions of the tables of the *LDLR* gene mutations in Russia (Meshkov

et al., 2021a). In our view, such a notion supports the relevance of the present review: it already mentions 203 pathogenic or likely pathogenic variants in the gene discussed.

Methods

All available literature concerning *LDLR* gene mutations in the Russian population was analyzed. As a result, a summarizing table was compiled that significantly expands our knowledge about the spectrum of mutations in Russia, as compared to previously published data (Mandelshtam et al., 1993, 1998a, b; Chakir et al., 1998a, b; Krapivner et al., 2001; Mandelshtam, Maslennikov, 2001; Tatishcheva et al., 2001; Zakharova et al., 2001, 2005, 2007; Meshkov et al., 2004, 2009, 2021a, b; Voevoda et al., 2008; Komarova et al., 2013a–c; Korneva et al., 2013–2016, 2017a, b; Shakhtshneider et al., 2017, 2019a, b, 2021; Averkova et al., 2018; Semenova et al., 2020) (Supplementary Table)¹.

The term ‘mutation’, used throughout the text, implies all rare variants of a gene (widespread polymorphisms excluded) that are potentially capable of causing a disease, including the variants with proven or highly probable pathogenicity. Synonymous substitutions are not considered in this review (their list is presented in Vasilyev et al., 2020).

Results and discussion

There are more than 4900 variants of the *LDLR* gene described in the world, as was already mentioned (Iacocca et al., 2018). This review reports 203 pathogenic or likely pathogenic mutations of this gene in Russia (see Suppl. Table). However, this diversity is not likely to represent the variability of the receptor gene in the Russian population, since GWS was introduced somewhat recently, and a systematic study of the FH genetics in quite a few regions of Russia has not been conducted. The studies were carried out mainly in large cities (Fig. 1). Currently most of the mutations found are specific for each of these cities, and a significantly smaller proportion is common with other regions. Thus, the largest number of pathogenic or probably pathogenic variants in Russia (101) was found only in Moscow (Krapivner et al., 2001; Meshkov et al., 2004, 2009, 2021a; Averkova et al., 2018; Semenova et al., 2020), 35 variants were found only in St. Petersburg (Mandelshtam et al., 1993; Zakharova et al., 2001, 2005, 2007; Tatishcheva et al., 2001), 23 – only in Novosibirsk (Voevoda et al., 2008; Shakhtshneider et al., 2017, 2019a, b), 11 – only in Petrozavodsk (Komarova et al., 2013a–c; Korneva et al., 2013, 2014, 2017a, b), 33 – in other regions, sometimes in several regions simultaneously (Meshkov et al., 2021b).

¹ Supplementary Table is available in the online version of the paper: http://vavilov.elpub.ru/jour/manager/files/Suppl_Vasilyev_engl.pdf

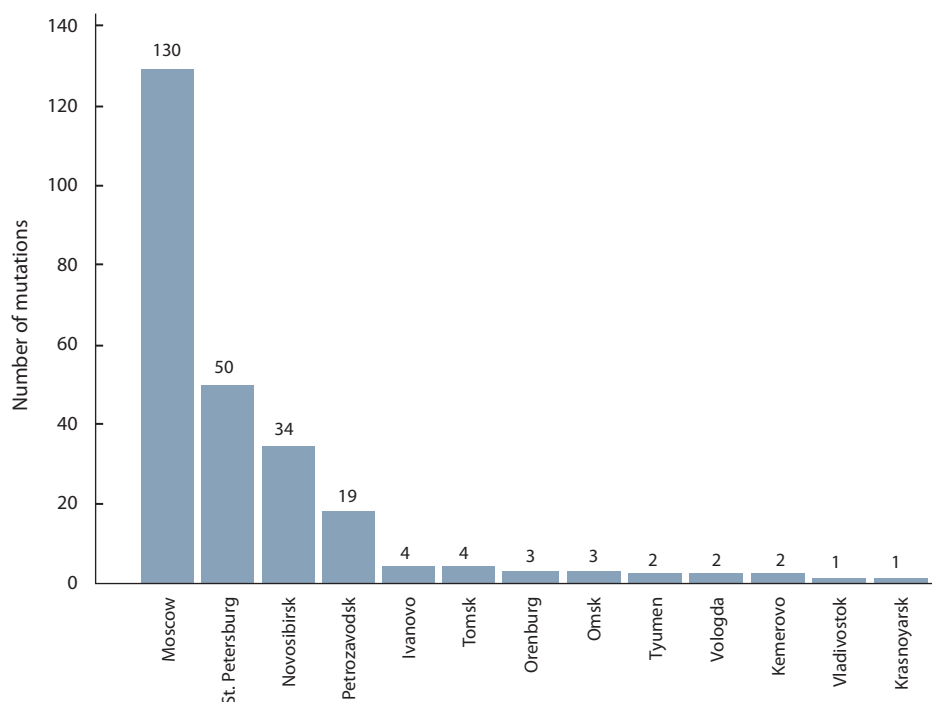


Fig. 1. The number of pathogenic and likely pathogenic variants in the *LDLR* gene found in Russian cities with examined populations (excluding common polymorphisms and benign variants).

Table 1. Analysis of the spectrum of pathogenic and likely pathogenic mutations of the *LDLR* gene in Russia and in the world

Mutation type	Total number of pathogenic variants found in Russia (%)	Number and proportion of variants specific for Russia (%)	Number and proportion of variants shared with other populations in the world (%)	Proportion of variants of this type in the world	
				Defesche et al., 2017	Chora et al., 2018
Large deletions	10 (5)	6 (60)	4 (40)	8–10	9
Splice site mutations	18 (9)	8 (44)	10 (56)	8–10	9
In-frame deletions and insertions	7 (3.5)	2 (29)	5 (71)	15–20	4
Frameshift mutations	27 (13.5)	19 (70)	8 (30)		18
Nonsense mutations	20 (10)	2 (10)	18 (90)	12–15	9
Missense mutations	121 (59)	43 (35)	78 (65)	40–50	46
Regulatory mutations	Not found	–	–	No data	2
Synonymous substitutions	Not considered	–	–	No data	1
Intron mutations	Not considered	–	–	No data	2
Total	203 (100)	80 (39.4)	123 (60.6)		100

Table 2. Pathogenic variants in the *LDLR* gene that were found in patients with FH from the Russian population in 10 or more families

Nucleotide change according to reference sequence NM_000527.5 (<i>LDLR</i>)	Predicted change in protein	Number of families	Nucleotide change according to dbSNP	Populations in Russia	References for Russia	Other countries in the world
c.478T > G	p.(Cys160Gly)	10	rs879254540	St. Petersburg, Novosibirsk, Moscow	Chakir et al., 1998a; Mandelshtam, Maslennikov, 2001; Meshkov et al., 2004, 2009, 2021a	None
c.654_656delTTGG	p.(Gly219del)	14	rs121908027	St. Petersburg, Novosibirsk, Moscow	Mandelshtam et al., 1998; Mandelshtam, Maslennikov, 2001; Zakharova et al., 2005; 2007; Meshkov et al., 2021a	The Czech Republic, Germany, UK, Israel, The Netherlands, Poland, RSA, USA, mainly in Ashkenazi Jews
c.986G > A	p.(Cys329Tyr)	13	rs761954844	St. Petersburg, Novosibirsk, Moscow, Petrozavodsk	Zakharova et al., 2005, 2007; Shakhtshneider et al., 2019b; Semenova et al., 2020b; Meshkov et al., 2021a, b; Miroshnikova et al., 2021	Canada, China, The Czech Republic, Philippines, Poland, Taiwan, The Netherlands
c.1202T > A	p.(Leu401His)	33	rs121908038	St. Petersburg, Novosibirsk, Moscow, Krasnoyarsk, Petrozavodsk	Zakharova et al., 2005; Shakhtshneider et al., 2019b; Meshkov et al., 2021a, b; Miroshnikova et al., 2021	Finland, The Netherlands, Brazil, Mexico, Norway
c.1775G > A	p.(Gly592Glu)	43	rs137929307	St. Petersburg, Novosibirsk, Moscow	Zakharova et al., 2001, 2007; Voevoda et al., 2008; Semenova et al., 2020; Meshkov et al., 2021a, b	Austria, Belgium, Brazil, Greece, Canada, Germany, The Czech Republic, Italy, The Netherlands, Norway, Poland, Portugal, Spain, USA, etc.

Table 3. Occurrence of Russian *LDLR* gene mutations in other countries

Country	Total number of mutations described	Reference	Number of mutations shared with Russia
Poland	99	Chmara et al., 2010	19
The Czech Republic	129	Tichý et al., 2012; Chora et al., 2018	23
The Netherlands	306	Fouchier et al., 2005; Chora et al., 2018	36
Spain	205	Mozas et al., 2004; Chora et al., 2018	12
Italy	251	Bertolini et al., 2013; Pirillo et al., 2017; Chora et al., 2018	28

At the moment, we can state a wide variety of mutations in Russia, of which more than one third (39.4 %) are specific for the local population and have not been found anywhere else in the world so far (Table 1). The distribution of mutations by type in Russia is very similar to that in the world (see Table 1).

From the analysis of Table 1 it follows that the underestimated percentage of large deletions is due to the fact that targeted sequencing was introduced only recently, and a targeted large-scale search for large deletions was not carried out: the researchers focused on exon screening, which determined a slightly higher percentage of missense mutations than in the world as a whole. The systematic search for large deletions in the *LDLR* gene began very recently (Shakhtshneider et al., 2021). It included patients with FH in whom high-throughput targeted sequencing did not reveal significant mutations in a panel of 43 lipid metabolism genes using multiplex ligase-dependent PCR (MLPA), which revealed two deletions of the *LDLR* gene in a studied sample of 80 patients with FH.

Only a few variants of the *LDLR* gene occur in several families, but unique mutations predominate. The majority of pathogenic mutations (142 out of 203 or 70 %) in Russia were also found in singular families, and only 61 types of mutations were found in two families or in more pedigrees. Around the world, the largest number of mutations is described in the 4th exon. Firstly, it is the largest of all exons in the *LDLR* gene. Secondly, it has the highest density of mutations, amounting to 0.882 variants per nucleotide (Chora et al., 2018). It is in this exon that the largest number of functionally characterized mutations was found, and almost all of those have a pathogenic effect. Our study showed that the largest number of mutations in the *LDLR* gene in the Russian population is localized in the largest exons, i. e. the 4th and 9th (Fig. 2). Considering all the information available, we conclude

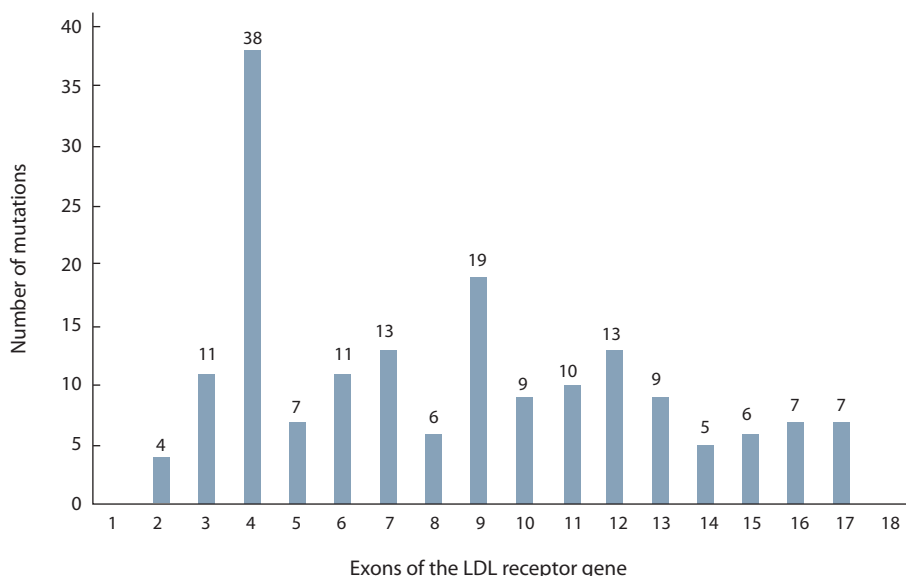


Fig. 2. Distribution of pathogenic and probably pathogenic variants by exons in the LDL receptor gene in patients with FH in Russia.

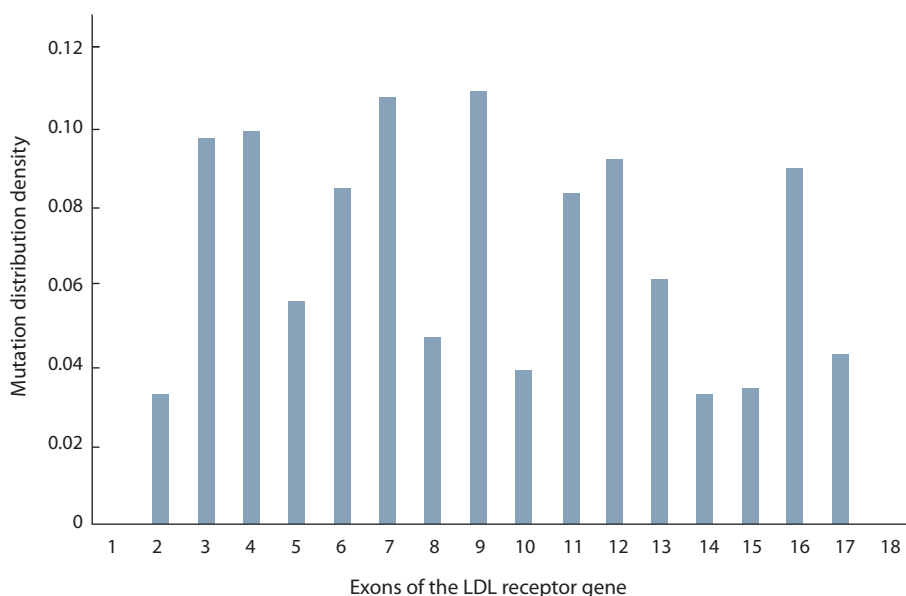


Fig. 3. Distribution density of pathogenic and likely pathogenic mutations in the exons of the LDL receptor gene per nucleotide in patients with FH in Russia.

that the highest mutation density per nucleotide (Fig. 3) is determined in the 9th, but not in the 4th exon, in contrast to other databases reported worldwide (Chora et al., 2018).

Only five pathogenic variants of the *LDLR* gene in Russia can be classified as major, found in 10 or more families (Table 2). Of these, only one is specific for Russia, while the rest are widespread in the world.

The greatest similarity in the spectrum of mutations in the *LDLR* gene in Russia is observed with Poland, the Czech Republic, the Netherlands, Spain and Italy, which is

partly determined by the fact that these populations are the best characterized (Table 3). This similarity probably results from the presence of widespread Caucasian race mutations in the world, but is not due to migration or the founder effect.

Conclusion

Thus, the success of further study of the mutation spectrum of the *LDLR* gene will depend on several factors, one of which is the formation of a complete nation-wide register of patients with FH, and the other is the introduction of targeted sequencing into routine practice.

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