The Role of Genetics in Cardiomyopathy

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1. Introduction

Cardiomyopathies can be defined as disorders of the myocardium which are associated with cardiac dysfunction and are aggravated by arrhythmias, heart failure and sudden death [Ricardson, 2006]. Genetics has played a very important role in the understanding of the different cardiomyopathies since, in 1957, Bridgen cited for the first time the word "cardiomyopathy" and in 1958, Teare, the British pathologist reported nine cases of septum hypertrophy (Teare, 1958).

The American Heart Association (AHA) has classified cardiomyopathies as primary cardiomyopathies (the heart is the only organ affected) and secondary cardiomyopathies (the heart is affected as part of a systemic disease). The European Society of Cardiology (ESC) has classified them according to morphological and functional phenotypes involving their pathophysiology (Maron, 2006; Maron, 2008; Elliott, 2008)

Primary cardiomyopathies are those which and can be genetic, nongenetic or acquired. Secondary cardiomyopathies are those in which the cardiomyopathy is found in a systemic disease. Primary cardiomyopathies can then be classified according to their anatomical and functional impairment in hypertrophic cardiomyopathy, dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), ion channel disorders. Secondary cardiomyopathies are those found in muscular dystrophies, mitochondrial disorders among others. The unclassified cardiomyopathies are non-compaction cardiomyopathy and takotsubo cardiomyopathy (Elliott, 2008;)

The genetic diagnosis has a close involvement in the management of primary and secondary cardiomyopathies and its development will have a key role in the understanding of the different molecular mechanisms that lead to a cardiomyopathy.

2. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a familial disease that in fifty percent of the cases is inherited in an autosomal dominant pattern. The disorder shows complete penetrance in most families although it depends on the age and the sex of the patients (Nimura, 1998, Richard, 2003, Richard, 2006).

As the prevalence of HCM is 1: 500, it can be stated that HCM is undoubtedly the most common cardiovascular disorder (Maron, 2002).

HCM has been traditionally described as an unexplained hypertrophy of the left ventricle that develops in the absence of systemic hypertension, valvular heart disease or amyloidosis. The left ventricular hypertrophy (LVH) is usually asymmetric and involves the septum.

The clinical presentation is variable. There can be varying degrees of clinical severity which can range from dyspnea, palpitations, atrial fibrillation, and syncopal episodes to congestive heart failure and sudden death. Many can be asymptomatic throughout their whole life, whereas others may even require heart transplantation. It is the most common cause of death in young athletes while practicing sports.

HCM generally has normal systolic function, impaired diastolic function and outflow ob-struction in about 25%. The histopathology shows myocyte disarray, interstitial fibrosis and hypertrophy (Richard, 2006, Ho, 2007).

Mutations in any of the thirteen sarcomeric genes lead to HCM. (See Table 1). The sarcomere has a complex structure where the proteins that form it interact among themselves. The different mechanisms that cause HCM are not yet completely understood. Most mutations in HCM are private of each family and there is clinical heterogeneity within family members (Richard, 2006 Hayashi, 2004; Frank, 2011).

3. Dilated cardiomyopathy

Dilated cardiomyopathy is the most common cause of congestive heart failure in young patients. The prevalence is ~36: 100,000 in the U.S. It is characterized by ventricular chamber enlargement, thin wall thickness, impaired left ventricular systolic function, and there is also, in some cases, secondary diastolic dysfunction. The most common feature is congestive heart failure, though, conduction impairment, syncope and sudden death may also occur. It is an important cause of cardiac transplantation (Sugrue, 1992).

The histological findings are nonspecific and they include myocyte loss and interstitial fibrosis. Familial cases of DCM were initially considered to be quite rare. However, careful screenings have shown that up to 35% of the probands´ relatives have a DCM familial disorder.

In these families, the pattern of inheritance is variable, so the patients present both locus heterogeneity and allellic heterogeneity. Mutations in many genes have been reported to cause

HCM gene	Symbol	Locus name	Chromosome locus	Protein
Beta-myosin heavy chain	MYH7	CMH1	14q2	Myosin heavy chain, cardiac muscle beta isoform
Myosin-binding protein C	MYBPC3	CMH4	11p11.2	Myosin-binding protein C, cardiac-type
Troponin T	TNNT2	CMH2	1q32	TroponinT, cardiac muscle
Troponin I	TNNI3	CMH7	19q13.4	TroponinI, cardiac muscle
Alpha-tropomyosin	TPM1	CMH3	15q22.1	Tropomyosin1 alpha chain
Regulatory myosin light chain	MYL2	CMH10	12q24.3	Myosin regulatory light chain 2, ventricular/ cardiac muscle isoform
Essential myosin light chain	MYL3	CMH8	3p21 5	Myosin light polypeptide 3
Actin	ACTC1	CMH11	15q14	Actin, alpha cardiac muscle 1
Cardiac troponin C	TNNC1	CMH13	3p21.1	Troponin C, slow skeletal and cardiac muscles
Titin	TTN	CMH9	2q24.3 2	Titin
Alpha-myosin heavy chain	MYH6	CMH14	14q12	Myosin heavy chain, cardiac muscle alpha isoform
Muscle LIM protein	CSRP3	CMH12	11p15.	Cysteine and glycine-rich protein 3, muscle LIM protein
Telethonin	TCAP	CMH11	17q12 1	Telethonin

Table 1. Sarcomeric genes that cause HCM

different forms of dilated cardiomyopathy. Therefore, autosomal dominant, autosomal recessive, and X-linked inheritance can be observed. (See Table 2) However, the autosomal dominant pattern is the most frequent mode of inheritance. It has been demonstrated that DCM has reduced penetrance. The age of onset shows great variability though it is usually appears in adulthood (Mangin, 1999). When the mutation is in one of the sarcomeric genes the affected patients are usually young adults (Aernout Somsen, 2012).

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

DCM gene	Symbol	Locus name	Chromosome locus	Protein	Mode of inheritance
TNNI3 gene	TNNI3	CMD1FF	19q13.4;	Troponin I,	AD
SDHA gene	SDHA	CMD1GG	5p15;	Succinate dehydrogenase complex subunit A	AD
BAG3 gene	BAG3	CMD1HH	10q25.2-q26.2	BCL2-associated athanogene 3	AD
TNNI3 gene	TNNI3	CMD2A,	19q13.42	Troponin I, cardiac muscle	AR
GATAD1 gene.	GATAD1	CMD2	7q21.2	GATA zinc finger domain containing protein 1	AR
Dystrophin gene	DMD	CMD3B	Xp21.2	dystrophin	X-linked
LAMP2 gene	LAMP2	Danon disease	Xq24	lysosome-associated membrane protein-2	X-linked
TAZ gene	TAZ		Xq28	dystrophin	X-linked

Table 2. Genes tha cause DCM

Mutations on the following genes *CMD1B* on 9q13; *CMD1H* on 2q14-q22; *CMD1K* on 6q12-q16; and *CMD1Q* on 7q22.3-q31.1 can also cause DCM.

4. Restrictive cardiomyopathy

Familial restrictive cardiomyopathy (RCM) is a rare disease which is inherited in autosomal dominant pattern with incomplete penetrance (Katritsis 1991). The exact prevalence of RCM is unknown (Elliott, 2008). In childhood, RCM accounts for 2–5% of cardiomyopathies and has a grave prognosis (Kaski, 2008.)

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 (Kushwaha, 1997).

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,

In many cases RCM can be observed overlapping with either HCM or DCM. (Kamisago, 2000; Olson, 2002; Zang, 2005; Kaski, 2008).

5. Arrhythmogenic right ventricular cardiomyopathy / dysplasia

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/ARVD) is a commonly inherited disorder with a family history in 30 to 50% of the cases (Klauke, 2010).

The prevalence has been estimated 1:2000 to 1:5000 in the general population (Peters 2006, Cox&Hauer, 2011).

ARVC is characterized by fibro-fatty replacement of the myocardium with a marked involvement of the right ventricle. ARVC can be defined by the presence either sectored or global right ventricular dysfunction. The left ventricular abnormalities which lead to DCM may take place later. Clinical features include tachyarrhythmias, electrocardiographic abnormalities, systolic heart failure, syncope and sudden death. ARVC is a frequent cause of sudden death in young people and athletes (Maron, 2006).

It is transmitted with an autosomal dominant pattern, though autosomal recessive families have also been reported. Incomplete penetrance and great variability in the symptoms have been observed (Hamid, 2002; Awad, 2008; Eliott, 2008; Klauke, 2010, Cox&Hauer, 2011).

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 3)

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 (Van Titelen, 2007; Vernengo, 2010; Klauke, 2010). Only recently has it been proven that seven members of the Swedish family with ARVC7 had the p.Pro419Ser mutation in *DES*, instead of a mutation linked to chromosome 10q23.2 (Melberg, 1999; Hedberg, 2012).

Naxos disease and Carvajal disease are ARVC 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 (Protonotarios, 1986; McKoy, 2000; Schonberger, 2001; Cox&Hauer, 2011).

6. Non–compaction cardiomyopathy

Non-compaction cardiomyopathy (NCCM) has been classified as a primary cardiomyopathy with a genetic etiology.The age of onset varies from neonatal to adult hood. There is variability in the clinical features which include heart failure, arrhythmias and thromboembolism, but patients can also be asymptomatic]. The most common congenital heart defects in NCCM are Ebstein's anomaly, septal defects and patent ductus arteriosus,

The patients have a thickened two-layered myocardium with a thin, compact, epicardial layer and a severely thickened endocardial layer with a 'spongy' appearance due to prominent

ARCV gene	Symbol	Locus name	Chromosome locus	Protein
Transforming growth factor beta- 3	TGFB3	ARVD1	14q2	Transforming growth factor beta-3
Ryanodine receptor 2	RYR2	ARVD2	1q43	RYR2
Unknown	Unknown	ARVD3	14q12-q22	Unknown
Unknown	Unknown	ARVD4	2q32 .1-q32.3	Unknown
transmembrane protein 43	TMEM43	ARVD5	3p25 .1	Transmembrane protein 43
Unknown	Unknown	ARVD6	10p14-p12	Unknownn
Desmin	DES	ARVD7	2q35	Desmin
Desmoplakin	DSP	ARVD8	6p24 .3	Desmoplakin
Plakophilin-2	PKP2	ARVD9	12p11 .21	Plakophilin-2
Desmoglein-2	DSG2	ARVD10	18q12 .1	Desmoglein-2
Desmocollin-2	DSC2	ARVD11	18q12 .1	Desmocollin-2
Junction plakoglobin	JUP	ARVD12	17q21 .2	Junction plakoglobin
Desmin	DES	ARVC	2q35	Desmin

Table 3. Genes that cause ARVC.

trabeculations and intertrabecular recesses (Hermida-Prieto, 2004; Freedom, 2005; Budde, 2007; Monserrat, 2007; Klaassen, 2008)

The majority of the patients have an autosomal dominant mode of inheritance.

Mutations in several genes coding for sarcomeric proteins have been described in NCCM, 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*). MYH7 has been reported to be the most frequent disease gene in NCCM in the absence of HCM (Ichida, 2001; Hermida-Prieto. 2004; Vatta, 2003; Shan, 2008).

7. Takotsubo cardiomyopathy

Takotsubo cardiomyopathy is characterized by an acute but transitient LV systolic dysfunction without atherosclerotic coronary artery disease and it is triggered by psychological stress (Sharkey, 2005; Sealove, 2008).

8. 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 (Aleong, 2007). These ion channel disorders include the Romano-Ward syndrome (long QT syndromes), the short-QT syndrome (SQTS), Brugada syndrome, and the catecholaminergic polymorphic ventricular tachycardia (CPVT). 5% to 10% of the sudden deaths in children can be associated to ion channel disorders (Modell & Lehmann, 2006).

The clinical diagnosis of the ion channelopathies can be often made by identification of alterations found on the ECG (Aleong, 2007; Kass, 2005).

8.1. Romano–Ward syndrome

RWS may be sporadic or transmitted as an autosomal-dominant trait with reduced penetrance. It is the most common form of inherited long QT syndrome. The prevalence of RWS has been estimated to be 1:3000 to 1:7000.

The Romano-Ward syndrome (RWS) is tipically identified in patients that present syncope, seizures, or sudden death due to episodic taquiarrhythmias, QT prolongation and T-wave abnormalities, interval torsade de pointes that lead to ventricular fibrillation and death.

RWS is associated with mutations in the following genes: *KCNQ1* on chromosome 11p15.5-p15.4, *KCNE1* on chromosome 21q22.12, *KCNE2* on chromosome 21q22.11, *KCNH2* on chromosome 7q36.1, *SCN5A* on chromosome *3p22.2, CAV3* on chromosome *3p25.3, SCN4B* on chromosome 11q23.3, *AKAP9* on chromosome 7q21.2, *SNTA1* on chromosome 20q11.21 and *KCNJ5* on chromosome *11q24.3* (Schwartz 1993; Schwartz 2001: Schwartz 2011).

8.2. Jervell and Lange–Nielsen syndrome

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 which tachiarrhythmias including torsade de pointes, ventricular fibrillation, syncope and sudden death.

Mutations in the *KCNQ1* gene on chromosome 11p15.5-p15.4, *KCNE1* gene on chromosome 21q22.12, have been reported in the affected individuals (Schwartz 2000; Schwartz 2006).

8.3. Timothy syndrome

Timothy syndrome is a rare autosomal dominant disorder are due to either a *de novo* mutation or parent germline mosaicism Mutations in the same gene *CACNA1C* cause the two forms of the disorder: the classic, type 1, and type 2. The reported cases of the patients suffering type 1 syndrome have shown complete penetrance (Splawski, 2004).

This complex multisystem disorder has a long QT syndrome associated with syndactily. Various forms of congenital heart defects such as tetralogy of Fallot, hypertrophic cardiomy-

opathy have been observed. The type 2 patients that have been reported did not have syndactily (Splawski, 2005)

Children died at age of 2.5 years due to ventricular tachycardia and ventricular fibrillation, infection or hypoglycemia (Reichenbach, 1992; Marks, 1995a; Marks 1995b; Splawski 2004; Lo-A-Njoe, 2005).

8.4. Brugada syndrome

The Brugada syndrome, which is inherited in an autosomal dominant pattern, 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 age of appearance ranges from a two- day- old patient to 85 years (Marks, 1995a; Marks, 1995b; Splawski, 2004; Huang, 2004; Lo-A-Njoe, 2005).

The cardiac differential diagnosis must be made with Duchenne muscular dystrophy, Friedreich ataxia and ARVC.

8.5. 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 7-9 years to the fourth decade of life.

It presents locus heterogeneity and in only approximatedly 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.

There is an autosomal dominant form caused by mutations in the RYR2 gene that encodes the ryanodine receptor 2, a calcium-release channel (George, 2003).

The autosomal recessive form is due to mutations in the calsequestrin 2 gene on chromosome 1p13.1 (Wilde, 2008).

8.6. 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, 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.

9. 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 (Hermans, 2012).

Cardiomyopathy occurs in myofibrillar myopathy, myotonic dystrophies, myotonic myopathies, dystrophinopathies, Emery-Dreifuss muscular dystrophy, and limb girdle muscular dystrophies (Hermans, 2012).

They are inherited in autosomal dominant, autosomal recessive and X-linked mode. (See Table 4, Table 5).

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 muscular dystrophies can cause hypertrophic, dilated or restrictive cardiomyopathy, 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. (De Ambroggi, 1995, Vicart 1998; Nguyen, 1998; Lazarus, 1999; Melacini, 1999; Barresi, 2000; Politano, 2001; Selcen, 2003; Fanin, 2001; Jefferies, 2005; Nakanishi, 2006; Connuck, 2008; Kaspar, 2009; Goldfarb, 2009; Lilienbaum, 2012; Hermans, 2012)

10. 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

Disease Name	Gene	Symbol	Locus name	Chromosome locus	Protein	Mode of inheritance
Desminopathy	Desmin	*DES*	MFM1	**2q35**	Desmin	AD/AR
Alpha-B crystallinopathy	CRYAB gene	*CRYAB*	MFM2	11q23.1	alpha-B-crystallin	AR/AD
Myotilinopathy	Myotilin	*MYOT (TTID)*	MFM3	5q31.2	Myotilin (titinmmunoglobuli n domain protein)	AD
ZASPopathy	ZASP	*LDB3*	MFM4	**10q23.2**	LIM domain-binding protein 3	AD
Filaminopathy	FilaminC	*FLNC*	MFM5	7q32.1	Filamin C	AD
BAG3-Related Myofibrillar Myopathy	BCL2-associated athanogen 3	*BAG3*	BAG3	***10q26.11***	BAG family molecular chaperone regulator 3	AD
Myotonic dystrophy type 1	myotonin-protein kinase (Mt-PK).	*DMPK*	DMPK	19q13.3	dystrophia myotonica-protein kinase	AD
Myotonic dystrophy type 2	zinc finger protein-9 gene	*CNBP*		*3q21.3*	zinc finger protein-9	AD
Duchenne/Becker muscular dystrophy	dystrophin	*DMD*	DMD	Xp21.2	dystrophin	X-linked
Emery-Dreyfuss Muscular Dystrophy1,X-linked	EMD gene	*EMD*	EMD1	Xq28	emerin	X-linked

Table 4. Genes that cause cardiomyopathy in muscular dystropies

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 (Walter, 2000; Carrasco, 2005; De Jonge, 2011).

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 (Walter, 2000; Carrasco, 2005; De Jonge, 2011).

Mitochondrial dysfunction and clinical symptoms appear when the heteroplasmic levels are above 80%-90% (Walter, 2000; Carrasco, 2005; De Jonge, 2011).

Disease Name	Gene	Symbol	Locus name	Chromosome locus	Protein	Mode of inheritance
LGMD2C	gamma sarcoglycan gene	*SGCG*	SGCG	13q12-q13	gamma sarcoglycan	AR
LGMD2D	alpha sarcoglycan gene	*SGCA*	SGCA	17q21	Alpha sarcoglycan	AR
LGMD2E	Beta sarcoglycan gene	*SGCB*	SGCB	4q12	Beta sarcoglycan	AR
LGMD2F	Delta sarcoglycan gene	*SGCD*	SGCD	5q33-q34	Delta sarcoglycan	AR
LGMD2I	fukutin related protein gene	*FKRP*	FKRP	19q13.32	fukutin related protein	AR

Table 5. Limb-girdle muscular dystrophies

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. Both hypertrophic and dilated cardiomyopathies have been reported (Holmgren, 2003, de Jonge, 2011).

11. Kearns-Sayre syndrome

The Kearns-Sayre syndrome (KSS) 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 (Roberts, 1979; Anan, 1995; Carrasco, 2005).

11.1. 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% (Hirano, 1994; Vydt, 2007; Wortmann, 2007). The first symptom the affected children have is the cardiomyopathy. The most common feature is a hypertrophic cardiomyopathy, although dilation has also been reported (Okajima, 1998).

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 (de Jonge, 2011).

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. When the protein is mutated in Friederich ´s ataxia, it does not allow the correct respiratory function.

Barth syndrome is a recessive X-linked inherited disease chacterized by cardiomyopathy and neutropenia. The cardiac disease presents a dilated cardiomyopathy, often with a degree of left myocardial thickening and, sometimes, endocardial fibroelastosis. The cardiac disease appears at birth or in the first few months of life

Mutations in the tafazzin gene are to be held responsible for this disorder because of the inhibition of this pathway leads to changes in mitochondrial architecture and function (Spencer, 2006, Schamme, 2006).

12. The impact of genetics in the understanding of cardiomyopathy

Although the diagnosis is based primarily on DNA analysis, a thorough clinical history and examination, blood tests, the ECG, echocardiography, electromyography, and muscle biopsy can also provide information that can be helpful for the diagnosis not only of the patients, but also of the asymptomatic carriers.

With the expansion in number of the different disorders that have myocardial involvement in conjunction with the development of their molecular and biochemical bases, it can be stated that these will play a most important role in the understanding of the pathophysiology of the syndromes.

The exact role and function each mutated protein has and the pathogenic mechanisms that lead to the different disorders still have to be elucidated, in spite of the fact that the mutations that cause them have been found.

It has also been observed that the mutations within the same gene and in the same family can give rise to distinct phenotypes in HCM, DCM and RCM. The pathogenesis of the three major types of cardiomyopathy can be linked to the the genetic mutations in the different sarcomeric proteins. These gene mutations are responsible to trigger the different pathways that lead to the remodeling of the heart. The mechanisms why this occurs are still unclear and the animal models are markedly distinct.

Since HCM is an autosomal dominant disorder most of the patients suffering from it are heterozygous. Mutations in MYH7 and/or MYBPC3 genes account for 80% of the mutations (Richard, 2006).

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* (Richard, 1999; Richard 2003; Van Driest, 2004; Ingles, 2005; Richard 2006).

The genotype-phenotype correlations have been linked to specific mutations (Richard, 2006).

The different mutations in the *MYH7* gene 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 (Ho, 2000; Richard, 2006; Overeem, 2007; Uro-Coste, 2009).

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, I79N are young, and even though they have a mild LVH, they died of sudden death. The F110I mutation does not seem to have a so severe development as the rest of the mutations in this gene (Watkins, 1995; Arian, 1998; Tardiff, 2005, Richard, 2006).

It is believed that patients having double mutations have a greater severity of the disorder due to a double dose effect (Ingles, 2005).

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 have not developed the disease. It is unknown whether carriers will develop the disorder at a certain age of their lives or will remain asymptomatic. 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 (Michels, 1992; Mestroni, 1999; Criley, 2003; Richard, 2006).

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 (Peddy, 2006; Menon, 2008).

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 and taffazin gene (*TAZ)* on chromosome Xq28 (Bleyt, 1997). It has been observed that when the mutations are in a sarcomeric gene, they give rise to a truncated protein and the onset of the disorder is during childhood. When there is an adult onset, there can be multiple mutations in a non sarcomeric gene thus the phenotype is more severe

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

In Timothy syndrome the molecular diagnosis of *CACNA1C* 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 (Becane, 2000; Brodsky, 2000)

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.

It has suggested that the mutations in the nuclear gene *RRM2B* gene cause 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 (Pitceathly, 2012).

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 (Di Mauro,2005).

13. What should the genetic counseling be in cardiomyopathy?

To provide genetic counseling to an individual that has a cardiomyopathy is not an easy task.

When a patient or a relative that has been diagnosed with cardiomyopathy comes for genetic counseling, the geneticist has to be forthright and explain that there are all sorts of disorders that cause it, locus heterogeneity and clinical variability.

It is very important that when a numerical value is provided the patient and/or his family understand what has been explained to them. It is necessary to be very clear that chance does not have a memory. It would be embarrassing to face a family that comes with a second affected child because they have misinterpreted the information provided to them.

It should also be pointed out that the molecular diagnosis of a disorder it is not only time consuming and a very expensive process, but also that, sometimes, there is not a specific mutation that stands out in the different disorders that cause a cardiomyopathy. Many patients do not have an identified causing gene defect.

Opinions differ about procedures when consultants are under 18 and asymptomatic, and at risk of having the disorder when adults, and there is not a causal treatment. Therefore, running

the molecular test of the disorder would be inappropriate. If a mutation is found, the children will not longer lead a normal life and it will also have a negative effect on family 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 analyses of *TNNT2, TNNT3, MYL2, MYL3, TPM1* and *ACTC* might clarify other cases.

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.

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

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

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

Timothy syndrome is due to either a *de novo* mutation or parental germline mosaicism. They do not live long enough to reproduce.

Only the siblings are at risk of inheriting the disorder.

When there is a *de novo* mutation, alternate paternity and maternity as well as whether the patient is adopted have to be ruled out.

The offspring of a patient suffering autosomal dominant familial cardiomyopathy has a 50% chance of inheriting the mutation. Families in which penetrance appears to be incomplete or reduced have been observed; therefore a 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 *de novo* mutations, so there is only one family member affected. The offspring of a male patient are not at risk whereas all females´ offspring

are at risk of inheriting the mutation. There is not risk that any other family member will inherit the disease.

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

A prenatal diagnosis for those patients there are at risk for any cardiomyopathy is possible, 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

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 sometimes deadly disorders.

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