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Review

Cardiomyopathies

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Summary. The most common cardiomyopathies often present to primary care physicians with similar symptoms, despite the fact that they involve a variety of phenotypes and etiologies (1). Many have signs and symptoms common in heart failure, such as reduced ejection fraction, peripheral edema, fatigue, orthopnea, exertion dyspnea, paroxysmal nocturnal dyspnea, presyncope, syncope and cardiac ischemia (1). In all cardiomyopathies, the cardiac muscle (myocardium) may be structurally and/or functionally impaired. They can be classified as hypertrophic, dilated, left-ventricular non compaction, restrictive and arrhythmogenic right ventricular cardiomyopathies. (www.actabiomedica.it)

Key words: Hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, left ventricular noncompaction, arrhythmogenic right ventricular cardiomyopathy

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (CMH) is characterized by an increase in the number of heart muscle cells. It is frequently caused by mutations in genes encoding sarcomeric proteins, leading to myocyte disarray, a hallmark of CMH (2).

Clinical symptoms range from asymptomatic left ventricular hypertrophy to progressive heart failure or sudden cardiac death, and vary from individual to individual even within the same family. Frequent symptoms include dyspnea, chest pain, palpitations, orthostasis, presyncope and syncope. Usually CMH becomes apparent during adolescence or early adulthood, although it may also develop in different stages of life such as old age, infancy or childhood (3).

Hypertrophic cardiomyopathy is a relatively common inherited heart disease with a prevalence of 1:500 in the population (4). Clinical diagnosis is based on patient history, physical examination, echocardiography and ECG to detect hypertrophy (2). The genetic test is useful for confirming diagnosis, and for differential diagnosis, recurrence risk evaluation and prenatal diagnosis in families with a known mutation. Differential diagnosis should consider acquired left ventricular hypertrophy, Danon disease, Fabry disease, cardiac amyloidosis, glycogen storage disease type II, Noonan syndrome and Friedreich ataxia (5).

The European Society of Cardiology recommends genetic testing in the following cases (6):

1 - patients meeting diagnostic criteria for CMH, when testing enables cascade genetic screening of their relatives;
2 - in first-degree adult relatives of patients with a definite disease-causing variant;
3 - in first-degree adult relatives, clinical screening with ECG and echocardiogram should be offered when genetic testing is not performed

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in the proband, or when genetic analysis fails to identify a definite mutation or reveals one or more genetic variants of unknown significance;

4 - children of patients with a definite disease-causing mutation should be considered for predictive genetic testing after pre-test family counseling when they are at least 10 years old;

5 - when there is a family history of childhood malignancies or early-onset disease or when children have heart symptoms or are involved in particularly demanding physical activity, clinical or genetic testing of first-degree child relatives may be considered before the age of 10 years.

Hypertrophic cardiomyopathy typically has autosomal dominant inheritance. Pathogenic variants may be missense, nonsense, splicing or small indels (Table 1). Large deletions/duplications have also been reported in the *NEXN*, *TNNI3*, *MYBPC3, CAV3* and *MYH7* genes.

The mutation detection rate for the most common mutant genes is ~56% (*MYBPC3* 20-30%; *MYH7* 20-30%; *TNNT2* 3-5%; *TNNI3* 3-5%; *TPM1* 1-3%) (7). MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes, and MLPA to detect duplications and deletions in *NEXN*, *TNNI3*, *MYBPC3*, *CAV3* and *MYH7*. Worldwide, 151 accredited medical genetic laboratories in the EU and 19 in the US, listed in the Orphanet (8) and GTR (9) databases, respectively, offer genetic tests for hypertrophic cardiomyopathy. The clinical guidelines for genetic testing are described in Genetics Home Reference (10), GeneReviews (5) and Clinical Utility Gene Card (7).

Dilated cardiomyopathy

Dilated cardiomyopathy (CMD) is a heart disorder characterized by dilation of at least one ventricle and systolic dysfunction. The ventricle wall becomes thinner and its contractile force decreases. Clinical signs are usually arrhythmias, thromboembolic events, such as stroke, and above all symptoms of heart failure, such as edema, orthopnea, dyspnea and fatigue. However, the symptoms take years to cause health problems and severity varies between affected individuals.

The etiology of CMD may include either inherited or acquired causes, such as myocardial infarction, valve disease, toxins, drugs, inflammatory conditions, long-standing severe hypertension and irradiation of the chest (11). Dilated cardiomyopathy is essentially an adult-onset disease, but has shown a highly variable age of onset (12). The prevalence is 1:2700 (13). It can be classified as acquired, syndromic or non syndromic.

Diagnosis is established when left ventricular enlargement and systolic dysfunction are both ascertained. Patient history, physical examination and echocardiography are also indispensable for the diagnostic process (12). The genetic test is useful for diagnosis confirmation, differential diagnosis, recurrence risk evaluation and prenatal diagnosis in families with a known mutation. Differential diagnosis should consider acquired dilated cardiomyopathies, syndromic forms and other cardiomyopathies that may present with left ventricular involvement (14). Syndromic forms include *HFE*-associated hereditary hemochromatosis, Emery-Dreifuss muscular dystrophy, Laing distal myopathy, Carvajal syndrome, Duchenne and Becker muscular dystrophy, Barth syndrome and mitochondrial dilated cardiomyopathies (15).

Dilated cardiomyopathy is a genetically heterogeneous disease and has different modes of inheritance (Table 2). Pathogenic variants may be missense, nonsense, splicing and small indels. Large deletions/duplications have also been reported in *LMNA, MYH7, SCN5A, BAG3, DES, EYA4, SGCD, MYBPC3, NEXN, PRDM16, PSEN1, TNNI3, DND, RAF1, FKTN* and *TAZ*. The mutation detection rates for the most frequently mutant CMD-related genes are *TTN* 18-25%, *LMNA* 6%, *MYH7* 4-5%, *MYH6* 3-4%, *MYBPC3* 2-4%, *TNNT2* 3%, *BAG3* 2-3%. (16).

Ourmulti-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes, MLPA to detect duplications and deletions in *LMNA, MYH7, SCN5A, BAG3, DES, EYA4, SGCD, MYBPC3, NEXN, PRDM16, PSEN1, TNNI3, DND, RAF1, FKTN* and *TAZ*.

Worldwide, 49 accredited medical genetic laboratories in the EU and 44 in the US, listed in the Orphanet (8) and GTR (9) databases, respectively, offer

Table 1. Genes associated with various forms of hypertrophic cardiomyopathy

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
MYH7	160760	CMH1	192600	AD	Beta heavy chain subunit of cardiac myosin
CAV3	601253	CMH1	192600	AD	Regulates voltage-gated K^+ channels and plays a role in sarcolemma repair in cardiomyocytes after mechanical stress
MYLK2	606566	CMH1	192600	AD	Cardiac Ca^{2+}/calmodulin-dependent myosin light chain
TNNT2	191045	CMH2	115195	AD	Ca^{2+}-dependent regulator of muscle contraction
TPM1	191010	CMH3	115196	AD	Ca^{2+}-dependent regulator of striated muscle contraction
MYBPC3	600958	CMH4	115197	AD	Cardiac isoform of myosin-binding protein C found in cross-bridge-bearing zone (C region) of A bands
PRKAG2	602743	CMH6	600858	AD	Energy-sensing enzyme that monitors cell energy status and functions. Inhibitor of de novo biosynthesis of fatty acids and cholesterol
TNNI3	191044	CMH7	613690	AD	Cardiac mediator of striated muscle relaxation
MYL3	160790	CMH8	608751	AD	Ventricular isoform of myosin light chain 3
TTN	188840	CMH9	613765	AD	Important for assembly and functioning of striated muscles, it connects microfilaments and contributes to balance of forces between two halves of sarcomere
MYL2	160781	CMH10	608758	AD	Regulatory light chain associated with cardiac myosin beta heavy chain, promoting cardiac myofibril assembly
ACTC1	102540	CMH11	612098	AD	ACTC1 is localized in contractile apparatus of muscle tissues
CSRP3	600824	CMH12	612124	AD	Positive regulator of myogenesis; transcription cofactor for myogenic bHLH transcription factors
TNNC1	191040	CMH13	613243	AD	TNNC1 encodes Tn-C that abolishes inhibitory action of Tn on actin filaments upon Ca^{2+} binding
MYH6	160710	CMH14	613251	AD	Alpha heavy chain subunit of cardiac myosin
VCL	193065	CMH15	613255	AD	VCL encodes an actin filament-binding protein that regulates cell-matrix adhesion, cell-cell adhesion, cell-surface E-cadherin expression, mechanosensing by E-cadherin complex, cell morphology and cell locomotion
MYOZ2	605602	CMH16	613838	AD	MYOZ2 encodes myozenin that binds proteins involved in linking Z line proteins and localizing calcineurin signaling to sarcomeres. May play a role in myofibrillogenesis

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Table 1 ***(continued)*****.** Genes associated with various forms of hypertrophic cardiomyopathy

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
JPH2	605267	CMH17	613873	AD	JPH2 is necessary for intracellular Ca^{2+} signaling in cardiac myocytes via ryanodine receptor-mediated Ca^{2+} release
PLN	172405	CMH18	613874	AD	Modulates contractility of heart muscle in response to physiological stimuli via ATP2A2 regulates Ca^{2+} re-uptake during muscle relaxation and Ca^{2+} homeostasis in heart muscle
CALR3	611414	CMH19 (?)	613875	AD	Ca^{2+}-binding chaperone localized in endoplasmic reticulum
NEXN	613121	CMH20	613876	AD	Essential for maintenance of sarcomere integrity
MYPN	608517	CMH22	615248	AD	Component of cardiac muscle sarcomere that links nebulette to alpha-actinin in Z lines
ACTN2	102573	CMH23 with or without LVNC	612158	AD	Localized in Z-disc of cardiac muscle where it anchors myofibrillar actin filaments
LDB3	605906	CMH24	601493	AD	Adaptor protein in striated muscle; couples protein kinase C-mediated signaling to cytoskeleton
TCAP	604488	CMH25	607487	AD	Muscle assembly regulating factor that mediates antiparallel assembly of titin molecules at sarcomere Z-disk
FLNC	102565	CMH26	617047	AD	Critical for myogenesis and structural integrity of muscle fibers

CMH=hypertrophic cardiomyopathy; LVNC=left ventricular non-compaction; AD=autosomal dominant; AR=autosomal recessive

genetic testing for CMD. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (10), GeneReviews (12) and Clinical Utility Gene Card (16).

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is a rare genetic heart disease characterized by restrictive ventricle filling and diastolic dysfunction due to cardiac muscle stiffness which leads to abnormal relaxation of the ventricles, although thicknesses and systolic function are usually normal until later stages of the disease (17). It can manifest at any time from childhood to adulthood. In children, the first signs may be failure to gain weight and thrive, fatigue and fainting. As the disease advances, there may be edema, ascites, hepatomegaly and lung congestion. Some children are totally asymptomatic and sudden death is the first manifestation. Adults with RCM first develop dyspnea, fatigue and reduced ability to exercise. Arrhythmia and palpitations are also typical of adults with RCM (18). Restrictive cardiomyopathy is uncommon: in the US and Europe, it accounts for less than 5% of all cardiomyopathies. Prevalence is unknown (19).

Table 2. Genes associated with various forms of dilated cardiomyopathies

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
LMNA	150330	CMD1A	115200	AD	Required for cardiac homeostasis
MYH7	160760	CMD1S	613426	AD	Beta heavy chain subunit of cardiac myosin
MYH6	160710	CMD1EE	613252	AD	Alpha heavy chain subunit of cardiac myosin.
SCN5A	600163	CMD1E	601154	AD	Mediates voltage-dependent Na^+ permeability of excitable membranes
ACTN2	102573	CMD1AA with/without LVNC	612158	AD	Localized in the Z-disc of cardiac muscle where it anchors myofibrillar actin filaments
DSG2	125671	CMD1BB	612877	AD	Ca^{2+}-binding transmembrane glycoprotein component of desmosomes between myocardial cells
LDB3	605906	CMD1C with/ without LVNC	601493	AD	Adaptor protein in striated muscle; couples protein kinase C-mediated signaling to cytoskeleton
TNNT2	191045	CMD1D	601494	AD	Ca^{2+}-dependent regulator of muscle contraction
RBM20	613171	CMD1DD	613172	AD	RNA-binding protein that regulates mRNA splicing of genes involved in heart development, such as TTN
TTN	188840	CMD1G	604145	AD	Important for striated muscle assembly and function, connects microfilaments, contributes to balance of forces between two halves of sarcomere
BAG3	603883	CMD1HH	613881	AD	Co-chaperone for HSP70 and HSC70 chaperone proteins in heart; triggers client/substrate protein release
DES	125660	CMD1I	604765	AD	Sarcomeric microtubule-anchoring protein that maintains sarcomere structure
CRYAB	123590	CMD1II	615184	AD	Has chaperone-like activity, preventing aggregation of proteins under stress conditions
EYA4	603550	CMD1J	605362	AD	Transcriptional regulator during organogenesis
LAMA4	600133	CMD1JJ	615235	AD	Mediates attachment, migration and organization of cells into tissues during embryo development by interacting with other extracellular matrix components
MYPN	608517	CMD1KK	615248	AD	Component of heart muscle sarcomere linking nebulette to alpha-actinin in Z lines
SGCD	601411	CMD1L	606685	AD	Component of sarcoglycan complex linking F-actin cytoskeleton and extracellular matrix
CSRP3	600824	CMD1M	607482	AD	Positive regulator of myogenesis; transcription cofactor for myogenic bHLH transcription factors
ABCC9	601439	CMD1O	608569	AD	Activates and regulates cardiac and smooth muscle-type KATP channels

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Table 2 ***(continued)*****.** Genes associated with various forms of dilated cardiomyopathies

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
PLN	172405	CMD1P	609909	AD	Modulates contractility of heart muscle in response to physiological stimuli via ATP2A2; regulates Ca^{2+} re-uptake during muscle relaxation and Ca^{2+} homeostasis in heart muscle
ACTC1	102540	CMD1R	613424	AD	Localized in contractile apparatus of muscle tissue
MYBPC3	600958	CMD1MM	615396	AD	Cardiac isoform of myosin-binding protein C found in cross-bridge-bearing zone (C region) of A bands
PRDM16	605557	CMD1LL	615373	AD	Transcriptional cofactor essential for heart development
PSEN1	104311	CMD1U	613694	AD	Expressed in heart and critical for heart development
PSEN2	600759	CMD1V	613697	AD	Expressed in heart and critical for heart development
TPM1	191010	CMD1Y	611878	AD	Ca^{2+}-dependent regulator of striated muscle contraction
VCL	193065	CMD1W	611407	AD	Encodes an actin filament-binding protein that regulates cell-matrix adhesion, cell-cell adhesion, cell-surface E-cadherin expression, mechanosensing by the E-cadherin complex, cell morphology and cell locomotion
TNNC1	191040	CMD1Z	611879	AD	Encodes Tn-C that abolishes inhibitory action of Tn on actin filaments upon Ca^{2+} binding
RAF1	164760	CMD1NN	615916	AD	Promotes cardiomyocyte survival
DSP	125647	CMD with woolly hair, keratoderma, tooth agenesis	615821, 605676	AD, AR	Obligate component of functional desmosomes
TCAP	604488	CMD	/	AD	Muscle assembly regulating factor that mediates antiparallel assembly of titin molecules at sarcomeric Z-disk
ANKRD1	609599	CMD	/	AD	Nuclear negative transcription factor that regulates expression of cardiac genes
TMPO	188380	CMD	/	AD	Regulates expression patterns of major cardiac transcription factors
ILK	602366	CMD	/	AD	Migration and survival of myocardial and endothelial cells
TNNI3	191044	CMD2A, CMD1FF	611880, 613286	AR	Cardiac mediator of striated muscle relaxation

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Table 2 ***(continued)*****.** Genes associated with various forms of dilated cardiomyopathies

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
GATAD1	614518	CMD2B	614672	AR	Regulates gene expression by binding to a histone modification site
FKTN	607440	CMD1X	611615	AR	Glycosylation of alpha-dystroglycan in skeletal muscle
SDHA	600857	CMD1GG	613642	AR	Major catalytic subunit of succinate-ubiquinone oxidoreductase located in mitochondrial respiratory chain
DMD	300377	CMD3B	302045	XLR	Anchors extracellular matrix to cytoskeleton via F-actin
TAZ	300394	CMD	/	XLR	Involved in cardiolipin metabolism

CMD=dilated cardiomyopathy, LVNC=left ventricular non-compaction AD=autosomal dominant; AR=autosomal recessive; XLR=X-linked recessive.

Clinical diagnosis is based on medical and family history, physical examination, chest X-ray, echocardiography, ECG, Holter monitoring, stress test, cardiac MRI, cardiac catheterization, coronary angiography and myocardial biopsy (18). Genetic testing is useful for confirming diagnosis, and for differential diagnosis, recurrence risk evaluation and prenatal diagnosis in families with a known mutation. Differential diagnosis should consider constrictive pericarditis, idiopathic forms, such as Loeffler eosinophilic endomyocardial disease, secondary forms, such as infiltrative disease (amyloidosis, sarcoidosis, hemochromatosis, Fabry disease, Danon disease and Friedreich ataxia) and treatment-induced RCM (post-irradiation fibrosis and drug-induced RCM) (19).

Restrictive cardiomyopathy typically has autosomal dominant inheritance (Table 3). Pathogenic variants may be missense, nonsense, splicing and small indels. Large deletions/duplications have been reported in *TNNI3, MYBPC3* and *MYH7*. MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes, and MLPA to detect duplications and deletions in the *TNNI3, MYBPC3* and *MYH7* genes. 6 accredited medical genetic laboratories in the US, listed in the GTR (9) database, offer genetic tests for RCM. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (10).

Left ventricular noncompaction

Left ventricular noncompaction (LVNC) is a heart disorder that affects the cardiac muscle, mostly the left ventricle, which acquires a thick spongy appearance. The disease is considered to be a consequence of an arrest in heart development during embryogenesis (20). The abnormal cardiac muscle does not function properly, leading to progressive systolic and diastolic dysfunction. LVNC may be isolated or an element of other heart diseases.

The disorder has a variety of symptoms. Some patients may be entirely asymptomatic, while others fall victim to sudden death. Other symptoms or signs may be arrhythmia, palpitations, abnormal blood clots, fatigue, dyspnea and lymphedema (21). Although the disease is genetic, age of onset is variable and diagnosis may be made from birth to late adulthood. The prevalence of LVNC is less than 0.25% (22).

Clinical diagnosis is mainly based on structural features observed by cardiac imaging. Echocardiography is used for diagnosis and follow-up. MRI can

Table 3. Genes associated with various forms of restrictive cardiomyopathy

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
TNNI3	191044	RCM1	115210	AD	Cardiac mediator of striated muscle relaxation
TNNT2	191045	RCM3	612422	AD	Ca2+-dependent regulator of muscle contraction
MYPN	608517	RCM4	615248	AD	Component of the heart muscle sarcomere linking nebulette to alpha-actinin in Z lines
FLNC	102565	RCM5	617047	AD	Critical for myogenesis and structural integrity of muscle fibers
ACTC1	102540	RCM	/	AD	Localized in contractile apparatus of muscle tissue
MYH7	160760	RCM	/	AD	Beta heavy chain subunit of cardiac myosin
MYBPC3	600958	RCM	/	AD	Cardiac isoform of myosin-binding protein C found in cross-bridge-bearing zone (C region) of A bands
TPM1	191010	RCM	/	AD	Ca^{2+}-dependent regulator of striated muscle contraction
MYL1	160780	RCM	/	AD	Regulatory light chain of myosin
MYL2	160781	RCM	/	AD	Regulatory light chain associated with cardiac myosin beta heavy chain, promoting cardiac myofibril assembly

RCM=restrictive cardiomyopathy; AD=Autosomal dominant.

be useful in cases with poor echocardiogram findings. Genetic testing is useful for confirming diagnosis and for differential diagnosis, recurrence risk evaluation and prenatal diagnosis in families with a known mutation. Differential diagnosis should consider dilated cardiomyopathy, hypertensive heart disease, apical hypertrophic cardiomyopathy, infiltrative cardiomyopathy, eosinophilic endomyocardial disease, localized left ventricular hypertrophy, left ventricular thrombi, cardiac metastases, endocardial fibroelastosis and Barth syndrome (23).

Left ventricular noncompaction is a genetically heterogeneous disorder with sporadic and familial forms (24). Autosomal dominant inheritance seems more common than X-linked inheritance (25). Autosomal recessive inheritance and mitochondrial inheritance have also been observed (26). Current evidence suggests that in most cases, an association with genetic cardiomyopathy (CMP) and/or congenital heart disease (CHD) is more likely than a causal role. Consequently, the genetic basis coincides or overlaps with those of CMP or CHD (27). LVNC has mostly autosomal dominant inheritance, but may also have autosomal recessive inheritance (Table 4).

Pathogenic variants may be sequence variations (missense, nonsense, splicing, small insertions and deletions, small indels). Large deletions/duplications have also been reported in *MYBPC3, MYH7, PKP2* and *PRDM16*. MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes, and MLPA to detect duplications and deletions in the same genes.

Worldwide, 40 accredited medical genetic laboratories in the EU and 4 in the US, listed in the Orphanet (8) and GTR (9) databases, respectively, offer genetic testing for LVNC. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (10).

Table 4. Genes associated with various forms of left ventricular noncompaction

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
MYH7	160760	LVNC5	613426	AD	Beta heavy chain subunit of cardiac myosin
MYBPC3	600958	LVNC10	615396	AD	Cardiac isoform of myosin-binding protein C found in cross-bridge-bearing zone (C region) of A bands
TPM1	191010	LVNC9	611878	AD	Ca^{2+}-dependent regulation of striated muscle contraction
PRDM16	605557	LVNC8	615373	AD	Transcriptional cofactor essential for heart development
MIB1	608677	LVNC7	615092	AD	Involved in heart looping process
TNNT2	191045	LVNC6	601494	AD	Ca^{2+}-dependent regulator of muscle contraction
ACTC1	102540	LVNC4	613424	AD	Localized in muscle tissue contractile system
LDB3	605906	LVNC3	601493	AD	Adapter protein in striated muscle; couples protein kinase C-mediated signaling to cytoskeleton
DTNA	601239	LVNC1	604169	AD	Component of dystrophin-associated protein complex; localized in sarcolemma
LMNA	150330	LVNC	/	AD	Required for cardiac homeostasis
SCN5A	600163	LVNC	/	AD	Mediates voltage-dependent Na^{+} permeability of excitable membranes
HCN4	605206	LVNC	/	AD	Necessary for heart pacemaking
PLEKHM2	609613	LVNC	/	AR	Regulates conventional kinesin activity
PKP2	602861	LVNC	/	AR	Plays a role in junctional plaques
SOX6	607257	LVNC	/	AR	Transcriptional activator required for maintenance of cardiac muscle cells
MT-ND1	516000	LVNC	/	MT	Core subunit of mitochondrial membrane respiratory chain NADH dehydrogenase

LVNC=left ventricular noncompaction; AD=Autosomal dominant; AR=Autosomal recessive; MT=Mitochondrial.

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic heart disease characterized by replacement of right ventricular myocytes with fibrous and fatty tissue. This predisposes young persons and athletes to ventricular tachycardia and even sudden death. Symptoms are not frequent in the early stages, but there is nevertheless risk of sudden death during intense exercise. When symptoms occur, they often include palpitations and syncope. Shortness of breath, swelling of the legs or heart failure are typical of a later stage of the disease. Patients usually develop symptoms between the second and fifth decade. The mean age at diagnosis is 31 years (28).

Prevalence of ARVC is estimated at 1:1000-1250

in the general population (29), but in countries with intensive family screening this disease appears to be much more common (30). Study of a population in which males and females were equally distributed revealed that males were 3.3-fold more likely to be associated with episodes of arrhythmia (31). Expression of the disease is variable, while penetrance is incomplete and age-related (32).

To establish diagnosis, an International Task Force proposed criteria for clinical diagnosis of ARVC/dysplasia that facilitated recognition and interpretation of its often nonspecific clinical features. Structural, histological, electrocardiographic, arrhythmic and familial features of the disease were incorporated into the criteria, divided into major and minor categories according to the specificity of their association with ARVC/dysplasia. This provided a standard on which to base clinical research and genetic studies (33). Differential diagnosis should consider idiopathic right ventricular outflow-tract tachycardia, cardiac sarcoidosis and congenital heart disease leading to right ventricular volume overload (34).

Arrhythmogenic right ventricular cardiomyopathy has mostly autosomal dominant inheritance and only rarely autosomal recessive or digenic inheritance (28). Pathogenic variants in the genes listed in Table 5

Table 5. Genes associated with various forms of arrhythmogenic right ventricular cardiomyopathy

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
TGFB3	190230	ARVC1	107970	AD	Involved in embryogenesis, differentiation, wound healing
RYR2	180902	ARVC2	600996	AD	Ca^{2+} channel that releases Ca^{2+} from sarcoplasmic reticulum into cytoplasm and triggers cardiac muscle contraction
TMEM43	612048	ARVC5	604400	AD	Maintains nuclear envelope structure
DSP	125647	ARVC8	607450	AD	Forms obligate component of functional desmosomes
PKP2	602861	ARVC9	609040	AD	Plays role in junctional plaques
DSG2	125671	ARVC10	610193	AD	Ca^{2+}-binding transmembrane glycoprotein components of desmosomes between myocardial cells
JUP	173325	ARVC12	611528	AD	Common constituent of desmosomes and intermediate junctions
CTNNA3	607667	ARVC13	615616	AD	Involved in formation of cell-cell adhesion complexes in muscle cells
TTN	188840	ARVC	/	AD	Important for striated muscle assembly and functioning; connects microfilaments and contributes to balance of forces between two halves of sarcomere
DES	125660	ARVC	/	AD	Sarcomeric microtubule-anchoring protein that maintains sarcomere structure
LMNA	150330	ARVC	/	AD	Required for cardiac homeostasis
DSC2	125645	ARVC11	610476	AD, AR	Major components of desmosomes (cell-cell junctions found in mechanically-stressed cells)

ARVC=arrhythmogenic right ventricular cardiomyopathy; AD=Autosomal dominant; AR=Autosomal recessive.

have autosomal dominant inheritance (35). Pathogenic variants may be missense, nonsense, splicing, small indels and gross deletions or duplications. MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes, and MLPA to detect duplications and deletions in *DSP* and *PKP2*.

Worldwide, 46 accredited medical genetic laboratories in the EU and 22 in the US, listed in the Orphanet (8) and GTR (9) databases, respectively, offer genetic testing for ARVC. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (10) and Clinical Utility Gene Card (35).

Conclusions

We created a NGS panel to detect nucleotide variations in coding exons and flanking regions of all the genes associated with cardiac disorders. When a suspect of cardiomyopathy is present, we perform the analysis of all the genes present in this short article.

In order to have a high diagnostic yield, we developed a NGS test that reaches an analytical sensitivity (proportion of true positives) and an analytical specificity (proportion of true negatives) of ≥99% (coverage depth ≥10x).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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