Inherited cardiomyopathies

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Abstract
The advent of molecular genetics — fuelled by the progress in DNA sequencing technologies and publication of the landmark Human Genome Project over a decade ago — has had a major impact on our understanding of the architecture of disease, opening up the prospect of personalized medicine based upon knowledge of an individual's genetic variants. Current management of patients with inherited cardiomyopathies is starting to integrate knowledge of an individual's genomic profile together with advancements in cardiovascular imaging. This has enhanced surveillance potential for high-risk individuals and has begun to facilitate diagnosis and, to a lesser extent, appropriate risk stratification and prognostication. This review introduces the reader to the inherited cardiomyopathies (hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy and dilated cardiomyopathy) — representing the first cardiac disorders to be accurately delineated at a molecular genetic level — and provides an insight into their molecular genetic and clinical complexity.

Keywords Arrhythmogenic right ventricular dysplasia; cardiomyopathy; dilated cardiomyopathy; genetic; hypertrophic; mutation; sudden cardiac death

What's new?

- MOGE(S) nomenclature aims to represent the complexity of inherited cardiomyopathies to facilitate individualized therapy
- Mutation analysis is used to make a genetic diagnosis in probands with suspected inherited cardiomyopathy, as well as allowing 'cascade' screening of at-risk family members
- Hypertrophic cardiomyopathy (HCM) is now recognized as a broad phenotypic response to cardiac energy deficiency
- Integration of genetics within clinical practice has led to the surveillance of genotype-positive phenotype-negative individuals, many of whom demonstrate subclinical phenotypes
- ARVC is a diagnosis within AC, as the underlying pathophysiology rarely occurs solely within the RV. LV and biventricular involvement has been demonstrated in a majority of cases

Cardiomyopathies — definition and classification

Traditional taxonomies classified cardiomyopathies largely on the basis of their gross morphofunctional appearances into hypertrophic, dilated or restrictive categories. While integrated morphofunctional assessment using state-of-the-art cardiac imaging remains an integral part of clinical assessment of patients with cardiomyopathy, growing appreciation for the molecular underpinnings that contribute towards this highly heterogeneous collection of heart muscle disorders has provoked a molecularly informed re-classification of their taxonomy, most recently through the World Heart Federation endorsed MOGE(S) nomenclature (Table 1).[1]

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Inspired by the TNM staging of tumours, the MOGE(S) classification builds on the previous European Society of Cardiology classification[2] by integrating morphofunctional characteristics (M), extent of organ involvement (O), genetic inheritance pattern (G), genetic aetiology (E) and functional status (S), and defines cardiomyopathies 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'. It is hoped that the MOGE(S) classification system will effectively capture the growing complexity of the inherited cardiomyopathies, and promote integration of genotype-based assessment to facilitate individualized treatment and follow-up decisions on affected probands and their relatives, as well as promote registry data collection and clinical research into cardiomyopathies. We discuss the aetiology and clinical management of inherited cardiomyopathies, namely hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy (AC) and dilated cardiomyopathy (DCM) (Table 2 and Figure 1).

Familial hypertrophic cardiomyopathy — a disease of sarcomeric proteins and energy deficiency producing hypertrophy

With a prevalence of 1 in 500, HCM is the most common inherited cardiomyopathy.[3] HCM is clinically recognized by unexplained left ventricular hypertrophy (LVH) and should be differentiated from acquired causes of LVH, such as systemic hypertension, aortic stenosis, infiltrative disorders (e.g. amyloidosis) or athlete's heart.

HCM may come to light following presentation with symptoms (including aborted sudden death), although many patients (up to 80%) remain asymptomatic. It may also appear through incidental identification on imaging or through cascade screening. Symptoms include dyspnoea, fatigue, chest pain, palpitations and pre-syncopal/syncopal episodes. The pathophysiological mechanisms responsible for these symptoms include impaired cardiac filling/diastolic function and/or emptying, microvascular dysfunction and arrhythmia. Whereas sudden cardiac death (SCD) is the most feared complication of HCM — with an annual event rate of 1–2% in children/adolescents and 0.5–1% in adults — up to 20% of patients experience

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The MOGE(S) nomenclature[1]

M, Morphofunctional phenotype[a]

D, dilated; H, hypertrophic; R, restrictive; ARVC, arrhythmogenic right ventricular cardiomyopathy; LVNC, left ventricular non-compaction cardiomyopathy; Overlapping, e.g. H + R, D + A, NC + H, H + D, D + NC, or more-complex combinations, such as H + R + NC; E, early, with type in parentheses; NS, nonspecific phenotype; NA, information not available; O, unaffected.

O, Organ or system involvement[b]

H, heart; M, muscle; S, skeletal; N, nervous; C, cutaneous; E, eye; A, auditory; K, kidney; G, gastrointestinal; S, skeletal; O, absence of organ or system involvement, for example, in family members who are healthy mutation carriers, the mutation is specified under 'Aetiological annotation', and inheritance is specified under 'Genetics'.

G, Genetics[c]

N, family history negative; U, family history unknown; AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive; XLD, X-linked dominant; XL, X-linked; M, matrilineal; DN, *de novo*; O, family history not investigated.

E, Aetiological annotation[d]

Genetic: G, genetic aetiology—add gene and mutation; NC, individual non-carrier plus the gene that tested negative; OC, obligate carrier; ONC, obligate non-carrier; DN, *de novo*; C, complex genetics with more than one mutation (provide additional gene and mutation); Neg, genetic test negative for known familial mutation; NA, genetic test not yet available; N, genetic defect not identified; O, no genetic test for any reason (e.g. no blood sample, no informed consent); A-*TTR*, genetic amyloidosis; *HFE*, haemochomatosis.

Nongenetic: M, myocarditis; V, viral infection (add the virus identified in affected heart); AI, autoimmune or 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 or drug); Eo, hypereosinophilic heart disease.

S, Stage[e]

ACC/AHA stage (A, B, C, D); NYHA functional class (I, II, III, IV).

[a] The morphofunction phenotype description can contain additional information using standard abbreviations, such as: AF, atrial fibrillation; AVR, atrioventricular block; LQT, prolongation of the QT interval; PR, short PR interval; R, low electrocardiogram voltages; WPW, Wolff—Parkinson—White syndrome.

[b] Organ involvement, in addition to the H for heart, should be expanded for the involvement of: A, auditory system; C, cutaneous; G, gastrointestinal system; K, kidney; L, liver; M, skeletal muscle; N, nervous system; O, ocular system, and other comorbidities, including MR, mental retardation.

[c] Genetics describes the available information about inheritance of the disease. It also provides complete information if the family history is not proven or is unknown, and if genetic testing has not been performed or was negative for the mutation or mutations identified in the family.

[d] The aetiological annotation provides the facility for the synthetic description of the specific disease gene and mutation, as well as description of non-genetic aetiology.

[e] The functional annotation or staging allows the addition of ACC/AHA stage and NYHA functional class.

A link for the practising clinician is available at: http://moges.biomeris.com/moges.html

Adapted from Arbustini E, Narula N, Dec GW et al. The MOGE(S) classification for a phenotype-genotype nomenclature of cardiomyopathy: endorsed by the World Heart Federation. *Journal of the American College of Cardiology*. Dec 3 2013; 62(22):2046—2072.

Table 1

early onset heart failure (HF) at a median age of 48 ± 19 years.[4] Heart failure in HCM is broadly attributable to (i) diastolic HF (~50% of patients); (ii) LV outflow-tract obstruction (LVOTO)-induced systolic dysfunction (~20%); or (iii) 'burnt out' HCM characterized by progressive LV dilatation, wall thinning and systolic dysfunction (~30%). One in five patients also experiences atrial fibrillation, associated with a high risk of embolic stroke. While pharmacological strategies fail to attenuate the risk of SCD, implantable cardiac defibrillators (ICD) play a key role in primary or secondary prevention of SCD due to malignant ventricular tachyarrhythmias.[5]

Clinical examination may be normal, particularly in individuals with minimal LVOTO. Those with resting LVOTO may exhibit HCM findings, including a bisferiens pulse, a forceful and sustained apical impulse, an audible S4 and a classical crescendo—decrescendo systolic murmur at the lower left sternal edge that increases with the Valsalva manoeuvre (due to reduced preload reducing LV filling and worsening LVOTO). Non-invasive imaging of cardiac structure and function plays a central role in diagnosis and the first step is usually transthoracic echocardiography. Unexplained left ventricular hypertrophy ≥15 mm, most commonly apparent in the basal anterior septum, is diagnostic of HCM. Electrocardiography should be performed in every patient suspected of having HCM and may reveal atrial fibrillation, pathological Q waves, left atrial abnormality or LVH by voltage criteria and associated widespread ST-T wave changes. Further relevant investigations include: ambulatory ECG monitoring as part of risk stratification of SCD; exercise testing to quantify functional capacity, to assess for inducible arrhythmia and dynamic LVOTO; cardiovascular magnetic resonance imaging; and genetic testing.

HCM is an autosomal dominant condition expressing variable penetrance and demonstrating substantial locus and allelic heterogeneity. Over 1400 mutations (often missense and private to a particular family) have been described within 13 genes, considered fundamental to effective cardiomyocyte functioning (Table 2). Mutations are found in between 40 and 60% of HCM patients with a clear family history of disease. Of those with known mutations, 70% of individuals harbour mutations within either β-myosin heavy chain (*MYH7*) or myosin-binding protein C (*MYBPC3*),[5] the former associated with high disease penetrance and moderate-severe LVH, the latter (manifest typically in mid-

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