The MOGE(S) Classification for a Phenotype—Genotype Nomenclature of Cardiomyopathy

Endorsed by the World Heart Federation

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In 1956, Blankerhorn and Gall [1] proposed the term *myocarditis* for ***inflammatory heart muscle disease***, and *myocardiosis* for ***other heart muscle diseases***. A year thereafter, Brigden [2] defined *cardiomyopathies* as ***uncommon, non-coronary heart muscle diseases***. Subsequently, Goodwin and Oakley [3] defined *cardiomyopathies* as ***myocardial diseases of unknown origin***, and proposed categorization of the disorders as dilated (DCM), hypertrophic (HCM), and restrictive (or obliterative) (RCM) cardiomyopathies. In 1980, the World Health Organization (WHO) and International Society and Federation of Cardiology (ISFC) established the definition of cardiomyopathies as ***myocardial diseases of unknown etiology***, reflecting the general lack of information about the mechanism(s) of disease [4]. Although WHO-ISFC retained the 3 morphological types of cardiomyopathies proposed by Goodwin and Oakley, it also introduced the term *specific heart muscle disease*, where the cause of myocardial dysfunction was known. The WHO-ISFC classification subsequently expanded the definition of cardiomyopathies by adding the functional component and defined cardiomyopathy as the ***diseases of myocardium associated with myocardial dysfunction***. Two additional classes, arrhythmogenic right ventricular cardiomyopathy (ARVC) and unclassified cardiomyopathy, were introduced during the revision, and the category of the specific heart muscle disease was excluded [5]. The ISFC changed its name to the World Heart Federation (WHF) in 1998 [6], and did not indulge in further revision of the recommendations for either diagnosis or management of cardiomyopathies.

A substantial increase in the knowledge of the genetic basis of cardiomyopathy has occurred, and noninvasive phenotypic characterization has become significantly more sophisticated. Therefore, the American Heart Association (AHA) [7] and the European Society of Cardiology (ESC) [8] in the last decade have proposed revisions to the classification of cardiomyopathic disorders. Whereas both systems have substantial similarities and have made important recommendations, the former has described cardiomyopathies starting from the genetic basis of the etiology followed by the phenotypic description of myocardial involvement. Conversely, the ESC has retained the description in original morphofunctional categories with further subclassification into genetic (familial) and nongenetic (nonfamilial) groups. Both classifications continue to exclude specific heart muscle disease (resulting from coronary, hypertensive, valvular, and congenital heart disease) from consideration as a cardiomyopathic disorder.

There is no denying the fact that most cardiomyopathies are genetic diseases, which in the real life are brought to clinical attention (and diagnosed and managed) based on a phenotypic diagnosis. More than 60 disease genes have been identified to date [9]; genes such as *MYBPC3* may be associated with different phenotypes (HCM, RCM, DCM), and genes such as *DYS* may cause a unique phenotype (DCM only). The penetrance of the genetic mutation is variable, and phenotypic manifestations are often age dependent. Most genetic cardiomyopathies are inherited as autosomal dominant traits, with a minority of families demonstrating autosomal recessive, X-linked recessive or dominant (rare), and matrilineal inheritance. Cascade family screening and follow-up have become mandatory [10]. It has become necessary for a more descriptive nosology to be developed that may encompass either all attributes of the individual patient cardiomyopathy or allow a common platform for collaborative research efforts. A number of experts, including clinical cardiologists, heart failure—transplantation physicians, geneticists, and cardiovascular imagers, have proposed a systematic nomenclature endorsed by the WHF Scientific Committee. The proposed classification is a descriptive presentation of the cardiomyopathic process, which is flexibly modifiable and expandable. This nosology is inspired from the TNM staging of tumors and is being simultaneously published by the *Journal of the American College of Cardiology* and the official journal of the WHF, *Global Heart*.

The AHA (2006) classification

In 2006, a scientific statement from the AHA redefined cardiomyopathy as a ***heterogeneous group of diseases of myocardium associated with mechanical and/or electrical dysfunction, which usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilation, due to a variety of causes that frequently are genetic*** [7]. The etiology of some cardiomyopathies originally classified as

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idiopathic or primary cardiomyopathy, or heart muscle disease of unknown cause had become known, and therefore, such entities could not be described as idiopathic any further. In the AHA 2006 definition, *primary cardiomyopathy* referred ***solely or predominantly to the involvement of heart***; the primary cardiomyopathy designation in the new definition did ***not*** mean *diseases of myocardium associated with myocardial dysfunction* as intended in the 1996 WHO-ISFC classification. The *secondary cardiomyopathy* in the AHA classification was applicable when the ***myocardial dysfunction was part of a systemic process***. The proposed classification is reproduced in Figure 1A. Myocardial dysfunction resulting from or associated with coronary, hypertensive, valvular, or congenital heart disease was not classified as cardiomyopathy. The WHF writing group applauds the efforts of the AHA 2006 writing committee for the first genuine attempt to introduce a genetic basis of classification of cardiomyopathies.

The ESC (2008) classification

Although recognizing the necessity for identifying the causative genetic defect as proposed by AHA (2006) nomenclature, the ESC classification emphasized that because the morphofunctional phenotype was the basis of the management of cardiomyopathy, it must also continue to be the basis of classification. ESC panelists emphasized that some of the so-called primary cardiomyopathies may be associated with extracardiac manifestations and may not justify the primary cardiomyopathy designation. Similarly, so-called secondary cardiomyopathy may occasionally involve the heart predominantly and defy designation as

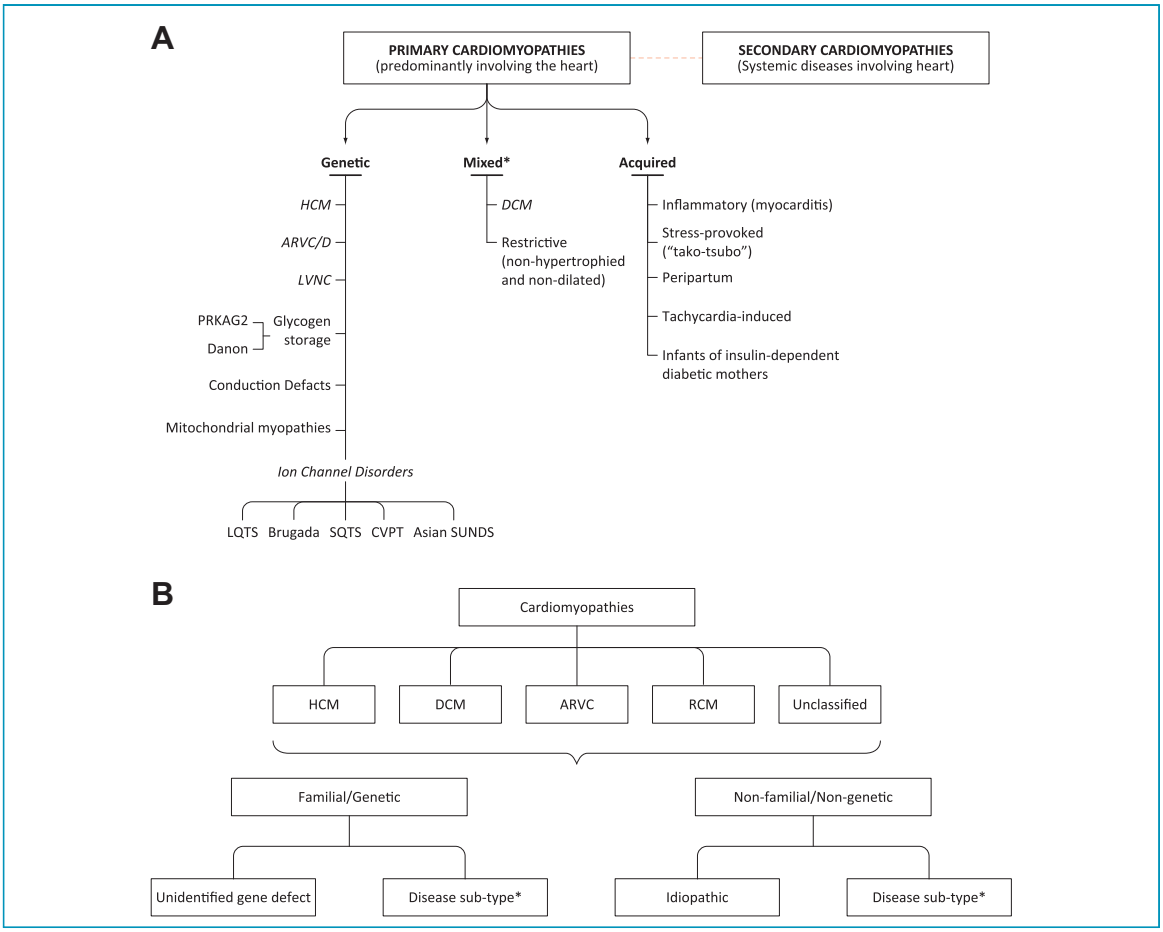


FIGURE 1. Current Classifications Of Cardiomyopathies. The 2006 American Heart Association classification proposes genetics-based classification (A). On the other hand, the 2008 European Society of Cardiology classification suggests first the morphofunctional phenotype and then the addition of inheritance information (B). ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia; CVPT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LVNC = left ventricular noncompaction; LQTS = long QT syndrome; RCM = restrictive cardiomyopathy; SQTS = short QT syndrome; SUNDS = sudden unexplained nocturnal death syndrome.

secondary cardiomyopathy [8]. In the ESC classification, *cardiomyopathy* was defined as a ***myocardial disorder in which the heart muscle is structurally and functionally abnormal***. Cardiomyopathy was grouped into morphofunctional phenotypes relevant for day-to-day clinical practice. These included dilated, hypertrophic, restrictive, and arrhythmogenic right ventricular cardiomyopathy and unclassified variety. Each of these types was further divided into familial genetic and nonfamilial, nongenetic forms. Ion channelopathies, a genetic subtype included in the AHA classification of primary cardiomyopathy, was not accepted as cardiomyopathy in this classification because genes encoding for ion channels might not result in morphofunctional phenotypes. However, similar to the AHA classification, myocardial dysfunction secondary to coronary, hypertensive, valvular, or congenital heart disease was not considered as cardiomyopathy. In the ESC 2008 classification, the cardiomyopathy was defined as familial when **present in more than 1 member of the family**. A genetic cardiomyopathy is sporadic when the causative mutation is de novo, namely occurring for the first time and exclusively in the affected family member. The proposed classification is reproduced in Figure 1B.

The proposed phenotype-genotype-based (2013) classification endorsed by WHF

In the last 10 years, knowledge of the genetics of cardiomyopathies has evolved exponentially, and at least 60 disease genes have been either confirmed or suspected as candidate genes (Table 1). The genetic heterogeneity is established, and the implementation of next-generation sequencing is further expected to increase the existing pool of knowledge. It is conceivable that although the diagnosis based on phenotype is still clinically useful, it is not sufficient to stratify prognosis in cardiomyopathies caused by mutations in different genes and that grouping cardiomyopathies per disease gene provides the basis for implementation of disease-specific research. The major clinical decisions (such as implantable cardioverter-defibrillator [ICD] implantation) are still based on functional (such as left ventricular [LV] ejection fraction [LVEF] in DCM) or morphological (such as maximal LV wall thickness in HCM) criteria regardless of the intrinsic disease risk related to the type of causative gene mutation [11–13]. Troponinopathies may not be associated with severe LV wall thickness but carry a high arrhythmogenic potential [14]. Similarly, laminopathies may not necessarily demonstrate severe LV dysfunction when their arrhythmogenic risk first manifests [15]. On the other hand, dystrophinopathies may display dramatically enlarged and dysfunctioning LV but are less susceptible to the risk of malignant arrhythmias; such patients, however, can deteriorate rather precipitously with as small an insult as a flu episode and deserve timely assistance [16]. Based on the underlying gene mutations, numerous new terms (such as *desmosomalopathies* [17], *cytoskeletalopathies* [18], *sarcomyopathies* [18], *channelopathies* [19], *cardiodystrophinopathies* [16], or *cardiolaminopathies* [20]), inspired by the general practice of myologists (such as *zaspopathies* [21], *myotilinopathies* [22], *dystrophinopathies* [23], *alphaB-crystallinopathies* [21], *desminopathies* [24], or *caveolinopathies* [25]), are being proposed that are likely to cloud the cardiomyopathy description, and it has become important that a uniform nomenclature be developed.

By the classification herein proposed, the cardiomyopathies are described as ***disorders characterized by morphologically and functionally abnormal myocardium in the absence of any other disease that is sufficient, by itself, to cause the observed phenotype***. In this nosology, although the conventional phenotypic subtype of the cardiomyopathy (e.g., dilated, hypertrophic) continues to provide the elements for the basic classification, a genotype-based assessment dictates the diagnostic work-up and treatment decisions in probands and relatives, as well as the follow-up plans. Figure 2 shows an example of the impact of an accurate genetic diagnosis on 2 patients with a similar phenotype at presentation. Once the genetic cause of the cardiomyopathy has been defined, the cascade family screening can help identify healthy mutation carriers that will eventually develop the phenotype over the ensuing years (Fig. 3) [10]. Avoidance of competitive sport activity and tailored monitoring with early medical treatment may favorably influence the natural history of the disease and the development of the manifest phenotype, as well as the risk of life-threatening arrhythmias. Identification of genetic diseases may also help subjects and alert physicians to refrain from the use of injurious agents. For instance, agents triggering malignant hyperthermia (succinyl choline) or volatile anesthetics (halothane and isoflurane) are to be avoided in emerinopathies and laminopathies causing muscular dystrophy [26]. Statins should be administered with caution in patients with genetic cardiomyopathies with possible involvement of the skeletal muscle, even when markers of myopathy are negative [27]. Patients with disorders of the respiratory chain may need surgeries in their long-term care, but anesthetics may interfere with metabolism and may trigger unexpected complications [28]. Patients with mitochondrial cardiomyopathy and epilepsy should not receive valproate because it could cause pseudoatrophy of brain [29]. Common indications for heart transplantation (HTx) in patients with end-stage cardiomyopathy should take into account the specific diagnosis; conditions such as Danon disease in males, or other comorbidities such as mental retardation, are a matter of debate about indications for HTx [30]. Finally, genotype-based diagnoses can be pooled in large international databases for future clinical trials and validation of novel management strategies.

THE MOGE(S) NOMENCLATURE SYSTEM

While waiting for the complete knowledge that may eventually support a genetic classification of cardiomyopathies (also the ultimate intent of the AHA and ESC classifications), we propose a nosology that addresses 5 simple

TABLE 1. List of Nuclear Genes Associated to Date With Cardiomyopathies

Nuclear Genes	MIM* Gene	Protein or Syndrome	HCM	RCM	DCM	ARVC	LVNC	Clinical Traits (Red Flags)	Phenotypes/Diseases Caused by Mutations of the Same Gene	Inheritance
ABCC9	601439	ATP-binding cassette, subfamily C, member 9			X			Hypertricosis	Cantu syndrome	AD
ABLIM1	602330	Limatin (actin-binding LIM domain protein)			X			LVNC		AD
ACTC1	102540	Cardiac actin alpha	X	X	X		X		Nemaline myopathy	AD
ACTN2	102573	Alpha-actinin 2	X		X					AD
ALMS1	606844	ALMS1-C			X			(70% DCM)	Alstrom syndrome	AR
ANO5	608662	Anoctamin 5			X			Dysphagia	Limb girdle muscular dystrophy, Gnathodiaphyseal dysplasia, Miyoshi muscular dystrophy 3	AR
ANKRD1	609599	Ankyrin repeat domain-containing protein 1			X					AD
BAG3	603883	*BCL2*-associated athanogene	X		X				*BAG3*-related myofibrillar myopathy, *CRYAB*-related myofibrillar myopathy, fatal infantile hypertrophy	AD
CALR3	611414	Calretinin 3	X							AD
CASQ2	114251	Calsequestrin 2			X		X			AD
CAV3	601253	Caveolin3	X		X				sCPK elevated; long QT syndrome-9; muscular dystrophy, limb-girdle; myopathy, distal, Tateyama type; rippling muscle disease	
CRYAB	123590	Alpha B crystallin	X	X	X			Cataract	Posterior polar cataract	AD
CSRP3	600824	Cysteine- and glycine-rich protein 3	X		X					AD
DES	125660	Desmin	X	X	X			AVB, ↑sCPK	Des-related myofibrillar myopathy, neurogenic scapuloperoneal syndrome, Kaeser type	AD
DMD	300377	Dystrophin			X			>sCPK/myopathy	Duchenne muscular dystrophy, Becker muscle dystrophy	X-linked recessive
DMPK	605377	Dystrophia myotonica protein kinase gene			X			AVB	(Dystrophia myotonica type 1) or Steinert's disease	AD
DOLK	610746	Dolichol kinase			X			Myopathy, possible ichthyosiform dermatitis	Congenital disorder of glycosylation, type Im	AR
DSC2	125645	Desmocollin 2			X	X			With and without mild palmoplantar keratoderma and woolly hair	AD
DSG2	125671	Desmoglein 2			X	X				AD
DSP	125647	Desmoplakin			X	X			Lethal acantholytic epidermolysis bullosa, keratosis palmoplantaris striata II, skin fragility—woolly hair syndrome	AD

DTNA	601239	Dystrobrevin alpha					X		With or without congenital heart defects	AD
EMD	300384	Emerin			X			AVB, myopathy, ↑sCPK	EDMD1, X-linked	X-linked recessive
EYA4	603550	Eyes absent 4			X			Deafness	Deafness, autosomal dominant	AD
FHL1	300163	Four-and-a-half LIM domains 1	X		X			Myopathy	EMDM 6, X-linked, myopathy, reducing body, childhood-onset and severe early-onset, myopathy with postural muscle atrophy, scapuloperoneal myopathy, X-linked dominant	X-linked recessive, X-linked dominant
GATAD1	614518	GATA zinc finger domain containing protein 1			X					AD
ILK	602366	Integrin-linked kinase			X					AD
JUP (*DP3*)	173325	Plakoglobin, desmoplakin III			X	X		Naxos traits		AD, AR
LMNA	150330	Lamin A/C			X	X		AVB, possible ↑sCPK	DCM with conduction disease plus 11 additional phenotypes	AD
LAMA4	600133	Laminin alpha 4			X					AD
LDB3	605906	LIM domain-binding 3	X		X		X	LVNC, hypertrabeculation; possible ↑sCPK	ZASP-related myofibrillar myopathy	AD
MYBPC3	600958	Myosin-binding protein C	X		X		X			AD
MYH6	160710	Alpha-myosin heavy chain 6	X		X				Atrial septal defect, sick sinus syndrome	AD
MYH7	160760	Beta-myosin heavy chain 7	X	X	X		X	Possible ↑sCPK	Laing distal myopathy; myosin storage myopathy; scapuloperoneal syndrome, myopathic type	AD
MYL2	160781	Myosin light chain 2	X							AD
MYL3	160790	Myosin light chain 3	X	X						AD, AR
MYOZ1	605603	Myozenin 1	X		X					AD
MYOZ2	605602	Myozenin 2	X							AD
MYPN	608517	Myopalladin			X					AD
NEBL	605491	Nebulette			X					AD
NKX2-5	600584	NK2 homeobox 5; cardiac-specific homeobox1			X			Possible conduction system disease		AD
PDLIM3	605889	PDZ LIM domain protein 3			X					AD
PLN	172405	Phospholamban			X					AR
PKP2	602861	Plakophilin 2			X	X				AD
PSEN1	104311	Presenilin 1			X				Acne inversa, familial, 3, Alzheimer disease, type 3, Frontotemporal dementia, Pick disease	AD
PSEN2	600759	Presenilin 2			X				Alzheimer disease	AD
RBM20	613171	RNA-binding protein 20			X					AD
RYR2	180902	Ryanodine receptor 2				X			Ventricular tachycardia, catecholaminergic polymorphic 1	AD

(continued)

TABLE 1. Continued

Nuclear Genes	MIM* Gene	Protein or Syndrome	HCM	RCM	DCM	ARVC	LVNC	Clinical Traits (Red Flags)	Phenotypes/Diseases Caused by Mutations of the Same Gene	Inheritance
SCN5A	600163	Sodium channel, voltage gated, type V, alpha subunit			X			Possible LQT or Brugada Syndrome	LQT3, Brugada 1, AF, SSS, familial VF	AD
SGCD	601411	Delta-sarcoglycan			X				Limb-girdle muscular dystrophy	AD
SYNE1	608441	Nesprin 1, synaptic nuclear envelop protein 1			X				EMD4, AD; Spinocerebellar ataxia, autosomal recessive	AD
TCAP	604488	Titin-cap; telethonin	X		X			↑sCPK	Muscular dystrophy, limb-girdle, type 2G	AD
TCF21	603306	Transcription factor 21, epicardin			X			Hearing loss	Hearing loss	AD
TGFB3	190230	Transforming growth factor beta-3			X	X				AD
TMEM43	612048	Transmembrane domain 43			X	X			Emery-Dreifuss muscular dystrophy, AD	AD
TMPO	188380	Thymopoietin			X					AD
TNNC1	191040	Cardiac troponin C1	X	X	X					AD
TNNI3	191044	Cardiac troponin I3	X	X	X					AD
TNNT2	191045	Cardiac troponin T2	X	X	X		X			AD
TPM1	191010	Tropomyosin 1	X	X	X					AD
TTN	188840	Titin	X		X				Limb-girdle muscular dystrophy, early-onset myopathy with fatal cardiomyopathy, proximal myopathy with early respiratory muscle involvement, tardive tibial muscular dystrophy	AD
VCL	193065	Vinculin	X		X					AD

AD = autosomal dominant; AF = atrial fibrillation; AR = autosomal recessive; ARVC = arrhythmogenic right ventricular cardiomyopathy; AVB = atrioventricular block; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LVNC = left ventricular noncompaction; LQT = long QT; MIM = Mendelian Inheritance in Man; RCN = restrictive cardiomyopathy; sCPK = serum creatine phosphokinase; SSS = sick sinus syndrome; VF = ventricular fibrillation.

*Also reported in Table 3 listing mitochondrial disorders.

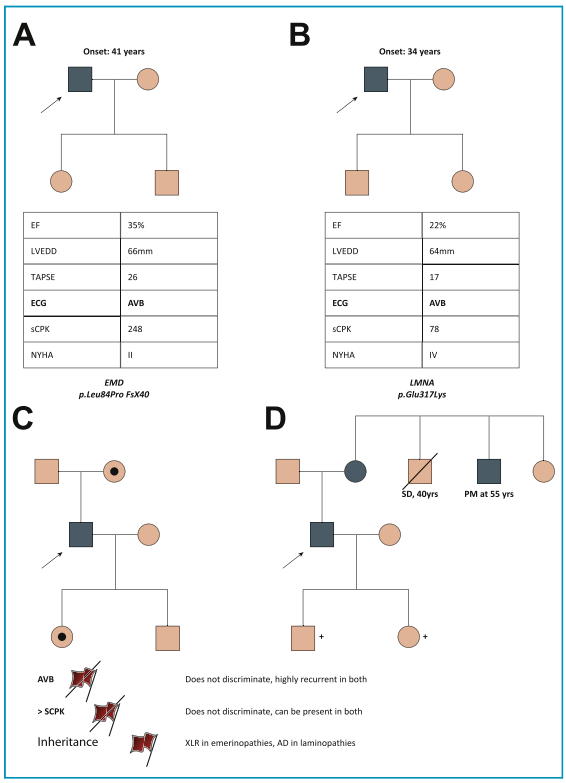


FIGURE 2. Importance of Genetic Information in DCM Patients. Two pedigrees with probands **(arrows)** demonstrate similar DCM phenotypes at the onset of disease. The identification of the causative genes and mutations underscores the importance of the genetic diagnosis on the management of the 2 families (A,B). In family A, the identification of a mutation in the *Emerin* (*EMD*) gene provides information about the genetic status of the offspring (C). The son of the proband is obligate negative because a male cannot transmit an X-linked defect to his son. On the other hand, the daughters of affected males in X-linked diseases are obligate carriers of the paternal mutations. (D) In family B, the identification of a mutation in the *Lamin A/C* (*LMNA*) gene provides evidence that offspring can inherit the mutation with 50% probability for each pregnancy (D). In this family in the **right panel**, both children inherited the paternal mutation **(+)**. Pedigree symbols for this and subsequent figures: **circles** for females, **squares** for males, **diagonal lines** represent deceased, **solid-dark gray symbols** denote cardiomyopathy, **dotted circles** denotes healthy carriers. AD = autosomal dominant; AVB = atrioventricular block; DCM = dilated cardiomyopathy; ECG = electrocardiogram; EF = ejection fraction; LVEDD = left ventricular end-diastolic dimension; NYHA = New York Heart Association; PM = pacemaker; sCPK = serum creatine phosphokinase; SD = sudden death; TAPSE = tricuspid annular plane systolic excursion; XLR = X-linked recessive.

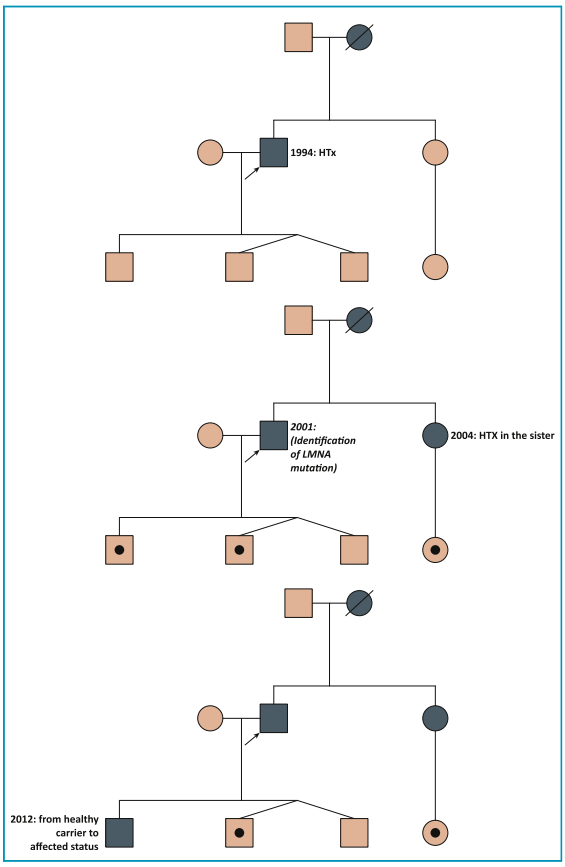


FIGURE 3. Genotype, DCM, and the Natural History. In 1994, a patient underwent heart transplantation (HTx) **(arrow)** for end-stage DCM associated with AVB. The patient had received a pacemaker 4 years earlier. His mother had died of heart failure due to DCM, and AVB was treated with pacemaker implantation. In 2001, the *LMNA* gene was discovered and was found to be the etiology of cardiomyopathy in this family with DCM and conduction disease. The cascade family screening further uncovered 2 sons of the proband and the daughter of his sister as the healthy mutation carriers. In 2004, the sister of the proband underwent HTx for DCM and AVB, and in 2012, the oldest son of the proband was diagnosed with *early* DCM. This 18-year-long follow-up highlights the importance of genetic characterization in cardiomyopathic disorders. Abbreviations as in Figure 2.

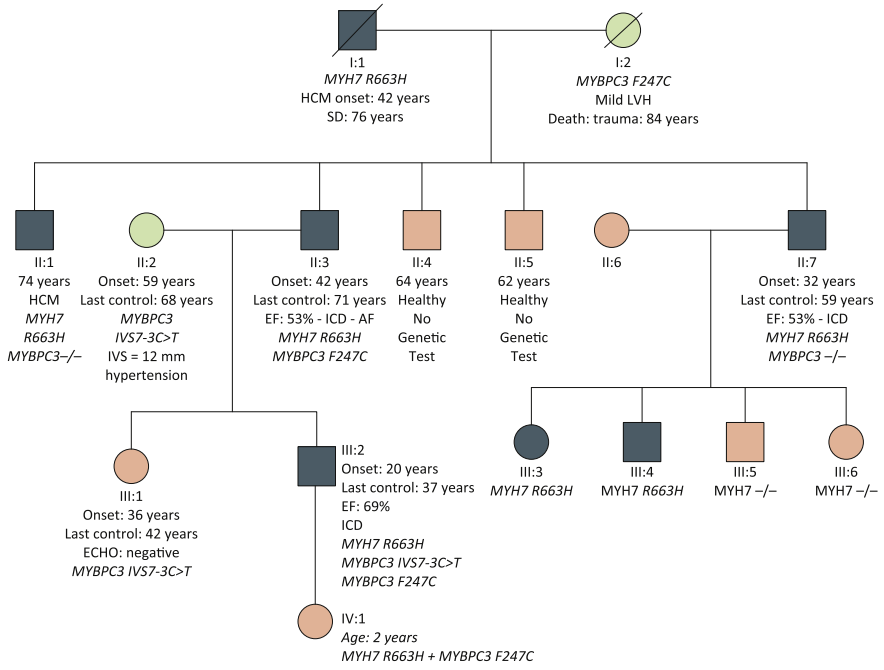
attributes of a cardiomyopathic disorder, including morphofunctional characteristic (M), organ involvement (O), genetic or familial inheritance pattern (G), and an explicit etiological annotation (E) with details of genetic defect or underlying disease/cause; information about the functional status (S) using the American College of Cardiology/American Heart Association (ACC/AHA) (A to D) stage and New York Heart Association (NYHA) (I to IV) functional classes may also be added. The addition of (S) has been left

optional, and should be used at the discretion of the physician. With the description of 5 attributes, the classification system is designated as MOGE(S).

- The **morphofunctional (M)** notation provides a descriptive diagnosis of the phenotype (M_D = dilated cardiomyopathy; M_H = hypertrophic cardiomyopathy; M_A = arrhythmogenic right ventricular (RV) cardiomyopathy; M_R = restrictive cardiomyopathy; M_{LVNC} = LV noncompaction). Description of combined/overlapping phenotypes (M_{D+R} or M_{H+D}) is easy to document, and disease-specific clinical markers can also be added, such as atrioventricular block (AVB), Wolff-Parkinson-White syndrome (WPW), epsilon wave ($M_{D\,[AVB]}$, $M_{H[WPW]}$, $M_{A[\varepsilon wave]}$). Although not likely, myocardial dysfunction with a nonspecific phenotype may be mentioned (M_{NS}). *Early* involvement or *no* involvement in a mutation carrier with affected family members should be documented as either with *early* imaging markers ($M_{E[H]}$ or $M_{E[D]}$) or *unaffected* (M_0) with the expected cardiac phenotype in brackets. When the information about the morphofunctional cardiac phenotype is *not available* (for example, in deceased relatives), the description is $M_{NA[H]}$.
- The **organ involvement (O)** is documented as *heart* only (O_H) or involvement of other organs/systems as below. The extracardiac involvement may be described by organ/system notations, such as skeletal *muscle* (O_{H+M}), *auditory* system (O_{H+A}), *kidney* (O_{H+K}), *nervous* system (O_{H+N}), *liver* (O_{H+L}), *gastrointestinal* system (O_{H+G}), *cutaneous* (O_{H+C}), eye, *ocular* system (O_{H+E}), or O_{H+MR} for *mental retardation*. Involvement of other organs may represent the systemic disease. Healthy mutation carriers can be described as (O_0), because the heart is not yet involved.
- The **genetic or familial inheritance (G)** provides information about *autosomal dominant* (G_{AD}), *autosomal recessive* (G_{AR}), *X-linked* (G_{XL}), *X-linked recessive* (G_{XLR}), *X-linked dominant* (G_{XLD}), or *matrilineal* (G_M) transmission. G_{XL} could also be used without recessive or dominant specification for conditions when an X-linked inheritance is strongly suspected on the basis of pedigree and family screening but is not yet supported by results of genetic testing and should be clarified in the E notation. *Sporadic* (G_S) indicates only a nonfamilial disease or a disease present in one family member when information or data on other family members are not (and will not be) available. Sporadic (G_S) notation is also applied in cases with possible de novo mutation not yet identified. G_N indicates *negative* family history, and G_U indicates *unknown* family history. G_0 indicates that family history has not been investigated so far.
- The **etiological annotation (E)** adds to the description of the underlying cause. For instance, *genetic* (E_G) etiology can be described by the specific disease gene and mutation(s) such as in the case of HCM ($E_{G\text{-}MYH7\,[p.Arg403Glu]}$), or familial amyloidosis ($E_{A\text{-}TTR[p.Val122Ile]}$), and so on. Etiological specification may include: *noncarrier* ($E_{G\text{-}Neg}$) when the disease gene tested negative; *obligate carrier* ($E_{G\text{-}OC}$); *obligate noncarrier* ($E_{G\text{-}ONC}$); presence of more than 1 mutation (or *complex* genetic defects, $E_{G\text{-}C}$ wherein all genetic information should be documented); genetic test *not available* yet, but the family data clearly indicate a genetic disease or the test is ongoing ($E_{G\text{-}NA}$); genetically orphan patients after completion of the screening of all known disease genes in familial disease ($E_{G\text{-}N}$); or genetic testing is *not done* or not feasible for any reason ($E_{G\text{-}0}$). All above may facilitate description of mutations that do not segregate with the phenotype or incomplete genotyping. Please see specific examples in the individual cardiomyopathy sections in the following text and in Figures 2 to 10.

On the other hand, the nongenetic etiology can be described as *viral* (V) adding the virus (e.g., Coxsackie B3 virus [CB3], human cytomegalovirus [HCMV], Epstein-Barr virus [EBV]) as ($E_{V\text{-}HCMV}$), ($E_{V\text{-}CB3}$) or ($E_{V\text{-}EBV}$). Similarly, *infectious nonviral* disease can be described as (E_I) with further specification of the infectious agent when possible. *Myocarditis* can be described as (E_M) when the myocarditis is the proven cause of the myocardial disease; specification about sarcoidosis or nonviral or noninfectious giant cell myocarditis should be added ($E_{M\text{-}sarcoidosis}$). *Autoimmune* etiology, either suspected or proven, can be added ($E_{AI\text{-}S}$) or ($E_{AI\text{-}P}$), respectively, after having excluded genetic and viral or toxic causes, especially in patients in whom a specific etiology may influence treatment. In the E annotation, nongenetic *amyloidosis* ($E_{A\text{-}K}$) or ($E_{A\text{-}L}$) or ($E_{A\text{-}SAAA}$) should be described with kappa, lambda, serum amyloid A, or other protein characterization. *Toxic* cardiomyopathies, either endogenous such as *pheochromocytoma*-related cardiomyopathy, or *drug*-induced cardiomyopathy, are described ($E_{T\text{-}Pheochromocytoma}$ or $E_{T\text{-}Chloroquine}$). The eosinophilic Loeffler endomyocarditis can be described according to the cause as either being *idiopathic* or a part of myeloproliferative disorder associated with the somatic chromosomal rearrangement of *PDGFR*$_\alpha$ or *PDGFR*$_\beta$ genes that generate a fusion gene encoding constitutively active PDGFR tyrosine kinases. The E annotation will be modified in the future as various conditions are excluded from the category of cardiomyopathic disorders or as the newer entities are recognized.

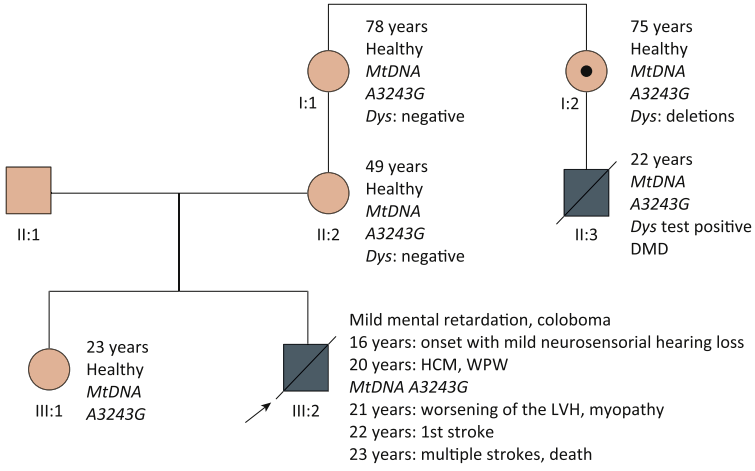
- It is proposed that **Heart Failure Stage (S)** may be provided pertaining to ACC/AHA stage (A to D) and NYHA functional class (I to IV) if deemed necessary. For instance, *stage A* disease with *functional class I* can be written as ($S_{A\text{-}I}$) or *stage C* disease in *functional class II* symptomatic subjects can be referred to as ($S_{C\text{-}II}$). Addition of the fifth descriptor (S) is optional, but may come in handy for the description of early cardiomyopathy. Early cardiomyopathy is a condition where the clinical criteria for diagnosis of the cardiomyopathy are not present, but genetic mutation has been confirmed and/or subclinical imaging evidence of myocardial



Family member	M O G E
I:1*	$M_H O_H G_{AD} E_{G\text{-}MYH7\ [p.R663H]}$
I:2	$M_H O_H G_U E_{G\text{-}MYBPC3\ [p.F247C]}$
II:1	$M_H O_H G_{AD} E_{G\text{-}C\text{-}MYH7\ [p.R663H]\ +\ MYBPC3\text{–}/\text{–}}$
II:2°	$M_H O_H G_N E_{G\text{-}MYBPC3\ [IVS7\text{-}3C>T]}$
II:3	$M_H O_H G_{AD} E_{G\text{-}C\text{-}MYH7\ [p.R663H]\ +\ MYBPC3\ [p.F247C]}$
II:4	$M_0 O_0 G_{AD} E_0$
II:5	$M_0 O_0 G_{AD} E_0$
II:7	$M_H O_H G_{AD} E_{G\text{-}MYH7\ [p.R663H]}$
III:1	$M_0 O_0 G_{AD} E_{G\text{-}MYBPC3\ [IVS7\text{-}3C>T]}$
III:2	$M_H O_H G_{AD} E_{G\text{-}C\text{-}MYH7\ [p.R663H]\ +\ MYBPC3\ [p.F247C]\ +\ MYBPC3\ [IVS7\text{-}3C>T]}$
III:3	$M_H O_H G_{AD} E_{G\text{-}MYH7\ [p.R663H]}$
III:4	$M_H O_H G_{AD} E_{G\text{-}MYH7\ [p.R663H]}$
III:5	$M_0 O_0 G_{AD} E_{G\text{-}Neg}$
III:6	$M_0 O_0 G_{AD} E_{G\text{-}Neg}$
IV:1	$M_0 O_O G_{AD} E_{G\text{-}C\text{-}MYH7\ [p.R663H]\ +\ MYBPC3\ [p.F247C]}$

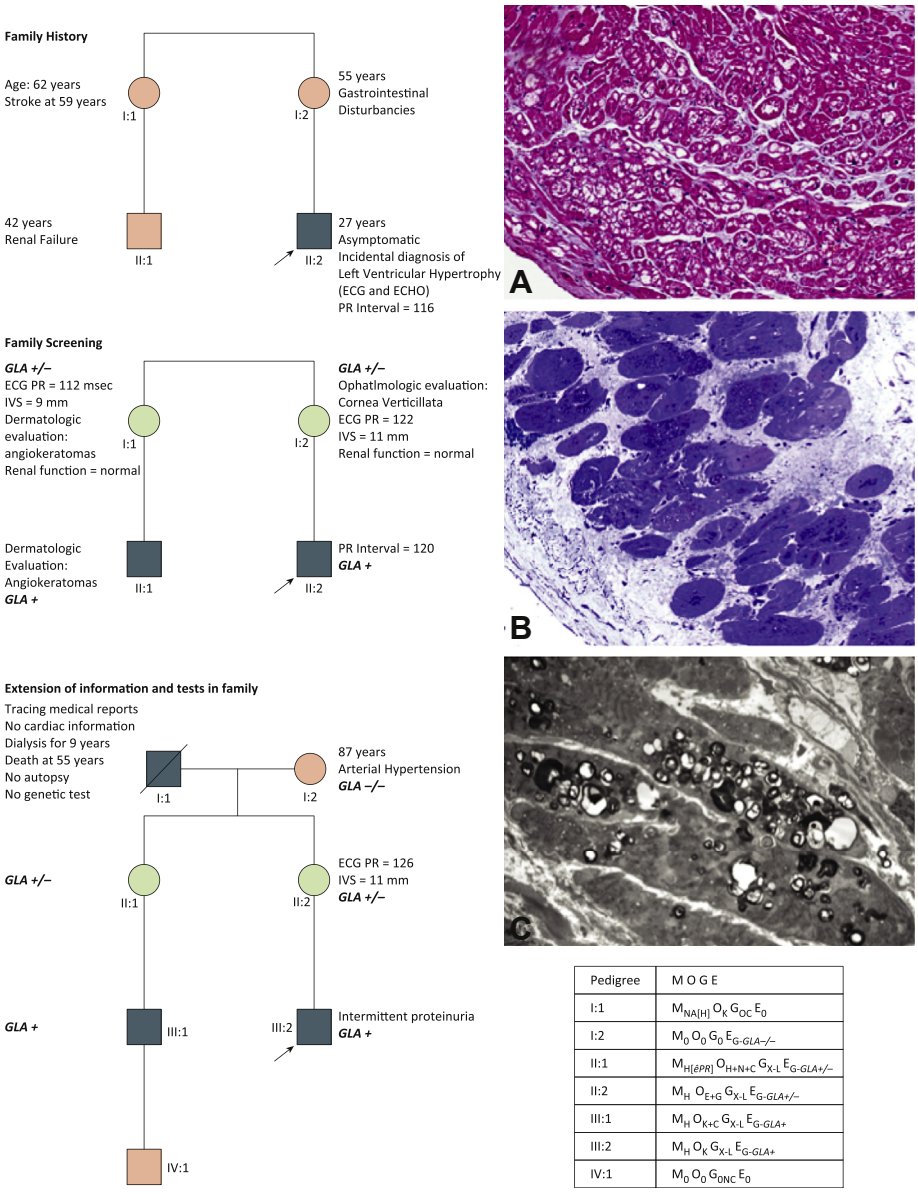
Individuals II:4 and II:5 are clinically unaffected ($M_0 O_0$), members of a family with AD HCM (G_{AD}): they are non-informative for segregation because they did not have genetic testing (E_0). IV:1 is a girl with normal ECG and echocardiographic study.
*two sibs likely affected, not proven (not shown).
°comorbidity = arterial hypertension.

FIGURE 4. The MOGE(S) in a Family With HCM. The MOGE(S) system allows presentation of all essential clinical and genetic information in a family with HCM and complex genetics. The pedigree shows the affected and nonaffected status of family members and the mutations identified in the family. The table **(bottom)** shows the application of the MOGE(S) system and the comprehensive description of the genetic make-up and phenotype expression in the members of different generations of the family. Although 3 mutations have been identified in this family, the HCM is inherited as autosomal dominant disease, and the mutation that occurs in all affected members is *MYH7* p.R663H; other mutations may contribute to worsen the phenotype but do not seem to cause, by themselves, HCM. In families demonstrating autosomal dominant inheritance, the segregation of the mutation from the phenotype is necessary to avoid labeling of the carriers of nondeterministic gene variants as possible future patients, and to provide a correct interpretation of results in case of prenatal diagnosis. Given the high prevalence of HCM in the general population (1:500), families carrying more than 1 mutation are not rare, and are expected to further increase with next-generation sequencing (NGS), that allows sequencing of several common and rare genes in a large number of patients simultaneously. AF = atrial fibrillation; ICD = implantable cardioverter-defibrillator; IVS = Intervening sequence; other abbreviations as in Figure 2. Green filled symbols: mild LVH.



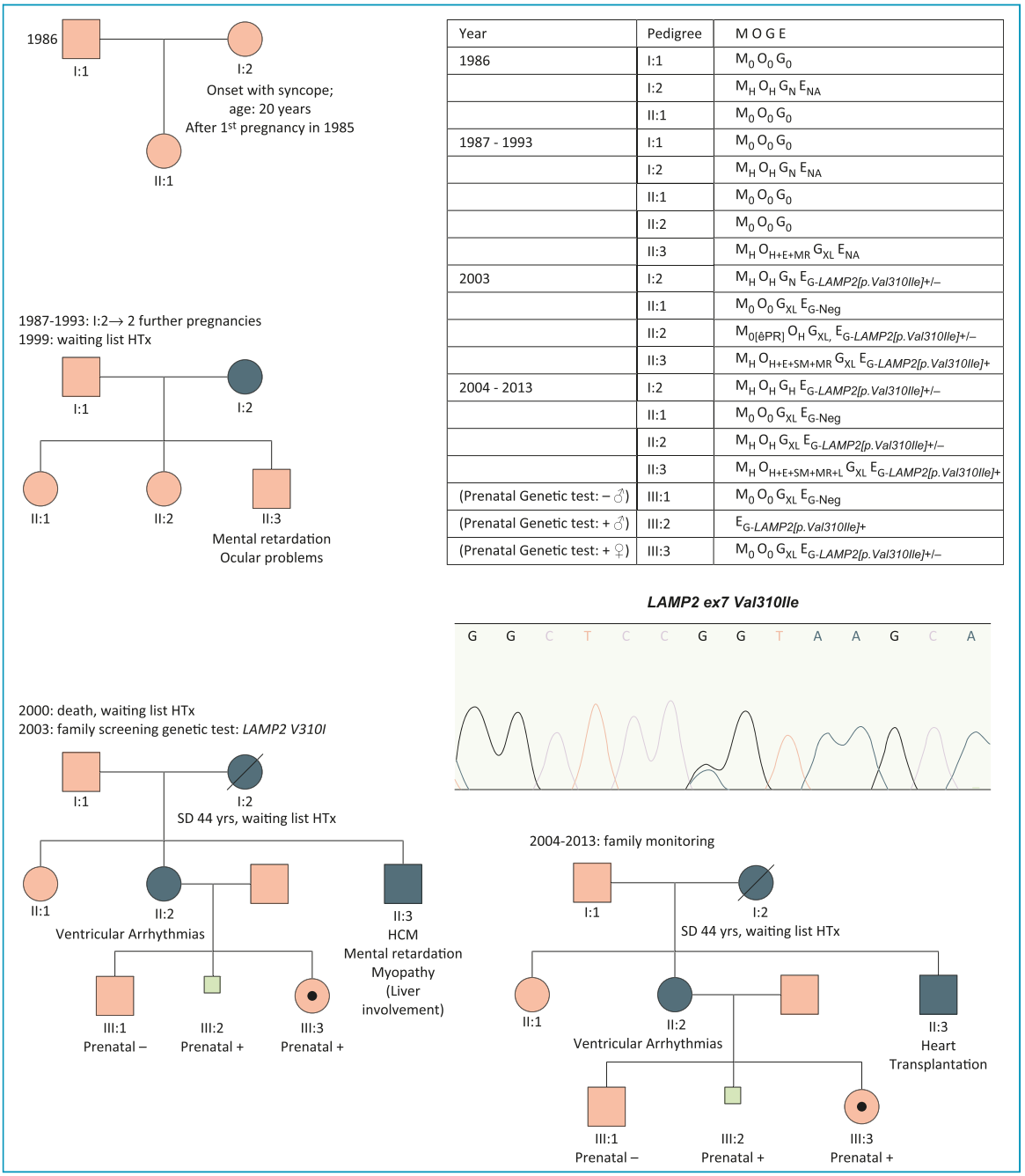
Year	Pedigree	M O G E
2007	I:1	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G}$
	I:2	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G;\ Dys\ Del\ +/-}$
	II:1	$M_0\,O_0\,G_N\,E_0$
	II:2	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G}$
	II:3	$M_D\,O_{H+M}\,G_{M,XLR,}\,E_{G\text{-}MtDNA\ A3243G;\ Dys\ Del\ +}$
	III:1	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G}$
	III:2	$M_{H[WPW]}\,O_{H+E+A+MR}\,G_M\,E_{G\text{-}MtDNA\ A3243G}$
2009	I:1	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G}$
	I:2	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G;\ Dys\ Del\ +/-}$
	II:1	$M_0\,O_0\,G_N\,E_0$
	II:2	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G}$
	III:1	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G}$
	III:2	$M_{H[WPW]}\,O_{H+E+A+MR}\,G_M\,E_{G\text{-}MtDNA\ A3243G}$
2011	I:1	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G}$
	I:2	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G;\ Dys\ Del\ +/-}$
	II:1	$M_0\,O_0\,G_N\,E_0$
	II:2	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G}$
	III:1	$M_0\,O_0\,G_M\,E_{G\text{-}MtDNA\ A3243G}$
	III:2	$M_{H[WPW]}\,O_{H+M+E+A+MR+N}\,G_M\,E_{G\text{-}MtDNA\ A3243G}$

FIGURE 5. MOGE(S) in a Family With Mitochondrial Cardiomyopathy: Evolution of the Disease in Family and Clarification of the Genetic Basis of Disease During Follow-Up. The pedigree illustrates the case of a young boy who was affected by mild mental retardation and bilateral coloboma. In 2007 he was first diagnosed with HCM and Wolff-Parkinson-White syndrome (WPW). His family history revealed the death of a maternal cousin at the age of 22 years for Duchenne muscular dystrophy (DMD). Based on family history and pedigree, the first hypothesis was an X-linked recessive disease, which was, however, unlikely because of the HCM phenotype, the WPW, and the mental retardation. The *DYS* gene tested negative in the proband (both multiplex ligation-dependent probe amplification [MLPA] and sequencing) as well as in the mother and maternal grandmother whose sister was healthy carrier of *DYS* mutation and mother of the young man with DMD. *LAMP2* was analyzed because of the HCM phenotype with WPW and cognitive impairment, and tested negative. Sequencing of the mitochondrial DNA (mtDNA) demonstrated the MT-TL1 MELAS/LS *A3243G* mutation [tRNA Leu (UUR)], heteroplasmic in all maternal relatives and in the boy. Endomyocardial biopsy was not performed. During the ensuing years, the patient showed worsening of HCM with evolution of left ventricular (LV) dysfunction (LVEF = 35%) and developed stroke-like episodes to result in death. The MOGE(S) system summarizes the clinical and genetic status of the family in 2011 and the key clinical traits of the disease. LVH = left ventricular hypertrophy; other abbreviations as in Figure 2.



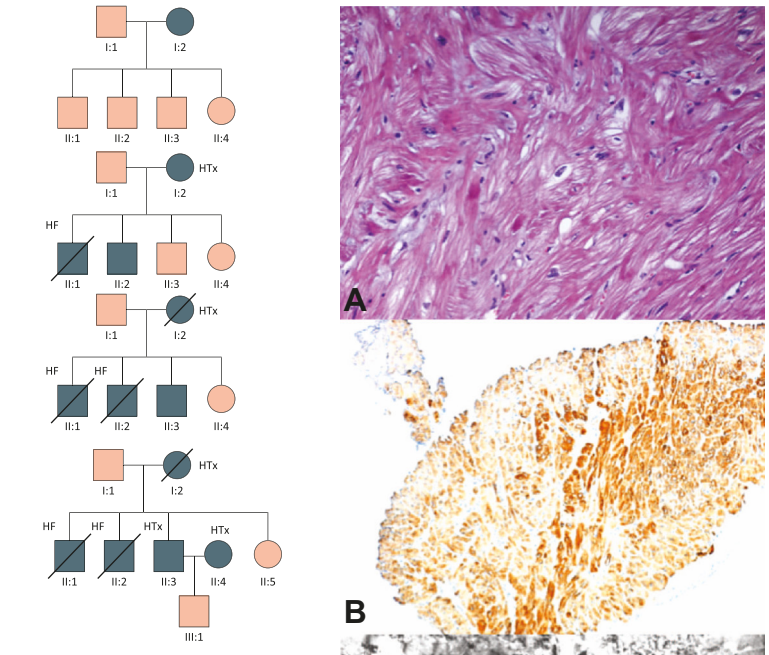
Pedigree	M O G E
I:1	$M_{NA[H]}\ O_K\ G_{OC}\ E_0$
I:2	$M_0\ O_0\ G_0\ E_{G\text{-}GLA\text{–}/\text{–}}$
II:1	$M_{H[\hat{e}PR]}\ O_{H+N+C}\ G_{X\text{-}L}\ E_{G\text{-}GLA+/\text{–}}$
II:2	$M_H\ O_{E+G}\ G_{X\text{-}L}\ E_{G\text{-}GLA+/\text{–}}$
III:1	$M_H\ O_{K+C}\ G_{X\text{-}L}\ E_{G\text{-}GLA+}$
III:2	$M_H\ O_K\ G_{X\text{-}L}\ E_{G\text{-}GLA+}$
IV:1	$M_0\ O_0\ G_{0NC}\ E_0$

FIGURE 6. MOGE(S) in a Family With AFD. On the **left** side of the figure, the example of Anderson-Fabry disease (AFD) highlights the importance of family study and demonstrates how simple is it to suspect the disease **(left)**. The proband **(arrow)** was brought to medical attention for the clinical suspicion of HCM. The family history, however, revealed long-lasting maternal gastrointestinal disturbances (common diseases causing such disorders had been excluded), a stroke in the maternal aunt, and renal failure in the maternal male cousin. Further screening of the family uncovered cornea verticillata in the mother and angiokeratomas in the male cousin. The serial examination of urine samples in the proband showed intermittent proteinuria, and the genetic testing confirmed the diagnosis of AFD. The MOGE(S) figure only summarizes the last clinical and genetic status of the family. Individual VI:1 is an obligate noncarrier, whereas individual I:1 (genetic test not performed) is an obligate carrier because the wife tested negative and both daughters carried the mutation. If the genetic test were available in I:1, it would not have been necessary in the daughters because both are naturally obligate carriers. In the **right half of the figure, from top to bottom**, the pathological features of AFD in endomyocardial biopsy are shown. (A) Hematoxylin and eosin stain shows a large number of vacuolated myocytes (glycosphingolipids are extracted in formalin-fixed, paraffin-embedded tissues); (B) the toluidine blue stain of the semi-thin sections from resin-embedded samples for electron microscopy show characteristic intramyocyte accumulation of osmiophilic bodies of the storage material; and (C) the ultrastructural panel confirms the typical lamellar and dense osmiophilic bodies. Abbreviations as in Figures 2. Grey filled symbols: mild LVH.



Year	Pedigree	M O G E
1986	I:1	$M_0\,O_0\,G_0$
	I:2	$M_H\,O_H\,G_N\,E_{NA}$
	II:1	$M_0\,O_0\,G_0$
1987 - 1993	I:1	$M_0\,O_0\,G_0$
	I:2	$M_H\,O_H\,G_N\,E_{NA}$
	II:1	$M_0\,O_0\,G_0$
	II:2	$M_0\,O_0\,G_0$
	II:3	$M_H\,O_{H+E+MR}\,G_{XL}\,E_{NA}$
2003	I:2	$M_H\,O_H\,G_N\,E_{G\text{-}LAMP2[p.Val310Ile]+/-}$
	II:1	$M_0\,O_0\,G_{XL}\,E_{G\text{-}Neg}$
	II:2	$M_{0[\hat{e}PR]}\,O_H\,G_{XL},\,E_{G\text{-}LAMP2[p.Val310Ile]+/-}$
	II:3	$M_H\,O_{H+E+SM+MR}\,G_{XL}\,E_{G\text{-}LAMP2[p.Val310Ile]+}$
2004 - 2013	I:2	$M_H\,O_H\,G_H\,E_{G\text{-}LAMP2[p.Val310Ile]+/-}$
	II:1	$M_0\,O_0\,G_{XL}\,E_{G\text{-}Neg}$
	II:2	$M_H\,O_H\,G_{XL}\,E_{G\text{-}LAMP2[p.Val310Ile]+/-}$
	II:3	$M_H\,O_{H+E+SM+MR+L}\,G_{XL}\,E_{G\text{-}LAMP2[p.Val310Ile]+}$
(Prenatal Genetic test: – ♂)	III:1	$M_0\,O_0\,G_{XL}\,E_{G\text{-}Neg}$
(Prenatal Genetic test: + ♂)	III:2	$E_{G\text{-}LAMP2[p.Val310Ile]+}$
(Prenatal Genetic test: + ♀)	III:3	$M_0\,O_0\,G_{XL}\,E_{G\text{-}LAMP2[p.Val310Ile]+/-}$

FIGURE 7. MOGE(S) in a Family With Danon Disease. The example of Danon disease caused by a mutation of the *LAMP2* gene and the natural history of the disease in the family from 1986 to 2013; the family history of 27 years is summarized in the table **(bottom right)**. Although Danon disease in its typical presentation affects males (*LAMP2* gene maps on the X chromosome) who show HCM, myopathy, and mental retardation (see the table), the cardiac phenotype is expressed also in adult female carriers who do not show myopathy and mental retardation. The II:3 male showed the typical phenotype; his sister who had 3 pregnancies and 3 prenatal diagnoses is now affected by cardiomyopathy. Her second pregnancy (a male fetus and a positive genetic test) ended in a voluntary interruption, whereas the third pregnancy (female fetus and positive genetic testing) ended in a Cesarean section due to worsening of ventricular arrhythmias during pregnancy. The girl is now well with normal electrocardiographic and echocardiographic features. The chromatogram shows the mutation identified in the *LAMP2* gene in I:2. Abbreviations as in Figure 2.



MOGE, 1987, proband 1:2, onset	
I:1	$M_0 O_0 G_0 E_0$
I:2	$M_{R\text{-}AVB} O_H G_U E_{G\text{-}NA}$
II:1	$M_0 O_0 G_0 E_{G\text{-}NA}$
II:2	$M_0 O_0 G_0 E_{G\text{-}NA}$
II:3	$M_0 O_0 G_0 E_{G\text{-}NA}$
II:4	$M_0 O_0 G_0 E_{G\text{-}NA}$

MOGE, 2013	
I:1	$M_0 O_0 G_0 E_0$
I:2	$M_{R\text{-}AVB} O_H G_U E_{G\text{-}DES\text{-}IVS3}$
II:1	$M_{R\text{-}AVB} O_H G_{AD} E_{G\text{-}NA}$
II:2	$M_{R\text{-}AVB} O_H G_{AD} E_{G\text{-}DES\text{-}IVS3}$
II:3	$M_{R\text{-}AVB} O_H G_{AD} E_{G\text{-}DES\text{-}IVS3}$
II:4	$M_D O_H G_N E_{M(\text{not proven})}$
II:5	$M_0 O_0 G_0 E_{G\text{-}0}$
III:1	$M_0 O_0 G_0 E_{G\text{-}0}$

FIGURE 8. MOGE(S) in RCM With Cardiac Desminopathy and Intramyocyte Storage of Desmin. Typical cardiac desminopathies with intramyocyte desmin accumulation are clinically characterized by RCM and AVB; the family history is presented in left panel and the typical pathologic features of the myocardium in the right panel. Individual I:1 underwent heart transplantation (HTx), as did her son II:3. The other 2 affected sons died of heart failure after diagnosis of RCM and pacemaker implantation. After transplantation II:3 married the unrelated II:4 (shown in blue letters in the MOGE, 2013 table) who also underwent HTx for DCM. II:4 had undergone HTx without family screening with a presumptive diagnosis of post-myocarditic DCM. However, her heart excised at transplantation did not show features of myocarditis, and the viral genome search was negative. The couple (II:3 and II:4) had a boy (III:1) in which the paternal *DES* mutation was excluded. However, in case the viral etiology of the DCM was wrong and the mother had a genetic DCM, the genetic status of the boy (although *DES* mutation is ruled out) remains incomplete, and the risk of developing DCM is unknown. The **right panel** shows (A) hematoxylin and eosin—stained myocardial samples in desminopathy. The eosinophilic bodies correspond to the accumulation of desmin, and myofibrillar disarray is present. (B) Anti-desmin immunostaining supports the diagnosis but remains nonconclusive in light microscopy study due to the variable orientation of myocytes in small EMB samples with procedure-related contraction bands. (C) Electron microscopy study is the gold standard for the pathological diagnosis. Abbreviations as in Figure 2.

involvement is apparent. The imaging alterations may include increased LV end-diastolic diameter and reduced longitudinal strain with still normal ejection fraction (EF) for DCM, or borderline LV thickening for HCM. The ACC/AHA guidelines include patients with a *family history of cardiomyopathy* in stage A. Therefore, the MOGE(S) can take advantage of the stage to describe individuals that show early markers of disease but do not fulfill the

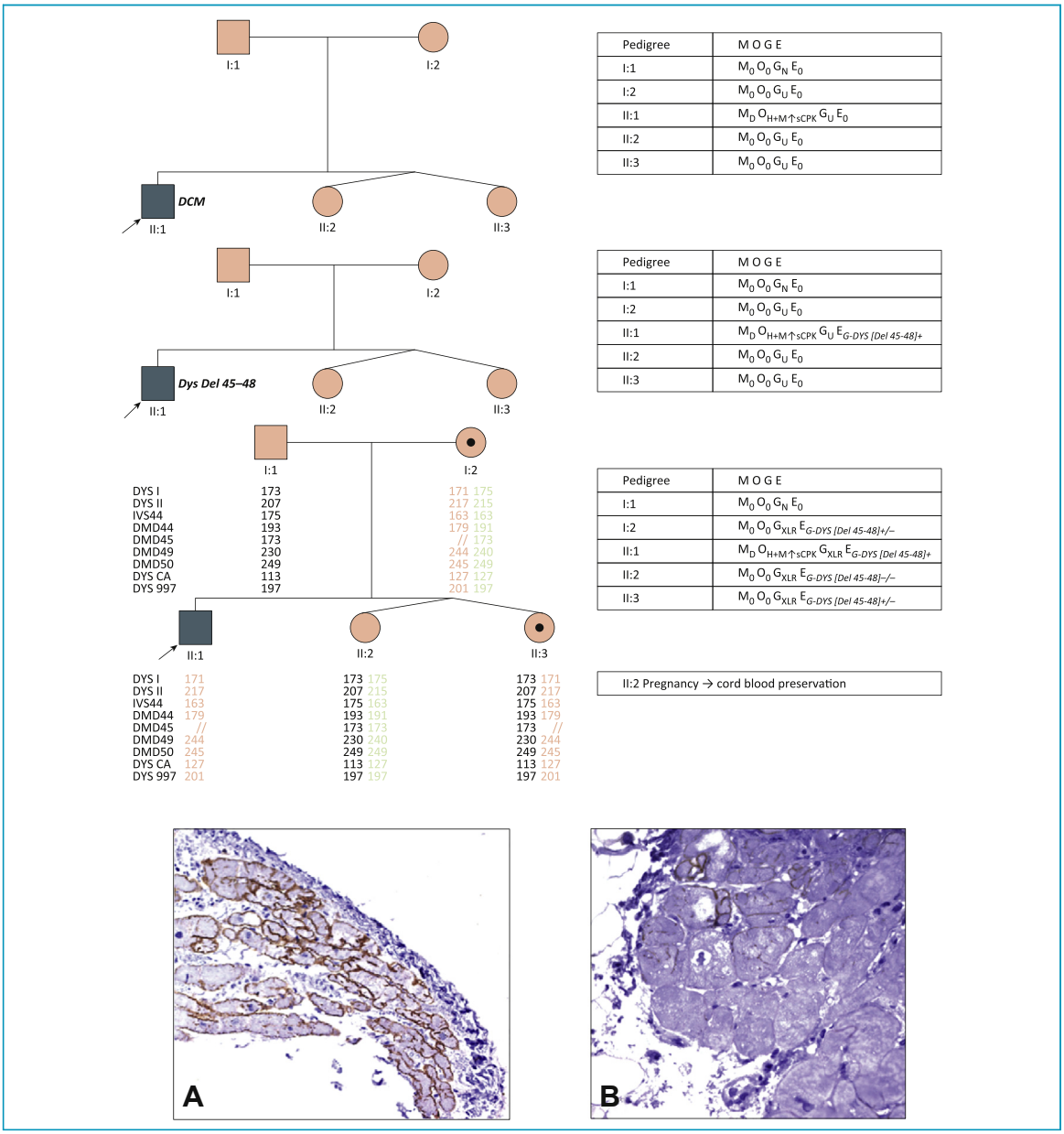


FIGURE 9. MOGE(S) in Dilated Cardiac Dystrophinopathy. The figure presents 3 diagnostic steps in a family with X-linked recessive DCM caused by deletion mutation of the *Dystrophin* gene. The proband showed an apparently sporadic DCM with severely dilated left ventricle and decreased EF; the presence of increased sCPK suggested the possibility of a Dystrophin defect. The MLPA demonstrated an in-frame deletion of exons 45 to 48. The noncarrier sister at her first pregnancy asked about private umbilical blood cord preservation for future stem cell (SC) transplantation in the affected brother. This request is increasing in Dystrophin families and, at present, regulatory bodies and scientific societies in different countries do not provide uniform recommendations. We realize that a definite donor cell engraftment is not yet proven, and such a request should only be considered in consultation with SC transplantation experts and specialized centers; private SC preservation with costs covered by the family is feasible. The family study documented the carrier status of the mother and of 1 of the sisters (II:3). **Bottom**: the myocardial pathology shows that the Dystrophin defect is associated with decreased expression of the protein (B) as compared to abundant expression (A) in a normal heart. **A** represents an endomyocardial biopsy specimen obtained from a donor heart before transplantation. Abbreviations as in Figure 2.

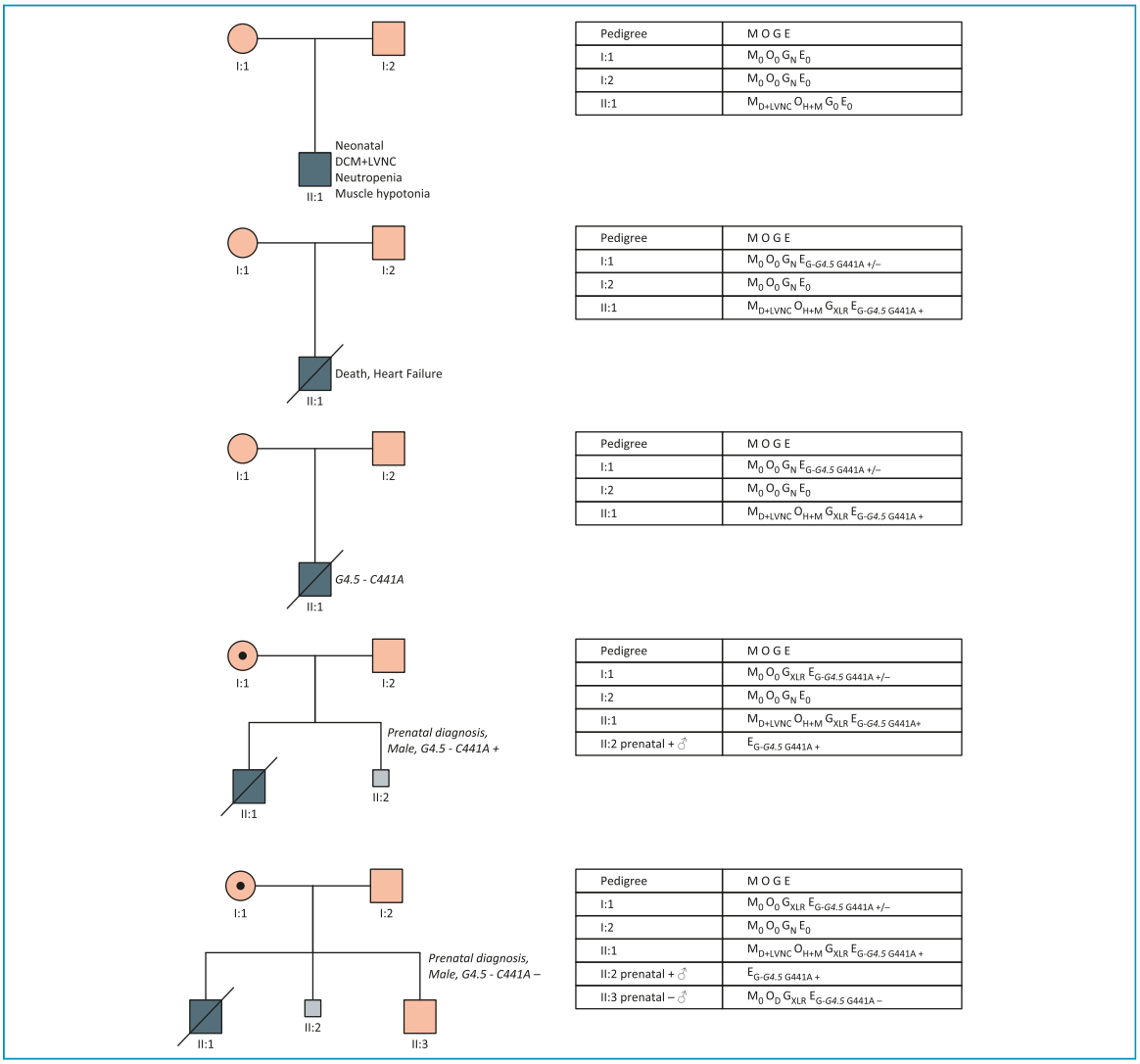


FIGURE 10. MOGE(S) in Barth Syndrome. The figure shows the case of a boy who demonstrated a severe and rapidly fatal neonatal dilated cardiomyopathy. The family history was negative: both parents were healthy, and there were no relatives affected by cardiac diseases. The presence of LVNC suggested the possibility of Barth syndrome. The genetic testing showed a hemizygous mutation in the *G.4.5* gene encoding the nuclear mitochondrial protein tafazzin. The mutation was inherited from the healthy mother whose clinical screening demonstrated a normal heart. At the second pregnancy, the prenatal diagnosis demonstrated a male fetus carrier of the mutation. The pregnancy was interrupted. At the third pregnancy, the prenatal diagnosis showed the male fetus a noncarrier of the mutation. The pregnancy was successful, and the boy is healthy. The mother did not show cardiac problems during or after the 3 pregnancies. Abbreviations as in Figure 2.

diagnostic criteria for the cardiomyopathy. In families with known mutation, the diagnosis of early cardiomyopathies can be further supported by the presence of the mutation(s), whereas in genetically orphan familial cardiomyopathies, only the early imaging markers of the disease can be highlighted. This description could be especially useful for sport worthiness that often requires physicians to provide a definitive recommendation, and (S) notation may allow the description of a gray diagnostic zone. Although criteria for early diagnosis of cardiomyopathy are not systematically described, the increasing family screening and monitoring have revealed that the cardiomyopathies likely serve a long *pre-clinical* or *subclinical* interval before the onset of symptoms or the manifestation of the clinical phenotype [31].

Table 2 shows the MOGE(S) system notations and modeling. The alphabetical components are likely going to

TABLE 2. The MOGE(S) Nomenclature: Some Common Examples Are Provided in the Lower Part of the Table

M Morphofunctional Phenotype*	O Organ/System Involvement†	G Genetic‡	E Etiological Annotation§	S Stage; ACC/AHA Stage, NYHA Functional Class‖
(D) Dilated	(H) Heart	(N) Family history negative	(G) Genetic etiology—add gene and mutation; (NC) Individual noncarrier plus the gene that tested negative	ACC/AHA stage represented as letter (A, B, C, D)
(H) Hypertrophic	(M) Muscle, skeletal	(U) Family history unknown		
(R) Restrictive	(N) Nervous	(AD) Autosomal dominant	(OC) Obligate carrier	
(A) ARVC	(C) Cutaneous	(AR) Autosomal recessive	(ONC) Obligate noncarrier	To be followed by NYHA functional class represented in Roman numerals (I, II, III, IV)
(NC) LVNC	(E) Eye	(XLR) X-linked recessive	(DN) De novo	
Overlapping (H+R), (D+A), (NC+H), (H+D), (D+NC) or more complex combinations such as (H+R+NC)	(A) Auditory	(XLD) X-linked dominant	(C) Complex genetics when >1 mutation (provide additional gene and mutation)	
	(K) Kidney	(XL) X-linked	(Neg) Genetic test negative for the known familial mutation	
	(G) Gastrointestinal	(M) Matrilineal	(NA) Genetic test not yet available	
	(S) Skeletal	(DN) De novo	(N) Genetic defect not identified	
(E) Early, with type in parentheses	(0) Absence of organ/system involvement, e.g., in family members who are healthy mutation carriers; the mutation is specified in E and inheritance in G	(0) Family history not investigated	(0) No genetic test, any reason (no blood sample, no informed consent, etc.)	
(NS) Nonspecific phenotype			Genetic amyloidosis (A-*TTR*) or hemochromatosis (*HFE*)	
(NA) Information not available			Nongenetic etiologies:	
(0) Unaffected			(M) Myocarditis	
			(V) Viral infection (add the virus identified in affected heart)	
			(AI) Autoimmune/immune-mediated; suspected (AI-S), proven (AI-P);	
			(A) Amyloidosis (add type of amyloidosis: A-K; A-L, A-*SAA*)	
			(I) Infectious, nonviral (add the infectious agent)	
			(T) Toxicity (add toxic cause/drug)	
			(Eo) Hypereosinophilic heart disease	
M_D, M_H, M_R, M_A, M_{NC}, M_0, M_{H+R}, M_{D+A}	O_H, O_M, O_K, O_C	G_N, G_U, G_{AD}, G_{AR}, G_{XLR}, G_{XLD}, G_{XD}, G_M, G_{DN}	$E_{G\text{-}MYH7[R403E]}$, $E_{G\text{-}HFE[Cys282Tyr+/+]}$, $E_{V\text{-}HCMV}$, $E_{G\text{-}A\text{-}TTR[V30M]}$, $E_{M\text{-}sarcoidosis}$	$S_{A\text{-}I}$, $S_{A\text{-}II}$

ACC/AHA = American College of Cardiology—American Heart Association; NYHA = New York Heart Association; other abbreviations as in Table 1.

*The morphofunctional phenotype description (M) may contain more information using standard abbreviations, such as AVB = atrioventricular block; WPW = Wolff-Parkinson-White syndrome; LQT = prolongation of the QT interval; AF = atrial fibrillation; ↓R = low electrocardiogram voltages; ↓PR = short PR interval.

†Organ (O) involvement in addition to the H subscript (for heart) should be expanded for the involvement of M = skeletal muscle, E = eye, ocular system, A = auditory system, K = kidney, L = liver, N = nervous system, C = cutaneous, G = gastrointestinal system, and other comorbidities, including MR = mental retardation.

‡Genetic (G) describes the available information about inheritance of the disease. It also provides complete information if the family history is not proven or unknown, and if genetic testing has not been performed or was negative for the mutation/mutations identified in the family.

§The etiologic annotation (E) provides the facility for the synthetic description of the specific disease gene and mutation, as well as description of nongenetic etiology.

‖The functional annotation or staging (S) allows the addition of ACC/AHA stage and NYHA functional class.

change in parallel with new scientific discoveries. As anticipated, the proposed nosology is modeled similarly to the universally accepted TNM staging of tumors, which has been consistently expanded and has allowed use of a common language of clinical comprehension and utility [32]. In **TNM staging**, the **T** describes the size of carcinoma and extent of local invasiveness, **N** stands for the status of lymph nodes, and **M** provides for the presence or absence of metastases. There are additional descriptors; for instance, the prefix **y** with T indicates that the cancer was resected after neoadjuvant therapy, **r** indicates recurrence of cancer, and **m** identifies multifocal cancer. Similarly the nodal status can be **i+** (isolated tumor cells), **mic** (micrometastatic, 0.2 to 2.0 mm), or **mac** (macrometastases, >2 mm). The clinical staging is designated as **cTNM** and the pathological staging of cancer as **pTNM**.

In the MOGE(S) nomenclature, ion channelopathies are not included, but can be incorporated if so needed in the future. The reason for the exclusion is that due to the high prevalence of genetic variations in ion channel genes and the ever-increasing genetic complexity of cardiomyopathy, it cannot be excluded that few available reports of ion channel mutations in patients with cardiomyopathy (in the absence of screening of all other disease genes) may in fact represent an incomplete genotyping. In a series of more than 100 DCM patients in whom the *SCN5A* gene was screened along with other genes, a single mutation was identified in 1 patient who was also carrier of the *PLN* mutation [33]. The channelopathies are nosologically well-defined arrhythmogenic disorders [34] without LV remodeling and with clinical needs that differ from those of cardiomyopathies. Giving the large spectrum of electrical phenotypes associated with mutations of ion channel genes, this group of diseases likely deserves a specific and independent nomenclature.

The MOGE(S) nomenclature in the diagnostic work-up of cardiomyopathies

It is expected that the clinical and imaging characterization of the phenotype (M) would be routinely defined on morphological (dilated, hypertrophic, LV noncompaction [LVNC]) and morphofunctional (restrictive, arrhythmogenic) traits, and the second descriptor (i.e., the organ involvement, O) would require to specify whether the heart is the only affected organ or other organs/systems are involved (Table 2). The disease may be systemic and the involvement of the heart a part of general disease process. This simple definition of the involvement of the heart only, of the heart as a component of systemic disease process, and the involvement of other organs provides useful clinically discriminatory information. The first combination of (M) and (O) can offer preliminary diagnostic clues. For instance, $M_H\ O_{H+SM+MR}$ suggests the possibility of HCM in either Danon or mitochondrial DNA–related disease; when additional details are available, such as $M_{H[WPW]}\ O_H$, a mutation of *PRKAG2* might be suspected. Similar clues could be available for dilated cardiolaminopathy $M_{D[AVB]}\ O_H$, dilated cardiodystrophinopathy $M_{D[\uparrow sCPK]}\ O_{H+M}$, or restrictive desminopathy $M_{R[AVB]}\ O_{H+M}$ and underscore the importance of identifying clinical indicators ("red flags") in the MOGE(S) nomenclature [35].

Data from family pedigrees, including investigation for the family history and the pattern of inheritance (G), add valuable leads for complete characterization of the cardiomyopathy. For example, a restrictive cardiomyopathy with autosomal dominant inheritance, but without conduction disease and involvement of other organ systems, suggests troponinopathy ($M_R\ O_H\ G_{AD}$). Information about G may help discriminate similar phenotypes: ($M_{H[WPW]}\ O_H\ G_{AD}$) might suggest an HCM associated with *PRKAG2* mutation, whereas ($M_{H[WPW]}\ O_{H+M+MR}\ G_{XL}$) suggests Danon disease, or ($M_{H[WPW]}\ O_{H+M+N}\ G_M$) mitochondrial DNA–related cardiomyopathy. The etiological annotation (E) provides a descriptive analysis of the genetic defect and/or underlying disease. For nongenetic and nonfamilial cardiomyopathy, the E annotation may include other etiologies.

Although it may seem a bit complex in the beginning, this nomenclature does provide an articulated configuration that is able to transmit all essential information for every cardiomyopathy type, patient, and family; a genetic tree and reference to family members per generation may be appended when needed (Fig. 4). An easy web application (app) for MOGE(S) nomeclature can be accessed from mobile phones and other devices (http://moges.biomeris.com). The app becomes handy for correct notation at least in the initial stages. The abbreviations applied here (such as AVB or WPW) are consistent with terminology systems such as Systematized Nomenclature of Medicine (SNOMED) [36] or SNOMED CT (SNOMED Clinical Terms) [37] and in the International Classification of Diseases (ICD) [38]. The proposed nomenclature reflects the diagnostic work-up of cardiomyopathies for evaluation of the phenotype, implementation of family screening strategies for diagnosis and prevention, and results of genetic testing in the Sanger and post-Sanger era.

MOGE(S) NOMENCLATURE FOR HCM

HCM phenotypically denotes a heterogeneous group of syndromes all sharing a cardiac trait of thickening of the LV wall; the 2 major groups include *sarcomeric* (up to 90% of all HCM caused by mutations of structural and regulatory genes of the sarcomere) and *nonsarcomeric* HCM (Table 1).

The diagnosis of sarcomeric HCM implies that a sarcomeric gene defect has been identified, and the mutation is duly noted in the etiological (E) annotation, such as $M_H\ O_H\ G_{AD}\ E_{G\text{-}MYH7[p.Arg403Glu]}$. Although earlier studies attempted to correlate distinct gene defects with the severity of the disease, little has been confirmed after 20 years of genotype to phenotype correlation studies [39]. Several disease genes have been identified; defects of *MYH7* and *MYBPC3* account for up to 70% of sarcomeric HCM, followed by troponin gene defects (*TNNI3*, *TNNT2*) and

TABLE 3. Major Mutations in MTDNA* and Nuclear Genes and Cardiac Phenotypes Reported to Date

MTDNA	Disease	Allele	Gene	HCM	DCM	RCM	LVNC
MTTL1	MMC/MELAS	*A3260G*	*tRNA$^{Leu(UUR)}$*	X	X		
MTTL1	MMC	*C3303T*	*tRNA$^{Leu(UUR)}$*	X	X		
MTTL1	MELAS	*A3243G*	*tRNA$^{Leu(UUR)}$*	X	X	X	X
MTTL1	MELAS	*G3244A*	*tRNA$^{Leu(UUR)}$*	X			
MTTL1	MM/HCM + RENAL TUBULAR DYSFUNCTION	*G3242A*	*tRNA$^{Leu(UUR)}$*	X	X		
MTTL1	MELAS	*A3252G*	*tRNA$^{Leu(UUR)}$*		X		
MTTL1	MELAS/myopathy	*T3258C*	*tRNA$^{Leu(UUR)}$*	X	X		
MTTL1	Myopathy	*A3280G*	*tRNA$^{Leu(UUR)}$*	X	X		
MTTL2	DCM/LS/failure to thrive and LA	*T12297C*	*tRNA$^{Leu(CUN)}$*		X		
MTTI	MHCM	*A4295G*	*tRNA^{Ile}*	X	X		
MTTI	MICM	*A4300G*	*tRNA^{Ile}*	X	X		
MTTI	FICP	*A4269G*	*tRNA^{Ile}*	X	X		
MTTI	HCM with hearing loss/possible hypertension factor	*A4316G*	*tRNA^{Ile}*	X			
MTTI	FICP	*A4317G*	*tRNA^{Ile}*	X	X		
MTTI	Varied familial presentation/spastic paraparesis	*G4284A*	*tRNA^{Ile}*	X	X		
MTTI	Mitochondrial encephalocardiomyopathy	*C4320T*	*tRNA^{Ile}*	X	X		
MTTK	Cardiomyopathy/SNHL	*A8348G*	*tRNA^{Lys}*	X	X		
MTTK	MERRF	*A8344G*	*tRNA^{Lys}*	X	X		
MTTK	MERRF/MICM+DEAF/autism/LS	*G8363A*	*tRNA^{Lys}*	X	X		
MTTG	MHCM	*T9997C*	*tRNA^{Gly}*		X		
MTTH	MICM	*G12192A*	*tRNA^{His}*		X		
MTTP	DCM	T16032TTCTCTGTTCTTTCAT (15 bp dup)	*tRNA^{Pro}*		X		
MTTQ	Possibly LVNC-associated	*T4373C*	*tRNA Gln*		X		
MTTV	LS	*C1624T*	*tRNA^{Val}*	X	X		
MTTV	Adult LS	*G1644T*	*tRNA^{Val}*	X			
MTRNR2	MELAS	*C3093G*	*16S rRNA*	X			
MTRNR1	Possibly LVNC-associated	*T921C*	*12S rRNA*				X
MTRNR1	Possibly LVNC-associated	*T850C*	*12S rRNA*				X
MTRNR1	DEAF, possibly LVNC-associated	*T961C*	*12S rRNA*				X
MTRNR1	Found in 1 HCM patient	*T1391C*	*12S rRNA*		X		
MTRNR1	Found in 1 HCM patient	*C1556T*	*12S rRNA*		X		
MTRNR2	Possibly LVNC-associated	*T2352C*	*16S rRNA*				X
MTRNR2	Possibly LVNC-associated	*G2361A*	*16S rRNA*				X
MTRNR2	Possibly LVNC-associated	*A2755G*	*16S rRNA*				X
MTCYB	HCM	*G15243A* (*G166E*)	*MTCYB*	X			
MTCYB	HCM/WPW,DEAF	*G15498A* (*G251D*)	*MTCYB*	X			
MTCO1	Idiopathic sideroblastic anemia	*T6721C* (*M273T*)	*MTCO1*	X			
MTCO1	Idiopathic sideroblastic anemia	*T6742C* (*I280T*)	*MTCO1*	X			
MTND4	Diabetes mellitus	*A12026G* (*I423V*)	*MTND4*	X			

(continued)

other less commonly involved genes (*ACTC1*, *CSRP3*, *CRYAB*, *CAV3*, *MYH6*, *MYL2*, *MYL*, *TNNC1*, *TCAP*, *MYOZ1*, *MYOZ2*) (Table 1). The extracardiac markers are conspicuously absent in autosomal dominant sarcomeric HCM. A minority of sarcomeric HCM may show associated myopathy, a feature that may be described as M_H O_{H+M} G_{AD} $E_{G\text{-}MYH7[p.Arg403Glu]}$. Autosomal recessive HCM is rare [40]: these families differ from those in which double or triple mutations are identified but inheritance is autosomal dominant. In fact, an increasingly greater proportion of patients with sarcomeric HCM are being recognized with double and compound mutations contributing to worse

TABLE 3. Continued

Nuclear Genes	Phenotype	Inheritance	HCM	DCM	RCM	LVNC
ANT1 (PEOA2)	AD-PEO, multiple mtDNA deletions	AD	X	X		
AGK	Sengers syndrome (HCM, cataract and myopathy)	AR	X			
COX10	Neonatal tubulopathy and encephalopathy, LS	AR		X		
COX15	Early-onset HCM, LS	AR	X			
DNAJC19	DCM and LVNC, early onset, anemia, ataxia, male genital anomalies and methylglutaconic aciduria type V	AR		X		X
FRDA	Friedreich ataxia, neuropathy, cardiomyopathy, diabetes	AR	X	X		
G4.5 (Tafazzin)	Barth syndrome, X-linked dilated cardiomyopathy	X-linked		X		X
MFN2	Charcot-Marie-Tooth disease type 2A2	AD		X		
POLG (PEOA1)	Alpers syndrome, AD-PEO and AR-PEO, male infertility, SANDO syndrome, SCAE	AD-AR	X	X		
NDUFS2	Encephalopathy	AR	X	X		
NDUFV2	Hypotonia, encephalopathy	AR	X			
SCO2	Neonatal cardio-encephalomyopathy	AR	X	X		

DEAF = maternally inherited deafness or aminoglycoside-induced deafness; FICP = fatal infantile cardiomyopathy plus, a MELAS-associated cardiomyopathy; LD = Leigh disease; LS = Leigh syndrome; LA = Lactic Acidosis; LVNC = left ventricular noncompaction; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF = myoclonic epilepsy and ragged red muscle fibers; MHCM = maternally inherited hypertrophic cardiomyopathy; MICM = maternally inherited cardiomyopathy; MMC = maternal myopathy and cardiomyopathy; mtDNA = mitochondrial DNA; PEO = progressive external ophthalmoplegia; SANDO = sensory ataxic neuropathy with dysarthria/dysphagia and ophthalmoplegia; SCAE = spinocerebellar ataxia with epilepsy; other abbreviations as in Table 1.

*http://www.mitomap.org; last accessed November 6, 2013. Short PR electrocardiogram intervals and pre-excitation recur in mitochondrial cardiac phenotypes, especially in the early phases of the disease. Atrioventricular block is more common in late phases of the disease.

phenotype and high arrhythmogenic risk regardless of the ventricular wall thickness; double (or compound) mutations detected by genetic testing may confer a genedose effect in HCM (such as M_H O_H G_{AD} $E_{G\text{-}MYH7[p.Arg403Glu]+MYBPC3[IVS7+1G>A]}$) and may predispose patients to adverse disease progression [41,42]. Some examples of MOGE(S) nomenclature for sarcomeric HCM are presented below.

M_H O_H G_{AD} $E_{G\text{-}MYH7[p.Arg403Glu]}$ $S_{B\text{-}I}$ represents: morphofunctional phenotype **(M)**: ***hypertrophic (H)*** cardiomyopathy; organ **(O)** involvement: ***heart (H)***; genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: ***genetic (G)*** and caused by the ***p.Arg403Glu*** mutation of the ***MYH7*** gene, ACC/AHA stage **(S)** ***B,*** NYHA ***I***.

$M_{E(H)}$ O_H G_{AD} $E_{G\text{-}MYH7[p.Arg403Glu]}$ $S_{A\text{-}I}$ represents morphofunctional phenotype **(M)**: "***early***" ***(E) hypertrophic (H)*** cardiomyopathy (for example, borderline LV thickness or early diastolic dysfunction or electrocardiographic (ECG) abnormalities suggesting hypertrophy with normal LV thickness); organ **(O)** involvement: ***heart (H)***; genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: ***genetic (G)*** and caused by the ***p.Arg403Glu*** mutation of the ***MYH7*** gene; ACC/AHA stage **(S)** ***A,*** NYHA ***I***.

$M_{E(H)}$ O_H G_{AD} $E_{G\text{-}NA}$ $S_{A\text{-}I}$ represents: morphofunctional phenotype **(M)**: "***early***" **(E)** ***hypertrophic (H)*** cardiomyopathy organ **(O)** involvement: ***heart (H)***; genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: genetic but the mutation is **not yet available (NA)** (either ongoing or to be done but feasible); ACC/AHA stage **(S)** ***A,*** NYHA ***I***.

M_0 O_0 G_{AD} $E_{G\text{-}MYH7[p.Arg403Glu]}$ $S_{A\text{-}I}$ represents: morphofunctional phenotype **(M)**: ***"unaffected" (0)*** by cardiomyopathy; organ **(O)** involvement: absence of any cardiac phenotype (zero, ***0***); in familial/genetic **(G)** ***autosomal dominant (AD)*** cardiomyopathy; etiology **(E)** ***genetic (G)***, healthy carrier of the ***p.Arg403Glu*** mutation of the ***MYH7*** gene that causes the disease in the family; ACC/AHA stage **(S)** ***A,*** NYHA ***I***.

Because the intrafamily variability of the phenotype may include different morphofunctional phenotypes (for example, HCM and DCM, the latter often representing the end-stage evolution of the original hypertrophic phenotype), a combination of morphofunctional phenotypes is possible **(H + D)**.

Nonsarcomeric HCM may show different types of inheritance, such as AD in *PRKAG2*-related HCM with WPW [43], AR in Friedrich ataxia [44], X-linked in Danon disease [45] and in Anderson Fabry disease (AFD) [46], AR in Pompe disease [47], or matrilineal (or maternal) in cardiomyopathies caused by mutations in the mitochondrial DNA [48,49] (Table 3, Fig. 5). Mitochondrial diseases constitute a large and heterogeneous group of complex diseases/syndromes (1 per 4,000 to 5,000 live births) caused by mutations of nuclear (inherited according to Mendelian rules) or mitochondrial (matrilineal inheritance with absence of male transmission) genes. Cardiologists encounter mitochondrial diseases in their routine practice either in patients presenting with HCM or DCM, or in patients referred by neurologists or myologists for consultation. The role of the cardiologists is essential for

TABLE 4. Most Common Metabolic Diseases Causing Cardiomyopathy Phenocopies and Synthetic Description of Involvements of Other Organs/Tissues

Disease	MIM # Phenotype	Inheritance	Age of Onset	Disease Gene	Cardiac Phenotype	Extracardiac Markers/ Major Involvement (Noncomprehensive) of Other Organs	Specific Treatment
Glycogen storage disease (GSD)							
GSDII (Pompe disease, glycogen storage disease II, acid alpha-glucosidase/acid maltase deficiency)	232300	AR	Infant to young adult	*GAA*	HCM	Skeletal muscle, liver	ERT (gene therapy; substrate reduction therapy)
GSDIII (Forbes or Cori disease, glycogen debranching enzyme)	232400	AR	Childhood	*AGL*	HCM	Liver, skeletal muscle, hypoglycemia, growth retardation	
GSD IV (Anderson disease, glycogen branching enzyme)	232500	AR	Perinatal, congenital, infant, childhood, adult	*GBE1*	DCM	Liver, skeletal muscle, brain	
GSD V (McArdle disease, glycogen phosphorylase)	232600	AR	Young adult	*PYGM*	DCM	Skeletal muscle; myoglobinuria	
GSD 0 (muscle) (muscle glycogen synthase	611556	AR	Childhood	*GYS1*	HCM	Skeletal muscle	
Other disorders of the glycogen metabolism							
PRKAG2-related disease Lethal congenital glycogen storage disease of heart	261740	AD	Young adult	*PRKAG2*	HCM	—	
PRKAG2-related familial hypertrophic cardiomyopathy	600858	AD	Young adult	*PRKAG2*	HCM	—	
Wolff-Parkinson-White syndrome	194200	AD	Young adult	*PRKAG2*	WPW with/without HCM	—	
Danon disease (lysosomal-associated membrane protein 2)	300257	XL	Childhood in males, young adult in females	*LAMP2*	HCM, HCM evolving through dilation and dysfunction, LVNC	Skeletal muscle, cognitive impairment in males, pigmentary retinopathy also in females	
Lysosomal storage diseases: sphingolipidoses							
Anderson-Fabry disease (alpha-galactosidase deficiency)	301500	XL	Childhood to adulthood	*GLA*	Symmetrical HCM	Renal, ocular, nervous, cutaneous, gastrointestinal systems	ERT
Anderson-Fabry disease—later onset, cardiac variant	301500	XL	Adult	*GLA*	HCM	—	ERT
GM1 gangliosidosis (beta-galactosidase deficiency)	230500	AR	Infancy (infantile form), childhood (late-infantile/ juvenile form), adult (chronic form)	*GLB1*	HCM, DCM	Neurological and skeletal systems, hepatosplenomegaly	

MLD (Metachromatic leucodystrophy)	250100	AD	Infancy (infantile form), childhood (juvenile form), adult (adult form)	*ARSA*	RCM/DCM	Skeletal muscle, nervous, ocular systems	
GM1 gangliosidosis with cardiac involvement (beta-galactosidase deficiency) [50—53]	230500	AR	Infancy (infantile form), childhood (juvenile form), adult (adult form)	*GLB1*	HCM/DCM, mitral valve thickening, CAD	Skeletal muscle, nervous, renal, ocular, and cutaneous systems	
GM2 gangliosidosis (Tay-Sachs disease)	272800	AR	Infancy (infantile form), childhood (juvenile form), adult (adult form)	*HEXA*	Valve disease	Nervous, ocular, auditory	
GM2 gangliosidosis (Sandhoff-Jatzkewitz disease) [54,55]	268800	AR	Infancy (infantile form), childhood (juvenile form), adult (adult form)	*HEXB*	HCM, Mitral and aortic valve disease	Nervous, skeletal muscle, ocular systems	
Gaucher disease (glucocerebrosidase deficiency), types I, II and III, perinatal lethal and type IIIC with cardiovascular calcifications (cardiac variant)	230800	AR	Childhood to young adult	*GBA* (*HK* gene)	Cardiovascular calcifications	Hemopoietic, nervous, bone, cutaneous systems, hepatosplenomegaly	ERT
Niemann-Pick disease (types C1, D) [56]	257220	AR	Infant, childhood, adult	*NPC1*	Coronary artery and valvular heart disease	Nervous, bone, cutaneous systems, hepatosplenomegaly, sea-blue histiocytes	
Lysosomal storage diseases: mucopolysaccaridoses (degradation defects of glycosaminoglycans)							
MPS I (Hurler and Scheie syndromes) (iduronidase enzyme deficiency)	607014, 607016, 607015	AR	Childhood to young adult	*DUA*	HCM	Nervous, skeletal and joints, ocular, cutaneous, respiratory systems	ERT
MPS II (Hunter syndrome)	309900	XLR	Late infancy to young adult	*IDS*	HCM	Nervous, skeletal, ocular, cutaneous, auditory systems	ERT
MPS III A (Sanfilippo syndrome A)	252900	AR	Infancy to young adult	*SGSH*	HCM, HF	Nervous, skeletal, cutaneous systems; abundant and coarse, often blond hair	
MPS III B (Sanfilippo syndrome B)	252920	AR		*NAGLU*	HCM, HF	Nervous; skeletal, ocular, auditory	
MPS III C (Sanfilippo syndrome C)	252930	AR		*HGSNAT*	HCM, HF	Nervous, skeletal, ocular, hypertrichosis	
MPS III D (Sanfilippo syndrome D)	252940	AR		*GNS*	HCM, HF	Nervous, skeletal, ocular, auditory, hypertrichosis	
MPS IV A (Morquio syndrome A)	253000	AR	Infancy to young adult	*GALNS*		Nervous, skeletal, ocular	
MPS IV B (Morquio syndrome B)	253010	AR	Infancy to young adult	*GLB1*	HCM	Nervous, skeletal, ocular	
MPS VI (Maroteux-Lamy syndrome)	253200	AR	Infancy to adult	*ARSB*	DCM	Skeletal, integumental, ocular, muscular, hepatosplenomegaly	ERT

(continued)

TABLE 4. Continued

Disease	MIM # Phenotype	Inheritance	Age of Onset	Disease Gene	Cardiac Phenotype	Extracardiac Markers/ Major Involvement (Noncomprehensive) of Other Organs	Specific Treatment
MPS VII (Sly syndrome)	253220	AR	Infancy to adult	*GUSB*	HCM	Skeletal, nervous, possible hepatomegaly and mild ocular	
MPS IX	601492	AR	Infancy to young adult	*HYAL1*	Heart involvement, NOS	Skeletal, nervous, ocular	
Lysosomal storage diseases: disorders of glycoprotein and glycosylation metabolism							
Galactosialidosis or Goldberg syndrome (cathepsin A defect)	256540	AR	Infancy (early and late infantile types), childhood, adult (juvenile/adult type)	*CTSA*	HCM in late infantile type, DCM	Nervous, skeletal, ocular, cutaneous, auditory systems; possible hepatosplenomegaly	
Mucolipidosis or sialidosis, type I and II	256550	AR	Infancy to adult	*NEU1*	DCM	Nervous, skeletal, ocular, cutaneous systems	
Fucosidosis	230000	AR	Infancy to adult	*FUCA1*	DCM, HF	Nervous, skeletal, ocular, cutaneous (angiokeratoma) systems	
Alpha-mannosidosis	248500	AR	Infancy to young adult	*MAN2B1*	Possible heart involvement, NOS	Nervous, skeletal, cutaneous, auditory	
Beta-mannosidosis	248510	AR	Infancy to young adult	*MANBA*	Possible heart involvement, NOS	Nervous, skeletal, auditory, cutaneous	
Aspartylglucosaminuria	208400	AR	Infancy to young adult	*AGA*	HCM	Nervous, skeletal, cutaneous	
Schindler disease juvenile (Kanzaki disease, adult form)	609241, 609241	AR	Childhood, adult	*NAGA*	HCM	Nervous, skeletal, muscle, cutaneous	
Disorders of amino acid and organic acid metabolism							
Methylmalonic aciduria	251000	AR	Infancy to young adult	*MUT*	DCM	Systemic	
Beta-ketothiolase deficiency	203750	AR	Infancy	*ACAT1*	DCM	Liver, kidney, ketoacidotic attacks, lethargy	
Tyrosinemia I	276700	AR	Infancy to young adult/adult	*FAH*	HCM	Liver, kidney, mental retardation	
Hyperoxaluria I (oxalosis I)	259900	AR	Infancy to childhood/adult	*AGXT*	HCM	Kidney	
Hyperoxaluria II (oxalosis II)	260000	AR	Infancy to childhood/adult	*GRHPR*	HCM	Kidney	
Alkaptonuria (homogentisate 1,2-dehydrogenase deficiency)	203500	AR	Infancy to old age	*HGD*	Aortic valve disease	Kidney	

Niemann-Pick ERT = enzyme replacement therapy; HF = heart failure; NOS = not otherwise specified; XLR = X-linked recessive; other abbreviations as in Table 1.

suspecting a mitochondrial disease in patients with cardiomyopathy at onset or as first clinical manifestation. Mitochondrial HCM initially shows symmetrical LV hypertrophy, and subsequently evolves through LV dysfunction and dilation. A number of cardiac (short PR interval, pre-excitation syndrome, AVB) or noncardiac (hearing loss, myopathy, palpebral ptosis, nonvascular neurological involvement, mental retardation) markers, or biochemical (elevated serum creatine phosphokinase [↑sCPK], lactacidemia) indicators in probands and relatives provide diagnostic clues [35].

The MOGE(S) system allows a comprehensive summary of the clinical and genetic status of the family once the diagnosis has been made and family screening completed. The availability of the functional status (S) becomes especially important in asymptomatic relatives with manifest causative gene defect. Both cardiac and extracardiac traits contribute to clinical recognition of phenocopies (Table 4) [35,50-56]. A systematic approach leads to better characterization of cardiomyopathic disorder and could identify the need for pathological confirmation of the etiological basis of the disease, such as in AFD (Fig. 6) and in Danon Disease (Fig. 7). An accurate diagnosis is mandatory for genetic counseling and disease management; for example, the availability of enzyme replacement therapy in AFD may change the natural history of the disease and prevent (or delay) the end-stage disease.

MOGE(S) NOMENCLATURE FOR RCM

RCM is clinically characterized by altered relaxation and abnormal LV filling, biatrial dilation, in the absence of significant LV hypertrophy (Table 2). The lack of hypertrophy distinguishes RCM from HCM with restrictive pattern. Troponinopathies and desminopathies are typical examples of pure RCM; the former is not associated with conduction disease, whereas the latter is associated with AVB. Troponinopathies are encountered as de novo or inherited as an AD disease, whereas the desminopathies are inherited as AD (50%), AR (25%), or de novo (25%) [57,58]. The differential diagnosis of desminopathy is based on the presence of AVB and its association with myopathy; a fine-needle biopsy of the skeletal muscle immunostained with anti-desmin antibodies may provide the final diagnosis. Alternatively, endomyocardial biopsy may demonstrate intracellular osmiophilic granulofilamentous inclusions that immunoreact with anti-desmin antibodies (Fig. 8). Pure RCM due to defects of troponin genes, *TNNI3* in particular, may show absence of myocyte hypertrophy on histology but the presence of myocyte disarray otherwise characteristic of sarcomeropathy [59]. The clinical distinction of the troponinopathy [60,61] and desminopathy is important because of the high arrhythmogenic risk in troponinopathy and the negligible risk in desminopathy. In a recent meta-analysis including desmin-related diseases, both myopathies and cardiomyopathies, sudden death was reported in 2 of 195

TABLE 5. Major Lipid Storage Disorders With Possible Myocardial Involvement

Disease	MIM# Phenotype	Inheritance	Age of Onset	Disease Gene	Cardiac Phenotype	Extracardiac Markers/Involvement of Other Organs	Treatment
Multiple acyl-CoA dehydrogenase deficiency							
Glutaric acidemia IIA	231680	AR	Neonatal	*ETFA*	DCM, neonatal	Nervous, skeletal, muscle, liver, kidney (often polycystic), metabolic acidosis, hypoglycemia	
Glutaric acidemia IIB	231680	AR	Neonatal, childhood	*ETFB*	Sudden neonatal death	Nervous, skeletal, muscle, liver	
Glutaric acidemia IIC	231680	AR	Childhood to adult	*ETFDH*	DCM	Nervous, skeletal, muscle, liver, kidney (often polycystic), lung, metabolic acidosis, hypoglycemia	
Primary, systemic, carnitine transporter deficiency	212140	AR	Childhood to adult	*SLC22A5*	DCM, HCM	< Total plasma carnitine, hypoketotic hypoglycemia, hepatomegaly, elevated transaminases, and hyperammonemia in infants; skeletal myopathy, > creatine kinase, in childhood; cardiomyopathy, arrhythmias, or fatigability in adulthood	Carnitine supplementation
Chanarin–Dorfman syndrome (NLSD-I)	275630	AR	Childhood to adult	*ABHD5*	DCM	Skin (ichthyosiform erythroderma), liver, muscle, nervous (with possible MR), ocular	Suggested: diet low in long-chain fatty acids; retinoids for skin in patients w/o liver dysfunction
Neutral lipid storage disease with myopathy (NLSD-M)	610717	AR	Childhood to adult	*PNPLA2**	DCM	Myopathy	

MR = mental retardation; other abbreviations as in Table 1.
*Noncompensable rate-limiting enzyme in free fatty acid mobilization.

DES mutation carriers [62]. On the other hand, desminopathy shows high risk of AVB. Both entities share a very high penetrance, and almost all mutated individuals demonstrate manifest disease by the age of 40 years [63]. MOGE(S) applies to RCM as follows.

$\mathbf{M_{R[AVB]}\ O_{H+M}\ G_{AD}\ E_{G\text{-}Des[p.Gly84Ser]}\ S_{C\text{-}III}}$ represents morphofunctional phenotype **(M)**: ***restrictive cardiomyopathy (R)*** with ***AVB***; organ **(O)** involvement: ***heart (H)*** and ***skeletal muscle (M)***; genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: ***genetic (G)*** caused by *the* ***p.Gly84Ser*** mutation in the ***Desmin*** gene; ACC/AHA stage **(S)** ***C,*** NYHA ***III***.

$\mathbf{M_{E(R)\ [AVB]}\ O_{H+M}\ G_{AD}\ E_{G\text{-}Des[p.Gly84Ser]}\ S_{A\text{-}I}}$ represents morphofunctional phenotype **(M)**: ***"early" (E)*** restrictive cardiomyopathy with AVB; organ **(O)** involvement: ***heart (H)*** and ***skeletal muscle (M)***; genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: ***genetic (G)*** caused by the ***p.Gly84Ser*** in the ***Desmin*** gene; ACC/AHA stage **(S)** ***A,*** NYHA ***I***.

$\mathbf{M_0\ O_0\ G_{AD}\ E_{G\text{-}Des[p.Gly84Ser]}\ S_{A\text{-}I}}$ represents morphofunctional phenotype **(M)**: ***"unaffected" (0)*** by cardiomyopathy; organ **(O)** involvement: none (=absence of any cardiac phenotype); genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: ***genetic*** and caused by the ***p.Gly84Ser*** mutation in the ***Desmin*** gene; ACC/AHA stage **(S)** ***A***, NYHA ***I***.

MOGE(S) CLASSIFICATION FOR AMYLOID HEART DISEASE

Amyloidosis represents a distinct and unique condition of extracellular infiltrative disease. Most cardioamyloidoses are in the context of systemic diseases (genetic or nongenetic). Its inclusion in MOGE(S) is supported by the cardiac phenotype and clinical presentation as HCM or RCM that must be distinguished from other HCM and RCM. Amyloid shows distinct staining properties (pink-violet color with hematoxylin and eosin, apple-green birefringence with Congo Red under polarized light, and magenta color with crystal violet) and ultrastructural characteristics (fibrils of 7.5- to 10-nm diameter), regardless of the amyloidogenic protein [64,65]. Amyloidosis may be systemic or localized, the former including primary (AL), secondary (AA), and genetic (multiple and different genes) forms. The heart shows infiltration in the interstitial spaces, vessel walls of epicardial coronary arteries and intramural small vessels, cardiac valves, and epicardial fat [66]. The heart is usually hypertrophied, with thickened cardiac valves, and shows a restrictive functional pattern. The typical patient is an adult or an old individual of either sex with a long-standing history of nonspecific symptoms; family history is positive for heart failure, renal or multiorgan failure in heritable forms. The children with familial Mediterranean fever caused by mutations of the gene *Marenostrin* (*MEFV*) may show amyloidosis of kidney, skin, thyroid; the heart is less likely to be involved [67].

In most cases of cardiac amyloidosis, there is an echo-ECG mismatch with increased LV wall thickness and decreased ECG voltages. The amyloidogenic protein can be identified by immunoelectron microscopy study of the endomyocardial biopsy (or the peri-umbilical fat in systemic forms). The genetic testing is mandatory in familial amyloidosis [68,69]; the investigation of the family members not only may provide early or pre-clinical diagnosis, but also contributes to understanding the natural history of the disease. The MOGE(S) system facilitates the description of the amyloid cardiomyopathy. MOGE(S) applies to cardiac amyloidosis as follows.

$\mathbf{M_{H+R(ECG\ voltages)}\ O_{H+K}\ G_N\ E_{A\text{-}L}\ S_{B\text{-}II}}$ represents morphofunctional phenotype **(M)**: ***hypertrophic cardiomyopathy*** with ***restrictive pattern (H+R), low ECG voltages***; organ **(O)** involvement: ***heart (H)*** and ***kidney (K)***; genetic/familial **(G)**: **negative** family history **(N)** (and/or screening); etiology **(E)**: ***amyloidosis (A)***, amyloidogenic **light chain lambda (L)**; ACC/AHA stage **(S)** ***B***, NYHA ***II***.

MOGE(S) NOMENCLATURE FOR DCM

DCM is characterized by the presence of LV dilation and LV systolic dysfunction in the absence of other disorders sufficient to cause global systolic impairment (Table 2). Right ventricular dilation and dysfunction can be present, but not necessary, for the diagnosis [8]. More than 50% of the DCM cases are familial [10]. Although all DCM phenotypically look alike, most of them are distinct genetic diseases. Mutations in more than 40 genes have been described (Table 1), leading to extreme genetic heterogeneity [70]. Most familial DCMs are AD, and a minority is X-linked recessive, autosomal recessive, or matrilineal [10]. The most common disease gene is *Lamin A/C*, and the laminopathy constitutes 8% of all DCMs. *Dystrophin* gene defects account for up to 7% of male patients with DCM; most of these patients show an increase in sCPK without apparent myopathy [16,71,72] (Fig. 9). About one-fourth of the DCM cases have been recently attributed to the mutations in the giant *Titin* (*TTN*) gene [73]. The elastic protein titin is expressed in cardiomyocytes in 2 main isoforms, N2B (stiffer spring) and N2BA (more compliant spring). Titin-isoform switching is considered a mechanism for increased myocardial passive stiffness found in patients with heart failure with preserved LVEF [74]. While waiting for confirmatory studies, *Titin* remains an important disease gene. DCM patients with *TTN* mutations do not show disease-specific clinical markers [73]. The laminopathies are clinically characterized by conduction tissue disease in up to 80% of patients; the remaining patients demonstrate atrial fibrillation or an ARVC-like phenotype [75]. Dystrophinopathy is associated with severely enlarged and dysfunctional ventricles, and increased sCPK [16,72]. Zaspopathies [76] and tafazzinopathies show either LVNC or increased trabeculations in the setting of DCM [77]; the tafazzinopathies typically occur in infancy and characteristically show cyclic neutropenia, oral

aphthous ulcers, and hypocholesterolemia [77]. A small number of DCM patients are characterized by autosomal recessive inheritance and are usually brought to the attention of cardiologists when being evaluated for lipid storage disease in a multidisciplinary context. Table 5 summarizes the known disease genes as well as the cardiac phenotypes typically expressed in these disorders [78–83]. Cardiomyopathy, mostly DCM, is one of the common traits recurring in these syndromes, and in some of them it may be the sole manifestation of the disease [79,84,85].

All aforesaid information, including the common cardiac phenotype, the clinical markers, or red flags that may occur in patients/carriers of mutations of the same gene, are systematically organized in the MOGE(S) system, thus generating a common pheno-molecular language that can be easily adopted by clinicians in their daily practice, without the risk of missing out on any necessary information. MOGE(S) applies to DCM as follows.

$M_{D[AVB]}$ O_H G_{AD} $E_{G\text{-}LMNA[p.Leu197ProfsX2]}$ $S_{C\text{-}II}$ represents morphofunctional phenotype **(M)**: ***dilated cardiomyopathy*** with ***atrioventricular block***; organ **(O)** involvement: ***heart (H)***; genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: ***genetic*** and caused by the ***p.Leu197Pro fs X2*** mutation in the ***LMNA*** gene; ACC/AHA stage **(S)** ***C,*** NYHA ***II***.

$M_{E(D)}$ O_H G_{AD} $E_{G\text{-}LMNA[p.\,Leu197ProfsX2]}$ $S_{A\text{-}I}$ represents morphofunctional phenotype **(M)**: ***"early" (E) dilated cardiomyopathy*** (for example, increased LV end-diastolic dimension with normal LV function, or borderline LV function); organ **(O)** involvement: ***heart (H)***; genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)** is ***genetic*** and caused by the ***p.Leu197Pro fs X2*** mutation in the ***LMNA*** gene; ACC/AHA stage **(S)** ***A,*** NYHA ***I***.

$M_{E(D)}$ O_H G_{AD} $E_{G\text{-}NA}$ $S_{A\text{-}I}$ represents morphofunctional phenotype **(M)**: ***"early" (E) dilated cardiomyopathy*** (see example in the preceding text); organ **(O)** involvement: ***heart (H)***; genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: ***genetic*** but the mutations is **not** yet **available (NA)** (genetic test either ongoing or to be done, but feasible); ACC/AHA stage **(S)** ***A,*** NYHA ***I***.

M_0 O_0 G_{AD} $E_{G\text{-}LMNA[p.\,Leu197ProfsX2]}$ $S_{A\text{-}I}$ represents morphofunctional phenotype **(M)**: ***"unaffected" (0)*** by cardiomyopathy; organ **(O)** involvement: ***none (0)*** (= absence of any cardiac phenotype); genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: ***genetic (G)***, healthy carrier of the ***p.Leu197Pro fs X2*** mutation in the ***LMNA*** gene that causes the disease in the family; ACC/AHA stage **(S)** ***A,*** NYHA ***I***.

The genetic testing in future is expected to influence clinical decision making for primary prevention of sudden death and ICD implantation. In the current guidelines the severely depressed LVEF constitutes the major indication for ICD implantation in patients with DCM [11–13]. It is now becoming increasingly evident that laminopathies carry high arrhythmogenic risk [15,20] even when they may not meet guideline recommendations for ICD implantation. On the other hand, some genes and genetic variants may not be at high risk even though they may result in low LVEF [16]. A group of DCM caused by mutations in genes typically related to ARVC have a high risk of life-threatening arrhythmias and may deserve ICD implantation even if they fall short of guideline-based recommendations [11–13]. As we accumulate more knowledge and experience, the indications for ICD implantation will be modified, made more specific, and personalized.

MOGE(S) NOMENCLATURE FOR ARVC

Although predominantly affecting the RV, the spectrum of ARVC now includes possible biventricular involvement as well as the left dominant arrhythmogenic cardiomyopathy [86], referred to as arrhythmogenic cardiomyopathy (ACM)/ARVC in the recent HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies [87]. Although all ACM/ARVC phenotypes are associated with mutations in desmosome genes [88,89], mutations in typically DCM-related genes have also been observed in ARVC-like phenotypes [75]. The practical implication of such genotype-phenotype correlative studies would be to determine whether the arrhythmogenic risk is better associated with the disease gene or the clinical phenotype. MOGE(S) applies to ARVC/ACM as follows.

$M_{A[\varepsilon]}$ O_H G_{AD} $E_{G\text{-}DSG2[p.Glu1020AlafsX18]}$ $S_{A\text{-}I}$ represents morphofunctional phenotype **(M)**: **ARVC** with ***ε wave***; organ **(O)** involvement: ***heart (H)***; genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: ***genetic (G)*** and caused by the ***p.Glu1020Ala fs X 18*** mutation in the ***DSG2*** gene; ACC/AHA stage **(S)** ***A,*** NYHA ***I***.

$M_{E(A)}$ O_H G_{AD} $E_{G\text{-}DSG2[p.Glu1020AlafsX18]}$ $S_{A\text{-}I}$ represents morphofunctional phenotype **(M)**: ***"early"*** **(E)** ***arrhythmogenic cardiomyopathy*** (for example, with minor ECG and/or echocardiographic criteria); organ **(O)** involvement: ***heart (H)***; genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: ***genetic (G)*** and caused by the ***p.Glu1020Ala fs X 18*** mutation in the ***DSG2*** gene that causes the disease in the family; ACC/AHA stage **(S)** ***A,*** NYHA ***I***.

M_0 O_0 G_{AD} $E_{G\text{-}DSG2[p.Glu1020AlafsX18]}$ $S_{A\text{-}I}$ represents morphofunctional phenotype **(M)**: ***"unaffected" (0)*** by cardiomyopathy; organ **(O)** involvement: ***none (0)*** (=absence of any cardiac phenotype); genetic/familial **(G)** with ***autosomal dominant (AD)*** transmission; etiology **(E)**: ***genetic (G)***, healthy carrier of the ***p.Glu1020Ala fs X 18*** mutation in the ***DSG2*** gene that causes the disease in the family; ACC/AHA stage **(S)** ***A,*** NYHA ***I***.

MOGE(S) NOMENCLATURE FOR LVNC

Left ventricular noncompaction (LVNC) is a morphological entity characterized by an excessive trabeculation of the LV

[90,91] (Table 2). Diagnostic criteria are based on echo and cardiac magnetic resonance imaging wherein the non-compacted ventricular muscle layer is substantially thicker than the compact layer [91]. Most LVNC patients are asymptomatic, and the diagnosis is often incidental. The LVNC can occur as isolated morphological phenotype [92] in association with LV systolic dysfunction or with LV hypertrophy. LVNC has been associated with both DCM and HCM, and with mutations in genes typically causing DCM and HCM [93]. LVNC is a typical trait in Barth syndrome [94] (Fig. 10), and it has been reported to occur more frequently in carriers of *LDB3* gene mutations. Although true LVNC is rare, hypertrabeculation of the LV is common and may be associated with increased thromboembolic risk. The MOGE(S) system distinguishes LVNC with LV dilation and dysfunction (M_{LVNC+D}) or with LV hypertrophy (M_{LVNC+H}) from pure LVNC (M_{LVNC}).

THE MOGE(S) CLASSIFICATION IN CLINICAL PRACTICE

The MOGE(S) system proposes a nosology that addresses 5 simple attributes of cardiomyopathies, including morphofunctional characteristic (M), organ involvement (O), genetic or familial inheritance pattern (G), and an explicit etiological annotation (E) with details of genetic defect or underlying disease/cause, followed by optional information about the functional status (S) using the ACC/AHA stage and NYHA functional class. Although the application of this nosology allows complete description of the diseases, the full notation may appear complex. It is expected that routine nomenclature will continue to be described by the standard, currently practiced morphology, and the proposed nosology is not meant to replace the morphological description. A dilated cardiomyopathy will be called dilated cardiomyopathy, but the complete description of the disease process would be best served by the descriptive terminology such as MOGE(S). In fact, AHA suggests genotyping to supersede the phenotypic description, which is opposed by the ESC; the proposed MOGE(S) system is a compromise. It is prudent to consider an example from the field of oncology. Pathological staging in a patient with lung cancer who has been treated with neoadjuvant therapy and still has multiple residual nodules in the ipsilateral lung and different lobes, has distant metastases, and lymph nodes show isolated tumor cells only, is described using TNM staging as follows: ypT4(m) N0 (i+) M1b G3 LVI + R2. y denotes that the patient has received neoadjuvant therapy prior to resection, p presents pathological stage after resection, T4 offers the extent of tumor which in this case has multiple residual tumor nodules (m) in different lobes of ipsilateral lung, N denotes the nodal status [N0(i+)] isolated tumor cells only in a lymph node that are considered node negative or N0, and M represents metastases where M1b means distant metastases (in contrast to M1a, which is thoracic metastases such as contralateral lung, pleural nodules or malignant pleural, or pericardial effusion). G in this staging is histological grade (1 = well differentiated; 2 = moderate; 3 = poorly differentiated), LVI + represents lymphovascular invasion (LVI−, absent), and R is residual disease after treatment (R0 = no residual disease; R1 = microscopic residual disease; R2 = grossly identified residual disease). Howsoever complex it may sound, oncologists are expected to use standard TNM staging. TNM nosology is constantly expanding, is very flexible, but ensures completeness. Simply looking at [ypT4(m) N0(i+) M1b G3 LVI+ R2] gives physicians all the information about the patient in question. However, in the common practice, this patient is considered to have *lung cancer*. Therefore, the MOGE(S) example $M_{D[AVB]}$ O_H G_{AD} $E_{G\text{-}LMNA[p.Arg190Trp]}$ is complete notation for a patient presenting with a specific DCM. The authors of the MOGE(S) nomenclature have developed an easy web-assisted application that can be conveniently used in daily clinical practice for complete and descriptive classification of cardiomyopathy (http://moges.biomeris.com).

CONCLUSIONS

We propose a descriptive nosology that combines morphofunctional trait and organ/system involvement with familial inheritance pattern, identified genetic defect, or other etiologies. As with the universal TNM staging for tumors, it is expected that this description will be improved, revised, modified, and made more comprehensive and user friendly. It will allow better understanding of the disease, allow easier communication among physicians, and help develop multicenter/multinational registries to promote research in diagnosis and management of cardiomyopathies.

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