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Chapter

The Role of Genetics in Cardiomyopathies: 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 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) classi-

| 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                                |
|                               | Tachycardia-induced                       |
|                               | Infants of insulin-dependent diabetic mothers |

Table 1. Primary Cardiomyopathies

| CARDIOMYOPATHIES | Genetic | Disease subtypes |
|------------------|---------|-----------------|
|                  | HCM                 | Unidentified gene defect |
|                  | DCM                 |                             |
|                  | ACM                 | Unidentified gene defect |
|                  | RCM                 | Unidentified gene defect |
|                  | Unclassified        | Unidentified gene defect   |

Table 2. European Society of Cardiology. Classification of the cardiomyopathies.
fication 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 Friedreich’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

| Morphofunctional phenotype | Organ involvement | Genetic pattern | Etiology | Stage |
|-----------------------------|------------------|----------------|---------|-------|
| Cardiomyopathy diagnosis   | 0: Absence of involvement | Inheritance | Index cases should be tested | The stage depicted by the letters A,B,C or D of the American College of cardiology- American Heart Association (ACC-AHA) |
| 1) HCM (H)                 | H: Heart         | A- Familial | 1. If Positive | Followed by the class of the New York Heart association |
| a) H (obs) non obstructive | M: Skeletal      | AD: autosomal dominant | relatives should also be tested | Heart association (NYHA) which is described by I, II, IV |
| b) H (noObs) non obstructive | Muscle          | AR: autosomal recessive | 2. If Negative | stands for the functional status (and functional class. (This is optional). |
| Obstructive (3)            | A: Auditory      | XLD: X-linked dominant | novel genes should be tested and | |
| 2) DCM (D)                 | C: Cutaneous     | XLR: X-linked recessive | relatives regular check-ups | |
| 3) RCM (R)                 | E: Eye, Ocular   | G: Gastrointestinal | G-OC: Obligate carrier | |
| 4) R EMP S)                | G: Kidney        | Mit: mitochondrial | G-HFE | |
| Endomyocardial fibrosis    | Li: Liver        | B: Non familial | G-ONC: Non carrier | |
| 6) ARVC/D (A)             | Lu: Lung         | Phenotypically sporadic I. | G-G-A: Genetic amyloidosis | |
| 7) LVNC (NC)              | N: Nervous       | Families | | |
| 8) Early                   | S: Skeletal      | a) Informative | Hemochromatosis | |
| (specifying the different subgroups) | | b) non Informative | DN De novo | |
| a) E(H)                    | | 2. Family | for an unknown mutation | |
| b) E(D)                    | | history not known by | G-N Neg Test Negative | |
| c) E (R)                   | | patient | for an unknown | |
| d) E (A)                   | | Family | G-N mutation not yet identified | |
| Channelopathies (are not included) | | screening | 1. affected asymptomatic | |
| 0 Unaffected               | | relatives who do not know they have the disorder | Non genetic etiologies | |
| NA not available           | | 2. Abnormal ECG and echocardiogram detected in relatives | Amelioroses (each type has to be stated) | |
| NS Non specific phenotype  | | 1. abnormal ECG and echocardiogram detected in relatives | A: amyloidosis | |
|                            |                  |                  |                  | |

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.

\[ M_{H(T \text{ wave abnormalities})} \] for hypertrophic cardiomyopathy and T wave abnormalities.

\[ O_{H_{M_{N_{L_{S}}}G_{AR}}} \quad \text{The organs affected were the heart, skeletal muscles, neurological, lung and skeletal problems,} \]

\[ E_{G_{FXN}} \quad \text{intron 1 GAA repeats >2000}. \]

\[ S_{C-II}. \]

Therefore, the patient could be classified as \( M_{H(T \text{ wave abnormalities})} \)

\[ O_{H_{M_{N_{L_{S}}}G_{AR}}}E_{G_{FXN}} \quad (\text{intron 1 GAA repeats > 2000}) \]

\[ S_{C-II}. \]

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.

\[ M_{D(AVB)} \]

\[ O_{H_{M_{N_{L_{S}}}G_{AR}}} \]

The organs affected were the heart and the skeletal muscles and had neurological, lung and skeletal problems,

\[ G_{AR} \quad \text{the disorder is a mitochondrial disorder.} \]

\[ E_{G_{0}} \quad \text{no molecular testing was run.} \]

\[ S_{C-II}. \]

The patient could be classified as followed \( M_{D(AVB)} \)

\[ O_{H_{M_{N_{E_{L_{G_{AB}}E_{G_{0}}}}}S_{C-II}}}. \]

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 unravel 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           | Troponin T, cardiac muscle                                             | AD                  | Definitive                           |
| alpha-tropomyosin      | TPM1   | CMH3       | 15q22.1          | Tropomyosin 1 alpha chain                                              |                     |                                      |
| Myosin-binding protein C | MYBPC3 | CMH4       | 11p11.2          | Myosin-binding protein C, cardiac type                                 | AD, AR              | Definitive                           |
| Troponin I             | TNNI3  | CMH7       | 19q13.42         | Troponin I, cardiac muscle                                             | AD                  | Definitive                           |
| Actin                  | ACTC1  | CMH11      | 15q14            | Actin, alpha cardiac muscle 1                                           | AD                  | Definitive                           |
| Regulatory myosin light chain | MYL2 | CMH10      | 12q24.11         | Myosin regulatory light chain 2, ventricular/ cardiac muscle 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 kinase 3         | 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  | CMH18      | 19p13.11         | Calreticulin                                                            | AD                  | Limited                              |
| Telethonin             | TCAP   | CMH25      | 17q12            | Telethonin                                                              | AD                  | Limited                              |
| MYOZ2 gene             | MYOZ2  | CMH16      | 4q26             | Myozin 2 (calsarcin 1)                                                  | AD                  | Limited                              |
| Titin                  | TTN    | CMH9       | 2q31.2           | Titin                                                                   | AD                  | Limited                              |
| Tripartite motif containing 63 | TRIM63 | 1p36.11     | Muscle ring finger protein 1                                           | AD                  | Limited                              |
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].

| 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 |
| Myovaldalin | MYPN | CMH22 | 10q21.3 | 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 | 20q11.21 | Myosin heavy chain α | AD | Limited |

Table 4. Genes that cause HCM.
| 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 | CMD1H | 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 |
| ARCC9 gene | ARCC9 | CMD1O | 12p12.1; | ATP-binding cassette, subfamily C, member 9 | AD |
| PLN gene | PLN | CMD1P | on 6q22.1; | Cardiac phospholamban | AD |
| ACTC1 gene | ACTC1 | CMD1Q | 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 |
| FKN | FKN | 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 | CMD1A | 1q42-q43; | Alpha-actinin-2 | AD |
| DSG2 gene | DSG2 | CMD1B | 18q12.1-q12.2; | desmoglein-2 | AD |
| NEXN gene | NEXN | CMD1C | 1p31.1 | Nelin | AD |
| RBM20 gene | RBM20 | CMD1D | 10q25.2; | RNA-Binding motif protein 20 | AD |
| MYH6 gene | MYH6 | CMD1E | 14q12 | Myosin 7 | AD |
| TNNI3 gene | TNNI3 | CMD1F | 19q13.4; | Troponin I, | AD |
| SDHA gene | SDHA | CMD1G | 5p15; | Succinate dehydrogenase complex subunit A | AD |
| BAG3 gene | BAG3 | CMD1H | 10q25.2-q26.2 | BCL2-associated athanogene 3 | AD |
| TNNI3 gene | TNNI3 | CMD2A, | 5q43.42 | Troponin I, cardiac muscle | AR |
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 factors play a role.
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 \( \text{DES} \) [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.

| 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 |
| Desmin                            | DES      | ARVD6       | 10p14-p12        | Unknown               |
| 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.*
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 outcome, 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 transient 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
severe QT prolongation (greater than 500 msec) which is associated with tachyarrhythmias including torsade de pointes, ventricular fibrillation, syncope and sudden death. Mutations in the \( \textit{KCNQ1} \) gene on chromosome 11p15.5-p15.4 and \( \textit{KCNE1} \) 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 \textit{de novo} mutation or parent germline mosaicism. Mutations in the gene \( \textit{CACNA1C} \) 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 \( \textit{KCNJ2} \) while type 2 is due to mutations in \( \textit{KCNJ5-GIRK4} \) 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.

9.3 Brugada syndrome

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, Friedreich’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.

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.

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. 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.
| Disease Name                | Gene          | Symbol | Locus name | Chromosome locus | Protein                          | Mode of inheritance | CMP   |
|-----------------------------|---------------|--------|------------|------------------|----------------------------------|---------------------|-------|
| Desminopathy                | Desmin        | DES    | MFM1       | 2q35             | Desmin                           | AD/AR               | HCM   |
| Alpha-B crystallinopathy    | CRYAB gene    | CRYAB  | MFM2       | 11q23.1          | alpha-B-crystallin               | AR/AD               | HCM   |
| Myotilinopathy              | Myotilin      | MYOT   | MFM3       | 5q31.2            | Myotilin (titinimmunoglobulin domain protein) | AD                 | HCM   |
| ZASPopathy                  | ZASP          | LDB3   | MFM4       | 10q23.2           | LIM domain-binding protein 3     | AD                 | HCD   |
| Filaminopathy               | FilaminC      | FLNC   | MFM5       | 7q32.1            | Filamin C                        | AD                 | HCM   |
| BAG3-Related Myofibrillar Myopathy | BCL2-associated athanogen 3 | BAG3 | BAG3 | 10q26.11       | BAG family molecular chaperone regulator 3 | AD | HCM   |
| 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        | Selensprotein 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 | SGC8 | SGC8 | 4q12             | Beta-sarcoglycan                  | AR                 | HCD   |
| LGMD2I                      | Fukutin-related protein | FKR8 |            |                   |                                   | AR                 | HCD   |
| LGMD2J                      | Titin         | TTN    | 2q.31.2    |                   |                                   | AD                 | HCM   |
| LGMD2M                      | Fukutin       | FKTN   | 9q.31.2    |                   |                                   | AR                 | HCD   |
| Barth syndrome              | Tafazzin      | TAZ    | Xq28       | Tazffin           |                                   | XLR                | HCM   |

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

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 \textit{de novo} mutation.

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

Timothy syndrome is due to either \textit{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 \textit{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.

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 \textit{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 \textit{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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References

[1] Richard P, Villard E, Charron P, Isnard R. The genetic bases of cardiomyopathies. J Am Coll Cardiol. 2006;48:A79–A78.

[2] Teare D. Asymmetrical hypertrophy of the heart Br heart J 1958;20:1–8 Postgrad Med J 1992;68 Suppl 1:S3–6.

[3] Dal Ferro, Severini G, Gigli M et al. Genetics of dilated cardiomyopathy: current knowledge and future perspectives. In Sinagra G, Merlo M, Pinamonti B, editors. Dilated Cardiomyopathy: From Genetics to Clinical Management, Chapter 5: Springer 2019.

[4] Spudich J. Three perspectives on the molecular basis of hypercontractility caused by hypertrophic cardiomyopathy mutations. Pflügers Archiv - European Journal of Physiology 2019; 471:701–717.

[5] Arbustini E, Narula N, Dec G et al. The MOGE(S) Classification for a Phenotype–Genotype Nomenclature of Cardiomyopathy. Journal of the American College of Cardiology 2013; 62: 2046–2072.

[6] Arbustini E, Narula N, Tavazzi L et al. The MOGE(S) Classification of Cardiomyopathy for Clinicians. Journal of the American College of Cardiology 2014; 64: 304–318.

[7] Elliott P, Andersson, B, Arbustini E et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Euro Heart Journal 2008; 29:270–276.

[8] Maron B, Towbin J, Thiene et al. Contemporary Definitions and Classification of the Cardiomyopathies an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006; 113: 1807-1816.

[9] Maron, B.J. The 2006 American Heart Association classification of cardiomyopathies is the gold standard. Circulation Heart Failure 2008; 1: 72-75.

[10] McCartan C, Mason R, Jayasinghe SR & Griffiths L. Cardiomyopathy Classification: Ongoing Debate in the Genomics Era. Biochemistry Research International 2012; Article ID 796926: 1-10.

[11] Cecchi F, Tomberli B, Olivotto I. Clinical and molecular classification of cardiomyopathies, Global Cardiology Science and Practice 2012:4.

[12] Vernengo L, Lilienbaum A, Agabulut O & Rodriguez, MM.. The role of geneties in cardiomyopathy .In Jos¨& Guiseppe Ambrosi, editors.: Cardiomyopathies. InTech 2013.

[13] Hazebroek M, Moors S, Dennert R et al. Prognostic Relevance of Gene-Environment Interactions in Patients With Dilated Cardiomyopathy. JACC 2015; 66: 1013–1023.

[14] Walsh R, Buchan R, Wilk A et al. Defining the genetic architecture of hypertrophic cardiomyopathy: re-evaluating the role of non-sarcomeric gene. European Heart Journal 2017a; 38, 3461–3468.

[15] Walsh R, Thomson K, Ware J et al. Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. Genet Med. 2017b; 19:192–203.
[16] Elkilan G. New Classification of Cardiomyopathy: Who are at Risk? Integrative Clinical Cardiology 2017; 1 (1): 001e.

[17] Richard P, Charron P, Carrier L, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation. 2003; 107:2227–2232.

[18] Ommen, SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evanovich LL, Hung J, Joglar JA, Kantor P, Kimmelstiel C, Kittleson M, Link MS, Maron MS, Martinez MW, Miyake CY, Schaff HV, Semsarian C, Soraja P. 2020 AHA/ACC Guideline for the diagnosis and treatment hypertrophic cardiomyopathy executive summary. Circ 2020; 142:e533–e557

[19] Lorenzini M, Norrish G, Field E et al. Penetrance of hypertrophic cardiomyopathy in sarcomere protein mutation carriers. J Am Coll Cardiol. 2020; 76: 550–559

[20] Elliott P, Anastasakis A, Borger M et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). European Heart Journal 2014; 35: 2733–2779.

[21] Branzi A, Romeo G, Specchia S et al. Genetic heterogeneity of hypertrophic cardiomyopathy. Int J Cardiol.1985; 7: 129–138.

[22] Niimura H, Bachinski L, Sangwatanaroj S et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. N Engl J Med 1998; 338:1248–1257.

[23] Seidman CE, Seidman JG. Identifying sarcomere gene mutations in hypertrophic cardiomyopathy: a personal history. Circ Res 2011; 108: 743–750.

[24] Wang, Y., Wang, Z., Yang, Q. et al. Autosomal recessive transmission of MYBPC3 mutation results in malignant phenotype of hypertrophic cardiomyopathy. PLoS One 8: e67087, 2013. Note: Electronic Article

[25] Hartmannova H; Kubanek M, Sramko M et al. Isolated X-Linked Hypertrophic Cardiomyopathy Caused by a Novel Mutation of the Four-and-a-Half LIM Domain 1 Gene. Circ Cardiovasc Genet. 2013; 6: 543-551.

[26] Lipshultz S, MD, Law Y, Asante-Korang A. Cardiomyopathy in Children: Classification and Diagnosis. A Scientific Statement From the American Heart Association. Circulation. 2019; 140: e9–e68.

[27] Bos JM, Towbin JA, Ackerman MJ. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. J Am Coll Cardiol 2009; 54:201–211.

[28] Maron BJ, Gardin JM, Flack JM et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. Circulation. 1995; 92: 785–789.

[29] Maron BJ, Shirani J, Poliac LC et al. Sudden death in young competitive athletes. JAMA 1996: 276; 199–204.

[30] Mavrogeni SI, Tsarouhas K, Spanidios DA et al. Sudden cardiac death in football players: Towards a new pre-participation algorithm. Exp Ther Med. (2019); 17:1143–1148.

[31] Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical...
perspectives. J Am Coll Cardiol 2012; 60: 705–715.

[32] Semsarian C, Ingles J, Maron M & Maron B. New Perspectives on the Prevalence of Hypertrophic Cardiomyopathy. JACC 2015; 65: 1249 – 1254.

[33] Sarkar S, Trivedi D, Morck M. et al. The hypertrophic cardiomyopathy mutations R403Q and R663H increase the number of myosin heads available to interact with actin. Sci. Adv. 2020; 6: eaax0069

[34] Frank D & Frey N. Cardiac Z-disc Signaling Network. JBC 2011 286; 12: 9897–9904

[35] Hayashi T, Arimura T, Itoh-Satoh M, et al. Tcap gene mutations in hypertrophic cardiomyopathy and dilated cardiomyopathy. J Am Coll Cardiol. 2004; 44:2192–2201.

[36] Marian A & Braunwald E. Hypertrophic Cardiomyopathy Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. Circ Res. 2017;121:749-770.

[37] Das KJ, Ingles J, Bagnall R et al. Determining pathogenicity of genetic variants in hypertrophic cardiomyopathy: importance of periodic reassessment. GenetMed. 2014; 16: 286–293.

[38] Furqan A, Arscot P, Girolami F et al. Care in specialized centers and data sharing increase agreement in hypertrophic cardiomyopathy genetic test interpretation. Circ Cardiovasc Genet. 2017; 10:e001700.

[39] Ga Overeem S, Schelhaas H, Blijham P et al. Symptomatic distal myopathy with cardiomyopathy due to a MYH7 mutation. Neuromuscul Disord 2007;17: 490–493.

[40] Ingles J, Goldstein J, Thaxton C et al. Evaluating the Clinical Validity of Hypertrophic Cardiomyopathy Genes. Circ Genom Precis Med. 2019;12; 57–64.

[41] Kelly MA, Caleshu C, Morales et al. Adaptation and validation of the ACMG/AMP variant classification framework for MYH7-associated inherited cardiomyopathies: recommendations by ClinGen’s Inherited Cardiomyopathy Expert Panel. Genet Med. 2018; 20: 351–359.

[42] Marian A, Roberts R. The molecular genetic basis for hypertrophic cardiomyopathy. J Mol Cell Cardiol 2001; 33:655.

[43] Rehm HL, Berg J, Brooks L et al; ClinGen. ClinGen—the Clinical Genome Resource. N Engl J Med. 2015; 372: 2235–2242.

[44] Moolman J, Corfield V, Posen B et al. Sudden death due to troponin T mutations. J Am Coll Cardiol 1997b;29: 549.

[45] Strande NT, Riggs E, Buchanan A et al. Evaluating the clinical validity of gene-disease associations: an evidence-based framework developed by the clinical genome resource. Am J Hum Genet. 2017;100: 895–906.

[46] Erdmann J, Daehmlow S, Wischke S et al. Mutation spectrum in a large cohort of unrelated consecutive patients with hypertrophic cardiomyopathy. Clin Genet. 2003 ; 64:339–349.

[47] Millat G, Bouvagnet P, Chevalier P. et al. Prevalence and spectrum of mutations in a cohort of 192 unrelated patients with hypertrophic cardiomyopathy. Eur J Med Genet. 2010; 53:261–267.

[48] Lilienbaum A & Vernengo L. Cardiomyopathies associated with myofibrillar myopathies. In Joseph Veselka, editor.: Cardiomyopathies – from basic research to clinical management InTech 2012; p.353–382.
[49] Miyamoto L. Molecular Pathogenesis of Familial Wolff-Parkinson-White Syndrome. Molecular Mechanisms of Cardiac Glycogen Regulation by AMPK. J Med Invest 2018; 65: 1-8.

[50] Elliott, P. Cardiomyopathy. Diagnosis and management of dilated cardiomyopathy. Heart 2000 84; 1; 106–112.

[51] Hershberger R, Givertz M, Ho C et al; ACMG Professional Practice and Guidelines Committee. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). GenetMed. 2018; 20: 899–909.

[52] Jefferies, J & Towbin, J. (2010). Dilated cardiomyopathy. Lancet 2010; 375:752–762.

[53] McNally E & Mestroni L. Dilated Cardiomyopathy: Genetic Determinants and Mechanisms. Circ Res. 2017; 121; 731–748.

[54] Park HY. Hereditary Dilated Cardiomyopathy: Recent Advances in Genetic Diagnostic. Korean Circ J 2017; 47: 291–298.

[55] Sugrue DD, Rodeheffer RJ, Codd MB, et al. The clinical course of idiopathic dilated cardiomyopathy: a population-based study. Ann Intern Med 1992;117:117–123.

[56] Paldino A, De Angelis G, Merlo M et al. Genetics of Dilated Cardiomyopathy: Clinical Implications. Curr Cardiol Rep 2018; 20: 83.

[57] Baig M, Goldman J, Caforio A et al. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. J Am Coll Cardiol 1998; 3:195–201.

[58] Lennermann D, Backs J, van den Hoogenhof MMG. New Insights in RBM20 Cardiomyopathy. Current Heart Failure Reports 2020; 17:234–246.

[59] Hershberger R, Lindenfeld J, Mestroni L et al Genetic evaluation of cardiomyopathy-A Heart Failure Society of America Practice Guideline J Cardiac Fail 2009;15:83–97.

[60] Mangin L, Charron P, Tesson F et al. Familial dilated cardiomyopathy: clinical features in French families. Eur J Heart Fail 1999; 14: 353–361.

[61] Aernout Somsen, Kees Hovingh G, Tulevski I. Familial dilated cardiomyopathy. In Baars H, van der Smagt, J, Doevendans P, editors. Clinical Cardiogenetics: Springer 2011; p. 63–78.

[62] Ortiz-Genga MF et al. Truncating FLNC Mutations Are Associated With High-Risk Dilated and Arrhythmogenic Cardiomyopathies. J Am Coll Cardiol. 2016; 68:2440–2451.

[63] Van den Hoogenhof M , Beqqali A, Amin A et al. RBM20 Mutations Induce an Arrhythmogenic Dilated Cardiomyopathy Related to Disturbed Calcium Handling. Circulation 2018; 138:1330–1342.

[64] Dek GW & Arbustini, E. Utilizing the MOGE(S) classification for predicting prognosis in dilated cardiomyopathy. JACC 2015; 66: 1324–1326.

[65] Katritsis D, Wilmshurst P, Wendon J et al. Primary restrictive cardiomyopathy: clinical and pathologic characteristics. J Am Coll Cardiol 1991; 18:1230–1235.

[66] Kaski J, Syrris P, Burch M, Tomé-Esteban M et al. Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes. Heart 2008a; 94:1478–1484.
[67] Kaski J, Syrris P, Burch M, Tomé-Esteban M et al. Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes. Heart 2008b; 94:1478–1484.

[68] Bahl A, Saikia U & Khullar Madhu. Idiopathic restrictive cardiomyopathy—perspectives from genetics studies. Is it time to Redefine these disorders. Cardiogenetics 2012: 2e4.

[69] Kushwaha S, Narula J, Narula N et al. Pattern of changes over time in myocardial blood flow and microvascular dilator capacity in patients with normally functioning cardiac allografts. Am J Cardiol. 1998; 82:1377-1381.

[70] Albakri A. Restrictive cardiomyopathy: A review of literature on clinical status and meta-analysis of diagnosis and clinical management. Pediatr Dimensions. 2018, 3: 1-14.

[71] Altmann HM, Tester DJ, Will ML, Middha S, Evans JM, Eckloff BW, Ackerman MJ. Homozygous/compound heterozygous triadin mutations associated with autosomal-recessive long-QT syndrome and pediatric sudden cardiac arrest: elucidation of the triadin knockout syndrome. Circulation. 2015; 131:2051–2060.

[72] Kamisago M, Sharma S, DePalma S et al. Mutations in sarcomere protein genes as a cause of dilated cardiomyopathy. New Eng. J. Med. 2000; 343: 1688–1696.

[73] Kirkels J & de Jonge N. Restrictive cardiomyopathy. In In Baars H, van der Smagt, J, Doevendans P, editors. Clinical Cardiogenetics: Springer 2011b; p130–139.

[74] Olson T; Illenberger S, Kishimoto N et al. Metavinculin mutations alter actin interaction in dilated cardiomyopathy. Circulation. 2002; 105: 431-437.

[75] Zhang J, Kumar A, Kaplan L et al. Genetic linkage of a novel autosomal dominant restrictive cardiomyopathy locus. J Med Genet 2005; 42: 663-665.

[76] Broddehl A., Ferrier, R, Hamilton S et al. Mutations in FLNC are associated with familial restrictive cardiomyopathy. Hum. Mutat. 2016; 37: 269–279.

[77] James C, Syrris P, van Tintelen J, Calkins H. The role of genetics in cardiovascular disease: arrhythogenic cardiomyopathy. European Heart Journal, 2020; 41, 1393–1400.

[78] Patel V, Asatryan B, Siripanthong B et al. State of the Art Review on Genetics and Precision Medicine in Arrhythogenic Cardiomyopathy. Int. J. Mol. Sci. 2020, 21, 6615–6762.

[79] Brun F., Barnes C, Sinagra G et al. Titin and desmosomal genes in the natural history of arrhythmogenic right ventricular cardiomyopathy. J Med Genet. 2014; 51: 669–676.

[80] Cox M & Hauer R. Arrhythmogenic right ventricular dysplasia/ cardiomyopathy from desmosome to disease. In Baars H, van der Smagt, J, Doevendans P, editors. Clinical Cardiogenetics: Springer 2011; p 80–96.

[81] Hamid M, Norman M, Quraishi A, et al. Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy/dysplasia reveals a need to broaden diagnostic criteria. J Am Coll Cardiol. 2002;40: 1445–1450.

[82] Klaue B, Kossmann S, Gaertner A et al. De novo desmin-mutation N116S is associated with arrhythmogenic right ventricular cardiomyopathy. Hum Mol Genet 2010; 19; 4595–4607.

[83] Peters S. Advances in the diagnostic management of arrhythmogenic right
ventricular dysplasia-cardiomyopathy. Int J Cardiol. 2006;113:4–11.

[84] Awad M, Calkins H, Judge D. Mechanisms of disease: molecular genetics of arrhythmogenic right ventricular dysplasia/cardiomopathy. Nat Clin Pract Cardiovasc 2008;5:258-267.

[85] Norgett E, Hatsell S, 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; 9:2761–2766.

[86] Protonotarios N, Tsatsopoulou A, Patsourakos P et al. Cardiac abnormalities in familial palmoplantar keratosis. Brit. Heart J. 1986; 56: 321–326.

[87] Schonberger J, Seidman CE. Many roads lead to a broken heart: the genetics of dilated cardiomyopathy. Am. J. Hum. Genet. 69: 249–260, 2001.

[88] McKoy G, Protonotarios N, Crosby A et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet 2000; 355: 2119-2124.

[89] Al-Jassar C, Knowles T, Jeeves M et al. The nonlinear structure of the desmoplakin plakin domain and the effects of cardiomyopathy-linked mutations. J Mol Biol. 2011 411:1049–1061.

[90] James C, Syrris P, van Tintelen JP & Calkins H. The role of genetics in cardiovascular disease: arrhythmogenic cardiomyopathy. Euro Heart Journal 2008; 41:1393–1400.

[91] Tintelen J., Entius M, Bhuiyan Z et al. Plakophilin-2 Mutations Are the Major Determinant of Familial Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. Circulation 2006; 113: 1650–1658.

[92] Van Tintelen J, Van Gelder I, Asimaki A et al. Severe cardiac phenotype with right ventricular predominance in a large cohort of patients with a single missense mutation in the DES gene. Heart Rhythm 2009; 6: 1574–1583.

[93] Vernengo L, Choubargi O, Panuncio A et al. Desmin myopathy with severe cardiomyopathy in a Uruguayan family due to a codon deletion in a new location within the desmin 1A rod domain. Neuromuscul Disord 2010; 20:178–187.

[94] Hedberg C, Melberg A, Kuhl A et al. Autosomal dominant myofibrillar myopathy with arrhythmogenic right ventricular cardiomyopathy 7 is caused by a DES mutation. Eur J Hum Genet 2012; 20:984–985.

[95] Melberg A, Oldfors, A, Blomstrom-Lundqvist C et al. Autosomal dominant myofibrillar myopathy with arrhythmogenic right ventricular cardiomyopathy linked to chromosome 10q. Ann. Neurol. 46: 684–692, 1999.

[96] Budde B, Binner P, Waldmuller S et al. Noncompaction of the ventricular myocardium is associated with a de novo mutation in the beta-myosin heavy chain gene. PLoS One.2007; 2:e1362.

[97] Freedom, R, Yoo, S, Perrin D et al. The morphological spectrum of ventricular noncompaction. Cardiology in the Young 2005;15:345–364.

[98] Hermida-Prieto MML, Castro-Beiras A, Laredo R et al. Familial dilated cardiomyopathy and isolated left ventricular noncompaction associated with Lamin A/C gene mutations. Am J Cardiol. 2004; 94:50–54.

[99] Klaassen S, Probst S, Oechslin E et al. Thierfelder L. Mutations in
sarcomere protein genes in left ventricular noncompaction. Circulation 2008; 117:2893–2901.

[100] Monserrat L, Hermida-Prieto M, Fernandez X et al. Mutation in the alpha-cardiac actin gene associated with apical hypertrophic cardiomyopathy, left ventricular noncompaction, and septal defects. Eur Heart J. 2007a; 28: 1953–1961.

[101] Monserrat L, Hermida-Prieto M, Fernandez X et al. Mutation in the alpha-cardiac actin gene associated with apical hypertrophic cardiomyopathy, left ventricular noncompaction, and septal defects. Eur Heart J. 2007b; 28: 1953–1961.

[102] Van Waning J, Caliskan K, Hoedemaekers Y et al. Genetics, Clinical Features, and Long-Term Outcome of Noncompaction Cardiomyopathy. JACC 2018; 7; 711-722.

[103] Dooijes D, Hoedemaekers Y, Michels M et al. Left ventricular noncompaction cardiomyopathy: disease genes, mutation spectrum and diagnostic implications. Submitted. 2009.

[104] Ichida F, Tsubata S, Bowles KR et al. Novel gene mutations in patients with left ventricular noncompaction or Barth syndrome. Circulation. 2001;103: 1256–1263.

[105] Shan L, Makita N, Xing Y et al. SCN5A variants in Japanese patients with left ventricular noncompaction and arrhythmia. Mol Genet Metab. 2008;93: 468–474.

[106] Vatta M, Mohapatra B, Jimenez S et al. Mutations in Cypher/ZASP in patients with dilated cardiomyopathy and left ventricular noncompaction. J Am Coll Cardiol 2003;42:2014–2027.

[107] Li S, Zhang C, Liu N et al. Clinical implications of sarcomere and nonsarcomere gene variants in patients with left ventricular noncompaction cardiomyopathy. Mol Genet Genomic Med. 2019;7:e874.

[108] Akashi Y, Goldstein D, Barbaro, G; Ueyama T. Takotsubo Cardiomyopathy A New Form of Acute, Reversible Heart Failure. Circulation. 2008;118:2754–2762.

[109] Borchert T, Hübscher D, Guessoum C et al. Catecholamine-Dependent β-Adrenergic Signaling in a Pluripotent Stem Cell Model of Takotsubo Cardiomyopathy. JACC 2017, 20: 975–991.

[110] Limongelli G, Masarone D, Maddaloni V et al. Genetics of Takotsubo Syndrome. Heart Fail Clin 2016; 12: 499–506.

[111] Sealove B, Tiiyagura S, & Fuster, V. Takotsubo cardiomyopathy. J of Gen Intern Med, 2008; 23; 1904–1908.

[112] Sharkey S., Lesser J, Zenovich et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. Circulation 2005; 111: 472–479

[113] Aleong, R.G., Milan, D.J. & Ellinor, P. The diagnosis and treatment of cardiac ion channelopathies: congenital long QT syndrome and Brugada syndrome. Curr Treat Opt in Cardio Med 2007; 9; 5:364–371.

[114] Garcia-Elias A & Benito B. Ion Channel Disorders and Sudden Cardiac Death. Int. J. Mol. Sci. 2018; 19, 692.

[115] Modell, S.M. & Lehmann, M.H. (2006). The long QT syndrome family of cardiac ion channelopathies: a HuGE review. Genet in Med 2006; 8;143–155.

[116] Nakano Y & Shimizu W. Genetics of long-QT syndrome. J Hum Genet 2016; 61:51–55.
[117] Ackerman M, Priori S, Willems Set al. HRS/ EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies. Europace 2011; 13: 1077–1109.

[118] Mizusawa Y, Horie M, Wilde A. Genetic and Clinical Advances in Congenital Long QT Syndrome. Circ J 2014; 78: 2827–2283

[119] Schulze-Bahr E, Wang Q, Wedekind H, Haverkamp W, Chen Q, Sun Y, et al. KCNE1 mutations cause Jervell and Lange-Nielsen syndrome. Nat Genet 1997 17:267–268.

[120] Splawski I, Timothy K, Sharpe L et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell 2004; 119:19-31.

[121] Splawski I, Timothy KW, Decher N et al. Severe arrhythmia disorder caused by cardiac L-type calcium channel mutations. Proc Natl Acad Sci 2005; 102: 8089–8096.

[122] Etheridge S, Bowles N., Arrington C et al. Somatic mosaicism contributes to phenotypic variation in Timothy syndrome. Am. J. Med. Genet. 155A: 2578–2583, 2011.

[123] Plaster N, Taiw1 R, Tristan M et al. Mutations in KIR2.1 cause the developmental and episodic electrical phenotypes of Andersen’s syndrome. Cell 2001 18;105: 511–519.

[124] Schwartz PJ, Stramba-Badiale M, Crotti et al. Prevalence of the congenital long-QT syndrome. Circulation 2009; 120:1761–1767.

[125] Marks M, Trippel D, Keating M. Long QT syndrome associated with syndactyly identified in females. Am J Cardiol. 1995a; 76:744–745.

[126] Marks ML, Whisler SL, Clericuzio C, Keating M. A new form of long QT syndrome associated with syndactyly. J Am Coll Cardiol. 1995b; 25:59–64.

[127] Lo-A-Njoe SM, Wilde AA et al. Syndactyly and long QT syndrome (CaV1.2 missense mutation G640R) is associated with hypertrophic cardiomyopathy. Heart Rhythm. 2005; 2:1365–1368.

[128] Nguyen HL, Pieper GH, Wilders R. Andersen-Tawil syndrome: clinical and molecular aspects. Int J Cardiol. 2013; 170: 1-16.

[129] Pérez-Riera A, Barbosa-Barros R, Samesina N et al. Andersen-Tawil Syndrome: A Comprehensive Review. Cardiol Rev. 2020.

[130] Campuzano O, Fernandez-Falgueras A, Lemus X. Short QT Syndrome: A Comprehensive Genetic Interpretation and Clinical Translation of Rare Variants. J. Clin. Med. 2015;8, 1035.

[131] Giustetto C, Scrocco C, Giachino D et al. Short QT syndrome. Cardiogenetics 2011;1(1), 21–27.

[132] Rudic B, Schimpf R, Borggreve M. Short QT Syndrome – Review of Diagnosis and Treatment. Arrhythmia & Electrophysiology Review 2011; 3:76–79.

[133] Al-Khatib S, Stevenson W, Ackerman et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2018; 72:e91–e220.

[134] Begoña B, Brugada J et al. The Brugada syndrome. In Baars H, van der Smagt, J, Doevendans P, editors.
Clinical Cardiogenetics: Springer 2011; p.165–188.

[135] Brugada R, Hong K, Dumaine R, Cordeiro J et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation. 2004; 109:30–35.

[136] Gourraud J, Barc J, A. Thollet A. The Brugada Syndrome: A Rare Arrhythmia Disorder with Complex Inheritance, Front. Cardiovasc. Med. 3 2016 9.

[137] Li K, Lee S, Yin C et al. Brugada syndrome: A comprehensive review of pathophysiological mechanisms and risk stratification strategies. IJC Heart & Vascular 2020a; 26: 1–10.

[138] Monasky M, Micaglio E, Ciconte G et al. Brugada Syndrome: Oligogenic or Mendelian Disease? Int. J. Mol. Sci. 2020, 21, 1687

[139] Ohno S, Zankov D, Ding W et al. KCNE5 (KCNE1L) Variants Are Novel Modulators of Brugada Syndrome and Idiopathic Ventricular Fibrillation. Circ Arrhythm Electrophysiol 2011; 4: 352–361.

[140] Li KHC, Lee S, Yin C et al. Brugada syndrome: A comprehensive review of pathophysiological mechanisms and risk stratification strategies IJC Heart & Vascular 2020b; 26; 100468.

[141] Juang JM & Huang SK. Brugada syndrome-an under-recognized electrical disease in patients with sudden cardiac death. Cardiology 2004; 101: 157-1687

[142] Al-Hassnan ZN, Tulbah S, Al-Manea W et al. The phenotype of a CASQ2 mutation in a Saudi family with catecholaminergic polymorphic ventricular tachycardia. Pacing Clin Electrophysiol. 2013; 36:140–142

[143] Behere S & Weindling S. Catecholaminergic polymorphic ventricular tachycardia: An exciting new era. 2016 Annals of Pediatric Cardiology. Annals of Pediatric Cardiology 2016; 136–147.

[144] Jensen HH, Brohus M, Nyegaard Met al Human calmodulin mutations. Front Mol Neurosci. 2018;11:396.

[145] Rooryck C, Kyndt F, Bozon D, et al. New family with catecholaminergic polymorphic ventricular tachycardia linked to the triadin gene. J Cardiovasc Electrophysiol. 2015 ; 26:1146–1150.

[146] Van der Zwaag, P, Jongbloed J, van den Berg M et al. A genetic variants database for arrhythmogenic right ventricular dysplasia/cardiomyopathy. Hum Mutat 2009; 30:1278–1283.

[147] Hermans M, Pinto Y, Merkies et al. Hereditary muscular dystrophies and the heart Neuromusc Disord 2010; 20: 479–492.

[148] Finsterer J, Stöllberger C , Wahb K. Cardiomyopathy in neurological disorders. Cardiovasc Pathol. 2013: 5,389-400.

[149] Meola G, Cardani R. Myotonic dystrophies: An update on clinical aspects, genetic, pathology, and molecular pathomechanisms. Biochim Biophys Acta. 2015; 1852: 594-606.

[150] Barresi R, Di Blasi C, Negri T, et al. Disruption of heart sarcoglycan complex and severe cardiomyopathy caused by beta sarcoglycan mutations. J Med Genet 2000; 37:102–107.

[151] Connuck D, Sleeper L, Colan S et al. Characteristics and outcomes of cardiomyopathy in children with Duchenne or Becker muscular dystrophy: a comparative study from the Pediatric Cardiomyopathy Registry. Am Heart J 2008; 155:998–1005.

[152] De Ambroggi L, Raisaro A, Marchiano V, Radice S, Meola G.
Cardiac involvement in patients with myotonic dystrophy: characteristic features of magnetic resonance imaging. Eur Heart J 1995;16:1007-1010.

[153] Fanin M, Melacini P, Boito C et al. LGMD2E patients risk developing dilated cardiomyopathy. Neuromuscul Disord 2003;13:303–309.

[154] Goldfarb L, Dalakas M. Tragedy in a heartbeat: malfunctioning desmin causes skeletal and cardiac muscle disease. J Clin Invest 2009; 119:1806–1813.

[155] Jefferies J, Eidem B, Belmont J et al. Genetic predictors and remodeling of dilated cardiomyopathy in muscular dystrophy. Circulation 2005; 112:2799–2804.

[156] Kaspar R, Allen H, Ray W et al. Alvarez CE, Kissel JT, Pestronk A, et al. Analysis of dystrophin deletion mutations predicts age of cardiomyopathy onset in Becker muscular dystrophy. Circ Cardiovasc Genet 2009a; 2:544–451.

[157] Kaspar R, Allen H, Ray W et al. Alvarez CE, Kissel JT, Pestronk A, et al. Analysis of dystrophin deletion mutations predicts age of cardiomyopathy onset in Becker muscular dystrophy. Circ Cardiovasc Genet 2009b; 2:544–551.

[158] Lazarus A, Varin J, Ounnoughene Z et al. Relationships among electrophysiological findings and clinical status, heart function, and extent of DNA mutation in myotonic dystrophy. Circulation 1999; 99:1041–1046.

[159] Melacini P, Fanin M, Duggan D et al. Heart involvement in muscular dystrophies due to sarcoglycan gene mutations. Muscle Nerve 1999; 22: 473–479.

[160] Nakanishi T, Sakauchi M, Kaneda Y et al. Cardiac involvement in Fukuyama-type congenital muscular dystrophy. Pediatrics 2006a;117:1187–1119.

[161] Nguyen H, Wolfe 3rd J, Holmes Jr D, Edwards W. Pathology of the cardiac conduction system in myotonic dystrophy: a study of 12 cases. J Am Coll Cardiol 1988a; 11:662–671.

[162] Nakanishi T, Sakauchi M, Kaneda Y et al. Cardiac involvement in Fukuyama-type congenital muscular dystrophy. Pediatrics 2006b;117:e1187–e1119.

[163] Nguyen H, Wolfe 3rd J, Holmes Jr D, Edwards W. Pathology of the cardiac conduction system in myotonic dystrophy: a study of 12 cases. J Am Coll Cardiol 1988b; 11:662–671.

[164] Politano L, Nigro V, Passamano L et al. Evaluation of cardiac and respiratory involvement in sarcoglycanopathies. Neuromuscul Disord 2001;11:178–185.

[165] Schoser B, Ricker, K, Schneider-Gold C et al. Sudden cardiac death in myotonic dystrophy type 2. Neurology 2004; 63: 2402–2404.

[166] Selcen D, Engel AG. Myofibrillar myopathy caused by novel dominant negative alpha B-crystallin mutations. Ann Neurol 2003; 54:804–810.

[167] Vicart P, Caron A, Guicheney P et al. A missense mutation in the alphaB-crystallin chaperone gene causes a desmin-related myopathy. Nat Genet 1998; 20:92–95.

[168] Lehman S, Tal-Grinspan L, Lynn M et al. Chronic Calmodulin-Kinase II Activation Drives Disease Progression in Mutation-Specific Hypertrophic Cardiomyopathy. Circulation 2019; 139: 1517-1529.

[169] Harris S, de Tombe P. Sarcomeric mutations in cardiac diseases. Pflugers Arch. 2019 ; 471: 659-660.
[170] Carrasco L, Vernengo L, Mesa R et al. Síndrome de Kearns-Sayre. Presentación de un caso clínico y revisión de la bibliografía. Arch. Inst. Neurol. 2005; 8(2):31–35. [Article in Spanish. Abstract in English].

[171] De Jonge N & Kirkels J. Restrictive cardiomyopathy. In Baars H, van der Smagt, J, Doevendans P, editors. Clinical Cardiogenetics: Springer 2011; p.123–128.

[172] Walter L, Nogueira V, Leverve X et al. Three classes of ubiquinone analogs regulate the mitochondrial permeability transition pore through a common site. J Biol Chem 2000; 275: 29521-29527.

[173] Behjati M, Sabri M, Far M et al. Cardiac complications in inherited mitochondrial diseases. Heart Fail Rev. 2021; 26: 391–403.

[174] Holgrem D, Wahlander H, Eriksson, B et al. Cardiomyopathy in children with mitochondrial disease: clinical course and cardiologigal findings. Eur Heart J 2003; 24:280–288.

[175] Annan R, Nakagawa M, Miyata M et al. Cardiac involvement in mitochondrial disease. A study of 17 patients with documental mitochondrial DNA defects. Circulation 1995; 91: 955–961.

[176] Roberts N, Perloff J, Kark R. A follow up study of myocardial involvement in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Heart 1998a; 80: 292-2955.

[177] Roberts N, Perloff J, Kark R. A follow up study of myocardial involvement in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Heart 1998b; 80:292-2955.

[178] Hirano M & Pavlakis S. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): current concepts. J Child Neurol. 1994; 9: 4-13

[179] Vydt T, de Coo R, Soliman O et al. Cardiac involvement in adults with m.3243A>G MELAS gene mutation. Am J Cardiol. 1997; 99: 264–269.

[180] Wortmann S, Rodenburg R, Backx A et al. Early cardiac involvement in children carrying the A3243G mtDNA mutation. Acta Paediatr. 2007; 96: 450–451.

[181] Kirkels J & de Jonge N. Mitochondrial cardiomyopathy. In Baars H, van der Smagt, J, Doevendans P, editors. Clinical Cardiogenetics: Springer 2011a; p123–128.

[182] Okajima Y, Tanabe Y, Takayanagi M & Aotsuka H. A follow up study of myocardial involvement in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Heart 1998; 80: 292-295.

[183] Spencer C, Bryant R, Day J et al. Cardiac and clinical phenotype in Barth syndrome. Pediatrics 2006;118:337–346.

[184] Jacoby D & McKenna W. Genetics of inherited cardiomyopathies. European Heart Journal 2012; 33: 296–304.

[185] Towbin JA. Inherited cardiomyopathies. Circ J. 2014;78:2347-2356.

[186] Ingles J, Doolan A, Chiu C et al. Compound and double mutations in patients with hypertrophic cardiomyopathy: implications for genetic testing and counselling. J Med Genet. 2005;42:e59.

[187] Richard P, Isnard R, Carrier L, et al. Double heterozygosity for mutations in the beta-myosin heavy chain and in the cardiac myosin binding protein C genes
in a family with hypertrophic cardiomyopathy. J Med Genet. 1999; 36: 542–545.

[188] Van Diest SL, Vasile VC, Ommen SR, Will ML, Jamil Tajik A, Gersh BJ, Ackerman MJ. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. J Am Coll Cardiol 2004;44:1903–1016 ;

[189] Ho C, Lever H, DeSanctis R, Farver C et al. Homozygous mutation in cardiac troponin T: implications for hypertrophic cardiomyopathy. Circulation 2000;102:1950–1955.

[190] Ingles J, Sarina T, Yeates L, et al. Clinical predictors of genetic testing outcomes in hypertrophic cardiomyopathy. Genet Med 2013; 15: 972–977.

[191] Uro-Coste E, Arne-Bes M, Pellissier J et al. Striking phenotypic variability in two familial cases of myosin storage myopathy with a MYH7 Leu1793pro mutation. Neuromuscul Disord 2009;19: 163–1636.

[192] Watkins H, McKenna W, Thierfelder L et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. N Engl J Med 1995; 332: 1058-1064.

[193] Landstrom, A. & Ackerman M. Mutation type is not clinically useful in predicting prognosis in hypertrophic cardiomyopathy. Circulation 2010; 22: 2441–2451.

[194] Tardiff JC. Sarcomeric proteins and familial hypertrophic cardiomyopathy: linking mutations in structural proteins to complex cardiovascular phenotypes. Heart Fail Rev 2005;10:237

[195] Fourey D, Care M, Siminovitch M et al. Prevalence and clinical implication in double mutation in hypertrophic cardiomyopathy: revisiting the gene dose effect. Circ Cardiovasc Genet. 2017;10: e001685.

[196] Maron B, Maron M, Semsarian C. Double or compound sarcomere mutations in hypertrophic cardiomyopathy: A potential link to sudden death in the absence of conventional risk. Heart Rhythm 2012b; 9: 57-63

[197] Crilley J, Boehm E, Blair E et al. Hypertrophic cardiomyopathy due to sarcomeric gene mutations is characterized by impaired energy metabolism irrespective of the degree of hypertrophy. J Am Coll Cardiol 2003;41: 1776–1787.

[198] Mestroni L, Rocco C, Gregori D, et al. Familial dilated cardiomyopathy: evidence for genetic and phenotypic heterogeneity. Heart Muscle Disease Study Group. J Am Coll Cardiol 1999; 34:181–190.

[199] Michels V, Moll P, Miller F et al. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. N Engl J Med 1992; 326:77–82.

[200] MacArthur DG, Manolio TA, Dimmock DP et al. Nature 2014. Guidelines for investigating causality of sequence variants in human disease. Nature 508, 469–476.

[201] Manrai AK, et al. Genetic misdiagnoses and the potential for health disparities. N Engl J Med. 2016; 375: 655–665.

[202] Moolman J, Corfield V, Posen B et al. Sudden death due to troponin T mutations. J Am Coll Cardiol 1997a;29: 549..
remodeling and restrictive physiology. Clin. Genet. 2008; 74: 445–454.

[204] Peddy S, Vricella L, Crosson J et al. Infantile restrictive cardiomyopathy resulting from a mutation in the cardiac troponin T gene. Pediatrics 2006; 117: 1830–1833.

[205] Hoedemaekers Y, Caliskan K, Michels M. The importance of genetic counseling, DNA diagnostics and cardiologic family screening in left ventricular noncompaction cardiomyopathy. Circ Cardiovasc Genet. 2010; 3:232–239.

[206] Becane H, Bonne G, Varnous S et al. High incidence of sudden death with conduction system and myocardial disease due to lamin A and C gene mutation. Pacing Clin Electrophysiol 2000; 23:1661–1666.

[207] Brodsky G, Muntoni F, Miocic S et al. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. Circulation 2000; 101:473–476.

[208] Emmanuele V, Silvers DS, Sotiriou E, Tanji K, DiMauro S, Hirano M. MERRF and Kearns-Sayre overlap syndrome due to the mitochondrial DNA m.3291T>C mutation. Muscle Nerve. 2011; 44:448-451.

[209] Pitceathly R, Fassone E, Taanman J et al. Kearns-Sayre syndrome caused by defective R1/p53R2 assembly. J Med Genet. 2011; 48: 610–617.

[210] Di Mauro S, Bonilla E, Zeviani M et al. Mitochondrial myopathies. Ann Neurol 1985; 17:521–538.

[211] Baltogiannis G, Lysitsas D; Di Giovanni G e al. CPVT: Arrhythmogenensis, therapeutic management, and future perspectives. A brief review of the literature. Front. Cardiovasc. Med. 12 July 2019.

[212] Hoedemaekers Y, Caliskan K, Majoor-Krakauer D. Non-compaction cardiomyopathy. In Baas H, van der Smagt, J, Doevendans P, editors. Clinical Cardiogenetics: Springer 2011; P.98–122.

[213] Hsu, YH.R., Yogasundaram, H., Parajuli, N. et al. MELAS syndrome and cardiomyopathy: linking mitochondrial function to heart failure pathogenesis. Heart Fail Rev 2016; 21: 103–116

[214] Kumar Singh B, Kolappa Pilla K et al. Classification and definitions of cardiomyopathies. In Joseph Veselka, editor.: Cardiomyopathies –from basic research to clinical management InTech 2012; p.3–20.

[215] Nimura H, Bachinski LL, Sangwatanaroj S, et al. Mutations in the gene for cardiac myosin binding protein C and late-onset familial hypertrophic cardiomyopathy. N Engl J Med 1998; 338: 1248–1257.

[216] Thierfelder, L., Watkins, H., MacRae, C et al .Alpha-tropomyosin and cardiac troponin T mutations cause familial hypertrophic cardiomyopathy: a disease of the sarcomere, Cell 1994; 77: 701–712.

[217] Van der Werf C & Wilde A. Catecholaminergic polymorphic ventricular tachycardia. In Baas H, van der Smagt, J, Doevendans P, editors. Clinical Cardiogenetics: Springer 2011; p.197–206.