Diagnostics in Cardiology and Grown-Up Congenital Heart Disease: GUCH

Mesihović Dinarević, Senka

2021-09

Academy of Sciences and Arts of Bosnia and Herzegovina

https://bastina.anubih.ba/items/ed834d90-5840-46fc-871c-bf98e2b0fac4

DOI: 10.5644/PI2021.199.01

GENETICS OF CARDIOMYOPATHY

Amina Kurtovic-Kozaric[1, 2]

[1]Clinical Centre of the University of Sarajevo, Sarajevo, Bosnia and Herzegovina,
[2]International Burch University, Sarajevo, Bosnia and Herzegovina

amina.kozaric@kcus.ba

Submitted: 2021, accepted: 2021, published: 2021

Abstract

Heart failure is a leading cause of morbidity and mortality. Around 4% of patients with heart failure carry a pathogenic genetic aberration that causes cardiomyopathy and subsequently leads to heart failure. There are five types of primary genetic cardiomyopathies that can give rise to heart failure: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, arrhythmogenic cardiomyopathy (ACM), restrictive cardiomyopathy (RCM), and left ventricular noncompaction (LVNC). If genetic cardiomyopathy is suspected, genomic/genetic testing is recommended because it provides the underlying cause for the diagnosis, prognostic parameters, and possibility to test family members at risk. Testing should be conducted as part of a multidisciplinary approach by a team of adult or paediatric cardiologists, geneticists, and genetic counsellors. Here we will discuss 1) different genomic testing approaches and the management of variants of uncertain significance, 2) management of patients with suspected genetic cardiomyopathy in a multidisciplinary team, and 3) the associations between genotypes and phenotypes of most commonly mutated genes such as *MYH7, TNNT2, TPM1, MYBPC3*, *TTN*, and others. In conclusion, genetic testing of patients with cardiomyopathies helps with proper diagnosis, prognosis, treatment, and identification of relatives at risk.

Key words: genetics, cardiomyopathy, hypertrophic cardiomyopathy, next generation sequencing, genetic counseling

Introduction

Cardiomyopathy represents heterogeneous group of diseases of the heart muscle, where the heart walls have changed by being thickened, stretched, or stiff. Subsequently, the heart function is affected. In 2006, the American Heart Association's Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care

and Outcomes of Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention recommended that cardiomyopathies can be most effectively classified as primary and secondary. Primary cardiomyopathies are driven by heart-specific factors (the heart is the primary affected organ), while secondary cardiomyopathies are part of a systemic disorder (the heart is affected along with other organs). Primary cardiomyopathies are further classified into: genetic, mixed (genetic and non-genetic), and acquired [1] (Figure 1). In this review, we will focus on the genetic causes of primary cardiomyopathies.

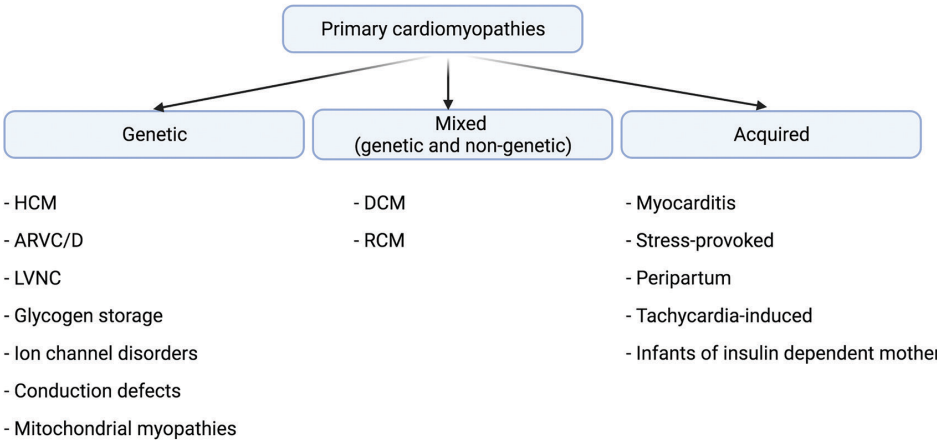

Figure 1. Primary cardiomyopathies are classified into genetic, mixed and acquired. Hypertrophic cardiomyopathy (HCM); arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D); left ventricular noncompaction - LVNC; dilated cardiomyopathy (DCM); restricted cardiomyopathy (RCM). Adapted from [1].

Primary genetic cardiomyopathies are: hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), and left ventricular non-compaction (LVNC), glycogen storage diseases, conduction defects, mitochondrial myopathies, and ion channel disorders (Brugada, LQTS, SQTS, CVPT, and Asian SUNDS) [1,2]. Mixed primary cardiomyopathies that have both genetic and non-genetic components include: dilated cardiomyopathy (DCM) and restrictive cardiomyopathy (RCM). Acquired primary cardiomyopathies can be: myocarditis, stress-provoked, peripartum, tachycardia-induced, infants of insulin-dependent diabetic mothers.

Secondary cardiomyopathies of genetic origin are for example Fabry disease (lysosomal storage disease caused by mutations in *GLA* gene), Noonan syndrome (*PTPN11*, *SOS1*, *RAF1*, *RIT1*, and *KRAS* genes), muscular dystrophy (DMD gene and others), Friedrich's ataxia (*FXN* gene), and hemochromatosis (*HFE* gene and others). Secondary cardiomyopathies of acquired causes are diabetes mellitus, hyperthyroidism, hypereosinophilic syndrome, sarcoidosis, etc.

As discussed above, primary cardiomyopathies can be caused by mutations in specific genes. Genes are long segments of DNA, which is situated within the nucleus of each cell in the body. DNA is a double helix consisting of two antiparallel chains made up of four building blocks: adenine, guanine, cytosine and thymine (Figure 2).

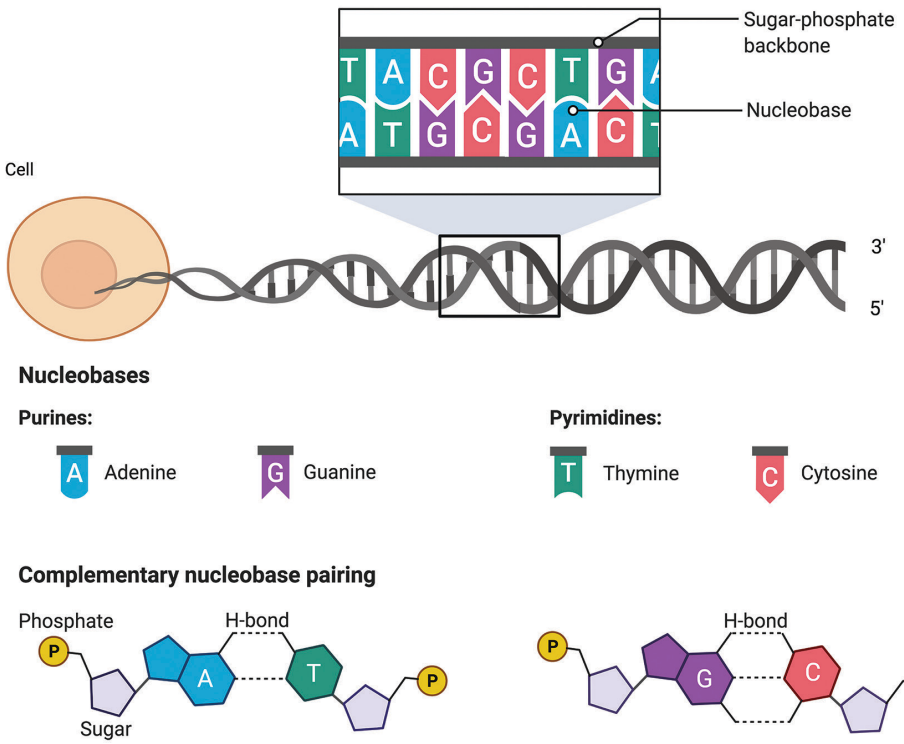

Figure 2. DNA is found in the nucleus of the cell. Building blocks of DNA are four bases: adenine, guanine, thymine, and cytosine, which are connected with a sugar phosphate backbone into a single molecular or chain. DNA has two antiparallel chains in the form of a double helix. Within the DNA helix, adenine pairs with thymine and cytosine pairs with guanine.

The DNA sequence in a gene is used to direct the correct sequence of proteins (the central dogma of biology: DNA-RNA-protein). Genes code for proteins that carry out various functions within the body including building organs or metabolizing various substances. Mistakes in the coded instructions (DNA) are called mutations, which can affect the proper structure and function of proteins (Figure 3). For example, DNA mutations in genes that code for proteins important for the function of heart cells can lead to cardiomyopathies.

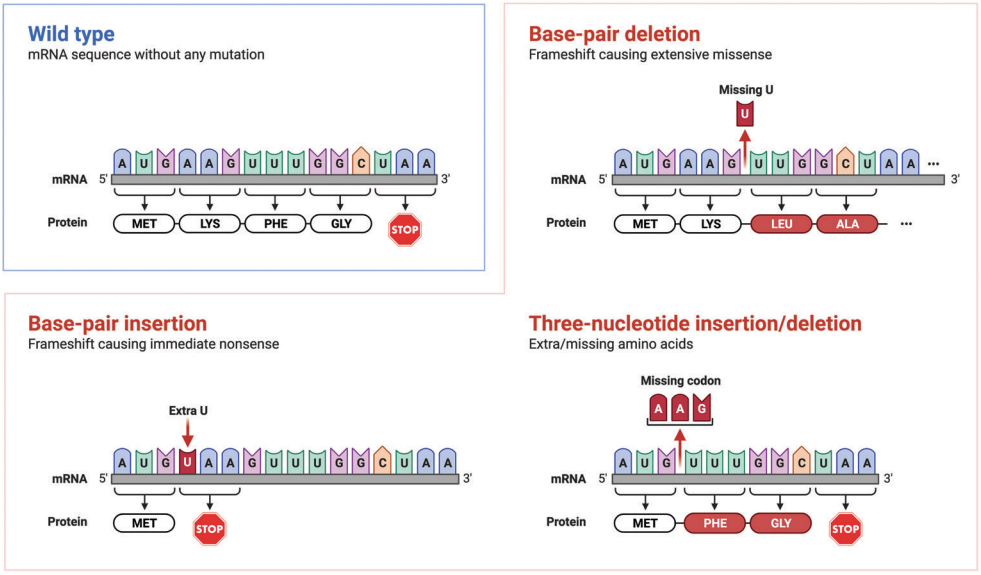

Figure 3. Mutations in DNA (or its copy in the form of RNA) can be single base pair mutations (not shown), duplications, deletions, insertions, or inversions (not shown). Mutation can have different effects on protein function: from no effect to deleterious effect, thus from benign to pathogenic effect.

Defining genomic terms and patterns of inheritance

The era of genomic medicine has impacted the field of cardiology as well, especially understanding the causes of cardiomyopathies. Mutations can be single point mutations, deletions, duplications, inversions, and insertions. Mutations in genes have five designations, depending on the effect on phenotype: pathogenic, likely pathogenic, variant of unknown significance, likely benign, and benign.

If an individual is a carrier of a germline mutation in genes associated with cardiomyopathy, they have a risk of passing the mutation to their offspring. Germline mutations can be inherited in autosomal dominant, autosomal recessive or X-linked manner. For autosomal dominant disorders, the patient has a DNA mutation in one copy of the gene, while the other copy is normal (wild type). Therefore, the offspring of that patient has a 50% chance to inherit the mutation. Autosomal dominant inheritance is defined as a disease where one copy of a mutation is sufficient to cause the disease. In a family with an autosomal dominant condition, offspring have a 50% chance of having the disease. In autosomal recessive disorders, both parents are carriers of a mutation, but they do not have the disease (carrier status, no disease). If their child inherits both copies of the mutated gene, the child will have the disease. If a child has a mutation in one copy of the gene, he is the carrier but does not manifest the disease. Children with autosomal recessive diseases have mutations in both copies of a specific gene, which they have inherited from both of their parents. A child with an autosomal recessive cardiomyopathy inherits a defective gene from each of his carrier parents. If both parents are carriers (have the mutation in one copy of the gene), the risk that other children (or future children) will have the cardiomyopathy is one in four, or 25%. Usually, the only individuals in the extended family at risk are brothers and sisters of the child with the cardiomyopathy.

Hypertrophic cardiomyopathy

HCM is a primary cardiomyopathy of genetic origin with heterogeneous clinical presentation [3]. It is a common disease, with prevalence of 1:500 to 1:200. It is an autosomal dominant disease, meaning that it is transmitted to 50% of patient's children and that it was inherited from one of patient's parents. HCM is also the most common cause of sudden cardiac death in younger people including athletes. Morphologically, the heart is hypertrophic with nondilated LV. There is no other underlying disease that could cause the hypertrophy such as hypertension or aortic valve stenosis. The first diagnosis is typically made by echocardiography or MRI; also, ECG alterations may be detected before hypertrophy. Any LV wall thickness, even when it is within normal limits, can be enough to refer the patient for DNA analysis.

HCM is caused by mutations in 11 genes that primarily encode proteins with function in heart cells, specifically contractile proteins in sarcomere. HCM was first associated with mutations in gene *MYH7* in 1989 [4-7]. About

70% of HCM patients have mutations in *MYH7* (β-myosin heavy chain) and *MYBPC3* (myosin-binding protein C). Other HCM genes include: *ACTC1*, *MYL2, MYL3, TNNT2, TNNI3, TPM1, CSRP3, JPH2,* and *TNNC1* (Table 1). There are no hot spot mutations and they are dispersed throughout the mentioned genes. So far, there are more than 1500 mutations identified.

Table 1. Genes involved in hypertrophic cardiomyopathy.

Gene Symbol	Encoded protein	Cellular Location
MYBPC3	Cardiac myosin binding protein C	Sarcomere, thick filament
MYH7	β-myosin heavy chain	Sarcomere, thick filament
MYL2	Regulatory myosin light chain	Sarcomere, thick filament
MYL3	Essential myosin light chain	Sarcomere, thick filament
TNNI3	Cardiac troponin I	Sarcomere, thin filament
TNNT2	Cardiac troponin T	Sarcomere, thin filament
TPM1	α-tropomyosin	Sarcomere, thin filament
ACTC1	Cardiac α-actin	Sarcomere, thin filament
CSRP3	Cardiac LIM protein	Sarcomere, Z line
JPH2	Junctophilin 2	Sarcomere, reticulum membrane
TNNC1	Troponin C1	Actin filament

The genetic cause for a majority of HCM is well established. However, the biochemical and functional mechanisms of how mutations affect sarcomere function disease remain less understood. Physiological mechanisms were better understood when HCM mutations were introduced into mice; for example, mutations in the myosin head region show enhancement of contraction, but inability for relaxation (myosin head region is the domain that generates force, hydrolyses ATP, and interacts with other sarcommeric proteins).

Genotype-phenotype relationship, or how specific mutation affects the clinical presentation and severity of disease, is not straightforward in HCM. Large families with specific HCM mutations have provided an insight into how genotype can affect phenotype. For example, it is known that poor clinical outcome is associated with several *MYH7* mutations: Arg403Gln, Arg719Trp, and Arg453Cys. Arg403Gln is associated with increased risk for sudden cardiac death, while Arg719Trp and Arg453Cys are associated with heart failure [8-10]. However, other mutations in *MYH7* have milder phenotype. Mutations in *MYBPC3* are associated with later onset and milder phenotype.

HCM can be found in other diseases such as Fabry (*GLA* gene), amyloidosis (*TTR* gene), Noonan syndrome (*PTPN11*, *SOS1*, *RAF1*, *RIT1*, and *KRAS* genes), glycogen storage disease (*PRKAG2*), Danon (*LAMP2*), and others. These diseases can have clinical presentation only in the heart and can mimic HCM. Thus, these genes should be considered for testing in appropriate clinical presentation. *PRKAG2* gene encodes the gamma-2-regulatory subunit of the AMP-activated protein kinase (*PRKAG2*) and is associated with variable degrees of LV hypertrophy and ventricular pre-excitation [11]. *LAMP2* is lysosome associated membrane protein 2 resulting in Danon-type storage disease [1]. Clinical manifestations are confined to the heart abnormalities, presenting with massive degrees of LV hypertrophy and ventricular pre-excitation. These disorders are now part of a subgroup of previously described infiltrative forms of LV hypertrophy such as Pompe disease and Fabry's disease, an X-linked recessive disorder of glycosphingolipid metabolism caused by a deficiency of alpha-galactosidase A [8]. Several other diseases associated with LV hypertrophy involve prominent thickening of the LV wall, occurring in infants and children less than 4 years of age, may resemble HCM caused by sarcomere mutations. These cardiomyopathies include Noonan syndrome, an autosomal dominant cardiofacial condition associated with a variety of cardiac defects.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)

ARVC/D is a rare form of heart disease (1:5000) that was first described about 20 years ago. It is regarded as a common cause of sudden death in athletes, diagnosed typically in third to fifth decade of life. It involves primarily the right ventricle with progressive loss of myocytes that are replaced by fibrofatty tissues. Clinical presentation usually involves ventricular tachyarrhythmias. ARCV/D can be transmitted in autosomal dominant or recessive manner, depending on the involved gene. In most cases, it is autosomal dominant inheritance but with incomplete penetrance. Four genes are primarily associated with ARCV/D: *RYR2, DSP, PKP2*, and *TGFB3*. Other genes associated with ARVC/D are: *ANK2, CTNNA3, DES, DSC2, DSG2, JUP, LMNA, SCN5A, TMEM43*, and *TTN* (Table 2). Plakophilin-2, *PKP2*, (ARVC9) gene mutations can be found in more than one third of ARVC patients [12, 13].

Table 2. Genes involved in Arrhythmogenic right ventricular cardiomyopathy/dysplasia.

Gene	Encoded Protein	Localization
RYR2	Ryanodine receptor 2	Sarcoplasmic reticulum
DSP	Desmoplakin	Carvajal syndrome
PKP2	Plakophilin 2	Nucleus, desmosome
TGFB3	Transforming Growth Factor Beta 3	extracellular matrix

JUP (Naxos syndrome), *DSP* (Carvajal syndrome), and *DSC* are inherited in autosomal recessive manner, and cause pulmoplanar keratoderma and woolly hair. Desmoplakin, *DSP* gene, was first identified and associated with ARVD (ARVD8) which causes Carvajal syndrome. The protein product of *DSP* gene is the key component of desmosomes and adherens junctions which are important for maintaining the tight adhesion. Once the junctions are disrupted, cell death and fibrofatty replacement take place [14]. Similarly to Carvajal syndrome, ARVD/C can also be associated with Naxos syndrome, an autosomal recessive disorder caused by mutations in the plakoglobin protein (*JUP* gene) with similar phenotypic presentation to Carvajal syndrome [15,16]. Like desmoplakin, plakoglobin is a key component of desmosomes and participates in maintaining tight cell-cell adhesion.

Left ventricular Noncompaction - LVNC

Left ventricular noncompaction is a recently discovered congenital cardiomyopathy with a characteristic morphological appearance of LV. It has prevalence of 0.05% to 0.3%. It often coexists with other cardiomyopathies. Three genes associated with LVNC are: *TAZ*, *MIB1*, and *MYH7*. Besides them, other genes are also associated with LVNC: *ACTC1, LDB3, LMNA, MYBPC3, TNNT2,* and *TPM1* (Table 3). TAZ (also known as *TAFAZZIN* or G4.5) is a gene that encodes a mitochondrial transacylase that catalyses remodelling of immature cardiolipin to its mature composition containing a predominance of tetralinoleoyl moieties. It is an X-linked condition and causes Barth syndrome.

Table 3. Genes involved in Left ventricular Noncompaction – LVNC

Gene	Encoded Protein	Associated findings or syndromes*
TAZ	Tafazzin	DCM, Barth syndrome
MIB1	Mindbomb homolog 1	None
MYH7	Myosin heavy chain	None

Metabolic disorders associated with primary cardiomyopathy

Glycogen storage diseases (GSD) are metabolic disorders caused by enzyme deficiencies affecting glycogen synthesis, glycogen breakdown, or glycolysis. There are at least 15 types of GSD, where two types are associated with primary HCM, namely Pompe disease caused by *GAA* mutations and *PRKAG2* syndrome (Table 4). *Pompe disease* (three forms: infantile, juvenile and adult-onset) is an autosomal recessive disorder that results from the deficiency in the enzyme acid alpha-glucosidase (GAA), causing the abnormal glycogen accumulation in all tissues [17]. *PRKAG2 syndrome* is a rare, early-onset autosomal dominant inherited disease, characterized by ventricular pre-excitation, supraventricular arrhythmias and cardiac hypertrophy. *PRKAG2* mutations are characterized by glycogen accumulation in the cardiac tissue.

Table 4. Genes involved in Metabolic disorders associated with primary cardiomyopathy

Gene	Encoded Protein	Disease	Inheritance
GLA	α-galactosidase A	Fabry disease	*X*-linked
LAMP2	Lysosome-associated membrane protein 2	Danon disease	*X*-linked
PRKAG2	AMP-activated protein kinase, g2 subunit (noncatalytic)	PRKAG2 cardiomyopathy	Autosomal dominant
GAA	α-glucosidase	Pompe disease	Autosomal recessive

Lysosomal storage disease associated with primary cardiomyopathy is *Danon syndrome* caused by lysosome associated membrane protein 2 (LAMP2) [18]. Clinical manifestations are confined to the heart abnormalities, presenting with massive degrees of LV hypertrophy and ventricular pre-excitation, as well as neurocognitive deficits and hepatic dysfunction with very poor prognosis and early triage to heart transplantation. It is an autosomal dominant disease.

GLA mutations cause Fabry disease with left ventricular hypertrophy as well as renal, eye, and skin manifestations [18]. Recognition of Fabry cardiomyopathy has critical therapeutic implications, because early treatment such as enzyme replacement therapy can be beneficial because it limits myocardial remodelling and maintains cardiac function [19-21].

Ion channelopathies

In the last several years, there has been a growing understanding of the rare congenital arrhythmia disorders that include LQTS (long QT syndrome),

SQTS (short-QT syndrome) Brugada syndrome, CPVT (catecholaminergic polymorphic ventricular tachycardia) and idiopathic ventricular fibrillation, that are all caused by mutations in ion channel genes responsible for defective functioning of sodium and potassium channels [1].

The most common ion channelopathy is LQTS, which can be inherited in autosomal recessive and autosomal dominant manner. Autosomal recessive forms are associated with deafness and are caused by mutations in *KCNQ1* gene (Jervell syndrome) and *KCNE1* gene (Lange-Nielsen syndrome). Autosomal dominant LQTS is caused by mutations in 8 genes: *SCN5A* (Na1.5, LQT3), *KCNQ1* (KvLQT1, LQT1), *ANKB* (LQT4), *KCNE1* (minK, LQT5), *KCNE2* (MiRP1, LQT6), *KCNH2* (HERG, LQT2) *KCNJ2* (Kir2.1, LQT7, Andersen's syndrome), and *CACNA1C* (Ca1.2, LQT8, Timothy syndrome) (Table 5).

Table 5. Genes involved in Brugada syndrome.

Gene name	Function
SCN5A	NaV1.5 – α subunit of the cardiac sodium channel carrying the sodium current
GPD1L	Glycerol-3-phosphate dehydrogenase like peptide
CACNA1C	CaV1.2 – α subunit of voltage-dependent calcium channel
CACNB2	CaVβ2B – β-2 subunit of the voltage-gated calcium channel
SCN1B	NaVβ1 – β-1 subunit of the sodium channel
KCNE3	MiRP2 – β subunit to voltage-gated potassium channels
SCN3B	NaVβ3 – β-3 subunit of the cardiac sodium channel
HCN4	Hyperpolarization Activated Cyclic Nucleotide Gated Potassium Channel 4
KCND3	KV4.3, α-subunit of the transient outward potassium channel
CACNA2D1	α2δ subunit of the voltage-gated calcium channel
RANGRF	MOG1
ABCC9	SUR2A, the adenosine triphosphate (ATP)-binding cassette transporter of the IK(ATP) channel
SCN2B	NaVβ2 – Beta-2 subunit of the cardiac sodium channel
SCN10A	NaV1.8 – α subunit of the neuronal sodium channel

Brugada syndrome was first described in 1992 and is characterized by distinct ECG pattern and increased risk of sudden cardiac death, especially SUDS [22-24]. It is an autosomal dominant disease, where the most common mutation is in *SCN5A* gene (20% of patients with Brugada syndrome, also called Brugada syndrome type 1). OMIM recognizes 9 types of Brugada syndrome. Type 2 is caused by mutation in *GPD1L*, type 3 by mutations in

CACNA1C, type 4 by mutations in CACNB2, type 5 *SCN1B*, type 6 by mutations in *KCNE3*, type 7 by mutations in *SCN3B* gene, type 8 by mutation in the *HCN4*, and type 9 by mutations in *KCND3*.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a primary cardiomyopathy of mixed origin, with both genetic and non-genetic (acquired) causes [25]. About 35% of DCM is genetic. Non-genetic causes include infectious, autoimmune, toxic, peripartum, drug-induced, and others. In DCM, wall thickness is normal, while left ventricular mass is increased due to enlarged myocytes, myocardial fibrosis that promotes arrhythmias and heart failure. Prevalence is about 1:250. Patients with DCM are the most frequent candidates for heart transplant [26]. DCM may be more difficult to diagnose genetically because clinical presentation may overlap with other cardiovascular diseases and some patients develop it late in life. Also, some gene panels are quite limiting, and may lead to missed DCM diagnoses.

More than 50 genes are involved in pathology of DCM with function in cytoskeleton, sarcomere, sarcolemma, etc. Most genes are involved in autosomal dominant inheritance. Mutations affecting sarcomere, such as *MYH7, TNNT2, TPM1, MYBPC3* and *TTN* are commonly mutated in DCM, where *TTN* accounts for up to 25% of all DCM mutations.

Table 6. Genes involved in dilated cardiomyopathy.

Gene	Protein	Percent mutated in DCM	Localization and coexistent phenotypes
TTN	Titin	15%-25%	None
MYH7	β-myosin heavy chain	10%	None
MYH6	α-myosin heavy chain	6%	Sarcomere
MYPN	Myopalladin	3%-4%	Sarcomere, Z disc
DSP	Desmoplakin	3%-4%	Desmosome
ACTC1	Cardiac α-actin	<1%	None
TNNT2	Cardiac troponin T	3%	None
TPM1	α-tropomyosin	<1%	None
TNNI3	Cardiac troponin I	<1%	None
BAG3	Bcl2-associated athanogene 3	<1%	None
DES	Desmin	<1%	Skeletal myopathy, conduction system disease

Gene	Protein	Percent mutated in DCM	Localization and coexistent phenotypes
DMD	Dystrophin	<1%	Duchenne's muscular dystrophy, Becker's muscular dystrophy
DNAJC19	DNAJ (Hsp40) homolog	<1%	DCMA
EMD	Emerin	<1%	Emery-Dreifuss muscular dystrophy type 1
LMNA	Lamin A/C	6%	Conduction system disease, Emery-Dreifuss muscular dystrophy type 2
PLN	Phospholamban	<1%	None
RBM20	RNA-binding protein, 20	5%	None
SCN5A	Voltage gated sodium channel type V, α-subunit	3%	Supraventricular and ventricular arrhythmias
TAZ	Tafazzin	<1%	Barth syndrome

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is the rarest form of primary cardiomyopathy, accounting for ~5% of primary cardiomyopathies [26]. It can be caused by genetic or non-genetic causes. Genes involved include troponin T (*TNNT2*), troponin I (*TNNI2*), α-actin (*ACTC1*), β-myosin heavy chain (*MYH7*), and filamin C (*FLNC*).

Patient management

Genetic testing and counselling are highly recommended for patients with suspected primary cardiomyopathy. Genetic counselling should be coordinated with a multidisciplinary team of cardiologists, genetic counsellors, and laboratory geneticists. The choice of a proper genetic test is important and should be discussed with the genetic counsellor and laboratory geneticist. There are 3 major test types: gene panel, WES (whole exome sequencing), and WGS (whole genome sequencing). Gene panels are tests that include sequencing of exons of many genes (up to ~100, depending on the company). Gene panels can be specific for a particular type of primary cardiomyopathy, such as HCM, DCM, etc. WES is a test that includes all genes, ~25000. WES is more expensive but gives more information and can be used to find mutations in rare genes, increasing the sensitivity of the test. On the contrary, besides cardiomyopathy-related findings, patient should be counselled that other genes might be picked up that carry mutations unrelated to the original indication.

Variants of unknown significance (VUS) may also be found, which can add additional complexity to the treatment algorithm. WGS is a comprehensive and expensive method to test all DNA, including genes, and other types of DNA including mitochondrial DNA, this being able to pick up rare intronic variants in cardiomyopathy-related genes. Often, WES and WGS are used for research purposes only and not in standard diagnostic setting; however, depending on the cost and insurance, clinicians may be more likely to order WES. ACC/AHA recommends using gene panel testing for HCM [3].

Regarding the interpretation of variants, ACMG (American College of Medical Genetics and Genomics) should be consulted, as well as ClinVar. If a patient carries a VUS, they should be re-evaluated every couple of years and ClinVar checked to see if the classification status has changed.

Testing of the proband, as it is the case in other genetic diseases, involves the family too. If the patient is a carrier of a pathogenic variant, their at-risk relatives should be informed as well.

Genotype-phenotype correlations are still largely unknown and may not be a part of routine genetic counselling session for primary cardiomyopathies. It is important to note that in primary cardiomyopathies, the same gene mutation (genotype) can have different phenotypes (DCM, HCM, RCM and ACM). For example, *MYH7* mutations can cause HCM, DCM, RCM or LVNC. Gene identification can also help with finding possible 'mimics' such as Fabry disease, glycogen storage disease, or others. Also, it can help with early start of proper therapy. Gene mutations can also identify patients with early onset of left ventricular arrhythmias. For example, *LMNA* mutation carriers have a higher risk of conduction disease, atrial and ventricular arrhythmias. DCM-associated genes *PLN, FLNC, TMEM43*, and DES have higher risk of ventricular arrhythmias, as well as *TTN* [27].

Similar to adults, families with a child diagnosed with cardiomyopathy are at an increased risk for another at-risk child or family member. When a pathogenic variant is diagnosed within the family, all of the family members (brothers, sisters, and parents) should be screened with an echocardiogram. Depending on the type of cardiomyopathy diagnosed, it may be necessary to repeat the echocardiogram periodically for younger children (childhood to mid-adult life). In infants, cardiomyopathies can be caused by inborn errors of metabolism that are inherited in an autosomal recessive fashion as discussed previously. Duchenne or Becker muscular dystrophy or Barth syndrome are

examples of X-linked inherited diseases that are found in males only, while females are carriers.

Primary cardiomyopathies are generally caused by genetic mutations leading to the development of HCM, DCM, RCM, LVNC and ARVC. Genetic testing is important for proper diagnosis, treatment as well as patient prognosis. Testing of at-risk relatives can identify those who will develop cardiomyopathy, helping to start early treatment.

References

1. Maron BJ, Towbin JA, Thiene G, Antzelevitch G, Corrado D, Arnett D, et al. Contemporary Definitions and Classification of the Cardiomyopathies. Circulation. 2006;113:1807–1816.
2. Seferović PM, Polovina M, Bauersachs J, Arad M, Gal TB, Lund LH, et al. Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019 May;21(5):553-576.
3. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliot P, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2020 Dec, 76 (25) e159–e240.
4. Jarcho JA, McKenna W, Pare JA, et al. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. N Engl J Med 1989; 321: 1372–1378.
5. Diederich, K. W., Eisele, I., Ried, T., Jaenicke, T., Lichter, P., Vosberg, H.-P. Isolation and characterization of the complete human beta-myosin heavy chain gene. Hum. Genet. 81: 214-220, 1989.
6. Yamauchi-Takihara, K., Sole, M. J., Liew, J., Ing, D., Liew, C. C. Characterization of human cardiac myosin heavy chain genes. Proc. Nat. Acad. Sci. 86: 3504-3508, 1989.
7. Geisterfer-Lowrance AA, Kass S, Tanigawa G, et al. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. Cell 1990;62:999–1006.
8. Anan R, Greve G, Thierfelder L, et al. Prognostic implications of novel beta cardiac myosin heavy chain gene mutations that cause familial hypertrophic cardiomyopathy. *J Clin Invest.* 1994;93:280–5.
9. Ko YL, Chen JJ, Tang TK, et al. Malignant familial hypertrophic cardiomyopathy in a family with a 453Arg–>Cys mutation in the beta-myosin heavy chain gene: coexistence of sudden death and end-stage heart failure. *Hum Genet.* 1996;97:585–90.
10. Tesson F, Richard P, Charron P, et al. Genotype-phenotype analysis in four families with mutations in β-myosin heavy chain gene responsible for familial hypertrophic cardiomyopathy. *Hum Mutat.* 1998;12:385–92.
11. Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. Bookshelf ID: NBK1768 PMID: 20301725.
12. Gerull B, Heuser A, Wichter T, et al. Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. Nat Genet 2004;36:1162–3.

13. van Tintelen JP, Entius MM, Bhuiyan ZA, et al. Plakophilin-2 mutations are the major determinant of familial arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation 2006; 113:1650–9.
14. Norgett EE, Hatsell SJ, Carvajal-Huerta L, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. Hum Mol Genet 2000; 9:2761–3.
15. Coonar AS, Protonotarios N, Tsatsopoulou A, et al. Gene for arrhythmogenic right ventricular cardiomyopathy with diffuse nonepidermolytic palmoplantar keratoderma and woolly hair (Naxos disease) maps to 17q21. Circulation 1998; 97:2049–51.
16. Rogaev EI, Rogaeva EA, Ginter EK, et al. Identification of the genetic locus for keratosis palmaris et plantaris on chromosome 17 near the RARA and keratin type I genes. Nat Genet 1993; 5:158–61.
17. Arad M, Maron BJ, Gorham JM et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. N Engl J Med 2005;352:362-72.
18. Nishino I, Fu J, Tanji K et al. Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). Nature 2000;406:906-10.
19. Eng CM, Guffon N, Wilcox WR, et al. International Collaborative Fabry Disease Study Group Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med.* 2001;345:9–16.
20. Banikazemi M, Bultas J, Waldek S, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med.* 2007;146:77–86.
21. Kampmann C, Perrin A, Beck M. Effectiveness of agalsidase alfa enzyme replacement in Fabry disease: cardiac outcomes after 10 years' treatment. *Orphanet J Rare Dis.* 2015;10:125.
22. Nademanee K, Veerakul G, Nimmannit S et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai me. Circulation 2007;96(8): 2595–2600.
23. Vatta M, Dumaine R, Varghese G et al. Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. Hum. Mol. Genet. 2002;11(3): 337–45.
24. Brugada J, Brugada P, Brugada R. The syndrome of right bundle branch block ST segment elevation in V1 to V3 and sudden death – the Brugada syndrome. 1999;1(3):156–66.
25. Burke MA, Cook SA, Seidman JG, Seidman CE. Clinical and Mechanistic Insights Into the Genetics of Cardiomyopathy. J Am Coll Cardiol. 2016;68(25):2871-2886.
26. Yogasundaram H, Alhumaid W, Dzwiniel T, Christian S, Oudit GY. Cardiomyopathies and Genetic Testing in Heart Failure: Role in Defining Phenotype-Targeted Approaches and Management. Can J Cardiol. 2021 Apr;37(4):547-559.
27. Gerull B, Gramlich M, Atherton J et al. Mutations of TTN, encoding the giant muscle filament titin, cause familial dilated cardiomyopathy. Nat Genet 2002;30:201-4.

GENETIKA KARDIOMIOPATIJE

Apstrakt

Zatajenje srca vodeći je uzrok morbiditeta i mortaliteta. Oko 4% pacijenata sa zatajenjem srca nosi patogenu genetsku aberaciju koja uzrokuje kardiomiopatiju, što posljedično dovodi do zatajenja srca. Postoji pet vrsta primarnih genetskih kardiomiopatija koje mogu uzrokovati zatajenje srca: hipertrofična kardiomiopatija (HCM), dilatativna kardiomiopatija, aritmogena kardiomiopatija (ACM), restriktivna kardiomiopatija (RCM) i nekompakcija lijeve komore (LVNC). Ako se sumnja na genetsku kardiomiopatiju, preporučuje se genomsko/genetsko testiranje, jer pruža temeljni uzrok za dijagnozu, prognostičke parametre i mogućnost testiranja rizičnih članova porodice. Testiranje bi trebalo biti provedeno kao dio multidisciplinarnog pristupa od strane tima kardiologa za odrasle ili za djecu, genetičara i genetskih savjetnika. U ovome radu ćemo raspravljati o: 1) različitim pristupima genomskom testiranju i upravljanju varijantama neizvjesnog značaja; 2) liječenju pacijenata sa sumnjom na genetsku kardiomiopatiju uz pomoć multidisciplinarnog tima; i 3) povezanosti između genotipova i fenotipova najčešće mutiranih gena poput *MYH7*, *TNNT2*, *TPM1*, *MYBPC3*, *TTN* i drugih. Zaključujemo da genetsko testiranje pacijenata s kardiomiopatijama pomaže u pravilnoj dijagnozi, prognozi, liječenju i identifikaciji ugrožene rodbine.

Ključne riječi: genetika, kardiomiopatija, hipertrofična kardiomiopatija, sekvenciranje sljedeće generacije, genetsko savjetovanje