Chapter

The Role of Genetics in Cardiomyopaties: A Review

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Abstract

Cardiomyopathies are defined as disorders of the myocardium which are always associated with cardiac dysfunction and are aggravated by arrhythmias, heart failure and sudden death. There are different ways of classifying them. The American Heart Association has classified them in either primary or secondary cardiomyopathies depending on whether the heart is the only organ involved or whether they are due to a systemic disorder. On the other hand, the European Society of Cardiology has classified them according to the different morphological and functional phenotypes associated with their pathophysiology. In 2013 the MOGE(S) classification started to be published and clinicians have started to adopt it. The purpose of this review is to update it.

Keywords: cardiomyopathy, primary and secondary cardiomyopathies, sarcomeric genes

1. Introduction

Cardiomyopathies can be defined as disorders of the myocardium associated with cardiac dysfunction and which are aggravated by arrhythmias, heart failure and sudden death [1]. The aim of this chapter is focused on updating and reviewing cardiomyopathies.

In 1957, Bridgen coined the word "cardiomyopathy" for the first time and in 1958, the British pathologist Teare reported nine cases of septum hypertrophy [2]. Genetics has played a key role in the understanding of these disorders. In general, the overall prevalence of cardiomyopathies in the world population is 3%.

The genetic forms of cardiomyopathies are characterized by both locus and allelic heterogeneity. The mutations of the genes which encode for a variety of proteins of the sarcomere, cytoskeleton, nuclear envelope, sarcolemma, ion channels and intercellular junctions alter many pathways and cellular structures affecting in a negative form the mechanism of muscle contraction and its function, and the sensitivity of ion channels to electrolytes, calcium homeostasis and how mechanic force in the myocardium is generated and transmitted [3, 4].

Panels of genes are performed to diagnose the different mutations of the genes that can be the cause of the disorders although it is not certain that these disorders might be caused by these mutations. Increasing insight has shown the overlapping of the different types of cardiomyopathies [3].

There are different ways of classifying them. In 2006, the American Heart Association classified them in either primary or secondary cardiomyopathies depending on whether the heart was the only organ involved or the disorder was a found in a systemic disease. On the other hand, in 2008, the European Society of

Cardiology classified them according to the different morphological and functional phenotypes associated with their pathophysiology. In 2013, the MOGE(S) classification was described [1, 5–11].

2. Classification

The American Heart Association (AHA) classified cardiomyopathies as primary those in which the heart is the only organ affected and can be genetic, mixed or acquired and secondary, those in which the heart is affected as part of a systemic disease. On the other hand, the European Society of Cardiology (ESC) classified them according to morphological and functional phenotypes involving their pathophysiology (**Tables 1** and **2**) [1, 7–12].

In 2013, MOGE(S), the new cardiomyopathy classification system, was developed. The MOGE(S) system, which is based on the TNM classification scheme for tumors, will be a useful tool for the diagnosis, management, and treatment of cardiomyopathies as well as the TNM classification is to the management of cancer. The nomenclature of the MOGE(S) classification system used in cardiomyopathies is easier to describe and understand. This latter configuration system has a descriptive language or code and it allows physicians to comprehend what the different types of cardiomyopathy are and what mutation each patient has It is a descriptive genotype–phenotype system. The MOGE(S) classification is based on five attributes and describes how it can be used on patients who have one of the disorders. Therefore, MOGE(S) stands for: (M) morphofunctional characteristic; (O) organ involvement; (G) genetic or familial inheritance pattern; (E) specific etiological characteristics; (S) Stage of heart failure (functional classes). The MOGE(S)

Genetic	Hypertrophic cardiomyopathy Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia Left Ventricular Noncompaction Conduction defects (Lenegre-Lev disease) Ion channels disorders: Long QT syndrome Brugada syndrome Short QT syndrome Catecholaminergic polymorphic ventricular tachycardia Mitochondrial defects.
Mixed	Dilated cardiomyopathy Restrictive cardiomyopathy
Acquired	Inflammatory (cardiac amyloidosis) Takotsubo Peripartum Tachicardia-induced Infants of insulin-dependent diabetic mothers

Table 1.
Primary Cardiomyopathies

CARDIOMYOPATHIES	HCM DCM ACM RCM Unclassified	Genetic	Disease subtypes Unidentified gene defect
		Non genetic	Disease subtypes Unidentified gene defect

Table 2.
European Society of Cardiology. Classification of the cardiomyopathies.

classification system will, undoubtedly, not only help in the diagnosis, but in the management of the different cardiomyopathies as well. It will definitely help to diagnose a cardiomyopathy in the early stages that is to say when the disorder is not yet present allowing to physicians to start treatment quickly (**Table 3**) [5, 6, 13–16].

Let us show a couple of examples regarding the several cases in which this classification can be applied.

Let us discuss a patient with Friedriech's ataxia. The patient was a Caucasian male who had normal milestones and at age 10 he started with progressive gait. On examination he had Babinski reflex, pes cavus. The disorder progressed very quickly. He had limb ataxia and pyramidal signs appear. He underwent surgery because of the scoliosis and had his spine braced. At age 15, he had dysarthria, distal

M **Morphofunctional phenotype**	**O** **Organ involvement**	**G** **Genetic pattern**	**E** **Etiology**	**S** **Stage**
Cardiomyopathy diagnosis 1)HCM (H) a) H (obs) obstructive b) H (noObs) non Obstructive3) 2)DCM (D) 3)RCM (R) 4 R EMF 5) Endomyocardial fibrosis 6)ARVC/D (A) 7)LVNC (NC) 8)Early (specifyiing the different subgroups) a)E(H) b)E(D) c)E (R) d)E (A) Channelopaties (are not included) 0 Unaffected NA not available NS Non specific phenotype	0: Absence of involvement H: Heart M Skeletal Muscle A: Auditory C: Cutaneous E: Eye, Ocular G: Gastrointestinal K: Kidney Li: Liver Lu: Lung N: Nervous S: Skeletal	Inheritance A- Familial: AD: autosomal dominant AR: autosomal recessive XLD: X-inked dominant XLR: X-inked recessive Mit: mitochondrial B.Non familial: Phenotipically sporadic 1. Families: a) Informative b) non Informative 2. Family history not known by patient Family screening 1. affected asymptomatic relatives who do not know they have the disorder. 2. Abnormal ECG and echocardiogram detected in relatives 3.Normal ECG and echocardiogram in relatives who have no symptoms.	Index cases should be tested 1. If Positive relatives should also be tested 2.If Negative novel genes should be tested and relatives regular check-ups G-OC: Obligate carrier G-ONC: Non carrier G-G-A-Genetic amyloidosis G-HFE Hemochromatosis DN *De novo* mutation G-Neg Test Negative for an unknown mutation G-N mutation not yet Identified 0 No genetic test performed *Non-genetic etiologies* A: amyloidosis (each type has to be stated) A: autimmune Eo: hypereosinophilic heart disease I: infectious diseases M: myocarditis V: viral infection state the gene that causes the disorder (if the molecular was performed) and the mutation found	The stage depicted by the letters A,B,C or D of the American College of cardiology- American Heart Association (ACC-AHA) NA: not applicable NU: not used Followed by the class of the New York Heart association (NYHA) which is described by I, II, II, IV stands for the functional status (and functional class. (This is optional).

Table 3.
The MOGE(S) system for classifying cardiomyopathy patients.

wasting, spasticity. The wasting of his muscles could be observed in his limbs. His fingers resembled aranodactyly.He was wheelchair-bound. Very intelligent person. Chest X ray: cardiomegaly. He never developed diabetes mellitus. He had several bouts of pneumonia. Serial ECGs showed repolarization wave abnormalities. Echocardiograms showed concentric left ventricular hypertrophy and normal ejection fraction. Pulmonary functional tests showed that he had restrictive pulmonary syndrome of scoliotic origin. Cranial CT scan demonstrated he had cerebellar atrophy. At age 19, he suffered from depression and he developed urinary urgency. Molecular test confirmed the diagnosis showing a GAA triplet repeat size over 2000.

$M_{H(T}$ wave abnormalities) for hypertrophic cardiomyopathy and T wave abnormalities.

$O_{H+M+N+Lu+S}$ The organs affected were the heart, skeletal muscles, neurological, lung and skeletal problems,

$G_{AR:}$ the disorder is inherited in an autosomal recessive pattern.

$E_{G\text{-}FXN}$ intron 1 GAA repeats >2000.

$S_{C\text{-}II}$.

Therefore, the patient could be classified as $M_{H(T\text{ wave abnormalities})}$ $O_{H+M+N+Lu+S}G_{AR}E_{G\text{-}FXN\ (intron\ 1\ GAArepeats\ >\ 2000)}$ $S_{C\text{-}II}$.

The other case is a 17-year-old Caucasian male who had a mitochondrial myopathy presenting the typical clinical features of KSS. The patient had intellectual disability, short stature and hypogrowth. Bilateral palpebral ptosis. External ophtalmoplegia. Dyspnea at rest. Pigmentary retinal degeneration Sensorineural loss. Muscle weakness. Cerebellar syndrome. Ataxia. He denied having a disease and did not want to have any more tests performed. Atrioventricular block appeared in the different ECGs. Echocardiograms showed dilated cardiomyopathy. Muscle biopsy showed ragged-red cells. Electron microscopy and no molecular test was performed. No other family member had the disease.

$M_{D(AVB)}$. for dilated cardiomyopathy with atrioventricular block.

$O_{H+M+N+Lu+S}$ The organs affected were the heart and the skeletal muscles and had neurological, lung and skeletal problems,

$G_{AR:}$ the disorder is a mitochondrial disorder.

$E_{G\text{-}0}$: no molecular testing was run.

$S_{C\text{-}II}$.

The patient could be classified as followed $M_{D(AVB)}$ $O_{H+M+N+E+Li}G_{Mit}E_{G\text{-}0}S_{C\text{-}II.}$

3. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) has commonly been described as an unexplained hypertrophy of the left ventricle which develops in the absence of systemic hypertension, valvular heart disease or amyloidosis. The left ventricular hypertrophy (LVH) is usually asymmetric and involves the septum leading to a decrease of the left ventricular chamber [1, 4, 10, 12, 17].

The 2020 AHA/ACC guideline has defined it as the common definition of primary cardiomyopathies in which the heart is the only organ involved [18] while Europeans do not take into account the loading conditions in adult patients, but the wall thickness of the left ventricle which has to be greater than 13 mm and two standard deviations from the predicted mean (z-score > 2) [19, 20].

HCM is a familial disease which has locus heterogeneity. It is inherited in an autosomal dominant pattern in fifty percent of the cases, but autosomal recessive and X-linked HCM have also been described [1, 12, 17, 21–26]. The clinical

presentation is variable and the clinical severity can even lead to, heart failure and sudden death. Many patients can be asymptomatic, whereas others will need a heart transplant [18, 27, 28]. It is the most common cause of death in young athletes while practicing sports [12, 27, 29, 30].

The prevalence of HCM varies from 1:200 to 1: 500 [4, 12, 31–33]. The cardiac sarcomere is a complex structure and it is a long way to completely unraveled the pathophysiology of HCM. Most mutations in HCM are private of each family thus presenting allelic heterogeneity, incomplete penetrance as well as myocyte hypertrophy and variable interstitial fibrosis. Genetic and environmental modifiers also play an important part in the development of the HCM [1, 4, 12, 18, 34–36].

A decade ago, there were thirty-three genes in the world literature that have been reported to be involved and caused the disease. The genetically based HCM are due to mutations in the cardiac sarcomere or the associated proteins (See **Table 4**). This has changed now and the classification of HCM is based on the ClinGen framework for evaluating gene-disease clinical validity. The genes that are considered to cause most likely HCM are *MYH7, TNNT2, TPM1, MYBPC3, ACTC1, TNNI3, MYL2* and *MYL3*. The different gene variants are now classified as definitive, strong, moderate, limited and no reported evidence. Conflicting evidence reported is defined when there is contradictory evidence reported and there are cases that were first described as HCM but later on they could not be confirmed [18, 19, 37–45].

There seems to be no correlation between the phenotype of the patients and the location of the mutations. Most of the mutations are usually missense with exception of the mutations in the *MYBPC3* gene in which it is common to find insertions, deletions and truncation mutations due to some frameshift mutations [1, 12, 17, 36, 46, 47].

There are syndromic phenotypes associated with HCM. Among them cardiofacial syndromes are commonly referred as RASopathies (Noonan, Leopard, Costello syndromes), neurological diseases (Frederich's ataxia which is caused by the expansion of GAA sequence in intron 1 of the frataxin gene), mitochondrial diseases caused by deletion syndromes (KSS, MELAS, MERFF; LOHN), metabolic disorders of lysosomal storage diseases (Anderson-Fabry disease (GLA mutations), Hurler's syndrome (absence of alpha-L-iduronidase,) and glycogen storage diseases (Wolf-Parkinson-White syndrome caused by mutations in the PRKAG2 gene), Forbes´ disease (mutations in the AGL gene) and Pompe disease [mutations in the alpha-1,4-glucosidase (GAA)]; infiltrative diseases (Danon disease that has mutations in LAMP2 gene). Other disorders that have HCM are Noonan syndrome caused by the syndromic genes PTPN11, RAF1 and RIT and myofibrillar myopathies caused by mutations in BAG3, FLNC and ZASP [11, 26, 36, 40, 48, 49].

4. Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by an enlargement of the left ventricular chamber with impaired left ventricular systolic function, which is progressive and, in some cases, has secondary diastolic dysfunction. The prevalence of DCM is greater than 1 in 2500. DCM is the most common cause of congestive heart failure in young patients. The prevalence is ~36: 100,000 in the U.S The most common feature is congestive heart failure, though, conduction impairment, syncope and sudden death may also occur. Cardiac transplantation is sometimes the only solution to the disease [12, 50–55].

HCM gene	Symbol	Locus name	Chromosome locus	Protein	Mode of inheritance	ClinGen Gene Validity Classification
Beta-myosin heavy chain	MYH7	CMH1	14q11.2	Myosin heavy chain, cardiac muscle beta isoform	AD	Definitive
Troponin T	TNNT2	CMH2	1q32.1	TroponinT, cardiac muscle	AD	Definitive
alpha-tropomyosin	TPM1	CMH3	15q22.1	Tropomyosin1 alpha chain		Definitive
Myosin-binding protein C	MYBPC3	CMH4	11p11.2	Myosin-binding protein C, cardiac-type	AD AR	Definitive
Troponin I	TNNI3	CMH7	19q13.42	TroponinI, cardiac muscle	AD	Definitive
Actin	ACTC1	CMH11	15q14	Actin, alpha cardiac muscle 1	AD	Definitive
Regulatory myosin light chain	*MYL2*	CMH10	12q.24.11	Myosin regulatory light chain 2, ventricular/ cardiacmuscle isoform	AD	Definitive
Essential myosin light chain	*MYL3*	CMH8	3p.21.31	Myosin light polypeptide 3	AD AR	Definitive
HGNC	*PLN*	CMH18	6q22.31	Phospholamban	AD	Definitive
Alpha kinase3	*ALPK3*	CMH27	15q25.3	Alpha-protein kinase 3	AR	Strong
Cysteine-rich protein 3	*CSRP3*	CMH12	11p15.1	Cysteine- and glycine-rich protein 3	AD	Moderate
slow-twitch skeletal	*TNNC1*	CMH13	3p21.1	Cardiac troponin C	AD	Moderate
junctophilin	*JPH2*	CMH17	20q13.12	Junctophilin-2	AD	Moderate
alpha-actinin-2	*ACTN2*	CMH23	1q43	Actinin, α2	AD	Moderate
NEXN gene	NEXN	CMH20	1p31.1	Nexilin	AD	Limited
Ankyrin repeat domain-containing 1	ARKD1		10q,21	Ankyrin repeat domain 1	AD	Limited
CALR3 gene	CALR3		19p13.11	Calreticulin	AD	Limited
Telethonin	TCAP	CMH25	17q.12	Telethonin	AD	Limited
MYOZ2 gene	*MYOZ2*	CMH16	4q26	Myozenin 2 (calsarcin 1)	AD	Limited
Titin	*TTN*	CMH9	2q.31.2	Titin	AD	Limited
Tripartite motif containing 63	*TRIM63*		1p36.11	Muscle ring finger protein 1	AD	Limited

HCM gene	Symbol	Locus name	Chromosome locus	Protein	Mode of inheritance	ClinGen Gene Validity Classification
Kruppel-like factor 10	KLF10		8q22.3		AD	Limited
Myosin heavy chain α gene	MYH6	CMH14	14q11.2	Myosin heavy chain α	AD	Limited
Myomesin 1	*MYOM1*		18p11.31		AD	Limited
Myoalladim	*MYPN*	CMH22	10q.21.3		AD	Limited
Obscurin	*OBSCN*		1q42.13		AD	Limited
	PDLIM3		4q35.1	PDZ and LIM domain protein 3	AD	Limited
Ryanodine	*RYR2*		1q43	Cardiac Ryanodine 2	AD	Limited
Myosin light chain kinase 2 gene	MYLK2	CMH1 digenic	20q11.21	Myosin heavy chain α	ADDD	Limited

Table 4.
Genes that cause HCM.

It is known that hypertension, valve disease, viral infections, toxins, drugs, metabolic disorders among others can cause DCM, but in almost 40% of DCM patients the cause of the disorder is due to a genetic mutation [12, 26, 53, 56].

The familial cases of DCM present autosomal dominant, autosomal recessive or X-linked inheritance so it can be stated that there is. both locus and allelic heterogeneity (See **Table 2**). The autosomal dominant pattern is undoubtedly the most frequent mode of inheritance. It has been demonstrated that DCM has reduced penetrance and expressivity is always variable. The mutations of the genes involved in DCM are those which encode cytoskeletal, sarcomeric, mitochondrial, desmosomal, nuclear membrane, and RNA-binding proteins [53, 54, 57, 58]. Generally speaking, the onset of DCM is in adulthood although its appearance has great variability [59, 60]. When the mutation is in one of the sarcomeric genes the affected patients are usually young adults [12, 61]. The most common genes that cause DCM are *FLNC*, *TTN* and *LMNA*. The truncating mutations found in *FLNC* and in *TTN* account for 4% and in 15–25% of the DCM cases respectively. 10% of cases are due to mutations in *LMNA*. It has been observed that patients with mutations in both *LMNA* and *FLNC* have a poor prognosis and are more susceptible to having an arrhythmogenic phenotype [12, 56, 62, 63].

The MOGE(S) classification can also be applied to patients that have been diagnosed with DCM and it has been observed there is a worse prognosis with the presence of multiple attributes [13, 64] (**Table 5**).

5. Restrictive cardiomyopathy

Familial restrictive cardiomyopathy (RCM) is a rare disease, which is inherited in autosomal dominant pattern with incomplete penetrance [65]. The exact prevalence of RCM is unknown [7]. In childhood, RCM accounts for 2–5% of cardiomyopathies and has a poor prognosis [10, 12, 66, 67].

DCM gene	Symbol	Locus name	Chromosome locus	Protein	Mode of inheritance
Lamin A/C gene	*LMNA*	CMD1A	1q21	lamin A and lamin C	AD
LDB3 gene		CMD1C	10q22-q23	LIM domain-binding protein 3	AD
TNNT2 gene	TNNT2	CMD1D	1q32	Troponin T, cardiac muscle	AD
SCN5A		CMD1E	3p	Sodium channel protein type 5 subunit alpha	AD
TTN gene	TTN	CMD1G	2q31	Titin	AD
DES gene	DES	CMD1I	2q35	Desmin	AD
EYA4 gene	EYA4	CMD1J	6q23-q24	Eyes absent homolog 4	AD
SGCD gene	SGCD	CMD1L	5q33	Delta-sarcoglycan	AD
CSRP3 gene	CSRP3	CMD1M	11p15.1	Cysteine and glycine-rich protein 3	AD
TCAP gene	TCAP	CMD1N	17q12;	Telethonin	AD
ABCC9 gene		CMD1O,	on 12p12.1;	ATP-binding cassette, subfamily C, member 9	AD
PLN gene	PLN	CMD1P	on 6q22.1;,	Cardiac phospholamban	AD
ACTC1 gene	ACTC1	CMD1R	15q14	Actin, alpha cardiac muscle 1	AD
MYH7 gene	MYH7	CMD1S	14q12;	Myosin 7	AD
TMPO gene	TMPO	CMD1T	12q22	Hymopoietin	AD
PSEN1 gene	PSEN1	CMD1U	14q24.3	Presenilin-1	AD
PSEN2 gene	PSEN2	CMD1V	1q31-q42;	Presenilin-2	AD
VCL		CMD1W	10q22-q23	Vinculin	AD
FKTN	FKTN	CMD1X	9q31	Fukutin	AR
TPM1 gene	TPM1	CMD1Y	15q22.1	tropomyosin-1	AD
TNNC1 gene	TNNC1	CMD1Z	3p21.3-p14.3	slow troponin-C	AD
ACTN2 gene	ACTN2	CMD1AA	1q42-q43;	Alpha-actinin-2	AD
DSG2 gene	DSG2	CMD1BB	18q12.1-q12.2;	desmoglein-2	AD
NEXN gene	NEXN	CMD1CC	1p31.1	Nelin	AD
RBM20 gene	RBM20	CMD1DD	10q25.2;	RNA-Binding motif protein 20	AD
MYH6 gene	MYH6	CMD1EE	14q12	Myosin 7	AD
TNNI3 gene	TNNI3	CMD1FF	19q13.4;	Troponin I,	AD
SDHA gene	SDHA	CMD1GG	5p15;	Succinate dehydrogenase complex subunit A	AD
BAG3 gene	BAG3	CMD1HH	10q25.2-q26.2	BCL2-associated athanogene 3	AD
TNNI3 gene	TNNI3	CMD2A,	*19q13.42*	Troponin I, cardiac muscle	AR

DCM gene	Symbol	Locus name	Chromosome locus	Protein	Mode of inheritance
GATAD1 gene.	GATAD1	CMD2	*7q21.2*	GATA zinc finger domain containing protein 1	AR
Dystrophin gene	*DMD*	CMD3B	Xp21.2	dystrophin	X-linked
LAMP2 gene	*LAMP2*	Danon disease	Xq24	lysosome-associated membrane protein-2	X-linked
TAZ gene	*TAZ*		Xq28	dystrophin	X-linked

Table 5.
Genes that cause DCM.

RCM is characterized by abnormal diastolic function, which has a restrictive filling pattern, a reduced diastolic volume of one of the ventricles or both ventricles, enlargement of the atria, pulmonary hypertension, and heart failure. In the early stages of the disorder the systolic function may be normal, but as the disease progresses, the systolic function generally declines [12, 68–70].

The list of RCM-associated genes includes sarcomeric and cytoskeletal genes often similar to those genes observed in HCM and DCM, but in total the genotyping success rate is quite low, corresponding approximately to 30%. The familial RCM is linked to the cardiac troponin genes. RCM1 is caused by a mutation in the *TNNI3* gene on chromosome 19q13. This gene encodes the cardiac muscle isoform of troponin 1. RCM2 has been mapped to chromosome 10q23. RCM3 is caused by mutation in the *TNNT2* gene. Mutations in the sarcomere gene, alpha-cardiac actin gene (ACTC) have also been reported to cause RCM. Cardiomyopathy, familial restrictive 5 is caused by mutations in the *FLNC* gene on chromosome 7q32. In many cases RCM can be observed overlapping with either HCM or DCM [10, 26, 66–68, 70–76].

Fabry's disease, Hurler syndrome, Gaucher's disease, haemochromatosis and glycogen storage diseases are among the diseases in which RCM can be observed [10, 26].

6. Arrhythmogenic cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) is a rather new word used to describe what previously was known as Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/ARVD). The prevalence has been estimated 1:5000 in the general population.

Later on, it was observed that in many cases the left ventricle was also affected (ALVC) thus this disorder started to be called ACM.

The age of onset is between 10 and 50 years old. The clinical features include ventricular tachyarrhythmias, electrocardiographic abnormalities, systolic heart failure, syncope and sudden death. It is a frequent cause of sudden death in young people and athletes ACM is characterized by fibro-fatty replacement of the myocardium, apoptosis and inflammation [8, 12, 77, 78].

It is transmitted most of the time in an autosomal dominant pattern; though autosomal recessive families have also been reported. The data has shown the inheritance could be even be oligogenic or multifactorial where environmental

ARCV gene	Symbol	Locus name	Chromosome locus	Protein
Transforming growth factor beta- 3	*TGFB3*	ARVD1	14q24.3	Transforming growth factor beta-3
Ryanodine receptor 2	RYR2	ARVD2	1q43	RYR2
Unknown	Unknown	ARVD3	14q12-q22	Unknown
Unknown	Unknown	ARVD4	2q32.1-q32.3	Unknown
transmembrane protein 43	*TMEM43*	ARVD5	3p25.1	Transmembrane protein 43
Unknown	Unknown	ARVD6	10p14-p12	Unknownn
Desmin	*DES*	ARVD7	2q35	Desmin
Desmoplakin	*DSP*	ARVD8	6p24.3	Desmoplakin
Plakophilin-2	*PKP2*	ARVD9	12p11.21	Plakophilin-2
Desmoglein-2	*DSG2*	ARVD10	18q12.1	Desmoglein-2
Desmocollin-2	*DSC2*	ARVD11	18q12.1	Desmocollin-2
Junction plakoglobin	*JUP*	ARVD12	17q21.2	Junction plakoglobin
Alpha-T-catenin	*CTNNA3*	ARVC13	10q21.3	Catenin
Cadherin2	*CDH2*	ARVC14	18q12.1	Cadherin

Table 6.
Genes that cause ARVC.

factors intertwine to cause the disease. Incomplete penetrance and great variability in the symptoms have been observed [7, 12, 77–84].

The two first disorders to be described were Naxos disease and Carvajal syndrome, which are inherited in an autosomal recessive pattern. The former is caused by mutations in the plakoglobin gene on chromosome 17q21,2 and the latter by mutations in the desmoplakin gene on chromosome 6p24 [12, 77, 78, 80, 85–88].

Desmosomes are intercellular junctions that link intermediate filaments to the plasma membrane and are essential to tissues that experience mechanical stress such as the myocardium. Mutations in the cardiac desmosome genes are to be held responsible for most of the cases that cause the disorder (See **Table 6**). The prognosis of those who have a mutation in these genes is much worse [12, 79, 89–91].

There are overlapping syndromes. Myofrillar myopathies genes such as filamin C can cause ARLV [77]. The mutations p.S13F, p.E114del and p.N116S in the desmin gene have the same ARVC cardiac phenotype. In transfection cells aggresome formation in the cytoplasm was observed [12, 82, 92, 93]. The members of the Swedish family who were diagnosed with ARVC7 linked to chromosome 10q23.2 had instead the p.Pro419Ser mutation in *DES* [94, 95]. In mutations in the SCN5A gene the mutations can cause ARVC with Brugada syndrome, long QT syndrome or DCM. In both Titin and lamin A/C ACM overlaps with DCM [12, 77].

7. Non-compaction cardiomyopathy

Non-compaction cardiomyopathy (NCCM) has been classified as a primary cardiomyopathy with a genetic etiology. The age of onset varies from neonatal to adult hood. There is variability in the clinical features which include heart failure, arrhythmias and thromboembolism, but patients can also be asymptomatic.

The most common congenital heart defects in NCCM are Ebstein's anomaly, septal defects and patent ductus arteriosus.

The patients have a thickened two-layered myocardium with a thin, compact, epicardial layer and a severely thickened endocardial layer with a 'spongy' appearance due to prominent trabeculations and intertrabecular recesses [96–102].

The majority of the patients have an autosomal dominant mode of inheritance. Mutations in several genes coding for sarcomeric proteins such as β-myosin heavy chain (MYH7), cardiac myosin-binding protein C (*MYBPC3*), α-cardiac actin *(ACTC1*), cardiac troponin T (*TNNT2*), α-tropomyosin (*TPM1*) and cardiac troponin I (*TNNI3).* have been described in NCCM.

While mutations in the tail domain of *MYH7* and *TTN* have been reported to be associated to NCCM with DCM and have a poor patient ouycome, mutations in *MYBPC3* are linked to NCCM with HCM. Mutations in *DES, DSP, FKTN, HCN4, KCNQ1, LAMP2, LMNA, MIB1, NOTCH1, PLN, RYR2, SCN5A,* and *TAZ* have also been described [12, 98, 102–107].

8. Takotsubo cardiomyopathy

Takotsubo cardiomyopathy is characterized by an acute but transitient LV systolic dysfunction without atherosclerotic coronary artery disease and it is triggered by psychological stress. It is more common to find it in women than in men. Although some genes are considered to be involved in developing the disorder there is controversy about this and many believe Takotsubo cardiomyopathy is not genetically determined [108–112].

9. Ion channel disorders

The cell membrane transit of sodium and potassium ions is ruled by the ion channel genes which encode proteins responsible for the right transit of these ions. Mutations in these proteins lead to a group of familial disorders [113]. These ion channel disorders include long QT syndromes (LQTS), of which the Romano Ward syndrome is the commonest, the short-QT syndrome (SQTS), Brugada syndrome, and the catecholaminergic polymorphic ventricular tachycardia (CPVT). 5–10% of the sudden deaths in children can be associated to ion channel disorders [78, 114–117]. Many of the mutations found in these genes overlap in the different traits.

9.1 Long QT syndromes (LQTS)

LQTS is an arrhythmia syndrome characterized by a prolonged QT interval ECG, torsades de pointes and a higher chance of sudden cardiac death. In most of the cases it is inherited in an autosomal dominant pattern. The prevalence is 1:2000. The most common syndromes are LQT1 (40–55%), LQT2 (30–45%) and LQT3 (5–10%). The autosomal dominant mutations are found in genes *KCNQ1, KCNH2* and *SCN5A* respectively whereas TRDN is an autosomal recessive gene (**Table** 7). While in LQT1 cardiovascular symptoms that can lead to sudden death occur during exercise, in LQT2 the symptoms appear with auditory stimuli and in LQT3 during rest or sleep [71, 114, 118].

The Jervell and Lange-Nielsen syndrome (JLNS) is inherited as an autosomal recessive trait. The affected children present symptoms before the age of three and they died before the age of 15 if they are not treated. The prevalence can vary considerably and it depends on the population studied. The patients have a more

Long QT syndromes	Gene	Protein
LQT1	*KCNQ1*	Kv7.1 potassium channel
LQT2	*KCNH2*	k_V11./hERG Kv11.1 potassium channel
LQT3	*LQT3*	NaV1.5 sodium channel
LQT4	*ANK2*	ankyrin B
LQT5	*KCNE1*	minK
LQT6	*KCNE2*	MiRP1
LQT7 (Andersen-Tawil syndrome)	*KCNJ2*	Kir2.1
LQT8 (Timothy syndrome)	*CACNA1C*	Ca_V1.2
LQT9	*CAV3*	Caveolin-3
LQT10	*SCN4B*	B4-subunit of the voltage-dependent Na + channel
LQT11	*AKAP9*	A-kinase anchor protein-9
LQT12	*SNTA1*	α1-syntrophin
LQT13	*KCNJ5*	Kir3.4
LQT14	*CALM1*	calmodulin
LQT15	*CALM2*	calmodulin
	CALM3	calmodulin
	TRDN	Triadin
	RYR2	ryanodine receptor 2
	TRPM4	Transient receptor potential melastatin 4

Table 7.
Genes that cause long QT syndromes.

severe QT prolongation (greater than 500 msec) which is associated which tachiarrhythmias including torsade de pointes, ventricular fibrillation, syncope and sudden death. Mutations in the *KCNQ1* gene on chromosome 11p15.5-p15.4 and *KCNE1* gene on chromosome 21q22.12, have been reported in the affected individuals [116, 119].

Timothy syndrome is a rare autosomal dominant disorder that is due to either a *de novo* mutation or parent germline mosaicism. Mutations in the gene *CACNA1C* cause the two forms of the disorder: the classic, type 1, and type 2. The reported cases of the patients suffering type 1 syndrome have shown complete penetrance [120]. This complex multisystem disorder has a long QT syndrome associated with various forms of congenital heart defects such as tetralogy of Fallot and hypertrophic cardiomyopathy Webbing of both fingers and toes have been observed. Type 2 patients did not have syndactily [121]. Children died at age of 2.5 years due to ventricular tachycardia and ventricular fibrillation, infection or malignant hypoglycemia.

The Andersen–Tawil syndrome (LQT7) presents with QT interval prolongation, hypokalemic periodic paralysis and facial dysmorphism. The type 1 disorder disease is caused by mutations in KCNJ2 while type 2 is due to mutations in KCNJ5-GIRK4 gene [119, 120, 122–129].

9.2 Short-QT syndrome

Short-QT syndrome is a familial disease that is characterized by a high incidence of sudden death. Patients with this disease have QT intervals that are <300 ms, and increased risk of atrial and ventricular arrhythmia.

It is an autosomal dominant inherited disorder that affects patients of 30 years of age, but the fibrillation can even be observed in newborns and young patients.

Missense mutations in the *KCNH2* gene on chromosome 7q36.1 and mutations in the *KCNQ1* gene on chromosome ***11p15.5-p15.*** and the *KCNJ2* gene on chromosome 17q24.3 have shown that this is a genetically heterogeneous disease There also different variants in mutations of the genes *CACNA2D1, KCNH2, KCNJ2, KCNQ1* and *SLC4A3* which have been described in SQTS, but most of them are VUS [130–132].

9.3 Brugada síndrome

The Brugada syndrome is associated with sudden death in young people as the patients have malignant ventricular tachyarrhythmias and sudden cardiac death. The heart is not affected by either a structural heart or systemic disease. The cardiac differential diagnosis must be made with Duchenne muscular dystrophy, Freidreich's ataxia and ARVC. The age of appearance ranges from a two- day- old patient to 85 years. It was believed to be inherited in an autosomal dominant pattern with incomplete penetrance. Up to eighty different mutations were identified in the SCN5A gene. A family with a pathogenic variant in *KCNE5* which is inherited in an X-linked recessive pattern. The genetic variants in SCN5A-SCN10A and HEY2 have also been described [120, 125–127, 133–141].

9.4 Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited tachyarrhythmia that is caused by acute adrenergic activation during exercise or acute emotion in young adolescents. The age of onset varies from 7 to 9 years to the fourth decade of life. It presents locus heterogeneity and in only approximately 50% of the cases the mutations in the genes causing the disease have been identified.

The prevalence of CPVT in the population is not known, but it could be estimated in approximately 1:10,000. In *CPVT, CALM1* and *RYR2* are inherited in an autosomal dominant manner while *CASQ2* and *TRDN* are inherited in an autosomal recessive manner [142–146].

10. Cardiomyopathy in muscular dystrophies

Muscular dystrophies are a heterogeneous group of inherited disorders, characterized by progressive weakness and wasting of the skeletal muscles. They are generally associated with cardiomyopathy. In many cases, there is no correlation between the skeletal myopathy and the involvement of the heart. The mutations of the genes that cause muscular dystrophies affect the skeletal and/or cardiac muscles. These include proteins which are associated with the dystrophin–glycoprotein complex, the nuclear lamina or the sarcomere [12, 147, 148].

Cardiomyopathy occurs in myofibrillar myopathy, myotonic dystrophies, myotonic myopathies, dystrophinopathies, Emery-Dreifuss muscular dystrophy, and limb girdle muscular dystrophies [147–149]. They are inherited in autosomal dominant, autosomal recessive and X-linked mode. (See **Table 4**). In this respect Duchenne muscular dystrophy and its allelic form Becker muscular dystrophy is of significant importance. These two conditions are the most common disorders in muscular dystrophies and cardiomyopathy can be a cardinal finding during the follow-up, thus requiring yearly evaluations.

The different forms of muscular dystrophies vary in the age of onset with no male or female prevalence and have different clinical features and severity.

Disease Name	Gene	Symbol	Locus name	Chromosome locus	Protein	Mode of inheritance	CMP
Desminopathy	Desmin	DES	MFM1	2q35	Desmin	AD/AR	HCM HCR
Alpha-B crystallinopathy	CRYAB gene	CRYAB	MFM2	11q23.1	alpha-B-crystallin	AR/AD	HCM
Myotilinopathy	Myotilinn	MYOT (TTID)	MFM3	5q31.2	Myotilin (titinmmunoglobulin domain protein)	AD	
ZASPopathy	ZASP	LDB3	MFM4	10q23.2	LIM domain-binding protein 3	AD	HCD
Filaminopathy	FilaminC	FLNC	MFM5	7q32.1	Filamin C	AD	HCM HCR
BAG3-Related Myofibrillar Myopathy	BCL2-associated athanogen 3	BAG3	BAG3	10q26.11	BAG family molecular chaperone regulator 3	AD	HCM HCD
Myotonic dystrophy type 1	myotonin-protein kinase (Mt-PK).	DMPK	DMPK	19q13.3	dystrophia myotonica-protein kinase	AD	HCD
Myotonic dystrophy type 2	zinc finger protein-9 gene	CNBP	ZNF9	3q21.3	zinc finger protein-9	AD	HCD
Duchenne/Becker muscular dystrophy	dystrophin	DMD	DMD	Xp21.2	emerin	X-linked	HCM
Rigid spine syndrome	Selenoprotein 1	SEPN1		1p36.11	Selenon	AR	HCD
LGMD1B	Lamin A/C	Lamin A		1q.22		AD	HCM
LGMD1C	Caveolin-3	CAV3				AR	HCM
LGMD2B	Dysferlin	Dysf		2p13.2	Dysferlin	AR	HCD
LGMD2E	Beta-sarcoglycan	SGCB	SGCB	4q12	Beta-sarcoglycan	AR	HCD
LGMD2I	Fukutin-related protein	FKRP				AR	HCD
LGMD2J	Titin	TTN		2q.31.2		AD AR	HCM
LGMD2M	Fukutin	FKTN		9q.31.2		AR	HCD
Barth syndrome	Tafazzin	TAZ		Xq28	Tazffin	XLR	HCM LVHT

Table 8.
Genes that cause cardiomyopathy in muscular dystrophies and limb girdle muscular dystrophies.

Mutations in the genes that are involved in muscular dystrophies can cause hypertrophic, dilated or restrictive cardiomyopathy depending on the mutations of the genes involved, but most cardiomyopathies in patients with a muscular dystrophy are of the dilated type. The progression of the disorders and life expectancy vary widely, even among different members of the same family. Patients die of sudden death due to conduction defects, and heart failure.

In dystrophinopathies, sarcoglycanopathies, and the disorders that are linked to mutations in the fukutin-related protein, the feature that stands out is the cardiomyopathy the patients suffer. In muscular dystrophies, the patients usually have a dilated cardiomyopathy. Hypertrophic cardiomyopathy can be observed in Danon disease, α-B crystallinopathy, and on patients or carriers of DMD and BMD. It has been proved that in spite of the fact that mutations in codon 92 (R92L and R92W) of the cardiac troponin T gene are in the same found in the same codon the severity and phenotypes are completely different due to fact that the mutated protein has a completely different function [4, 12, 48, 147, 148, 150–169] (**Table 8**).

11. Mitochondrial disorders

Mitochondrial disorders are a heterogeneous group of disorders that have common clinical features and are caused by the different mutations found in either the nuclear or mitochondrial DNA (mtDNA) genes which regulate the mitochondrial respiratory chain, the essential final common pathway of aerobic metabolism, tissues and organs. mtDNA is maternally inherited and the disorders can appear at any age. All the mitochondria have multiple copies of their own mtDNA and the mutation rate is much higher than in nuclear DNA [170–173].

Many mitochondrial disorders involve multiple organ systems such as the brain, the heart, the liver, and the skeletal muscles which are, therefore, affected due to the fact they depend on the energy and they are especially susceptible to energy metabolism impairment [170–173].

Mitochondrial dysfunction and clinical symptoms appear when the heteroplasmic levels are above 80–90% [170–172].

The different mitochondrial cardiomyopathies are a result of the heart being commonly affected. Sometimes, the cardiomyopathy is diagnosed during the first year of life even before the mitochondrial disorder has been diagnosed. HCM, DCM, LVNC cardiomyopathies have been reported [171, 173, 174].

11.1 Kearns-Sayre syndrome

The Kearns-Sayre syndrome (KSS), a mitochondrial deletion syndrome, is characterized by the triad: onset of the disorder before the age of 20, progressive external ophthalmoplegia and pigmentary retinopathy. A cerebrospinal fluid protein concentration greater than 100 mg/d, and a commonly elevated lactate and pyruvate concentrations in blood and cerebrospinal fluid are found.

The KSS has cardiac involvement with conduction defects such as right bundle branch block, left anterior hemiblock or complete A-V block. These patients can develop a cardiomyopathy usually dilated [170, 173, 175–177].

11.2 MELAS

It is a multisystem disorder with onset in childhood with mitochondrial encephalomyopathy, lactic acidosis, and recurrent stroke-like episodes. The

variability of symptoms and the severity of the syndrome make it difficult to confirm the diagnosis.

MELAS is transmitted by maternal inheritance.

The cardiac involvement is considered to be 18–100% [178–180]. The first symptom the affected children have is the cardiomyopathy. The most common feature is a hypertrophic cardiomyopathy, although dilation has also been reported [134, 181, 182].

Mutations in the nuclear genes that also encode mitochondrial proteins can cause cardiomyopathies. These disorders are sometimes not considered among the group of mitochondrial primary disorders. Two of the most well-known disorders are Friedreich's ataxia and Barth syndrome [12, 171, 173, 183].

Friedreich's ataxia is an autosomal recessive disorder. Frataxin, the protein encoded by *FXN,* is involved in the mitochondrial transport and is needed for the synthesis of the enzymes of the respiratory chain complexes I – III and aconitase. HCM is found in this disorder [173].

In Barth syndrome, abnormal mitochondria and DCM are described as well as neutropenia [173].

12. The impact of genetics in the understanding of cardiomyopathy

Genetics started to play a key role with the advent of molecular genetics therefore physicians should not only base themselves on the family history of a patient, but with molecular genetics they have a tool that they could use and help them to diagnose and understand the disorders. Every year, new pathogenic mutations in the different genes are described, but it has not yet been figured out what the specific function and the pathogenic mechanisms the mutated proteins are.

The fact a molecular analysis can be performed does not mean the different steps physicians follow to evaluate and diagnose a cardiomyopathy should be left out, if one takes into account the fact that cardiomyopathies are in many cases inherited disorders. Therefore, a three generation family history looking for cardiac symptoms is essential as well as a thorough examination. Blood tests, ECGs, echocardiograms, cardiovascular magnetic resonance imaging, electromyography, and muscle biopsy should be carried out in order to provide us with the information that can help us to diagnose a cardiomyopathy. The suspected cardiomyopathy will have to be confirmed by DNA analysis not only in the patients, but also in asymptomatic carriers [12, 18, 51, 53, 59].

Multigene panels for molecular testing have been developed which allow physicians to diagnose the different disorders. If these tests are negative, exome sequencing, looking for point mutations and insertions as well as exome arrays checking for deletions and duplications should be performed. When performing the genetic testing the genes that should be tested are those that are considered to be the most common ones and are held responsible for the disorder. Cascade genetic testing of first degree relatives at risk seeking for a mutation that has been previously found in a patient should be performed. In children and adolescents, screening by means of serial ECGs, echocardiograms and genetic testing should be done every year or every two years while in adults it should be performed every three years There should be a lifelong surveillance of family members [18, 19, 51, 53, 54].

It has been observed that mutations in the same gene and in the same family can give rise to HCM; DCM, RCM, the three major types of cardiomyopathy, which in many cases overlap. It can be said that the different mutations of the genes plus modifier genes are liable to trigger the different pathways that lead to the

remodeling of the heart. The different mechanisms are 11. still not clear and have to be cleared up [1, 12, 184, 185].

HCM is an autosomal dominant disorder in which mutations in the *MYH7, TNNT2, TPM1, MYBPC3, ACTC1, TNNI3, MYL2* and *MYL3* have been classified as definitive according to the new classification and most of the patients suffering from it are heterozygous. Mutations in MYH7 and/or MYBPC3 genes account for 80% of the mutations [1, 12, 40]. In some cases, patients have two different mutations, usually in MYH7 and/or MYBPC3 genes. These mutations result in the patients being compound heterozygous. The double heterozygotes that have also been observed have mutations in the MyBP-C/β –MHC, MyBP-C/TNNT2, MyBP-C/TNNT3, MyBP-C/TPM, β-MHC/TNNT2 genes. Sometimes, the patients can be homozygous for a mutation in the genes MyBP-C, β -MHC, and TNNT2 [1, 12, 17, 51, 186–188]. The genotype–phenotype correlations have been linked to specific mutations [1]. The different mutations in the MYH7gene show great variability in symptomatology. Patients with the R403Q, R719W and R719Q mutations have complete penetrance, severe hypertrophy and short life expectancy, whereas those with the V606M mutation have a mild progression [1, 12, 39, 189–191]. All the patients that have mutations in the TNNT2 gene seem to have a more severe course. In most cases, the affected patients carrying the mutations R92W, R92Q, TNNT2-I79N are young, and even though they have a mild LVH, they died of sudden death. The F110I mutation does not seem to have so severe a development as the rest of the mutations in this gene Arian, 1998; [1, 12, 192–194].

It was believed that patients having double mutations in HCM have a greater severity of the disorder due to a double dose effect [186], but in a study carried out later on the data has demonstrated that this is apparently not so with the exception of double mutations in *MYBPC3* [195, 196].

Incomplete or reduced penetrance has been observed in many cases (20 to 30%) as there are parents that are carriers of the mutations, but they do not develop the disease. It is unknown whether carriers will develop the disorder at a certain age or will remain asymptomatic throughout their lives. Symptoms show a great variability among the patients that have the same mutation and suffer the disorder. These may be due to gene interaction, environmental factors and modifier genes. After 15-year follow-up it is likely carriers will develop the disorder though it is not certain [1, 19, 197–199]. False positive reports have led to the misdiagnosis of HCM [200, 201]. It is the most common cause of sudden death in young people [12, 27–30, 44, 202].

In many cases RCM can be observed overlapping with either HCM or DCM. *An* autosomal dominant cardiomyopathy has been described where the single sarcomere *TNNT2* gene mutation can cause idiopathic RCM in some patients, or HCM or DCM in others. All affected members of a RCM-associated family have *the* I79N mutation in the *TNNT2* gene, thus showing the variability of the disorders [12, 203, 204].

It is very difficult to assess the genotype-phenotype correlation in NCCM. It seems that when there are mutations in the alpha-dystrobrevin gene (*DTNA)* on chromosome 18q12.1 taffazin gene on chromosome Xq28 (Barth syndrome), lamin A/C gene, *ZASP* and *SCN5A* gene can develop the disorder [12, 205].

As soon as the patients are diagnosed with the myopathies mentioned above they should be cardiac check-up should be performed and treated immediately as the cardiac therapy improves the cardiac involvement and life expectancy.

In the ion channels disorders the molecular diagnosis of Timothy syndrome where the gene *CACNA1C* gene is mutated it should be performed in several tissues, including sperm.

It has been observed that mutations in the lamin A/C gene cause CMD1A, LGMD1B or EDMD2 in the same family [12, 206, 207].

The mitochondrial deletion syndromes are generally not inherited. The *de novo* deletions that take place in the mother's oocytes during germline development or in the embryo during embryogenesis are to be held responsible for these syndromes. 90% of the patients with KSS have deletions of mtDNA. The deletions are present in all tissues in individuals with KSS. There is no correlation between the size or the location of the mtDNA deletion and the phenotype and penetrance because there are related to the mutation load. An overlap between KKS and MERRF has been observed due to point mutation in the tRNA [tRNALeu(UUR)] [208].

It has been suggested that the mutations in the nuclear gene *RRM2B* gene cause KSS following a Mendelian mode of inheritance. The patient had multiple mtDNA deletions and a normal left ventricular function with an increased thickness of the interventricular septum and left posterior ventricular wall [209].

Approximately 80% of cases of MELAS are due to mutations in the mtDNA gene *MT-TL1* which encodes tRNA leucine. The mutations in *MT-ND5* gene which encodes the NADH–ubiquinone oxidoreductase subunit 5 have also been found in individuals with MELAS or with overlap syndromes [181, 210].

In spite of the fact that there has been considerable improvement in the molecular diagnosis of the different mutations that lead to cardiomyopathies, we still have to learn more about the pathophysiology of these disorders. Genetic testing for these inherited disorders has provided us with an insight into the prevalence of the underlying mutations of the different cardiomyopathies. Even though many genes which cause cardiomyopathies have been identified and have led to a better understanding of the pathogenesis of cardiomyopathies, mutation analyses affecting the patients have proven not to be the panacea for the different family members [211]. Different variants within a specific gene can be associated with many different phenotypes, even within the same family, preventing physicians from having a clear genotype–phenotype correlation. It seems it is a long way ahead to unravel completely the pathophysiology of the different cardiomyopathies [212, 213].

13. What should the genetic counseling be in cardiomyopathy?

Genetic counseling to patients with cardiomyopathy is very complex due to the fact that there is locus heterogeneity and clinical variability. The geneticist has to be clear and explain that there are all sorts of disorders that cause it.

It is very important that when a numerical value is provided the patient and/or his family clearly understand that the value given it is the probability of having a another a child affected with the disorder. It is imperative they understand that chance has no memory. The numerical value given to them will be the same for every new offspring of an affected parent. It would be embarrassing to face a family that comes with a second affected child because they have misinterpreted the information given to them.

The different opinions regarding what steps should be taken when the consultants are less than 18 years of age and have a genetic disorder. Should we tell them when they are asymptomatic and are at risk of having the disorder when they are adults? If a mutation is found, the children will no longer lead a normal life and it will also have a negative effect on family life. In ACM, it is advised that the genetic test be run when the consultant is over 10 years of age. The decision will have to be made on the fact on whether the treatment could help to lead a better life.

In HCM, the first step the geneticist should take is to order the molecular analyses of *MYH7* and *MYBPC3*, the two genes that carry most of the mutations.

Should the mutations not be in these two genes, the genetic analysis has to be focused on those genes that are considered definite.

Sometimes, if no mutations are found in any of the genes tested, the disorder cannot be ruled out because it is likely that a new gene not yet discovered can be the cause of the disorder.

In DCM, the mode of inheritance has to be defined in order to provide a correct counseling as there is locus and allelic heterogeneity.

In the autosomal dominant cardiomyopathies most individuals diagnosed have an affected parent. However, the index case may have the disorder as the result of a *de novo* mutation [214].

In HCM, it is not known the number of cases that are caused by these *de novo* gene mutations. While in Brugada syndrome and in RWS *de novo* mutations are low, and in CPVT is almost 40%.

Timothy syndrome is due to either de *novo* mutations or parental germline mosaicism. The affected patients do not have offspring because they do not reach adult life. The siblings are at risk of inheriting the disorder. When there is a *de novo* mutation, alternate paternity and maternity as well as whether the patient is adopted have to be ruled out.

The offspring of a patient suffering autosomal dominant familial cardiomyopathy has a 50% chance of inheriting the mutation. Families in which penetrance appears to be incomplete or reduced have been observed; therefore, the parent with a mutation that causes the disorder is not affected whereas the son or daughter is. The severity and age of onset cannot be predicted [215–217].

The siblings of the index case depend on the genetic condition of their parents. If a parent is affected or has the mutation that causes the disorder, the risk to inherit the mutated allele is 50%.

In the cases reported where more than one mutation in one the genes encoding a sarcomere protein has been identified in a patient with HCM, it is very difficult to assess the mode of inheritance and makes it arduous for the geneticist to give an accurate risk assessment to another family member.

It is essential to provide patients and relatives that are at risk, the potential risk their offspring might have in these disorders and the reproductive options they have.

In the autosomal recessive traits, the parents are obligate carriers. The offspring of a patient suffering an autosomal recessive familial cardiomyopathy will be obligate carriers. The siblings have a 25% chance of inheriting the mutation.

The deletions in mtDNA are usually due to *de novo* mutations, so there is only one family member affected. The offspring of a male patient are not at risk whereas all females´ offspring are at risk of inheriting the mutation. There is not risk that any other family member will inherit the disease.

When there are multiple mtDNA deletions the analysis of *RRM2B* should be performed because it conditions the genetic counseling.

A prenatal diagnosis can be performed in those patients there are at risk of having any cardiomyopathy, if the mutation carried by the parents or the proband has been previously identified.

Preimplantation genetic diagnosis (PGD) may be available for families in which the mutation that causes the disorder has already been identified.

14. Conclusion

Genetic testing has undoubtedly broadened our knowledge of the mechanisms of cardiomyopathy and has to a certain extent helped physicians to understand to a certain extent the genotype–phenotype correlation. By having a deeper

understanding of this genotype–phenotype correlation, it will be easier to get a clinical management of the patients. It has also aided to diagnose symptomatic and asymptomatic patients, be able to treat them when it is possible and to perform genetic counseling of the affected patients, their offspring and first degree relatives.

When a genetic test is performed and a patient is diagnosed with a disorder genetic counseling is essential for the patient and relatives at risk since this will allow an early identification of relatives who are at risk.

Not all the mutations that have been described over the last twenty have proven to be pathogenic. The new classification allows us to understand what mutations are really pathogenic. A deeper understanding of the genotype–phenotype correlation is necessary, because this could imply what steps should be taken in order to deal with the correct management of the patients.

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