Genetic Cardiomyopathies
While the contribution that diseases of the heart and blood vessels make to human morbidity and mortality has been acknowledged for decades, the health burden associated with inherited cardiovascular disorders has been recognized comparatively recently. This change has been driven partly by advances in genomic medicine that have provided major insights into the pathogenesis of inherited cardiovascular disorders, and also by greater awareness of genetic mechanisms amongst cardiovascular specialists. Cardiomyopathies, or diseases of heart muscle unexplained by abnormal loading conditions or coronary artery disease, constitute the largest group of Mendelian cardiovascular disorders. They present at all ages with cardiovascular symptoms, cause sudden cardiac death often in minimally symptomatic individuals, and result in a gradual deterioration in ventricular function and end-stage heart failure. The commonest forms of cardiomyopathy are inherited as autosomal dominant traits with highly variable intra- and interfamilial disease expression and incomplete clinical penetrance. This clinical heterogeneity is partially explained by genetic locus and allelic heterogeneity, but it is increasingly clear from family studies that other mechanisms such as modifier genes, epigenetics, post-transcriptional and post-translational modifications must play a role.

Clinicians that wish to understand the genetic complexity of cardiomyopathy are blessed with many well-written textbooks and online resources and this textbook edited by three experts in the field, provides a concise and accessible update on the genetic architecture of cardiomyopathy. The major difference between this book and most other sources is its highly original structure that puts clinical method firmly at its core by emphasising the concept of diagnostic clues or “red flags” that can be used to guide rational selection of diagnostic tests including genetic analysis. This seemingly simple idea is in fact a major departure from the more typical approach of protocol-driven evaluation which often fails to identify an underlying disease mechanism. Inevitably, gaps in knowledge and the capricious nature of disease phenotypes mean that this cardiomyopathy-oriented mind-set is also imperfect, but its adoption will increase the chance that disorders with very specific management strategies can be identified.
For the ordinary physician, the pace and sheer scale of the genetic revolution can appear totally removed from the everyday practicalities of clinical medicine. The authors of this excellent book are to be commended for showing that clinical acumen and a systematic approach to diagnosis are as important in the genomic era as they have ever been.

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Abbreviations

AD  Autosomal Dominant
AF  Atrial Fibrillation
AR  Autosomal Recessive
ARVC/ARVD Arrhythmogenic Right Ventricular Cardiomyopathy
AV block Atrio-Ventricular block
CK  Creatine kinase. Note: ↑ - ↑↑ - ↑↑↑ = mild, moderate or severe increase in serum creatine kinase levels
CMP Cardiomyopathy
DCM Dilated Cardiomyopathy
ECG Electrocardiogram
HCM Hypertrophic Cardiomyopathy
ICD Implantable cardioverter-defibrillator
LQTS Long-QT Syndrome
LVNC Left Ventricular Non-Compaction
MPS Mucopolysaccharidoses
mtDNA Mitochondrial DNA
RCM Restrictive Cardiomyopathy
SQTS Short-QT Syndrome
SSS Sick Sinus Syndrome
SVT Supraventricular Tachycardia
VF Ventricular Fibrillation
VT Ventricular Tachycardia
WPW Wolff Parkinson White
XL X-linked
? Unknown or uncertain entries
% % before OMIM number indicates that the number refers to the phenotype description
Cardiomyopathies (CMPs) are myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of conditions such as coronary artery disease, hypertension or valvular disease, sufficient to cause the observed myocardial abnormalities [1]. The disease may be localized involving the myocardium only or predominantly (“primary CMPs” in the classification by Maron et al. [2]) or it may be associated, in a complex form, with systemic multi-organ disorders (“secondary CMPs”) [2]. When considering the etiology, many CMPs have a genetic origin, some are acquired (inflammation, alcohol, drugs, etc.), while others may have a mixed origin [2]. In recent years researchers have identified the genetic background of many diseases involving the myocardium, and many CMPs are considered to have a genetic origin. New problems and new responsibilities need to be considered by the clinical cardiologist in this emerging medical field, in which the goal is to provide a precise diagnosis, stratify the risk and treat patients correctly, and advise them on personal and family choices.

Hypertrophic cardiomyopathy (HCM) is a genetic disease usually caused by mutations in genes encoding sarcomeric proteins. More than 15 genes related to sarcomere and myofilament disease, and hundreds of different mutations, have been identified [3, 4]. HCM phenocopies are caused by disorders of different genetic origin; for example: those resulting from mutations in the genes encoding protein kinase AMP-activated, gamma-2 non-catalytic subunit (PRKAG2) and lysosome-associated membrane protein 2 (LAMP2) (Danon disease); or the disease caused by alpha-galactosidase deficiency (Fabry disease). Moreover a HCM phenotype may be present in other congenital diseases such as Noonan syndrome, mitochondrial syndromes, etc. (Table 1.1).
Dilated cardiomyopathy (DCM) may be the consequence of clearly defined etiologic factors, such as viral infections, toxins, drugs, metabolic disorders, etc., but at least 30–40% of cases have a genetic origin [5]. DCM is characterized by a high level of genetic complexity and by an involvement of different structures of the myocytes. Initially DCM was considered to be a disease of the cytoskeleton, but later it was demonstrated that other structures (sarcomere, Z-disc, cytoskeleton, nuclear skeleton, mitochondria, desmosomes, sodium and potassium channels, lysosomal membrane), as well as a transcriptional coactivator may be involved [5, 6] (Table 1.2).

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is another CMP of genetic origin, usually characterized by mutations in genes encoding different proteins involved in the intercellular junctions. These proteins (plakoglobin, desmoplakin, plakophilin, desmoglein, desmocollin) are localized in the desmosomes and are important for the maintenance of tissue architecture and integrity. Also in this disease a high genetic complexity is suggested by the fact that ARVC may be linked to genes unrelated or not directly related to the cell-adhesion complex; for example, the genes encoding cardiac ryanodine receptor 2 (RYR2) and transforming growth factor B3 (TGFB3) (Table 1.3).

Moreover, other rare forms of genetically determined CMPs have been identified, including restrictive cardiomyopathy and left ventricular non-compaction (Tables 1.4 and 1.5).

The relationships between gene mutations and the phenotype are complex and not always clear. It is well known that mutations in the same gene may cause different types of cardiomyopathies (Fig. 1.1) and may be characterized by great variation in clinical phenotypes. For example, in lamin A/C gene (LMNA) mutation carriers, up to ten different phenotypes (“laminopathies”) have been described with variable involvement of skeletal and/or cardiac muscle and also of white fat, peripheral nerves, bones or premature aging [7]. In addition, in patients affected by CMP, great variation can be observed in age of onset, severity and evolution of the disease in the same family or in different families [7]. Furthermore, in a minority of cases (25% of mutation carriers according to Sylvius and Tesson [7]) subjects may remain asymptomatic.

From a clinical point of view in familial CMPs, the definition of the genetic diagnosis and the genotype determination may have potential advantages, as this information allows early diagnosis, risk stratification and guided screening of at-risk relatives, better determination of the correct treatment, and accurate clinical and genetic counseling. An early genetic diagnosis is clearly important and these patients will need a strict follow-up to identify and treat disease at its onset rather than later in its course. Importantly, when an apparently healthy member of an affected family is found to be free of the CMP mutation for that family, there can be reassurance and cessation of periodic clinical screening. Moreover, molecular genetic assessment can be useful in cases of uncertain diagnosis in order to give a better definition of the disease.

Early diagnosis is clinically useful when considering the possibility of early pharmacological treatment with angiotensin converting enzyme
Fig. 1.1 Cardiomyopathies and genetic complexity. Mutations within the same gene may cause different phenotypes. Gene acronyms: see Tables 1.1–1.5 and Glossary. ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular non-compaction; RCM, restrictive cardiomyopathy
inhibitors and beta blockers in cases of asymptomatic ventricular dysfunction. Some studies have demonstrated indeed the beneficial effect of early treatment in patients with asymptomatic left ventricular dysfunction [8]. The possibility of a prophylactic treatment is also important, especially in some CMPs characterized by a high risk of severe arrhythmias and sudden death even before the appearance of heart failure [9–12]. For example, symptomatic patients carrying LMNA mutations are characterized by a significantly worse prognosis in comparison with other forms of DCM [13–15] and may die at a young age. In these cases prophylactic therapy with an implantable cardioverter–defibrillator appears to prevent sudden death [11], even when the ejection fraction is largely preserved. However, reliable predictors of sudden death in this patent population are currently unknown, often making the clinical decision challenging.

The importance of a patient-based approach, which should orientate the clinical cardiologist trying to integrate basic knowledge and clinical science, has been stressed [1, 6] with the aim of identifying the etiology, the genetic origin and the possible type of genetic involvement. Indeed the characteristics of disease presentation and progression might suggest the involvement of specific genes [16] and knowledge of the phenotype–genotype relationship will be useful in some CMPs (for example, DCM in which there is extensive genetic heterogeneity).

The clinical approach should define the characteristics of the CMP and should also explore, when present, the characteristics of involvement of other organs and systems. This requires a broad-minded cardiologist with a solid knowledge base in basic science and clinical cardiology, as well as internal medicine, who can recognize key symptoms and clues in the family history when they are present. This comprehensive approach will help to define the etiological diagnosis and a rational selection of diagnostic tests, especially the molecular genetic tests for identification of genetic mutations. A typical example is a patient with DCM in whom the initial symptomatology is characterized by supraventricular arrhythmias, atrioventricular conduction delay and, possibly, elevated creatine kinase levels. In this case a LMNA gene mutation should be considered highly likely and should prompt molecular genetic testing of LMNA.
<table>
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<th>Gene</th>
<th>Locus</th>
<th>OMIM no.</th>
<th>Protein</th>
<th>Inheritance pattern</th>
<th>Estimated fraction of HCM (when available) (%)</th>
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