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ОБЗОР
REVIEW

Biological and psychological approach to familial hypercholesterolemia

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Abstract. *Relevance.* Familial hypercholesterolemia (FH) is a monogenic hereditary disorder characterized by impaired lipid metabolism. The prevalence of FH in the general population averages 0.32% (95% CI: 0.26–0.39%). The disease can have both autosomal dominant and autosomal recessive inheritance patterns. Eight FH phenotypes associated with mutations in the *LDLRAP1*, *PCSK9*, *APOA2*, *APOB*, *GHR*, *GSBS*, *EPHX2*, and *LDLR* genes are known, which can lead to early manifestation of the pathology. The aim of this review is to comprehensively analyze current literature data on the molecular genetics, biological, and psychological aspects of FH. Analysis of signaling pathways in FH revealed three clusters of genes and their encoded proteins responsible for the following processes: assembly, remodeling, and clearance of plasma lipoproteins (genes: *LDLR*, *LDLRAP1*, *VLDLR*, *NPC1L1*, *APOC1*, *LPA*, *CETP*, *MTTP*, *APOB*, *PCSK9*); cholesterol metabolism (gene: *PPP1R17*); regulation of plasma lipoprotein particle levels (gene: *ANGPTL3*). The proteins PCSK9, APOB, and MTTP were identified as key elements (central hubs) of these metabolic networks. The PPP1R17 protein is involved in the mechanisms of long-term depression, a form of synaptic plasticity. Furthermore, the literature describes an association of FH with five other genes: *ABCG5*, *ABCG8*, *STAP1*, *CYP7A1*, *LIPA*, and *PNPLA5*. *Conclusion.* Thus, for the early diagnosis and effective management of patients with FH, it is necessary to consider not only the expanded spectrum of associated genes and proteins but also the psychological state of patients, particularly their levels of anxiety, depression, and stress.

Keywords: familial hyperholestorelomia, associated genes, proteins, metabolic pathways, anxiety, stress, depression

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D.D. Bekoeva— reviewing the manuscript. All authors have made significant contributions to the manuscript preparation, read, and approved final version before publication.

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Introduction

The comprehensive study of biological, molecular-genetic, psychological, and social aspects of hereditary cardiovascular diseases (CVD) remains a critical challenge in modern theoretical and practical biology and medicine. Cardiovascular diseases are the leading cause of morbidity worldwide, surpassing all other pathologies. Among these, multifactorial or polygenic disorders, such as ischemic heart disease, atherosclerosis, arterial hypertension, and others, are the most prevalent. Both hereditary predisposition and lifestyle factors play significant roles in the development and progression of these diseases. Key lifestyle risk factors include tobacco use, unhealthy diet and obesity, physical inactivity, excessive alcohol consumption, and chronic stress [1]. Additionally, conditions such as elevated blood pressure, diabetes, and hyperlipidemia serve as major contributors to CVD. Psychological and social factors, including chronic stress, anxiety, depression, and personality types (e.g., Type A behavior pattern), disrupt neurohumoral regulation and elevate cortisol and catecholamine levels [2]. These physiological changes contribute to the development of hypertension, arrhythmias, and the progression of atherosclerosis.

In addition to numerous multifactorial cardiovascular diseases, there exist a significant number of monogenic disorders affecting the cardiovascular system. The cause of these hereditary syndromes is the expression of a mutation in an associated gene. These inherited syndromes most commonly follow Mendelian inheritance patterns. One of the most prevalent hereditary cardiovascular pathologies is familial hypercholesterolemia (FH)**.** The inheritance pattern can be either autosomal dominant or, less commonly, autosomal recessive**.**

For all index cases/probands, genetic testing is recommended to identify the disease-causing DNA variant. This enables accurate diagnosis, risk assessment, and personalized treatment strategies for patients and their families.

The autosomal dominant inheritance pattern of FH was first described by the Norwegian physician Carl Müller in 1938 [3]. In the early 1970s and 1980s, Dr. Joseph Goldstein and Dr. Michael Brown investigated the genetic cause of FH. Their research focused on the process of low-density lipoprotein (LDL) binding to its receptor and the metabolic consequences of impaired binding, which was identified as the primary mechanism underlying FH [4]. For their discovery of the LDL receptor (LDL-R) and its role in lipoprotein metabolism, they were awarded the Nobel Prize in Medicine in 1985**.**

The prevalence of FH in the general population is approximately 1:313 [5], highlighting its significance as a common genetic disorder requiring widespread

screening and management. If an individual has biallelic (homozygous or compound heterozygous) pathogenic variants in one of these three genes — a condition known as homozygous FH — the symptoms are more severe and appear at an earlier age [6].

In modern psychology, two primary approaches to CVD prevention are recognized globally. The first, and historically earlier approach, has become the more conventional one. It targets prevention by influencing the professional, social, and psychological factors that contribute to CVD development. This model relies on objective data regarding an individual's vocational training and education — data that can be verified through testing, examinations, or other documentation. The core premise is that these factors significantly impact the disease course and are key contributors to poor patient adherence to treatment. The second approach is termed the competency-based model**.** It is founded on the novel concept of "competence," which describes a high level of professional capability in both healthcare providers and patients. Within this framework, disease prevention is linked to inherent personal factors, such as a genetic predisposition to conditions like hypercholesterolemia. These factors are more challenging to formalize and assess compared to the verifiable qualifications emphasized in the first approach.

Very recently, a targeted therapy addressing the disease's pathogenesis has been developed. Two effective strategies for reducing LDL levels have emerged:

suppressing the synthesis of lipoproteins in the liver by blocking the expression of apolipoprotein B and inhibiting the activity of the microsomal triglyceride transfer protein (MTP) [7].

According to the recommendations of the European Atherosclerosis Society, cholesterol screening should be performed for all individuals in the population before they reach the age of 20. In cases of a family history of FH or early-onset CHD, measurement of serum total cholesterol should be initiated from the age of 2 years [8].

The aim of our research is to analyze the molecular genetics and psychosocial features of FH.

Etiology and pathogenesis of familial hypercholesterolemia

HYPERCHOLESTEROLEMIA, FAMILIAL, 1; FHCL1 (OMIM # 143890 (Online Catalog of Human Genes and Genetic Disorders) — is a monogenic hereditary disease. Other associated clinical features include hyperbetalipoproteinemia, tuberous xanthoma, and tendon xanthoma. A mutation in one of the genes associated with FH is the underlying cause of the disease, which most often manifests at a young age. Furthermore, the mutation can be inherited in an autosomal dominant pattern or, much less frequently, in an autosomal recessive pattern. Table 1 presents the phenotypes, their associated genes, and the inheritance patterns of these syndromes.

It is known that the pathogenetic basis of the clinical manifestations of FH is atherosclerosis, which results from high concentrations of low-density lipoprotein cholesterol (LDL–C). In the small intestine, under the influence of bile acids and pancreatic lipase, dietary fats are emulsified and hydrolyzed. They are then packaged into chylomicrons, whose primary apolipoprotein is apoB-48. Through the action of lipoprotein lipase, which is activated by apolipoprotein C–II (apoC–II), chylomicrons are broken down into triglycerides (TG) and remnant particles. The apoC–II is then transferred back to high-density lipoprotein (HDL).

The remnant particles are taken up by the liver via receptor-mediated interaction and hydrolyzed, releasing free cholesterol. Endogenous cholesterol synthesis occurs primarily in the liver. The liver is also the main site for the receptor-mediated catabolism of LDL–C. LDL receptors located on hepatocytes remove LDL–C from the bloodstream by binding to LDL particles. The resulting complex, through interaction with the LDL receptor adapter protein (LDLRAP1), enters the cell via endocytosis and is directed to the lysosome, where the LDL particles are degraded.

The binding of PCSK9 to the LDL receptor on the hepatocyte surface promotes the degradation of the receptor, preventing its recycling back to the cell membrane [9].

Table 1

Relationship between Phenotype and Genes Associated with Familial hypercholesterolemia (OMIM data)

№	Phenotype	Phenotype MIM number	Inheritance	Gene	Gene name	Aliases	Gene MIM number	Locus
1	Hypercholesterolemia, familial, 4	603813	AR	*LDLRAP1*	Low density lipoprotein receptor adaptor protein 1	*ARH, FHCB2, FHCB1, FHCL4*	605747	1p36.11
2	Low density lipoprotein cholesterol level QTL 1 Hypercholesterolemia, familial, 3	603776	AD	*PCSK9*	Proprotein convertase, subtilisin/kexin-type,9	*NARC1, HCHOLA3, FH3, LDLCQ1, FHCL3*	607786	1p32.3
3	Hypercholesterolemia,familial, modifier of Apolipoprotein A-IIdeficiency	143810	AD, AR	*APOA2*	Apolipoprotein A-II	*ApoA-II*	107670	1q23.3
4	Hypercholesterolemia, familial, 2	144010	AD	*APOB*	Apolipoprotein B (in- cluding Ag(x) antigen)	*FLDB, LDLCQ4 FCHL2*	107730	2p24.1
	Hypobetalipoproteinemia	615558	AR					
5	Hypercholesterolemia,familial, modifier of	143890	AD, AR	*GHR*	Growth hormone receptor	*GHIP*	600946	5p13.1
	Growth hormone insensi- tivity, partial	604271	AD					
	Increased responsiveness to growth hormone	604271	AD					
	Laron dwarfism	262500	AR					
6	Hypercholesterolemia, susceptibility to	143890	AD, AR	*GSBS*	G-substrate	*PPP1R17*	604088	7p14.3
7	Hypercholesterolemia, familial, due to LDLR defect, modifier of	143890	AD, AR	*EPHX2*	Epoxide hydrolase 2, cytoplasmic	*ABHD 20 SEH*	132811	8p21.2
8	Hypercholesterolemia, familial, 1	143890	AD, AR	*LDLR*	Low density lipoprotein receptor	*FHCL1, FHC, FH, LDLCQ2*	606945	19p13.2

FH is classified as a disorder of lipid metabolism. It is characterized by impaired metabolism of LDL particles, leading to elevated levels of LDL–C in the blood. This abnormal accumulation of lipids facilitates their infiltration into the arterial walls. Consequently, cholesterol plaques (atherosclerotic lesions) form, which impair blood circulation and lead to atherosclerosis. This condition, in turn, is a primary cause of myocardial infarctions and strokes.

The main causes of dyslipidemia include hormonal disorders, cholecystitis, pancreatitis, an unbalanced diet, a sedentary lifestyle, smoking, and alcohol consumption, among others. However, a hereditary factor plays a crucial role in the pathogenesis of FH. The presence of a mutation in one of the genes involved in lipoprotein metabolism results either in insufficient clearance of LDL–C from the bloodstream or in increased degradation of the LDL receptor. Individuals with FH are considered to be at high risk for developing cardiovascular complications [8–11].

FH often remains asymptomatic for many years. The most common associated pathology is the development of ischemic heart disease (atherosclerosis of the coronary arteries). Cerebral vessels can also be affected, which may lead to transient ischemic attacks or stroke. Individuals with FH are also at risk for sudden cardiac death.

In some cases, patients with FH may exhibit external signs such as xanthomas — benign, yellowish-white, doughy-consistency skin growths — and corneal arcus (a white or grayish-white ring of lipid deposits around the cornea).

The condition is characterized not only by an elevated level of total serum cholesterol, which was the first factor recognized as responsible for the initiation and progression of atherosclerosis and its complications, but also by high levels of TG, elevated levels of LDL–C, and reduced levels of HDL–C [12].

Family history is a cornerstone of FH diagnosis due to its autosomal dominant inheritance pattern. A first-degree relative (parent, sibling, or child) with known coronary artery disease (e.g., heart attack, angina) or other vascular disease (e.g., stroke, peripheral artery disease) at an early age (typically <55 years for men and <60 years for women), with physical signs like tendon xanthomas**.** The patient's own history of premature atherosclerosis is a strong indicator. Documented evidence of CAD (e.g., heart attack, revascularization procedure like stent or bypass) at a young age. A physical exam can reveal visible signs of long-term, severe cholesterol elevation. Tendon Xanthomas: These are nodular, cholesterol-rich deposits in the tendons, most commonly observed in the Achilles tendons and the knuckles of the hands. They are a pathognomonic sign of FH. Arcus Cornealis**:** A white or grayish ring around the cornea of the eye. While it can be a normal sign of aging (arcus senilis), its appearance in a person under 45 years of age is a significant suggestive sign of FH.

The measurement of LDL–C is critical. The higher the level, the more likely the diagnosis of FH, especially in the absence of secondary causes. Levels are interpreted in the context of age and pre-treatment status. The following table illustrates how LDL–C levels are typically scored in diagnostic criteria like the DLCN: very strong evidence for Definite FH: LDL–C level >8.5 mmol/L.

The underlying cause of the clinical signs is the excessively high level of LDL–C in the blood. These lipoproteins infiltrate the artery walls, where they are engulfed by immune cells called macrophages. The macrophages, overloaded with cholesterol, become "foamy cells," which are the primary building blocks of atherosclerotic lesions (plaques) that narrow arteries and cause cardiovascular disease [11]. By combining the findings from all these domains into a scoring system, a clinician can reach a final diagnosis: Definite FH: Typically (DLCN), presence of a pathogenic genetic mutation, or tendon xanthomas in the patient or a relative, probable FH, unlikely FH. This structured approach ensures an accurate diagnosis, which is essential for initiating aggressive treatment and conducting family screening (cascade testing).

Epidemiology of FH

The conducted meta-analysis of 44 studies, encompassing a total of 10,921,310 subjects (of which 33,036 had FH), established the pooled prevalence

of familial hypercholesterolemia at 0.32% (95% CI: 0.26–0.39%) in the general population. No significant differences were found in prevalence estimates when using genetic diagnostic methods compared to clinical ones. A critical limitation is the lack of data on FH prevalence for 178 countries (91% of the total), which underscores the necessity for further epidemiological research on a global scale [13] (Figure 1).

One of the leading risk factors for the development of cardiovascular diseases is hyperlipidemia. According to data from the ESSE-RF epidemiological study, which included 13 regions from various parts of the Russian Federation, up to 60% of men and women in the Russian population have hypercholesterolemia LDL–C level of more than 3 mmol/L or a total cholesterol (TC) level of more than 5 mmol/L. The prevalence of elevated total cholesterol levels in the Russian regions was higher than in the USA; this difference was even more pronounced for LDL–C levels, which in the Russian regions were more than twice as high as the corresponding figure in the US population [14].

Among the causes of mortality in Russia, as in most developed countries, CVD hold the leading position. CVD account for 18.8% of the overall disease structure, ranking first. Among the working-age population, CVD account for more than a third of all deaths. The mortality rate from CVD among men exceeds that among women by 4.7 times overall, by 7.2 times for ischemic heart disease (IHD), by 9.1 times for myocardial infarction, and by 3.4 times for cerebrovascular diseases [15].

The most dangerous CVD leading to fatal outcomes are IHD, including myocardial infarction, cerebrovascular diseases, and hypertensive disease. 60% of cardiovascular mortality is attributable to risk factors: arterial hypertension, disorders of carbohydrate and lipid metabolism, obesity, smoking, excessive alcohol consumption, and low physical activity [16].

Biological aspects of FH

Characteristics Proteins Associated with FH

To date, a large number of genes associated with FH have been identified. The characteristics of a number of these genes, such as *APOA2, APOB, EPHX2, LDLR, LDLRAP1, GHR, GSBS, PCSK9*, are summarized in Table 1. The characteristics of the proteins associated with FH are listed below.

Apolipoprotein A-II

Apolipoprotein (apo-) A-II (APOA2) is the second most abundant protein of high-density lipoprotein particles. The protein is found in plasma as a monomer,

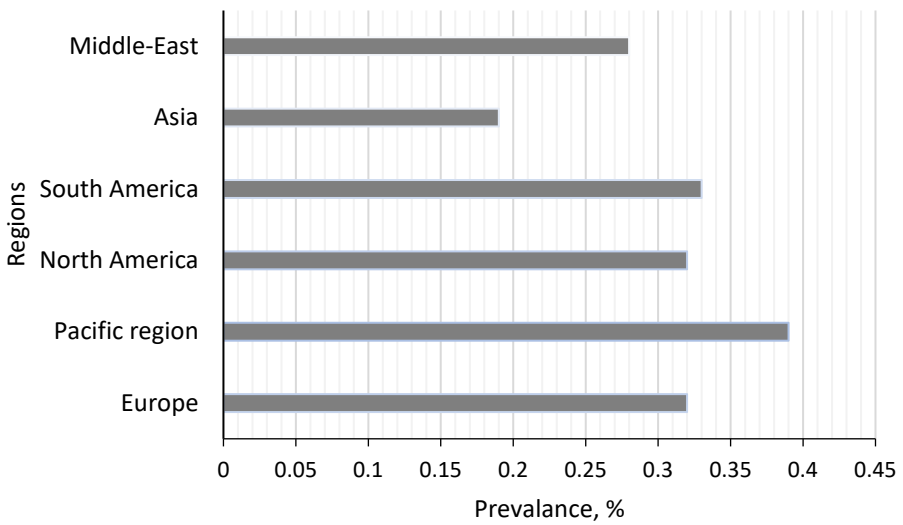

Fig. 1. FH prevalence of the different worldwide regions

homodimer, or heterodimer with apolipoprotein D. Defects in this gene can lead to a deficiency of apolipoprotein A-II or hypercholesterolemia [17].

Apolipoprotein B

It is the main apolipoprotein of chylomicrons and low-density lipoproteins (LDL) and serves as a ligand for the LDL receptor. It is found in plasma in the form of two main isoforms, apoB-48 and apoB-100: the former is synthesized exclusively in the intestine, while the latter is synthesized in the liver. The intestinal and hepatic forms of apoB are encoded by a single gene from one very long mRNA. The two isoforms share a common N-terminal sequence. Mutations in the APOB gene account for 5 to 10% of cases of familial hypercholesterolemia [18].

Epoxide Hydrolase 2

Epoxide hydrolase 2 (EPHX2) — a protein member of the epoxide hydrolase family, found in both the cytosol and peroxisomes, binds to specific epoxides and converts them into the corresponding dihydrodiols. This bifunctional enzyme has mutations in this gene associated with familial hypercholesterolemia. Alternatively spliced transcript variants have been described [19]. The C-terminal domain plays an important role in the metabolism of xenobiotics by degrading potentially toxic epoxides (by analogy). It also determines stable levels of physiological mediators.

Low density lipoprotein receptor

The low-density lipoprotein receptor (LDLR) consists of surface cell proteins involved in receptor-mediated endocytosis of specific ligands. The structure of LDLR is organized into 5 different domains, including the EGF precursor homology domain, which plays a key role in the release of lipoproteins and the recycling of receptors. The encoded protein is typically associated with the cell membrane, where it binds low-density lipoproteins/cholesterol and transports them into cells via endocytosis, entering the cell [20]. The LDL-R is a mosaic protein consisting of 839 amino acids. The most common genetic cause of FH is a mutation in the LDL-R gene *LDLR* which is primarily located on the surface of hepatocytes and plays a key role in binding and clearing circulating LDL particles from the bloodstream [21].

Low Density Lipoprotein Receptor Adaptor Protein 1

Low Density Lipoprotein Receptor Adaptor Protein 1 (LDLRAP1) in humans is encoded by the *LDLRAP*1 gene. The protein encoded by this gene is a cytosolic protein that contains a phosphotyrosine-binding (PTB) domain. The PTB domain has been found to interact with the cytoplasmic tail of the LDL-R [22]. Mutations in this gene lead to dysfunction of the LDL-R protein and cause autosomal recessive hypercholesterolemia [23].

Growth hormone receptor

Human Growth hormone receptor (GHR Protein (RP 00251)) is a transmembrane receptor for growth hormone. This receptor is integrated into the outer membrane of cells throughout the body and is most abundant in liver cells. The growth hormone receptor consists of three main parts: an extracellular region that protrudes from the cell surface, a transmembrane region that anchors the receptor to the cell membrane, and an intracellular region that transmits signals inside the cell [24]. The binding of growth hormone triggers signaling through the intracellular region of the receptor, which stimulates cell growth and division.

Protein Phosphatase 1 Regulatory Subunit 17

Protein phosphatase 1 regulatory subunit 17 is primarily found in Purkinje cells of the cerebellum, where it functions as an inhibitor of protein phosphatase. The encoded protein is a substrate for cyclic GMP-dependent protein kinase. An allele of this gene has been found that increases susceptibility to hypercholesterolemia. Two transcript variants encoding different isoforms have been identified for this gene [25].

Proprotein convertase subtilisin/kexin type 9

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is expressed in the tissues of the liver, intestine, and kidneys and accompanies specific receptors for lysosomal degradation [26]. It plays a role in cholesterol

and fatty acid metabolism. Mutations that increase the functional activity of *PCSK9* with a recessive inheritance pattern led to accelerated degradation of LDL-R, resulting in a reduced number of receptors on the cell surface and impaired capture of LDL [27]. Mutations in the *PCSK9* gene occur in less than 5% of cases of FH [28]. Alternative splicing results in the appearance of multiple transcript variants.

Signaling Pathways in FH

Figure 2 presents a diagram of signaling pathways in FH, constructed using the program http;// string-db.org. The analysis revealed three main clusters of genes and proteins, whose brief characteristics are provided in Table 2.

The first cluster combines 10 proteins key to the processes of plasma lipoprotein assembly, remodeling, and clearance. These include the products of the *LDLR, LDLRAP1, VLDLR, NPC1L1, APOC1, LPA, CETP, MTTP, APOB,* and *PCSK9* genes. It should be noted that four of these (*LDLR, LDLRAP1, APOB, PCSK9*) were characterized earlier in Table 1. The second cluster includes the protein PPP1R17, which is involved in cholesterol metabolism. The third cluster is represented by the protein ANGPTL3, which plays a role in regulating the level of plasma lipoprotein particles.

More detailed information on the functions of the proteins involved in the metabolic pathways in FH is summarized in Table 3. The proteins LDLR, LDLRAP1, APOB, *and* PCSK9, as mentioned above, are not duplicated in this table since their description was provided previously.

Figure 2 demonstrates that the protein PPP1R17 of the second cluster interacts with proteins of the first cluster via three key players: PCSK9, MTTP, and APOB. PPP1R17, which is primarily expressed in cerebellar Purkinje cells, functions as a protein phosphatase inhibitor and is a substrate for cGMP-dependent protein kinase. It is also actively involved in long-term

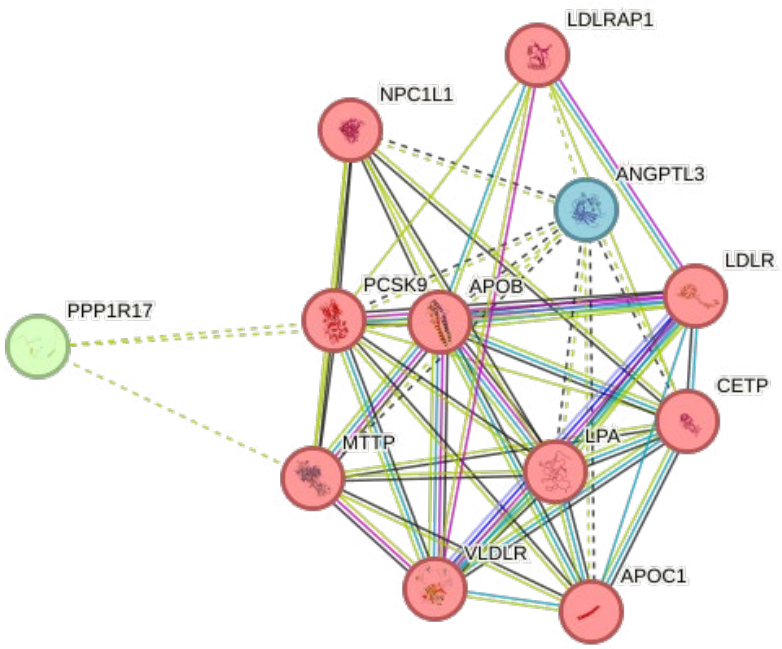

Fig. 2. Signaling pathways of FH. Three clusters: 1. Plasma lipoprotein assembly, remodeling, and clearance (in red); 2. Cholesterol metabolism (in green); 3. Regulation of plasma lipoprotein particle levels (in blue)

Table 2

Characteristics of genes involved in signaling pathways in FH

Cluster	Name/Gene ID	Description	Gene location	Aliases	MIM
1	*LDLRID: 3949*	low density lipoprotein receptor	16q13	*FH, FHC, FHCL1, LDLCQ2*	606945
	LDLRAP1ID: 26119	low density lipoprotein receptor adaptor protein 1	1p36.11	*ARH, ARH1, ARH2, FHCB1, FHCB2, FHCL4*	605747
	VLDLRID: 7436	very low density lipoprotein receptor	9p24.2	*CAMRQ1, CARMQ1, CHRMQ1, VLDL-RCH, VLDLR*	192977
	NPC1L1ID: 29881	NPC1 like intracellular cholesterol transporter 1	7p13	*LDLCQ7, NPC11L1, SLC65A2*	608010
	APOC1ID: 341	apolipoprotein C1	19q13.32	*APOC1B, Apo-CI, ApoC–I, apo-CIB, apoC–IB*	107710
	LPAID: 4018	lipoprotein(a)	6q25.3-q26	*AK38, APOA, LP*	152200
	CETPID: 1071	cholesteryl ester transfer protein	16q13	*BPIFF, HDLCQ10*	118470
	MTTPID: 4547	microsomal triglyceride transfer protein	4q23	*ABL, MTP*	157147
	APOBID: 338	apolipoprotein B	2p24.1	*FCHL2, FLDB, LDLCQ4,apoB-100, apoB-48*	107730
	PCSK9ID: 255738	proprotein convertase subtilisin/ kexin type 9	1p32.3	*FH3, FHCL3, HCHOLA3, LDLCQ1, NARC-1, NARC1, PC9*	607786
2	*PPP1R17ID: 10842*	protein phosphatase 1 regulatory subunit 17	7p14.3	*C7orf16, GSBS*	604088
3	*ANGPTL3ID: 27329*	angiopoietin like 3	1p31.3	*ANG-5, ANGPT5, ANL3, FHBL2*	604774

Table 3

Characteristics of Protein Clusters Involved in Metabolic Pathways in FH

Cluster	Proteins	Characteristics
1. Plasma lipoprotein assembly, remodeling, and clearance	LDLR	described earlier in part 1
	LDLRAP1	described earlier in part 1
	VLDLR	The Very Low-Density Lipoprotein Receptor (VLDLR) is primarily responsible for binding and internalizing VLDL particles via clathrin-mediated endocytosis, facilitating their cellular uptake. Beyond its role in lipid metabolism, the VLDLR also functions in neuronal signaling. It acts as a receptor for Reelin, and upon binding, it induces tyrosine phosphorylation of the adaptor protein Dab1, which modulates Tau protein phosphorylation and influences neuronal migration (By similarity).
	APOC1	Truncated apolipoprotein C–I (apoC–I) is a multifunctional inhibitor of lipid metabolism. It primarily functions by blocking the binding of lipoproteins to several receptors, including the low-density lipoprotein (LDL) receptor, the LDL receptor-related protein, and the very low-density lipoprotein (VLDL) receptor.This protein is found associated with both high-density lipoproteins (HDL) and triacylglycerol-rich lipoproteins in the plasma, constituting approximately 10% of VLDL protein and 2% of HDL protein.A key regulatory role of apoC–I is its function as the major plasma inhibitor of cholesteryl ester transfer protein (CETP). Furthermore, it directly interferes with cellular fatty acid uptake by binding free fatty acids, thereby reducing their intracellular esterification.
	NPC1L1	The NPC1-like intracellular cholesterol transporter 1 (NPC1L1) is a key player in maintaining cholesterol homeostasis. It is critically important for the absorption of dietary cholesterol, facilitating its uptake across the plasma membrane of intestinal enterocytes.This protein is of direct clinical significance as it is the molecular target of the drug ezetimibe, which inhibits cholesterol absorption by blocking NPC1L1. Dysfunction of NPC1L1 results in multiple lipid transport abnormalities. Beyond its primary role in cholesterol uptake, NPC1L1 appears to have a broader function in the transport and homeostasis of multiple lipids, potentially playing a critical role in regulating overall lipid metabolism. It also acts as a negative regulator of the NPC2 protein, inhibiting its expression and secretion.

Ending Table 3

Cluster	Proteins	Characteristics
1. Plasma lipoprotein assembly, remodeling, and clearance	LPA	Apolipoprotein(a) (Apo(a)) is the defining protein component of Lipoprotein(a) (Lp(a)). It exhibits serine protease activity and is capable of autoproteolysis. A key pathophysiological function of Apo(a) is its inhibition of tissue-type plasminogen activator 1 (tPA), linking Lp(a) to both atherosclerosis and impaired fibrinolysis. Furthermore, Lp(a) may act as a ligand for the megalin/gp330 receptor. Apo(a) belongs to the plasminogen subfamily within the peptidase S1 family.
	CETP	Cholesteryl Ester Transfer Protein (CETP) is an enzyme that swaps fats between different cholesterol-carrying particles in the blood. It moves cholesteryl esters from "good" HDL cholesterol to "bad" VLDL cholesterol, and triglycerides in the opposite direction. This process is essential for reverse cholesterol transport, which helps clear excess cholesterol from the body. CETP is part of the BPI/LBP/Plunc protein superfamily.
	MTTP	The Microsomal Triglyceride Transfer Protein (MTTP) large subunit is critical for the production of lipoproteins containing apolipoprotein B (e.g., VLDL). It enables this by catalyzing the transport of lipids (triglycerides, cholesteryl esters, phospholipids) necessary for the particle's formation. Without functional MTTP, these lipoproteins cannot be secreted.
	APOB	described earlier in part
	PCSK9	described earlier in part 1
2. Cholesterol metabolism	PPP1R17	The Protein Phosphatase 1 Regulatory Subunit 17 (PPP1R17) functions as an inhibitor, suppressing the phosphatase activities of both protein phosphatase 1 (PP1) and protein phosphatase 2A (PP2A) complexes.
3. Regulation of plasma lipoprotein particle levels	ANGPTL3	Angiopoietin-related protein 3 (ANGPTL3) is a hepatokine that regulates lipid and glucose metabolism. A key function is to elevate plasma triglyceride (TG) levels by inhibiting the activity of lipoprotein lipase (LPL), the enzyme responsible for TG clearance. This inhibition occurs indirectly; ANGPTL3 recruits proprotein convertases PCSK6 and FURIN to LPL, leading to its cleavage and inactivation. It is also proposed to direct energy substrates to storage or oxidative tissues in response to feeding (By similarity).

depression (LTD), a form of synaptic plasticity. This interaction network suggests a potential, visually apparent link between disruptions in lipid metabolism and neurological processes like depression.

The third cluster includes the protein ANGPTL3, which shows extensive interactions with multiple proteins of the first cluster: LDLRAP1, NPC1L1, PCSK9, APOB, MTTP, LPA, APOC1, and CETP. This protein, a member of the angiopoietin-like family, is predominantly expressed in the liver and functions as a hepatokine regulating lipid and glucose metabolism. It inhibits endothelial lipase, leading to elevated plasma levels of HDL-cholesterol and phospholipids, and promotes lipolysis in adipocytes. Notably, ANGPTL3 contributes to lower plasma LDL-cholesterol levels through a pathway independent of APOE and LDLR. Mutations in its gene are associated with familial hypobetalipoproteinemia type

In conclusion, the proteins PCSK9, APOB, and MTTP can be identified as central hubs within these metabolic networks. They exhibit a high degree of connectivity within the first cluster and also serve as critical interaction points for the regulatory proteins of the second (PPP1R17) and third (ANGPTL3) clusters, thereby positioning them as key integrators of regulatory influences on the core metabolic pathways.

Other genes and proteins associated with FH

Other genes associated with FH have been described in the literature. These include *ABCG5*, *ABCG8*, *STAP1*, *CYP7A1*, *LIPA* and *PNPLA5*. A brief description of these genes is provided in Table 4.

The characteristics of other FH-related proteins are presented below.

ATP binding cassette subfamily G member 5 and member 8

The ABC transporter superfamily includes proteins that participate in the transport of various molecules across cellular membranes. ATP binding cassette subfamily G member 5 and member 8 (ABCG5 and ABCG8) consist of a magnesium-dependent ATP-binding domain at the N-terminus (containing the conserved peptide motifs Walker A and B) and a transmembrane domain that includes six trans-

Table 4

Description of other genes associated with FH

Name/Gene ID	Description	Gene location	Aliases	MIM
ABCG5ID: 64240	ATP Binding Cassette Subfamily G Member 5	2p21	*STSL; STSL2*	605459
ABCG8ID: 64241	ATP Binding Cassette Subfamily G Member 8	2p21	*GBD4, STSL, STSL1*	605460
STAP1ID: 26228	Signal Transducing Adaptor Family Member 1	4q13.2	*BRDG1; STAP-1*	604298
CYP7A1ID: 1581	Cytochrome P450 Family 7 Subfamily A Member 1	8q12.1	*CP7A; CYP7; CYPVII*	118455
LIPAID: 3988	Lipase A, Lysosomal Acid Type	10q23.31	*LAL; CESD*	613497
PNPLA5ID: 150379	Patatin Like Phospholipase Domain Containing 5	22q13.31	*GS2L; dJ388M5; dJ388M5.4*	611589

membrane helices. The protein encoded by this gene functions to prevent the entry of non-cholesterol sterols at the intestinal level, promote the excretion of cholesterol and sterols into bile, and facilitate the transport of sterols back into the intestinal lumen. It is expressed in a tissue-specific manner in the liver, intestine, and gallbladder [29].

Signal Transducing Adaptor Family Member 1

Signal Transducing Adaptor Family Member 1 (STAP1) protein, depending on alternative splicing of mRNA, consists of either 295 or 314 amino acid residues (aa) and contains several phosphorylation sites and an N-terminal proline-rich region (Pro6–Pro11). STAP1 is involved in the anti-inflammatory activation of glia and thus may contribute to apoptosis and neurodegeneration. [30]. Rare variants of CHCS can be caused by mutations in the STAP1 gene [31]. The protein encoded by this gene contains a proline-rich region. This protein is a substrate for the tyrosine-protein kinase Tec, and its interaction with the tyrosine-protein kinase Tec depends on phosphorylation. Variants of this gene are associated with autosomal dominant hypercholesterolemia (ADH) [32]. Alternative splicing results in the emergence of multiple transcript variants.

Subfamily A, family 7 of cytochrome P450

Subfamily A, family 7 of cytochrome P450 (CYP7A1) is synthesized in liver cells and functions as cholesterol 7-α monooxygenase. This endoplasmic reticulum membrane protein catalyzes the first step of the main metabolic pathway of cholesterol in the human body: the conversion of cholesterol into bile acids by attaching a hydroxyl group at position 7-α [33]. This reaction is the primary mechanism for removing cholesterol from the body [34].

Patatin Like Phospholipase Domain Containing 5 P

Patatin Like Phospholipase Domain Containing 5 (PNLA5) patatin-like phospholipase inhibits transacylation. PNPLA5 expression is found in the brain, skin, and gallbladder, while moderate expression has been recorded in the liver [35] and adipose tissue [36]. The protein is found in the cytoplasm and is typically located on the surface of lipid droplets, which are conserved organelles composed of lipids in the form of triacylglycerols and sterol esters, enclosed in a monolayer membrane [37]. The lipids found in these droplets likely serve as an energy depot for the cell and precursors for membranes for autophagosomes. Rare variants of SGHCS may be caused by mutations in the *PNPLA5* gene.

Psychological aspects of FH

It is currently known that psychological factors influence the clinical course of CVD [38]. Potential psychological risk factors for the development of cardiovascular diseases can be divided into three groups. The first consists of negative affective states, including depression, anxiety, stress, and anger; the second includes types of behavior and personality; the third involves social factors, including socio-economic status and social support. Anxiety and depression rank third among the leading risk factors for the development of IHD. Depression in young patients is associated with a double risk, while anxiety is linked to an earlier onset

of myocardial infarction. The relationship between anxiety and hypertension is better understood today. Increased anxiety is an important risk factor for the development of cardiovascular diseases.

However, recent studies present evidence that in ischemic heart disease, anxiety may increase the risk of serious cardiac events and mortality. Genetic variants in the serotonin system are associated with depression and cardiovascular diseases [39]. Loci associated with an increased risk of depression are also linked to an increased risk of ischemic heart disease and elevated levels of total cholesterol, low-density lipoproteins, and C-reactive protein. Six loci of the genes *CD83, CX3CR1, STAT4, COL1A2,* and *SH2D1B* are associated with both mental disorders and IHD [40]. Prolonged exposure to stress can contribute to elevated cholesterol levels and increase the risk of cardiovascular diseases and predisposition to ischemic heart disease. A number of studies have shown that depression is often associated with endothelial dysfunction, chronic inflammatory processes in the vessel walls, and the effect of blood thickening. These factors play a significant role in the development of atherosclerosis, which, in turn, worsens the prognosis of cardiovascular diseases [41]. According to WHO assessments, depression ranks second among the ten leading diseases causing disability (after ischemic heart disease). The prevalence of depression is approximately 50% higher among women than among men [42].

Numerous studies in recent decades have shown a widespread prevalence of depression among patients with various cardiovascular diseases, such as unstable angina, acute myocardial infarction, and congestive heart failure [43, 44]. Those who have recently suffered an acute myocardial infarction are at increased risk of developing depression and mental disorders [45].

The pathophysiological mechanism of stress, like that of other psychological factors, includes an increase in blood pressure, neurohumoral excitation, and hormonal shifts [46]. Physiological responses to stress play a fundamental role in the risk of cardiovascular diseases. Corticolimbic areas of the brain are involved in regulation. Differences in regulatory pathways explain individual differences in relation to stress. In clinical practice and prevention, the psychological assessment of real-life situations that lead to stress remains insufficiently acknowledged [47]. In the modern world, a person is constantly exposed to stress. Stress and anxiety can lead to elevated cholesterol levels, while low cholesterol levels, on the contrary, may contribute to the development of depression and anxiety disorders, as cholesterol is involved in the synthesis of serotonin, the 'happiness hormone.'

The results of epidemiological studies in the regions of the Russian Federation show that anxiety and depressive states in cardiovascular pathology contribute to an increased frequency of complications. Numerous studies indicate that depression, anxiety, personality traits, social support, and stress significantly influence the onset, course, and prognosis of cardiovascular diseases [48, 49]. In some clinical guidelines, stress is already recognized as a preventive measure for people at high overall risk of cardiovascular diseases or with documented cardiovascular conditions. Stress in adulthood plays an important role as a trigger for disease in individuals who already have a significant number of atherosclerotic plaques and as a factor determining prognosis and outcomes in those who already have cardiovascular or cerebrovascular diseases [50, 51].

The Mendelian randomization study showed that depression may have a genetic predisposition and can influence cardiovascular diseases, such as myocardial infarction. Additionally, smoking and lipid levels may be causes of depression [52]. These data were also confirmed by the largest genome-wide association studies (GWAS) or meta-analyses of depression GWAS. The genetic correlation between depressive symptoms and blood lipid levels ranged from 10% to 31% [53].

Conclusion

Thus, when discussing the biological features of FH, it should be noted that to date, 8 genes (*LDLRAP1, PCSK9, APOA2, APOB, GHR, GSBS, EPHX2, LDLR*) have been identified that are closely associated with this hereditary disease and the phenotypes listed in Table 1.

Analysis of signaling pathways in FH has led to the identification of three clusters of genes and their encoded proteins. The involvement of the second cluster

protein, PPP1R17, in the mechanisms of long-term depression (LTD)—a form of synaptic plasticity — points to a potential, visually traceable link between lipid metabolism disorders and neurological processes such as depression.

The third cluster protein, ANGPTL3, a member of the angiopoietin-like protein family, is predominantly expressed in the liver and acts as a hepatokine, regulating lipid and glucose metabolism. Notably, ANGPTL3 contributes to lowering plasma LDL–C levels through a pathway independent of APOE and LDLR. Mutations in its gene are associated with familial hypobetalipoproteinemia. The proteins PCSK9, APOB, and MTTP can be defined as central hubs of these metabolic networks. They serve as critically important interaction points for the regulatory proteins of the second (PPP1R17) and third (ANGPTL3) clusters, allowing them to integrate regulatory influences on core metabolic pathways.

Regarding psychological aspects, patients with FH, as with other CVDs, most frequently exhibit stress, depression, and anxiety. These conditions are often accompanied by social maladjustment.

Therefore, for the early diagnosis of individuals at risk of developing hypercholesterolemia, it is crucial to investigate a broader spectrum of genes and mandatory to consider the psychological characteristics of patients.

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Биологические и психологические аспекты семейной гиперхолестеренемии

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Аннотация. Семейная гиперхолестеринемия (СГ) — это моногенное наследственное заболевание с нарушением метаболизма липидов. Распространенность СГ в общей популяции в среднем составляет 0,32% (95% ДИ: 0,26–0,39%). Заболевание может иметь как аутосомно-доминантный, так и аутосомно-рецессивный типы наследования. Известно 8 фенотипов СГ, связанных с мутациями в генах *LDLRAP1*, *PCSK9*, *APOA2*, *APOB*, *GHR*, *GSBS*, *EPHX2* и *LDLR*, которые могут приводить к раннему проявлению патологии. Целью данного обзора является комплексное исследование данных современной литературы по молекулярно-генетическим, биологическим и психологическим аспектам СГ. Анализ сигнальных путей при СГ выявил три кластера генов и кодируемых ими белков, ответственных за следующие процессы: сборку, ремоделирование и клиренс липопротеинов плазмы (гены: *LDLR*, *LDLRAP1*, *VLDLR*, *NPC1L1*, *APOC1*, *LPA*, *CETP*, *MTTP*, *APOB*, *PCSK9*); метаболизм холестерина (ген: *PPP1R17*); регуляцию уровня частиц липопротеинов плазмы (ген: *ANGPTL3*). Белки PCSK9, APOB и MTTP идентифицированы как ключевые элементы (центральные узлы) этих метаболических сетей. Белок PPP1R17 вовлечен в механизмы долговременной депрессии, формы синаптической пластичности. Кроме того, в литературе описана ассоциация СГ с пятью другими генами: *ABCG5*, *ABCG8*, *STAP1*, *CYP7A1*, *LIPA* и *PNPLA5*. Таким образом, для ранней диагностики и эффективного ведения пациентов с СГ необходимо учитывать не только расширенный спектр ассоциированных генов и белков, но и психологическое состояние пациентов, в частности уровень их тревожности, депрессии и стресса.

Ключевые слова: *семейная гиперхолестеринемия, гены, белки, метаболические пути, тревога, стресс, депрессия*

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