Genetics: Genotype/Phenotype Correlations in Cardiomyopathies

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2.1 Introduction

When considering etiology, many cardiomyopathies (CMP) have a genetic origin; some are acquired (inflammation, alcohol, drugs, etc.), whereas others may have a mixed origin [1]. The relationships between gene mutations and phenotype are complex and not always clear. One challenging point is the observation that mutations in the same gene may cause different types of CMP; moreover, the various CMP are characterized by great heterogeneity in clinical phenotypes. The key features to note for different inheritance patterns are as follows:

- Autosomal dominant inheritance is characterized by the presence of affected individuals in every generation, with the possibility of male-to-male transmission and a 50 % risk to offsprings of affected parents.
- Autosomal recessive inheritance is the least common pattern in heart-muscle diseases. It should be suspected when both parents of the proband are unaffected and consanguineous. Males and females are equally affected. Parents of an affected child are obligate carriers, with a 25 % risk of having a carrier son/daughter in each pregnancy.

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- X-linked inheritance should be suspected if males are the only or most severely affected individuals. In X-linked inheritance, all daughters of an affected father will be carriers and no male–male transmission is observed. A female carrier has a 50 % risk of having affected sons and a 50 % risk of daughters that carry the gene defect. In some X-linked disorders, such as Anderson–Fabry disease, female carriers can develop milder and later disease because of unfavorable inactivation of the X-chromosome (lionization) [2].
- Matrilineal (or mitochondrial) inheritance in which women but not men transmit the disease to offspring (male and female) is typical of mutations in mitochondrial DNA.

Although differences exist in the classification of major cardiac organizations, genetic CMP have historically been broken down into several major phenotypic categories: hypertrophic, dilated, arrhythmogenic, and restrictive [3].

2.2 Genetic Approach: From Genotype to Phenotype

2.2.1 Dilated Cardiomyopathy

Most genetic dilated cardiomyopathy (DCM) inheritance follows an autosomal dominant pattern, although X-linked, recessive, and mitochondrial patterns of inheritance occur as well. At least 30–50 % of DCM cases are familial, suggesting the involvement of a defective gene [4]. X-linked DCM results from mutations in the dystrophin gene. It may be clinically indistinguishable from idiopathic DCM (IDCM) [5]. Creatine kinase levels are usually (but not always) elevated.

DCM is characterized by a high level of genetic complexity and involvement of different structures of myocytes. Initially, DCM was considered to be a disease of the cytoskeleton; later, it was demonstrated that other structures may be involved, such as sarcomere, Z-disc, nucleoskeleton, mitochondria, desmosomes, sodium and potassium channels, and lysosomal membrane [4, 6]. Mutations in >30 genes across a wide variety of cellular components and pathways have been associated with DCM. The most common sarcomeric mutations are reported in *MYH7*, in *TNNT2*, in *MYBPC3* [7, 8] and alpha-myosin heavy chain (*MYH6*). Hershberger et al. also found rare variants in genes of the sarcomeric complex that “likely” or “possibly” caused the disease in their study population [4]. Herman et al. reported a high frequency of “deleterious variants” in the titin gene in a large, multicenter DCM cohort [9]. Among known sarcomeric genes involved in DCM pathogenesis, some, when mutated, can cause hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and left ventricular (LV) noncompaction (LVNC). An inevitable limitation is the considerable overlap encountered between categories into which diseases have been segregated (overlap phenotypes). Merlo et al. found that carriers of rare sarcomeric gene variants represented a subgroup of DCM patients with a particularly severe phenotype characterized by a high frequency of

ventricular arrhythmias, a high incidence of cardiovascular events, and pump failure [10]. Furthermore, in lamin A/C (*LMNA*) gene mutation carriers, up to ten different phenotypes (laminopathies) have been described, with variable involvement of skeletal and/or cardiac muscle and also of white fat, peripheral nerves, bones, or premature aging [11]. In this peculiar CMP, conduction disease can precede development of DCM in some families, whereas in other families, DCM occurs first. The practical significance is that individuals who may have mild DCM caused by *LMNA* mutations may be at risk of sudden death (SD), whereas this scenario is highly unlikely with most sarcomeric and all cytoskeletal abnormalities. Therefore, when SD is seen in a family with mild DCM, testing for *LMNA* mutations may be helpful and lead to early consideration for implanted cardiac defibrillator (ICD) therapy [12]. Reports of increased arrhythmogenicity in *SCN5A-associated* [13] and desmosomal-associated [14] DCM indicate that a similar approach may be taken when these mutations are identified.

2.2.2 Hypertrophic Cardiomyopathy

HCM is a genetic disease usually caused by mutations in genes encoding sarcomeric and nonsarcomeric proteins. HCM is usually inherited as an autosomal dominant trait; de novo mutations are rare. The major group includes sarcomeric mutations (up to 90 %), in which 15 different genes have been identified [15]; nonsarcomeric (Z-disc or calcium-handling proteins) account for <1 % of cases, and a further 5 % of patients have metabolic disorders, neuromuscular disease, chromosome abnormalities, and genetic malformation syndromes [16].

After two decades of molecular research, the relationship between sarcomere mutations and clinical outcome in patients with HCM has proven to be unreliable, largely attributable to phenotypic heterogeneity, highly variable intra- and interfamily expressivity, and incomplete penetrance. Among several sarcomeric genes identified, defects of beta-myosin heavy-chain (*MYH7*) and myosin-binding protein C (*MYBPC3*) account for up to 70 % of HCM, followed by troponin T gene defects (*TNNI3, TNNT2*) and other less commonly involved genes (*ACTC1, CSRP3, CRYAB, CAV3, MYH6, MYL2, MYL, TNNC1, TCAP, MYOZ1, MYOZ2*) [17].

Specific mutations in *MYH7* (*Arg403Gln, Arg453Cys, and Arg719Trp*) appear convincingly associated with adverse outcomes; however, data suggests that at-risk patients carrying these mutations also display clinical risk factors at the time of events, limiting the added prognostic benefit of genetic diagnosis [18].

An exception to this is HCM caused by mutations in cardiac *TNNT2*, which may cause ventricular arrhythmias and SD in the absence of impressive morphological (mild LV hypertrophy) or hemodynamic features (obstruction, diastolic dysfunction) [19]. Moreover, possible exceptions are emerging, including preliminary data suggesting that double, triple, or compound sarcomere mutations (evident in 5 % of patients with HCM) [20] could be associated with greater disease severity,

including SD, also in the absence of conventional risk factors [21]. In addition, complicating the scenario, some HCM phenocopies, characterized by infiltrative and storage CMP, can be caused by disorders of different genetic origin; for example, those resulting from mutations in genes encoding protein kinase adenosine monophosphate (AMP)-activated, gamma-2 noncatalytic subunit (*PRKAG2*) [22], lysosome-associated membrane protein 2 (*LAMP2*) (Danon disease), alpha-galactosidase deficiency (Fabry disease), and transthyretin (TTR) protein (familial amyloid TTR CMP). Moreover, an HCM phenotype may be present in other congenital diseases, such as Noonan syndrome and mitochondrial syndromes. Finally, several studies have shown the important influences exerted by modifying genes and lifestyle in HCM expression. Indeed, in some cases, modifier genes are neither necessary nor sufficient to cause HCM because environmental influences, such as diet, lifestyle, and exercise, can have a predominant role [23].

2.2.3 Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is another disease of genetic origin and is usually characterized by mutations in genes encoding different proteins mainly involving intercellular junctions (see Chaps. 19, 20, 21, 22, and 23). These proteins (plakoglobin, desmoplakin, plakophilin, desmoglein, desmocollin) are localized in the desmosomes and are important for maintaining tissue architecture and integrity. In addition, nondesmosomal genes are described and include transforming growth factor beta 3 (TGFβ3) and transmembrane protein 43 (TMEM43). Inheritance patterns are mainly autosomal dominant, but rare recessive forms (Naxos disease and Carvajal syndrome) are also observed and well described. In this disease, a high genetic complexity is suggested by the fact that ARVC may be linked to genes related (or not) to the cell-adhesion complex: for example, genes encoding cardiac ryanodine receptor 2 (*RYR2*) and transforming growth factor β3 (*TGFB3*). Furthermore, in ARVC5, *TMEM43* gene mutation causes a fully penetrant disease variant with lethal arrhythmic outcome [24]. In a large ARVC cohort, Rigato et al confirmed that carriers of more than one gene mutation (compound-digenic heterozygosity) have a high risk factor for lifetime major arrhythmic events and *SD* [25]. Moreover, Taylor et al provide evidence that titin mutations can also cause ARVC, given that structural impairment of the titin spring constitutes a novel mechanism underlying myocardial remodelling and SD [26].

2.2.4 Other Cardiomyopathies

RCM and LVNC have been classified individually, but evidence exists for considerable overlap between these syndromes and HCM and DCM. Familial RCM is increasingly recognized as a specific phenotype within the HCM spectrum [27]. Similarly, LVNC is an imaging diagnosis with profound overlap with both DCM and HCM phenotypes and their disease-causing mutations [28]. For LVNC, the

definition of the clinical phenotype remains under debate, and population prevalence varies widely depending on the cohort examined and the diagnostic criteria utilized [29].

In conclusion, genetic testing is becoming an important tool for a personalized medical approach to CMP. However, it must not be viewed as a simple blood test: a negative genetic test can never, by itself, rule out the presence of the CMP. Likewise, a positive genetic test must be carefully considered as only one component of a comprehensive cardiogenetic evaluation, together with an accurate clinical diagnosis, an understanding of the probabilistic nature of genetic testing, and an accurate family history [30].

2.3 Clinical Approach: From Phenotype to Genotype

The clinical approach should define the characteristics of CMP and should also explore, when present, the characteristics of involvement of other organs and systems. This approach does not necessarily involve the use of novel or particularly sophisticated tests; however, it requires a detailed analysis of the proband and an in-depth assessment of family background. The construction of a three- four-generation family pedigree must record not only the presence or absence of CMP in relatives, but also other features that support the diagnosis of a genetic cardiovascular disorder (SD, heart failure, cardiac transplantation, insertion of pacemakers or ICD, and stroke at a young age). Noncardiac manifestations in relatives, such as neuromuscular disease, osteoarticular disorder, mental retardation, abnormal craniofacial features, sensorineural hearing loss, visual impairment, skin and hair abnormalities, chronic kidney disease, hematopoietic, endocrine, and genital disorders, also provide diagnostic clues (Tables 2.1 and 2.2).

CMP may also be a feature of rare congenital dysmorphic syndromes that are diagnosed during infancy and childhood [31]. A detailed description of these disorders is outside of the aim of this chapter. It is evident that CMP are a common feature of multisystem diseases. The mechanisms of multiorgan involvement are heterogeneous, and a complete evaluation includes researching red flags, such as the following [32, 33]:

- Physical examination (Tables 2.1 and 2.2)
- Electrocardiogram abnormalities (Table 2.3)
- Laboratory tests (Table 2.4)
- Echocardiography/cardiac magnetic resonance: hypertrophy pattern, pericardial effusion, valve thickening, bulging, sacculations, sparkling myocardium texture, late gadolinium enhancement (LGE) (Table 2.5). Some typical features are described, such as LGE localized to the inferolateral wall in patients with Anderson–Fabry disease or dystrophinopathies and to the circumferential subendocardial wall in cardiac amyloidosis. The echocardiogram remains the first-line imaging tool in patients with suspected CMP. It has a central role in defining the morphological and functional phenotype and in guiding treatment decisions.

Table 2.1 Examples of signs and symptoms that should raise suspicion of specific diagnoses grouped according to the main cardiac features

Phenotypic finding	Cardiac features	Diseases to consider
Sensorineural deafness	HCM	Mitochondrial diseases
		Anderson–Fabry disease
		LEOPARD syndrome
	DCM	Epicardin mutation
		Mitochondrial diseases
Muscle weakness	HCM	Mitochondrial diseases
		Glycogenosis
	DCM	Dystrophinopathies
		Sarcoglycanopathies
		Laminopathies
		Myotonic dystrophy
		Desminopathies
	RCM	Desminopathies
Learning difficulties, mental retardation	HCM	Mitochondrial diseases
		Noonan Syndrome
		Danon disease
	DCM	Dystrophinopathies
		Mitochondrial diseases
		Myotonic dystrophy
		FKTN mutations
	RCM	Noonan syndrome
Myotonia (involuntary muscle contraction with delayed relaxation)		Myotonic dystrophy (type 1 and type 2)
Paraesthesia/sensory abnormalities/ neuropathic pain	HCM	Amyloidosis
		Anderson–Fabry disease
	RCM	Amyloidosis

HCM hypertrophic cardiomyopathy, *DCM* dilated cardiomyopathy, *RCM* restrictive cardiomyopathy, *LEOPARD syndrome* lentigines, echocardiograph conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness, *FKTN* fukutin

As with all imaging modalities, echocardiography rarely suggests a specific etiology, but it can be helpful in the context of a number of features in directing further investigation.

- Others: exercise test, nuclear imaging, endomyocardial biopsy

The key to diagnostic success is, therefore, a CMP-centered approach to clinical assessment coupled with a systematic stepwise use of cardiac and noncardiac diagnostic tests. The comparative diagnosis between different forms is also important from a prognostic and sometimes therapeutic point of view. Some clinical features of CMP can also vary within the same family, a phenomenon that indicates that sometimes there is not a clear-cut relationship between the mutation and its clinical consequences [34, 35].

Table 2.2 Examples of skin/eyes signs that should raise suspicion of specific cardiac features

Phenotypic finding	Cardiac features	Disease to be considered
Visual impairment	HCM	TTR-related amyloidosis (vitreous opacities, cotton wool type) Danon disease (retinitis pigmentosa) Anderson–Fabry disease (cataracts, corneal opacities)
	DCM	*CRYAB* (polar cataract) type 2 myotonic dystrophy (subcapsular cataract)
Carpal tunnel syndrome (bilateral)	HCM	TTR-related amyloidosis
	RCM	Amyloidosis
Lentigines/café au lait spots	HCM	LEOPARD syndrome
Angiokeratoma hypohidrosis	HCM	Anderson–Fabry disease
Palmoplantar keratoderma, woolly hair	ARVC	Naxos and Carvajal syndromes

HCM hypertrophic cardiomyopathy, *DCM* dilated cardiomyopathy, *RCM* restrictive cardiomyopathy, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *TTR* transthyretin protein, *LEOPARD syndrome* lentigines, echocardiograph conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness

Table 2.3 Laboratory findings that should raise the suspicion of specific cardiac features

High serum creatine kinase (CK)	HCM	Mitochondrial diseases Glycogenosis Danon disease
	DCM	Dystrophinopathies Sarcoglycanopathies Zaspopathies (*LDB3* gene) Laminopathies Myotonic dystrophy *FKTN* mutations
	RCM	Desminopathies Myofibrillar myopathies
Proteinuria with/without low glomerular filtration rate	HCM RCM	Anderson–Fabry disease Amyloidosis
High transaminase	HCM	Mitochondrial diseases Glycogenosis Danon disease
High transferrin saturation/ hyperferritinemia	DCM RCM	Hemochromatosis
Lactic acidosis	HCM DCM	Mitochondrial diseases
Myoglobinuria	HCM DCM	Mitochondrial diseases
Leukocytopenia	HCM DCM	Mitochondrial diseases (*TAZ* gene/Barth syndrome)

HCM hypertrophic cardiomyopathy, *DCM* dilated cardiomyopathy, *RCM* restrictive cardiomyopathy, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *TTR* transthyretin protein, *LEOPARD syndrome* lentigines, echocardiograph conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness, *FKTN* fukutin, *TAZ* tafazzin

Table 2.4 Examples of electrocardiographic (ECG) abnormalities that should raise the suspicion of specific diagnoses grouped according to the main cardiac features

Phenotypic finding	Cardiac features	Diseases to be considered
Short PR/pre-excitation (WPW like)	HCM	Glycogenosis Danon *PRKAG2* Anderson–Fabry Mitochondrial disease
AV block	HCM	Amyloidosis Danon disease
	DCM	Laminopathy Emery Dreifuss Sarcoidosis Desminopathy
	RCM	Desmin-related cardiomyopathy Amyloidosis
Extreme LV hypertrophy (Sokolow criteria)	HCM	Danon disease Pompe disease
Low QRS voltage	HCM	Amyloidosis
Low P wave amplitude atrial standstill	DCM	Emery Dreifuss
Q waves in posterolateral leads	DCM	Dystrophin-related cardiomyopathy Limb-girdle muscular dystrophy Sarcoidosis
Inverted T waves in inferolateral leads Epsilon waves in inferolateral leads	ARVC	ARVC with biventricular involvement

WPW Wolff-Parkinson-White syndrome, *AV* arteriovenous, *LV* left ventricular, *HCM* hypertrophic cardiomyopathy, *DCM* dilated cardiomyopathy, *RCM* restrictive cardiomyopathy, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *PRKAG2* protein kinase, AMP-activated, gamma 2 noncatalytic subunit

Table 2.5 Echocardiographic diagnostic clues grouped according to main morphological phenotype

Phenotypic findings	Cardiac features	Diseases to be considered
Increased interatrial septum thickness	HCM	Amyloidosis
Increased atrioventricular valve thickness		Amyloidosis; Anderson–Fabry disease
Increased RV free-wall thickness		Amyloidosis, myocarditis, Anderson–Fabry disease
Mild–moderate pericardial effusion		Amyloidosis, myocarditis
Ground-glass appearance of ventricular myocardium		Amyloidosis
Concentric LVH		Glycogenosis, Anderson–Fabry disease
Extreme concentric LVH		Danon disease, Pompe disease
Global hypokinesia (with/without LV dilatation)		Anderson–Fabry; mitochondrial disease; TTR-related amyloidosis; *PRKAG2* mutations; Danon disease; myocarditis; end-stage sarcomeric HCM

Table 2.5 (continued)

Phenotypic findings	Cardiac features	Diseases to be considered
LV noncompaction	DCM	Genetic DCM (more frequently sarcomeric mutations)
Posterolateral akinesia/dyskinesia		Dystrophin-related cardiomyopathy
Mild (absent) dilatation + akinetic/dyskinetic segments with noncoronary distribution		Myocarditis; sarcoidosis
Coexistent LV segmental dysfunction	ARVC	Biventricular ARVC
Partial LV or RV apical obliteration	RCM	Endomyocardial fibrosis/hypereosinophilia

LVH left ventricular hypertrophy, *LV* left ventricle, *RV* right ventricle, *HCM* hypertrophic cardiomyopathy, *DCM* dilated cardiomyopathy, *RCM* restrictive cardiomyopathy, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *PRKAG2* protein kinase

Conclusions

Genotype–phenotype relationships are not always simple and clear, and diagnostic approach and possible interpretations may be complex. Different mutations in the same gene can cause apparently identical phenotypes as well as be associated with phenotypes that are radically different one from the other. It is necessary to bring genetics closer to clinical practice, to create a bridge between clinical observation and molecular genetics, thus helping identify a possible specific genetic background. Clinical assessment should not be restricted to cardiological examinations; indeed, CMP represent a challenging interface between cardiology and many other medical specialties. Another important aspect is recognizing red flags, which guide rational selection of further diagnostic tests, including genetic analysis, and thereby identification of specific CMP subtypes. Arbustini et al. proposed a descriptive nosology that combines morphofunctional traits and organ-system involvement with familial inheritance patterns, identified genetic defects, or other etiologies [36]. The current body of knowledge suggests a genetic basis for understanding CMP pathophysiology, provides potential targets for therapeutic intervention, contributes to diagnosis, allows for cascade screening, and occasionally informs prognosis [33].

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