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Phenotype variation of hypertrophic cardiomyopathy in carriers of the p.Arg870His pathogenic variant in the *MYH7* gene

Kucher A.N.[1], Valiakhmetov N.R.[1], Salakhov R.R.[1, 3], Golubenko M.V.[1], Pavlyukova E.N.[2], Nazarenko M.S.[1, 3]

[1] Research Institute of Medical Genetics, Tomsk National Research Medical Center (NRMC), Russian Academy of Sciences
10, Ushaika Embankment Str., Tomsk, 634050, Russian Federation

[2] Cardiology Research Institute, Tomsk National Research Medical Center (NRMC), Russian Academy of Sciences
111a, Kievskaya Str., Tomsk, 634012, Russian Federation

[3] Siberian State Medical University
2, Moscow Trakt, Tomsk, 634050, Russian Federation

ABSTRACT

The review analyzes variability of clinical manifestations of p.Arg870His in the *MYH7* gene, which is repeatedly registered in patients with hypertrophic cardiomyopathy (HCM). The analysis involves the data from scientific publications obtained as a search result in the PubMed, ClinVar, and eLibrary.ru databases, as well as authors' own results. A wide range of phenotypic manifestations have been revealed in carriers of p.Arg870His, from the asymptomatic to severe course, rapid progression, and early death. The review considers possible factors that modify the effect of the pathogenic variant (i.e. dosage of the pathogenic variant, the presence of other unfavorable genetic variants, etc.). The importance of accumulating information on the clinical features of HCM in the carriers of specific gene variants is emphasized in order to clarify their pathogenicity and to identify factors modifying the clinical outcome, which is important for the choice of the treatment strategy for HCM.

Keywords: hypertrophic cardiomyopathy (HCM), myosin heavy chain 7 (*MYH7*) gene

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Фенотипическая вариабельность гипертрофической кардиомиопатии у носителей патогенного варианта p.Arg870His гена *MYH7*

Кучер А.Н.[1], Валиахметов Н.Р.[1], Салахов Р.Р.[1, 3], Голубенко М.В.[1], Павлюкова Е.Н.[2], Назаренко М.С.[1, 3]

[1] Научно-исследовательский институт (НИИ) медицинской генетики, Томский национальный исследовательский медицинский центр (НИМЦ) Российской академии наук
Россия, 634050, г. Томск, ул. Набережная реки Ушайки, 10

✉ *Kucher Aksana N.,* aksana-kucher@medgenetics.ru

[2] *Научно-исследовательский институт (НИИ) кардиологии, Томский национальный исследовательский медицинский центр (НИМЦ) Российской академии наук*
Россия, 634012, г. Томск, ул. Киевская, 111а

[3] *Сибирский государственный медицинский университет (СибГМУ)*
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

Обзор посвящен анализу вариабельности клинических проявлений неоднократно зарегистрированного у пациентов с гипертрофической кардиомиопатией (ГКМП) патогенного варианта p.Arg870His гена *MYH7*. К анализу привлечены данные научных публикаций, полученных в результате поиска в базах данных PubMed, ClinVar, eLibrary.ru, а также собственные результаты. Выявлен широкий спектр фенотипических проявлений у носителей патогенного варианта p.Arg870His: от бессимптомного носительства до тяжелого течения, быстрого прогрессирования и ранней смерти. Обсуждаются возможные факторы, модифицирующие эффект патогенного варианта (доза патогенного варианта, наличие других неблагоприятных генетических вариантов и др.). Подчеркивается важность накопления информации о клинических особенностях течения ГКМП у носителей конкретных вариантов генов с целью уточнения их патогенности, выявления модифицирующих клиническую картину факторов, что имеет значение для определения тактики ведения пациентов с ГКМП, уточнения прогноза, определения стратегии обследования членов их семей.

Ключевые слова: гипертрофическая кардиомиопатия (ГКМП), ген тяжелой цепи миозина (*MYH7*)

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a myocardial disease with hypertrophy of the left and / or right ventricle. The development of the disease cannot be explained by extra load, arterial hypertension, the presence of another heart pathology, systemic disease, or other conditions associated with left ventricular hypertrophy. Asymmetric thickening of the interventricular septum is the most common form of the disease [1]. Symptoms include dyspnea, heart pain, faints, dizziness, tachycardia, and sudden cardiac death. HCM is diagnosed with a frequency of 1: 500 [2], which may be underestimated due to the asymptomatic course of the disease in some patients. Estimated disease prevalence may vary in different populations. Thus, HCM prevalence was estimated as 0.19% in Spain [3], and as 0.031% in Korea [4].

According to the modern concepts, HCM is a hereditary disease characterized by high genetic heterogeneity and clinical polymorphism [5–7]. In the curated database ClinGen [8], HCM genes are classified according to the strength of the association with the disease: proven, or strong (*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC1*, *MYL2,* and *MYL3* genes), moderate (*CSRP3*, *TNNC1*, *JPH2* genes), and weak (16 genes). Genes with a proven, strong and moderate association with the disease encode proteins of thick and thin filaments of the sarcomere, Z-disc, and sarcoplasmic reticulum complex [9].

The online resource ClinVar lists 40 genes [10], whose rare variants are considered to cause the development of this disease. Among them, there are 427 pathogenic variants in 29 genes and 408 likely pathogenic variants in 31 genes. The most significant contribution to the genetic causes of HCM is made by pathogenic (P) / likely pathogenic (LP) variants localized in two genes of sarcomeres – *MYBPC3* and *MYH7* [10–14]. In addition, about

6,000 variants with uncertain significance (VUS) in 110 genes have been described, but the HCM-related data are contradictory [10]. At the same time, pathogenicity estimates for particular genetic variants are regularly reviewed as new clinical data on the variant carriers and their family members are accumulated. In particular, such a revision in relation to *MYH7* gene variants led to a decrease in the number of VUS from 42 to 30%. [15]. In some cases, variants were initially categorized as "benign", i.e. non-pathogenic, but later were detected in patients with severe HCM [16, 17].

A number of studies have assessed correlations between genotype and phenotype in HCM [11–13, 18–27]. For example, they focused on HCM patients with pathogenic mutations in the *MYH7* and *MYBPC3* genes. The study revealed more surgical interventions, a higher risk of sudden cardiac death, and a shorter life expectancy in patients with pathogenic variants in the *MYH7* gene, compared with carriers of the *MYBPC3* gene variants. During 6 years of follow-up, 26% of patients with pathogenic variants in the *MYH7* gene had clinical manifestations of HCM, while those with the *MYBPC3* gene variants remained asymptomatic [28]. Another study showed that patients with pathogenic variants in the *MYH7* gene, compared with the *MYBPC3* gene, had a larger left atrium, a high risk of atrial fibrillation, and a worse disease prognosis [24]. In addition, myectomy or percutaneous alcohol septal ablation was more often performed in individuals with pathogenic variants in the *MYH7* gene [29]. The meta-analysis (which included 51 studies with 7675 HCM patients) showed that *MYH7* pathogenic variants, on average, led to earlier HCM development and a more severe course, compared with patients with HCM associated with other genes. Besides, the incidence of impaired cardiac conduction, ventricular arrhythmias, and heart transplantation is higher in patients with pathogenic variants in the *MYH7* gene than in those with variants in the *MYBPC3* gene [13]. In case of pathogenic variants in the sarcomeric genes (*MYBPC3*, *MYH7*, *TNNT2*, *MYL2*, *MYL3*, *TNNI3*, *ACTC1*, *TNNC1*), the disease manifests earlier than in patients who do not have mutations in these genes [26].

However, given the high genetic heterogeneity of HCM and, therefore, a small number of patients with the same mutation, some questions still remain unresolved. In this regard, the role of some pathogenic variants in HCM development is questionable, and the factors contributing to the development of pathogenic phenotypes and the disease course remain unclear. The problem of HCM phenotypic description and variability, as well as pathogenicity estimates of genetic variants is actively discussed in the scientific and clinical community [30].

HCM is an autosomal dominant disease, and the vast majority of patients have a single pathogenic variant. At the same time, cases of compound heterozygotes and even homozygotes for particular mutations have been described. Such patients usually have an earlier onset and a more severe course of the disease.

One of the mutations repeatedly identified in HCM patients is the p.Arg870His amino acid replacement in the beta-myosin heavy chain protein encoded by the *MYH7* gene. Cases of both the disease and asymptomatic carriage of this variant are known. One study describes a pedigree where two members, who are descendants of closely related marriages, were found to be homozygous for the pathogenic variant [18]. In our practice of HCM genetic diagnosis, this mutation was also registered and showed incomplete penetrance [31]. Thus, this variant is of interest for a detailed analysis of the clinical characteristics in patients from different families.

The aim of the study was to systematically review publications describing the phenotypic features of HCM in carriers of the pathogenic p.Arg870His variant in the *MYH7* gene, including the use of our own findings.

MATERIALS AND METHODS

Articles were found in the PubMed, ClinVar, and eLibrary databases using the following keywords and their combinations: hypertrophic cardiomyopathy (HCM), myosin heavy chain 7 (*MYH7*) "p.Arg870His", without any restrictions by the study design and native language of authors. Titles and abstracts were checked in order to assess whether studies corresponded with the topic of the review. All the clinical data from the articles were included in the table: diagnosis, gender, age, family history, description of the main symptoms, NYHA classification of heart failure, data of instrumental heart

examinations (echocardiography (Echo-CG), interventricular septum (IVS), left ventricular posterior wall (LVPW), ejection fraction (EF), peak gradient in the left ventricular outflow tract (LVOT), and electrocardiography (ECG)).

RESULTS

In total, we found 66 publications mentioning the pathogenic genetic variant p.Arg870His of the *MYH7* gene in HCM patients. Only 6 studies [18–20, 32–34] described clinical characteristics of the disease in patients. Except for the case described by us [31], there were no Russian publications that provided information on the clinical characteristics of patients with this mutation (based on the information given in the scientific electronic library eLibrary.ru). Several studies lacked some instrumental methods for assessing the heart state (Echo-CG and ECG).

CLINICAL CHARACTERISTICS OF HYPERTROPHIC CARDIOMYOPATHY IN CARRIERS OF THE PATHOGENIC P.ARG870HIS VARIANT IN THE *MYH7* GENE

A single-nucleotide variant 2609:G>A in exon 22 of the *MYH7* gene results in an arginine to histidine substitution at codon 870 (p. Arg870His, R870H, rs36211715) in the alpha-helical S-2 domain of the beta-myosin heavy chain protein. The p. Arg870His substitution is one of the most frequently reported pathogenic variants detected in patients with HCM. Even though the amino acids arginine and histidine are both positively charged, they differ in several properties (hydrophilicity, size, donor – acceptor properties) [35], which can determine the structural and functional features of the protein. Amino acid substitutions in this region can affect myofilament assembly, protein stability, tensile strength, and stiffness [34, 36]. The p.Arg870His variant causes a drastic decrease (more than ten-fold) in the binding affinity of the C1–C2 domains of *MYBPC3* (MyBP-C) [37]. The variant reduces the relative sliding velocity between actin and myosin filaments [38]. The mutation destabilizes the interactions (as well as the structure) between *MYH7* and *MYL3* and between *MYH7* and *MYL2* [34].

The p. Arg870His substitution is very rarely registered in populations (with frequency corresponding to the rate of mutational events, – 4×10^{-6}–1.6×10^{-5}) [39], but it is detected in HCM patients of various nationalities (both in sporadic and familial cases) [18–21, 32, 33, 40–44]. Although most researchers consider this pathogenic variant relatively benign, carriers of p. Arg870His show a wide range of phenotypic manifestations. These are cases of asymptomatic carriage [20, 32], severe clinical manifestations of HCM [33], as well as cases of sudden cardiac death in families with this pathogenic variant [19, 21] (Table).

Clinical symptoms in carriers of this variant vary both between members of the same family and between members of different families. Extensive information was obtained in the study of a large Indian family with HCM, with the p.Arg870His substitution as the cause of the disease [18, 32] (Table). The authors described high clinical heterogeneity of HCM in the carriers (from asymptomatic carriage, usually in younger people, to early death). The age of onset also varies widely. However, as some authors note [32], the onset age is accurately established only for the probands, since the health status of other carriers is assessed during subsequent family screening (i.e., the age of onset must be earlier). Among members of the family with HCM from India, 75% of men and 44% of women with the p.Arg870His variant had clinical symptoms of HCM. The average penetrance of the variant was 59% [32].

In general, asymptomatic carriage of this variant is typical of young people. In the elderly, clinical symptoms of this pathology were recorded even in the absence of HCM echocardiographic signs. The age of diagnosis varied from 16 to 47 years in men and from 20 to 69 years in women (Table). Some female carriers of the pathogenic variant of different age (19, 48, and 55 years) with normal heart ultrasound results had HCM symptoms (dyspnea, palpitations). Furthermore, one woman aged 25 years was diagnosed with HCM according to echocardiographic data but had no disease symptoms.ECG changes in carriers of the pathogenic p.Arg870His variant are typical of HCM (Q waves, depression of the ST segment, T wave inversions (Table)) [45]. Sometimes ECG changes precede clinical manifestations of the disease [19, 20, 46–48]. At the same time, ECG changes arising in already diagnosed HCM patients indicate a high risk of ventricular tachyarrhythmia and sudden cardiac death [49].

Table

Phenotype variation of HCM in carriers of the p.Arg870His pathogenic variant in the *MYH7* gene

Population	Pathology (type)	Case	Sex	Age at the examination	Genotype	Clinical symptoms	NYHA	Echo-CG				ECG	Source
								IVS, mm	LVPW, mm	LVOT, mm Hg	EF,%		
Russia	HCM (O)	P-mother	f	45	het	Syncope, dyspnea, weakness	III	20	9	105	63	ST depression in leads I, II, aVL, aVF, V5–V6	Own data
				53		Deterioration of the condition	–	24	16	70.8	91	–	
				53[a]		Surgical treatment	–	15	11	12	55	–	
				54		–	–	19	13	8.43	62	–	
				57		–	–	18	12	8.8	65	–	
	Normal	P-daughter	f	27	het	No	–	7.8	7.6	–	72	–	
India	HCM	P1	m	69	het	Palpitations, syncope	II	15	10	–	69	Enlarged LA	[32]
	Normal	P1	f	55	het	Palpitations, angina, dyspnea	II	10	9	–	73	WNL	
	Normal	P1	f	48	het	Palpitations, dyspnea	II	12	10	–	65	WNL	
	HCM	P1	f	58	het	Dyspnea	II	17	11	–	65	Abnormal Q wave	
	HCM (O)	P1	m	52	het	Dyspnea, syncope	III	21	11	40	75	–	
	HCM	P1	m	47	het	Dyspnea, palpitations, angina	II	16	10	–	65	T wave inversion	
	HCM (NO), ASH	P1[b]	m!	37 (30)	homo	Palpitations, syncope	III	20	11	–	55	T wave inversion, abnormal Q wave	
	HCM	P1	f	34	het	Palpitations	II	13	8	–	73	T wave inversion	
	HCM (O)	P1	m!	32 (31)	het	Palpitations, dyspnea	III	23	13	64	76	Enlarged LA, left axis deviation	
	HCM	P1	f	25	het	No	I	14	11	–	78	Short PR interval	
	HCM (NO), ASH	P1	m!	23 (19)	homo	Dyspnea, syncope	III	19	10	–	76	T wave inversion, abnormal Q wave, lower ischemia	
	Normal	P1	f	20	het	No	I	11	9	–	80	WNL	
	Normal	P1	m	16	het	No	I	12	10	–	82	WNL	
	HCM	P1	f	20	het	Dyspnea	I	13	10	–	78	WNL	
	Normal	P1	m	17	het	No	I	8	7	–	81	WNL	
	Normal	P1	f	19	het	Dyspnea	I	10	9	–	72	WNL	
	Normal	P1	f	16	het	No	I	7	7	–	75	WNL	
	HCM (O)	S[c]	m!	36 (34)	het	No	II	32	21	–	70	–	

Table (continued)

Population	Pathology (type)	Case	Sex	Age at the examination	Genotype	Clinical symptoms	NYHA	Echo-CG				ECG	Source
								IVS, mm	LVPW, mm	LVOT, mm Hg	EF,%		
Japan	HCM, ASH	P2/father	m	40	het	–	–	20	11	–	78	Complete right bundle branch block	[20]
	HCM, ASH	P2/son	m	16	het R870H+ Arg54 Ter	–	–	20	11	–	83	Abnormal Q waves in leads II, III, aVF, V5–V6, T wave inversion in leads I and aVL	
				19				25	12	–	82	Abnormal Q waves in leads II, III, and aVF disappeared, ST depression with T wave flattening in V5 and V6 emerged	
Spain	HCM (NO), ASH	P7/sister	f	65 (59)	het	–	II	–	20	–	–	–	[19]
	HCM, ASH	P7/brother[d]	m	50 (38)	–	–	–	–	22	–	–	–	
Czech Republic	Severe HCM	S	–	36	het	Chronic atrial fibrillation, chest pain, fatigue, dyspnea	–	–	28	60	–	–	[33]
Italy	Arrhythmogenic cardiomyopathy	P8/father	m	43 (2005)	het (*de novo*)	Syncope, sustained ventricular tachycardia	–	–	–	–	–	Tachycardia, wide QRS complex	[34]
				45 (2007)		Syncope, implantable cardioverter – defibrillator	–	–	–	–	–	Monomorphic ventricular tachycardia after syncope	
				59 (2021)		Ventricular arrhythmias were not registered for 13 years	II	–	–	–	60	Epsilon wave in V3–V4, T wave inversion in V3–V6, and Q wave in V5–V6	
	Normal	P8/daughter	f	18	het	Syncope, palpitations	I	WNL (not given)				Episodes of sinus tachycardia during palpitations and syncopal episodes	

Note: P – familial case; S – sporadic case; (O) – obstructive form of HCM; (NO) – non-obstructive form of HCM; ASH – asymmetric septal hypertrophy; het – heterozygous carrier of the pathogenic variant; homo – homozygous carrier of the pathogenic variant; WNL – within normal limits; IVS – interventricular septum thickness; LVPW – left ventricular posterior wall thickness; LVOT – left ventricular outflow tract gradient; EF – ejection fraction; NYHA – class of heart failure; a – medical examination data after septal myectomy with mitral valve repair; b – the patient died due to heart failure a few months after the pacemaker was implanted; c – the patient served in the armed forces for more than 10 years (prolonged physical activity); d – after 12 years of follow-up, the patient developed severe systolic dysfunction resulting in sudden cardiac death; ! – proband.

In general, only 6% of individuals with apparent echocardiographic evidence of HCM at the time of diagnosis did not have ECG changes. Patients with abnormal ECG had more severe symptoms, higher peak pressure gradients in the LVOT, and a greater degree of ISW thickness. They were more likely to have severe syncopal symptoms requiring surgical myectomy and / or implantation of a cardioverter – defibrillator [45]. In addition, ECG results may change during the follow-up of patients with HCM (Table).

Interestingly, in a recent study [34], the pathogenic p.Arg870His variant of the *MYH7* gene was considered to be the cause of arrhythmogenic cardiomyopathy (Table). A 43-year-old man had a syncopal episode while taking amiodarone, and ECG showed a wide QRS complex and complex tachycardia. Two years later, he was implanted with a cardioverter- – defibrillator due to the monomorphic ventricular tachycardia following syncope (registered by ECG). The pathogenic p.Arg870His variant of the *MYH7* gene in this man arose *de novo* and was inherited by his daughter. At the age of 18, she showed no abnormalities, according to echocardiography and Holter ECG monitoring, as well as heart computed tomography. However, dyspnea, palpitations, and episodes of sinus tachycardia with palpitations and syncope were observed [34].

Despite the fact that most studies describe a relatively mild clinical course of the disease for p.Arg870His in the *MYH7* gene, some HCM families with this mutation had early and (or) sudden deaths, including deaths of homozygous patients [18, 19, 44].

It should also be noted that the HCM course may differ depending on an amino acid that was replaced in the protein structure, even if it occurred in the same codon. Thus, when cysteine replaces arginine at codon 870 (p.Arg870Cys), it leads to a severe course of HCM with an early onset and a high risk of sudden cardiac death [44].

Data on the follow-up of carriers with HCM-inducing pathogenic genetic variants are also interesting. Such studies are scarce, and the results of dynamic observation of groups with individual pathogenic mutations are rarely published [20, 50]. At the same time, pharmacotherapy and (or) surgery can change the clinical presentation of HCM (Table).

Thus, the spectrum of phenotypic manifestations of the p.Arg870His mutation shows that carriers of the same pathogenic variant may have a wide range of HCM clinical symptoms as well as other forms of cardiomyopathies. In this regard, it is important to establish the factors that can modify clinical symptoms in the pathogenic variant carriers.

FACTORS MODIFYING THE CLINICAL PRESENTATION OF HCM

Causes of clinical variability in the manifestation of pathological signs in carriers of pathogenic mutations (including p.Arg870His in the *MYH7* gene) may include both genetic and epigenetic factors, as well as lifestyle.

Genetic factors influencing the clinical course include gene dosage (homozygous and (or) heterozygous genotype for the pathogenic variant), the presence of other P- and LP-variants in the same or another HCM gene [12, 17, 19, 20, 51–54], as well as a set of genetic variants in other genes [55, 56]. A rare case was described for the p.Arg870His mutation: two patients homozygous for this mutation were born in two different inbred marriages in the same pedigree [32, 18]. One of them died suddenly at the age of 36, a few months after the implantation of the pacemaker due to the developed heart failure. Another patient was diagnosed with HCM (asymmetric septal hypertrophy without obstruction) at the age of 19 and had abnormal T and Q waves on the ECG (Table).

One of the first published cases combining two mutations in the *MYH7* gene, i.e., a compound heterozygous genotype, was also associated with the p.Arg870His mutation. In addition to that variant, the patient had a nonsense mutation in exon 3, which formed a stop codon at codon 54 (p.Arg54Ter). This variant combination led to the early development of HCM (at the age of 16) and rapid progression of the disease (worse ECG and Echo-CG results) [20]. The pathogenic p.Arg870His variant was inherited from the father (who developed the disease at the age of 40). The second variant, p.Arg54Ter, was inherited from the maternal grandmother (both the grandmother and mother were healthy). Thus, the combination of the two mutations inherited from parents led to HCM development at an early age and its more severe course. In addition, the authors supposed that heterozygous nonsense mutations in

the *MYH7* gene did not lead to the disease manifestation. That study identified the p.Arg870His variant in three pedigrees, and 9 out of 10 variant carriers had myocardial hypertrophy at the time of the medical examination [20].

As we are accumulating more and more data on HCM gene sequencing, it turns out that patients with more than one pathogenic variant are not so rare [12, 53, 57]. For example, the combination of pathogenic variants p.Arg787His and p.Ile736Thr in the *MYH7* gene led to severe HCM [19]. It is interesting that the probands with compound heterozygous variants in the *MYH7* gene demonstrated a higher left ventricular myocardium mass and higher QRS, SV1, and RV5 + SV1 amplitudes on ECG than those with double mutations on the same chromosome [58].

Based on the study of mutations in the *MYH7*, *MYBPC3*, *TNNT2*, and *TNNI3* genes, Y. Zou et al. [12] concluded that neither a specific gene nor a specific mutation were correlated with the clinical phenotype of HCM, while the number of mutations was associated with the maximum thickness of the left ventricular wall. Multiple pathogenic variants (either in the same or in different sarcomeric genes) were registered in 9.5% of HCM patients. Another study of 2,912 HCM probands showed that 8% of probands had more than one pathogenic (P) or likely pathogenic (LP) variant or variant of uncertain significance (VUS); 0.6% of probands had 2 or more P / LP variants (including homozygous ones, and 1 proband had 3 P / LP variants, the age of such patients was 10 years younger than that of patients with single variants). 5% of probands had 1 P / LP and at least 1 VUS, and 2.4% had 2 or more VUS [53].

In addition to the combined effect of P and LP variants, the phenotype may be influenced by rare polymorphic variants in sarcomeric genes. For example, in 60 HCM patients without pathogenic variants in the genes of sarcomeric proteins, functionally significant variants in the intron and 3'UTR of the *MYH7* gene were identified. They were localized in the promoter region at the binding sites of transcription factors [59]. So, the clinical presentation of HCM is determined not only by individual mutations in the sarcomeric genes, but also by a combination of mutations and (or) variants in several genes (not only sarcomeric). Therefore, HCM is more and more often referred to as not a monogenic but an oligogenic disease [7]. A detailed examination and genotyping of patients with severe HCM (as well as other cardiomyopathies) for the presence of other P / LP genetic variants is essential for predicting the course of the disease both in probands and in their relatives who inherited these variants and (or) their combinations.

The potential significance of the general genetic background for the clinical presentation of the disease may be evidenced by the data of genome-wide association studies (GWAS) for HCM [55, 56]. Thus, a study by A.R.Harper et al. [55] identified 12 loci associated with HCM. Moreover, single nucleotide polymorphisms affect the HCM severity in carriers of mutations in the genes of sarcomeric proteins [55, 60].

The spectrum of genes modifying the clinical presentation of HCM is constantly expanding [61, 62]. Thus, the presence of mutations in the genes of ion channels (*KCNQ1*, *KCNH2*, *CACNA1C*, *SCN5A*, and *ANK2*) in HCM patients increases the risk of life-threatening arrhythmias and sudden cardiac death and affects their prognosis and treatment [63]. At the same time, the genes modifying the clinical course of HCM may differ in men and women, as has been shown for the development of cardiac fibrosis in this disease [61].

The influence of environmental and epigenetic factors on the penetrance of pathogenic variants and the HCM course is described by data from twin studies. Monitoring the HCM progression in 11 pairs of monozygotic twins (with 9 pairs having pathogenic variants in the sarcomeric genes) for 5–14 years revealed inconsistency of morphological changes (thickness of the left ventricular wall, left atrial diameter, and left ventricular ejection fraction). It led the authors to the conclusion that epigenetics and environmental factors play an essential role in the progression of this disease [64]. Behavioral features (such as doing sports, physical activity, etc.) can also act as factors modifying the clinical presentation of HCM [32].

Unfortunately, modifying factors (multiple pathogenic variants, effects of regulatory elements and polymorphic variants of different genes, whose products ensure functioning of the cardiovascular system, general genetic background, epigenetic

modifications, etc.) have not been sufficiently studied despite the clinical significance of possible results of such studies.

CONCLUSION

The complexity of describing the genetic component of HCM and assessing the pathogenetic significance of individual variants is due to the fact that this disease is characterized by incomplete age-dependent penetrance and variability of the clinical course even in carriers of the same pathological variant [14, 27, 32, 64–66]. For instance, it was demonstrated by the pathogenic p.Arg870His variant in the *MYH7* gene. Sometimes HCM develops without a clear clinical presentation, and sudden cardiac death may be its first manifestation. According to epidemiological data, sudden cardiac death in individuals with even minor signs of HCM often occurs in case of a sedentary lifestyle or light activity (66%), often in bed or during sleep (32%), less often during physical activity (22%), including participation in competitions [67].

Accurate pathogenicity classification of variants in HCM genes is of great clinical importance. Thus, it is known that patients with P / LP variants in HCM genes had a lower survival rate compared with patients with no such variants in these genes [28]. At the same time, genetic testing in HCM allows not only to confirm the clinical diagnosis, but also to identify family members with pathogenic variants who are at risk of developing the disease, which opens up the possibility of prevention [68, 69]. Moreover, examining relatives of HCM patients with a genetically determined cause sometimes helps to identify mutation carriers already having HCM manifestations [70]. Therefore, if pathogenic variants in cardiomyopathy genes are detected in an individual (even in the absence of complaints), it is recommended to examine relatives and start cascade genetic screening, if pathological phenotypes are detected [69].

In the future, accumulation and analysis of data on the phenotypic variability in carriers of specific pathogenic variants will help to determine the conditions of mutation penetrance and predict features of the disease course more accurately. In this regard, the ClinVar expert group proposed to expand and unify the criteria used for the phenotypic description of patients in order to clarify the pathogenicity of variants [30], which will contribute to improving the care provided to patients with this pathology.

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Authors contribution

Kucher A.N. – conception and design; drafting of the manuscript; substantiation of the manuscript or critical revision of the manuscript for important intellectual content; final approval of the manuscript for publication. Valiakhmetov N.R., Salakhov R.R., Golubenko M.V., Pavlyukova E.N. – analysis and interpretation of the data; drafting of the manuscript; substantiation of the manuscript or critical revision for important intellectual content. Nazarenko M.S. – conception and design; substantiation of the manuscript or critical revision of the manuscript for important intellectual content; final approval of the manuscript for publication.

Authors information

Kucher Aksana N. – Dr. Sci. (Biol.), Professor, Leading Researcher, Laboratory of Population Genetics, Research Institute of Medical Genetics, Tomsk NRMC, Tomsk, aksana-kucher@medgenetics.ru, http://orcid.org/0000-0003-3824-3641

Valiakhmetov Nail R. – Post-Graduate Student, Laboratory of Population Genetics, Research Institute of Medical Genetics, Tomsk NRMC, Tomsk, valiakhmetov.nail@medgenetics.ru, http://orcid.org/0000-0001-7969-7020

Salakhov Ramil R. – Cand. Sci. (Med.), Researcher, Laboratory of Population Genetics, Research Institute of Medical Genetics, Tomsk NRMC, Tomsk; Associate Professor, Biochemistry and Molecular Biology Division with Clinical Laboratory Diagnostics Course, Siberian State Medical University, Tomsk, ramil.salakhov@medgenetics.ru, http://orcid.org/0000-0002-9789-9555

Golubenko Maria V. – Cand. Sci. (Biol.), Senior Researcher, Laboratory of Population Genetics, Research Institute of Medical Genetics, Tomsk NRMC, Tomsk, maria-golubenko@medgenetics.ru, http://orcid.org/0000-0002-7692-9954

Pavlyukova Elena N. – Dr. Sci (Med.), Professor, Head of the Atherosclerosis and Ischemic Heart Disease Department, Cardiology Research Institute, Tomsk NRMC, Tomsk, pavluk@cardio-tomsk.ru, http://orcid.org/0000-0002-3081-9477

Nazarenko Maria S. – Dr. Sci. (Med.), Professor, Head of the Laboratory of Population Genetics, Research Institute of Medical Genetics, Tomsk NRMC, Tomsk; Professor, Medical Genetics Division, Siberian State Medical University, Tomsk, maria.nazarenko@medgenetics.ru, http://orcid.org/0000-0002-0673-4094

(✉) **Kucher Aksana N.,** aksana-kucher@medgenetics.ru

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