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Monogenic diseases associated with cardiomyopathy genes and their phenotypic manifestations

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ABSTRACT

The aim of the present study was to summarize the data on the spectrum of genetic diseases and their phenotypic manifestations in case of structural and functional defects in 75 genes, pathogenic variants of which are associated with the formation of different types of cardiomyopathy (CMP). The search for scientific publications was carried out in foreign (PubMed) and Russian (eLibrary) digital libraries. The data analysis was performed using the Simple ClinVar, An Online Catalog of Human Genes and Genetic Disorders, and STRING databases.

It was shown that the vast majority of CMP genes are pleiotropic. Monogenic diseases caused by mutations in CMP genes are characterized by a wide range of pathological manifestations in various organs and systems (cardiovascular, nervous, endocrine, musculoskeletal systems, connective tissue, skin and appendages, organs of vision and hearing, kidneys) as well as by metabolic and immune disorders. Therefore, if a patient (regardless of the primary diagnosis) has pathogenic / likely pathogenic variants or variants of uncertain significance in the CMP genes, we recommend a detailed and comprehensive clinical examination. This is important for clarifying the effects of rare genetic variants, identifying significant clinical and prognostic features for CMP and monogenic diseases associated with CMP genes, and identifying risk groups and controllable triggers that contribute to the manifestation of pathogenic genetic variants.

Keywords: cardiomyopathy genes, monogenic diseases, phenotypic manifestations

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Спектр фенотипических проявлений моногенных заболеваний, связанных с генами кардиомиопатий

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РЕЗЮМЕ

Цель настоящего исследования заключалась в обобщении данных о спектре наследственных заболеваний и их фенотипических проявлениях при структурно-функциональных нарушениях в 75 генах, патогенные варианты которых связаны с формированием различных типов кардиомиопатий (КМП). Поиск научных публикаций проведен в зарубежных (PubMed) и отечественных (eLibrary) электронных библиотеках. Анализ данных выполнен с использованием баз Simple ClinVar, An Online Catalog of Human Genes and Genetic Disorders, а также интернет-ресурса STRING.

Показано, что подавляющее большинство генов КМП обладают плейотропизмом и при моногенных заболеваниях, вызванных мутациями в данных генах, регистрируют широкий спектр патологических проявлений в различных системах органов (сердечно-сосудистой, нервной, эндокринной, костно-мышечной системы и соединительной ткани, кожи и придатков, органов зрения и слуха, почек), а также нарушения метаболизма и иммунитета. В связи с этим вне зависимости от первичного диагноза при выявлении у пациентов в генах КМП патогенных / вероятно патогенных вариантов или вариантов с неопределенной значимостью рекомендуется проведение детального и комплексного клинического обследования. Это имеет важное значение для уточнения эффектов редких вариантов генов, выделения клинически и прогностически значимых признаков для КМП и моногенных заболеваний, связанных с генами КМП, а также выявления групп риска и управляемых триггеров, способствующих проявлению патогенных генетических вариантов.

Ключевые слова: гены кардиомиопатий, моногенные заболевания, фенотипические проявления

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INTRODUCTION

One of the key problems of modern biomedical research is to understand the regularities of implementation of the genetic program and identify the mechanisms of formation of genetically determined phenotypes, including pathological ones [1, 2]. Advances in the field of molecular genetic research, systems biology, and systems medicine allow to take a fresh look at the issue of transformation from genotype to phenotype [3].

Cardiomyopathies (CMPs) represent a clinically and etiologically heterogeneous group of myocardial pathologies and are a remarkable example of the complexity of pathological phenotype formation. CMPs can have a monogenic, oligogenic or polygenic basis [4–6], which develops into a pathological phenotype over decades (and is manifested more often in adults) and in some cases only under certain environmental triggers [5, 6]. Clinically, CMPs can be separated into hypertrophic (HCM), dilated (DCM), restrictive (RCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC); dysfunctions of certain genes are often considered to be their causes [6–8].

However, similar myocardial disorders can be caused by both external and internal environmental factors (for example, drug-induced, diabetic, peripartum, stress-induced, inflammatory (myocarditis) CMP, etc.), and pathogenic variants in genes thought to cause CMPs are also detected in patients with these conditions [9–11]. In some cases, there is a combination of several types of CMP or a transition from one form to another as the disease progresses [12–14], and CMPs can also represent a symptom of other complex pathological phenotypes [11, 15].

Dozens of genes are known, pathogenic / likely pathogenic variants of which can lead to one of the types of CMP. The number and spectrum of causative genes vary for different CMPs, but negative variants in the same genes (and even the same variants) can lead to both different and same types of CMPs [16]. There is a growing body of evidence that, on the one hand, mutations in different genes can lead to the development of similar phenotypes (in particular, to CMP), and, on the other hand, pathological variants in the same gene can contribute to the formation of different clinical phenotypes and traits, even not associated with the

underlying pathology [4, 6, 17, 18]. Identification of phenotype features, as well as clarification of the spectrum of possible disorders in the presence of pathogenic gene variants is of interest not only from a fundamental point of view (to determine the scope of specific genes), but also has clinical significance, in particular for translational medicine [3, 19]. The aim of this study was to summarize the data on the spectrum of genetic diseases and their phenotypic manifestations in structural and functional defects of the CMP genes.

DATA SOURCE AND ANALYTICAL TOOLS

Information about the genes of primary CMPs does not completely match in different sources (ClinGen, SimpleClinVar, Online Mendelian Inheritance in Man (OMIM) databases, etc.), which is due to differences in the criteria used for classifying genes as significant. In the present study, the Simple ClinVar database (https://simple-clinvar.broadinstitute.org/, accessed on February 2023), was used as a source of information on CMP genes.

The analysis of the scope of the CMP genes was performed on the basis of Online Mendelian Inheritance in Man (OMIM) (https://www.omim.org/) data on monogenic diseases that can be caused by mutations in the CMP genes under discussion. To describe the features of phenotypic manifestations of monogenic diseases caused by mutations in the CMP genes, we used MeSH, a vocabulary thesaurus used for indexing citations in MEDLINE (https://www.ncbi.nlm.nih.gov/mesh/). The online STRING (https://string-db.org/) resource was also used to characterize the CMP genes. The search for scientific publications was carried out in foreign (PubMed) and Russian (eLibrary) digital libraries.

CHARACTERISTICS OF THE PRIMARY CARDIOMYOPATHY GENES

According to Simple ClinVar, pathogenic / likely pathogenic variants of 75 genes can lead to one of the forms of primary CMPs; 40 of these genes are reported for HCM, 50 genes for DCM, 11 genes for ARVC, and 7 genes for RCM (Figure). Most of the CMPs genes are protein-coding genes, *FLNC-AS1* and *TTN-AS1* belong to non-coding RNA genes. Along with specific genes (which are characterized as causal to one type of CMP), there are genes variants of which can lead to different types of CMPs. For example, variants in the *ACTN2*, *DES*, *LMNA*, and *TMEM43* genes are considered causal for HCM, DCM, and ARVC; variants in the *MYH7*, *TNNI3*, *TNNT2*, and *TTN* are considered causal for HCM, DCM, and RCM (Figure). In other words, pathogenic variants in the same CMP genes can lead to different pathological phenotypes affecting the functioning of the heart.

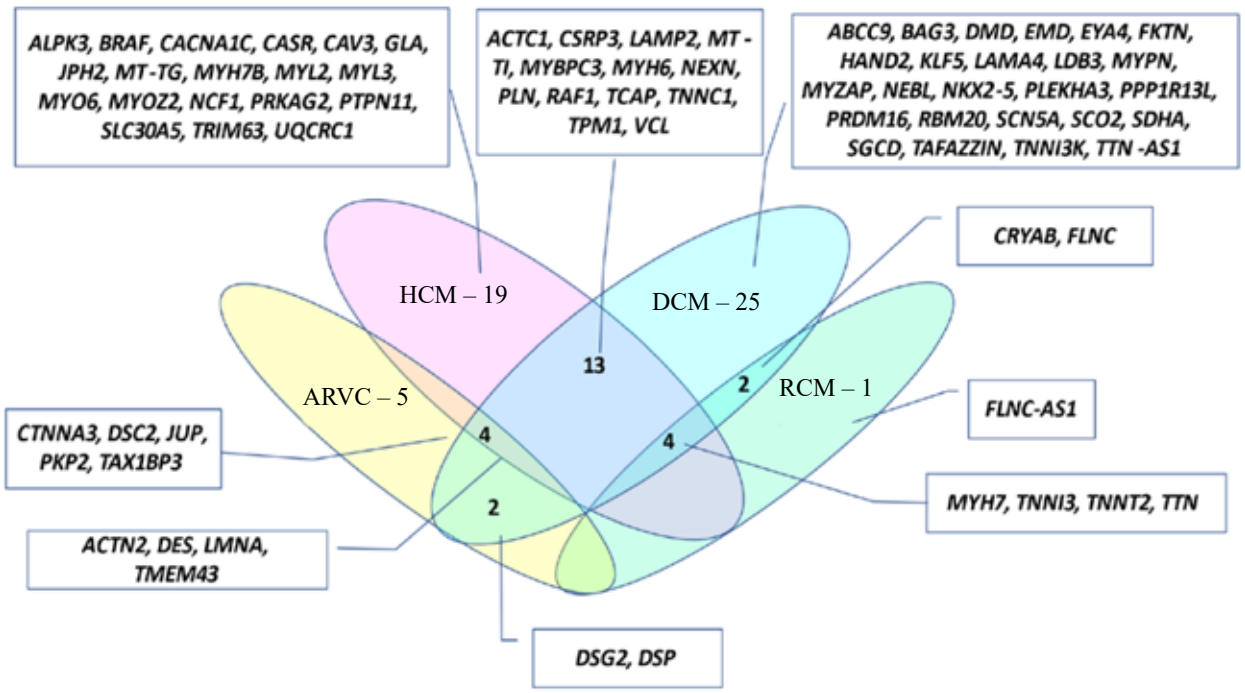

Figure. Common and specific genes for different monogenic CMPs

According to the Tissue Expression Database (https://tissues.jensenlab.org/) and STRING [20, 21], the CMP genes under discussion are expressed in many tissues, including various parts of the heart (right ventricle, cardiac muscle, left and right atrium, ventricle, atrium), embryonic tissues (21 genes), tissues of the female reproductive system (17 genes), testicles (9 genes), fetus (13 genes), sensory organs (6 genes), rectum (5 genes), gallbladder (3 genes), in adipocytes (2 genes), platelets (4 genes), etc. [20, 21]. In particular, the *PKP2*, *UQCRC1*, *VCL*, *RAF1*, *MYH7B*, *SDHA*, *DSC2*, *NCF1*, *TMEM43*, *FLNC*, *PTPN11*, *MYPN*, *HAND2*, *DMD*, *LMNA*, *BAG3*, *EMD*, *KLF5*, *JUP*, *MYH6*, *LAMP2* genes are expressed in embryonic structures (BTO:0000174 according to [20]), the *BAG3*, *DMD*, *VCL*, *SDHA*, *NCF1*, *PTPN11* genes are expressed in the sensory organs, etc. Expression in different types of tissues and at different stages of ontogenesis suggests that dysfunction in CMP genes can affect the functioning of not only the cardiovascular, but also other organ systems.

According to STRING [21], 71 proteins encoded by the CMP genes were functionally related (the average local clustering coefficient is 0.656), a total of 683 functional or physical interactions were registered (on average, 19.2 per protein) with the expected 35 interactions (protein-protein interactions enrichment $p < 1.0e\text{-}16$). The protein products of only 7 genes were not included into the network: *NCF1*, *TAX1BP3*, *KLF5*, *SLC30A5*, *PLEKHA3*, *PRDM16* and *CASR*. The integration of proteins encoded by the CMP genes into a single network is expected due to criteria for their selection for analysis, but this also implies the possibility of involvement of these genes in common pathological conditions when other organ systems are affected.

THE SPECTRUM OF MONOGENIC DISEASES ASSOCIATED WITH THE CMP GENES (ACCORDING TO OMIM) AND THEIR CLINICAL MANIFESTATIONS

Monogenic diseases are not indicated for 13 genes in the Online Mendelian Inheritance in Man (OMIM) database: for the *HAND2*, *KLF5*, *MT-TG*, *MT-TI*, *MYH7B*, *MYZAP*, *NEBL*, *PLEKHA3*, *PPP1R13L*, *SLC30A5*, *TAX1BP3*, *TRIM63*, *TTN-AS1* genes [22]. For the 62 remaining genes, a total of 191 diseases are listed, with only two pathologies being reported as predisposition (the *CASR* gene – to idiopathic generalized epilepsy; *SCN5A* gene – to sudden infant death syndrome). In most cases, autosomal dominant (72.8%) or autosomal recessive (17.3%) inheritance is noted, less frequently – mixed autosomal dominant / autosomal recessive (4.0%), autosomal dominant / digenic dominant (1.2%), and X-linked (4.6%) inheritance of the disease in the presence of pathological variants are observed. In five cases, somatic mutations are considered as the cause of the pathology (for cancers).

The CMP genes are characterized both by a different number of monogenic diseases and by their diversity. The largest number of diseases (from 5 to 11) was registered for *LMNA*, *SCN5A*, *MYH7*, *BRAF*, *NKX2-5*, *DSP*, *TTN, CASR*, *CAV3* genes (Table 1).

Table 1

CMP genes characterized by the largest number of monogenic diseases according to OMIM

Gene	Monogenic diseases
LMNA	DCM, 1A; Charcot – Marie – Tooth disease, type 2B1; Emery– Dreifuss muscular dystrophy type 2, (AD); Emery – Dreifuss muscular dystrophy type 3, (AR); heart – hand syndrome, Slovenian type; Hutchinson – Gilford progeria syndrome; familial partial lipodystrophy, type 2; Malouf syndrome; mandibuloacral dysplasia; muscular dystrophy, congenital; restrictive dermopathy 2 – **11 diseases in total**
SCN5A	Atrial fibrillation, familial, 10; Brugada syndrome 1; DCM, 1E; heart block, nonprogressive; heart block, progressive, type IA; long QT syndrome 3; sick sinus syndrome 1; ventricular fibrillation, familial, 1; susceptibility to sudden infant death syndrome **– 9 diseases in total**
MYH7	DCM, 1S; HCM, 1; Laing distal myopathy; left ventricular noncompaction 5; myosin storage congenital myopathy (AD and AR); scapuloperoneal myopathy **– 7 diseases in total**
BRAF	Lung adenocarcinoma, somatic; cardiofaciocutaneous syndrome; colorectal cancer, somatic; LEOPARD syndrome 3; melanoma, malignant, somatic; non-small cell lung cancer, somatic; Noonan syndrome 7 – **7 diseases in total**
NKX2-5	Atrial septal defect 7, with or without AV conduction defects; conotruncal heart malformations, variable; hypoplastic left heart syndrome 2; hypothyroidism, congenital nongoitrous, 5; tetralogy of Fallot; ventricular septal defect 3 **– 7 diseases in total**
DSP	Arrhythmogenic right ventricular dysplasia 8; DCM with woolly hair and keratoderma; dilated cardiomyopathy with woolly hair, keratoderma, and tooth agenesis; epidermolysis bullosa, lethal acantholytic; palmoplantar keratodermas striata II; woolly hair-skin fragility syndrome **– 6 diseases in total**

Table 1 (continued)

Gene	Monogenic diseases
TTN	DCM, 1G; HCM, 9; muscular dystrophy, limb-girdle, (AR) 10; myopathy, myofibrillar, 9, with early respiratory failure; congenital myopathy-5 with cardiomyopathy; tardive tibial muscular dystrophy – **6 diseases in total**
CASR	Hyperparathyroidism, neonatal; hypocalcemia (AD); hypocalcemia (AD) with Bartter syndrome; hypocalciuric hypercalcemia, type I; predisposition to idiopathic generalized epilepsy 8, late onset – **5 diseases in total**
CAV3	HCM, familial; creatine phosphokinase, elevated serum; long QT syndrome 9; distal myopathy, Tateyama type; rippling muscle disease 2 – **5 diseases in total**

Note. AD and AR designate autosomal dominant and autosomal recessive inheritance, respectively.

Four monogenic diseases were associated with 14 genes (*ABCC9*, *ACTC1*, *ACTN2*, *CACNA1C*, *CRYAB*, *FKTN*, *FLNC*, *LDB3*, *MYH6*, *MYO6*, *MYPN*, *PTPN11*, *SDHA*, *TNNT2*), and the number of diseases indicated in OMIM does not exceed three for the remaining genes.

From the above list of monogenic diseases for the CMP genes (Table 1), it is obvious that pathological manifestations of mutations in these genes are detected not only in the cardiovascular system, but also in other organs. In MeSH terminology, genetic diseases caused by pathogenic variants in the CMP genes can manifest as symptoms of damage to various organ systems (Table 2). According to OMIM and MeSH data, damage to the cardiovascular system accompanies monogenic diseases caused by 56 CMP genes, damage to the musculoskeletal system and connective tissue is caused by 24 CMP genes, skin and appendages, and metabolic disorders – by 8 genes each, pathology of the central nervous system is associated with 6 CMP genes. In addition, endocrine system disorders, pathology of the kidneys, eyes, immunity, hearing, and some other disorders were recorded with mutations in 4 or less genes.

It is worth noting that the "ranking" of CMP genes by the number of nosologies indicated in OMIM is not fully consistent with the that in relation to the organ systems in which such disorders occur. Full accordance is observed only for the *LMNA* gene (maximum number of inherited diseases and the number of affected systems) and a number of genes with a small number of monogenic diseases indicated in OMIM (for example, for the *ALPK3*, *CSRP3*, *JPH2*, *LAMA4*, *CTNNA3* and some others genes, only cardiovascular system is indicated). Similar estimates were obtained for the *BRAF*, *CASR*, and *CAV3* genes, which have a high "ranking" both in terms of the number of nosologies and the number of disorders in monogenic diseases of affected organ systems (Table 1, 2). It is important to emphasize that the list of disorders presented in MeSH that are characteristic of monogenic diseases caused by pathogenic variants in the CMP genes is not complete and does not take into account all pathological features that are characteristic of the respective diseases.

The table does not include the MeSH "Immune System Diseases" category, which is found only for the *NCF1* gene (characterized by Phagocyte bactericidal dysfunction).

A variety of clinical manifestations in monogenic diseases caused by pathogenic variants in the CMP genes is also registered within individual organ systems (Table 2) [22]. CMP genes dysfunction can lead to other heart pathologies (various arrhythmias, heart and vascular defects, etc.). Thus, variants in the *ABCC9* and *SCN5A* genes lead to atrial or ventricular fibrillation. A number of CMP genes (*CTNNA3*, *DSC2*, *DSG2*, *DSP*, *PKP2*, *TMEM43*) act as causative factors for the development of arrhythmogenic right ventricular dysplasia or arrhythmias among symptoms, syndromes, and diseases. For example, tachycardia is caused by *SCN5A* and *CACNA1C* in Brugada syndrome, and by *PRKAG2* gene in Wolff – Parkinson – White syndrome [22].

According to clinical observations, atrial fibrillation may represent the initial stage of cardiomyopathy manifestation (in particular in carriers of pathogenic / likely pathogenic variants in CMP genes) [23], and the phenotype of arrhythmogenic CMP may occur in other genetically determined cardiomyopathies [24]. However, arrhythmias do not always manifest in patients with monogenic CMPs even in the presence of the same pathogenic variant, as was observed, in particular, in patients with HCM caused by the p.Gln1233Ter substitution in the *MYBPC3* gene [25].

It should be highlighted that out of 62 CMP genes associated with monogenic diseases according to OMIM, no diseases manifested by the pathology of the cardiovascular system are mentioned for 6 genes – *CASR*, *SCO2*, *EMD*, *LAMP2*, *NCF1,* and *UQCRC1*. This indicates that information in the OMIM database about possible monogenic diseases caused by pathogenic variants in the CMP genes is incomplete.

Table 2

Examples of phenotypic manifestations* of monogenic diseases caused by pathogenic variants in the CMP genes according to MeSH

Genes	OMIM {total nosologies}	CVD	Musculoskeletal / connective tissue diseases	Nervous system diseases	Skin and appendages	Neoplasia	Traits	Metabolism	Endocrine system diseases	Kidney diseases	Eye diseases	Hearing disorders	Total MeSH Terms
LMNA	115200, 605588, 181350, 616516, 610140, 176670, 151660, 212112, 248370, 613205, 619793 **{11}**	CMP, CHD	MD, hand deformities, mandibuloacral dysplasia	Motor and sensory neuropathy	Restrictive dermopathy	–	–	Progeria, lipid metabolism D.	Gonadal dysgenesis	Urogenital A.	–	–	7
BRAF	211980, 115150, 114500, 613707, 155600, 211980, 613706 **{7}**	CHD	Muscle and skeletal A. Connective tissue A.	–	Ectodermal dysplasia, pigmentation D.	Lung Cr, Colorectal Cr, melanoma	Feeding difficulties, face and skull A.	–	–	–	–	–	5
PTPN11	151100, 607785, 156250, 163950 **{4}**	CHD	Muscle and skeletal A. Connective tissue A.	–	Ectodermal dysplasia, pigmentation D.	Bone and cartilage Cr.; leukemia	Feeding difficulties, face and skull A.	–	–	–	–	–	5
SDHA	613642, 252011, 619259, 614165 **{4}**	CMP	–	Neurodegeneration, ataxia	–	Paraganglioma	–	Mitochondrial diseases	–	–	ONA	–	5
RAF1	615916, 611554, 611553 **{3}**	CMP, CHD	Muscle and skeletal A. Connective tissue A.	–	Ectodermal dysplasia, pigmentation D.	–	Feeding difficulties, face and skull A.	–	–	–	–	–	4
CACNA1C	611875, 618447, 620029, 601005 **{4}**	Ar.	Skeletal A.	Seizures, autism	–	–	Neuromuscular manifestations	–	–	–	–	–	4

Table 2 (continued)

Genes	OMIM {total nosologies}	CVD	Musculoskeletal / connective tissue diseases	Nervous system diseases	Skin and appendages	Neoplasia	Traits	Metabolism	Endocrine system diseases	Kidney diseases	Eye diseases	Hearing disorders	Total MeSH Terms
CASR	239200, 601198, 601198, 145980, 612899 **{5}**	–	–	Epilepsy	–	–	–	Calcium metabolism P.	P. of parathyroid and adrenal glands	D. of transport in tubules	–	–	4
FKTN	611615, 253800, 613152, 611588 **{4}**	CMP	MD	Brain A.	–	–	–	–	–	–	Eye A.	–	4
ABCC9	614050, 608569, 239850, 619719 **{4}**	CMP, Ar., cardiomegaly	MP, osteochondrodysplasia	–	Hypertrichosis	–	–	–	–	–	–	–	3
CAV3	192600, 123320, 611818, 614321, 606072 **{5}**	CMP, Ar.	MD	–	–	–	CPK level	–	–	–	–	–	3
CRYAB	615184, 613763, 608810, 613869 **{4}**	CMP	MP	–	–	–	–	–	–	–	Cataract	–	3
TMEM43	604400, 619832, 614302 **{3}**	CMP	MD	–	–	–	–	–	–	–	–	Auditory neuropathy	3

Note. CMP – cardiomyopathy; CHD – congenital heart disorder; Ar. – arrhythmia; MD – muscular dystrophy; MP – myopathy; CPK – creatine phosphokinase; ONA – optic nerve atrophy, A. – anomalies; P. – pathology; Cr. – cancer; D.– disorders.

The musculoskeletal system and connective tissue are the second most frequently affected tissues by the presence of pathogenic variants in the CMP genes. Anomalies of the muscles, skeleton, and connective tissue, muscular dystrophy, myopathies, and some other disorders were registered for mutations in 24 genes (Table 2). In particular, various forms of myopathy are caused by mutations in the *ACTN2* gene (congenital myopathy with structured cores and Z-line abnormalities; distal myopathy, type 6, with adult onset), *BAG3* (myofibrillar myopathy, type 6), etc. [22].

Pathogenic variants in the CMP genes are also associated with the development of other monogenic diseases, manifested by pathological changes in the skin and hair (including restrictive dermopathy, skin pigmentation disorders, keratosis, woolly hair, etc.), cancers (melanoma, leukemia and other cancers), neurological disorders (neurodegenerative changes, seizures, epilepsy, ataxia, autism, etc.), metabolic (changes in lipid metabolism, mitochondrial pathology, storage diseases, etc.) and endocrine disorders (pathology of the parathyroid gland and adrenal glands) (Table 2), as well as various syndromes characterized by a wide range of structural and functional disorders. At the same time, on the one hand, complex clinical phenotypes are registered in some types of CMP, and, on the other hand, cardiomyopathies (or other myocardial disorders) can act as a symptom of a genetic disease or syndrome [22].

Thus, DCM caused by pathogenic variants in the *DSP* gene is combined with woolly hair and keratoderma; a left ventricular noncompaction can be registered in DCM and HCM (in both cases, the causative variant is localized in the *ACTN2* gene). CMP as a symptom is observed in Barth syndrome (DCM, neutropenia, proximal myopathy, physical and motor development delay are registered; the causative gene is *TAFAZZIN*); Danon disease (HCM, myopathy, mental retardation, the causative gene is *LAMP2*), LEOPARD syndrome (characterized by myocardial hypertrophy, multiple lentigines, electrocardiography conduction abnormalities, hypertelorism, pulmonary stenosis, abnormal genitalia, growth retardation, and sensorineural deafness; pathogenic variants of *PTPN11*, *RAF1*, *BRAF* can act as causative genes); Malouf syndrome (DCM, skeletal anomalies, reproductive disorders, mental retardation, where the causative gene is *LMNA*), Naxos disease (arrhythmogenic right ventricular dysplasia, palmoplantar keratoderma and woolly hair, the causative gene is *JUP*) and others [22].

It is worth noting that damage to other organ systems is observed in monogenic diseases caused by different CMP genes. Thus, skin and hair structure disorders were detected in arrhythmogenic right ventricular dysplasia (the causative gene is *DSC2*); cardiofaciocutaneous syndrome (*BRAF*); lethal acantholytic epidermolysis bullosa, striate palmoplantar keratoderma II (*DSP* gene), Cantú syndrome (*ABCC9* gene), restrictive dermopathy 2 (*LMNA* gene), etc. Mutations in the CMP genes can lead to sensory organ damage both as isolated phenotypes (*EYA4*, *MYO6* cause deafness; *CRYAB* causes cataract) and as individual symptoms (mutations in the *GLA*, *PTPN11*, *RAF1*, *BRAF*, *FKTN* genes) [22].

Cancers are caused by somatic mutations in the *BRAF* gene (adenocarcinoma, colorectal cancer, melanoma, non-small cell lung cancer) and the *PTPN11* gene (juvenile myelomonocytic leukemia), and pathogenic variants in the *SDHA* gene lead to paraganglioma 5. In addition, it should be noted that for syndromes caused by mutations in the CMP genes, malformations of various organ systems, physical and mental retardation, and disorders in the reproductive system are observed [22].

As already noted, the data provided in MeSH on phenotypic manifestations in monogenic diseases caused by mutations in the CMP genes cannot be considered complete, and as these patients are described in more detail, their phenotypic features and, accordingly, the scope of the genes will be refined. Thus, significant associations were found between pathogenic variants in the *PTPN11* gene and pulmonary stenosis (both valvular and supravalvular) and pulmonary valve dysplasia [2]. It has been shown that children and young adults with Noonan syndrome, who have pathogenic variants in the *PTPN11* gene, despite their slim build, are characterized by an unfavorable metabolic profile (low level of high-density lipoproteins, a trend toward higher triglyceride levels, higher HOMA-IR median, impaired glucose metabolism according to glucose tolerance test) [17]. Rare cases of early-onset cardiomyopathy associated with pathogenic variants in the *ALPK3* gene (DCM, HCM, mixed DCM/HCM phenotype with progression to HCM) combined with craniofacial anomalies have been described [13].

The spectrum of monogenic diseases caused by pathogenic variants in CMP genes is expanding. Thus, based on the expression patterns and study of protein - protein interaction networks using *in silico* tools, the *TTN* gene is considered as a candidate for arthrogryposis type 10 (a congenital disease of the musculoskeletal system manifested by joint

contractures, muscle underdevelopment, and changes in the spinal cord) [26].

In general, based on the summarized data on the phenotypic features of monogenic diseases caused by pathogenic variants in the CMP genes and taking into account the functional connectivity of the proteins encoded by these genes, we can expect the involvement of CMP genes in normal variability and formation of predisposition to pathological conditions of the cardiovascular, musculoskeletal, nervous, endocrine, and other organ systems. The traits associated with these organ systems may be of interest for a more detailed study in patients with various CMPs, including monogenic forms.

CONCLUSION

Despite the fact that the data are incomplete (due to the peculiarities of formation of any information resources), the information above allows to make several generalizations. Firstly, it is obvious that the CMP genes are pleiotropic, and pathogenic variants localized in these genes can lead to disorders in various organ systems. Secondly, the expression in various organs and the functional connectivity of the proteins encoded by CMP genes suggest the involvement of many genes in determining the structural and functional features of organ systems for which changes were registered in the already known monogenic diseases. Thirdly, monogenic diseases are caused by pathogenic gene variants with a strong effect, and, accordingly, monogenic diseases are characterized by extreme phenotypic manifestations (even in the case of incomplete penetrance and expressivity). Therefore, that polymorphic variants of these genes can make a certain contribution to the normal variability of traits of the relevant organ systems and take part in the formation of a polygenic basis of various disease determinations.

This statement is confirmed by the data of genome-wide association studies (GWAS), according to which polymorphic variants of the CMP genes are involved in the formation of variability not only of parameters reflecting the functional state of cardiovascular system (ECG and Echo parameters, blood pressure, etc.), but also in disorders of various organ systems (endocrine, urogenital, musculoskeletal, organs of vision and hearing, etc.), biochemical parameters and blood cell composition [27]. In our opinion, taking into account the complexity of genetic determination (from monogenic to polygenic component), incomplete penetrance and expressivity of genetic variants, and the possible modifying effect of various genetic factors on the clinical presentation of CMP [25, 28, 29], this aspect requires more detailed consideration.

In addition, the data above also define some important areas of research that may have significant clinical relevance in the future. First of all, this concerns a detailed clinical examination of patients with a diagnosed genetic disease, which is or may be caused by CMP genes. The examination should be comprehensive and not limited to the detailed characterization of previously described symptoms and traditionally examined parameters or systems of organs. So, V. Lodato et al. [3] note that physicians observing CMP in children “can face the most bizarre scenarios”. And the diagnostic process requires knowledge in cardiology, pediatrics, metabolism, radiology, and genetics (both clinical and molecular) and personalized management. As such data accumulate, it will be possible to identify clinically and prognostically significant traits for CMPs and other monogenic diseases associated with CMP genes, as well as markers that may contribute to the phenotypic manifestation of the pathogenic genetic variant. A detailed phenotypic description of patients is important to clarify the effects of rare variants of the CMP genes detected by molecular genetic testing, as well as variants of uncertain significance (VUS). This approach may allow for early identification of risk groups and manageable triggers that contribute to the manifestation of pathogenic gene variants.

This study was based on the analysis of CMP genes. At the same time, it seems appropriate to assess the scope of the genes of other monogenic diseases, as well as a to perform a deeper, comprehensive examination of individuals with an established or suspected diagnosis of various hereditary diseases.

REFERENCES

1. Nussinov R., Tsai C.J., Jang H. Protein ensembles link genotype to phenotype. *PLoS Comput. Biol*. 2019;15 (6):e1006648. DOI: 10.1371/journal.pcbi.1006648.
2. Leoni C., Blandino R., Delogu A.B., De Rosa G., Onesimo R., Verusio V. et al. Genotype-cardiac phenotype correlations in a large single-center cohort of patients affected by RASopathies: Clinical implications and literature review. *Am. J. Med. Gene.t A*. 2022;188(2):431–445. DOI: 10.1002/ajmg.a.62529.
3. Lodato V., Parlapiano G., Calì F., Silvetti M.S., Adorisio R., Armando M. et al. Cardiomyopathies in children and systemic disorders when is it useful to jook beyond the heart? *J. Cardiovasc. Dev. Dis*. 2022;9(2):47. DOI: 10.3390/jcdd9020047.
4. Cerrone M., Remme C.A., Tadros R., Bezzina C.R., Delmar M. Beyond the one gene-one disease paradigm: complex genetics and pleiotropy in inheritable cardiac disorders. *Circulation*.

2019;140(7):595–610. DOI: 10.1161/CIRCULATIONAHA.118.035954.
5. Hershberger R.E., Cowan J., Jordan E., Kinnamon D.D. The complex and diverse genetic architecture of dilated cardiomyopathy. *Circ Res*. 2021; 128 (10): 1514–1532. DOI: 10.1161/CIRCRESAHA.121.318157.
6. McKenna W.J., Judge D.P. Epidemiology of the inherited cardiomyopathies. *Nat. Rev. Cardiol*. 2021;18(1):22–36. DOI: 10.1038/s41569-020-0428-2.
7. Brieler J., Breeden M.A., Tucker J. Cardiomyopathy: an overview. *Am. Fam. Physician*. 2017;96(10):640–646.
8. El Hadi H., Freund A., Desch S., Thiele H., Majunke N. Hypertrophic, dilated, and arrhythmogenic cardiomyopathy: Where are we? *Biomedicines*. 2023;11(2):524. DOI: 10.3390/biomedicines11020524.
9. Povysil G., Chazara O., Carss K.J., Deevi S.V.V., Wang Q., Armisen J. et al. Assessing the role of rare genetic variation in patients with heart failure. *JAMA Cardiol*. 2021;6(4):379–386. DOI: 10.1001/jamacardio.2020.6500.
10. Koziol K.J., Aronow W.S. Peripartum cardiomyopathy: current understanding of pathophysiology, diagnostic work-up, management, and outcomes. *Curr. Probl. Cardiol*. 2023;48 (8):101716. DOI: 10.1016/j.cpcardiol.2023.101716.
11. Paul C., Peters S., Perrin M., Fatkin D., Amerena J. Non-ischaemic dilated cardiomyopathy: recognising the genetic links. *Intern. Med. J*. 2023;53(2):178–185. DOI: 10.1111/imj.15921.
12. Komissarova S.M., Rineyskaya N.M., Chakova N.N., Niyazova S.S. Overlapping Phenotype: Left Ventricular non-Compaction and Hypertrophic Cardiomyopathy. *Kardiologiia*. 2020; 60 (4): 137–145 (in Russ.). DOI: 10.18087/cardio.2020.4.n728.
13. Ding W.W., Wang B.Z., Han L., Li Z.P., Zhang W., Wang H. et al. ALPK3 gene-related pediatric cardiomyopathy with craniofacial-skeletal features: a report and literature review. *Zhonghua Er Ke Za Zhi – Chinese Journal of Pediatrics*. 2021;59(9):787–792. [Chinese]. DOI: 10.3760/cma.j.cn112140-20210222-00150.
14. Gonçalves L., Pires I., Santos J., Correia J., Neto V., Moreira D. et alOne genotype, two phenotype: Hypertrophic cardiomyopathy with left ventricular non-compaction. *Cardiol. J*. 2022;29 (2):366–367. DOI: 10.5603/Cj.2022.0020.
15. Joury A., Faaborg-Andersen C., Quintana R.A., da Silva-de-Abreu A., Nativi-Nicolau J. Diagnostic tools for cardiac amyloidosis: a pragmatic comparison of pathology, imaging and laboratories. *Curr. Probl. Cardiol*. 2023;48(5):101106. DOI: 10.1016/j.cpcardiol.2022.101106.
16. Simple ClinVar. URL: https://simple-clinvar.broadinstitute.org/
17. Noronha R.M., Villares S.M.F., Torres N., Quedas E.P.S., Homma T.K., Albuquerque E.V.A. et al. Noonan syndrome patients beyond the obvious phenotype: A potential unfavorable metabolic profile. *Am. J. Med. Genet. A*. 2021;185(3):774–780. DOI: 10.1002/ajmg.a.62039.
18. Rimskaya E.M., Novikov P.S., Salami H.F., Golitsyn S.P. Brugada syndrome and early repolarization syndrome: various clinical forms of J-wave syndrome in one family. *Russian Cardiology Bulletin*. 2022;17(2):81–87 (in Russ.). DOI: 10.17116/Cardiobulletin20221702181.
19. Yu C., Deng X.J., Xu D. Gene mutations in comorbidity of epilepsy and arrhythmia. *J.* Neurol. 2023;270(3):1229–1248. DOI: 10.1007/s00415-022-11430-2.
20. Tissue expression database. URL: https://tissues.jensenlab.org/
21. STRING. URL: https://string-db.org/
22. Online Mendelian Inheritance in Man. URL: https://omim.org/
23. Yoneda Z.T., Anderson K.C., Quintana J.A., O'Neill M.J., Sims R.A., Glazer A.M. et al. Early-onset atrial fibrillation and the prevalence of rare variants in cardiomyopathy and arrhythmia genes. *JAMA Cardiol*. 2021;6(12):1371–1379. DOI: 10.1001/jamacardio.2021.3370.
24. Cipriani A., Perazzolo Marra M., Bariani R., Mattesi G., Vio R., Bettella N. et al. Differential diagnosis of arrhythmogenic cardiomyopathy: phenocopies versus disease variants. *Minerva Med*. 2021;112(2):269–280. DOI: 10.23736/S0026-4806.20.06782-8.
25. Salakhov R.R., Golubenko M.V., Valiakhmetov N.R., Pavlyukova E.N., Zarubin A.A., Babushkina N.P. et al. Application of long-read nanopore sequencing to the search for mutations in hypertrophic cardiomyopathy. *Int. J. Mol. Sci*. 2022;23(24):15845. DOI: 10.3390/ijms232415845.
26. Biswas A., Nath S.D., Ahsan T., Hossain M.M., Akhteruzzaman S., Sajib A.A. *TTN* as a candidate gene for distal arthrogryposis type 10 pathogenesis. *J. Genet. Eng. Biotechnol*. 2022;20(1):119. DOI: 10.1186/s43141-022-00405-5.
27. GWAS Catalog. The NHGRI-EBI Catalog of human genome-wide association studies. URL: https://www.ebi.ac.uk/gwas/
28. Kucher A.N., Valiakhmetov N.R., Salakhov R.R., Golubenko M.V., Pavlyukova E.N., Nazarenko M.S. Phenotype variation of hypertrophic cardiomyopathy in carriers of the p.Arg870His pathogenic variant in the *MYH7* gene. *Bulletin of Siberian Medicine*. 2022;21(3):205–216 (in Russ.). DOI: 10.20538/1682-0363-2022-3-205-216. DOI: 10.20538/1682-0363-2022-3-205-216.
29. Kucher A.N., Sleptsov A.A., Nazarenko M.S. The genetic landscape of dilated cardiomyopathy. *Russian Journal of Genetics*. 2022;58(4):371–387 (in Russ.). DOI: 10.31857/S0016675822030080. DOI: 10.1134/S1022795422030085.

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