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Cardiomyopathies – genetic and molecular issues

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Abstract

Cardiomyopathy is a condition that may have a genetic basis. It is a serious ailment because it affects almost half of the individuals who die suddenly in childhood, adolescence, or related to heart transplant procedures. The inheritance patterns of this disease can vary. For example, as described in the work on HCM and ARVC, they are inherited in an autosomal dominant manner. De novo mutations may involve genes related to myofilaments, Z-discs, components related to cellular calcium handling, or desmosomes, among others. However, detailed molecular aspects should be correlated with clinical features because changes within a single gene may be associated with diverse abnormalities. Depending on the manifestation of the action of certain allele changes, they may range from microscopic deviations to causing heart failure and impaired blood flow through other organs, thereby disrupting the functionality of the entire body, hindering daily life and lowering its quality. Currently, the analysis of the degree of interaction of genetic determinants in cardiomyopathy is becoming increasingly accessible due to modernization and improvement of tools in the field of diagnosing anomalies in gene sequences and expression. A more precise understanding of causative mutations and associated conditions may contribute to determining strategic points for the future regarding the most beneficial course of action in specific circumstances and evaluating the effectiveness of the steps taken in the long run. In addition to mutations typically causing cardiomyopathy, there are also mutations contributing to their development within the spectrum of other diseases. This includes the PRKAG2-related cardiac syndrome, associated with abnormal metabolism, Danon disease, mitochondrial disorders, ion channelopathies, or conduction disorders.

Running title: Cardiomyopathies review

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Introduction

Cardiomyopathy is a condition that affects almost half of those who suddenly lose their lives in childhood, adolescence, or as a result of heart transplant surgery [1]. Therefore, it can be easily argued that there is a profound impact of this disease on the population – not only adults but also pediatric patients [2,3]

It might seem that the history began in 1891 when Krehl reported incidents of myocardial diseases whose causes were unknown, but the term cardiomyopathy was first used by Wallace Brigden in 1957, who described them as non-coronary diseases involving the myocardium with an unspecified causative factor [4].

The identification in 1990 of mutations in the MYH7 gene, located at 14q11.2-q12, encoding the beta-myosin heavy chain by Christine Seidman and Jonathan Seidman marked a turning point in understanding the genetic influences on the development of cardiomyopathy [1,5,6].

Considering the distinct mechanisms underlying specific diseases within this group, the interactions between them appear to be of interest. Dilated cardiomyopathy (DCM) ranks first among primary myocardial diseases and is detected in 6 out of 10 patients with cardiomyopathies [7]. In addition to dilated cardiomyopathy, hypertrophic cardiomyopathy (HCM) is also among the most common types. Other existing types such as arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive (RCM), and unclassified cardiomyopathies are less common. Among the general adult population, the diagnosis of HCM, the most common inherited cardiomyopathy, and DCM affects about 0.2-0.4%. The prevalence of ARVC in this population is associated with 0.02-0.05%, while RCM falls even lower in these statistics [8].

The modernization and continuous improvement of tools for diagnosing abnormalities in gene sequences and expression now includes the possibility of analyzing the degree of interaction of hereditary determinants in cardiomyopathy [9].

However, molecular details should be confronted with observable characteristics, as separate mutations in one gene may result in different abnormalities – changes in adjacent amino acids within the beta-myosin heavy chain leads to hypertrophic or dilated cardiomyopathy [10]. Lifestyle can also influence the phenotypic picture and disease progression in the case of identical mutations, and the same disease entity may result from various disorders in the same gene [11].

Given the significance and breadth of the topic under discussion, the authors of many publications continue to emphasize the need for broader analysis and the necessity of conducting additional research.

Description

The term cardiomyopathy refers to a group of disorders affecting the heart muscle, resulting in impaired function. Abnormalities may also involve the pericardium and endocardium [12]. The classification of cardiomyopathies is currently based on diagnoses related to morphology and functioning of the chambers. Further division involves the influence of familial factors and potential lack of association with genetic predisposition [13,14]. Thus, a distinction is made between primary and secondary cardiomyopathies, with the latter being associated with the influence of external factors – such as high blood pressure [15]. According to the American Heart Association, the classification within primary cardiomyopathies includes genetic, mixed, and acquired cardiomyopathies. The categorization of cardiomyopathies is problematic, and existing divisions are not uniform [12].

Regarding the genetic aspects and the diversity of allele actions of specific genes, cardiomyopathies can manifest variations at the microscopic level in cardiac muscle cells or lead to cardiac dysfunction, consequently impairing blood flow to other organs [16].

Hypertrophic cardiomyopathy

Encountered in the highest number of cases – 1:200 to 1:500 asymptomatic patients and 1:3000 symptomatic ones – the genetically based heart disease is HCM [14]. The condition is defined as an increase in the thickness of the left ventricular wall to 15 mm or more, not resulting from abnormal loading [17].

Genetic causes of HCM affect 34% of patients, and mutations associated with this condition are described as autosomal dominant, focusing on the sarcomere and associated proteins. They can involve myofilaments, the Z-disc, or elements related to cellular calcium handling [6]. Within 11 sarcomeric genes, over 1400 mutations contributing to HCM have been identified. These mutations not only affect peptide function but also folding and molecular interactions within the cell [18]. Therefore, it is noteworthy that while mutations in sarcomeric protein components theoretically causing HCM can be found in a larger population, not all carriers of the defective gene will clinically develop the manifested condition [19].

Attention should also be paid to the possibility of phenotypic characteristics appearing long after the onset of the mutation [6].

MYBPC3 gene has been found to have at least 350 mutations resulting in HCM. Their large number leads to a decrease in protein molecule length [10,20] There have been multiple reports linking mutations in other genes such as MYH7, TNNT2, TPM1, TNNI3 and TNNC1 to cause HCM [21].

MYBPC3 gene contains 34 exons, and its product is MyBP-C, whose cardiac isoform (cMyBP-C) has

additional features: a C0 domain at the N-terminus, phosphorylation regions between the C1 and C2 domains, and a 28-amino acid insertion in C5, distinguishing it from the other two isoforms [20].

The sarcomere, the basic unit of cardiomyocyte, comprises two main components: thick and thin filaments. The former includes myosin, consisting of two heavy chains (beta- or alpha-myosin) and 4 light chains, while the latter is associated with actin, which interacts with troponin T, I, C, and alpha-tropomyosin. MyBP-C regulates interactions between these parts [22]. cMyBP-C interacts with the carboxyl and amino terminals of myosin and actin, limiting interactions. Increased ATPase activity and actin actions and the opposite result in myosin, caused by phosphorylation of the N-terminus of cMyBP-C, lead to forceful cross-bridge formation [23].

Mutations within MYBPC3 involve frameshifts, missense changes, insertions, or deletions. The large number of mutations results in a decrease in protein molecule length. Loss of normal product function due to the existence of premature termination codons (PTCs) and Nonsense-Mediated Decay (NMD) leads to decreased MyBP-C levels, which in turn leads to HCM development [24].

MYH7, encoding the heavy chain of beta-myosin, which includes the head, alpha-helical rod, and hinge region, shows distinct outcomes depending on the mutation location. Mutations in this regard most commonly involve missense changes [22].

Mutations in the third gene most strongly associated with HCM-TNNT2, encoding troponin T, anchoring troponin C and troponin I and serving as a signal transducer for Ca2+-rarely cause such strong ventricular hypertrophy as in other cases but contribute to a high risk of sudden cardiac arrest (SCA). Particularly, the missense mutation TNNT2 I79N +/- is associated with an increased likelihood of SCA at a young age [18,25].

In addition to troponin T, troponin I and C play important roles. The former, divided into 6 functional regions, stabilized under low Ca2+ concentrations, prevents actin and myosin interaction. Contraction results from changes in Ca2+ concentration from 100 nmol/l to 1 mmol/l.

Mutations in the TNNI3 gene, encoding troponin I, most commonly involve replacing a positively or negatively charged amino acid with a neutral or hydrophobic one. 40% of events are associated with arginine inclusion.

Changes in the TNNC1 gene, associated with the second of them – troponin C – disrupt the harmony of cellular mechanisms and the degree of Ca2+ binding strength [18].

Disorders in TPM1, encoding alpha-tropomyosin, condition abnormal myocardial contractility also through the aforementioned element.

Broadly defined calcium handling dysfunctions contribute to HCM development [26]. The level of junctophilin-2 (JPH2) – a protein anchoring the sarcoplasmic reticulum in T-tubules, allowing proper calcium ion flow – is reduced in affected cardiac muscle. Studies in a mouse model have shown that downregulation affects both protein and mRNA JPH2 [27].

Phospholamban (PLN) also participates in calcium handling regulation, and its mutations contribute to the development of inherited cardiomyopathies [28]. Phospholamban is a main protein regulating the Ca2+-ATPase of cardiac sarcoplasmic reticulum [29]. Its phosphorylation is associated with the cessation of inhibitory influence on the sarcoplasmic reticulum-associated pump (SERCA2a) and the accumulation of Ca2+ in the ER [28].

Genes associated with the myofilament mechanism, subject to mutations less frequently, include TTN, located on chromosome 2, responsible for titin formation, MYL3 on chromosome 3, encoding ventricular essential myosin light chain 3, MYL2 on chromosome 12, associated with ventricular regulatory myosin light chain 2, and ACTC on chromosome 15, encoding alpha-cardiac actin [6].

Genes associated with Z-disc proteins, ensuring proper sarcomere construction, also contribute to HCM: ACTN2 (alpha-actinin 2), FLNC (filamin C), MYPN (myopalladin), TCAP (telethonin), LDB3 (ZASP) [30].

Alpha-actinin 2 is a protein that is responsible for creating connection within the opposite oriented actin filaments. This molecule also binds N-terminal titans and therefore maintains sarcomere stability [31].

Filamin C protein is one of the isoforms of filamin that enables cross-connection within the actin filaments. It is also responsible for binding with over 90 different structures [32].

Myopalladin is a protein that plays a major role in regulation and maintenance of sarcomere structure [33].

Telethonin is a Z-disc protein that is responsible for binding with other proteins in the T-tubule membrane. Tcap is essential in maintaining structure, and functionality of the t-tubule, even more so under mechanical overload [34].

ZASP is a cytoskeletal protein present in the sarcomere. The molecule is responsible for preservation of the structural coherence of the Z-line [35].

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) is caused by changes in the intercalated discs that allow cardiac cells to communicate with each other, specifically affecting the portion of the intercalated disc called the desmosome [36].

Structural and functional abnormalities observed in ARVC may be explained by disturbances in signal transduction, intercellular communication, as well as cell proliferation and differentiation [37].

The classic form of ARVC is autosomal dominantly inherited. It is believed to be responsible for 30-50% of cases with a variable proportion of individuals with a particular genotype expressing the phenotypic effect in a given environment [38].

There are 8 genes, the pathological variants of which account for most ARVC cases. These are five desmosomal genes (PKP2, DSP, DSG2, DSC2, and JUP) and three non-desmosomal genes (TMEM43, DES, and PLN) [39].

PKP2 is one of the most important genes associated with ARVC. PKP2 encodes plakophilin-2, a protein consisting of 881 amino acids with an ARM domain, which has a structure similar to plakoglobin encoded by JUP [40]. To date, over 150 pathogenic mutations in PKP2 have been identified, making it the primary gene responsible for the disease (about 35%-40% of all ARVC cases) [41]. Studies of ARVC patients suggest that there are many PKP2 mutations (insertions, deletions, nonsense, missense changes) leading to haploinsufficiency and consequently to a reduction in PKP2 protein levels in the heart [42]. The most common mutations in the PKP2 gene are small deletions/insertions with a frame shift (40%), nonsense mutations (25%), missense changes (20%), and splicing site mutations (15%) [41]. New research suggests a greater involvement of RNA, specifically RNA splicing modification, which leads to altered levels of PKP2 in RNA form, and these changes play a crucial role in the pathogenesis of ARVC in patients with ARVC who have PKP2 mutations [42].

DSC2 is the gene encoding desmocollin 2, which, of all desmocollins, is most prevalent in tissues, including cardiomyocytes. Monoallelic mutations in DSC2 are associated with an autosomal dominant version of ARVC [43]. Mutations in DSG2 were first associated with ARVC in 2006 [40].

DSG2 is the only desmoglein present in the heart, which plays a heterodimerization role with DSC2 to ensure cell stability. Therefore, there is no possibility of compensating for the loss of DSG2 function in the heart with another desmoglein subtype. DSG2 mutations are present in about 10% of ARVC patients [44]. Over 50 pathogenic mutation variants associated with ARVC have been found. About 60% of all of them were missense mutations, about 20% were small insertions/deletions, and the remaining 20% accounted for splicing site changes. Although most identified mutations show a dominant inheritance pattern, recessive inheritance modes of mutations have also been indicated in ARVC patients [41].

Mutations in the gene encoding JUP as well as PKP2, functioning in the outer, dense desmosomal plaques, lead to a similar cardiac phenotype in ARVC. Both mutations manifest ARVC during adolescence with a proportion of individuals with a particular genotype expressing the phenotypic effect in a given environment of 55% in carriers of PKP2 mutations and 100% in homozygous carriers of the JUP gene mutation [45].

Desmoplakin (DSP) is a structural protein that connects the cardiac desmosome with intermediate filaments and is also essential for proper transmis-

TABLE 1 Affected genes and corresponding proteins

DISEASE	GENE	PRODUCT
HCM	MYH7	Heavy chain of beta-myosin
	TNNT2	Cardiac troponin T
	TPM1	Alfa-tropomyosin
	TNNI3	Cardiac troponin I
	TNNC1	Cardiac troponin C
	MYBPC3	MyBP-C
	TTN	Titin
	MYL3	Ventricular essential myosin light chain,
	MYL2	Ventricular regulatory myosin light chain
	ACTC	α-cardiac actin
	ACTN2	α-actinin ۲
	FLNC	Filamin C
	MYPN	Myopalladin
	TCAP	Telethonin
	LDB3	ZASP
	JPH2	Junctophilin-2
	PLN	Phospholamban
ARVC	PKP2	Plakophilin-2
	DSP	Desmoplakin
	DSG2	Desmoglein-2
	DSC2	Desmocollin-2
	JUP	Junction plakoglobin

sion of excitation in cardiac muscle [46]. Data suggest that DSP expression in cardiomyocytes is essential for maintaining cardiac tissue integrity, and abnormalities in DSP function will be responsible for ARVC – specifically cardiomyocyte death, changes in lipid metabolism, and defects in heart development. DSP mutations leading to ARVC are mainly autosomal and dominant [47].

Affected genes and corresponding proteins summarized in **table 1**.

Left ventricular noncompaction (LVNC)

Left ventricular noncompaction (LVNC) is a cardiomyopathy characterized by the formation of abnormal trabeculations in the left ventricle, typically in the apex region. The condition may be associated with dilatation or hypertrophy, systolic and diastolic dysfunction, and even various forms of congenital heart diseases [48]. From 17%, to as much as 50% of LVNC patients have a relative with another primary cardiomyopathy. Moreover, the yield of genetic testing ranges from 9% to 41%, depending on patient selection and the number of genes tested [49]. The American Heart Association classified LVNC in the genetic section of primary cardiomyopathies in 2006. It is a heterogeneous disease associated with many clinical symptoms and can be inherited autosomally or X-linked or linked to genome in mitochondria. LVNC is the third most common cardiomyopathy after dilated and hypertrophic cardiomyopathy, and its prevalence ranges from 0.05% to 0.3% in the population. The molecular-level mechanisms involved in LVNC are still unknown. Genetic mutations of sarcomere and chaperone proteins, cell skeleton, ion channels and nuclear membranes are present and are consisted with this condition. [50].

PRKAG2-associated cardiac syndrome and danon disease

PRKAG2-associated cardiac syndrome, specifically with its catalytically inactive Gamma 2 subunit, is characterized by glycogen accumulation in heart tissue [51]. This syndrome also presents with left ventricular hypertrophy, Wolff-Parkinson-White syndrome, atrial tachyarrhythmia, and abnormal cardiac conduction [52], and sometimes skeletal myopathy [53].

PRKAG2-related gene disease is a disorder involving abnormal metabolism in the heart [54]. AMPK is a serine-threonine kinase, composed of catalytic α subunits, regulatory β subunits, and γ subunits. It is allosterically activated by increasing levels of AMP and by phosphorylation of the α subunit under conditions of substrate shortages, hypoxia, physical exertion, and heat stroke, where it then modifies enzymatic activity in metabolic pathways related to both ATP production and consumption and regulates necessary systems to maintain homeostasis [55]. New compelling evidence regarding PRKAG2 mutations suggests "gain-of-function" in the basal activity of AMPK, at least in the early stages of the disease, leading to excessive glucose uptake and pathological glycogen storage in the heart. The end result is usually a lethal cardiac phenotype [54].

Distinguishing PRKAG2 cardiomyopathy from hypertrophic cardiomyopathy is one of the most important tasks in medicine. It results not only from the clinical presentation of diseases but also from their long-term outcomes. Sudden death in the case of PRKAG2 mutations is more common [52]. So far, only a small number of cases have been reported and documented, so the biological history of this disease is still not fully understood [56].

Danon syndrome (DD) is a rare, dominant, X-linked disease characterized by a deficiency of lysosome-associated membrane protein-2 (LAMP-2) [57]. LAMP-2 is needed for correct evolvement of autophagosomes by fusion with lysosomes [58]. Cardiomyopathy, skeletal myopathy, and intellectual disability are the triad of symptoms of this disease [57]. Primary deficiency of this protein disrupts the process of autophagy, leading to impaired fusion of lysosomes and autophagosomes and lysosome biogenesis [59]. The inability to remove old mitochondria causesenergy deficits and oxidative stress [60]. There are three main types of autophagy: macroautophagy, chaperone-mediated autophagy, and microautophagy. Macroautophagy is the most common form of autophagy and the most affected in Danon disease [61].

In women, both HCM and DCM were present. In this sex, isolated heart disease was present, whereas in men, DD typically presented as HCM and often was a multi-level disease [62].

Mitochondrial cardiomyopathies

According to estimates, cardiomyopathies affect 20-40% of the youngest individuals diagnosed with mitochondrial disorders and are simultaneously the most common cardiac manifestation associated with them. Typically, hypertrophic cardiomyopathies are observed, but dilated cardiomyopathies, restrictive cardiomyopathies, LVNC, or histiocytoid cardiomyopathy associated with this mechanism are also encountered. Mitochondrial mutations contributing to the development of cardiomyopathies may affect genes related to, among others, complex I (e.g., MTND1, MTND2), II (e.g., SDHA, SDHD), III (e.g., MTCYB), IV (e.g., MTCO1, MTCO2) electron transport, mtRNA, mrRNA, mtDNA, factors necessary in translation, and Q10 synthesis [63,64].

Ion channelopathies and conduction disorders

Ion channelopathies are diseases caused by dysfunction of ion channels, which can have a genetic basis or result from acquired pathological factors [65]. Channelopathies often manifest as harmful arrhythmias resulting from dysfunction of ion chan-

nels or proteins associated with them. Studies have shown that about 30% of autopsies of young individuals that did not reveal a precise cause of death could be explained by pathological variations in genes related to channelopathies [66].

Each channelopathy has its own electrocardiographic pattern, typical symptom model, and the most common gene associated with this condition. For long QT syndrome type 1, it is the KCNQ1 gene; for catecholaminergic polymorphic ventricular tachycardia, which usually presents as sudden cardiac arrest during physical activity in young males, it is the RYR2 gene; for long QT syndrome type 2, most commonly occurring in adult females shortly after childbirth, it is the KCNH2 gene; while for long QT syndrome type 3 and Brugada syndrome, which most commonly manifest at night in young adult males, it is the SCN5A gene [67].

KCNQ1 encodes voltage-gated potassium channel subunit alpha [68]. The most major roles of KCNQ1 channels are providing a repolarization wave after an action potential and also managing water and salt transportation in epithelial tissues [69]. KCNH2 gene encodes a different alpha subunit of voltage-gated channel protein [70].

RyR2 gene encodes ryanodine receptor which plays a major role in regulating Ca2+ release from sarcoplasmic reticulum. This protein has multitudinous functional domains, all of which have specified roles [71].

Interestingly, it turns out that abnormalities in ion channels can lead to dilated cardiomyopathy (DCM). There are cases of DCM associated with mutations in the SCN5A gene [72], which encodes a component of the heart sodium channel responsible for ion conduction and hence the excitability of heart tissue. Mutations within SCN5A causing DCM may increase sodium ion flow and limit channel function [73].

Mutations in ABCC9, encoding SUR2A, which is responsible for regulating ATP-sensitive K+ channels, are associated with susceptibility to DCM. In these cases, rhythm disturbances were observed. Dysfunction of channels caused by ABCC9 mutation involves impaired signal flow due to abnormal ATP hydrolysis [74].

Conclusions

A review of numerous studies suggests the existence of various mutations causing cardiomyopathies, which inherit in different ways, such as autosomal dominant inheritance observed in HCM and ARVC. Depending on the expression of alleles of certain genes, changes may be limited to the microscopic level or may condition serious cardiac performance disorders [14, 16, 38]. The American Heart Association has also classified LVNC in the genetic section of cardiomyopathies. Besides mutations typically conditioning cardiomyopathies, there are also those contributing to their development within the spectrum of other diseases, such as PRKAG2-associated cardiac syndrome, Danon disease, ion channelopathies, and mitochondrial disorders. With the contemporary advancement of genetic research techniques, we hope for the possibility to identify new genes responsible for the conditions described, which may bring future benefits in the form of targeted patient care and determination of the most favorable clinical procedures in specific mutation cases.

Ethical approval
This study is not related to either human or animal use.

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Conflict of interest
The authors declare no conflict of interest.

References

1. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. Circ Res. 2017;121(7):722-30; DOI:10.1161/CIRCRESAHA.117.309711.
2. Ware SM, Wilkinson JD, Tariq M, Schubert JA, Sridhar A, Colan SD, Shi L, Canter CE, Hsu DT, Webber SA, Dodd DA, Everitt MD, Kantor PF, Addonizio LJ, Jefferies JL, Rossano JW, Pahl E, Rusconi P, Chung WK, Lee T, Towbin JA, Lal AK, Bhatnagar S, Aronow B, Dexheimer PJ, Martin LJ, Miller EM, Sleeper LA, Razoky H, Czachor J, Lipshultz SE, Pediatric Cardiomyopathy Registry Study Group. Genetic causes of cardiomyopathy in children: first results from the pediatric cardiomyopathy genes study. J Am Heart Assoc. 2021;10(9):e017731; DOI:10.1161/JAHA.120.017731.
3. Monda E, Rubino M, Lioncino M, Di Fraia F, Pacileo R, Verrillo F, Cirillo A, Caiazza M, Fusco A, Esposito A, Fimiani F, Palmiero G, Pacileo G, Calabrò P, Russo MG, Limongelli G. Hypertrophic cardiomyopathy in children: pathophysiology, diagnosis, and treatment of non-sarcomeric causes. Front. Pediatr. 2021;9:632293; DOI:10.3389/fped.2021.632293.
4. Salemi VMC, Mohty D, de Altavila SLL, de Melo MDT, Kalil Filho R, Bocchi EA. Insights into the classification of cardiomyopathies: past, present, and future directions. Clinics. 2021;76:e2808; DOI:10.6061/clinics/2021/e2808.
5. Marian AJ. Molecular genetic basis of hypertrophic cardiomyopathy. Circ Res. 2021;128(10):1533-53; DOI:10.1161/CIRCRESAHA.121.318346.
6. Geske J, Ommen S, Gersh B. Hypertrophic cardiomyopathy: clinical update. JACC Heart Fail. 2018;6(5):364-75; DOI:10.1016/j.jchf.2018.02.010.
7. Posafalvi A, Herkert JC, Sinke RJ, van den Berg MP, Mogensen J, Jongbloed JD, van Tintelen JP. Clinical utility gene card for: dilated cardiomyopathy (CMD). Eur J Hum Genet. 2013;21(10); DOI:10.1038/ejhg.2012.276.
8. Schaufelberger M. Cardiomyopathy and pregnancy. Heart. 2019;105(20):1543-51; DOI:10.1136/heartjnl-2018-313476.
9. Kosobudzki M, Bortkiewicz A. Genetyczne uwarunkowania chorób układu krążenia. Forum Medycyny Rodzinnej. 2012;6(1):1-13.
10. Watkins H, Ashrafian H, Redwood C. Dziedziczne kardiomiopatie. Kardiologia po Dyplomie. 2011;10(9):12-29.
11. Burke MA, Cook SA, Seidman JG, Seidman CE. Clinical and mechanistic insights into the genetics of cardiomyopathy. J Am Coll Cardiol. 2016;68(25):2871-86; DOI:10.1016/j.jacc.2016.08.079.
12. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB, American Heart Association, Council on Clinical Cardiology Heart Failure and Transplantation Committee, Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups, Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology,

Heart Failure and Transplantation Committee, Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups, Council on Epidemiology and Prevention. Circulation. 2006;113(14):1807-16; DOI:10.1161/CIRCULATIONAHA.106.174287.
13. Elliott P, Andersson B, Arbustini E, Bilińska Z, Cecchi F, Charron P, Dubourg O, Kühl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Klasyfikacja kardiomiopatii. Stanowisko Grupy Roboczej Chorób Mięśnia Sercowego i Osierdzia Europejskiego Towarzystwa Kardiologicznego. Kardiol Pol. 2008;66(5):533-40; DOI: 10.33963/v.kp.80540.
14. Yamada T, Nomura S. Recent findings related to cardiomyopathy and genetics. Int J Mol Sci. 2021;22(22):12522; DOI:10.3390/ijms222212522.
15. Kimura A. Molecular genetics and pathogenesis of cardiomyopathy. J Hum Genet. 2016;61(1):41-50; DOI:10.1038/jhg.2015.83.
16. Brieler J, Breeden MA, Tucker J. Cardiomyopathy: an overview. Am Fam Physician. 2017;96(10):640-6.
17. Maj K, Major K, Lelonek M. HFpEF mimics: hypertrophic cardiomyopathy in light of the 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure with Preserved Ejection Fraction. Folia Cardiol. 2023;18(4):182-6; DOI:10.5603/fc.96348.
18. Marques MA, de Oliveira GA. Cardiac troponin and tropomyosin: structural and cellular perspectives to unveil the hypertrophic cardiomyopathy phenotype. Front Physiol. 2016;7:429; DOI:10.3389/fphys.2016.00429.
19. Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2015;65(12):1249-54; DOI:10.1016/j.jacc.2015.01.019.
20. Carrier L, Mearini G, Stathopoulou K, Cuello F. Cardiac myosin-binding protein C (MYBPC3) in cardiac pathophysiology. Gene. 2015;573(2):188-97; DOI:10.1016/j.gene.2015.09.008.
21. Wolf CM. Hypertrophic cardiomyopathy: genetics and clinical perspectives. Cardiovasc Diagn Ther. 2019;9(Suppl 2):S388-S415; DOI:10.21037/cdt.2019.02.01.
22. Akhtar M, Elliott P. The genetics of hypertrophic cardiomyopathy. Glob Cardiol Sci Pract. 2018;2018(3):36; DOI:10.21542/gcsp.2018.36.
23. Toepfer CN, Wakimoto H, Garfinkel AC, McDonough B, Liao D, Jiang J, Tai AC, Gorham JM, Lunde IG, Lun M, Lynch TL 4th, McNamara JW, Sadayappan S, Redwood CS, Watkins HC, Seidman JG, Seidman CE. Hypertrophic cardiomyopathy mutations in MYBPC3 dysregulate myosin. Sci Transl Med. 2019;11(476):eaat1199; DOI:10.1126/scitranslmed.aat1199.
24. Tudurachi BS, Zăvoi A, Leonte A, Ţăpoi L, Ureche C, Bîrgoan SG, Chiuariu T, Anghel L, Radu R, Sascău RA, Stătescu C. An update on MYBPC3 gene mutation in hypertrophic cardiomyopathy. Int J Mol Sci. 2023;24(13):10510; DOI:10.3390/ijms241310510.
25. Shafaattalab S, Li AY, Gunawan MG, Kim B, Jayousi F, Maaref Y, Song Z, Weiss JN, Solaro RJ, Qu Z, Tibbits GF. Mechanisms of arrhythmogenicity of hypertrophic cardiomyopathy-associated troponin T (TNNT2) variant I79N. Front Cell Dev Biol. 2021;9:787581; DOI:10.3389/fcell.2021.787581.
26. Dorsch LM, Kuster DWD, Jongbloed JDH, Boven LG, van Spaendonck-Zwarts KY, Suurmeijer AJH, Vink A, du Marchie Sarvaas GJ, van den Berg MP, van der Velden J, Brundel BJJM, van der Zwaag PA. The effect of tropomyosin variants on cardiomyocyte function and structure that underlie different clinical cardiomyopathy phenotypes. Int J Cardiol. 2021;323:251-8; DOI:10.1016/j.ijcard.2020.08.101.
27. Beavers DL, Landstrom AP, Chiang DY, Wehrens XH. Emerging roles of junctophilin-2 in the heart and implications for cardiac diseases. Cardiovascular Res. 2014;103(2):198-205; DOI:10.1093/cvr/cvu151.
28. Hof IE, van der Heijden JF, Kranias EG, Sanoudou D, de Boer RA, van Tintelen JP, van der Zwaag PA, Doevendans PA. Prevalence and cardiac phenotype of patients with a phospholamban mutation. Neth Heart J. 2019;27(2):64-9; DOI:10.1007/s12471-018-1211-4.
29. Simmerman HK, Jones LR. Phospholamban: protein structure, mechanism of action, and role in cardiac function. Physiol Rev. 1998;78(4):921-47; DOI:10.1152/physrev.1998.78.4.921.
30. Wadmore K, Azad AJ, Gehmlich K. The role of Z-disc proteins in myopathy and cardiomyopathy. Int J Mol Sci. 2021;22(6):3058; DOI:10.3390/ijms22063058.
31. Ranta-Aho J, Olive M, Vandroux M, Roticiani G, Dominguez C, Johari M, Torella A, Böhm J, Turon J, Nigro V, Hackman P, Laporte J, Udd B, Savarese M. Mutation update for the ACTN2 gene. Hum Mutat. 2022;43(12):1745-56; DOI:10.1002/humu.24470.
32. Mao Z, Nakamura F. Structure and function of filamin C in the muscle Z-disc. Int J Mol. Sci. 2020;21(8):2696; DOI:10.3390/ijms21082696.
33. Bang ML, Mudry RE, McElhinny AS, Trombitás K, Geach AJ, Yamasaki R, Sorimachi H, Granzier H, Gregorio CC, Labeit S Myopalladin, a novel 145-kilodalton sarcomeric protein with multiple roles in Z-disc and I-band protein assemblies. J Cell Biol. 2001;153(2):413-28; DOI:10.1083/jcb.153.2.413.
34. Ibrahim M, Siedlecka U, Buyandelger B, Harada M, Rao C, Moshkov A, Bhargava A, Schneider M, Yacoub MH, Gorelik J, Knöll R, Terracciano CM. A critical role for Telethonin in regulating t-tubule structure and function in the mammalian heart. Hum Mol Genet. 2013;22(2):372-83, DOI:10.1093/hmg/dds434.
35. Li Z, Ai T, Samani K, Xi Y, Tzeng HP, Xie M, Wu S, Ge S, Taylor MD, Dong JW, Cheng J, Ackerman MJ, Kimura A, Sinagra G, Brunelli L, Faulkner G, Vatta M. A ZASP missense mutation, S196L, leads to cytoskeletal and electrical abnormalities in a mouse model of cardiomyopathy. Circ Arrhythm Electrophysiol. 2010;3(6):646-56; DOI:10.1161/CIRCEP.109.929240.
36. Marcus FI, Edson S, Towbin JA. Genetics of arrhythmogenic right ventricular cardiomyopathy: a practical guide for physicians. J Am Coll Cardiol. 2013;61(19):1945-8; DOI:10.1016/j.jacc.2013.01.073
37. Jacoby D, McKenna WJ. Genetics of inherited cardiomyopathy. Eur Heart J. 2012;33(3):296-304; DOI:10.1093/eurheartj/ehr260.
38. Kim KH, Pereira NL. Genetics of cardiomyopathy: clinical and mechanistic implications for heart failure. Korean Circ J. 2021;51(10):797; DOI:10.4070/kcj.2021.0154.
39. Krahn AD, Wilde AAM, Calkins H, La Gerche A, Cadrin-Tourigny J, Roberts JD, Han HC. Arrhythmogenic right ventricular cardiomyopathy. JACC Clin Electrophysiol. 2022;8(4):533-53; DOI:10.1016/j.jacep.2021.12.002.
40. Ohno S. The genetic background of arrhythmogenic right ventricular cardiomyopathy. J Arrhythm. 2016;32(5):398-403; DOI:10.1016/j.joa.2016.01.006.
41. Campuzano O, Alcalde M, Allegue C, Iglesias A, García-Pavía P, Partemi S, Oliva A, Pascali VL, Berne P, Sarquella-Brugada G, Brugada J, Brugada P, Brugada R. Genetics of arrhythmogenic right ventricular cardiomyopathy. J Med Genet. 2013;50(5):280-9; DOI:10.1136/jmedgenet-2013-101523.
42. Bradford WH, Zhang J, Gutierrez-Lara EJ, Liang Y, Do A, Wang TM, Nguyen L, Mataraarachchi N, Wang J, Gu Y, McCulloch A, Peterson KL, Sheikh F. Plakophilin 2 gene therapy prevents and rescues arrhythmogenic right ventricular cardiomyopathy in a mouse model harboring patient genetics. Nat Cardiovasc Res. 2023;2(12):1246-61; DOI:10.1038/s44161-023-00370-3.
43. Lee JYW, McGrath JA. Mutations in genes encoding desmosomal proteins: spectrum of cutaneous and extracutaneous abnormalities. Br J Dermatol. 2021;184(4):596-605; DOI:10.1111/bjd.19342.
44. Schlipp A, Schinner C, Spindler V, Vielmuth F, Gehmlich K, Syrris P, Mckenna JW, Dendorfer A, Hartlieb E, Waschke J. Desmoglein-2 interaction is crucial for cardiomyocyte cohesion and function. Cardiovasc Res. 2014;104(2):245-57; DOI:10.1093/cvr/cvu206.
45. Antoniades L, Tsatsopoulou A, Anastasakis A, Syrris P, Asimaki A, Panagiotakos D, Zambartas C, Stefanadis C, Mckenna WJ, Protonotarios N. Arrhythmogenic right ventricular cardiomyopathy caused by deletions in plakophilin-2 and plakoglobin (Naxos disease) in families from Greece and Cyprus: genotype–phenotype relations, diagnostic features and prognosis. Eur Heart J. 2006;27(18):2208-16; DOI:10.1093/eurheartj/ehl184.
46. Smith ED, Lakdawala NK, Papoutsidakis N, Aubert G, Mazzanti A, McCanta AC, Agarwal PP, Arscott P, Dellefave-Castillo LM, Vorovich EE, Nutakki K, Wilsbacher LD, Priori SG, Jacoby DL, McNally EM, Helms AS. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. Circulation. 2020;141(23):1872-84; DOI:10.1161/CIRCULATIONAHA.119.044934.
47. Yang Z, Bowles NE, Scherer SE, Taylor MD, Kearney DL, Ge S, Nadvoretskiy VV, DeFreitas G, Carabello B, Brandon LI, Godsel LM, Green KJ, Saffitz JE, Li H, Danieli GA, Calkins H, Marcus F, Towbin JA. Desmosomal dysfunction due to mutations in desmoplakin causes arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Res. 2006;99(6):646-55; DOI:10.1161/01.RES.0000241482.19382.c6.
48. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. Lancet. 2015;386(9995):813-25; DOI:10.1016/S0140-6736(14)61282-4.
49. Lorca R, Martín M, Pascual I, Astudillo A, Molina BD, Cigarrán H, Cuesta-Llavona E, Avanzas P, Reguero JJR, Coto E, Morís C, Gómez J. Characterization of left ventricular non-compaction cardiomyopathy. J. Clin. Med. 2020;9(8):2524; DOI:10.3390/jcm9082524.
50. Dong X, Fan P, Tian T, Yang Y, Xiao Y, Yang K, Liu Y, Zhou Y. Recent advancements in the molecular genetics of left ventricular noncompaction cardiomyopathy. Clinica Chimica Acta. 2017;465:40-4; DOI:10.1016/j.cca.2016.12.013.
51. Banankhah P, Fishbein GA, Dota A, Ardehali R. Cardiac manifestations of PRKAG2 mutation. BMC Med Genet. 2018;19(1):1-4, DOI:10.1186/s12881-017-0512-6.

52. Sternick EB. PRKAG2 cardiomyopathy. Arq Bras Cardiol. 2022;119(5):689-90; DOI:10.36660/ABC.20220694.
53. Gong X, Yu P, Wu T, He Y, Zhou K, Hua Y, Lin S, Wang T, Huang H, Li Y. Controversial molecular functions of CBS versus non-CBS domain variants of PRKAG2 in arrhythmia and cardiomyopathy: A case report and literature review. Mol Genet Genomic Med. 2022;10(7):e1962; DOI:10.1002/MGG3.1962.
54. Gollob MH. Modulating phenotypic expression of the PRKAG2 cardiac syndrome. Circulation. 2008;117(2):134-5; DOI:10.1161/CIRCULATIONAHA.107.747345.
55. Wolf CM, Arad M, Ahmad F, Sanbe A, Bernstein SA, Toka O, Konno T, Morley G, Robbins J, Seidman J, Seidman C, Berul C. Reversibility of PRKAG2 glycogen-storage cardiomyopathy and electrophysiological manifestations. Circulation. 2008;117(2):144-54; DOI:10.1161/CIRCULATIONAHA.107.726752.
56. Lopez-Sainz A, Dominguez F, Lopes LR, Ochoa JP, Barriales-Villa R, Climent V, Linschoten M, Tiron C, Chiriatti C, Marques N, Rasmussen TB, Espinosa MA, Beinart R, Quarta G, Cesar S, Field E, Garcia-Pinilla JM, Bilinska Z, Muir AR, Roberts AM, Santas E, Zorio E, Peña-Peña ML, Navarro M, Fernandez A, Palomino-Doza J, Azevedo O, Lorenzini M, García-Álvarez MI, Bento D, Jensen MK, Méndez I, Pezzoli L, Sarquella-Brugada G, Campuzano O, Gonzalez-Lopez E, Mogensen J, Kaski JP, Arad M, Brugada R, Asselbergs FW, Monserrat L, Olivotto I, Elliott PM, Garcia-Pavia P, Barriales R, Larrañaga-Moreira JM, Alonso-García D, Cárdenas-Reyes IJ, Cicerchia M, García-Ferro G, García-Hernández S, Nöel-Bröger M, Ortiz M, Azevedo P, Bispo J, Mota T, Fernandes R, Costa H, Doza JP, Salguero-Bodes R, Valverde-Gomez M, Espinosa MA, Mendez I, Cobo-Marcos M, Domínguez F, Escobar L, González-López E, López-Sainz Á, Segovia-Cubero J, Vilches S, Garcia-Pinilla JM, Robles-Mezcua A, López-Garrido M, Hidalgo LM, Abad VD, Sabater-Molina M, Gimeno-Blanes JR, Barton PJ, Cook SA, Ware JS, Syrris P, Truszkowska G, Michalak E, Ploski R, Bilinska Z, Asselbergs F, Baas AF, Dooijes D. Clinical features and natural history of PRKAG2 variant cardiac glycogenosis. J Am Coll Cardiol. 2020;76(2):186-97; DOI:10.1016/J.JACC.2020.05.029.
57. Cheng Z, Fang Q. Danon disease: focusing on heart. J Hum Genet. 2012;57(7):407-10; DOI:10.1038/jhg.2012.72.
58. Endo Y, Furuta A, Nishino I. Danon disease: a phenotypic expression of LAMP-2 deficiency. Acta Neuropathol. 2015;129(3):39188; DOI:10.1007/s00401-015-1385-4.
59. Cenacchi G, Papa V, Pegoraro V, Marozzo R, Fanin M, Angelini C. Review: Danon disease: review of natural history and recent advances. Neuropathol Appl Neurobiol. 2020;46(4):303-22; DOI:10.1111/nan.12587.
60. Arad M. Cardiac Danon disease: insights and challenges. Int J Cardiol. 2017;245:211-2; DOI:10.1016/j.ijcard.2017.07.106.
61. Rowland TJ, Sweet ME, Mestroni L, Taylor MRG. Danon disease – dysregulation of autophagy in a multisystem disorder with cardiomyopathy. J Cell Sci. 2016;129(11):2135-43; DOI:10.1242/jcs.184770.
62. Brambatti M, Caspi O, Maolo A, Koshi E, Greenberg B, Taylor MRG, Adler E. Danon disease: gender differences in presentation and outcomes. Int J Cardiol. 2019;286:92-8; DOI:10.1016/J.IJCARD.2019.01.020.
63. El-Hattab AW, Scaglia F. Mitochondrial cardiomyopathies. Front Cardiovasc Med. 3:(25); DOI:10.3389/fcvm.2016.00025.
64. Meyers DE, Haseeb F, Basha I, Koenig MK. Mitochondrial cardiomyopathy. Tex Heart Inst J. 2013;40(4):385-94.
65. Abriel H, Zaklyazminskaya E V. Cardiac channelopathies: genetic and molecular mechanisms. Gene. 2013;517(1):1-11; DOI:10.1016/J.GENE.2012.12.061.
66. Fernández-Falgueras A, Sarquella-Brugada G, Brugada J, Brugada R, Campuzano O. Cardiac channelopathies and sudden death: recent clinical and genetic advances. Biology. 2017;6(1):7; DOI:10.3390/BIOLOGY6010007.
67. Skinner JR, Winbo A, Abrams D, Vohra J, Wilde AA. Channelopathies that lead to sudden cardiac death: clinical and genetic aspects. Heart Lung Circ. 2019;28(1):22-30; DOI:10.1016/J.HLC.2018.09.007.
68. Dotzler SM, Kim CSJ, Gendron WAC, Zhou W, Dan Ye, Bos JM, Tester DJ, Barry MA, Ackerman MJ. Suppression-replacement KCNQ1 gene therapy for type 1 long QT syndrome. Circulation. 2021;143(14):1411-25; DOI:10.1161/CIRCULATIONAHA.120.051836.
69. Jespersen T, Grunnet M, Olesen SP. The KCNQ1 potassium channel: from gene to physiological function. Physiology. 2005;20(6):408-16; DOI:10.1152/physiol.00031.2005.
70. Kekenes-Huskey PM, Burgess DE, Sun B, Bartos DC, Rozmus ER, Anderson CL, January CT, Eckhardt LL, Delisle BP. Mutation-specific differences in Kv7.1 (KCNQ1) and Kv11.1 (KCNH2) channel dysfunction and long QT syndrome phenotypes. Intern J of Molec Scien 2022;23(13):7389; DOI:10.3390/ijms23137389.
71. Fowler ED, Zissimopoulos S. Molecular, subcellular, and arrhythmogenic mechanisms in genetic RyR2 disease. Biomolecules. 2022;12(8):1030; DOI:10.3390/biom12081030.
72. McNair WP, Ku L, Taylor MR, Fain PR, Dao D, Wolfel E, Mestroni L, Familial Cardiomyopathy Registry Research Group. SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. Circulation. 2004;110(15):2163-7; DOI:10.1161/01.CIR.0000144458.58660.BB.
73. Wilde AAM, Amin AS. Clinical spectrum of SCN5A mutations: long QT syndrome, Brugada syndrome, and cardiomyopathy. J Am Coll Cardiol EP. 2018;4(5):569-79; DOI:10.1016/j.jacep.2018.03.006.
74. Bienengraeber M, Olson TM, Selivanov VA, Kathmann EC, O'Cochlain F, Gao F, Karger AB, Ballew JD, Hodgson DM, Zingman LV, Pang YP, Alekseev AE, Terzic A. ABCC9 mutations identified in human dilated cardiomyopathy disrupt catalytic KATP channel gating. Nat Genet. 2004;36(4):382-7; DOI:10.1038/ng1329.