# Genetic Cardiomy

A Clinical Approach

# Genetic Cardiomyopathies

Gianfranco Sinagra • Luisa Mestroni •
Fulvio Camerini
Editors

# Genetic Cardiomyopathies

## A Clinical Approach

Foreword by Perry Elliott

Springer

*Editors*
Gianfranco Sinagra, MD, FESC
Professor of Cardiology
Chief of Cardiovascular
Department and Postgraduate
School of Cardiovascular Sciences
Ospedali Riuniti and
University of Trieste, Italy

Luisa Mestroni, MD, FACC, FESC
Professor of Cardiology
Director Molecular Genetics
Cardiovascular Institute
University of Colorado Denver Anschutz
Medical Campus, Aurora, USA

Fulvio Camerini, MD, EFESC
Professor of Cardiology
Ospedali Riuniti and
University of Trieste, Italy

ISBN 978-88-470-2756-5 ISBN 978-88-470-2757-2 (eBook)

DOI 10.1007/978-88-470-2757-2

Springer Milan Dordrecht Heidelberg London New York

Library of Congress Control Number: 2012941333



9 8 7 6 5 4 3 2 1 2013 2014 2015 2016

Cover design: Ikona S.r.l., Milan, Italy
Typesetting: Graphostudio, Milan, Italy
Printing and binding: Grafiche Porpora, Segrate (Milan), Italy

Springer-Verlag Italia S.r.l. – Via Decembrio 28 – I-20137 Milan
Springer is a part of Springer Science+Business Media (www.springer.com)

# Foreword

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.

London, September 2012

Professor Perry Elliott FRCP, FESC, FACC
Director, Inherited Cardiac Disease Unit
The Heart Hospital, University College
London, UK

# Contents

# Contributors

**Stefano Bardari** MD, Cardiovascular Department, Ospedali Riuniti and University of Trieste, Italy

**Francesca Brun** MD, Cardiovascular Department, Ospedali Riuniti and University of Trieste, Italy

**Rossana Bussani** MD, Department of Pathology and Morbid Anatomy, Ospedali Riuniti and University of Trieste, Italy

**Fulvio Camerini** MD, EFESC, Cardiovascular Department, Ospedali Riuniti and University of Trieste, Italy

**Andrea Di Lenarda** MD, FESC, Cardiovascular Center, Azienda per i Servizi Sanitari No. 1, Trieste, Italy

**Enrico Fabris** MD, Cardiovascular Department, Ospedali Riuniti and University of Trieste, Italy

**Marco Merlo** MD, Cardiovascular Department, Ospedali Riuniti and University of Trieste, Italy

**Luisa Mestroni** MD, FACC, FESC, Cardiovascular Institute, University of Colorado, Aurora, Colorado, USA

**Michele Moretti** MD, Cardiovascular Department, Ospedali Riuniti and University of Trieste, Italy

**Bruno Pinamonti** MD, Cardiovascular Department, Ospedali Riuniti and University of Trieste, Italy

**Gianfranco Sinagra** MD, FESC, Cardiovascular Department, Ospedali Riuniti and University of Trieste, Italy

**Matthew R. G. Taylor** MD, PhD, Cardiovascular Institute, University of Colorado, Aurora, Colorado, USA

# 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 |

# Introduction

# 1

Fulvio Camerini, Gianfranco Sinagra and Luisa Mestroni

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).

G. Sinagra (✉)
Cardiovascular Department,
Ospedali Riuniti and University of Trieste, Italy
email: gianfranco.sinagra@aots.sanita.fvg.it

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_1, © Springer-Verlag Italia 2013

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, plakophillin, 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

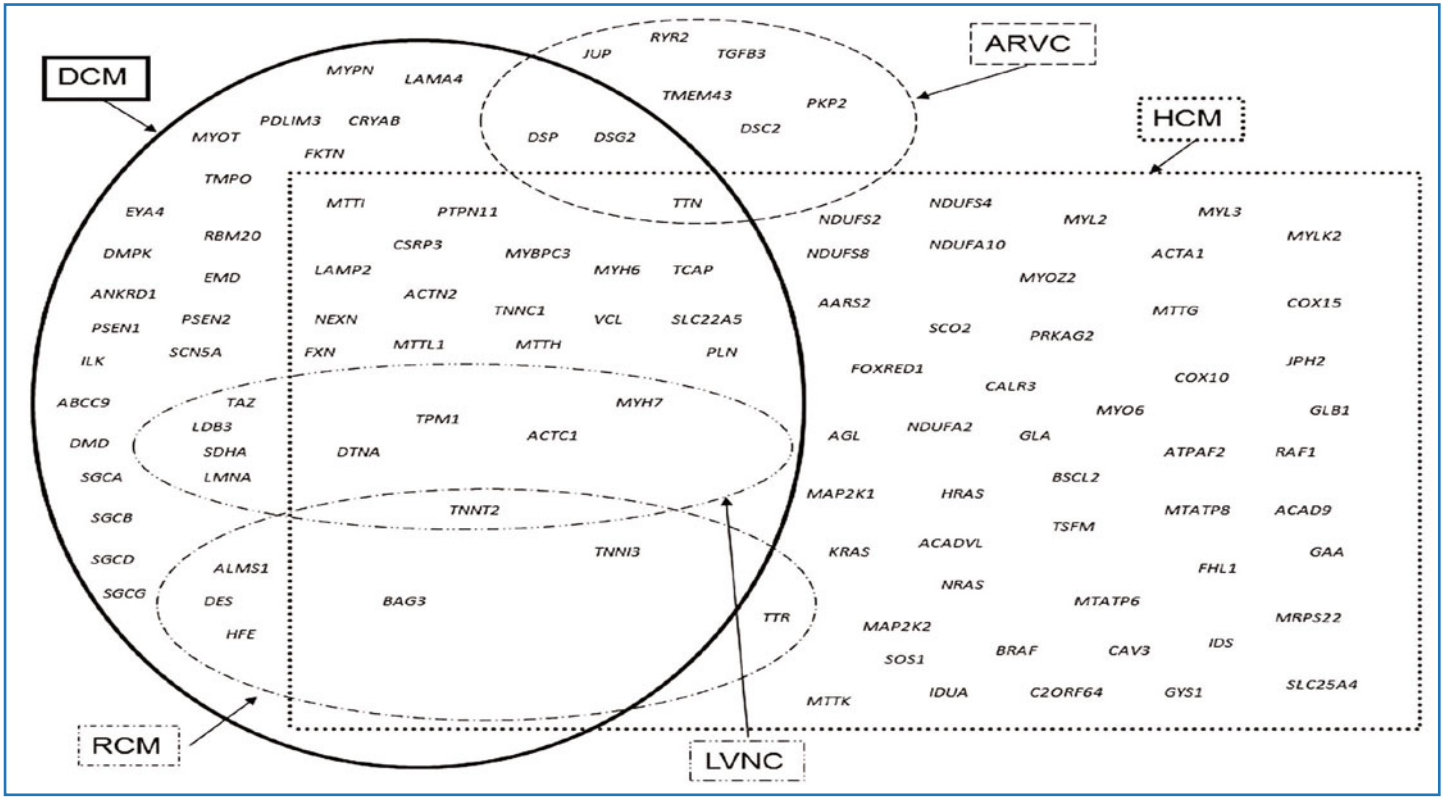



**Fig. 1.1** Cardiomyopathies and genetic complexity. Mutations within the same gene may cause different phenotypes. Gene acronyms: see Tables 1.1–1.5 and Glossary. *ARVC*, arrhythmogenic right ventricular cardiomyopathy; *DCM*, dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy; *LVNC*, left 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 1.1** Hypertrophic cardiomyopathy

| Gene | Locus | OMIM no.[a] | Protein | Inheritance pattern | Estimated fraction of HCM (when available) (%)[b] | Other cardiac phenotypes |
|---|---|---|---|---|---|---|
| **Sarcomere and sarcomere-associated proteins** | | | | | | |
| *MYH6* | 14q11.2 | 160710 | Myosin heavy chain 6, alpha | AD | | DCM |
| *MYH7* | 14q11.2 | 160760 | Myosin heavy chain 7, beta | AD | 40 | DCM, LVNC |
| *MYBPC3* | 11p11.2 | 600958 | Myosin-binding protein C | AD | 40 | DCM |
| *TTN* | 2q31.2 | 188840 | Titin | AD | | DCM, ARVC |
| *TCAP* | 17q12 | 604488 | Titin-cap (Telethonin) | AD | | DCM |
| *TNNT2* | 1q32.1 | 191045 | Troponin T2, cardiac | AD | 5 | DCM, RCM, LVNC |
| *TNNI3* | 19q13.42 | 191044 | Troponin I, cardiac | AD | 5 | DCM, RCM |
| *TPM1* | 15q22.2 | 191010 | Tropomyosin 1 | AD | 2 | DCM, LVNC |
| *MYL2* | 12q24.11 | 160781 | Myosin, light chain 2, regulatory, cardiac, slow | AD | | |
| *MYL3* | 3p21.31 | 160790 | Myosin, light chain 3, alkali, ventricular, skeletal, slow | AD | 1 | |
| *ACTC1* | 15q14 | 102540 | Actin, alpha, cardiac muscle | AD | | DCM, LVNC |
| *CSRP3* | 11p15.1 | 600824 | Cysteine and glycine-rich protein 3 | AD | | DCM, endocardial fibroelastosis |
| *ACTN2* | 1q43 | 102573 | Alpha-actinin-2 | AD | | DCM |
| *TNNC1* | 3p21.1 | 191040 | Troponin C, slow | AD | | DCM |
| *ACTA1* | 1q42.13 | 102610 | Actin, alpha, skeletal muscle 1 | AD | | |
| *VCL* | 10q22.2 | 193065 | Vinculin | AD | | DCM |
| *MYLK2* | 20q11.21 | 606566 | Myosin light chain kinase 2 | ? | | |
| *MYOZ2* | 4q26 | 605602 | Myozenin-2 | AD | | |

(*cont.*) →

**Table 1.1** Hypertrophic cardiomyopathy *(continued)*

| Gene | Locus | OMIM no.[a] | Protein | Inheritance pattern | Estimated fraction of HCM (when available) (%)[b] | Other cardiac phenotypes |
|---|---|---|---|---|---|---|
| **Other proteins** | | | | | | |
| *JPH2* | 20q13.12 | 605267 | Junctophilin-2 | ? | | |
| *CALR3* | 19p13.11 | 611414 | Calreticulin-3 | ? | | |
| *RAF1* | 3p25.2 | 164760 | V-RAF-1 murine leukemia viral oncogene homolog 1 | AD | | |
| *MYO6* | 6q14.1 | 600970 | Myosin-VI | AD | | |
| *KRAS* | 12p12.1 | 190070 | V-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog | AD | | |
| *FHL1* | Xq26.3 | 300163 | Four-and-a-half LIM domains 1 | XL | | |
| *HRAS* | 11p15.5 | 190020 | V-HA-RAS Harvey rat sarcoma viral oncogene homolog | AD | | |
| *BSCL2* | 11q12.3 | 606158 | Seipin (or Bernardinelli–Seip congenital lipodystrophy type 2 protein) | AR | | |
| *BAG3* | 10q26.11 | 603883 | BCL2-associated athanogene 3 (BAG family molecular chaperone regulator 3) | AD | | DCM, RCM |
| *PTPN11* | 12q24.13 | 176876 | Protein-tyrosine phosphatase non-receptor type 11 | AD | | |
| *NEXN* | 1p31.1 | 613121 | Nexilin, rat, homolog of | AD | | DCM |
| *DTNA* | 18q12.1 | 601239 | Dystrobrevin alpha | AD | | LVNC, DCM |
| *SLC22A5* | 5q31.1 | 603377 | Solute carrier family 22 organic cation transporter, member 5 | AR | | DCM |
| *CAV3* | 3p25.3 | 601253 | Caveolin-3 | AD | | LQTS type 9 |
| *SLC25A4* | 4q35.1 | 103220 | Solute carrier family 25 (mitochondrial carrier, adenine nucleotide translocator), member 4 | AD | | |
| *PLN* | 6q22.31 | 172405 | Phospholamban | AD | | DCM |
| *SOS1* | 2p22.1 | 182530 | Son of sevenless, drosophila, homolog 1 | AD | | |
| *NRAS* | 1p13.2 | 164790 | Neuroblastoma RAS viral oncogene homolog | AD | | |

(*cont.*) ↓

| | | | | | | |
|---|---|---|---|---|---|---|
| *BRAF* | 7q34 | 164757 | V-RAF murine sarcoma viral oncogene homolog B1 | AD | | |
| *MAP2K1* | 15q22.31 | 176872 | Mitogen-activated protein kinase kinase 1 | AD | | |
| *MAP2K2* | 19p13.3 | 601263 | Mitogen-activated protein kinase kinase 2 | AD | | |
| **Mitochondrial / respiratory chain genes and proteins** | | | | | | |
| *NDUFA2* | 5q31.3 | 602137 | NADH-ubiquinone oxidoreductase 1 alpha subcomplex, 2 | AR | | |
| *NDUFA10* | 2q37.3 | 603835 | NADH-ubiquinone oxidoreductase 1 alpha subcomplex, 10 | AR | | |
| *NDUFS2* | 1q23.3 | 602985 | NADH-ubiquinone oxidoreductase Fe-S protein 2 | AR | | |
| *NDUFS4* | 5q11.2 | 602694 | NADH-ubiquinone oxidoreductase Fe-S protein 4 | AR | | |
| *NDUFS8* | 11q13.2 | 602141 | NADH-ubiquinone oxidoreductase Fe-S protein 8 | AR | | |
| *FOXRED1* | 11q24.2 | 613622 | FAD-dependent oxidoreductase domain-containing protein 1 | AR | | |
| *AARS2* | 6p21.1 | 612035 | Alanyl-tRNA synthetase 2 | AR | | |
| *SCO2* | 22q13.33 | 604272 | SCO2, *S. cerevisiae*, homolog of | AD | | |
| *ACADVL* | 17p13.1 | 609575 | Acyl-CoA dehydrogenase, very long-chain | AR | | |
| *COX10* | 17p12 | 602125 | Cytochrome C oxidase assembly protein COX10 | AR | | |
| *COX15* | 10q24.2 | 603646 | Cytochrome C oxidase assembly protein COX15 | AR | | |
| *ATPAF2* | 17p11.2 | 608918 | ATP synthase, mitochondrial F1 complex, assembly factor 2 | AR | | |
| *TSFM* | 12q14.1 | 604723 | Ts translation elongation factor, mitochondrial | ? | | |
| *ACAD9* | 3q21.3 | 611103 | Acyl-CoA dehydrogenase family, member 9 | AR | | |
| *MRPS22* | 3q23 | 605810 | Mitochondrial ribosomal protein S22 | AR | | |
| *C2ORF64* | 2q11.2 | 613920 | Chromosome 2 open reading frame 64 | AR | | |
| *FXN* | 9q21.11 | 606829 | Frataxin | AR | | DCM |
| *MTATP6* | mtDNA | 516060 | ATP synthase 6 | Mit | | |
| *MTATP8* | mtDNA | 516070 | ATP synthase 8 | Mit | | |
| *MTTI* | mtDNA | 590045 | Transfer RNA, mitochondrial, isoleucine | Mit | | DCM |
| *MTTL1* | mtDNA | 590050 | Transfer RNA, mitochondrial, leucine, 1 | Mit | | DCM |

(*cont.*) →

**Table 1.1** Hypertrophic cardiomyopathy *(continued)*

| Gene | Locus | OMIM no.[a] | Protein | Inheritance pattern | Estimated fraction of HCM (when available) (%)[b] | Other cardiac phenotypes |
|---|---|---|---|---|---|---|
| *MTTH* | mtDNA | 590040 | Transfer RNA, mitochondrial, histidine | Mit | | DCM |
| *MTTG* | mtDNA | 590035 | Transfer RNA, mitochondrial, glycine | Mit | | |
| *MTTK* | mtDNA | 590060 | Transfer RNA, mitochondrial, lysine | Mit | | |
| **Metabolic/storage disorders** | | | | | | |
| *LAMP2* | Xq24 | 309060 | Lysosome-associated membrane protein 2 | XL | | DCM |
| *PRKAG2* | 7q36.1 | 602743 | Protein kinase, AMP-activated, non-catalytic, gamma-2 | AD | | WPW syndrome |
| *GLA* | Xq22.1 | 300644 | Galactosidase, alpha | XL | | |
| *GLB1* | 3p22.3 | 611458 | Galactosidase, beta-1 | AR | | DCM |
| *GYS1* | 19q13.33 | 138570 | Glycogen synthase 1 | AR | | |
| *GAA* | 17q25.3 | 606800 | Glucosidase, alpha, acid | AR | | |
| *AGL* | 1p21.2 | 610860 | Amylo-1,6-glucosidase, 4-alpha-glucanotransferase | AR | | |
| *IDUA* | 4p16.3 | 252800 | Alpha-L-iduronidase | AR | | Endocardial fibroelastosis |
| *IDS* | Xq28 | 300823 | Iduronate 2-sulfatase | XL | | |
| *SGSH* | 17q25.3 | 605270 | *N*-sulfoglucosamine sulfohydrolase | AR | | |
| *NAGLU* | 17q21.2 | 609701 | *N*-acetylglucosaminidase, alpha | AR | | |
| *GALNS* | 16q24.3 | 612222 | Galactosamine-6-sulfate sulfatase | AR | | |
| *GLB1* | 3p22.3 | 611458 | Galactosidase, beta-1 | AR | | |
| *ARSB* | 5q14.1 | 611542 | Arylsulfatase B | AR | | |
| *GUSB* | 7q11.21 | 611499 | Beta-glucuronidase | AR | | |
| *AGXT* | 2q37.3 | 604285 | Alanine-glycoxylate aminotransferase | AR | | DCM, RCM |

(*cont.*) ↓

| | | | | | | |
|---|---|---|---|---|---|---|
| *GNPTAB* | 12q23.2 | 607840 | *N*-acetylglucosamine-1-phosphotransferase, alpha/beta subunits | AR | | DCM, RCM |
| *ATP7B* | 13q14.3 | 606882 | ATPase, $Cu^{++}$-transporting, beta-polypeptide | AR | | DCM |
| **Extracellular/secreted proteins** | | | | | | |
| *TTR* | 18q21.1 | 176300 | Transthyretin | AD | | RCM |

Genes reported in association with hypertrophic cardiomyopathy (HCM): isolated, syndromic and multi-system forms. HCM is defined as the presence of increased ventricular wall thickness or mass in the absence of loading conditions sufficient to cause the observed abnormality.
*AD*, autosomal dominant; *AR*, autosomal recessive; *ARVC*, arrhythmogenic right ventricular cardiomyopathy; *DCM*, dilated cardiomyopathy; *LQTS*, long-QT syndrome; *LVNC*, left ventricular non-compaction; Mit, mitochondrial; *RCM*, restrictive cardiomyopathy; *WPW*, Wolff–Parkinson–White; *XL*, X-linked.
[a]Online Mendelian inheritance in man [17].
[b]Estimated fraction according to Cirino and Ho [18].

**Table 1.2** Dilated cardiomyopathy

| Gene | Locus | OMIM no.[a] | Protein | Inheritance pattern | Other cardiac phenotypes |
|---|---|---|---|---|---|
| **Sarcomere and sarcomere-associated proteins** | | | | | |
| *MYH6* | 14q11.2 | 160710 | Myosin heavy chain 6, alpha | AD | HCM |
| *MYH7* | 14q11.2 | 160760 | Myosin heavy chain 7, beta | AD | HCM, LVNC |
| *MYBPC3* | 11p11.2 | 600958 | Myosin-binding protein C | AD | HCM |
| *MYPN* | 10q21.1 | 608517 | Myopalladin | AD | |
| *MYOT* | 5q31.2 | 604103 | Titin immunoglobulin domain protein (myotilin) | AD | |
| *TTN* | 2q31.2 | 188840 | Titin | AD | HCM, ARVC |
| *TCAP* | 17q12 | 604488 | Titin-cap (telethonin) | AD | HCM |
| *TNNT2* | 1q32.1 | 191045 | Troponin T2, cardiac | AD | HCM, RCM, LVNC |
| *VCL* | 10q22.2 | 193065 | Vinculin | AD | HCM |
| *ACTN2* | 1q43 | 102573 | Alpha-actinin-2 | AD | HCM |
| *TPM1* | 15q22.2 | 191010 | Tropomyosin 1 | AD | HCM, LVNC |
| *TNNC1* | 3p21.1 | 191040 | Troponin C, slow | AD | HCM |
| *TNNI3* | 19q13.42 | 191044 | Troponin I, cardiac | AD | HCM, RCM |
| *CSRP3* | 11p15.1 | 600824 | Cysteine and glycine-rich protein 3 | AD | HCM, endocardial fibroelastosis |
| *ACTC1* | 15q14 | 102540 | Actin, alpha, cardiac muscle | AD | HCM, LVNC |
| *NEBL* | 10p12.31 | 605491 | Nebulette | ? | |
| **Cytoskeletal proteins** | | | | | |
| *LDB3 (CYPHER; ZASP)* | 10q23.2 | 605906 | LIM domain-binding 3 (cypher; ZASP) | AD | LVNC |
| *CRYAB* | 11q23.1 | 123590 | Crystallin alpha-B | AD | |

(*cont.*) ↓

| | | | | | |
|---|---|---|---|---|---|
| *DES* | 2q35 | 125660 | Desmin | AD | RCM |
| *PDLIM3* | 4q35.1 | 605889 | PDZ and LIM domain protein 3 | AD | |
| *DMPK* | 19q13.32 | 605377 | Dystrophia myotonica protein kinase | AD | |
| *LAMP2* | Xq24 | 309060 | Lysosome-associated membrane protein 2 | XL | HCM |
| *NEXN* | 1p31.1 | 613121 | Nexilin, rat, homolog of | AD | HCM |
| *ALMS1* | 2p13.1 | 606844 | Alstrom syndrome protein 1 | AR | RCM |
| **Nucleus and nuclear membrane proteins** | | | | | |
| *LMNA* | 1q22 | 150330 | Lamin A/C | AD | LVNC |
| *TMPO (LAP2)* | 12q23.1 | 188380 | Thymopoietin (lamina-associated polypeptide 2) | AD | |
| *RBM20* | 10q25.2 | 613171 | RNA-binding motif protein 20 | AD | |
| *ANKRD1* | 10q23.31 | 609599 | Ankyrin repeat domain-containing protein 1 | AD | |
| *EMD* | Xq28 | 300384 | Emerin | XL | Atrial arrhythmias, atrial standstill, conduction defects (DCM?) |
| **Membrane proteins and ion channels** | | | | | |
| *PLN* | 6q22.31 | 172405 | Phospholamban | AD | HCM |
| *PSEN1* | 14q24.2 | 104311 | Presenilin-1 | AD | |
| *PSEN2* | 1q42.13 | 600759 | Presenilin-2 | AD | |
| *ILK* | 11p15.4 | 602366 | Integrin-linked kinase | AD | |
| *SLC22A5* | 5q31.1 | 603377 | Solute carrier family 22 organic cation transporter, member 5 | AR | HCM |
| *HFE* | 6p22.2 | 613609 | Hereditary hemochromatosis protein | AR | RCM |
| *ATP7B* | 13q14.3 | 606882 | ATPase, $Cu^{++}$-transporting, beta-polypeptide | AR | HCM |

(*cont.*) →

**Table 1.2** Dilated cardiomyopathy *(continued)*

| Gene | Locus | OMIM no.[a] | Protein | Inheritance pattern | Other cardiac phenotypes |
|---|---|---|---|---|---|
| *ABCC9 (SUR2)* | 12p12.1 | 601439 | ATP-binding cassette sub-family C member 9 (sulfonylurea receptor 2) | AD | |
| *SCN5A* | 3p22.2 | 600163 | Sodium channel, type 5 alpha subunit | AD | Brugada syndrome, LQTS, SSS, AV block, familial AF, familial VF |
| *KCNJ2* | 17q24.3 | 600681 | Potassium channel, inwardly rectifying, subfamily J, member 2 | AD | Familial AF, LQTS, SQTS |
| *TAZ* | Xq28 | 300394 | Tafazzin | XL | LVNC, endocardial fibroelastosis |
| **Dystrophin–glycoprotein complex** | | | | | |
| *DMD* | Xp21.2 -p21.1 | 300377 | Dystrophin | XL | |
| *SGCA* | 17q21.33 | 600119 | Alpha-sarcoglycan | AR | |
| *SGCB* | 4q12 | 600900 | Beta-sarcoglycan | AR | |
| *SGCD* | 5q33.3 | 601411 | Delta-sarcoglycan | AR | |
| *SGCG* | 13q12.12 | 608896 | Gamma-sarcoglycan | AR | |
| *DTNA* | 18q12.1 | 601239 | Dystrobrevin alpha | AD | LVNC, HCM |
| **Desmosomes** | | | | | |
| *DSP* | 6p24.3 | 125647 | Desmoplakin | AD | ARVC |
| *DSG2* | 18q12.1 | 125671 | Desmoglein-2 | AD | ARVC |
| **Mitochondrial proteins** | | | | | |
| *FXN* | 9q21.11 | 606829 | Frataxin | AR | HCM |
| *SDHA* | 5p15.33 | 600857 | Succinate dehydrogenase flavoprotein subunit A | AR | LVNC |
| *MTTI* | mtDNA | 590045 | Transfer RNA, mitochondrial, isoleucine | Mit | HCM |

(*cont.*) ↓

| | | | | | |
|---|---|---|---|---|---|
| *MTTL1* | mtDNA | 590050 | Transfer RNA, mitochondrial, leucine, 1 | Mit | HCM |
| *MTTH* | mtDNA | 590040 | Transfer RNA, mitochondrial, histidine | Mit | HCM |
| **Extracellular matrix** | | | | | |
| *LAMA4* | 6q21 | 600133 | Laminin alpha-4 | AD | |
| *FKTN* | 9q31.2 | 607440 | Fukutin | AR | |
| **Other** | | | | | |
| *BAG3* | 10q26.11 | 603883 | BCL2-associated athanogene 3 (BAG family molecular chaperone regulator 3) | AD | HCM, RCM |
| *GBE1* | 3p12.2 | 607839 | Glycogen branching enzyme | AR | |
| *AGTX* | 2q37.3 | 604285 | Alanine-glycoxylate aminotransferase | AR | HCM, RCM |
| *GNPTAB* | 12q23.2 | 607840 | *N*-acetylglucosamine-1-phosphotransferase, alpha/beta subunits | AR | HCM, RCM |
| *GLB1* | 3p22.3 | 611458 | Galactosidase, beta-1 | AR | HCM |
| *EYA4* | 6q23.2 | 603550 | Eyes absent 4 | AD | |

Genes reported in association with dilated cardiomyopathy: isolated, syndromic and multisystem forms.
*AD,* autosomal dominant; *AF,* atrial fibrillation; *AR,* autosomal recessive; *ARVC,* arrhythmogenic right ventricular cardiomyopathy; *AV,* atrioventricular; *HCM,* hypertrophic cardiomyopathy; *LQTS,* long-QT syndrome; *LVNC,* left ventricular non-compaction; *Mit,* mitochondrial; *RCM*, restrictive cardiomyopathy; *SSS,* sick sinus syndrome; *SQTS,* short-QT syndrome; *VF,* ventricular fibrillation.
[a]Online Mendelian inheritance in man [17].

**Table 1.3** Arrhythmogenic right ventricular cardiomyopathy

| Gene | Locus | OMIM no.[a] | Protein | Inheritance pattern | Estimated fraction of ARVC (when available) (%)[b] | Other cardiac phenotypes |
|---|---|---|---|---|---|---|
| **Desmosomal proteins** | | | | | | |
| *DSP* (ARVC/D 8) | 6p24.3 | 125647 | Desmoplakin | AD/AR | 3 | Carvajal disease: autosomal recessive DCM with woolly hair and keratoderma |
| *PKP2* (ARVC/D 9) | 12p11.21 | 602861 | Plakophilin-2 | AD | 78 | |
| *DSG2* (ARVC/D 10) | 18q12.1 | 125671 | Desmoglein-2 | AD | 13 | DCM |
| *DSC2* (ARVC/D 11) | 18q12.1 | 125645 | Desmocollin-2 | AD | 4 | |
| *JUP* (ARVC/D 12) | 17q21.2 | 173325 | Junction plakoglobin | AD/AR | 1 | Naxos disease: autosomal recessive ARVC with woolly hair and keratoderma |
| **Membrane proteins and ion channels** | | | | | | |
| *RYR2* (ARVC/D 2) | 1q43 | 180902 | Ryanodine receptor 2 | AD | ? | Catecholaminergic polymorphic ventricular tachycardia, "atypical" LQTS |
| *TMEM43* (ARVC/D 5) | 3p25.1 | 612048 | Transmembrane protein 43 | AD | 1 | |
| **Extracellular/secreted proteins** | | | | | | |
| *TGFB3* (ARVC/D 1) | 14q24.3 | 190230 | Transforming growth factor, beta-3 | AD | ? | |
| **Sarcomere and sarcomere-associated proteins** | | | | | | |
| *TTN* | 2q31.2 | 188840 | Titin | AD | ? | HCM, DCM |

(*cont.*) ↓

| | | | | | | |
|---|---|---|---|---|---|---|
| **Other** | | | | | | |
| *?* (ARVC/D 3) | 14q12-q22 | %602086 | Unknown | AD | | |
| *?* (ARVC/D 4) | 2q32.1-q32.3 | | %602087 | Unknown | AD | |
| *?* (ARVC/D 6) | 10p14-p12 | %604401 | Unknown | AD | | |
| *?* (ARVC/D 7) | 10q22.3 | %609160 | Unknown | AD | | |

Genes reported in association with arrhythmogenic right ventricular cardiomyopathy.
*AD*, autosomal dominant; *AR*, autosomal recessive; *ARVC*, arrhythmogenic right ventricular cardiomyopathy; *DCM*, dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy; *LQTS*, long-QT syndrome.
[a]Online Mendelian inheritance in man [17].
[b]Estimated fraction according to Kapplinger et al. [19].

**Table 1.4** Restrictive cardiomyopathy

| Gene | Locus | OMIM no.[a] | Protein | Inheritance pattern | Other cardiac phenotypes |
|---|---|---|---|---|---|
| **Sarcomere and sarcomere-associated proteins** | | | | | |
| *TNNT2* | 1q32.1 | 191045 | Troponin T2, cardiac | AD | HCM, DCM, LVNC |
| *TNNI3* | 19q13.42 | 191044 | Troponin I, cardiac | AD | HCM, DCM |
| **Cytoskeletal proteins** | | | | | |
| *DES* | 2q35 | 125660 | Desmin | AD | DCM |
| *ALMS1* | 2p13.1 | 606844 | Alstrom syndrome protein 1 | AR | DCM |
| **Membrane proteins** | | | | | |
| *HFE* | 6p22.2 | 613609 | Hereditary hemochromatosis protein | AR | DCM |
| **Extracellular/secreted proteins** | | | | | |
| *TTR* | 18q21.1 | 176300 | Transthyretin | AD | HCM |
| **Other** | | | | | |
| *BAG3* | 10q26.11 | 603883 | BCL2-associated athanogene 3 | AD | HCM, DCM |
| *AGTX* | 2q37.3 | 604285 | Alanine-glycoxylate aminotransferase | AR | HCM, DCM |
| *GNPTAB* | 12q23.2 | 607840 | *N*-acetylglucosamine-1-phosphotransferase, alpha/beta subunits | AR | HCM, DCM |

Genes reported in association with restrictive cardiomyopathy.
*AD*, autosomal dominant; *AR*, autosomal recessive; *DCM*, dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy; *LVNC*, left ventricular non-compaction.
[a]Online Mendelian inheritance in man [17].

**Table 1.5** Left ventricular non-compaction

| Gene | Locus | OMIM no.[a] | Protein | Inheritance pattern | Other cardiac phenotypes |
|---|---|---|---|---|---|
| **Sarcomere and sarcomere-associated proteins** | | | | | |
| *MYH7* | 14q11.2 | 160760 | Myosin heavy chain 7, beta | AD | HCM, DCM |
| *TNNT2* | 1q32.1 | 191045 | Troponin T2, cardiac | AD | HCM, RCM, DCM |
| *TPM1* | 15q22.2 | 191010 | Tropomyosin 1 | AD | HCM, DCM |
| *ACTC1* | 15q14 | 102540 | Actin, alpha, cardiac muscle | AD | HCM, DCM |
| **Cytoskeletal proteins** | | | | | |
| *LDB3 (CYPHER; ZASP)* | 10q23.2 | 605906 | LIM domain-binding 3 (Cypher; ZASP) | AD | DCM |
| **Nucleus and nuclear membrane proteins** | | | | | |
| *LMNA* | 1q22 | 150330 | Lamin A/C | AD | DCM |
| *NKX2-5* | 5q35.1 | 600584 | NK2 homeobox 5 | AD | |
| **Membrane proteins and ion channels** | | | | | |
| *DTNA* | 18q12.1 | 601239 | Dystrobrevin alpha | AD | DCM, HCM |
| *TAZ* | Xq28 | 300394 | Tafazzin | XL | DCM, endocardial fibroelastosis |
| **Mitochondrial proteins** | | | | | |
| *SDHA* | 5p15.33 | 600857 | Succinate dehydrogenase subunit A flavoprotein | AR | DCM |
| **Other** | | | | | |
| *?* (LVNC2) | 11p15 | %609470 | Unknown | AD | |

Genes reported in association with left ventricular non-compaction.
*AD,* autosomal dominant; *AR,* autosomal recessive; *DCM,* dilated cardiomyopathy; *HCM,* hypertrophic cardiomyopathy; *RCM*, restrictive cardiomyopathy; *XL,* X-linked.
[a]Online Mendelian inheritance in man [17].

## References


1. Elliott P, Andersson B, Arbustini E et al (2008) Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 29:270–276. doi:10.1093/eurheartj/ehm342
2. Maron BJ, Towbin JA, Thiene G et al (2006) Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 113:1807–1816. doi:10.1161/circulationaha.106.174287
3. Watkins H, Ashrafian H, McKenna WJ (2008) The genetics of hypertrophic cardiomyopathy: Teare redux. Heart 94:1264–1268. doi:10.1136/hrt.2008.154104
4. Wang L, Seidman JG, Seidman CE (2010) Narrative review: harnessing molecular genetics for the diagnosis and management of hypertrophic cardiomyopathy. Ann Intern Med 152:513–520, W181. doi:10.1059/0003-4819-152-8-201004200-00008
5. Hershberger RE, Cowan J, Morales A, Siegfried JD (2009) Progress with genetic cardiomyopathies: screening, counseling, and testing in dilated, hypertrophic, and arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Heart Fail 2:253–261. doi:10.1161/CIRCHEARTFAILURE.108.817346
6. Sinagra G, Di Lenarda A, Moretti M et al (2008) The challenge of cardiomyopathies in 2007. J Cardiovasc Med (Hagerstown) 9:545–554. doi:10.2459/JCM.0b013e3282f2c9f9
7. Sylvius N, Tesson F (2006) Lamin A/C and cardiac diseases. Curr Opin Cardiol 21:159–165. doi:10.1097/01.hco.0000221575.33501.58
8. The SOLVD Investigators (1992) Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 327:685–691. doi:10.1056/NEJM199209033271003
9. Sakata K, Shimizu M, Ino H et al (2005) High incidence of sudden cardiac death with conduction disturbances and atrial cardiomyopathy caused by a nonsense mutation in the STA gene. Circulation 111:3352–3358. doi:10.1161/CIRCULATIONAHA.104.527184
10. Bonne G, Levy N (2003) LMNA mutations in atypical Werner's syndrome. Lancet 362:1585–1586; author reply 1586. doi:10.1016/S0140-6736(03)14761-7
11. Meune C, Van Berlo JH, Anselme F, Bonne G, Pinto YM, Duboc D (2006) Primary prevention of sudden death in patients with lamin A/C gene mutations. N Engl J Med 354:209–210. doi:10.1056/NEJMc052632
12. Corrado D, Leoni L, Link MS et al (2003) Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation 108:3084–3091. doi:10.1161/01.CIR.0000103130.33451.D2
13. Arbustini E, Pilotto A, Repetto A et al (2002) Autosomal dominant dilated cardiomyopathy with atrioventricular block: a lamin A/C defect-related disease. J Am Coll Cardiol 39:981–990
14. Taylor MR, Fain PR, Sinagra G et al (2003) Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. J Am Coll Cardiol 41:771–780
15. Sylvius N, Bilinska ZT, Veinot JP et al (2005) In vivo and in vitro examination of the functional significances of novel lamin gene mutations in heart failure patients. J Med Genet 42:639–647. doi:10.1136/jmg.2004.023283
16. Hershberger RE, Lindenfeld J, Mestroni L et al (2009) Genetic evaluation of cardiomyopathy–a Heart Failure Society of America practice guideline. J Card Fail 15:83–97. doi:10.1016/j.cardfail.2009.01.006
17. Online Mendelian inheritance in man. http://www.omim.org/. Accessed 18 May 2012
18. Cirino AL, Ho C (2011) Familial hypertrophic cardiomyopathy overview. In: Pagon RA, Bird TD, Dolan CR et al (eds) GeneReviews. University of Washington, Seattle. http://www.ncbi.nlm.nih.gov/books/NBK1768/. Accessed 18 May 2012
19. Kapplinger JD, Landstrom AP, Salisbury BA et al (2011) Distinguishing arrhythmogenic right ventricular cardiomyopathy/dysplasia-associated mutations from background genetic noise. J Am Coll Cardiol 57:2317–2327

# Family History

# 2

Michele Moretti, Matthew R. G. Taylor, Marco Merlo and Luisa Mestroni

The clinical cardiologist who examines a case of cardiomyopathy (CMP) should systematically consider the possibility of a genetic origin of the disease. After the clinician has excluded other known causes of heart muscle disease (hypertension, ischemia, drugs such as anthracyclines that may damage the myocardium, myocarditis, etc.), the family history has a critical role in the determination of a genetic origin of the disease.

An important goal of the family history [1] is the identification of other family members known to be affected or at least in whom there is the suspicion of a myocardial disease (e.g., a history of sudden death). A "negative" family history does not exclude a genetic etiology because the disease may be the result of a "de novo" mutation (approximately 10% of cases of sarcomeric hypertrophic cardiomyopathy [HCM] [1]) or, more frequently, a previously unrecognized myocardial disease may be present in the family [2].

If the family history is "positive", other important data should be analyzed, such as age of onset, sex, age and causes of death, association with abnormalities of other organs or systems, and the presence of syndromic forms of CMP.

A family history questionnaire is useful for the construction of a pedigree and at least three generations should be investigated [1]. In addition, expansion of the family history beyond the third generation, as well as the collection of clinical data from relatives with suspected or manifest myocardial disease, might be highly informative [3].

Morales et al. [1] considered the pedigree as "the most effective tool for practical application of genetic knowledge into clinical care" in familial CMP. Indeed with the pedigree it is possible to view multiple generations, to evaluate the number and sex of affected and non-affected relatives, and fre-

L. Mestroni (✉)
Cardiovascular Institute, University of Colorado, Aurora, Colorado, USA
e-mail: luisa.mestroni@ucdenver.edu

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_2, 

quently to develop an understanding of the likely inheritance pattern for a given family.

## 2.1 Patterns of Inheritance

The following patterns of inheritance are possible (Fig. 2.1).

### 2.1.1 Autosomal Dominant

In autosomal patterns the gene defect is localized in one of the 22 non-sex chromosomes (called *autosomes*). Dominant inheritance means that the subject can express the disease by inheriting a single copy (*heterozygous*) of a particular mutant gene (or *allele*, see Glossary below), even though the matching gene inherited from the other parent is normal. Thus, if one parent has the gene defect, each child has a 50% chance of inheriting the mutation.

Typical characteristics of this pattern are:

- Affected individuals in multiple generations;
- Male-to-male transmission (father-to-son) may occur;
- Males and females are usually equally affected.

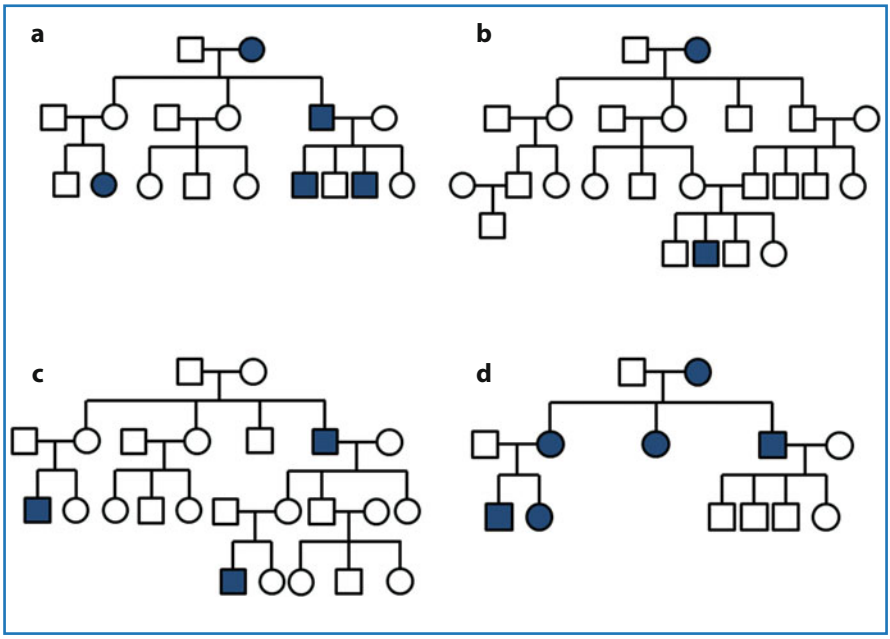



**Fig. 2.1** Pedigrees of different patterns of inheritance. **a** Autosomal-dominant inheritance. **b** Autosomal-recessive inheritance. **c** X-linked inheritance. **d** Mitochondrial inheritance

The likelihood of transmitting the mutant allele is 50% for each pregnancy, however, the actual number of affected offspring is usually lower than 50% because of incomplete *penetrance*. Penetrance refers to the proportion of carriers of a gene mutation that manifest the disease.

Autosomal dominant is the most common pattern of transmission of genetic CMPs.

### 2.1.2 Autosomal Recessive

As in autosomal-dominant inheritance, the gene defect is localized in one of the 22 non-sex chromosomes, but in autosomal-recessive inheritance both alleles must be mutated in order to express the phenotype. Individuals with only one mutant allele are considered to be *carriers*. Thus parents of an affected child are clinically unaffected, and both are carriers of a gene mutation. In this case, the risk of transmitting both mutant alleles to the child is 25%, while the chance of having a carrier child is 50% for each pregnancy. Males and females have the same chance of inheriting and expressing the trait.

This inheritance pattern should be suspected when both parents of the *proband* are unaffected, and its occurrence is increased in families where parents of an affected individual are related to each other (consanguineous union).

This is the least common inheritance pattern in heart muscle diseases.

### 2.1.3 X-linked Inheritance

In this pattern, the gene defect causing the trait is localized on the sex chromosome X. Usually X-linked inheritance refers to recessive forms. Since females have two X chromosomes and males have one X and one Y chromosome, the phenotype is expressed in males only (*hemizygotes*), while female individuals are *heterozygote* carriers. In females the random inactivation of one of the two X chromosomes is a normal process known as *lyonization*. Sometimes the X-inactivation process is non-random and female carriers who preferentially inactivate their X chromosomes carrying the normal allele, may present with the clinical phenotype, often in a milder form than affected males.

This pattern should be suspected if the pedigree is characterized by a pattern in which only males or predominantly males are affected (i.e., brothers, uncles and male cousins). No male-to-male transmission is observed. Moreover, all daughters of an affected male are obligate carriers, while the risk of having an affected son from a carrier mother is 50%.

X-linked dominant disorders are less common than X-linked recessive disorders, and require only one mutant allele in order to express the disease. In these rare forms, the pedigree may show more affected females than males.

### 2.1.4 Mitochondrial Inheritance

Also known as "matrilinear" inheritance, this pattern refers to mutations in mitochondrial DNA that can be transmitted from only the mother to the offspring. The ovum has about 100,000 copies of mitochondrial DNA, while the sperm has fewer than 100 copies and these are probably lost at fertilization. Thus males cannot transmit the disease to sons or daughters, while virtually the entire offspring of an affected mother will be affected.

## 2.2 Clinical Impact of Family History

The family history is an essential tool in clinical cardiology, and a source of valuable information. By analyzing the family pedigree, it is possible to have a comprehensive view of multiple generations, to identify additional family members and assess the number of affected relatives, to obtain information on the age of onset of clinical symptoms, variability of expression and penetrance of the disease, and occurrence and modalities of death, and, finally, to identify patients at risk.

The study of the family history (as well as an extensive family evaluation of relatives who are at risk but who have undiagnosed signs of CMP) is particularly important in some CMPs, taking into account the clinical–genetic correlations, and potential prophylactic and therapeutic consequences.

As an example, familial HCMs are characterized by a marked phenotypic heterogeneity: variable factors are the severity of hypertrophy, left ventricular obstruction, and age of onset of symptoms and complications.

In the majority of cases the prognosis is relatively benign; however, the risk of sudden death is around 1% per year in adults, and 2–5% of cases develop heart failure as a result of pump failure and/or restrictive physiology. Many of these features do not have a direct genetic correlation [4]; however, some data suggest clinical correlations in selected patients with HCM caused by mutations in the gene encoding cardiac troponin T (*TNNT2*) [5]. Sudden death or cardiac arrest with successful resuscitation has been observed in young, apparently unaffected, subjects carrying *TNNT2* mutations. These data, although controversial [6], may indicate a more aggressive approach to using an early implantable cardioverter-defibrillator (ICD) in patients with *TNNT2* mutations but with moderate or absent hypertrophy (also in the absence of traditional risk factors). However, translation of the molecular genetic data to the clinical setting has many limitations, and the possibility of identifying a "benign" mutation has not been confirmed [7].

Jacoby and McKenna also stress the importance of family assessment in HCM patients with multiple sarcomeric mutations [4]. Frequently these patients have a disease that is inherited from both parents and the disease is more severe and may be evident at an earlier age. Multiple sarcomeric muta-

tions have been identified in 5–10% of HCM patients, and in these the disease was found to be frequently more severe and more precocious in onset than for other members of the family [8–10].

In some cases observed by Girolami et al. [9] where individuals carried three mutations, the disease had an earlier onset and was more severe (cardiac arrest, heart failure, cardiac transplantation) in comparison with other members of the family who carried one or two mutations.

Some specific mutations in myosin heavy chain 7 (*MYH7),* such as R403Q or R453C, appear to be associated with adverse events, but, considering the presence in these patients of clinically evident risk factors, it is probable that the genetic data do not contribute to a better prognosis and treatment [4].

The family history is also important in some forms of DCM caused by mutations of lamin A/C gene (*LMNA*). In these cases, arrhythmias are frequent and there is a high incidence of sudden death (see Chap. 4). Sudden death has also been observed in *LMNA* mutation carriers who have preserved left ventricular function. In these cases it has been suggested that early ICD implantation may be important [11]. Similarly, an increased tendency for genetically inherited arrhythmias has been observed in CMPs resulting from *SCN5A* or desmosomal gene mutations.

## Glossary

**Allele:** one of the two copies of a gene.

**Autosome:** non-sex chromosome (22 pairs).

**Carrier:** heterozygous individual.

**Dominant:** a trait which is expressed when a single mutant allele is present.

**Hemizygosity:** presence of only one allele of the gene, in the sex chromosomes (x and y).

**Heterozygosity:** presence of two different alleles of the gene.

**Homozygosity:** presence of two identical alleles of the gene.

**Lyonization:** inactivation on one of the two X chromosomes in females.

**Penetrance:** proportion of individuals who carry a particular gene mutation and also express the phenotype.

**Proband:** first affected family member who seeks medical attention for a genetic disorder.

**Recessive:** a trait that can be expressed only when both alleles are mutated.

## References


1. Morales A, Cowan J, Dagua J, Hershberger RE (2008) Family history: an essential tool for cardiovascular genetic medicine. Congest Heart Fail 14:37–45
2. Watkins H, Ashrafian H, McKenna WJ (2008) The genetics of hypertrophic cardiomyopathy: Teare redux. Heart 94:1264–1268. doi:10.1136/hrt.2008.154104
3. Hershberger RE, Lindenfeld J, Mestroni L et al (2009) Genetic evaluation of cardiomyopathy – a Heart Failure Society of America practice guideline. J Card Fail 15:83–97. doi:10.1016/j.cardfail.2009.01.006
4. Jacoby D, McKenna WJ (2012) Genetics of inherited cardiomyopathy. Eur Heart J 33:296–304. doi:10.1093/eurheartj/ehr260
5. Watkins H, McKenna WJ, Thierfelder L et al (1995) Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. N Engl J Med 332:1058–1064. doi:10.1056/NEJM199504203321603
6. Anan R, Shono H, Kisanuki A et al (1998) Patients with familial hypertrophic cardiomyopathy caused by a Phe110Ile missense mutation in the cardiac troponin T gene have variable cardiac morphologies and a favorable prognosis. Circulation 98:391–397
7. Van Driest SL, Ackerman MJ, Ommen SR et al (2002) Prevalence and severity of "benign" mutations in the beta-myosin heavy chain, cardiac troponin T, and alpha-tropomyosin genes in hypertrophic cardiomyopathy. Circulation 106:3085–3090
8. Richard P, Charron P, Carrier L et al (2003) Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation 107:2227–2232. doi:10.1161/01.CIR.0000066323.15244.54
9. Girolami F, Ho CY, Semsarian C et al (2010) Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. J Am Coll Cardiol 55:1444–1453. doi:10.1016/j.jacc.2009.11.062
10. Millat G, Bouvagnet P, Chevalier P et al (2010) Prevalence and spectrum of mutations in a cohort of 192 unrelated patients with hypertrophic cardiomyopathy. Eur J Med Genet 53:261–267. doi:10.1016/j.ejmg.2010.07.007
11. Meune C, Van Berlo JH, Anselme F et al (2006) Primary prevention of sudden death in patients with lamin A/C gene mutations. N Engl J Med 354:209–210. doi:10.1056/NEJMc052632

# The Role of Clinical Observation: Red Flag 1 – Cardiomyopathies and Skeletal Muscle Involvement

3

Gianfranco Sinagra, Fulvio Camerini and Enrico Fabris

Genetic mutations can cause specific changes to cardiomyopathy (CMP) phenotype, and these changes may be associated with a variety of abnormalities of different organs and systems. Therefore, the clinical approach is very important, as is the presence of "red flags", which are potentially useful for better characterization of the genetic background of the CMP.

## 3.1 Red Flag 1: Cardiomyopathies and Skeletal Muscle Involvement

Many types of CMP are associated with different forms of skeletal muscle disease (Table 3.1). Examples of such associations can be found in muscular dystrophies (discussed later in this chapter), in systemic diseases (such as glycogenosis and mitochondriopathies) and in diseases of neurogenic origin (Friedrich ataxia), as well as in clearly defined syndromes. Muscular dystrophies (broadly defined as muscle weakness arising from a defect in the muscle itself [1]) are considered to be a spectrum of genetically heterogeneous diseases (there are more than 20 monogenic causes). They are frequently associated with dilated cardiomyopathy (DCM), caused by an intrinsic defect of the cardiomyocytes, but also to important arrhythmias and conduction defects, which may contribute to morbidity and mortality.

It should be noted that also in this group of diseases mutations in one gene may cause different phenotypic traits and that, as a result of the genetic mutations, skeletal muscle involvement in familial CMPs may be variable, absent, mild or severe [2].

In the following sections, the different types of muscular dystrophy associated with CMP are categorized according to their genetic background and molecular pathogenesis.

G. Sinagra (✉)
Cardiovascular Department,
Ospedali Riuniti and University of Trieste, Italy
email: gianfranco.sinagra@aots.sanita.fvg.it

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_3, © Springer-Verlag Italia 2013

### 3.1.1 Dystrophin (DMD)

Mutations of the gene encoding dystrophin are the cause of Duchenne muscular dystrophy, an X-linked cardiac and skeletal muscle disease affecting approximately 1 in 6,000 boys. The dystrophin protein, in conjunction with the dystrophin glycoprotein complex, has an important role in force transmission, being integral to the mechanical link between the intracellular cytoskeleton and the extracellular matrix [3]. In dystrophinopathies caused by reduced levels of, or abnormal, dystrophin protein (Fig. 3.1), increased sarcolemmal per-

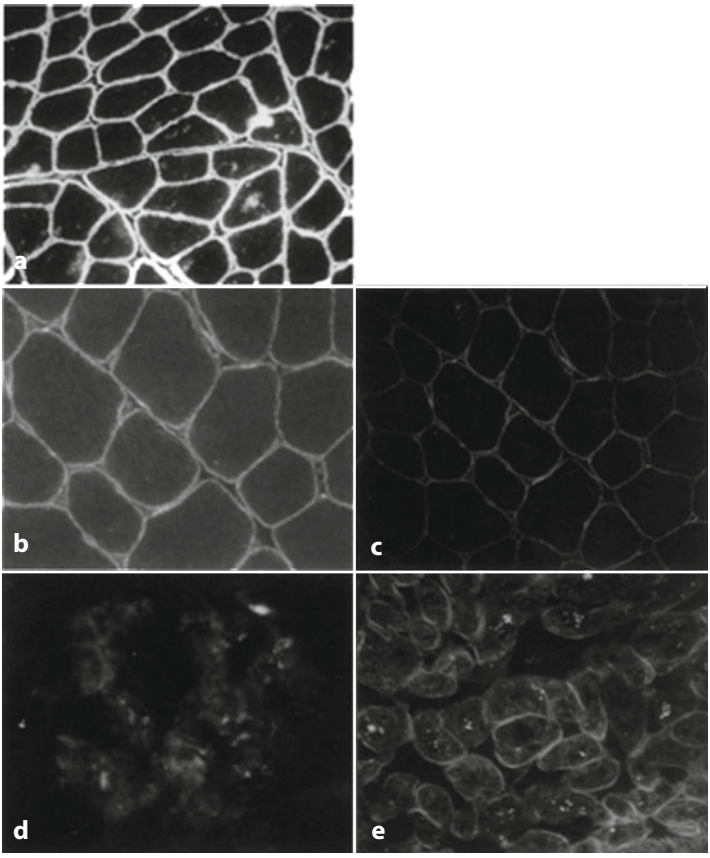



**Fig. 3.1** Immunocytochemistry of skeletal and heart muscle in Duchenne muscular dystrophy. **a** Cryostat sections of skeletal muscle from a normal individual were immunolabeled with antibodies to the C-terminal region of dystrophin. The cryostat sections of the skeletal muscle of the patient with Duchenne muscular dystrophy were labeled with antibodies against the N terminus (**b**) and the C terminus (**c**). These antibodies show reduced but structurally preserved staining of the muscle of the patient compared with that of the normal control (×180). **d** The cryostat section of the cardiac muscle from the patient immunostained with antibodies to the N terminus shows complete absence of dystrophin (×250). **e** Weak reactivity was detected with antibodies against the C terminus of the protein (×250). Modified from Milasin J et al. [57], with permission

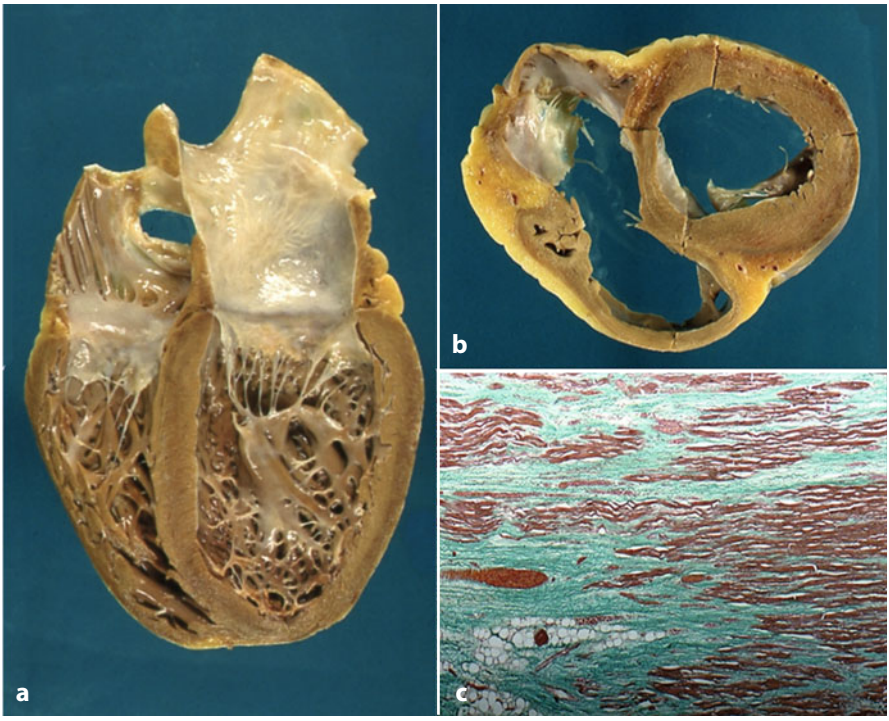



**Fig. 3.2** Dilated cardiomyopathy in a 27-year-old man with Duchenne muscular dystrophy. **a**,**b** Severe biventricular dilatation. **c** Histopathology: Azan–Mallory staining (×10) showing severely damaged myocardial fibers with a large area of fibrotic tissue

meability resulting from membrane injury or stretch induces increased trafficking across ion channels, and this leads to muscle dysfunction and progressive cell death. Mutations in the dystrophin gene, which is located on chromosome Xp21, cause two forms of X-linked skeletal myopathy: a severe form (Duchenne muscular dystrophy), and a milder, later-onset form (Becker muscular dystrophy). In both forms, the disease process begins in childhood. Boys affected with Duchenne muscular dystrophy are typically wheelchair-bound before 12 years of age [4], while in Becker muscular dystrophy the disease process begins later and has a slower evolution (boys are wheelchair-bound after 16 years of age). In both forms, the skeletal myopathy shows pseudohypertrophy of the calf muscles, and the disease is associated with elevated levels of plasma creatine kinase (CK) [5].

In the majority of patients, Duchenne muscular dystrophy is complicated by a progressive form of DCM (Fig. 3.2), which competes with respiratory muscle failure as the main cause of morbidity; in Becker muscular dystrophy, cardiac involvement is less frequent (about 70%) [5]. However, in patients affected by subclinical or mild forms of Becker muscular dystrophy, overt

dilated DCM may be the main clinical feature and manifestation of the disease [6]. Abnormal Q waves in lead I, aVL, V6, or in lead II, lead III, aVF have been described [7]. Supraventricular arrhythmias, atrioventricular (AV) block and right bundle branch block may be present. It should also be noted that about 10% of female carriers of dystrophin gene mutations (Duchenne or Becker type) may develop a DCM in the absence of clinical involvement of skeletal muscle [8, 9].

X-linked DCM is a form of genetically inherited DCM that results from mutations in the dystrophin gene. It may be clinically indistinguishable from "idiopathic" DCM. There is no muscular weakness in this form of the disease, but CK levels are usually (but not always) elevated [10].

### 3.1.2 The Sarcoglycans

The sarcoglycan proteins (and the genes encoding them) comprise alpha-sarcoglycan (*SGCA*), beta-sarcoglycan (*SGCB*), gamma-sarcoglycan (*SGCG*) and delta-sarcoglycan (*SGCD)*. From a clinical point of view, mutations of these genes can cause a clinical pattern characterized by limb-girdle muscular dystrophy and/or DCM. Mutations of *SGCD* can be the cause of apparently isolated DCM, as described by Tsubata et al. [11]; however, this is a rare occurrence (no mutations were found in *SGCB* and *SGCD* in 99 cases with sporadic or familial DCM [12]), while the prevalence of mutations of the delta-sarcoglycan gene is less than 1% in "idiopathic" DCM, according to Sylvius et al. [12].

Limb-girdle muscular dystrophy with proximal leg muscular involvement was associated with DCM in two cases described by Barresi et al. [13] and considered to be a result of mutations in the beta-sarcoglycan gene; cardiac involvement appeared years after the skeletal muscle symptoms and it was severe [13]. The possibility of more frequent involvement of the heart in muscular dystrophy caused by mutations in sarcoglycan genes was demonstrated by Melacini et al. [14] who studied 13 patients with mutations of the genes encoding alpha-, beta- and gamma-sarcoglycan, and they found electrocardiogram (ECG) or echocardiogram abnormalities in about 30% of cases affected by severe muscular dystrophy. The cardiac involvement was not severe and there was no correlation between the presence of cardiac abnormalities and the type of mutation of the sarcoglycan gene involved. In CMPs caused by sarcoglycan gene mutations, sudden death has been reported [11].

In DCM resulting from sarcoglycan gene mutations, ECGs are frequently abnormal, with increased R waves in V1, similar to those sometimes observed in dystrophin DCM (e.g., Duchenne muscular dystrophy).

### 3.1.3 Titin (*TTN*)

Mutations of the gene encoding titin can be the cause of isolated DCM [15] and isolated hypertrophic cardiomyopathy (HCM) [16]. Moreover, Carminac et al. [17] reported a novel form of "titinopathy" of congenital onset involving both heart and skeletal muscle in a Moroccan family (three siblings). Delayed motility was present in the first year of life, while in the first decade muscle weakness (involving the lower and the upper limbs, neck and trunk flexors, and facies) was present. Poor muscle bulk in the upper limbs contrasted with relative pseudohypertrophy in the lower limbs, and ptosis was a constant finding. In all three siblings, global motor performance was stable or tended to improve, but between 5 and 12 years a severe progressive form of DCM developed. All the patients died or received heart transplants between 8 and 15 years after the onset of the cardiac symptoms. Complex supraventricular or ventricular arrhythmias were present in all the patients. A similar clinical picture was found to be present in two siblings of a Sudanese family.

### 3.1.4 Lamin A/C (*LMNA*)

Mutations in lamin A/C gene may cause at least ten different phenotypes ("laminopathies"). In patients with these mutations, involvement of the myocardium, skeletal muscle, distribution of white fat, bones, peripheral nerves and premature ageing, and also mandibuloacral dysplasia and multisystem dystrophy syndrome, have been observed [18, 19]. However, there is not always a clear relationship between genotype and phenotype.

Mutations in the *LMNA* gene were first described in Emery–Dreifuss muscular dystrophy [20–22]. In this disease, the association of cardiac abnormalities and skeletal muscle dystrophy may be very variable. Sometimes both systems are clearly involved and skeletal muscle involvement can have different severity and characteristics, such as in Emery–Dreifuss muscular dystrophy or limb-girdle muscular dystrophy [23]. Sometimes the CMP is apparently isolated [2, 19, 24]. Moreover, in some cases, the skeletal muscle disease may be subclinical, with an increase in the level of the serum CK [24] as the only sign of the underlying muscular pathology. Muscular dystrophies, whether clinically evident or subclinical, can be associated with DCM and with sinus node and/or AV conduction abnormalities [24]. Finally, mutations in *LMNA* have been identified in a few patients affected by a combination of DCM, muscular dystrophy, lipodystrophy and supraventricular arrhythmias [25] or CMP, lipoatrophy, diabetes, leukomelanodermic papules and liver steatosis [26].

### 3.1.5 Emerin (*EMD*)

Mutations in the *EMD* gene, which is localized on chromosome Xq28 and encodes emerin, is a cause of Emery–Dreifuss muscular dystrophy, a geneti-

cally heterogeneous disorder (*LMNA* mutations are another important cause of this type of muscular dystrophy, as described above). Emery–Dreifuss syndrome is transmitted by an X-linked recessive mechanism, and also by an X-linked dominant mechanism [27], and it can be characterized by a phenotype that includes complex supraventricular arrhythmias. In two families with Emery–Dreifuss muscular dystrophy, Sakata et al. [27] identified 16 carriers with a nonsense mutation in exon 6 of the *EMD* gene (also known as *STA*) [27]. Five of these patients showed signs of mild skeletal muscle involvement, associated with supraventricular arrhythmias. A clinical picture of DCM was not present, although two male carriers had left ventricular dilatation with normal systolic function. The occurrence of a more extensive ventricular involvement, with heart failure [28] and also treatment with a heart transplant [29], in patients with a clinical phenotype of Emery–Dreifuss muscular dystrophy has been noted in the literature, although in these patients the demonstration of an emerin mutation was not possible. It should be noted that Cartegni et al. [30] localized emerin in the desmosomes and fasciae adherents, and this specific localization could account for the characteristic conduction defects (and perhaps right ventricular involvement) observed by Buckley et al. [31].

### 3.1.6 Fukutin (*FKTN*)

Mutations of the *FKTN* gene are considered to be the cause of Fukuyama-type muscular dystrophy, a disease that is usually observed in Japan, and which is characterized by a combination of severe muscular dystrophy and structural brain abnormalities with mental retardation, and rarely by cardiac involvement. The disease is associated with glycosylation defects of alpha-dystroglycans, which are very important for intracellular and extracellular membrane linkage. Fukutin is a protein that is probably involved in modifying cell-surface molecules, such as glycoproteins and glycolipids, and mutant fukutin may have different effects on glycosylation of alpha-dystroglycan in skeletal and cardiac muscle. These effects may explain the observations by Murakami et al. [32] who identified six patients in four families affected by DCM in the absence of, or with only minimal, limb-girdle muscle involvement and normal intelligence. DCM was frequently severe (a heart transplant at 18 years of age in one patient, and death for severe heart failure in a 12-year-old child) and the CK level was usually found to be elevated. The authors concluded that the clinical spectrum caused by fukutin mutations is much wider than previously perceived and that it is important to consider mutation in *FKTN* in the diagnosis of familial DCM, although it is rare outside Japan. The frequency of cardiac involvement in Fukuyama muscular dystrophy is not clear, although Saito [33] suggested that a slowly progressive cardiac involvement is frequent in individuals who have lived for more than ten years; this was documented by the presence of fibrosis of the myocardium, as observed in postmortem examination [34, 35].

### 3.1.7 Dystrophia Myotonica Protein Kinase (*DMPK*)

A mutation of the *DMPK* gene is the cause of myotonic muscular dystrophy type 1 (Steinert disease), a multi-system disorder and the most common form of muscular dystrophy in adults. Cardiovascular involvement is frequent. Myotonic muscular dystrophy type 1 (the more severe and more common form of the two major types of myotonic muscular dystrophy) is the consequence of a genetic abnormality characterized by a trinucleotide repeat expansion (cytosine, thymine, guanine, CTG) in the dystrophia myotonica protein kinase gene (*DMPK*). The disease is characterized by frequent involvement of different organs and systems.

Cardiac involvement is frequently characterized by ECG abnormalities and arrhythmias, while symptomatic DCM and heart failure have been reported rarely (4–6% in patients with severe ECG abnormalities in an extensive study on 406 adult patients with genetically confirmed myotonic dystrophy type 1 [36]).

### 3.1.8 Zinc Finger Protein 9 (*ZFN9*)

A mutation of the cellular retroviral nucleic acid-binding protein 1 (*CNBP*) gene (also known as *ZFN9)* is the cause of myotonic muscular dystrophy type 2 (alternative name: proximal myotonic myopathy, PROMM). In this disease, muscular involvement is usually less severe and cardiac abnormalities are less common [37]. In the three familial cases described by Von Zur Muhlen et al. [37], atrioventricular and intraventricular conduction defects were present, and in one patient they were associated with severe sustained ventricular tachycardia. No signs of heart failure were reported, but left ventricular function was slightly reduced in one patient, and myocardial hypertrophy and some endocardial fibrosis were present at endomyocardial biopsy. This disease is considered to be a multi-system disorder.

### 3.1.9 D4Z4

D4Z4 repeat motif contraction, at chromosome 4q35, is associated with facioscapulohumeral muscular dystrophy, which is another form of muscular dystrophy, and the third most frequent after Duchenne and myotonic muscular dystrophy. Cardiac abnormalities are rarely present and usually not severe. Supraventricular arrhythmias and AV blocks have been described [38, 39]. In a group of 100 patients studied by Laforet et al. [39], minor and non-specific ECG changes were present in 38%, while more severe conduction abnormalities and arrhythmias were present in five patients. Interestingly, one patient was apparently affected by arrhythmogenic right ventricular cardiomyopathy. Abnormalities of different organs or systems have also been described.

## 3.2 The Myofibrillar Myopathies and Cardiomyopathies

The myofibrillar myopathies are a group of skeletal muscle disorders that are considered to be a morphologically distinct subset of muscular dystrophies, and they are clinically and genetically heterogeneous. The myofibrillar myopathies are characterized by a common pathological pattern, which includes early disintegration of the Z-discs and then of myofibrils, followed by aggregation of degraded myofibrillar products into pleomorphic granular or hyaline inclusions. The molecular basis of myofibrillar myopathies is heterogeneous, but there is a common background (i.e., the causative mutations are localized in genes encoding sarcomeric proteins, which are an integral part of the Z-disc or closely associated with it [40, 41]). The genes and the sarcomeric Z-disc proteins that have been studied are desmin (*DES*), LIM-domain binding 3 (*LDB3*) (also known as Cypher/ZASP), titin immunoglobulin domain protein (*MYOT)* (also known as myotilin), alpha-B-crystallin (*CRYAB*) and Bcl2-associated athanogene 3 (*BAG3*).

The clinical heterogeneity is characterized by an autosomal-dominant or autosomal-recessive mode of inheritance, different age of onset, and variability of clinical associations, such as neural involvement, cardiomyopathy, etc. CMPs (hypertrophic, restrictive, dilated) have been observed in all types of myofibrillar myopathies, with the exception of those caused by filamin mutations.

### 3.2.1 Desmin (*DES*)

Mutations in the gene encoding desmin are also thought to be the cause of a wide spectrum of phenotypes, such as as CMPs of different types (dilated, restrictive), skeletal myopathies, and mixed skeletal and cardiac myopathies. Desmin myopathy, a distinct subgroup in the family of myofibrillar myopathies, is a rare disease characterized by muscle weakness, initially distal, which usually begins in middle age (mean age 28 years in the Dalakas et al. series of patients [42]). The disease subsequently extends to proximal muscles and progressively limits walking, raising arms and using hands. Dysphagia, and weakness of facial, neck and respiratory muscles may occur. In some patients CMP, usually characterized by conduction defects and occasionally heart failure, precedes skeletal muscle involvement (by a mean of 12 years in the Dalakas et al. series [42]); contrasting symptoms are also possible (cardiac conduction defects developing years after skeletal muscle disease). In some patient series [43, 44], cardiac involvement with a phenotype of DCM was apparently isolated, with no clinical involvement of skeletal muscles. CK was not evaluated in these cases. Desmin mutations account for 1–2% of all cases of DCM [44].

### 3.2.2 LIM-Domain Binding 3 (*LDB3*)

Mutations in the gene encoding LIM-domain binding 3 (*LDB3*; also known as *Cypher/ZASP*), identified in 2003 by Vatta et al. [45], are thought to be the cause of pure forms of DCM or DCM associated with left ventricular non-compaction [45]. In all 16 cases described by Vatta et al. [45], and in the family observed by Arimura et al. [46], there were no clinical or laboratory signs of skeletal involvement. In contrast, in a group of 11 patients with mutations in the *ZASP* gene, Selcen et al. [47] observed cardiac involvement in four patients with skeletal myofibrillar myopathy: arrhythmias, ECG changes, and low ejection fraction in one patient (with coronary disease).

### 3.2.3 Titin Immunoglobulin Domain Protein (*MYOT*)

Titin immunoglobulin domain protein (also known as myotilin), a Z-disc associated protein, is produced in large amounts in skeletal muscle and low amounts in cardiac muscle. A mutation in the *MYOT* gene is a cause of skeletal myofibrillar myopathy [48], and also of some cases of CMP, probably DCM [49].

In Selcen and Engel's series [49], muscle weakness was sometimes slowly progressive, and more prominent distally than proximally, but the opposite symptomatology was also possible. The age of onset ranges from 50 to 77 years, and evidence of peripheral nerve involvement is apparent in all patients.

### 3.2.4 Alpha-B-Crystallin (*CRYAB*)

Expression of the gene encoding alpha-B-crystallin was initially demonstrated in the lens, but the protein is also produced in skeletal and cardiac muscle and it functions as a chaperone for desmin and actin [50, 51]. Alpha-B-Crystallin also contributes to the maintenance of integrity of the cytoskeleton and it has a role in other cellular processes, such as the degradation of proteins. *CRYAB* mutations are rare, and associated in about 50% of cases with cataracts, and less frequently with distal myopathy, dysphonia and/or dysarthria. Rare cases of skeletal myopathy associated with CMP have been observed [52, 53].

Clinical signs of muscle involvement usually appear in middle age, and subjects presenting with isolated myopathy may develop CMP later in the evolution of the disease.

### 3.2.5 Bag 3 Protein (*BAG3*)

Bag 3 protein (also known as bcl2-associated athanogene3) encoded by *BAG3* is considered by Selcen et al. [40] to be a candidate for myofibrillar myopathy

because it localizes to and co-chaperones the Z-disc in skeletal and cardiac muscle, and because its targeted deletion is the cause of a fulminant myopathy in mice. Those authors identified a *BAG3* mutation in three young patients (aged 11–17 years), all with limb and axial muscle weakness and severe respiratory deficiency: two with rigid spine and one with a peripheral neuropathy. In all three patients, a CMP was present, which was restrictive in two patients (one received a heart transplant at age 13 years, and one died at 12 years of age), while the third had hypertrophic cardiomyopathy. The authors concluded that a mutation in the Bag family of proteins is the cause of a new form of childhood muscle dystrophy and CMP.

## 3.3 Familial Restrictive Cardiomyopathies and Skeletal Muscle Involvement

Familial restrictive cardiomyopathies (RCMs) can be caused by mutations in the gene encoding the cardiac muscle isoform of troponin I (*TNNI3*) on chromosome 19q13 (RCM1), while another form, RCM3, is caused by a mutation in the *TNNT2* gene. Another form, RCM2, has been mapped to chromosome 10q23. From a clinical point of view, few cases of familial RCM associated with proximal and distal skeletal myopathy have been described [54–56]. A form of RCM associated with myofibrillar myopathy caused by a *BAG3* mutation has been described (see *BAG3)*.

## 3.4 Notes

Mutations in genes encoding telethonin and dystrobrevin have been identified in muscular dystrophy and CMPs, but, at present, no cases with simultaneous skeletal and heart muscle disease have been described.

**Table 3.1** Cardiomyopathies with skeletal muscle involvement and/or arrhythmias

| Gene | Protein | Cardiac phenotype(s) | ECG abnormalities and arrhythmias | Type of skeletal muscle disorder | Possible associated phenotypes |
|---|---|---|---|---|---|
| *DMD* | Dystrophin | DCM<br><br>**Cardiac involvement in 90–95% of cases**; age of onset: 10–13 years, severe DCM and heart failure after 20 years of age; cause of death in 20% of DMD and in 50% of BMD cases | Abnormal Q waves<br><br>SVT, AV block, bundle branch block | **DMD**: progressive proximal muscular dystrophy with characteristic pseudohypertrophy of the calves; CK↑↑↑; age of onset: before 5 years; wheelchair dependency before 12 years of age; death in the second or third decade<br><br>**BMD**: similar to DMD in the distribution of proximal muscle wasting and weakness, but with preservation of neck flexor muscle strength; CK ↑↑; age of onset: around 12 years, but also later in life (frequently in second or third decade); wheelchair dependency after age 16 years; death in the fourth or fifth decade<br><br>**X-linked DCM**: no clinically evident muscular disorder; CK normal or ↑ | **DMD**: possible mental retardation (severe in 20% of cases)<br><br>**BMD**: possible mental retardation (less common and severe than DMD) |
| *SGCA*<br>*SGCB*<br>*SGCG*<br>*SGCD* | Sarcoglycan complex | DCM<br><br>(Heart involvement is variable, but less severe than DMD or BMD) | Increased R waves in V1<br><br>Sudden death | **Limb-girdle muscular dystrophy, type 2D, 2E, 2F**: progressive weakness and wasting restricted to the limb musculature, proximal (shoulder, pelvic girdle, upper thighs, and upper arms) greater than distal (lower legs and feet, lower arms and hands); calf pseudohypertrophy is frequent; CK ↑↑/↑↑↑; age of onset: early childhood; progression can be severe (similar to DMD) or mild with later onset (similar to BMD); wheelchair dependency after age 15 years | |

(*cont.*) →

**Table 3.1** Cardiomyopathies with skeletal muscle involvement and/or arrhythmias (*continued*)

| Gene | Protein | Cardiac phenotype(s) | ECG abnormalities and arrhythmias | Type of skeletal muscle disorder | Possible associated phenotypes |
|---|---|---|---|---|---|
| *TTN* | Titin | DCM | Complex SVT or VT<br><br>Sudden death | **Early onset diffuse muscular dystrophy** (lower and upper limbs, neck, trunk, facies, palpebral ptosis) | |
| *LMNA* | Lamin A/C | DCM | SVT, AF or atrial flutter, SSS, AV block<br><br>Sudden death | **Emery–Dreifuss type 2 and 3 muscular dystrophy**: see Emery–Dreyfuss type 1 muscular dystrophy; CK normal or ↑<br>**Limb-girdle muscular dystrophy, type 1B**: proximal lower limb weakness; age of onset: third decade; CK normal or ↑ | Broad spectrum of human diseases, more than ten different clinical syndromes described, associated or not associated with DCM |
| *EMD* | Emerin | DCM (?) | SVT (junctional tachycardia), AF, SSS, AV block<br><br>Sudden death | **Emery–Dreifuss type 1 muscular dystrophy**: slow progressive muscle weakness and wasting initially in a humeroperoneal distribution and later extending to the scapular and pelvic girdle muscles, associated with joint contractures (elbows, Achilles tendons and postcervical muscles); mild pectus excavatum; no muscle pseudohypertrophy or involvement of the forearm muscles; CK normal or ↑/↑↑; age of onset: early childhood | |
| *FKTN* | Fukutin | DCM (age of onset over 10 years) | | **Muscular dystrophy-dystroglycanopathy**: broad spectrum of severity, from mild limb-girdle muscular dystrophy to severe generalized hypotonia and symmetric muscle weakness (congenital forms); CK ↑↑/↑↑↑; age of onset: childhood or congenital; death in first or second decade<br>Note: cardiac involvement observed especially in milder forms | Severe brain and eye abnormalities in congenital form; no extramuscular abnormalities described in milder forms |

(*cont.*) ↓

| | | | | | |
|---|---|---|---|---|---|
| *DMPK* | Dystrophia myotonica-protein kinase | DCM | Abnormal Q waves<br><br>SVT, AF or atrial flutter, AV blocks, intraventricular conduction defects, VT<br>Sudden death | **Myotonic dystrophy type 1 or Steinert's disease**: distal leg, hand, neck and face muscle weakness; myotonia and grip myotonia; in newborn: hypotonia, generalized and facial muscle weakness, positional malformations including club foot, respiratory insufficiency; CK normal or ↑; age of onset: from adolescence to third decade (classic form), adulthood (mild form) or congenital | Minor intellectual deficits, elevated transaminases, cataract, diabetes mellitus, balding |
| *ZNF9 (CNBP)* | Zinc finger protein 9 (cellular nucleic acid-binding protein) | DCM (?), HCM (?), endocardial fibroelastosis (?) | AV and intraventricular conduction defects, VT | **Myotonic dystrophy type 2 or proximal myotonic myopathy (PROMM)**: arm and neck muscle weakness, muscle pain and stiffness; myotonia; CK normal or ↑; age of onset: third decade | Subcapsular cataracts, hypogammaglobulinemia, insulin-insensitive type 2 diabetes mellitus and testicular failure |
| *D4Z4 (FSHMD1A)* see also *DUX4* | Double homeobox protein 4 | ARVC (?) | SVT, VT, AV blocks, intraventricular conduction defects | **Facioscapulohumeral muscular dystrophy**: slow progressive weakness of the facial, scapular and dorsiflexors of the foot muscles; severity is highly variable (20% of cases require a wheelchair); age of onset: before 20 years; CK normal or ↑; life expectancy not reduced | Retinal vasculopathy (with normal vision) (40–60% of cases); high-tone sensorineural hearing loss (60% of cases) |
| *DES* | Desmin | DCM, RCM | Conduction defects (frequently requiring pacemaker implantation) | **Myofibrillar myopathy type 1**: slow progressive weakness that can involve both proximal and distal muscles; distal muscle weakness is more frequent and more severe than proximal; possible sensory symptoms, muscle stiffness, aching or cramps; CK normal or ↑/↑↑; age of onset: usually middle age | Peripheral neuropathy (20%) |

(*cont.*) →

**Table 3.1** Cardiomyopathies with skeletal muscle involvement and/or arrhythmias (*continued*)

| Gene | Protein | Cardiac phenotype(s) | ECG abnormalities and arrhythmias | Type of skeletal muscle disorder | Possible associated phenotypes |
|---|---|---|---|---|---|
| *LDB3* | LIM domain-binding protein 3 (Cypher/ZASP) | DCM, LVNC | Abnormal ECG, SVT, right bundle branch block, LQTS | **Myofibrillar myopathy type 4** (see myofibrillar myopathy type 1); age of onset: adult (fourth to seventh decade) | Peripheral neuropathy (20%) |
| *MYOT* | Titin immuno-globulin domain protein (myotilin) | DCM | | **Myofibrillar myopathy type 3** (see myofibrillar myopathy type 1); age of onset: adult (fifth to seventh decade) | Peripheral neuropathy (20%) |
| *CRYAB* | Crystallin alpha-B | DCM | | **Myofibrillar myopathy type 2** (see myofibrillar myopathy type 1); age of onset: adult (third to fifth decade) | Peripheral neuropathy (20%); polar cataract |
| *BAG3* | BCL2-associated athanogene 3 | HCM, RCM | | **Myofibrillar myopathy type 6** (see myofibrillar myopathy type 1); age of onset: first to second decade; fatality: high | Peripheral neuropathy (20%); rigid spine |
| *DTNA* | Dystrobre-vin alpha | LVNC "HCM-DCM" | AF Sudden death | | |
| *SCN5A* | Sodium channel protein type 5 subunit alpha | DCM | SSS, AF, AV and intraventricular conduction defects | | |

(*cont.*) ↓

| | | | | | |
|---|---|---|---|---|---|
| *KCNJ2* | Potassium channel, inwardly rectifying, subfamily J, member 2 | DCM | Familial AF, LQTS, SQTS | **Andersen–Tawil syndrome**: episodic flaccid muscle weakness that occurs spontaneously or may be triggered by prolonged rest. Mild permanent weakness is common; CK normal; hypokalemia or hyperkalemia; age of onset: first or second decade | Low-set ears, ocular hypertelorism, small mandible, fifth-digit clinodactyly, syndactyly, short stature and scoliosis |
| *ABCC9 (SUR2)* | ATP-binding cassette, sub-family C, member 9 (sulfonylurea receptor 2) | DCM | VT | | |
| *PSEN1 PSEN2* | Presenilin 1 and presenilin 2 | DCM | 1 degree AV block, AF, left bundle branch block Syncope | | |

Note: sketelal muscle involvement as part of a genetic multi-system disease has not been considered in this table (see Tables 9.1, 9.2 and 9.3 for multi-organ disorders).

*AF,* atrial fibrillation; *ARVC,* arrhythmogenic right ventricular cardiomyopathy; *AV,* atrioventricular; *BMD,* Becker muscular dystrophy; *CK,* creatine kinase; *DCM,* dilated cardiomyopathy; *DMD,* Duchenne muscular dystrophy; *ECG,* electrocardiogram; *HCM,* hypertrophic cardiomyopathy; *LQTS,* long-QT syndrome; *LVNC,* left ventricular non-compaction; *RCM,* restrictive cardiomyopathy; *SSS,* sick sinus syndrome; *SQTS,* short-QT syndrome; *SVT,* supraventricular tachycardia; *VT,* ventricular tachycardia.

## References


1. McNally EM, MacLeod H (2005) Therapy insight: cardiovascular complications associated with muscular dystrophies. Nat Clin Pract Cardiovasc Med 2:301–308. doi:10.1038/ncpcardio0213
2. Taylor MR, Fain PR, Sinagra G et al (2003) Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. J Am Coll Cardiol 41:771–780
3. Lapidos KA, Kakkar R, McNally EM (2004) The dystrophin glycoprotein complex: signaling strength and integrity for the sarcolemma. Circ Res 94:1023–1031. doi:10.1161/01.RES.0000126574.61061.25
4. Brooke MH, Fenichel GM, Griggs RC et al (1989) Duchenne muscular dystrophy: patterns of clinical progression and effects of supportive therapy. Neurology 39:475–481
5. Jefferies JL, Eidem BW, Belmont JW et al (2005) Genetic predictors and remodeling of dilated cardiomyopathy in muscular dystrophy. Circulation 112:2799–2804. doi:10.1161/CIRCULATIONAHA.104.528281
6. Melacini P, Fanin M, Danieli GA et al (1996) Myocardial involvement is very frequent among patients affected with subclinical Becker's muscular dystrophy. Circulation 94:3168–3175
7. Mestroni L, Miyamoto SD, Taylor MR (2007) Genetics of dilated cardiomyopathy conduction disease. Prog Pediatr Cardiol 24:3–13
8. Mirabella M, Servidei S, Manfredi G et al (1993) Cardiomyopathy may be the only clinical manifestation in female carriers of Duchenne muscular dystrophy. Neurology 43:2342–2345
9. Politano L, Nigro V, Nigro G et al (1996) Development of cardiomyopathy in female carriers of Duchenne and Becker muscular dystrophies. JAMA 275:1335–1338
10. Arbustini E, Diegoli M, Morbini P et al (2000) Prevalence and characteristics of dystrophin defects in adult male patients with dilated cardiomyopathy. J Am Coll Cardiol 35:1760–1768
11. Tsubata S, Bowles KR, Vatta M et al (2000) Mutations in the human delta-sarcoglycan gene in familial and sporadic dilated cardiomyopathy. J Clin Invest 106:655–662. doi:10.1172/JCI9224
12. Sylvius N, Duboscq-Bidot L, Bouchier C et al (2003) Mutational analysis of the beta- and delta-sarcoglycan genes in a large number of patients with familial and sporadic dilated cardiomyopathy. Am J Med Genet A 120A:8–12. doi:10.1002/ajmg.a.20003
13. Barresi R, Di Blasi C, Negri T et al (2000) Disruption of heart sarcoglycan complex and severe cardiomyopathy caused by beta sarcoglycan mutations. J Med Genet 37:102–107
14. Melacini P, Fanin M, Duggan DJ et al (1999) Heart involvement in muscular dystrophies due to sarcoglycan gene mutations. Muscle Nerve 22:473–479
15. Gerull B, Gramlich M, Atherton J et al (2002) Mutations of TTN, encoding the giant muscle filament titin, cause familial dilated cardiomyopathy. Nat Genet 30:201–204. doi:10.1038/ng815
16. Satoh M, Takahashi M, Sakamoto T et al (1999) Structural analysis of the titin gene in hypertrophic cardiomyopathy: identification of a novel disease gene. Biochem Biophys Res Commun 262:411–417. doi:10.1006/bbrc.1999.1221
17. Carmignac V, Salih MA, Quijano-Roy S et al (2007) C-terminal titin deletions cause a novel early-onset myopathy with fatal cardiomyopathy. Ann Neurol 61:340–351. doi:10.1002/ana.21089
18. Sylvius N, Tesson F (2006) Lamin A/C and cardiac diseases. Curr Opin Cardiol 21:159–165. doi:10.1097/01.hco.0000221575.33501.58
19. Karkkainen S, Helio T, Miettinen R et al (2004) A novel mutation, Ser143Pro, in the lamin A/C gene is common in Finnish patients with familial dilated cardiomyopathy. Eur Heart J 25:885–893. doi:10.1016/j.ehj.2004.01.020
20. Emery AE, Dreifuss FE (1966) Unusual type of benign x-linked muscular dystrophy. J Neurol Neurosurg Psychiatry 29:338–342
21. Bonne G, Di Barletta MR, Varnous S et al (1999) Mutations in the gene encoding lamin A/C cause autosomal dominant Emery–Dreifuss muscular dystrophy. Nat Genet 21:285–288. doi:10.1038/6799
22. Raffaele Di Barletta M, Ricci E et al (2000) Different mutations in the LMNA gene cause au-

tosomal dominant and autosomal recessive Emery–Dreifuss muscular dystrophy. Am J Hum Genet 66:1407–1412. doi:10.1086/302869
23. Brodsky GL, Muntoni F, Miocic S et al (2000) Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. Circulation 101:473–476
24. Fatkin D, MacRae C, Sasaki T et al (1999) Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. N Engl J Med 341:1715–1724. doi:10.1056/NEJM199912023412302
25. van der Kooi AJ, Bonne G, Eymard B et al (2002) Lamin A/C mutations with lipodystrophy, cardiac abnormalities, and muscular dystrophy. Neurology 59:620–623
26. Caux F, Dubosclard E, Lascols O et al (2003) A new clinical condition linked to a novel mutation in lamins A and C with generalized lipoatrophy, insulin-resistant diabetes, disseminated leukomelanodermic papules, liver steatosis, and cardiomyopathy. J Clin Endocrinol Metab 88:1006–1013
27. Sakata K, Shimizu M, Ino H et al (2005) High incidence of sudden cardiac death with conduction disturbances and atrial cardiomyopathy caused by a nonsense mutation in the STA gene. Circulation 111:3352–3358. doi:10.1161/CIRCULATIONAHA.104.527184
28. Yoshioka M, Saida K, Itagaki Y, Kamiya T (1989) Follow up study of cardiac involvement in Emery–Dreifuss muscular dystrophy. Arch Dis Child 64:713–715
29. Rees W, Schuler S, Hummel M, Hetzer R (1993) Heart transplantation in patients with muscular dystrophy associated with end-stage cardiomyopathy. J Heart Lung Transplant 12:804–807
30. Cartegni L, di Barletta MR, Barresi R et al (1997) Heart-specific localization of emerin: new insights into Emery–Dreifuss muscular dystrophy. Hum Mol Genet 6:2257–2264
31. Buckley AE, Dean J, Mahy IR (1999) Cardiac involvement in Emery Dreifuss muscular dystrophy: a case series. Heart 82:105–108
32. Murakami T, Hayashi YK, Noguchi S et al (2006) Fukutin gene mutations cause dilated cardiomyopathy with minimal muscle weakness. Ann Neurol 60:597–602. doi:10.1002/ana.20973
33. GeneTests: Medical Genetics Information Resource (1993–2010) University of Washington, Seattle. http://www.genetests.org. Accessed 8 May 2012
34. Miura K, Shirasawa H (1987) Congenital muscular dystrophy of the Fukuyama type (FCMD) with severe myocardial fibrosis. A case report with postmortem angiography. Acta Pathol Jpn 37:1823–1835
35. Osawa M, Arai Y, Ikenaka H et al (1991) Fukuyama type congenital progressive muscular dystrophy. Acta Paediatr Jpn 33:261–269
36. Groh WJ, Groh MR, Saha C et al (2008) Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. N Engl J Med 358:2688–2697. doi:10.1056/NEJMoa062800
37. von zur Muhlen F, Klass C, Kreuzer H et al (1998) Cardiac involvement in proximal myotonic myopathy. Heart 79:619–621
38. Shen EN, Madsen T (1991) Facioscapulohumeral muscular dystrophy and recurrent pacemaker lead dislodgement. Am Heart J 122:1167–1169
39. Laforet P, de Toma C, Eymard B et al (1998) Cardiac involvement in genetically confirmed facioscapulohumeral muscular dystrophy. Neurology 51:1454–1456
40. Selcen D, Muntoni F, Burton BK et al (2009) Mutation in BAG3 causes severe dominant childhood muscular dystrophy. Ann Neurol 65:83–89. doi:10.1002/ana.21553
41. Reilich P, Schoser B, Schramm N et al (2010) The p.G154S mutation of the alpha-B crystallin gene (CRYAB) causes late-onset distal myopathy. Neuromuscul Disord 20:255–259. doi:10.1016/j.nmd.2010.01.012
42. Dalakas MC, Park KY, Semino-Mora C et al (2000) Desmin myopathy, a skeletal myopathy with cardiomyopathy caused by mutations in the desmin gene. N Engl J Med 342:770–780. doi:10.1056/NEJM200003163421104
43. Li D, Tapscoft T, Gonzalez O et al (1999) Desmin mutation responsible for idiopathic dilated cardiomyopathy. Circulation 100:461–464
44. Taylor MR, Slavov D, Ku L et al (2007) Prevalence of desmin mutations in dilated cardiomyopathy. Circulation 115:1244–1251. doi:10.1161/CIRCULATIONAHA.106.646778

45. Vatta M, Mohapatra B, Jimenez S et al (2003) Mutations in Cypher/ZASP in patients with dilated cardiomyopathy and left ventricular non-compaction. J Am Coll Cardiol 42:2014–2027
46. Arimura T, Hayashi T, Terada H et al (2004) A Cypher/ZASP mutation associated with dilated cardiomyopathy alters the binding affinity to protein kinase C. J Biol Chem 279:6746–6752. doi:10.1074/jbc.M311849200
47. Selcen D, Engel AG (2005) Mutations in ZASP define a novel form of muscular dystrophy in humans. Ann Neurol 57:269–276. doi:10.1002/ana.20376
48. Hauser MA, Horrigan SK, Salmikangas P et al (2000) Myotilin is mutated in limb girdle muscular dystrophy 1A. Hum Mol Genet 9:2141–2147
49. Selcen D, Engel AG (2004) Mutations in myotilin cause myofibrillar myopathy. Neurology 62:1363–1371
50. Bagneris C, Bateman OA, Naylor CE et al (2009) Crystal structures of alpha-crystallin domain dimers of alphaB-crystallin and Hsp20. J Mol Biol 392:1242–1252. doi:10.1016/j.jmb.2009.07.069
51. Wang X, Klevitsky R, Huang W et al (2003) AlphaB-crystallin modulates protein aggregation of abnormal desmin. Circ Res 93:998–1005. doi:10.1161/01.RES.0000102401.77712.ED
52. Pilotto A, Marziliano N, Pasotti M et al (2006) alphaB-crystallin mutation in dilated cardiomyopathies: low prevalence in a consecutive series of 200 unrelated probands. Biochem Biophys Res Commun 346:1115–1117. doi:10.1016/j.bbrc.2006.05.203
53. Sacconi S, Feasson L, Antoine JC et al (2012) A novel CRYAB mutation resulting in multisystemic disease. Neuromuscul Disord 22:66–72. doi:10.1016/j.nmd.2011.07.004
54. Fitzpatrick AP, Shapiro LM, Rickards AF et al (1990) Familial restrictive cardiomyopathy with atrioventricular block and skeletal myopathy. Br Heart J 63:114–118
55. Katritsis D, Wilmshurst PT, Wendon JA et al (1991) Primary restrictive cardiomyopathy: clinical and pathologic characteristics. J Am Coll Cardiol 18:1230–1235
56. Ishiwata S, Nishiyama S, Seki A, Kojima S (1993) Restrictive cardiomyopathy with complete atrioventricular block and distal myopathy with rimmed vacuoles. Jpn Circ J 57:928–933
57. Milasin J et al (1996) A point mutation in the 54 splice site of the dystrophin gene first intron responsible for X-linked dilated cardiomyopathy. Human Molecular Genetics 5(1):73–79

# The Role of Clinical Observation: Red Flag 2 – Cardiomyopathies and Arrhythmias

4

Fulvio Camerini, Gianfranco Sinagra and Stefano Bardari

Arrhythmias and/or conduction defects can complicate some types of cardiomyopathy (CMP) and might represent a useful clue to a specific gene defect (Table 3.1). The presence of these arrhythmias can be important from a diagnostic point of view because they may be the first sign of myocardial disease, and sometimes they are associated with a more severe prognosis, as for example in *LMNA* gene mutations, in which there is a marked incidence of sudden death, even before overt myocardial dysfunction [1].

In familial CMP, cardiac arrhythmias may be associated with skeletal muscle involvement, and in these cases a careful clinical approach should be considered an important contribution toward a more definite etiological diagnosis.

## 4.1 Lamin A/C (*LMNA*)

Mutations of the gene encoding lamin A/C may be characterized by age-dependent onset of cardiac arrhythmias, which may precede the onset of dilated cardiomyopathy (DCM) and/or heart failure. In many cases asymptomatic electrocardiogram (ECG) changes in cardiac rate and rhythm observed during routine physical examination and ECG are the first evident abnormalities [2]. Cardiac arrhythmias are characterized by the presence of supraventricular paroxysmal tachycardia, atrial flutter or fibrillation, and sick sinus syndrome, and they are frequently complicated by a first- or second-degree or complete heart block [3–5], which may require pacemaker implantation [4, 5]. Taylor et al. [3] reported a high mortality, more frequent need of heart transplantation, and an increased rate of major events in *LMNA* mutation carriers compared

G. Sinagra (✉)
Cardiovascular Department,
Ospedali Riuniti and University of Trieste, Italy
email: gianfranco.sinagra@aots.sanita.fvg.it

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_4, © Springer-Verlag Italia 2013

with patients with DCM who did not carry an *LMNA* mutation. In a meta-analysis published by Van Berlo et al. [6], cardiac arrhythmias were present in 92% of patients with an *LMNA* mutation after the age of 30 years, and heart failure was present in 64% of patients after the age of 50 years, contributing to death in 12% of patients. However, the most frequent mode of death was sudden death, as reported in 46% of cases [6]. There was no difference in the risk of sudden death between patients with apparent isolated CMP and those with skeletal muscle involvement. Knowledge of the relationships between *LMNA* mutations, supraventricular arrhythmia, conduction defects and sudden death is important when considering the report by Meune et al. [7] who demonstrated the importance of early use of an implanted cardioverter–defibrillator (ICD) for the prevention of sudden death in *LMNA* mutation carriers who had preserved ejection fraction [7]. In a recent paper, Van Rijsingen et al. [8], who studied 269 *LMNA* mutation carriers, confirmed a high rate of sudden cardiac death, ventricular arrhythmias and progression to heart failure in the study group, and they identified four independent clinical and genetic factors that predict malignant ventricular arrhythmias. The four independent risk factors are: non-sustained ventricular tachycardia, left ventricular ejection fraction <45% at the first clinical contact, male sex and non-missense mutations. The authors suggested that it seems to be prudent to consider use of an ICD in a person with two or more or the four risk factors.

As mentioned in Chap. 3, associated skeletal involvement in *LMNA* mutation carriers may be variable, absent, subclinical or clinically evident (Emery–Dreifuss muscular dystrophy or limb-girdle muscular dystrophy phenotype), but it is usually mild [2].

Knowledge of these findings is important because the presence of skeletal muscle disease, supraventricular arrhythmias and conduction defects in a patient with DCM has to be considered an important predictor of an *LMNA* mutation.

## 4.2 Emerin (*EMD*)

In Emery–Dreifuss muscular dystrophy, an X-linked form of muscular dystrophy with mild and slowly progressive locomotor involvement, cardiac involvement is usually evident in the second decade of life. It is characterized by sinus node dysfunction, atrial or junctional tachyarrhythmias or bradyarrhythmias, atrial fibrillation, atrial standstill and atrioventricular (AV) block, and it is frequently treated with pacemaker implantation. Unexplained sudden death occurred in three subjects (out of 16 carriers) reported by Sakata et al. [9], but it did not occur in 13 patients treated with pacemaker implantation. In female carriers, cardiac involvement was found to be less frequent, occurring at an older age, and neuromuscular symptoms were absent. No patients showed progression toward DCM, but presumably this could occur with a more prolonged follow-up.

## 4.3 Desmin (*DES*)

Mutations in the gene encoding desmin are the cause of a wide spectrum of phenotypes of different types of CMPs (DCM, restrictive cardiomyopathy), skeletal myopathies and mixed skeletal and cardiac myopathies [10].

DCM is observed in patients with or without skeletal muscle involvement. In the series of Dalakas et al. [11], 6 of 12 patients in whom mutations were identified in the *DES* gene had cardiac conduction defects, and in five of these patients a cardiac pacemaker was implanted. In four patients, CMP preceded skeletal myopathy by a mean of 12 years (range 3–20 years), but the opposite was also observed (severe and rapidly progressive myopathy followed by CMP) [11]. In the experience of Taylor et al. [10], all six patients with a *DES* mutation had "pure" DCM with no skeletal muscle involvement, and conduction system abnormalities were present in all of the patients.

## 4.4 Alpha-Dystrobrevin (*DTNA*)

Mutations in alpha-dystrobrevin, a protein in the dystrophin-associated glycoprotein complex, have been found in some rare forms of muscular dystrophies and in patients with left ventricular non-compaction, "hypertrophic DCM" or DCM [12]. Hichida et al. [12] described a Japanese family of six members with left ventricular non-compaction, which was associated with congenital heart defects in three members of the family. In some of the patients, atrial arrhythmias (atrial fibrillation) and sudden cardiac death were observed.

## 4.5 Cardiac Sodium Channel (*SCN5A*)

In 2004, McNair et al. [13] reported a large family in which the disease showed an autosomal-dominant pattern of inheritance, and it was characterized by sinus node dysfunction and frequent atrial fibrillation that culminated in most cases in left or bi-atrial dilatation and right or biventricular dilatation and dysfunction [13]. A mutation in *SCN5A* gene was considered to be the cause of the disease. Subsequently, Olson et al. [14] described a multi-generational family, as well as other families and sporadic cases, in which DCM was typically preceded by sinus node dysfunction, atrial fibrillation and conduction block; mutations of *SCN5A* were demonstrated in these patients. It is interesting that mutations in *SCN5A* have been described previously [13] in various genetically induced rhythm disorders [1] such as progressive conduction delay (Lenegre syndrome), sick sinus syndrome and AV block, long QT, Brugada syndrome and idiopathic ventricular fibrillation [1]. In a recent survey of 289 families with DCM, McNair et al. [15] confirmed that *SCN5A* mutations are found in approximately 2% of patients with DCM, and that these patients have a peculiar phenotype characterized by an arrhythmogenic trait

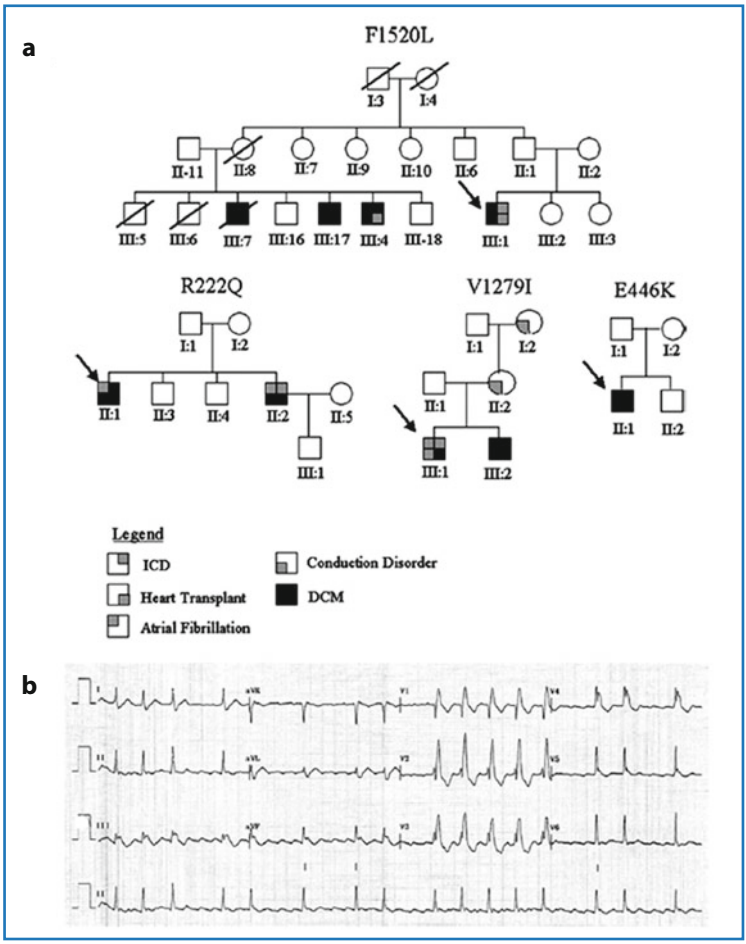



**Fig. 4.1** Dilated cardiomyopathy in sodium channel mutations. **a** Pedigrees of patients with dilated cardiomyopathy and *SCN5A* mutations. Generations are denoted by *roman numerals*. *Black arrows* show probands for each pedigree. **b** Early arrhythmia in *SCN5A* mutation carriers. Electrocardiogram of an affected individual, showing atrial fibrillation when the patient had a normal left ventricular ejection fraction (74%). Modified from McNair et al. [22], with permission

(Fig. 4.1). The most frequent arrhythmias were supraventricular arrhythmias, including sick sinus syndrome and atrial fibrillation, ventricular tachycardia and conduction disease.

At present it is not clear how mutations in the same gene may cause different clinical syndromes and what is the link between supraventricular arrhythmias and ventricular dysfunction, dilatation and heart failure. Mestroni et al. [1] reported the possibility that a shift in the activation curve of sodium channel conductance toward more positive voltages may result in reduced excitability of myocytes [16]. Moreover Olson et al. [14] suggested other pos-

sible mechanisms that are essentially based on the concept that electrical signals trigger calcium release and contraction; therefore, it seems reasonable that ion channel abnormalities are a possible cause of decreased contractile function [17], as a result of decreased intracellular calcium, with impairment of calcium-mediated myocellular force production. An interesting fact is that mutations in other cardiac ion channels may be the cause of combined electrophysiologic and contraction abnormalities. An example is Andersen–Tawil syndrome, a rare disorder characterized by ventricular arrhythmias, periodic paralysis, dysmorphic features and severe ventricular dysfunction caused by mutations in the *KCNJ2* gene [18].

In conclusion, it seems clear that different mutations of the *SCN5A* gene may cause different phenotypes (Brugada syndrome, long QT, conduction disease, lone atrial fibrillation, etc.) and that, in some cases, severe degenerative changes of the conduction system may be associated with a pattern of DCM.

## 4.6 ATP-binding Cassette, Subfamily C, Member 9 (*ABCC9*)

In a group of 323 patients affected by idiopathic DCM with heart failure and rhythm disturbances, Bienengraber et al. [19] identified two families with mutations in *ABCC9* (also known as *SUR*), which encodes the regulatory sulfonylurea receptor 2 (SUR2A) subunit of the cardiac ATP-sensitive potassium channel. The two index patients (and the father carrier of one of the patients) had a severely dilated heart and episodes of ventricular tachycardia at ECG monitoring (no details).

## 4.7 Presenilin

Presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*) are two molecules associated with familial early onset Alzheimer disease. Presenilins are also produced in the heart and are critical for cardiac development. Li et al. [20] studied the sequence variations of *PSEN1* and *PSEN2* in a group of 315 index patients affected by DCM. Those authors found a novel missense *PSEN1* mutation in one family, and a single *PSEN2* missense mutation in two other families. In all three families, the mutations were present in affected patients and segregated with DCM and heart failure. In the family with a *PSEN1* mutation, the disease was severe, whereas a milder form with a more favorable prognosis was associated with the *PSEN2* mutation in the two other families. In these patients some arrhythmias were noted: first degree AV block (two cases), atrial fibrillation, left bundle branch block and syncope. In one patient an ICD was implanted. It is interesting to note that two cases of dementia were identified within the three families.

## 4.8 Dystrophia Myotonica Protein Kinase (*DMPK*)

In myotonic muscular dystrophy type 1 (Steinert Disease), asymptomatic ECG abnormalities (prolongation of PR interval and QRS duration) and/or arrhythmias (sinus node dysfunction, sick sinus syndrome, atrial tachycardia, flutter or fibrillation, AV blocks and ventricular tachycardias) are frequent as a result of degeneration (fibrous and fatty infiltration) of the sinus node and the conduction tissue. Q waves that are not caused by myocardial infarction are common. Sudden death is common; in a group of 406 patients reported by Groh et al. [21], 81 (20%) died and in one-third of these patients death was sudden. The presence of severe ECG abnormalities and the clinical diagnosis of atrial tachyarrhythmias were the only independent predictors of sudden death [21].

## References

1. Mestroni L, Miyamoto SD, Taylor MR (2007) Genetics of dilated cardiomyopathy conduction disease. Prog Pediatr Cardiol 24:3–13
2. Fatkin D, MacRae C, Sasaki T et al (1999) Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. N Engl J Med 341:1715–1724. doi:10.1056/NEJM199912023412302
3. Taylor MR, Fain PR, Sinagra G et al (2003) Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. J Am Coll Cardiol 41:771–780
4. Hershberger RE, Hanson EL, Jakobs PM et al (2002) A novel lamin A/C mutation in a family with dilated cardiomyopathy, prominent conduction system disease, and need for permanent pacemaker implantation. Am Heart J 144:1081–1086. doi:10.1067/mhj.2002.126737
5. Kärkkäinen S, Heliö T, Miettinen R et al (2004) A novel mutation, Ser143Pro, in the lamin A/C gene is common in Finnish patients with familial dilated cardiomyopathy. Eur Heart J 25:885–893. doi:10.1016/j.ehj.2004.01.020
6. van Berlo JH, de Voogt WG, van der Kooi AJ et al (2005) Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do lamin A/C mutations portend a high risk of sudden death? J Mol Med (Berl) 83:79–83. doi:10.1007/s00109-004-0589-1
7. Meune C, Van Berlo JH, Anselme F et al (2006) Primary prevention of sudden death in patients with lamin A/C gene mutations. N Engl J Med 354:209–210. doi:10.1056/NEJMc052632
8. van Rijsingen IA, Arbustini E, Elliott PM et al (2012) Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a European cohort study. J Am Coll Cardiol 59:493–500. doi:10.1016/j.jacc.2011.08.078
9. Sakata K, Shimizu M, Ino H et al (2005) High incidence of sudden cardiac death with conduction disturbances and atrial cardiomyopathy caused by a nonsense mutation in the STA gene. Circulation 111:3352–3358. doi:10.1161/CIRCULATIONAHA.104.527184
10. Taylor MR, Slavov D, Ku L et al (2007) Prevalence of desmin mutations in dilated cardiomyopathy. Circulation 115:1244–1251. doi:10.1161/CIRCULATIONAHA.106.646778
11. Dalakas MC, Park KY, Semino-Mora C et al (2000) Desmin myopathy, a skeletal myopathy with cardiomyopathy caused by mutations in the desmin gene. N Engl J Med 342:770–780. doi:10.1056/NEJM200003163421104
12. Ichida F, Tsubata S, Bowles KR et al (2001) Novel gene mutations in patients with left ventricular noncompaction or Barth syndrome. Circulation 103:1256–1263
13. McNair WP, Ku L, Taylor MR et al (2004) SCN5A mutation associated with dilated cardiomyopathy, conduction disorder, and arrhythmia. Circulation 110:2163–2167. doi:10.1161/01.CIR.0000144458.58660.BB

14. Olson TM, Michels VV, Ballew JD et al (2005) Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. JAMA 293:447–454. doi:10.1001/jama.293.4.447
15. McNair WP, Sinagra G, Taylor MR et al (2011) SCN5A mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. J Am Coll Cardiol 57:2160–2168. doi:10.1016/j.jacc.2010.09.084
16. Groenewegen WA, Firouzi M, Bezzina CR et al (2003) A cardiac sodium channel mutation cosegregates with a rare connexin40 genotype in familial atrial standstill. Circ Res 92:14–22
17. Adler E, Fuster V (2005) SCN5A – a mechanistic link between inherited cardiomyopathies and a predisposition to arrhythmias? JAMA 293:491–493. doi:10.1001/jama.293.4.491
18. Schoonderwoerd BA, Wiesfeld AC, Wilde AA et al (2006) A family with Andersen–Tawil syndrome and dilated cardiomyopathy. Heart Rhythm 3:1346–1350. doi:10.1016/j.hrthm.2006.07.021
19. Bienengraeber M, Olson TM, Selivanov VA et al (2004) ABCC9 mutations identified in human dilated cardiomyopathy disrupt catalytic KATP channel gating. Nat Genet 36:382–387. doi:10.1038/ng1329
20. Li D, Parks SB, Kushner JD et al (2006) Mutations of presenilin genes in dilated cardiomyopathy and heart failure. Am J Hum Genet 79:1030–1039. doi:10.1086/509900
21. Groh WJ, Groh MR, Saha C et al (2008) Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. N Engl J Med 358:2688–2697. doi:10.1056/NEJMoa062800
22. McNair WP, Sinagra G, Taylor MR et al (2011) SCN5A mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. J Am Coll Cardiol;57:2160–2168

# 5 The Role of Clinical Observation: Red Flag 3 – Cardiomyopathies, Wolff–Parkinson–White Syndrome and Other Electrocardiogram Abnormalities

Gianfranco Sinagra, Fulvio Camerini, Andrea Di Lenarda and Michele Moretti

## 5.1 Wolff–Parkinson–White Syndrome and Short PR

In patients with a hypertrophic cardiomyopathy (HCM) phenotype, study of the electrocardiogram (ECG) can sometimes suggest a specific diagnosis (Table 5.1). For example, an ECG pattern of ventricular pre-excitation can be found in storage diseases, such as those characterized by abnormalities of muscle glycogen.

In Danon disease, abnormal storage is caused by defects in *LAMP2* (lysosome associated membrane protein 2). In this X-linked disease, severe concentric left ventricular hypertrophy is usually present in young men, and characterized by exceptionally high voltages of the QRS complex, associated with a pattern of ventricular pre-excitation in the ECG [1] (Fig. 5.1). Pre-excitation (observed by many authors [2–4]) associated with severe left ventricular hypertrophy and high voltage in the ECG was found in six of seven patients with *LAMP2* mutations [4]. The presence of this pattern in a patient with a clinical diagnosis of HCM is highly suggestive of Danon disease.

Another form of cardiac hypertrophy that is not caused by sarcomere protein gene defects is a result of a genetic mutation in *PRKAG2*, encoding the regulatory γ subunit of AMP-activated protein kinase. In this condition, insidious glycogen accumulation in the myocardium can result in myocardial hypertrophy, which is probably secondary to glycogen-filled vacuoles. Also, left ventricular hypertrophy can be associated with an ECG pattern of ventricular pre-excitation in this disease (9 of 32 patients observed by Arad et al. [4]). However, a review of the literature indicates that *PRKAG2* gene mutations can

G. Sinagra (✉)
Cardiovascular Department,
Ospedali Riuniti and University of Trieste, Italy
email: gianfranco.sinagra@aots.sanita.fvg.it

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_5, © Springer-Verlag Italia 2013

**Table 5.1** Cardiomyopathies associated with Wolff–Parkinson–White syndrome or short PR

| Disease/syndrome | Type of CMP |
|---|---|
| Danon disease | HCM, DCM |
| *PRKAG2* gene mutation | HCM |
| Pompe disease | HCM |
| Fabry disease | HCM |
| Duchenne/Becker muscular dystrophy | DCM |
| MELAS syndrome | HCM, DCM |
| Kearns–Sayre syndrome | DCM |
| LHON | ? |
| Leigh syndrome | HCM, DCM |
| MERRF syndrome | HCM, DCM |
| Oncocytic CMP | HCM |

*CMP,* cardiomyopathy; *DCM,* dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy; *LHON,* Leber's hereditary optic neuropathy; *MELAS,* mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; *MERRF*, myoclonic epilepsy with ragged red fibers

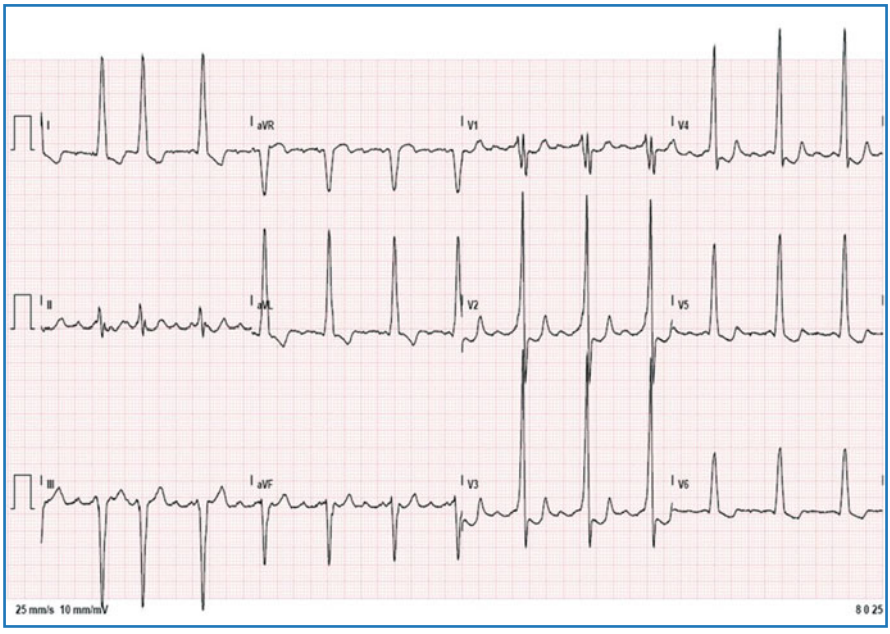



**Fig. 5.1** Electrocardiogram of a 30-year-old man with Danon disease. The electrocardiogram shows atrial flutter, right bundle branch block, and very high voltage of R waves in lead DI, aVL and precordial left ventricular leads. Note the delta wave, which is particularly evident in V3 (Courtesy of Dr Daniela Miani, Department of Cardiovascular Sciences, S. Maria della Misericordia Hospital, Udine, Italy)

cause a spectrum of phenotypic patterns ranging from apparently "isolated" HCM to HCM with pre-excitation [5] (sometimes with a marked propensity toward early dilatation of the ventricle). Moreover, Gollob et al. [6] reported a few cases of a novel *PRKAG2* mutation causing Wolff–Parkinson–White (WPW) syndrome associated with conduction defects with onset in childhood, but with absent cardiac hypertrophy. As for the ECG patterns, various terminologies have been used, from "extremely short PR" [4], to pre-excitation [4, 5] and WPW with delta wave [2].

The mechanism of pre-excitation appears to be the result of an interruption of the annulus fibrosus by glycogen-filled myocytes, causing a bypass of the atrioventricular (AV) node and ventricular pre-excitation. In some cases, electrophysiological studies have shown accessory AV connections [4] treated with ablation [4, 5]. A similar pattern has been described in Pompe disease (a hereditary deficiency of alpha-1,4-glucosidase, which is lysosomal acid), in Fabry disease (deficiency of alpha-galactosidase) and in "oncocytic" cardiomyopathy (CMP), a rare neonatal CMP characterized by refractory tachyarrhythmias and by the presence in the myocardium of islands of large cells with vacuolated, granular or foamy cytoplasm, resembling histiocytes [7]. The mechanisms causing WPW syndrome appear to be confirmed by the experimental data of Arad et al. [8] who developed transgenic mice overexpressing mutant *PRKAG2*. These mice developed massive left ventricular hypertrophy with ventricular pre-excitation and sinus node dysfunction. Cardiac histology revealed that the annulus fibrosus was disrupted by glycogen-filled myocytes. The possibility that the pathogenesis of ventricular pre-excitation might have an alternative explanation is suggested by the observations of Gollob et al. [6] who described patients with mutations of the *PRKAG2* gene and familial WPW syndrome, but without ventricular hypertrophy. In those cases, the investigators hypothesized that a mutation could cause an abnormality of AV septation during cardiogenesis, leading "to the presence of accessory atrio-ventricular fibers responsible for ventricular pre-excitation" [6].

In addition, WPW pattern or a short PR can be found in other disease scenarios such as DCM complicating Duchenne muscular dystrophy [9], and in mitochondrial diseases possibly with similar anatomical substrates.

## 5.2 Q Waves

The presence of abnormal Q waves is usually considered an important indicator of coronary artery disease. However, abnormal (in depth and/or duration) Q waves may be present in different types of CMP and are sometimes useful for an early diagnosis (Table 5.2). Abnormal Q waves have been observed in HCM (Fig. 5.2), in leads DI, aVL and anterior precordial leads and/or in DIII and aVF, although these have occurred in a minority of cases (9% in a series of 200 patients [10], 8–9% in a group of 56 patients [11], and 18.1% of 110 patients [12]). The explanation for these abnormalities in this disease may be

**Table 5.2** Cardiomyopathies and pathological Q waves in the electrocardiogram

| Disease/syndrome | Type of CMP |
|---|---|
| Myotonic dystrophy type 1 or Steinert disease | DCM |
| Duchenne/Becker muscular dystrophy | DCM |
| Sarcoglycan mutation (elevated R waves in V1) | DCM |
| Friedrich ataxia | HCM, DCM |
| Left ventricular aneurysm | |
| Sarcoidosis | |
| HCM | |

Characteristics of Q waves: those in hypertrophic cardiomyopathy are usually "narrow and clean", while those associated with infiltrative disorders and myocyte death may be similar to necrotic Q waves. *CMP*, cardiomyopathy; *DCM*, dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy.

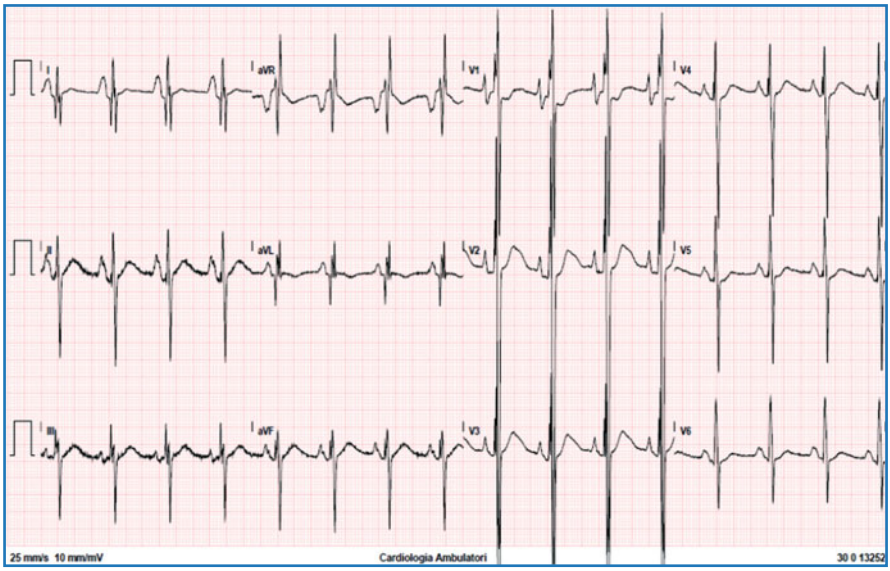



**Fig. 5.2** Electrocardiogram of a 40-year-old woman with hypertrophic cardiomyopathy. The electrocardiogram shows sinus rhythm, biatrial dilatation, right ventricular conduction delay and biventricular hypertrophy. Note the high voltage and narrow Q waves in lead I and aVL

an abnormal direction of the initial QRS vector resulting from increased electrical forces produced by the pathological hypertrophy or, in some cases, a localized loss of electrical forces because of transmural fibrosis [13].

Abnormal Q waves have been observed in other types of CMP in addition to DCM (a few cases, usually associated with left ventricular aneurysm), and in DCM with a defined etiology, such as in cardiac sarcoidosis [14–16]. Finally, frequent abnormalities of Q waves classified as "prominent" [9] or

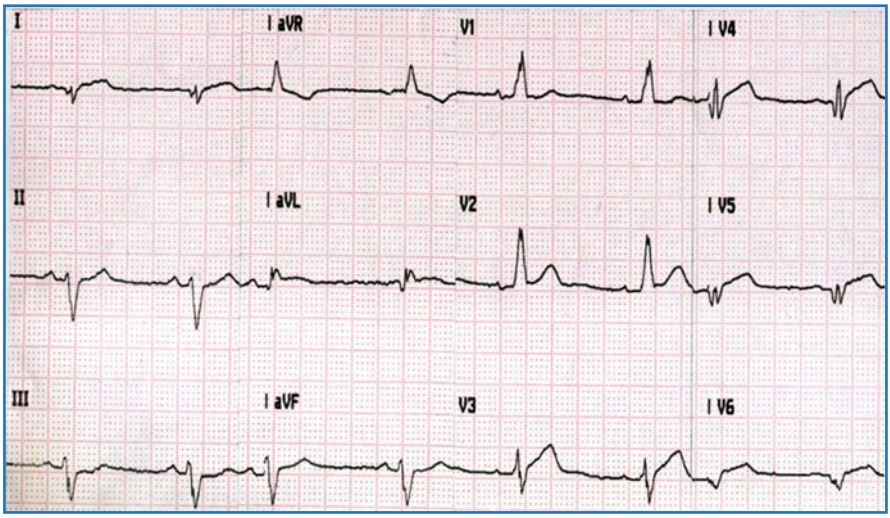



**Fig. 5.3** Electrocardiogram of a patient with Becker muscular dystrophy and dilated cardiomyopathy. The electrocardiogram shows sinus bradycardia, P waves suggestive of left atrial enlargement, right bundle branch block, and "necrotic" Q waves in DI, aVL, V4–V6 with prominent R waves in V1–V2 suggestive of lateral and posterior necrosis

deep [17] or abnormal [18] have been described in CMPs resulting from Duchenne muscular dystrophy or Becker muscular dystrophy (Fig. 5.3), as well as CMP in Friedrich ataxia.

## 5.3 T Waves in Apical Hypertrophic Cardiomyopathy

A specific variant of HCM is apical HCM in which the hypertrophy is confined to the cardiac apex. The apical variant is present in 3–14% of patients with HCM [19], with the exception of Japanese patients who show a higher prevalence of this variant [20].

The ECG in apical HCM is characterized by the presence of negative T waves in precordial leads, usually V4–V6, and in 50% of cases negative T waves are "giant" [19] (giant T wave negativity is defined as a voltage of negative T waves ≥1 mV = ≥10 mm) (Fig. 5.4 and 5.5).

In patient cohorts with apical HCM, the percentage of positive genotypes varies between 13% [19] and 47% [21]. Mutations in the myosin heavy chain 7 (*MYH7*) and myosin binding protein C (*MYBPC3*) sarcomere genes are those most frequently found [19], but some apparently rare mutations such as alpha-actin (*ACTC*) [21] can also be observed. According to Gruner et al. [19], who studied 61 patients with apical HCM (as part of a population of 429 patients affected by HCM who underwent genetic testing), there is no significant genotype–phenotype correlation in this form of CMP.

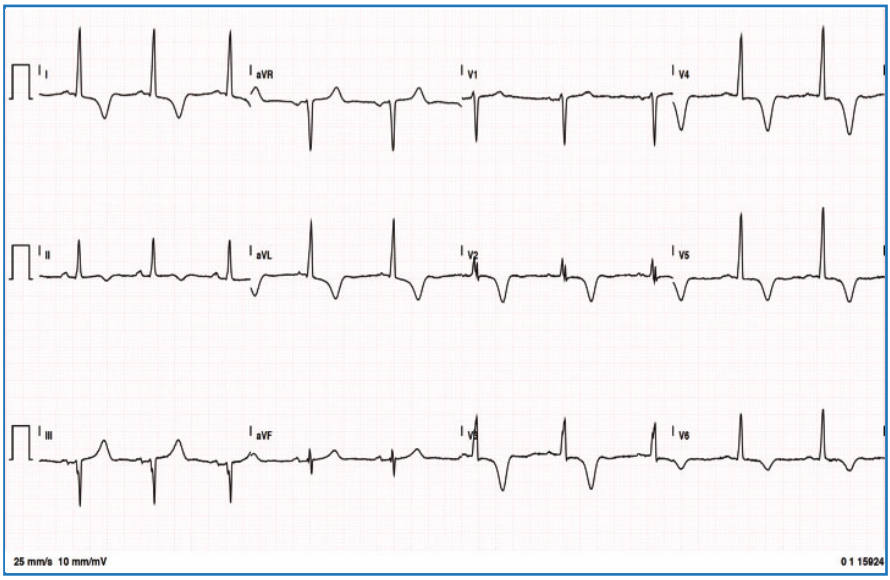



**Fig. 5.4** Electrocardiogram of a patient with apical hypertrophic cardiomyopathy. The electrocardiogram shows sinus rhythm. Note the negative deep symmetric negative T waves in V2–V6

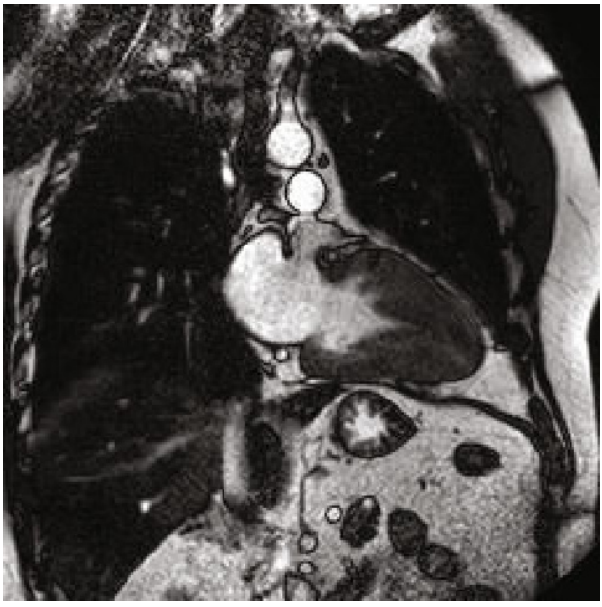


**Fig. 5.5** Magnetic resonance imaging: steady state free precession image of a patient with apical hypertropic cardiomyopathy; two chamber views

## References


1. Taylor MR, Ku L, Slavov D et al (2007) Danon disease presenting with dilated cardiomyopathy and a complex phenotype. J Hum Genet 52:830–835. doi:10.1007/s10038-007-0184-8
2. Balmer C, Ballhausen D, Bosshard NU et al (2005) Familial X-linked cardiomyopathy (Danon disease): diagnostic confirmation by mutation analysis of the LAMP2 gene. Eur J Pediatr 164:509–514. doi:10.1007/s00431-005-1678-z
3. Charron P, Villard E, Sebillon P et al (2004) Danon's disease as a cause of hypertrophic cardiomyopathy: a systematic survey. Heart 90:842–846. doi:10.1136/hrt.2003.029504
4. Arad M, Maron BJ, Gorham JM et al (2005) Glycogen storage diseases presenting as hypertrophic cardiomyopathy. N Engl J Med 352:362–372. doi:10.1056/NEJMoa033349
5. Blair E, Redwood C, Ashrafian H et al (2001) Mutations in the gamma(2) subunit of AMP-activated protein kinase cause familial hypertrophic cardiomyopathy: evidence for the central role of energy compromise in disease pathogenesis. Hum Mol Genet 10:1215–1220
6. Gollob MH, Seger JJ, Gollob TN et al (2001) Novel PRKAG2 mutation responsible for the genetic syndrome of ventricular preexcitation and conduction system disease with childhood onset and absence of cardiac hypertrophy. Circulation 104:3030–3033
7. Bird LM, Krous HF, Eichenfield LF et al (1994) Female infant with oncocytic cardiomyopathy and microphthalmia with linear skin defects (MLS): a clue to the pathogenesis of oncocytic cardiomyopathy? Am J Med Genet 53:141–148. doi:10.1002/ajmg.1320530205
8. Arad M, Moskowitz IP, Patel VV et al (2003) Transgenic mice overexpressing mutant PRKAG2 define the cause of Wolff–Parkinson–White syndrome in glycogen storage cardiomyopathy. Circulation 107:2850–2856. doi:10.1161/01.CIR.0000075270.13497.2B
9. Thrush PT, Allen HD, Viollet L, Mendell JR (2009) Re-examination of the electrocardiogram in boys with Duchenne muscular dystrophy and correlation with its dilated cardiomyopathy. Am J Cardiol 103:262–265. doi:10.1016/j.amjcard.2008.08.064
10. Ohmoto-Sekine Y, Suzuki J et al (2007) Gender-specific clinical characteristics of deep Q waves in hypertrophic cardiomyopathy. Gend Med 4:274–283
11. Satoh M, Takahashi M, Sakamoto T et al (1999) Structural analysis of the titin gene in hypertrophic cardiomyopathy: identification of a novel disease gene. Biochem Biophys Res Commun 262:411–417. doi:10.1006/bbrc.1999.1221
12. Furuki M, Kawai H, Onishi T, Hirata K (2009) Value of convex-type ST-segment elevation and abnormal Q waves for electrocardiographic-based identification of left ventricular remodeling in hypertrophic cardiomyopathy. Kobe J Med Sci 55:E16–29
13. Koga Y, Yamaga A, Hiyamuta K et al (2004) Mechanisms of abnormal Q waves in hypertrophic cardiomyopathy assessed by intracoronary electrocardiography. J Cardiovasc Electrophysiol 15:1402–1408. doi:10.1046/j.1540-8167.2004.04314.x
14. Homsi M, Alsayed L, Safadi B et al (2009) Fragmented QRS complexes on 12-lead ECG: a marker of cardiac sarcoidosis as detected by gadolinium cardiac magnetic resonance imaging. Ann Noninvasive Electrocardiol 14:319–326. doi:10.1111/j.1542-474X.2009.00320.x
15. Mestroni L, Morgera T, Miani D et al (1994) Idiopathic left ventricular aneurysm: a clinical and pathological study of a new entity in the spectrum of cardiomyopathies. Postgrad Med J 70 Suppl 1:S13–20
16. Xia S, Wu B, Zhang X, Hu X (2009) Left ventricular aneurysm in patients with idiopathic dilated cardiomyopathy: clinical analysis of six cases. Neth Heart J 17:475–480
17. Takami Y, Takeshima Y, Awano H et al (2008) High incidence of electrocardiogram abnormalities in young patients with Duchenne muscular dystrophy. Pediatr Neurol 39:399–403. doi:10.1016/j.pediatrneurol.2008.08.006
18. Santos MA, Costa Fde A, Travessa AF et al (2010) [Duchenne muscular dystrophy: electrocardiographic analysis of 131 patients]. Arq Bras Cardiol 94:620–624
19. Gruner C, Care M, Siminovitch K et al (2011) Sarcomere protein gene mutations in patients with apical hypertrophic cardiomyopathy. Circ Cardiovasc Genet 4:288–295. doi:10.1161/CIRCGENETICS.110.958835

20. Kitaoka H, Doi Y, Casey SA et al (2003) Comparison of prevalence of apical hypertrophic cardiomyopathy in Japan and the United States. Am J Cardiol 92:1183–1186
21. Arad M, Penas-Lado M, Monserrat L et al (2005) Gene mutations in apical hypertrophic cardiomyopathy. Circulation 112:2805–2811. doi:10.1161/CIRCULATIONAHA.105.547448

# The Role of Clinical Observation: Red Flag 4 – Cardiomyopathies and Sensorineural Hearing Loss

6

Fulvio Camerini and Gianfranco Sinagra

Early onset hearing loss is frequently of genetic origin and usually caused by cochlear hair cell and/or neuronal malfunction. Associated heart and hearing abnormalities may be found in different syndromes, frequently in association with diseases of other organs, but cardio-auditory diseases [1] in the absence of other organ involvement are rare. A typical example is Jervell and Lange–Nielsen syndrome, characterized by congenital deafness, long QT and cardiac arrhythmias, but "normal" cardiac structure. In 2000, Schönberger et al. [1] reported two families with many members affected by sensorineural hearing loss, which occurred mostly in early adulthood and preceded the appearance of dilated cardiomyopathy (DCM), which usually occurred in the fourth decade [1]. The cardiac involvement in these patients was severe and was the cause of death or it necessitated a heart transplant, in all affected patients. Schönberger et al. [1] considered the gene encoding epicardin (a transcription factor expressed in the myocardium and the cochlea) to be a candidate gene, but a specific mutation was not identified. In a later study, Schönberger et al. [2] found a deletion in the *EYA4* gene, which was present in all affected family members and absent in 300 control chromosomes. In contrast to the sarcomeric/cytoskeletal genes involved in DCM that encode structural proteins, *EYA4* encodes a transcriptional coactivator.

A similar phenotype with sensorineural hearing loss, progressive and late onset, associated with HCM and usually characterized by mild or absent symptoms can be caused by a mutation of the gene encoding myosin 6 (*MYO6*), one of the so-called "unconventional" myosin genes encoding a protein responsible for actin-based molecular-motor driven movement of intracellular vesicles and for organelle transport [3]. Finally, hearing loss or deafness is frequently observed in complex syndromes caused by mitochondrial defects (see Chap. 9).

G. Sinagra (✉)
Cardiovascular Department,
Ospedali Riuniti and University of Trieste, Italy
email: gianfranco.sinagra@aots.sanita.fvg.it

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_6, © Springer-Verlag Italia 2013

## References

1. Schönberger J, Levy H, Grunig E et al (2000) Dilated cardiomyopathy and sensorineural hearing loss: a heritable syndrome that maps to 6q23-24. Circulation 101:1812–1818
2. Schönberger J, Wang L, Shin JT et al (2005) Mutation in the transcriptional coactivator EYA4 causes dilated cardiomyopathy and sensorineural hearing loss. Nat Genet 37:418–422. doi:10.1038/ng1527
3. Mohiddin SA, Ahmed ZM, Griffith AJ et al (2004) Novel association of hypertrophic cardiomyopathy, sensorineural deafness, and a mutation in unconventional myosin VI (MYO6). J Med Genet 41:309–314

# 7 The Role of Clinical Observation: Red Flag 5 – Right Ventricular Involvement, Arrhythmogenic Right Ventricular Cardiomyopathy and Associated Phenotypes

Bruno Pinamonti, Fulvio Camerini, Enrico Fabris and Gianfranco Sinagra

Studies relating to arrhythmogenic right ventricular cardiomyopathy (ARVC) have demonstrated that mutations in genes encoding different components of the desmosome, a major cell-adhesion structure, are the main genetic cause of the disease, which is histologically characterized by right ventricular myocellular atrophy with characteristic fibro-fatty replacement [1]. From a structural point of view, as observed by imaging techniques such as echocardiography (Fig. 7.1) and cardiac magnetic resonance imaging, the pathological hallmark of the disease is a thin right ventricle usually with bulges and sacculations, which are typically located in the "triangle of dysplasia" (apex, outflow tract and subtricuspid areas). Symptomatic or asymptomatic arrhythmias of right ventricular origin are usually present, and in more advanced cases a severe right ventricular enlargement with systolic dysfunction can be present.

In ARVC, left ventricular involvement can be present and is sometimes clinically relevant [2] (Figs. 7.2, 7.3, 7.4, 7.5 and 7.6). Long-term follow-up studies have demonstrated that some patients with initially localized right ventricular involvement may progressively develop more extensive right ventricular disease and later left ventricular involvement [2, 3].

In a study correlating clinical and postmortem (or post-transplantation) data, Corrado et al. [4] showed that ARVC is a progressive disease of heart muscle that can be characterized initially by a "silent" or "overt" right ventricular disease, which might extend to the left ventricle later. Left ventricular involvement may be progressive and lead to an end-stage biventricular cardiomyopathy, mimicking dilated cardiomyopathy, and leading to congestive heart failure and sometimes heart transplantation (Fig. 7.5). Histological or macroscopic left ventricular involvement was found to be frequent in the

B. Pinamonti (✉)
Cardiovascular Department,
Ospedali Riuniti and University of Trieste, Italy
email: bruno.pinamonti@gmail.com

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_7, © Springer-Verlag Italia 2013

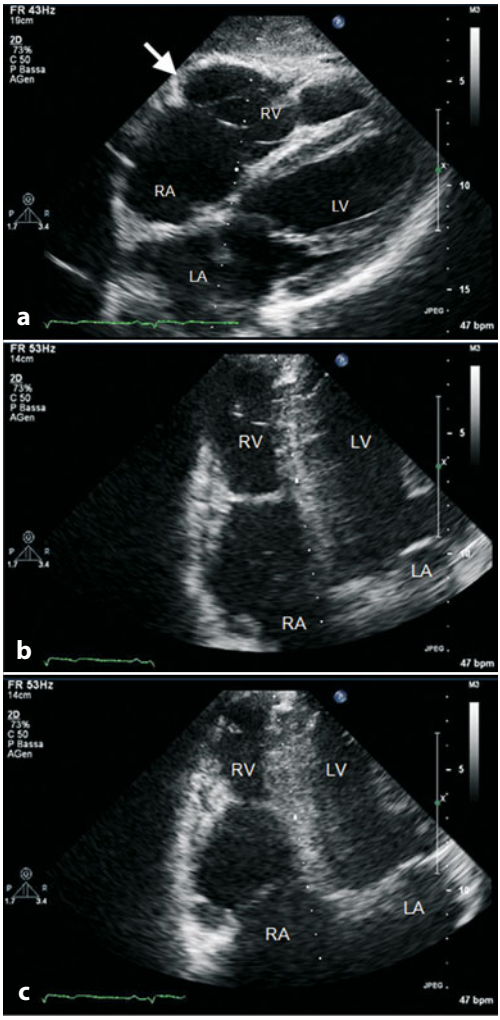



**Fig. 7.1** Two-dimensional echocardiogram in a patient with familial arrhythmogenic right ventricular cardiomyopathy. The disease is localized in the right ventricle. **a** Subcostal four-chamber view, end-diastolic frame. A wall aneurysm is evident in a subtricuspid area (*arrow*). **b,c** Apical four-chamber view, end-diastolic and end-systolic frames, respectively. A severe right ventricular dysfunction is evident (fractional area contraction of RV: 22%). *LA,* left atrium, *LV,* left ventricle, *RA,* right atrium, *RV,* right ventricle

series reported by Corrado et al. [4]. In that study of 42 hearts (from autopsies, or explanted hearts), left ventricular involvement was characterized by areas of transmural and/or subepicardial fibro-fatty replacement. The lesions extended from the outer layers to the inner layers of the left ventricular wall, a pattern similar to that observed in the right ventricle. Interestingly, the left ventricular involvement was age dependent and was more common in patients with a long-standing clinical history of the disease. Diagnosis of the disease in patients with ARVC and biventricular involvement may be difficult because these patients might show symptoms that are similar to those in patients affected by dilated cardiomyopathy (DCM). The concept is that ARVC is a disease with a potential progressive evolution from an early concealed phase to a second phase characterized by more or less severe electrical disorders, and to a third phase with

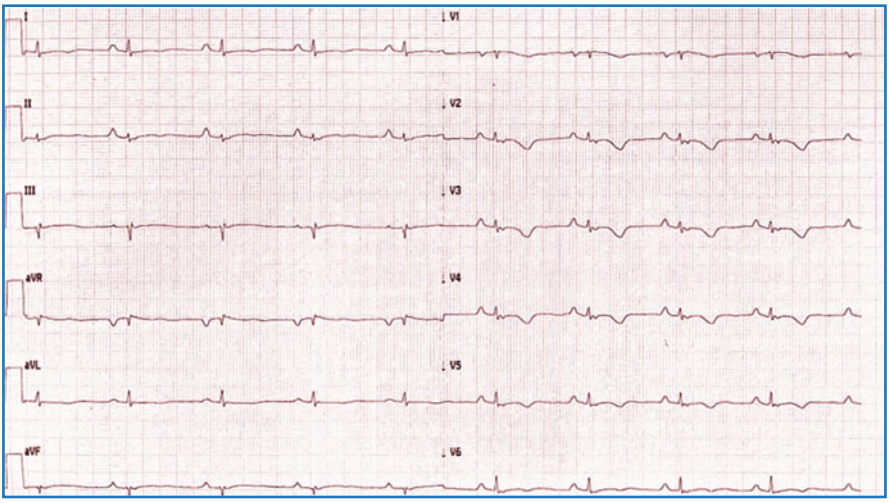



**Fig. 7.2** Electrocardiogram of a patient with arrhythmogenic right ventricular cardiomyopathy with left ventricular involvement. Sinus rhythm and abnormalities of P waves; inverted T waves in right precordial leads; negative T waves from V4 to V6, suggestive of left ventricular involvement

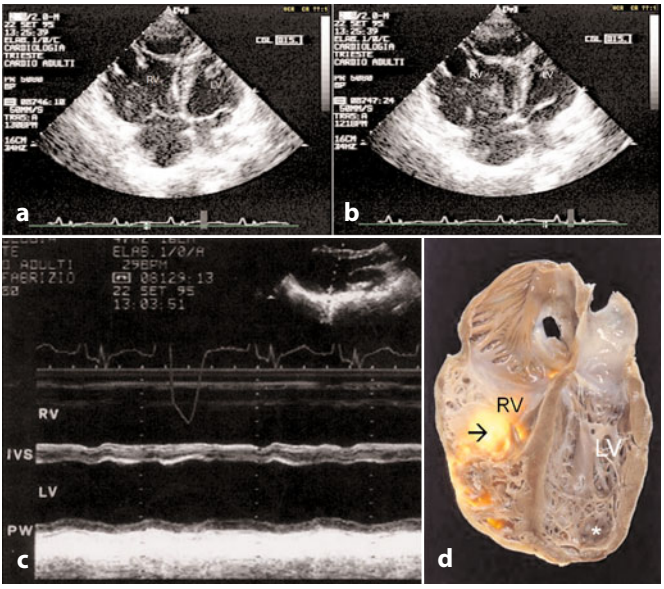



**Fig. 7.3** Arrhythmogenic right ventricular cardiomyopathy with left ventricular involvement. The patient died in refractory heart failure. End-systolic frame (**a**) and end-diastolic frame (**b**) of two-dimensional echocardiography, apical four-chamber view oriented to the right ventricle (*RV*). The RV is severely dilated and diffusely hypokinetic with multiple akinetic bulges of the free wall; systolic function was severely depressed. The left ventricle (*LV*) is not enlarged, but diffusely hypokinetic. **c** M-mode echocardiogram (parasternal approach) at the level of the ventricles. The RV is enlarged (end-diastolic diameter 45 mm). The LV is not enlarged (end-diastolic diameter 55 mm), but severely hypokinetic (fractional shortening 18%). **d** Severe RV dilatation with fatty infiltration shown by transillumination (*arrow*). In the LV, there is a small apical aneurysm (*asterisk*). *IVS*, interventricular septum, *PW*, posterior wall

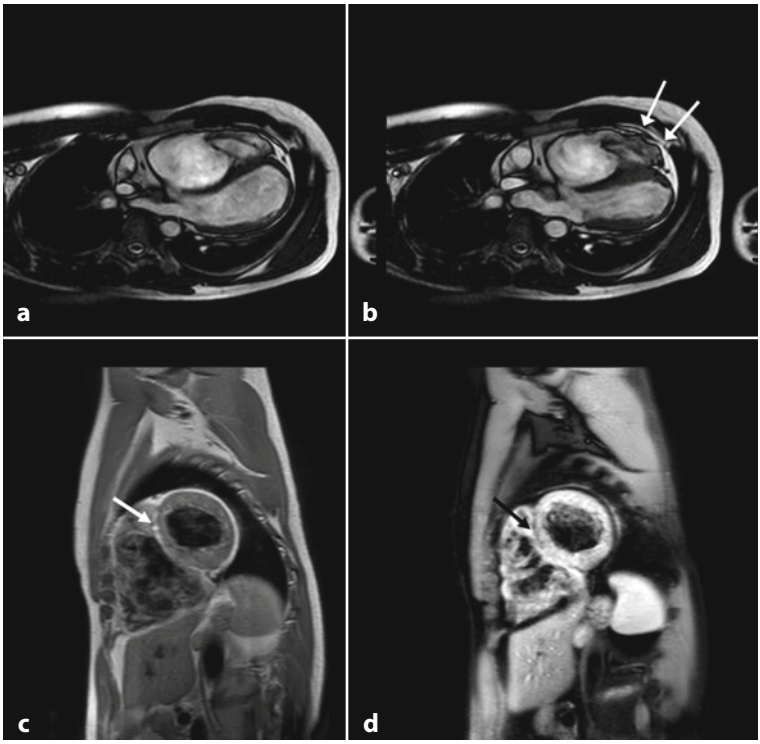



**Fig. 7.4** Magnetic resonance images of arrhythmogenic right ventricular cardiomyopathy in a 40-year-old patient. End-diastolic (**a**) and systolic (**b**) still-frames obtained from four-chamber stack steady-state free precession cine-imaging, showing systolic bulging of multiple small aneurysms (*arrows*) of the right ventricle (*RV*) free wall in the apex and subtricuspid area. The volume calculations showed RV dilatation and severe systolic dysfunction. T1 without (**c**) and with (**d**) fat saturation showing fatty infiltration of the anterior interventricular septum (*arrow*). The fatty infiltration appears to be hyperintense in T1, and dark in the fat saturation images

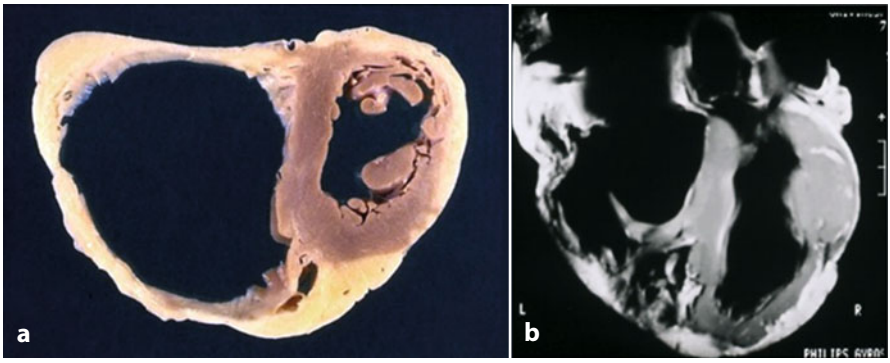



**Fig. 7.5** Post-explantation findings in a patient with arrhythmogenic right ventricular cardiomyopathy and left ventricular involvement. A basal transversal section (**a**) and a longitudinal section (**b**). Note the presence of a massive fatty substitution of the right ventricle, and also of the left ventricular free wall and posterior wall

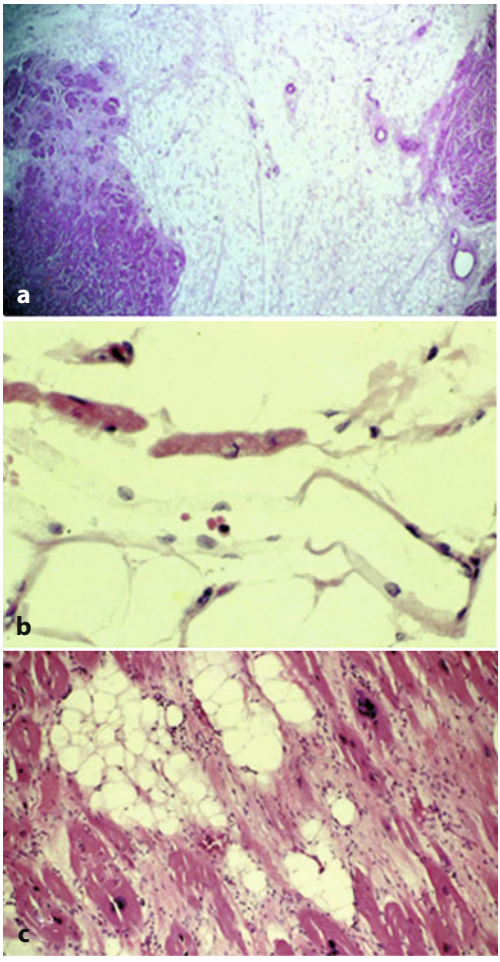



**Fig. 7.6** Arrhythmogenic right ventricular cardiomyopathy with left ventricular involvement. **a** Interventricular septum with extensive fatty substitution (×2.5). **b** Apex: massive presence of fat with few atrophic myocells (×63). **c** Fatty substitution in the posterior wall of the left ventricle. The myocells are hypertrophic and hypotrophic (×20). H&E

more severe right ventricular disease and left ventricular involvement.

The data of Corrado et al. [4] were essentially based on clinical and pathological observations and long-term follow-up, and the diagnosis of left ventricular involvement was essentially based on an echocardiogram. More recently, the extensive use of cardiac magnetic resonance as a "surrogate for anatomic examination" [5] has demonstrated that involvement of the left ventricle is more common than initially thought. In the study by Sen-Chowdhry et al. [5] of a group of 200 patients affected by ARVC, 168 (84%) had cardiac magnetic resonance evidence of left ventricular involvement; late enhancement was the most frequent (92%) indicator of the left ventricular myocardial abnormality, while the occurrence of myocardial fat (43%), left ventricular dilatation (40%) and reduced left ventricular ejection fraction (18%) was less frequent. These findings suggest that left ventricular involvement is a common

phenomenon in ARVC, not just a late complication, and that it might also occur (40% of the cohort) in the presence of preserved right ventricular systolic function.

## 7.1 Patterns of ARVC

The high frequency of left ventricular involvement, the possible, although rare, predominance of left ventricular phenotype, the timing of its involvement, and the common origin connected to desmosomal gene mutations, all suggest that ARVC is not a unique entity but a disease characterized by three patterns of disease expression: the classic (39%), the left dominant (5%) and the biventricular forms (56%) [5]. Although it is widely accepted, the term ARVC is inadequate to express the complexity of the disease, and for these reasons Sen-Chowdhry et al. [5] have suggested the term "arrhythmogenic cardiomyopathy" to better express the multiple phenotypes.

If we consider the natural history and clinical features in the advanced phases of ARVC, all three forms of "arrhythmogenic cardiomyopathy" may be confused with DCMs. However, some criteria are thought to be helpful in the differential diagnosis. Within the "classic" subgroup of ARVC, an increased right ventricle to left ventricle volume ratio, a more severely affected right ventricle, and the evolution of the disease with a progressive late involvement of the left ventricle might help distinguish the disease from DCM.

The "left ventricular dominant" forms are rare, but well documented in the literature [6, 7]. From a clinical point of view, the following clinical observations might help in the diagnosis [5]:

1. Presence in the electrocardiogram of negative T waves in (infero)-lateral leads
2. Extensive left ventricular late enhancement
3. Arrhythmias of left ventricular or biventricular origin
4. Isolated left ventricular dilatation or dysfunction
5. Right ventricle to left ventricle volume <1
6. Presence of wall motion abnormalities or aneurysms in the right ventricle
7. Family history of ARVC

Finally, the "biventricular forms" are characterized by a combination of "classic" features and left ventricle features (with different degree of severity) [5].

This classification is probably rigid and there are superimpositions and overlaps between different forms of ARVC, but it seems to be useful for a better understanding of the complexity of the disease.

## 7.2 Gene Mutations Associated with ARVC

ARVC has been associated with mutations of genes encoding proteins of the desmosomes [1], which are structures responsible for cell–cell junctions in

myocardial and epithelial cells. Desmosomes, together with gap and adherence junctions, play an important role in mechanical and electrical stability of the cells, as well as in cell signaling, proliferation and differentiation (see Glossary). Mutations in genes coding for proteins of the desmosomes have been identified, although in a systematic study of 156 patients Sen-Chowdhry et al. [5] could identify mutations of desmosomal genes only in 39 subjects (about 30% of cases). A comparison between groups of subjects who were positive or negative for a desmosomal gene mutation and between carriers of mutations in the three desmosomal genes (encoding plakophilin 2, desmoglein-2 and desmoplakin) did not show significant differences in the observed phenotype between the different groups, with one exception, i.e., carriers of the desmoplakin mutations had echocardiographic, cardiac magnetic resonance and electrocardiographic signs indicating a more severe involvement of the left ventricle.

A study of three families from Ecuador reported a mutation in the gene encoding desmoplakin, causing a syndrome characterized by palmoplantar hyperkeratosis, woolly hair and "dilated left ventricular cardiomyopathy" (Carvajal syndrome) [8, 9]. Mutations in the desmoplakin gene may cause a typical ARVC as a part of a syndrome that is characterized by woolly hair and skin features localized in the extremities, with vesicular lesions histologically similar to pemphigus foliaceus (Naxos-like syndromes) [10]. Indeed, this phenotype resembles the true Naxos disease, which is characterized by autosomal-recessive ARVC associated with palmoplantar keratoderma and woolly hair, and is caused by a deletion in the desmosomal gene encoding plakoglobin [11–13].

Last, in a group of 100 unrelated patients, all affected by idiopathic DCM, Elliot et al. [14] found three missense mutations in the gene encoding plakophilin 2, and two novel mutations in the gene encoding desmoplakin. An autopsy performed in one of the patients showed the presence of biventricular fibro-fatty infiltration. It was concluded that mutations of genes encoding desmosomal proteins might contribute to the pathogenesis of DCM.

It should also be noted that mutations of the following non-desmosomal genes have been implicated in the development of some forms of ARVC: the *TGFB3* gene, which encodes transforming growth factor β3 [15], and the *TMEM43* gene, which encodes transmembrane protein 43. *TMEM43* was identified in a genetically isolated population and the disease is characterized by high lethality, male preponderance, fibro-fatty replacement of the myocardium, and heart failure as a late manifestation [16]. There are some potential connections between these genes and the mechanisms of cell–cell adhesion because the *TGFB3* gene encodes a cytokine that stimulates fibrosis and modulates cell adhesion [17]. Moreover *TGFB3* modulates expression of genes encoding desmosomal proteins [18]. As for the *TMEM43* gene, its role in the mechanisms of ARVC is not clear, but it is important to note that this gene contains a response element for adipogenic transcription factor, and this might explain (at least partially) the fibro-fatty replacement of the myocardium.

Mutations in the *RYR2* gene, which encodes ryanodine receptor 2, important in regulatory mechanisms of calcium handling, have been reported as a cause of polymorphic ventricular tachycardia [19–22]. In four families, different mutations of this gene have been described as the cause of ARVC (ARVC 2) [23] and of a more extended spectrum of clinical phenotypes characterized by polymorphic ventricular tachycardia, and also sino-atrial node and atrioventricluar node dysfunction, atrial fibrillation, atrial standstill and DCM [24]. In the families reported by Tiso et al. [23] and Bauce et al. [25], there was a high prevalence of polymorphic ventricular arrhythmias and sudden death during exercise. The involvement of the right ventricle was segmental and mostly confined to the apex of the right ventricle.

Finally, mutations in the gene encoding the giant protein titin (*TTN*) have recently been associated with ARVC, a finding that expands the origin of the disease beyond desmosomal proteins. In these cases, a structural impairment of titin, which connects to the transitional junction at intercalated disks, was thought to be a likely cause of ARVC, and it constitutes a novel mechanism underlying the occurrence of myocardial remodeling and sudden cardiac death [26].

## References

1. Corrado D, Thiene G (2006) Arrhythmogenic right ventricular cardiomyopathy/dysplasia: clinical impact of molecular genetic studies. Circulation 113:1634–1637. doi:10.1161/CIRCULATIONAHA.105.616490
2. Pinamonti B, Sinagra G, Salvi A et al (1992) Left ventricular involvement in right ventricular dysplasia. Am Heart J 123:711–724
3. Pinamonti B, Di Lenarda A, Sinagra G et al (1995) Long-term evolution of right ventricular dysplasia-cardiomyopathy. The Heart Muscle Disease Study Group. Am Heart J 129:412–415
4. Corrado D, Basso C, Thiene G et al (1997) Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. J Am Coll Cardiol 30:1512–1520
5. Sen-Chowdhry S, Syrris P, Ward D et al (2007) Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. Circulation 115:1710–1720. doi:10.1161/CIRCULATIONAHA.106.660241
6. De Pasquale CG, Heddle WF (2001) Left sided arrhythmogenic ventricular dysplasia in siblings. Heart 86:128–130
7. Norman M, Simpson M, Mogensen J et al (2005) Novel mutation in desmoplakin causes arrhythmogenic left ventricular cardiomyopathy. Circulation 112:636–642. doi:10.1161/CIRCULATIONAHA.104.532234
8. Duran M, Avellan F, Carvajal L (2000) [Dilated cardiomyopathy in the ectodermal dysplasia. Electro-echocardiographic observations in palmo-plantar keratoderma with woolly hair]. Rev Esp Cardiol 53:1296–1300
9. Norgett EE, Hatsell SJ, Carvajal-Huerta L et al (2000) Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. Hum Mol Genet 9:2761–2766
10. Alcalai R, Metzger S, Rosenheck S et al (2003) A recessive mutation in desmoplakin causes arrhythmogenic right ventricular dysplasia, skin disorder, and woolly hair. J Am Coll Cardiol 42:319–327

11. McKoy G, Protonotarios N, Crosby A et al (2000) Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet 355:2119–2124. doi:10.1016/S0140-6736(00)02379-5
12. Protonotarios N, Tsatsopoulou A (2004) Naxos disease and Carvajal syndrome: cardiocutaneous disorders that highlight the pathogenesis and broaden the spectrum of arrhythmogenic right ventricular cardiomyopathy. Cardiovasc Pathol 13:185–194. doi:10.1016/j.carpath.2004.03.609
13. Protonotarios N, Tsatsopoulou A, Anastasakis A et al (2001) Genotype–phenotype assessment in autosomal recessive arrhythmogenic right ventricular cardiomyopathy (Naxos disease) caused by a deletion in plakoglobin. J Am Coll Cardiol 38:1477–1484
14. Elliott P, O'Mahony C, Syrris P et al (2010) Prevalence of desmosomal protein gene mutations in patients with dilated cardiomyopathy. Circ Cardiovasc Genet 3:314–322. doi:10.1161/CIRCGENETICS.110.937805
15. Beffagna G, Occhi G, Nava A (2005) Regulatory mutations in transforming growth factor-beta3 gene cause arrhythmogenic right ventricular cardiomyopathy type 1. Cardiovasc Res 65:366–373. doi:10.1016/j.cardiores.2004.10.005
16. Merner ND, Hodgkinson KA, Haywood AF et al (2008) Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. Am J Hum Genet 82:809–821. doi:10.1016/j.ajhg.2008.01.010
17. Sporn MB, Roberts AB (1992) Transforming growth factor-beta: recent progress and new challenges. J Cell Biol 119:1017–1021
18. Kapoun AM, Liang F, O'Young G et al (2004) B-type natriuretic peptide exerts broad functional opposition to transforming growth factor-beta in primary human cardiac fibroblasts: fibrosis, myofibroblast conversion, proliferation, and inflammation. Circ Res 94:453–461. doi:10.1161/01.RES.0000117070.86556.9F
19. Laitinen PJ, Brown KM, Piippo K et al (2001) Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. Circulation 103:485–490
20. Swan H, Piippo K, Viitasalo M et al (1999) Arrhythmic disorder mapped to chromosome 1q42-q43 causes malignant polymorphic ventricular tachycardia in structurally normal hearts. J Am Coll Cardiol 34:2035–2042
21. Lehnart SE, Wehrens XH, Laitinen PJ et al (2004) Sudden death in familial polymorphic ventricular tachycardia associated with calcium release channel (ryanodine receptor) leak. Circulation 109:3208–3214. doi:10.1161/01.CIR.0000132472.98675.EC
22. Priori SG, Napolitano C, Tiso N et al (2001) Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation 103:196–200
23. Tiso N, Stephan DA, Nava A et al (2001) Identification of mutations in the cardiac ryanodine receptor gene in families affected with arrhythmogenic right ventricular cardiomyopathy type 2 (ARVD2). Hum Mol Genet 10:189–194
24. Bhuiyan ZA, van den Berg MP, van Tintelen JP et al (2007) Expanding spectrum of human RYR2-related disease: new electrocardiographic, structural, and genetic features. Circulation 116:1569–1576. doi:10.1161/CIRCULATIONAHA.107.711606
25. Bauce B, Nava A, Rampazzo A et al (2000) Familial effort polymorphic ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy map to chromosome 1q42-43. Am J Cardiol 85:573–579
26. Taylor M, Graw S, Sinagra G et al (2011) Genetic variation in titin in arrhythmogenic right ventricular cardiomyopathy-overlap syndromes. Circulation 124:876–885. doi:10.1161/CIRCULATIONAHA.110.005405

# The Role of Clinical Observation: Red Flag 6 – Left Ventricular Non-Compaction

8

Fulvio Camerini, Luisa Mestroni, Gianfranco Sinagra and Michele Moretti

Left ventricular non-compaction (LVNC) is characterized by a pseudohypertrophic "spongy" left ventricle with deep trabeculations. It is considered to be a rare cardiomyopathy (CMP), with a prevalence of approximately 1:2,000 to 1:7,000 individuals. The condition shows excessive and unusually trabeculated myocardium within the mature heart muscle in the apical and midlateral/inferior portions of the left ventricle, which is usually hypokinetic (Fig. 8.1). LVNC represents a developmental failure of the heart to form the fully compact myocardium during the later stages of cardiac development.

LVNC is defined by the American Heart Association classification [1] as a genetic CMP; however, in a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, LVNC is considered to be an "unclassified cardiomyopathy" because "it is not clear whether LVNC is a separate cardiomyopathy, or merely a congenital or acquired morphological trait shared by many phenotypically distinct cardiomyopathies" [2]. The disease may be associated with the presence of other CMPs, usually the phenotype of dilated cardiomyopathy [3] or hypertrophic cardiomyopathy [4].

According to Stöllberger et al. [5], the term "isolated" LVNC might be misleading because other cardiac abnormalities could be present [6]: syndromic cases are usually seen in pediatric patients and have been associated with mutations in the genes encoding tafazzin [7], alpha-dystrobrevin [8] and NK2 homeobox 5 [9]. Recently, the association of "isolated" LVNC with genes of the sarcomere has been reported [10]. An echocardiographic diagnosis of LVNC should prompt research into the presence of possible overlapping entities.

In conclusion, LVNC is characterized by genetic heterogeneity and poor genotype–phenotype correlation, and it does not seem to be a distinct CMP, but rather a morphological expression of different diseases [10].

G. Sinagra (✉)
Cardiovascular Department,
Ospedali Riuniti and University of Trieste, Italy
email: gianfranco.sinagra@aots.sanita.fvg.it

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_8, © Springer-Verlag Italia 2013

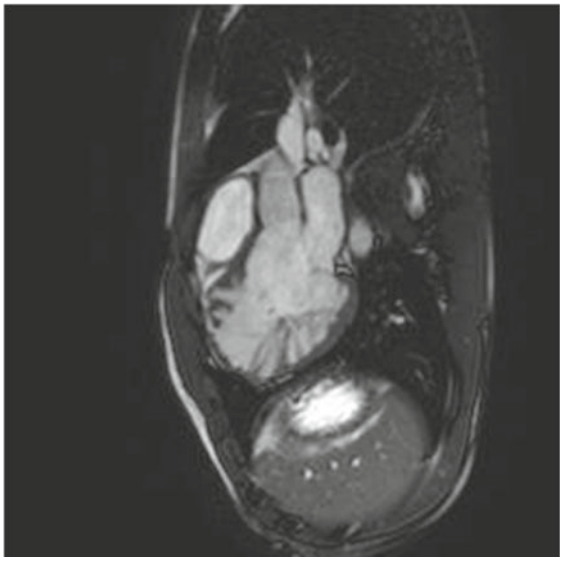


**Fig. 8.1** Left ventricular non-compaction. Cardiac magnetic resonance: end-diastolic still frame obtained from three-chamber steady-state free precession cine imaging, showing increased trabeculation of the left ventricle and an increased ratio of non-compacted to compacted myocardium

## References


1. Maron BJ, Towbin JA, Thiene G et al (2006) Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 113:1807–1816. doi:10.1161/CIRCULATIONAHA.106.174287
2. Elliott P, Andersson B, Arbustini E et al (2008) Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 29:270–276. doi:10.1093/eurheartj/ehm342
3. Vatta M, Mohapatra B, Jimenez S et al (2003) Mutations in Cypher/ZASP in patients with dilated cardiomyopathy and left ventricular non-compaction. J Am Coll Cardiol 42:2014–2027
4. Monserrat L, Hermida-Prieto M, Fernandez X et al (2007) Mutation in the alpha-cardiac actin gene associated with apical hypertrophic cardiomyopathy, left ventricular non-compaction, and septal defects. Eur Heart J 28:1953–1961. doi:10.1093/eurheartj/ehm239
5. Stollberger C, Finsterer J, Blazek G (2002) Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. Am J Cardiol 90:899–902
6. Ritter M, Oechslin E, Sutsch G et al (1997) Isolated noncompaction of the myocardium in adults. Mayo Clin Proc 72:26–31
7. Pignatelli RH, McMahon CJ, Dreyer WJ et al (2003) Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. Circulation 108:2672–2678. doi:10.1161/01.CIR.0000100664.10777.B8
8. Ichida F, Tsubata S, Bowles KR et al (2001) Novel gene mutations in patients with left ventricular noncompaction or Barth syndrome. Circulation 103:1256–1263
9. Pauli RM, Scheib-Wixted S, Cripe L et al (1999) Ventricular noncompaction and distal chromosome 5q deletion. Am J Med Genet 85:419–423
10. Oechslin E, Jenni R (2011) Left ventricular non-compaction revisited: a distinct phenotype with genetic heterogeneity? Eur Heart J 32:1446–1456. doi:10.1093/eurheartj/ehq508

# The Role of Clinical Observation: Red Flag 7 – Syndromic and Multi-system Cardiomyopathies

9

Gianfranco Sinagra, Fulvio Camerini, Michele Moretti and Luisa Mestroni

In some patients, the phenotype of a cardiomyopathy (CMP) may be associated with the involvement of multiple organs, and with systemic clinical manifestations. These genetically determined diseases are characterized by complex, unusual and sometimes bizarre clinical pictures. The associations observed are not surprising, considering that in these diseases the defective gene is expressed in different structures or tissues. This is for example the case in the mitochondrial genes where production of abnormal proteins can cause multiform tissue abnormalities and/or dysfunction of different organs.

## 9.1 Syndromic Cardiomyopathies

CMPs have been observed in many genetic syndromes, the most important of which are described below (Table 9.1).

### 9.1.1 Friedreich Ataxia

Friedreich ataxia is a disease that is anatomically characterized by degeneration of the posterior columns and the corticospinal and posterior spinocerebellar tracts, and clinically by ataxia, dysarthria, loss of deep tendon reflexes, sensory abnormalities, skeletal deformities and diabetes mellitus. Neurological signs begin around puberty, and are constant and frequently severe before the age of 20–25 years. While the most important symptoms of the disease are usually secondary to neuronal degeneration, the involvement of

G. Sinagra (✉)
Cardiovascular Department,
Ospedali Riuniti and University of Trieste, Italy
email: gianfranco.sinagra@aots.sanita.fvg.it

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_9, © Springer-Verlag Italia 2013

the heart is considered to be an independent site of primary degeneration [1].

The *FXN* gene mutation is localized in chromosome 9 and frataxin is the protein involved. The most common genetic abnormality is a GAA trinucleotide repeat expansion in intron 1 of the *FXN* gene. In the majority of cases, patients with Friedreich ataxia have between 66 and 1,500 GAA repeats (in normal subjects there are fewer than 33 repeats). There is a correlation between the size of GAA expansion and left ventricular hypertrophy [1].

Cardiac involvement is very frequent (more than 90% in neurologically symptomatic patients), and it is characterized by left ventricular hypertrophy, usually concentric, sometimes asymmetric, with or without a left ventricular outflow gradient. Dilated cardiomyopathy (DCM) is rare and is probably a late evolution of hypertrophic cardiomyopathy (HCM). The presence of Q waves identifies a subgroup of patients with wall-motion abnormalities that make them prone to developing a hypokinetic dilated left ventricle [2] (Figs. 9.1, 9.2).

### 9.1.2 Barth Syndrome

Barth syndrome is an X-linked inherited disorder characterized by skeletal myopathy, granulocytopenia, lactic acidemia, increased levels of 3-methylglutaconic acid 2-ethyl hydracrylic acid in the urine, and abnormal mitochondria. Reported heart involvement is variable, ranging from endocardial fibroelastosis to congenital DCM (sometimes with infantile congestive heart failure) and left ventricular non-compaction (LVNC) [3]. Christodoulou et al. [4] mentioned the possibility of progressive improvement of left ventricular function after the first year of life, when it can become subclinical and normal. In Barth syndrome, mutations in the gene encoding tafazzin (*TAZ*) (initially called G4.5) have been identified as a cause of the disease [5].

### 9.1.3 Costello Syndrome

Costello syndrome is another rare syndrome characterized by the association of multiple abnormalities: coarse facies, short stature, distinctive hand posture and appearance, and feeding difficulties. The skin of the neck, palm, toes and fingers is redundant. Papillomata around mouth and mental retardation occur frequently. There is also an increased risk of malignancies. Cardiac abnormalities are frequent [6] (63% in 94 patients), and these are characterized by HCM (34%), cardiac malformations, most commonly pulmonary stenosis (30%), and frequent rhythm abnormalities (usually atrial tachycardia). In this syndrome, Hinek et al. [7] noticed at postmortem that the cardiomyocytes were characterized by pericellular and intracellular accumulation of glycosaminoglycans bearing chondroitin 6-sulfate moieties, with lower than normal deposition of chondroitin 4-sulfate. In Costello syndrome, there is usually a mu-

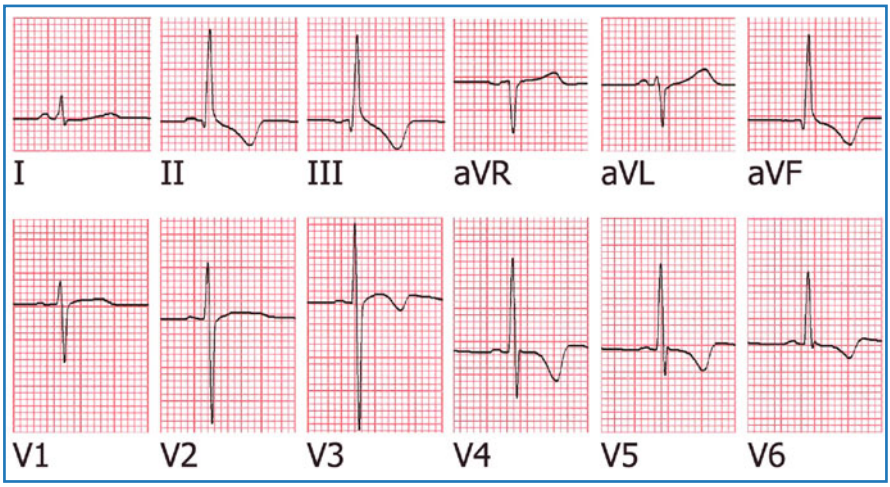



**Fig. 9.1** Electrocardiogram (ECG) of an 8-year-old boy with Friedreich ataxia. The ECG shows sinus rhythm, normal conduction, and alterations of the repolarization phase

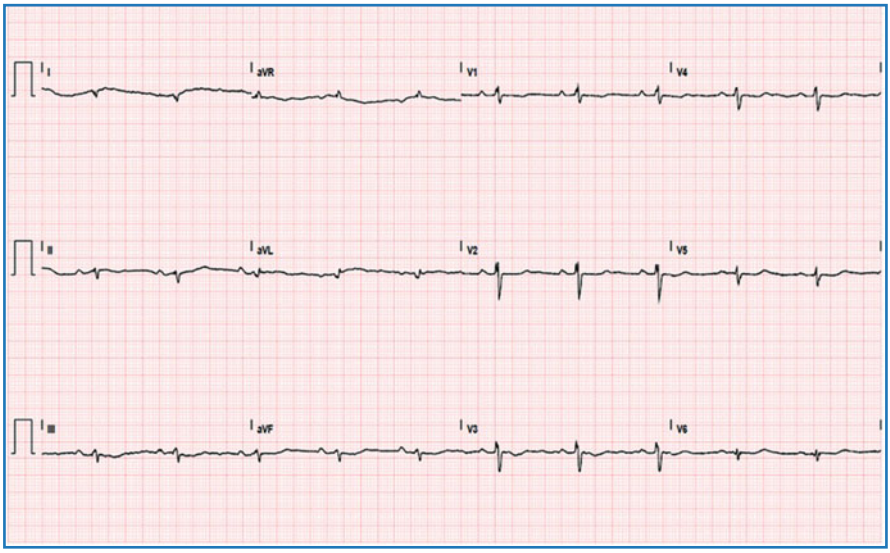


**Fig. 9.2** Electrocardiogram (ECG) of a 27-year-old man with Friedreich ataxia and hypertrophic non-obstructive cardiomyopathy. The patient has severe systolic and diastolic left ventricular dysfunction (ejection fraction 36%). The ECG shows sinus rhythm, diffuse low voltage, rs complexes in V1, and abnormal Q waves in aVL and qs in lead I

tation in the *HRAS* gene. Finally, the syndrome shows phenotypic overlaps with cardiofaciocutaneous syndromes caused by mutations in the *KRAS* gene, and Noonan syndrome caused by mutations in the *PTPN11* gene.

### 9.1.4 LEOPARD Syndrome

LEOPARD is an acronym for Lentiginosis (multiple), ECG abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness. The syndrome is autosomal dominant [8], and in the majority of cases it is caused by mutations in the *PTPN11* gene on chromosome 12q24.13, and therefore it is allelic to Noonan syndrome. Another form of LEOPARD syndrome is caused by mutation in the *RAF1* gene, which also causes a form of Noonan syndrome.

HCM is frequently present in the syndromes described above [9–11], but other congenital cardiac defects (pulmonary stenosis, bundle branch block, AV block, family history of sudden death) have also been described [11, 12].

### 9.1.5 Noonan Syndromes

Noonan syndrome 1 (NS1) is an autosomal-dominant dysmorphic syndrome characterized by abnormalities involving various organs. NS1 is caused more frequently by mutations in the *PTPN11* gene, which maps to chromosome 12q24.13. Rare forms of the syndrome are Noonan syndrome 2, which is probably autosomal recessive, Noonan syndrome 3 (caused by mutations in the *KRAS* gene), Noonan syndrome 4 (mutations in the *SOS1* gene), Noonan syndrome 5 (mutations in the *RAF1* gene), and Noonan syndrome 6 (mutations in the *NRAS* gene).

Different congenital cardiac abnormalities have been described in NS1: patent ductus arteriosus, pulmonary stenosis, coarctation of the aorta, and also HCM, restrictive cardiomyopathy (RCM) and "spongy myocardium" (LVNC) [13, 14]. The HCM phenotype seems to be more frequent in Noonan syndrome 2 [15]; it has also been observed in Noonan syndrome 6 [16], and particularly in Noonan syndrome 5 [17].

### 9.1.6 Cardiofaciocutaneous Syndrome

Cardiofaciocutaneous syndrome is caused by gain of function mutations in different genes. One of four genes is involved: *KRAS, BRAF, MEK1 (MAP2K1)* or *MEK2 (MAP2K2)*. The protein products of these genes interact in a common pathway that regulates cell differentiation, proliferation and apoptosis [18]. Cardiofaciocutaneous syndrome is characterized by multiple complex congenital anomalies, such as a distinctive facial appearance that includes a high forehead with bitemporal constriction, hypoplastic supraorbital ridges, downslanting palpe-

bral fissures, depressed nasal bridge and posteriorly angulation [18]. Congenital heart defects are frequently present; these include pulmonary stenosis, atrial septal defects and HCM [18]. A phenotypic overlap between cardiofaciocutaneous syndrome and Noonan and Costello syndromes has been described [18].

### 9.1.7 Cardioencephalomyopathy (Fatal, Infantile Due to Cytochrome c Oxidase Deficiency)

Fatal infantile cardioencephalomyopathy is a disease characterized by the presence of hypotonia, respiratory difficulties, and increased levels of lactate in the blood and cerebrospinal fluid at birth. Cardiac involvement is usually characterized by a HCM phenotype. The disease is the result of cytochrome c oxidase (COX) deficiency caused by a mutation in the *SCO2* gene, which is a COX assembly gene on chromosome 22q13.13. *SCO2* mutations have been associated with early spontaneous abortion [19].

### 9.1.8 Alstrom Syndrome

Alstrom syndrome is an autosomal-recessive disorder caused by a mutation in the *ALMS1* gene. Many organs can be affected, although truncal obesity, progressive sensory-neural hearing loss, retinitis pigmentosa and insulin-resistant diabetes seem to be the most frequent manifestations of the disease. From a cardiac point of view, the presence of DCM has been reported with variable frequency. According to Marshall et al. [20], who studied a large cohort of patients (250 affected individuals from different countries), the frequency of DCM was 57.8%, and in two-thirds of these patients it was observed during infancy. Russell Eggitt et al. [21] described 18 cases of infantile CMP in a group of 22 children studied at Great Ormond Street Hospital, London, over a period 10 years; however, other authors have reported a lower incidence [20, 22]. The occurrence of DCM is usually observed in infancy. It has to be noted that also cases of RCM have been observed in this syndrome [23].

## 9.2 Metabolic and Storage Diseases

Metabolic and storage disorders are described below, and in Table 9.2.

### 9.2.1 Danon Disease

Danon disease is an X-linked dominant lysosomal disease caused by a mutation in the gene encoding lysosome-associated membrane protein 2 (*LAMP2*), and it is characterized histologically by the presence, in cardiac and skeletal

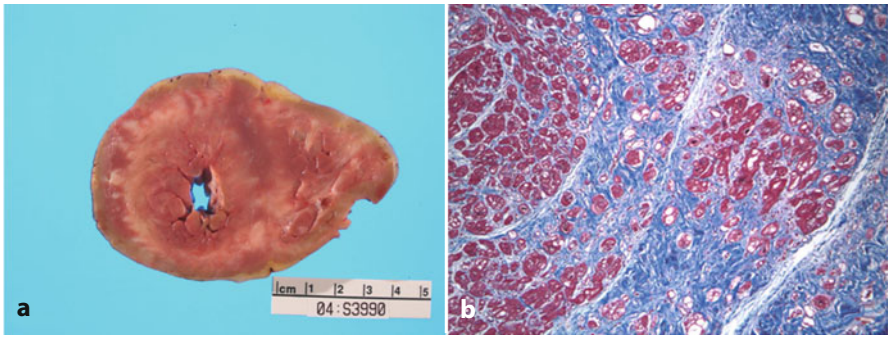



**Fig. 9.3** Danon disease. **a** Cardiac muscle specimen from a patient with Danon disease aged 14 years: a cross-section of explanted heart showing biventricular hypertrophy and fibrosis. **b** Photomicrograph (Trichrome stain) showing extensive fibrosis (*blue*), severely damaged cardiomyocytes (*red*) and vacuolization. Modified from Taylor et al. [29], with permission

muscle cells, of intracytoplasmic vacuoles containing autophagic material and glycogen [24, 25]. The accumulation of glycogen initially led to the classification of Danon disease as a glycogen storage disease [26]; however, according to Nishino [27], Danon disease is not a true glycogen storage disease because the level of glycogen is not always increased.

The disease is diagnosed on the basis of clinical features and muscle pathology: CMP, skeletal muscle weakness (usually mild), elevated creatine kinase, and the presence of intracytoplasmic vacuoles containing autophagic material and glycogen in cardiac and skeletal muscle, with no acid maltase deficiency. Intellectual disabilities and, in some cases, retinal involvement are present, with a severe decrease in visual acuity resulting from choriocapillary ocular atrophy [28] or retinal pigment disease (in female carriers) [29]. Affected females usually show a later onset and a less severe form of CMP, usually DCM. Cardiac involvement is sometimes apparently isolated [26, 28], and is frequently of early onset (less than 20 years of age) [25, 26, 28] and has a poor prognosis. Symptoms are usually similar to those present in HCM. Echocardiography shows a concentric left ventricular hypertrophy, which may be massive (Fig. 9.3). In the electrocardiogram (ECG), as an expression of the massive hypertrophy, left ventricular voltage is greatly increased (nearly the double than that found in patients with sarcomere gene mutations), and in some series there has been frequent occurrence of ventricular pre-excitation [26] (see Fig. 5.1). In the majority of cases, the evolution of the disease is toward a progressive deterioration of left ventricular dysfunction and congestive heart failure.

### 9.2.2 Fabry Disease

Fabry disease is an X-linked disorder caused by a mutation in the gene encoding alpha-galactosidase (*GLA*). The deficient or absent activity of alpha-galac-

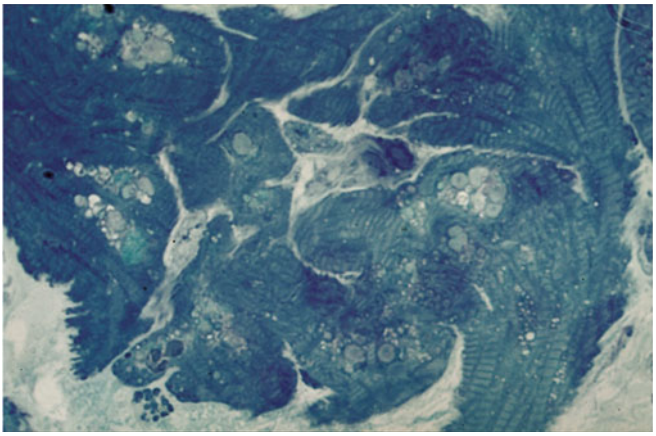


**Fig. 9.4** Fabry disease. Multiple osmiophilic bodies, which represent sphingolipid accumulation, are present in the myocardium. Azur II stain, semifine section, ×200

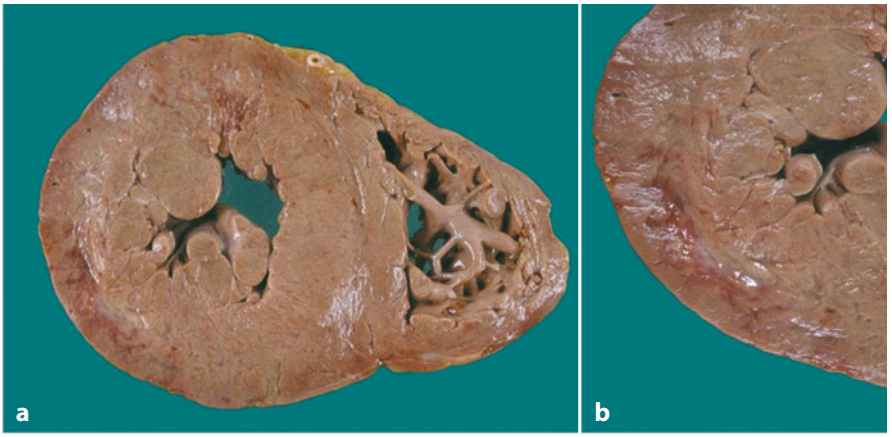



**Fig. 9.5 a,b** Fabry disease in a 53-year-old man with hypertrophic cardiomyopathy. Note the massive left ventricular hypertrophy with areas of fibrotic tissue in the posterior third of the septum

tosidase, a lysosomal enzyme, leads to systemic accumulation of globotriaosylceramide and other glycosphingolipids in lysosomes of many cells of different organs (Fig. 9.4). Skin, kidneys, nerves and eyes are usually involved. The condition affects males, and also heterozygous and homozygous females. Males experience a more severe clinical symptomatology, while in females the symptoms vary from mild or virtually absent to symptoms as serious as those in males. Cardiac involvement in females seems to be rare.

Cardiac involvement is characterized by left ventricular hypertrophy (Figs. 9.5, 9.6 and 9.7), ECG changes with high voltages (Romhilt–Estes scores indicative of cardiac hypertrophy are present in 80% of cases), and frequently by short PR (40% of cases) [30]. Chronic hypertension and luminal narrowing

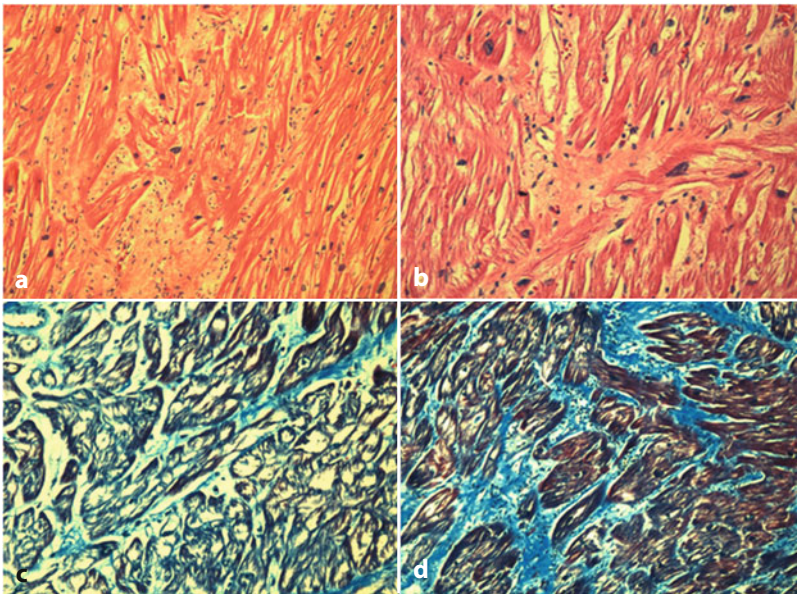



**Fig. 9.6** Fabry disease. Microscopic view of cardiac sections in Fabry disease. **a** Myocyte hypertrophy and disarray, with partial replacement of normal myocardium by fibrotic areas. H&E, ×10. **b** Myocardium with diffuse interstitial fibrosis. Note the severe myocellular hypertrophy. H&E, ×20. **c** Extensive myocyte vacuolation and diffuse interstitial fibrosis. Azan Mallory, ×20. **d** Severe plessiform fibrosis and myocyte disarray. Azan Mallory, ×20

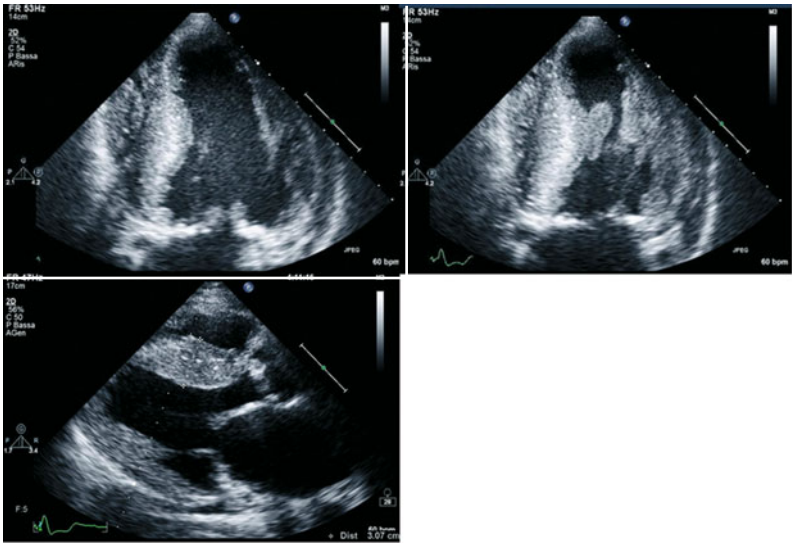


**Fig. 9.7** Two-dimensional echocardiogram from a 52-year-old man with Fabry disease and cardiac involvement. *Upper panels* apical four-chamber views, end-diastolic and end-systolic frames. *Lower panel* parasternal long-axis view, end-diastolic frame. The left ventricle is severely hypertrophic (interventricular septum thickness 29 mm) and moderately dilated (end-diastolic volume 175 ml); an apical hypokinesis is present. A "granular sparkling" appearance of ventricular myocardium is evident. The global systolic function is at the lower limits of normality (ejection fraction: 51%). There is moderate thickening of valve leaflets without significant stenosis

of coronary arteries can cause myocardial ischemia, while structural changes in mitral and aortic valves may favor the deterioration of systolic function. Cardiologists should consider a diagnosis of Fabry disease in patients, especially males, with left ventricular hypertrophy, mitral and aortic valve thickening on echocardiography, short PR and conduction defects on the ECG, in particular when associated with involvement of other organs (typical skin lesions, and kidney and cerebrovascular disease). In a few cases, manifestations of Fabry disease may be limited to the heart [31], or an HCM phenotype can be the first manifestation of the disease [32].

### 9.2.3 Glycogen Storage Diseases

Glycogen storage diseases (also known as glycogenoses) are a group of genetic disorders that are the result of deficiencies of enzymes necessary for glycogen metabolism. Glycogen is a highly branched polymer of glucose with a tree-like structure, and it undergoes addition and removal of residues at its periphery. Glucose is mobilized from glycogen by complex reactions induced by different enzymes that are encoded by different genes.

More than 10 different forms of glycogenosis have been described, and in at least three forms the myocardium is affected. Examples include: glycogen storage disease type II or Pompe disease (caused by a mutation of the *GAA* gene), glycogen storage disease type III or Cori–Forbes disease (caused by a mutation of the *AGL* gene), and glycogen storage disease type IV or Andersen disease (caused by a mutation of the *GBE1* gene).

### 9.2.4 Carnitine Deficiency

Carnitine is a quaternary ammonium compound required for the transport of fatty acids from the cytosol into the mitochondria. Fatty acids are a major source of energy for heart and muscles. Systemic carnitine deficiency can have different causes such as deficiency of intake or synthesis, or it can be the result of abnormalities in fatty acid metabolism. However, the most important clinical form of carnitine deficiency is “primary carnitine deficiency” caused by a mutation in the *SLC22A5* gene. This gene encodes a protein known as OCTN2, which transports carnitine into the cells. Mutations in the *SLC22A5* gene are the cause of a dysfunctional (or absent) OCTN2 protein. As a consequence, there is a deficiency of carnitine within the cells and reduced energy production. The phenotype is characterized by neurologic, skeletal muscle and metabolic symptoms, and laboratory findings. Heart involvement is characterized by the presence of a variable phenotype (HCM or DCM). Moreover, sudden infant deaths have been observed in a family with mutation of *SLC22A5* [33]. Importantly, treatment with carnitine supplementation may cause dramatic improvements in cardiac symptoms.

### 9.2.5 Hemochromatosis

Hemochromatosis is an autosomal-recessive disorder of iron metabolism characterized by iron deposition in many organs. From a clinical point of view, excess iron deposition can be the cause of complex illnesses, including liver cirrhosis, diabetes mellitus, hypogonadotropic hypogonadism and arthritis. Diagnosis is confirmed by increased ferritin and transferrin saturation levels in the absence of evidence for other causes of iron overload.

Arrhythmias (supraventricular and ventricular) may be the first sign of heart involvement, but congestive heart failure caused by left ventricular dysfunction with low ejection fraction is frequently present. Occasionally a restrictive pattern on echocardiography and/or cardiac catheterization can be demonstrated. Low voltage of the QRS complex is a frequent ECG finding. Familial hemochromatosis is usually caused by mutations in the *HFE* gene on chromosome 6p21.3.

### 9.2.6 Wilson Disease

Wilson disease is a rare autosomal-recessive disorder characterized by toxic copper accumulation, especially in the liver and central nervous system. This syndrome typically presents with liver cirrhosis, degenerative changes in the brain (especially in the basal ganglia), Kayser–Fleischer corneal rings, low serum copper concentration, decreased serum ceruloplasmin level, increased urinary copper, and deposition of copper in various tissues [34]. The age of onset ranges from 3 years to over 50 years. It can present with hepatic, neurologic or psychiatric disturbances, or a combination of these.

Cardiac involvement is an uncommon feature of the disease; nevertheless, cardiac hypertrophy and increased cardiac copper concentration have been described [35, 36]. Cardiac manifestations in Wilson disease include arrhythmias, HCM or DCM, cardiac death and autonomic dysfunction [37]. ECG abnormalities have been described in approximately one-third of patients, and they include left ventricular hypertrophy, biventricular hypertrophy, early repolarization, ST depression and T inversion. Arrhythmias include premature atrial or ventricular beats, atrial fibrillation, sinoatrial block, Mobitz type 1 atrioventricular block and ventricular fibrillation [37]. Asymptomatic orthostatic hypotension and an abnormal response to the Valsalva maneuver have also been described [37].

The disease is caused by mutations (more than 260) in the *ATP7B* gene. This gene encodes a protein known as copper-transporting ATPase 2, which is part of the P-type ATPase family, a group of proteins that transports metals into and out of cells. Copper-transporting ATPase 2 plays a role in the transport of copper from the liver to other parts of the body, and it is also important for the removal of excess copper from the body.

### 9.2.7 Mucopolysaccharidoses

Mucopolysaccharidoses (MPSs) are metabolic disorders caused by absent or defective activity of one of the lysosomal enzymes that catabolize complex carbohydrates known as mucopolysaccharides (or glycosaminoglycans). In patients with MPS, there is insufficient or abnormal activity of these enzymes, and this limits the breakdown of mucopolysaccharides into simpler molecules. Mucopolysaccharides collect in the cells of different organs, and blood and connective tissue to produce progressive cellular damage (nervous system, eyes, skeleton, liver and spleen).

Seven types and numerous subtypes of MPS have been identified. The phenotypes of these diseases are different and patients, after a period of apparent normal development, frequently show progressive physical and/or mental deterioration.

The cardiac manifestations of MPS may be insidious initially, but they are usually progressive as a result of engorgement of cells and tissues by macromolecular material; acute cardiac failure in the first weeks or months of life has also been described [38].

#### 9.2.7.1 MPS Type 1 (Hurler Syndrome) (*IDUA* Gene)

Cardiac involvement is present in almost all individuals with severe MPS type 1 (MPS-1). Thickening and stiffening of the mitral and aortic valve leaflets can lead to valve incompetence, which may become hemodynamically important in the more advanced stages of the disease. CMP (hypertrophic) and sudden death from arrhythmias and coronary artery disease can occur [39]. Donaldson et al. [38] described five children of three families with MPS-1 affected by a severe form of CMP, with a heart that was dilated and hypertrophic in the majority of cases. In two patients studied at postmortem, endomyocardial fibrosis of the left ventricle was present, as well as (in one patient) intimal thickening of the coronary arteries.

Hurler syndrome is caused by a defect in the gene that encodes alpha-L-iduronidase. This defect can be the cause of three major clinical entities: Hurler syndrome (MPS-1H), Shaie syndrome (MPS-1S) and Hurler–Shaie syndrome (MPS-1HS). MPS-1H is the most severe form of the disease, MPS-1S is relatively mild, while MPS-1HS is intermediate in phenotypic expression. In MPS-1S and MPS-1HS, involvement of mitral and aortic valves has been observed [38].

#### 9.2.7.2 MPS Type 2 (Hunter Syndrome) (*IDS* Gene)

In MPS type 2 (MPS-2), echocardiography shows valvular involvement, with mitral and aortic regurgitation and/or stenosis, in about 50% of cases [40]. CMP is much less common and may be associated with an increased risk of cardiac arrhythmias [41]. In a case described by Hishitani et al. [41], a complete atrioventricular block was the cause of sudden death; patchy fibrosis was

present in the myocardium, and fibrosis and infiltration of lymphocytes and macrophages were present in the penetrating portion of the His bundle.

#### 9.2.7.3 MPS Type 3 (Sanfilippo Syndrome) (*SGSH, NAGLU* Genes)

In Sanfilippo type A syndrome, the symptoms are mainly neurologic and can appear in early childhood; the majority of patients die of end-stage neurodegenerative disease within the second decade of life. Cardiac involvement is rare; however, asymmetrical septal hypertrophy [42] and severe HCM [43] have been observed, while DCM seems to be very rare [39]. Moreover, Van Hove et al. [44] described apparently isolated severe HCM, involving both ventricles, in a woman who did not show neurologic symptoms. Percutaneous endomyocardial biopsy showed ballooned cardiomyocytes with perinuclear storage vacuoles, displacing the myofibrils peripherally. Specific staining identified the storage material as acid mucopolysaccharides. The diagnosis of Sanfilippo type A syndrome was documented by the excess of heparan sulfate in the urine, deficient enzyme activity and reduction in the level of heparan sulfamidase. The patient died after a cardiac transplant at age 56 years, and the authors correlated the relatively advanced age to a significant residual heparan sulfamidase activity.

#### 9.2.7.4 MPS Type 4 (Morquio Syndrome Type A and B) (*GALNS, GLB1* Gene)

Cardiac involvement in MPS type 4 (Morquio syndrome) is usually characterized by involvement of the mitral and aortic valves. The valves can appear thickened, insufficient or stenotic, but in the majority of cases the lesions are hemodynamically mild [45]. In 2 of 10 patients studied by John et al. [45], biventricular hypertrophy or apical hypertrophy (apparently not explained by the severity of the valvular lesions) was present.

#### 9.2.7.5 MPS Type 6 (Maroteaux–Lamy Syndrome) (*ARSB* Gene)

MPS type 6 is a form of MPS characterized by the development of different types of heart disease and cardiac dysfunction, which can be the cause of serious problems in the majority of these patients [46]. An acute form of CMP with severe heart failure has been observed in the first year of life by Miller and Partridge [47], Fong et al. [48] and Hayflick et al. [49]. In these cases, the heart was enlarged with or without ventricular hypertrophy, but with severe dilatation and reduced left ventricular function. Endomyocardial fibroelastosis is usually present. Severe myocardial involvement seems to be present only in the first year of life, while signs of mitral and/or aortic incompetence and/or stenosis are very frequent at a more advanced age (96% of 121 patients reported by Swiedler et al. [50]). Tricuspid regurgitation has been frequent in some echocardiographic studies [51]. Symptomatic coronary artery disease is rare, although sclerosis of the intima, foamy cells between collagen fibers in the coronary arteries, has been observed [52].

#### 9.2.7.6 MPS Type 7 (Sly Syndrome) (*GUSB* Gene)

Valvular heart disease has been observed in this form of MPS.

### 9.2.8 Mucolipidoses

Mucolipidoses are a group of inherited metabolic disorders characterized by a pathological accumulation of carbohydrates and lipids in cells. The mucolipidoses are lysosomal storage diseases and they are classified in four types: sialidosis (sometimes referred to as mucolipidosis type I), types II, III, and IV.

#### 9.2.8.1 Mucolipidosis Type 2 Alpha/Beta (*GNPTAB* Gene)

Mucolipidosis type 2 is an autosomal-recessive disorder caused by deficiency of multiple lysosomal hydrolases, which are active in the degradation of lipids and mucopolysaccharides. The disorder is characterized clinically by short stature, skeletal abnormalities, developmental delay and cardiovascular changes. The cardiovascular changes are similar to those observed in MPS: aortic valve prolapse with insufficiency, mitral and tricuspid prolapse [53], as well as accumulation of foam cells in the myocardium. Patients affected by mucolipidosis type 2 can present with a phenotype of DCM, dilatation of the left ventricle and signs of endocardial fibroelastosis [54]. "Marked muscular hypertrophy of the left ventricle" has also been described [55], in which microscopy showed hypertrophied myocardial fibers, while the "sarcoplasm was vacuolated".

### 9.2.9 Gangliosidoses

Gangliosidoses are a group of inherited metabolic disorders characterized by abnormal accumulation of lipids (gangliosides) within the cells.

#### 9.2.9.1 Gangliosidosis, Type 1 (*GLB1* Gene)

Gangliosidosis type 1 is an autosomal-recessive lysosomal storage disease, caused by a mutation in the gene encoding beta-galactosidase 1. The disease is characterized by accumulation of ganglioside substrates in lysosomes, and three main clinical variants have been described. It is a rare condition, and a form of the disease with heart involvement has been observed in an infant who died at the age of 8 months [56], when it was characterized by hypertrophy of both ventricles and endocardial fibroelastosis. In another infant "cardiomyopathy", vacuolated and hypertrophic myofibers, thick and nodular mitral valve leaflets, and partial occlusion of the right coronary artery by an atherosclerotic plaque containing ballooned cells were present [57]. Finally Morrone et al. [58] described eight patients with infantile severe form of the disease, and out of these patients six presented cardiac involvement (DCM, "HCM and DCM", intraventricular conduction delay).

### 9.2.10 Oxalosis

Oxalosis is caused by generalized deposition of calcium oxalate, in renal and extrarenal tissues.

#### 9.2.10.1 Hyperoxaluria Primary, Type I; HP1 (*AGXT* Gene)

Oxalosis is a rare autosomal-recessive disorder caused by a mutation in the gene encoding alanine-glyoxylate aminotransferase (*AGXT*). Decreased amounts or absent *AGXT* activity (and a failure to transaminate glyoxylate) causes the accumulated glyoxylate to be oxidized to oxalate. Non-soluble calcium oxalate accumulates in many organs, especially the kidney, and frequently results in renal failure. The heart is the site of clinically relevant deposition of oxalate crystals, and this might be the etiologic factor in different forms of CMP.

Severe RCM has been described by Shulze et al. [59], and "infiltrative cardiomyopathy" with heart failure has been described by Van Driessche et al. [60]. Yoshioka et al. [61] observed a concentric thickening of myocardial wall in a case of oxalosis, while DCM with a severe reduction in ejection fraction was reported by Robdby et al. [62] and Detry et al. [63]. In both of the latter cases, there was a relevant improvement in cardiac function after kidney and liver transplantation.

## 9.3 Mitochondrial Diseases

Mitochondria are structures localized in the cytoplasm of the cells, and their function is to provide substrates (such as ATP) for intracellular metabolic pathways. Mitochondrial DNA encodes several components of metabolic pathways, including Krebs cycle, beta oxidation, and lipid and cholesterol synthesis. Considering the fundamental role of these pathways, defects of mitochondrial function can have very severe consequences [64]. Most DNA is packaged in chromosomes of the nucleus, but mitochondria also contain a limited amount of DNA (mtDNA). Human mtDNA is a circular double-stranded molecule, which is much smaller than most nuclear genes. mtDNA contains 37 genes, 13 of which are involved in oxidative phosphorylation. The 13 proteins encoded by human mtDNA are involved in the respiratory chain and oxidative phosphorylation system [64].

The remaining 24 mitochondrial genes provide instructions for producing molecules such as transfer RNA (tRNA) and ribosomal RNA (rRNA), which are structures that help in assembling amino acids into functioning proteins.

Inherited or spontaneous mutations in mtDNA or in nuclear DNA (nDNA) can cause an alteration in the functions of proteins or rRNA molecules. Since the mitochondria are located in the cytoplasm, they are transmitted to the embryo through the maternal oocyte. Therefore, mitochondrial diseases are transmitted from the mother to children of both sexes (matrilineal transmis-

sion). As a consequence, altered functions in different tissues can cause a broad spectrum of diseases, with many possible combinations. However, considering the characteristics of the mitochondrial proteins in different diseases, it is currently difficult to explain the different patterns of affected organs and systems.

Considering the fact that mitochondria perform many different functions in different tissues, the spectrum of mitochondrial diseases can be variable, and they can have a multi-system nature and be of particular relevance to many medical specialities. Furthermore, identical mtDNA mutations may not produce identical diseases, and conversely different mutations in mtDNA and nDNA can lead to apparently undistinguishable diseases. Typical of this is Leigh syndrome [65], in which there is extensive genetic heterogeneity, with mutations identified in both nuclear-encoded and mitochondrial-encoded genes that are involved in energy metabolism.

Santorelli et al. [66] first introduced the concept of mitochondrial CMP. These CMPs are caused by different mutations of different genes (mtDNA deletions, mtDNA point mutations, and mutations that can induce multiple mtDNA deletions or depletions). These mitochondrial CMPs are rarely isolated, but frequently associated with skeletal myopathies and multi-organ involvement. The characteristics of these CMPs, and other cardiac abnormalities and the most frequent syndromic diseases are described in Table 9.3.

### 9.3.1 Defects of the Respiratory Chain Complex

Mutations involving genes encoding subunits of the mitochondrial respiratory chain complex may be the cause of heterogeneous phenotypes in which associated CMP has been described [67]. HCM without obstruction, often detected in early infancy, is the characteristic form encountered [67]. Hypertrophy of the myocardium appears to result from swelling of the cardiomyocytes caused by accumulation of mitochondria [67]. It has been suggested that mitochondrial proliferation is an attempt by the cardiac muscle cell to compensate for deficient energy production [68].

Defects in any of the five complexes (I [69], II [70], III [71], IV [72] and V [73]) of the respiratory chain have been associated with HCM. HCM is usually part of complex syndromes characterized by a variable combination of metabolic acidosis, and involvement of skeletal muscle (psychomotor delay, generalized hypotonia, etc.) and the central nervous system.

The relationship between phenotypes, biochemical defects and molecular genetic findings is poorly understood. Furthermore, in patients with mtDNA mutations involving tRNA genes, biochemical studies in muscle have shown multiple defects of the respiratory chain, most frequently complexes I and IV [74, 75].

**Table 9.1** Cardiomyopathies with multi-organ involvement: syndromes

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| *FXN* | Frataxin | HCM, DCM | **Friedreich ataxia (FRDA)**<br>***Typical form (75% of cases of FRDA)***:<br>**Onset/natural history**: mean age of onset: 10–15 years; average time from symptom onset to wheelchair dependence: 10 years; average time from symptom onset to death: 36 years<br>**CNS**: progressive ataxia in childhood or in the early teens, starting with poor balance when walking (gait ataxia), followed by slurred speech and upper-limb ataxia. Spinocerebellar degeneration, loss of proprioception. "Scanning" dysarthria. Mixed axonal peripheral neuropathy. Muscle weakness, most prominent in hip extensors and abductors, progressing to distal limb muscles. Lower limb spasticity. Optic nerve atrophy<br>**Psychomotor development**: cognition is usually normal, slow motor and mental reaction times. Intelligence profile: concrete thinking, poor capacity in concept formation and visuospatial reasoning with reduced speed of information processing<br>**Eyes**: optic nerve atrophy, nystagmus, irregular ocular pursuit, dysmetric saccades, saccadic latency, square wave jerks, ocular flutter, poor vestibulo-ocular reflex gain and increased latency<br>**Auditory system**: sensorineural hearing loss, auditory neuropathy<br>**Osteoarticular system**: scoliosis, pes cavus<br>**Metabolic disorders**: diabetes mellitus (30% of cases)<br>***Atypical forms (25% of cases of FRDA)***:<br>**Late-onset FRDA** (approximately15%)<br>Mean age of onset: 26–39 years, slow progression<br>**Very late-onset FRDA**<br>Mean age of onset: over 40 years, slow progression<br>**FRDA with retained reflexes** (approximately 12%)<br>Brisk tendon reflexes accompanied by clonus. Tendon reflexes may be retained for | |

(*cont.*) ↓

| | | | | |
|---|---|---|---|---|
| | | | more than ten years after the onset of the disease. Later age of onset and lower incidence of secondary skeletal involvement and cardiomyopathy<br>**FRDA in Acadians**<br>Acadians with FRDA have a later age of onset and of wheelchair confinement, and a much lower incidence of cardiomyopathy | |
| *TAZ* | Tafazzin | DCM, LVNC, endocardial fibroelastosis | **Barth syndrome**<br>**Onset**: neonatal period to childhood (most develop DCM before 10 years of age)<br>**Perinatal history and growth**: fetal cardiac failure, fetal hydrops and miscarriage or stillbirth during the 2nd/3rd trimester of pregnancy. Tendency to hypoglycemia during the neonatal period. Postnatal growth delay, delayed puberty<br>**Skeletal myopathy**: hypotonia, muscle weakness (mostly proximal) and exertional fatigue. CK normal or ↑<br>**Metabolic disorders**: 3-methylglutaconic aciduria type II<br>**Hematopoietic disorders**: neutropenia (risk of septicemia, severe bacterial sepsis, mouth ulcers and painful gums), mild anemia<br>**Other**: abnormal mitochondria<br>**Craniofacial features**: chubby cheeks, deep-set eyes, prominent ears | |
| *HRAS* | V-HA-RAS Harvey rat sarcoma viral oncogene homolog | HCM | **Costello syndrome**<br>**Onset**: can be diagnosed in utero but more frequently recognized during childhood<br>**Perinatal history and growth**: increased fetal nuchal thickness, polyhydramnios. Increased birth weight (as a result of edema, not true macrosomia), weight loss resulting from resolution of edema, severe postnatal feeding difficulties, failure to thrive, short stature<br>**Craniofacial features and voice**: relative macrocephaly, coarse facial features, full cheeks, full lips, large mouth, macroglossia, epicanthal folds, wide nasal bridge, short full nose, short webbed neck, deep/hoarse or whispery voice<br>**Eyes**: strabism, palpebral ptosis, epicanthal folds<br>**Skin and hair**: curly or sparse, fine hair, loose and soft skin (cutis laxa), increased pigmentation, deep palmar and plantar creases, papillomata of face and perianal region (typically absent in infancy, but may appear in childhood and confirm the diagnosis in doubtful cases), premature aging, hair loss | **Congenital defects**: pulmonic stenosis<br>**Arrhythmias**: SVT (chaotic atrial rhythm/ multifocal atrial tachycardia or ectopic atrial tachycardia) |

(*cont.*) →

**Table 9.1** Cardiomyopathies with multi-organ involvement: syndromes (*continued*)

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| | | | **Skeletal myopathy**: diffuse hypotonia<br>**Osteoarticular system**: diffuse joint laxity, ulnar deviation of wrists and fingers, splayed fingers resulting in characteristic hand posture, spatulate finger pads, abnormal fingernails, tight Achilles tendons (often developing throughout childhood), positional foot deformity, vertical talus, kyphoscoliosis, pectus carinatum, pectus excavatum, asymmetric rib cage<br>**Respiratory system**: recurrent pneumothorax, respiratory failure<br>**CNS**: Arnold–Chiari type I malformation (may develop over time), hydrocephalus, seizures, tethered cord, mental retardation<br>**Psychomotor development**: developmental delay or intellectual disability, sociable and outgoing personality<br>**Tumors**: increased occurrence of malignant solid tumors<br>**Metabolic disorders**: elevated urine catecholamine metabolites | |
| *PTPN11*<br><br><br><br><br>*RAF1*<br><br><br><br><br>*KRAS* | Protein-tyrosine phosphatase non-receptor type 11<br><br><br><br><br>V-RAF-1 murine leukemia viral oncogene homolog 1<br><br><br><br><br>V-KI-RAS2 Kirsten rat sarcoma viral | HCM<br><br><br><br><br>HCM<br><br><br><br><br>HCM | **Noonan syndrome (NS)**<br>(*PTPN11*: 50%, *SOS1*: 10-13%, *RAF1*: 3-17%, *KRAS* <5%, *BRAF* <2%, *MAP2K1* <2%, *NRAS*: rare)<br>**Perinatal history and growth**: transient or persistent cystic hygroma, polyhydramnios and hydrops fetalis (rare). Normal or mildly elevated birth weight, transient neonatal edema, feeding difficulties, failure to thrive (usually self-limited), growth delay (infancy and adolescence, short stature)<br>**Craniofacial features**:<br>• **Neonate**: tall forehead, hypertelorism, downslanting palpebral fissures, low-set posteriorly rotated ears with a thickened helix, deeply grooved philtrum with high and wide peaks to the vermillion border of the upper lip, short neck with excess nuchal skin and low posterior hairline<br>• **Infancy and childhood**: prominent eyes with horizontal fissures, hypertelorism, thickened or ptotic lids, depressed nose root with wide base and bulbous tip, facial appearance often lacking in expression | **Congenital defects**: pulmonary valve stenosis (often with dysplasia, 20–50% of patients with NS), atrial and ventricular pulmonary artery stenosis tetralogy of Fallot, coarctation of the aorta |

(*cont.*) ↓

| | | | | |
|---|---|---|---|---|
| | oncogene homolog | | • **Adolescence**: facial shape is an inverted triangle, wide at the forehead and tapering to a pointed chin. Eyes are less prominent and features are sharper. The neck lengthens, accentuating skin webbing or prominence of the trapezius muscle | |
| *NRAS* | Neuroblastoma RAS viral oncogene homolog | HCM | • **Adult**: nasolabial folds are prominent, and the skin appears transparent and wrinkled<br>**Skin and hair**: apparently low-set nipples, follicular keratosis over extensor surfaces and face, low posterior hairline, woolly hair (possible), café-au-lait spots and lentigines (possible)<br>**Psychomotor development**: mild mental retardation, language impairment | |
| *BRAF* | V-RAF murine sarcoma viral onco gene homolog B1 | HCM | **Urinary**: dilatation of the renal pelvis, duplex collecting systems, minor rotational anomalies, distal ureteric stenosis, renal hypoplasia, unilateral renal agenesis, unilateral renal ectopia, bilateral cysts with scarring<br>**Genital**: possible delayed or inadequate male puberty, cryptorchidism (60–80% of males), hypergonadotrophic hypogonadism. Possible delayed puberty in females, with normal fertility | |
| *MAP2K1* | Mitogen-activated protein kinase 1 | HCM | **Bleeding diathesis**: coagulation defects with abnormal bleeding or bruising<br>**Lymphatic**: dorsal limb (top of the foot and back of the hand) lymphedema, intestinal, pulmonary or testicular lymphangiectasia; chylous effusions of the pleural space and/or peritoneum; localized lymphedema of the scrotum or vulva | |
| *SOS1* | Son of sevenless, drosophila, homolog 1 | HCM | **Eyes**: vivid blue or blue-green irises, strabismus, refractive errors, amblyopia, nystagmus (up to 95% of cases)<br>**CNS**: Arnold–Chiari type I malformation<br>**Hematopoietic disorders**: hepatosplenomegaly (related to subclinical myelodysplasia)<br>**Auditory system**: hearing loss, low-set posteriorly rotated ears<br>**Osteoarticular system**: pectus carinatum, pectus excavatum, cubitus valgus, chinodactyly, brachidactyly<br>**Tumors**: juvenile myelomonocytic leukemia (in *PTPN11* mutations), acute lymphoblastic leukemia, acute myeloid leukemia, rhabdomyosarcoma, neuroblastoma, myeloproliferative disorders, Noonan-like/multiple giant-cell lesion syndrome | |

(*cont.*) →

**Table 9.1** Cardiomyopathies with multi-organ involvement: syndromes (*continued*)

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| *PTPN11*<br>*RAF1*<br>*BRAF* | (See Noonan syndrome)<br>(See Noonan syndrome)<br>(See Noonan syndrome) | HCM<br>HCM<br>HCM | **LEOPARD syndrome**<br>(*PTPN11*: 90%, *RAF1*: <5%, *BRAF*: <5%)<br>multiple **L**entigines, **E**lectrocardiographic conduction abnormalities, **O**cular hypertelorism, **P**ulmonic stenosis, **A**bnormal genitalia, **R**etardation of growth, and sensorineural **D**eafness.<br>**Perinatal history and growth**: normal or mildly elevated birth weight, postnatal growth retardation and short stature.<br>**Skin and hair**: multiple lentigines (dispersed, flat, black-brown macules), mostly on the face, neck and upper part of the trunk with sparing of the mucosa. In general, lentigines do not appear until age 4–5 years but then greatly increase by puberty. Café au lait spots (up to 70–80% of cases), usually preceding the appearance of lentigines. Skin hyperelasticity<br>**Eyes**: ocular hypertelorism, downslanting palpebral fissures<br>**Genitourinary**: cryptorchidism (30% of affected males), hypospadias, urinary tract defects, ovarian abnormalities (rare)<br>**Auditory system**: sensorineural hearing loss<br>**Craniofacial features**: similar to NS (although usually milder)<br>**Psychomotor development**: mild intellectual disability and cognitive defects (30% of cases) | **Congenital defects**: similar to NS |
| *BRAF*<br>*KRAS*<br>*MAP2K1* | (See Noonan syndrome)<br>(See Noonan syndrome)<br>(See Noonan syndrome) | HCM<br>HCM<br>HCM | **Cardiofaciocutaneous syndrome (CFC)**<br>(*BRAF*: approximately 75%, *MAP2K1* and *MAP2K2*: approximately 25%; *KRAS*: <2–3%)<br>**NS** and **CFC** have a great overlap in features. With respect to **NS**, **CFC** presents: More severe intellectual disability, with higher likelihood of structural CNS anomalies<br>More severe skin pathology (xerosis; hyperkeratosis of arms, legs and face; ichthyosis; keratosis pilaris; ulerythema ophryogenes; eczema; hemangiomas; café-au-lait macules; erythema; pigmented moles; palmoplantar hyperkeratosis | **Congenital defects**: pulmonary stenosis, atrial septal defects, ventricular septal defects, heart valve dysplasia, tricuspid valve dysplasia, and bicuspid aortic valve); rhythm disturbances |

(*cont.*) ↓

| | | | | |
|---|---|---|---|---|
| | | | over pressure zones)<br>More severe gastrointestinal problems, gastroesophageal reflux, aspiration, vomiting, oral aversion, dysmotility, intestinal malrotation, hernia, constipation, hepatosplenomegaly<br>Coarser facial appearance, with increased frequency of dolichocephaly and absent eyebrows<br>Less frequent blue or blue-green irises<br>Less frequent bleeding diathesis (rare) | |
| *MAP2K2* | Mitogen-activated protein kinase 2 | HCM | | |
| *ALMS1* | Alstrom syndrome protein 1 | DCM, RCM | **Alstrom syndrome**<br>**Onset**: from birth to 15 months of life (ocular manifestations); from 2 weeks to 4 months (DCM); adolescence/adulthood (RCM)<br>**Perinatal history and growth**: normal birth weight, hyperphagia and excessive weight gain during the first year of life resulting in childhood truncal obesity. Accelerated skeletal maturity and low-serum growth hormone concentrations result in adult short stature<br>**Eyes**: progressive cone dystrophy resulting in visual impairment, photophobia, nystagmus; posterior subcapsular cataract; retinitis pigmentosa<br>**Auditory system**: progressive bilateral sensorineural hearing loss, initially in the high frequency range<br>**Metabolic disorders**: insulin resistance, type 2 diabetes mellitus, hyperlipidemia, hypertriglyceridemia<br>**Psychomotor development**: delay in early developmental milestones, delay in gross and fine motor skills and in expressive and receptive language, learning disability, cognitive impairment (rare)<br>**Osteoarticular system**: scoliosis or kyphosis, flat feet, dental abnormalities<br>**Endocrine and genital**: hypogonadotropic hypogonadism. In males: delayed puberty, low plasma testosterone concentration, atrophic fibrotic seminiferous tubules, small penis and testes, gynecomastia in adolescence. In females: reduced plasma gonadotropin concentrations, hirsutism, cystic ovaries, precocious puberty, endometriosis, irregular menses, amenorrhea | |

(*cont.*) →

**Table 9.1** Cardiomyopathies with multi-organ involvement: syndromes (*continued*)

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| | | | **Kidneys**: interstitial fibrosis, tubulo-interstitial disease, progressive renal failure<br>**Urinary**: detrusor-urethral dyssynergia (lack of coordination of bladder and urethral muscle activity), urgency and long intervals between voiding, hesitancy, poor urinary flow, incontinence or retention, recurrent urinary infections<br>**Liver**: macrovesicular steatosis, hepatomegaly, progressive hepatic failure, portal hypertension, ascites, splenomegaly, esophageal varices<br>**Gastrointestinal**: epigastric pain and gastroesophageal reflux disease<br>**Respiratory system**: chronic bronchitis, frequent pneumonia, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial fibrosis | |

*CK,* creatine kinase; *CNS,* central nervous system; *DCM,* dilated cardiomyopathy; *HCM,* hypertrophic cardiomyopathy; *LVNC,* left ventricular non-compaction.

**Table 9.2** Cardiomyopathies with multi-organ involvement: metabolic cardiomyopathies

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| *LAMP2* | Lysosome-associated membrane protein 2 | HCM, DCM | **Danon disease**<br>**Onset/natural history**: median age at diagnosis: 16 years (males) and 30 years (females); median age at death: 18 years (males) and 37 years (females)<br>**Skeletal myopathy**: vacuolar myopathy with proximal muscle weakness (upper arms and neck). CK↑/↑↑<br>**CNS**: mental retardation<br>**Eyes**: choriocapillary ocular atrophy, retinal pigment disorder, retinal dysfunction with visual impairment. | **ECG**: WPW syndrome associated with massive left ventricular hypertrophy |
| *GLA* | Galactosidase, alpha | HCM | **Fabry disease**<br>**Onset/natural history**:<br>• ***Male, classic form***: onset during childhood or adolescence. Mean age of death: 41 years (Residual α-galactosidase activity: <1%)<br>• ***Male, renal variant***: onset over 25 years of age. Mean age of death: >60 years (Residual α-galactosidase activity: >1%)<br>• ***Male, cardiac variant***: onset over 40 years of age. Mean age of death: >60 years. (Residual α-galactosidase activity: >1%)<br>• ***Female, "carrier" form***: age of onset and clinical history are variable (from asymptomatic throughout a normal lifespan to as severe as affected males). (Residual α-galactosidase activity: variable and unreliable for the diagnosis)<br>**Skin**: angiokeratomas (clusters of individual punctate, dark red to blue-black angiectasis in the superficial layers of the skin, may be flat or slightly raised and do not blanch with pressure), frequently clustering between the umbilicus and the knees and commonly involve the hips, back, thighs, buttocks, penis and scrotum, and tend to be bilaterally symmetric. The oral mucosa, conjunctiva and other mucosal areas are commonly involved. Number and size of angiokeratomas progressively increase with age.<br>Anhidrosis or hypohidrosis<br>**Peripheral nervous system**: pain (acroparesthesias) occurring as episodic crises of agonizing, burning pain in the distal extremities, lasting from minutes to several days | **ECG**: short PR, conduction defects<br>**Other**: aortic and mitral valve thickening; coronary artery stenosis |

(*cont.*) →

**Table 9.2** Cardiomyopathies with multi-organ involvement: metabolic cardiomyopathies (*continued*)

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| | | | and usually triggered by exercise, fatigue, emotional stress or rapid changes in temperature and humidity. The crises usually decrease in frequency and severity with increasing age<br>**CNS**: multifocal small cerebral vessel thrombosis, transient ischemic attacks, basilar artery ischemia and aneurysm, seizures, hemiplegia, hemianesthesia, aphasia, labyrinthine disorders, cerebral hemorrhage<br>**Eyes**: cornea verticillata (corneal opacity, found in affected males and most heterozygous females). Granular anterior capsular or subcapsular deposit, lenticular opacity ("Fabry cataract"), (30% of affected males). Corneal and lenticular opacities do not interfere with visual acuity. Aneurysmal dilatation and tortuosity of conjuctival and retinal vessels (possible)<br>**Kidneys**: typical urinary sediment during childhood and adolescence (proteins, casts, red cells and birefringent lipid globules with characteristic "Maltese crosses"). Progressive proteinuria, isosthenuria, and renal failure occur with advancing age<br>**Gastrointestinal**: episodic diarrhea, nausea, vomiting, bloating, cramping abdominal pain and/or intestinal malabsorption. Achalasia and jejunal diverticulosis (may lead to perforation of the small bowel)<br>**Respiratory system**: chronic obstructive disease, chronic bronchitis, wheezing, dyspnea<br>**Auditory system**: high-frequency hearing loss, tinnitus and dizziness<br>**Psychological**: depression, anxiety, severe fatigue and other psychosocial manifestations | |
| *GAA* | Glucosidase, alpha, acid | HCM | **Glycogenosis type II or Pompe disease**<br>Onset/natural history:<br>• ***Classic infantile form***: onset in utero or before the age of 3 months. Death within the first year of life (without enzyme replacement therapy)<br>• ***Non-classic variant of infantile form***: onset within the first year of life, slow progression. Death (for ventilatory failure) in early childhood<br>• ***Late-onset forms:*** childhood, juvenile and adult-onset | **ECG**: WPW syndrome |

(*cont.*) ↓

| | | | | |
|---|---|---|---|---|
| | | | **Perinatal history and growth**: growth delay<br>**Skeletal myopathy**: hypotonia, hyporeflexia, generalized muscle weakness, feeding and swallowing difficulties, calf pseudohypertrophy, macroglossia; CK ↑↑.<br>**Respiratory system**: relapsing respiratory infections and respiratory failure<br>**Osteoarticular system**: hyperlordosis and/or scoliosis<br>**Liver**: hepatomegaly<br>**Auditory system**: hearing loss | |
| *AGL* | Amylo-1,6-glucosidase, 4-alpha-gluca-notransferase | HCM | **Glycogenosis type III or Cori–Forbes disease**<br>**Onset**: first year of life/childhood (liver disorders), childhood/adolescence (cardiac and skeletal muscle disorders)<br>**Perinatal history and growth**: growth delay (secondary to poor metabolic control)<br>**Skeletal myopathy**: slowly progressive generalized muscle weakness (severe in the third–fourth decade). CK normal or ↑<br>**Metabolic disorders**: ketotic hypoglycemia, hyperlipidemia<br>**Osteoarticular system**: osteoporosis and osteopenia<br>**Liver**: hepatomegaly and elevated hepatic transaminases<br>**Genital**: polycystic ovary disease with normal fertility | |
| *GBE1* | Glycogen branching enzyme | DCM | **Glycogenosis type IV or Andersen disease (neuromuscular forms)**<br>**Onset**: from fetal to adult age (earlier forms are the most severe)<br>**Perinatal history and growth**: the most severe form starts before birth with decrease or absence of fetal movements, arthrogryposis, hypoplastic lungs, polyhydramnios, fetal hydrops and perinatal death. Congenital forms have severe hypotonia, cardiomyopathy, depressed respiration and neuronal involvement<br>**Skeletal myopathy**: severe diffuse myopathy characterized by hypotonia, hyporeflexia and diffuse muscular atrophy involving respiratory muscles. "Myopathic face", waddling gait with hyperlordosis. Later-onset forms may present with a limb-girdle muscular dystrophy with hyperlordotic posture, waddling gait and proximal limb weakness greater in the arms than in the legs<br>**Respiratory system**: absence of spontaneous breathing at birth, respiratory failure<br>**CNS**: from subclinical neuropathy to widespread upper and lower motor neuron lesions | |

(*cont.*) →

**Table 9.2** Cardiomyopathies with multi-organ involvement: metabolic cardiomyopathies (*continued*)

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| *SLC22A5* | Solute carrier family 22 organic cation transporter, member 5 | DCM, HCM Sudden infant death syndrome | **Primary carnitine deficiency**<br>**Onset**: infancy to childhood<br>**Skeletal myopathy**: underdeveloped muscles with generalized muscle weakness. CK normal<br>**Metabolic disorders**: severally decreased plasma carnitine levels, hypoketotic hypoglycemia<br>**Liver**: hepatomegaly<br>**CNS**: mental retardation | |
| *HFE* | Hereditary hemochromatosis protein | DCM, RCM | **Hereditary hemochromatosis**<br>**Onset**: without therapy, males may develop symptoms between 40 and 60 years of age and females after menopause. In most of cases, however, they are identified before symptoms develop<br>**Liver**: hepatomegaly, liver cirrhosis, portal hypertension, hepatocellular carcinoma, end-stage liver disease<br>**Osteoarticular system**: arthropathy involving the metacarpophalangeal joints, joint stiffness and pain<br>**Endocrine and genital**: impotence from pituitary dysfunction in males, diabetes mellitus (pancreatic iron deposits)<br>**Skin**: progressive skin pigmentation resulting from deposits of melanin and iron<br>**Gastrointestinal**: aspecific abdominal pain<br>**Other**: weakness, lethargy, weight loss | Supraventricular and ventricular arrhythmias |
| *ATP7B* | Copper-transporting ATPase 2 | HCM, DCM | **Wilson disease**<br>**Onset**: ranges from 3 to over 50 years<br>**Liver**: hepatomegaly, atypical or prolonged hepatitis, hepatic cirrhosis, hepatic coma.<br>**Eyes**: Kayser-Fleischer ring (result from copper deposition in Descemet's membrane of the cornea)<br>**Kidneys**: renal tubular dysfunction, renal calculi | **Arrhythmias**: premature atrial or ventricular beats, atrial fibrillation, sino-atrial block, Mobitz type 1 atrio-ventricular block and ventricular fibrillation |

(*cont.*) ↓

| | | | | |
|---|---|---|---|---|
| | | | **CNS**: movement disorders (tremors, poor coordination, loss of fine-motor control, chorea, choreoathetosis) or rigid dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement).<br>**Psychiatric disturbance**: depression, neurotic behaviors, disorganization of personality and occasionally intellectual deterioration<br>**Osteoarticular system**: osteoporosis, osteomalacia, chondrocalcinosis, osteoarthritis, joint hypermobility<br>**Endocrine**: hypoparathyroidism<br>**Skin**:blue lunulae, acanthosis nigricans, and pretibial hyperpigmentation | |
| *IDUA* | Alpha-L-iduronidase | HCM | **Mucopolysaccharidosis type I or Hurler syndrome**<br>**Onset/natural history**: mean age of diagnosis (severe forms): 9 months. Death by cardiorespiratory failure usually occurs within the first decade<br>**Perinatal history and growth**: infants usually appear normal at birth but may have inguinal or umbilical hernias. Mild dysostosis, particularly of the hip, as well as thickening of the ribs, can be detected on radiographs at birth<br>Intellectual developmental delay by age 18 months. By age 3 years linear growth ceases<br>**Craniofacial features and voice**: coarse facies, facial bone dysostosis, thickening of the alae nasi, lips, ear lobules and tongue (becomes apparent within the first 2 years). Macrocephaly and scaphocephaly. Chronic recurrent rhinitis. Upper airway complications, narrowed trachea, thickened vocal cords, redundant tissue in the upper airway, enlarged tongue. The voice may be deep and gravelly<br>**Skin and hair**: facial and body hypertrichosis (by age 24 months), scalp hair is coarse, straight and thatch-like<br>**Liver and spleen**: massive hepatosplenomegaly (often with protuberance of the abdomen) without organ dysfunction<br>**Osteoarticular system**: progressive skeletal dysplasia (dysostosis multiplex) involving all bones. Gibbus deformity (dorsolumbar kyphosis) apparent within the first 14 months. Short stature. Spinal deformity with spinal nerve entrapment, acute spinal injury and atlanto-occipital instability. Short, thickened and irregular clavicles. Long bones are short with wide shafts; the knees are prone to valgus and varus deformities. Endochondral growth plates are thickened and disordered. Deformed pelvis. | **Valves**: mitral and aortic regurgitation secondary to progressive thickening and stiffening of the valve leaflets (may become hemodynamically significant in the later stages of disease)<br>**Arrhythmias**: sudden death<br>Other: coronary artery disease, early-onset fatal endocardiofibroelastosis |

(*cont.*) →

**Table 9.2** Cardiomyopathies with multi-organ involvement: metabolic cardiomyopathies (*continued*)

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| | | | Small femoral heads and coxa valga leading to progressive and debilitating hip deformity. Progressive arthropathy leading to severe joint deformity, joint stiffness (by age 2 years). Claw hand deformity (phalangeal dysostosis and synovial thickening). Carpal tunnel syndrome. Poor hand function<br>**Eyes**: progressive corneal clouding leading to severe visual impairment. Open-angle glaucoma. Retinal degeneration resulting in decreased peripheral vision and progressive blindness. Optic nerve compression and atrophy<br>**Auditory system**: hearing loss resulting from frequent middle ear infection (eustachian tube dysfunction), dysostosis of the ossicles of the middle ear, scarring of the tympanic membrane and damage to the eighth nerve<br>**Gastrointestinal**: inguinal and umbilical hernias. Periodic diarrhea alternating with periods of severe constipation (may or may not diminish with age)<br>**CNS**: hydrocephalus with increase in intracranial pressure (can cause rapid cognitive decline in some individuals). Severe intellectual disability, limited language skills (developmental delay, chronic hearing loss and enlarged tongue).<br>Seizures (uncommon). Placid behavior | |
| *IDS* | Iduronate-2-sulfatase | HCM | **Mucopolysaccharidosis type II or Hunter syndrome**<br>**Onset/natural history**: median age of onset of symptoms: 1.5 years; median age of diagnosis: 3.5 years. Death in the first or second decade of life (severe forms)<br>**Perinatal history and growth**: the appearance of newborns is usually normal. Early developmental milestones may be within the normal range. Delay in global developmental milestones in children with nervous system involvement, developmental regression between 6 and 8 years of age. Postnatal growth delay, short stature<br>**Craniofacial features and voice**: coarse facies, macroglossia, prominent supraorbital ridges, broad nose, broad nasal bridge, large rounded cheeks and thick lips (generally between ages 18 months and 4 years). Macrocephaly. Hypertrophic adenoids and tonsils, ankylosis of the temporomandibular joint. Swallowing difficulties. Hoarse voice. Irregular-shaped teeth, gingival overgrowth | **Valves**: mitral and aortic regurgitation secondary to progressive thickening and stiffening of the valve leaflets (may become hemodynamically significant in the later stages of disease)<br>**Arrhythmias**: sudden death<br>**Other:** coronary artery disease, early onset fatal endocardiofibroelastosis |

(*cont.*) ↓

| | | | | |
|---|---|---|---|---|
| | | | **CNS**: progressive cognitive deterioration, behavior problems. Chronic communicating hydrocephalus. Seizures. Narrowing of the spinal canal (spinal stenosis), particularly in the cervical region, with spinal cord compression<br>**Eyes**: discrete corneal lesions (not affecting vision), optic nerve head swelling, optic atrophy, progressive retinal dysfunction, visual field loss<br>**Auditory system**: conductive and sensorineural hearing loss, recurrent ear infections, otosclerosis<br>**Osteoarticular system**: joint contractures (especially of the phalangeal joints), dysostosis multiplex (generalized thickening of most long bones, particularly the ribs, with irregular epiphyseal ossification centers in many areas), notching of the vertebral bodies, hip dysplasia. Carpal tunnel syndrome<br>**Respiratory**: frequent upper respiratory tract infections (secondary to airway obstruction, thickening of respiratory secretions and stiffness of the chest wall), sleep apnea requiring positive pressure assistance and eventually tracheostomy<br>**Liver and spleen**: hepatomegaly and/or splenomegaly<br>**Gastrointestinal**: inguinal and umbilical hernias. Periodic diarrhea | |
| *SGSH*<br><br>*NAGLU* | *N*-sulfoglucosamine sulfohydrolase (type A)<br>*N*-acetylglucosaminidase, alpha (type B) | HCM | **Mucopolysaccharidosis type III or Sanfilippo syndrome (type A and B)**<br>**Onset and natural history**: onset between 2 and 6 years of age. Death because of end-stage neurodegenerative disease within the second decade<br>**CNS**: behavioral disorders (hyperkinesia, aggressiveness) and intellectual deterioration, sleep disorders. Seizures, loss of motor milestones and communication problems (around 10 years of age)<br>**Craniofacial features**: very mild dysmorphism<br>**Liver and spleen**: hepatomegaly and/or splenomegaly (usually mild)<br>**Laboratory**: *N*-acetyl-α-D-glucosaminidase deficiency in fibroblasts, heparan sulfate excretion in urine | |
| *GALNS*<br><br>*GLB1* | Galactosamine-6-sulfate sulfatase (type A)<br>Galactosidase, beta-1 (type B) | HCM | **Mucopolysaccharidosis type IV or Morquio syndrome (type A and B)**<br>**Onset**: second year of life<br>**Perinatal history and growth**: growth arrest at around 8 years of age, definitive size of 1–1.5 m<br>**Osteoarticular system**: spondylo-epiphyso-metaphyseal dysplasia, platyspondyly, | **Valves**: mitral and aortic valve thickening with regurgitation and/or stenosis (usually not severe). Endocardial fibroelastosis |

(*cont.*) →

**Table 9.2** Cardiomyopathies with multi-organ involvement: metabolic cardiomyopathies (*continued*)

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| | | | kyphosis, scoliosis, pectus carinatum, genu valgum, long bone deformities, joint hyperlaxity with frequent luxations (hips, knees), impairment in walking and daily activities<br>**CNS**: risk of spinal cord compression (secondary to cervical vertebra instability)<br>**Liver**: hepatomegaly<br>**Auditory system**: hearing loss<br>**Eyes**: corneal clouding | |
| *ARSB* | Arylsulfatase B | DCM (?), "acute CMP", endocardial, fibroelastosis | **Mucopolysaccharidosis type VI or Maroteaux–Lamy syndrome**<br>**Onset/natural history**: rapid progression form: onset at birth, death before the 2nd or 3rd decade; slow progression form: later onset, death in the 4th or 5th decade<br>**Perinatal history and growth**: postnatal growth delay, short stature<br>**Craniofacial features**: macrocephaly, coarse facies, frontal bossing, depressed nasal bridge, enlarged tongue, gingival hypertrophy, delayed dental eruption, hypertrichosis<br>**Auditory system**: conductive and sensorineural hearing loss, recurrent ear infections, otosclerosis<br>**Metabolic**: elevated urinary glycosaminoglycans (generally >100 μg/mg creatinine in rapid progression forms, <100 μg/mg creatinine in slow progression forms)<br>**Osteoarticular system**: short stature, dysostosis multiplex, degenerative joint disease, thoracic deformity (pectus carinatum), scoliosis or kyphosis (gibbus malformation)<br>**Respiratory**: frequent upper respiratory tract infections (secondary to airway obstruction, thickening of respiratory secretions and stiffness of the chest wall), sleep apnea, severe pulmonary obstruction and respiratory failure requiring tracheostomy (usually after 10 years of age)<br>**Eyes**: progressive visual impairment secondary to slowly increasing corneal clouding and optic nerve atrophy<br>**CNS**: chronic communicating hydrocephalus, usually normal intellectual development. May have intellectual impairment secondary to severe visual/hearing disabilities in infancy. Cervical spinal cord compression and lesions<br>**Liver**: hepatomegaly | **Valves**: mitral, aortic and tricuspid valve insufficiency or stenosis often requiring substitution in rapid progression forms (after 10 years of age)<br>**Other**: coronary artery disease (rare) |

(*cont.*) ↓

| | | | | |
|---|---|---|---|---|
| *GUSB* | Beta-glucuronidase | ? | **Mucopolysaccharidosis type VII or Sly syndrome**<br>**Onset/natural history**: from severe prenatal/perinatal forms to mild forms with later onset (adolescence)<br>**Perinatal history and growth**: non-immune hydrops fetalis, short stature<br>**Craniofacial features**: dysmorphism of variable degree<br>**Liver and spleen**: hepatomegaly and/or splenomegaly<br>**Osteoarticular system**: club feet, dysostosis, thoracic kyphosis<br>**CNS**: severe hypotonia, neurological disorders, severe intellectual deficit | **Valves**: mitral and aortic valve thickening with regurgitation and/or stenosis |
| *GNPTAB* | *N*-acetylglucosamine-1-phosphotransferase, alpha/beta subunits | HCM, DCM | **Mucolipidosis type II alpha/beta**<br>**Onset/natural history**: clinical onset at birth, fatal outcome often in early childhood<br>**Perinatal history and growth**: low to borderline normal birth weight. Postnatal growth is limited and often ceases during the second year of life. Failure to thrive. Length decrease over time (hip and knee contractures). Head size is proportional to body size<br>**Craniofacial features**: flat midface, flat nasal bridge, shallow orbits, prominent mouth, coarse facial features, gingival hypertrophy, prominent periorbital tortuous veins, telangiectatic capillaries over the cheeks<br>**Eyes**: epicanthal folds, corneal haziness<br>**Auditory system**: recurrent otitis media, conductive hearing loss<br>**Respiratory**: narrow airways, progressive mucosal thickening, respiratory insufficiency<br>**Osteoarticular system**: thoracic deformity, kyphosis, clubfeet, deformed long bones, dislocation of the hips<br>**CNS**: delayed early motor milestones, unaided walking is never achieved, expressive language is late and limited to single words, impaired cognitive function | **Valves**: mitral and aortic valve thickening and insufficiency. Pulmonary hypertension |
| *GLB1* | Galactosidase, beta-1 | HCM, DCM | **Gangliosidosis type 1**<br>**Onset/natural history**: onset within the first 3 months of life, death in infancy<br>**Perinatal history and growth**: retardation or arrest of development during the first 6 months of life, followed by progressive neurological deterioration. Dwarfism<br>**Craniofacial features**: coarse facies, full forehead, flat nose, gingival hyperplasia, short neck | **Valves**: mitral valve thickening with vacuolated histiocytes and fibrous tissue<br>**Other:** coronary artery disease |

(*cont.*) →

**Table 9.2** Cardiomyopathies with multi-organ involvement: metabolic cardiomyopathies (*continued*)

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| | | | **Eyes**: macular cherry red spots, amaurosis, hypertelorism, clear cornea<br>**Osteoarticular system**: kyfoscoliosis, hypoplastic vertebral bodies, beaked vertebral bodies, joint stiffness, thick ribs<br>**Liver/spleen**: hepatomegaly and splenomegaly<br>**Kidneys**: Glomerular epithelial cytoplasmic vacuolization<br>**CNS**: progressive encephalopathy with mental retardation and cerebral degeneration<br>**Auditory system**: conductive and sensorineural hearing loss, recurrent ear infections, otosclerosis<br>**Metabolic**: no mucopolysaccharidu ria, β-galactosidase-1 deficiency, elevated urinary oligosaccharide levels | |
| *AGXT* | Alanine-glycoxylate aminotransferase | HCM, DCM, RCM | **Primary hyperoxaluria type I**<br>**Onset**: onset of symptoms ranges from 1 to 57 years of age<br>**Kidneys**: early nephrocalcinosis and renal failure (infantile form), recurrent urolithiasis and progressive renal failure (late onset forms), hematuria, pyelonephritis, hydronephrosis<br>**Osteoarticular system**: multiple fractures, osteosclerosis<br>**Eyes**: retinopathy, optic atrophy<br>**Nervous system**: peripheral neuropathy<br>**Hematologic**: pancytopenia<br>**Liver and spleen**: hepatosplenomegaly<br>**Endocrine**: hypothyroidism | |

*CK,* creatine kinase; *CMP,* cardiomyopathy; *CNS,* central nervous system; *DCM,* dilated cardiomyopathy; *ECG,* electrocardiogram; *HCM,* hypertrophic cardiomyopathy; *WPW,* Wolff–Parkinson–White.

**Table 9.3** Cardiomyopathies with multi-organ involvement: mitochondrial cardiomyopathies

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| *MTTL1* | Transfer RNA, mitochondrial, leucine, 1 | HCM, DCM | **MELAS syndrome** (**M**itochondrial myopathy, **E**ncephalopathy, **L**actic **A**cidosis, **S**troke-like episodes)<br>(**MELAS** syndrome can be caused by mutations in several mtDNA genes, but CMPs are described only for the genes listed in the first column) | **ECG and arrhythmias**: WPW syndrome, conduction blocks |
| *MTTH* | Transfer RNA, mitochondrial, histidine | HCM, DCM | **Onset**: typically in childhood (between 2 and 10 years of age), possible late onset (until age 40 years)<br>**Growth**: short stature<br>**Skeletal myopathy**: mitochondrial myopathy with lactic acidosis and/or ragged red fibers on muscle biopsy, exercise intolerance, proximal limb weakness | |
| *MTTK* | Transfer RNA, mitochondrial, lysine | HCM | **CNS**: generalized tonic-clonic seizures, recurrent headaches, stroke-like episodes, transient or permanent hemiparesis or cortical blindness, impaired mentation, dementia, drop attacks, nausea, vomiting, learning disability, elevated CSF proteins, basal ganglia calcification, myoclonus, episodic coma, cerebellar signs<br>**Eyes**: optic atrophy, pigmentary retinopathy, hemianopsia, progressive external ophthalmoplegia<br>**Auditory system**: sensorineural hearing loss<br>**Metabolic disorders**: diabetes mellitus<br>**Gastrointestinal**: recurrent vomiting, anorexia | |
| *NDUFA2* | NADH-ubiquinone oxidoreductase 1 alpha subcomplex, 2 | HCM | **Leigh syndrome**<br>(**Leigh** syndrome can be caused by mutation in several mtDNA genes, but CMPs are described only for the genes listed in the first column)<br>**Onset/natural history**: typically between 3 and 12 months of age (often following a viral infection). Mean age of death: 2–3 years. Later onset forms (from 1 year of age to adulthood) in up to 25% of cases (with slower progression)<br>**Growth**: poor feeding, failure to thrive, developmental delay<br>**CNS**: progressive neurodegenerative disorder (subacute necrotizing | **ECG**: cardiac conduction defects, pre-excitation, prolongation of QT interval |
| *NDUFA10* | NADH-ubiquinone oxidoreductase 1 alpha subcomplex, 10 | HCM | | |

(*cont.*) →

**Table 9.3** Cardiomyopathies with multi-organ involvement: mitochondrial cardiomyopathies (*continued*)

| Gene | Protein | Main cardiac phenotype | Multi-organ involvement | Other cardiac disorders and arrhythmias |
|---|---|---|---|---|
| *NDUFS4* | NADH-ubiquinone oxidoreductase Fe-S protein | HCM | encephalomyelopathy) characterized by hypotonia, spasticity, dystonia, muscle weakness, hypo- or hyperreflexia, seizures (myoclonic or generalized tonic-clonic), infantile spasms, movement disorders (including chorea), cerebellar ataxia, and peripheral neuropathy. Brain stem lesions may cause respiratory difficulty (apnea, hyperventilation, or irregular respiration), swallowing difficulty, persistent vomiting, and abnormalities of thermoregulation (hypothermia and hyperthermia)<br>**Psychomotor development**: psychomotor retardation or regression<br>**Kidneys**: renal tubulopathy or diffuse glomerulocystic kidney damage<br>**Liver**: hepatomegaly, hepatic failure<br>**Eyes**: nystagmus, ophthalmoplegia, strabism, optic atrophy<br>**Gastrointestinal**: recurrent vomiting | |
| *NDUFS8* | NADH-ubiquinone oxidoreductase Fe-S protein 8 | HCM | | |
| *COX15* | Cytochrome c oxidase assembly protein COX15 | HCM | | |
| *FOXRED1* | FAD-dependent oxidoreductase domain -containing protein 1 | HCM | | |
| *SDHA* | Succinate dehydrogenase flavoprotein subunit A | DCM | | |
| *MTTL1* | Transfer RNA, mitochondrial, leucine, 1 | HCM, DCM | **MERRF syndrome** (**M**yoclonic, **E**pilepsy with **R**agged **R**ed **F**ibers) (**MERRF** syndrome can be caused by mutations in several mtDNA genes, but CMPs are described only for the genes listed in the first column)<br>**Onset**: typically in childhood, after a normal early development<br>**Growth**: normal early development, short stature<br>**Skeletal myopathy**: generalized myopathy with ragged red fibers on muscle biopsy, exercise intolerance, lactic acidosis<br>**CNS**: myoclonus, generalized epilepsy, dementia, peripheral neuropathy | **ECG**: WPW syndrome |
| *MTTH* | Transfer RNA, mitochondrial, histidine | HCM, DCM | | |
| *MTTK* | Transfer RNA, mitochondrial, lysine | HCM | | |

(*cont.*) ↓

| | | | |
|---|---|---|---|
| | | **Eyes**: optic atrophy, pigmentary retinopathy, ophthalmoparesis<br>**Auditory system**: sensorineural hearing loss | |
| *MTTL1* (see page 106)<br>*Multiple mtDNA deletions* | DCM | **Kearns–Sayre syndrome (KSS)**<br>(note: more than 150 different mtDNA deletions, ranging in size from 1.1 kb to 10 kb, have been associated with KSS)<br>**Onset**: childhood to adolescence (before 20 years of age)<br>**Growth**: short stature<br>**Eyes**: pigmentary retinopathy (fundus oculi: atypical "salt and pepper" retinopathy), progressive external ophtalmoplegia, palpebral ptosis<br>**CNS**: cerebellar ataxia, basal ganglia calcifications, diffuse signal abnormality of central white matter, intellectual disability, dementia, seizures, sensory neuropathy, motor neuropathy, CSF protein >100 mg/dl<br>**Skeletal myopathy**: oropharyngeal and esophageal dysfunction, exercise intolerance, proximal more than distal limb muscle weakness<br>**Auditory system**: sensorineural hearing loss<br>**Endocrine**: diabetes mellitus, hypoparathyroidism, growth hormone deficiency, Addison disease<br>**Kidneys**: renal tubular acidosis, Fanconi syndrome | **ECG**: AV blocks and conduction defects, WPW |
| *18 known allelic variants associated with many missense mutations in the mtDNA* | ? (no definite CMP has been documented) | **LHON syndrome** (**L**eber **H**ereditary **O**ptic **N**europathy)<br>**Onset**: young adult (typically in the second to third decade). More frequent in **males** (male/female ratio: 4:1 to 5:1)<br>**Eyes**: bilateral, painless, subacute visual failure with characteristic enlarging dense central or centrocecal scotoma. Develops in young adult life and rapidly evolves to optic discs atrophy and blindness<br>**CNS**: postural tremor, peripheral neuropathy, movement disorders<br>**Skeletal myopathy**: from non-specific myopathy to muscular dystrophy-like disease (more frequent in women) | **ECG**: cardiac conduction defects, pre-excitation, prolongation of QT interval |

*AV,* atrioventrcular; *CK*, creatine kinase; *CMP,* cardiomyopathy; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *DCM,* dilated cardiomyopathy; *ECG,* electrocardiogram; *HCM,* hypertrophic cardiomyopathy; *mtDNA,* mitochondrial DNA; *WPW*, Wolff–Parkinson–White.

## References


1. Isnard R, Kalotka H, Durr A et al (1997) Correlation between left ventricular hypertrophy and GAA trinucleotide repeat length in Friedreich's ataxia. Circulation 95:2247–2249
2. Casazza F, Morpurgo M (1996) The varying evolution of Friedreich's ataxia cardiomyopathy. Am J Cardiol 77:895–898. doi:10.1016/S0002-9149(97)89194-1
3. Barth PG, Valianpour F, Bowen VM et al (2004) X-linked cardioskeletal myopathy and neutropenia (Barth syndrome): an update. Am J Med Genet A 126A:349–354. doi:10.1002/ajmg.a.20660
4. Christodoulou J, McInnes RR, Jay V et al (1994) Barth syndrome: clinical observations and genetic linkage studies. Am J Med Genet 50:255–264. doi:10.1002/ajmg.1320500309
5. Bione S, D'Adamo P, Maestrini E et al (1996) A novel X-linked gene, G4.5. is responsible for Barth syndrome. Nat Genet 12:385–389. doi:10.1038/ng0496-385
6. Lin AE, Grossfeld PD, Hamilton RM et al (2002) Further delineation of cardiac abnormalities in Costello syndrome. Am J Med Genet 111:115–129. doi:10.1002/ajmg.10558
7. Hinek A, Teitell MA, Schoyer L et al (2005) Myocardial storage of chondroitin sulfate-containing moieties in Costello syndrome patients with severe hypertrophic cardiomyopathy. Am J Med Genet A 133A:1–12. doi:10.1002/ajmg.a.30495
8. Gorlin RJ, Anderson RC, Blaw M (1969) Multiple lentigenes syndrome. Am J Dis Child 117:652–662
9. St John Sutton MG, Tajik AJ, Giuliani ER et al (1981) Hypertrophic obstructive cardiomyopathy and lentiginosis: a little known neural ectodermal syndrome. Am J Cardiol 47:214–217
10. Digilio MC, Sarkozy A, de Zorzi A et al (2006) LEOPARD syndrome: clinical diagnosis in the first year of life. Am J Med Genet A 140 (7):740–746. doi:10.1002/ajmg.a.31156
11. Limongelli G, Sarkozy A, Pacileo G et al (2008) Genotype-phenotype analysis and natural history of left ventricular hypertrophy in LEOPARD syndrome. Am J Med Genet A 146A:620–628. doi:10.1002/ajmg.a.32206
12. Peter JR, Kemp JS (1990) LEOPARD syndrome: death because of chronic respiratory insufficiency. Am J Med Genet 37:340–341. doi:10.1002/ajmg.1320370309
13. Lemire EG (2002) Noonan syndrome or new autosomal dominant condition with coarctation of the aorta, hypertrophic cardiomyopathy, and minor anomalies. Am J Med Genet 113:286–290. doi:10.1002/ajmg.10782
14. Croonen EA, van der Burgt I, Kapusta L, Draaisma JM (2008) Electrocardiography in Noonan syndrome PTPN11 gene mutation—phenotype characterization. Am J Med Genet A 146:350–353. doi:10.1002/ajmg.a.32140
15. van Der Burgt I, Brunner H (2000) Genetic heterogeneity in Noonan syndrome: evidence for an autosomal recessive form. Am J Med Genet 94:46–51
16. Cirstea IC, Kutsche K, Dvorsky R et al (2010) A restricted spectrum of NRAS mutations causes Noonan syndrome. Nat Genet 42:27–29. doi:10.1038/ng.497
17. Pandit B, Sarkozy A, Pennacchio LA et al (2007) Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy. Nat Genet 39:1007–1012. doi:10.1038/ng2073
18. Roberts A, Allanson J, Jadico SK et al (2006) The cardiofaciocutaneous syndrome. J Med Genet 43:833–842. doi:10.1136/jmg.2006.042796
19. Tay SK, Shanske S, Kaplan P, DiMauro S (2004) Association of mutations in SCO2, a cytochrome c oxidase assembly gene, with early fetal lethality. Arch Neurol 61:950–952. doi:10.1001/archneur.61.6.950
20. Marshall JD, Hinman EG, Collin GB et al (2007) Spectrum of ALMS1 variants and evaluation of genotype-phenotype correlations in Alstrom syndrome. Hum Mutat 28:1114–1123. doi:10.1002/humu.20577
21. Russell-Eggitt IM, Clayton PT, Coffey R et al (1998) Alstrom syndrome. Report of 22 cases and literature review. Ophthalmology 105:1274–1280. doi:10.1016/S0161-6420(98)97033-6
22. Michaud JL, Heon E, Guilbert F et al (1996) Natural history of Alstrom syndrome in early childhood: onset with dilated cardiomyopathy. J Pediatr 128:225–229

23. Marshall JD, Paisey RB, Carey C et al (2003 – updated 2012 May 31) Alström Syndrome. In: Pagon RA, Bird TD, Dolan CR (eds) Gene Reviews (Internet). University of Washington, Seattle, 1993
24. Danon MJ, Oh SJ, DiMauro S, Manaligod JR et al (1981) Lysosomal glycogen storage disease with normal acid maltase. Neurology 31:51–57
25. Sugie K, Yamamoto A, Murayama K et al (2002) Clinicopathological features of genetically confirmed Danon disease. Neurology 58:1773–1778
26. Arad M, Maron BJ, Gorham JM et al (2005) Glycogen storage diseases presenting as hypertrophic cardiomyopathy. N Engl J Med 352:362–372. doi:10.1056/NEJMoa033349
27. Nishino I, Fu J, Tanji K et al (2000) Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). Nature 406:906–910. doi:10.1038/35022604
28. Charron P, Villard E, Sebillon P et al (2004) Danon's disease as a cause of hypertrophic cardiomyopathy: a systematic survey. Heart 90:842–846. doi:10.1136/hrt.2003.029504
29. Taylor MR, Ku L, Slavov D et al (2007) Danon disease presenting with dilated cardiomyopathy and a complex phenotype. J Hum Genet 52:830–835. doi:10.1007/s10038-007-0184-8
30. Senechal M, Germain DP (2003) Fabry disease: a functional and anatomical study of cardiac manifestations in 20 hemizygous male patients. Clin Genet 63:46–52
31. Ogawa K, Sugamata K, Funamoto N et al (1990) Restricted accumulation of globotriaosylceramide in the hearts of atypical cases of Fabry's disease. Hum Pathol 21:1067–1073
32. Nagao Y, Nakashima H, Fukuhara Y et al (1991) Hypertrophic cardiomyopathy in late-onset variant of Fabry disease with high residual activity of alpha-galactosidase A. Clin Genet 39:233–237
33. Melegh B, Bene J, Mogyorosy G et al (2004) Phenotypic manifestations of the OCTN2 V295X mutation: sudden infant death and carnitine-responsive cardiomyopathy in Roma families. Am J Med Genet A 131:121–126. doi:10.1002/ajmg.a.30207
34. Gilbert-Barness E, Barness LA (1999) Disorders of metal metabolism. Eaton Press, Natick, Massachusetts
35. Bottiger LE, Mollerberg H (1959) Increased copper content of hypertrophic myocardium. Acta Med Scand 165:413–416
36. Azevedo EM, Scaff M, Barbosa ER et al (1978) Heart involvement in hepatolenticular degeneration. Acta Neurol Scand 58:296–303
37. Kuan P (1987) Cardiac Wilson's disease. Chest 91:579–583
38. Donaldson MD, Pennock CA, Berry PJ et al (1989) Hurler syndrome with cardiomyopathy in infancy. J Pediatr 114:430–432
39. Dangel JH (1998) Cardiovascular changes in children with mucopolysaccharide storage diseases and related disorders – clinical and echocardiographic findings in 64 patients. Eur J Pediatr 157:534–538
40. Wraith JE, Scarpa M, Beck M et al (2008) Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy. Eur J Pediatr 167:267–277. doi:10.1007/s00431-007-0635-4
41. Hishitani T, Wakita S, Isoda T et al (2000) Sudden death in Hunter syndrome caused by complete atrioventricular block. J Pediatr 136:268–269
42. Gross DM, Williams JC, Caprioli C et al (1988) Echocardiographic abnormalities in the mucopolysaccharide storage diseases. Am J Cardiol 61:170–176
43. Cleary MA, Wraith JE (1993) Management of mucopolysaccharidosis type III. Arch Dis Child 69:403–406
44. Van Hove JL, Wevers RA, Van Cleemput J et al (2003) Late-onset visceral presentation with cardiomyopathy and without neurological symptoms of adult Sanfilippo A syndrome. Am J Med Genet A 118A:382–387. doi:10.1002/ajmg.a.20068
45. John RM, Hunter D, Swanton RH (1990) Echocardiographic abnormalities in type IV mucopolysaccharidosis. Arch Dis Child 65:746–749
46. Golda A, Jurecka A, Tylki-Szymanska A (2011) Cardiovascular manifestations of mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome). Int J Cardiol. doi:10.1016/j.ijcard.2011.06.097

47. Miller G, Partridge A (1983) Mucopolysaccharidosis type VI presenting in infancy with endocardial fibroelastosis and heart failure. Pediatr Cardiol 4:61–62
48. Fong LV, Menahem S, Wraith JE, Chow CW (1987) Endocardial fibroelastosis in mucopolysaccharidosis type VI. Clin Cardiol 10:362–364
49. Hayflick S, Rowe S, Kavanaugh-McHugh A Golda A, Jurecka A (1992) Acute infantile cardiomyopathy as a presenting feature of mucopolysaccharidosis VI. J Pediatr 120:269–272
50. Swiedler SJ, Beck M, Bajbouj M et al (2005) Threshold effect of urinary glycosaminoglycans and the walk test as indicators of disease progression in a survey of subjects with Mucopolysaccharidosis VI (Maroteaux–Lamy syndrome). Am J Med Genet A 134A:144–150. doi:10.1002/ajmg.a.30579
51. Azevedo AC, Schwartz IV, Kalakun L et al (2004) Clinical and biochemical study of 28 patients with mucopolysaccharidosis type VI. Clin Genet 66:208–213. doi:10.1111/j.1399-0004.2004.00277.x
52. Keller C, Briner J, Schneider J et al (1987) [Mucopolysaccharidosis 6-A (Maroteaux-Lamy disease): comparison of clinical and pathologico-anatomic findings in a 27-year-old patient]. Helv Paediatr Acta 42:317–333
53. Satoh Y, Sakamoto K, Fujibayashi Y et al (1983) Cardiac involvement in mucolipidosis. Importance of non-invasive studies for detection of cardiac abnormalities. Jpn Heart J 24:149–159
54. Schulz R, Vogt J, Voss W, Hanefeld F (1987) [Mucolipidosis type II (I-cell disease) with unusually severe heart involvement]. Monatsschr Kinderheilkd 135:708–711
55. Nagashima K, Sakakibara K, Endo H et al (1977) I-cell disease (mucolipidosis 11). Pathological and biochemical studies of an autopsy case. Acta Pathol Jpn 27:251–264
56. Benson PF, Barbarik A, Brown SP, Mann TP (1976) GM1-generalized gangliosidosis variant with cardiomegaly. Postgrad Med J 52:159–165
57. Hadley RN, Hagstrom JW (1971) Cardiac lesions in a patient with familial neurovisceral lipidosis (generalized gangliosidosis). Am J Clin Pathol 55:237–240
58. Morrone A, Bardelli T, Donati MA et al (2000) Beta-galactosidase gene mutations affecting the lisosomal enzyme and the elastin-binding protein in GM1-gangliosidosis patients with cardiac involvement. Hum Mutat 15(4):354-66
59. Schulze MR, Wachter R, Schmeisser A, Fischer R, Strasser RH (2006) Restrictive cardiomyopathy in a patient with primary hyperoxaluria type II. Clin Res Cardiol 95:235–240. doi:10.1007/s00392-006-0362-2
60. Van Driessche L, Dhondt A, De Sutter J (2007) Heart failure with mitral valve regurgitation due to primary hyperoxaluria type 1: case report with review of the literature. Acta Cardiol 62:202–206
61. Yoshioka J, Park YD, Tanaka Y et al (2001) Echocardiographic features in a patient with primary oxalosis. Echocardiography 18:599–602
62. Rodby RA, Tyszka TS, Williams JW (1991) Reversal of cardiac dysfunction secondary to type 1 primary hyperoxaluria after combined liver-kidney transplantation. Am J Med 90:498–504
63. Detry O, Honore P, DeRoover A et al (2002) Reversal of oxalosis cardiomyopathy after combined liver and kidney transplantation. Transpl Int 15:50–52. doi:10.1007/s00147-001-0364-y
64. Schapira AH (2006) Mitochondrial disease. Lancet 368:70–82. doi:10.1016/S0140-6736(06)68970-8
65. Leigh D (1951) Subacute necrotizing encephalomyelopathy in an infant. J Neurol Neurosurg Psychiatry 14:216–221
66. Santorelli FM, Tessa A, D'Amati G, Casali C (2001) The emerging concept of mitochondrial cardiomyopathies. Am Heart J 141:E1. doi:10.1067/mhj.2001.112088
67. Guenthard J, Wyler F, Fowler B, Baumgartner R (1995) Cardiomyopathy in respiratory chain disorders. Arch Dis Child 72:223–226
68. Hoppel CL, Kerr DS, Dahms B, Roessmann U (1987) Deficiency of the reduced nicotinamide adenine dinucleotide dehydrogenase component of complex I of mitochondrial electron transport. Fatal infantile lactic acidosis and hypermetabolism with skeletal-cardiac myopathy and encephalopathy. J Clin Invest 80:71–77. doi:10.1172/JCI113066

69. Moreadith RW, Batshaw ML, Ohnishi T et al (1984) Deficiency of the iron-sulfur clusters of mitochondrial reduced nicotinamide-adenine dinucleotide-ubiquinone oxidoreductase (complex I) in an infant with congenital lactic acidosis. J Clin Invest 74:685–697. doi:10.1172/JCI111484
70. Reichmann H, Angelini C (1994) Single muscle fibre analyses in 2 brothers with succinate dehydrogenase deficiency. Eur Neurol 34:95–98
71. Papadimitriou A, Neustein HB, Dimauro S et al (1984) Histiocytoid cardiomyopathy of infancy: deficiency of reducible cytochrome b in heart mitochondria. Pediatr Res 18:1023–1028
72. Sacconi S, Salviati L, Sue CM et al (2003) Mutation screening in patients with isolated cytochrome c oxidase deficiency. Pediatr Res 53:224–230
73. Holme E, Greter J, Jacobson CE et al (1992) Mitochondrial ATP-synthase deficiency in a child with 3-methylglutaconic aciduria. Pediatr Res 32:731–735
74. Zeviani M, Gellera C, Antozzi C et al (1991) Maternally inherited myopathy and cardiomyopathy: association with mutation in mitochondrial DNA tRNA(Leu)(UUR). Lancet 338:143–147
75. Antozzi C, Zeviani M (1997) Cardiomyopathies in disorders of oxidative metabolism. Cardiovasc Res 35:184–199

# The Role of Clinical Observation: Red Flag 8 – Cardiomyopathies in the First Year of Life and Pediatric Cardiomyopathies

10

Fulvio Camerini, Enrico Fabris, Rossana Bussani and Gianfranco Sinagra

Pediatric cardiomyopathies (CMPs) are complex and present challenges to both cardiologists and pediatricians.

The incidence of pediatric CMPs is significantly higher in the first year of life than at an older age. In a study by Lipshultz et al. [1], who analyzed data from the pediatric CMP registry (467 cases) sponsored by the National Heart Lung and Blood Institute, 41% of cases had received a diagnosis of CMP in the first 12 months of life. More specifically, in comparison with the groups of children between 1 and 18 years old, the annual incidence of CMPs in infants less than 1 year old was markedly higher (8.3 versus 0.7 per 100,000 children). A similar conclusion was reached for all types of CMP (with the exception of few cases of restrictive CMP) in an epidemiological study carried out in Australia [2], with peak incidence occurring before the age of 3 months.

All types of CMP may be present in early childhood. The most frequent type is dilated cardiomyopathy (DCM), while familial hypertrophic cardiomyopathy (HCM) caused by contractile protein abnormalities usually develops, at least in some series, after the first decade of life [2].

Considering the etiology, in the first year of life the majority of cases of DCM have been classified as "idiopathic" [3]. More specifically, in a group of 591 patients diagnosed with DCM in the first year of life, 460 (77.8%) had a diagnosis of idiopathic DCM, 26 (4.3%) had a diagnosis of familial DCM, and 65 (10.9%) had a diagnosis of myocarditis, while in the remaining patients (6.7%) the DCM was associated with skeletal muscle disorders, inborn errors of metabolism or malformation syndromes. Similar data have been observed in studies of patients with HCM [4]; in a group of 855 patients of less than 18 years of age, the majority (74.2%) had idiopathic HCM, and in 35.8% of these children the diagnosis was made in the first year of life. Systematic use of pre-

G. Sinagra (✉)
Cardiovascular Department,
Ospedali Riuniti and University of Trieste, Italy
email: gianfranco.sinagra@aots.sanita.fvg.it

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_10, © Springer-Verlag Italia 2013

natal and neonatal echocardiography will probably increase the number of patients with a diagnosis of HCM (Figs. 10.1, 10.2 and 10.3).

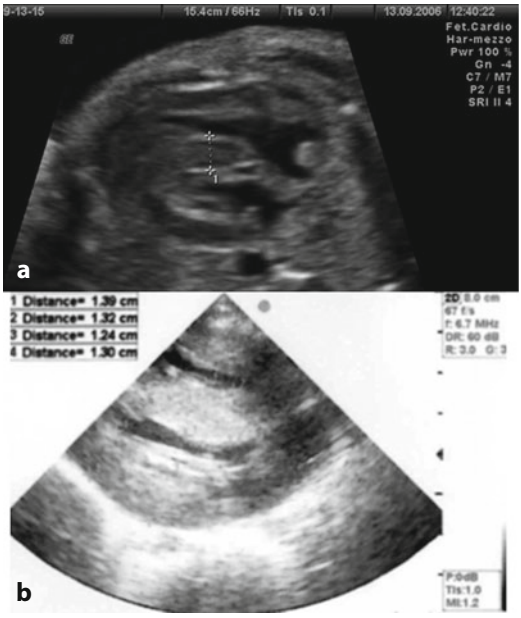
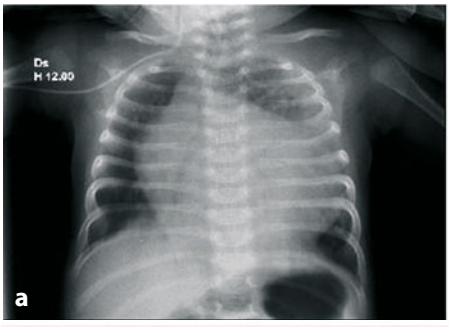



**Fig. 10.1** Prenatal and neonatal hypertrophic cardiomyopathy. **a** Fetal echocardiogram at 30 weeks of age. Note left ventricular septum hypertrophy (0.65 cm). **b** Echocardiogram at 2 months of age. Note massive biventricular hypertrophy (Courtesy of Dr Alessandra Benettoni, Institute for Maternal and Child Health-IRCCS Burlo Garofolo, Trieste, Italy)



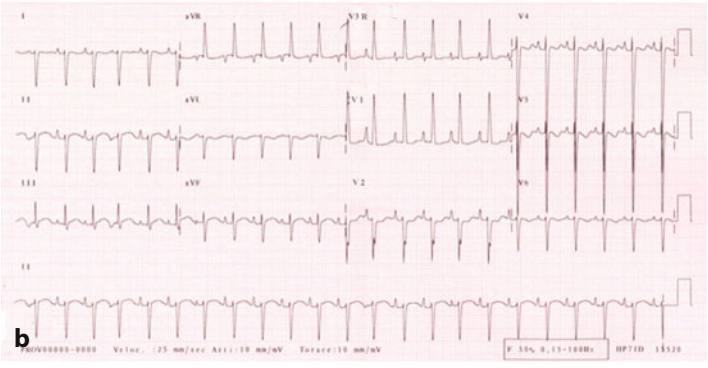




**Fig. 10.2** Prenatal and neonatal hypertrophic cardiomyopathy (same patient as in Fig. 10.1). **a** Chest X-ray showing severe enlargement of the heart. **b** Electrocardiogram showing sinus tachycardia 120 bpm, P waves suggestive of right atrial dilatation, and biventricular hypertrophy (Courtesy of Dr Alessandra Benettoni, Institute for Maternal and Child Health-IRCCS Burlo Garofolo, Trieste, Italy)

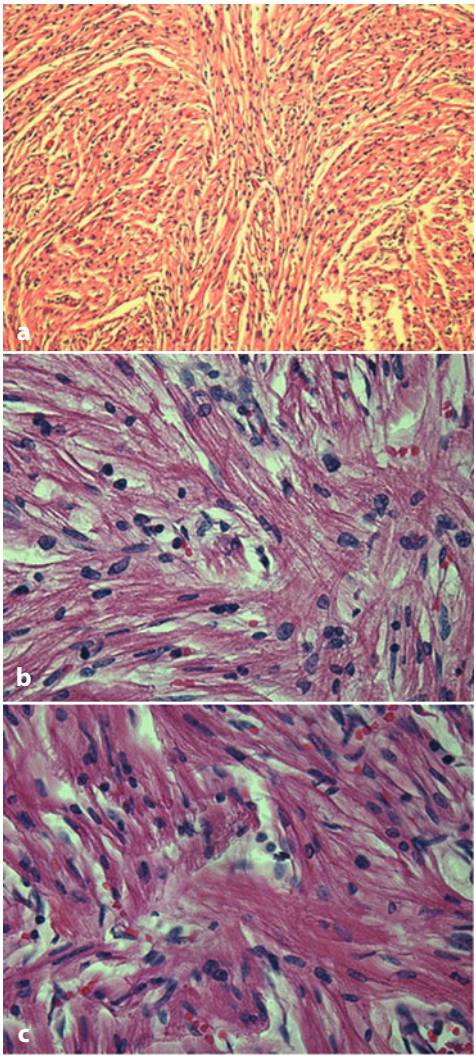



**Fig. 10.3** Prenatal and neonatal hypertrophic cardiomyopathy (same patient as in Figs 10.1 and 10.2). **a**,**b**,**c** Postmortem histological findings. H&E, ×10 (**a**), ×40 (**b**,**c**). Note the hypertrophy of the myocells and evident myocellular disarray

Among the recognizable genetic conditions associated with CMP in the first year of life, inborn errors of metabolism comprise the largest group [5]. Inborn errors of metabolism are characterized by defects in enzymes involved in intermediary metabolism (breakdown of proteins, lipids and carbohydrates) or energy production (e.g., oxidative phosphorylation) [6]. Inborn errors of metabolism are complex and multiform, and many distinct disorders have been identified [6]. The majority of cases are inherited in autosomal-recessive manner, while a few are X-linked.

The clinical consequences are more often evident in the neonatal period, and in about 5% of cases inborn errors of metabolism may be complicated by CMP, which is more frequently hypertrophic, but dilated and mixed forms have also been observed [6].

It is rare that the heart is the only organ affected in pediatric CMP of metabolic etiology; the CMP is usually part of a complex multiform clinical syndrome. According to Cox et al. [6], different types of inborn errors of metabolism are frequently associated with specific "types" of CMP. Disorders of glycogen metabolism are usually characterized by a HCM phenotype; the most common is Pompe disease, which is usually clinically evident in the first few months of life, and is associated with hypotonia and muscle weakness. In contrast, in the DCM group, oxidative phosphorylation defects and systemic carnitine deficiency are the most common causes.

In fact, Cox et al. [6] suggested that, from a pathogenetic point of view, diseases associated with a storage of glycogen, fat or lysosomal substrates frequently manifest themselves with a phenotype of HCM, while DCM is often present in inborn errors of metabolism characterized by "an excess of acid metabolites, such as organic acidemias, aminoacidopathies and systemic carnitine deficiency".

It also seems that, at least in some cases, the same "error of metabolism" may cause different types of heart muscle disease.

When heart involvement is present, the clinical approach should be directed toward the identification of signs of a multi-systemic pathology: peculiar physical appearance, neurological abnormalities, skeletal myopathies, abnormalities of the skeleton, etc. Laboratory findings are also very important; for example, the presence of hypoglycemia, metabolic acidosis, hyperammonemia, carnitine levels or ketoacidosis, as well as the detection of specific metabolites in the urine.

In this complex field of pediatric cardiology, which needs a strict cooperation between pediatricians, genetists and cardiologists, an early diagnosis is important, considering the fact that energy source, diet, dietary supplements, avoidance of fasting, replacement of missing enzymes, stem cells and organ transplantation may improve the prognosis of these disorders. Sometimes dramatic improvements can be seen, such as with the administration of high doses of carnitine in children with carnitine deficiency [6].

## References

1. Lipshultz SE, Sleeper LA, Towbin JA et al (2003) The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 348:1647–1655. doi:10.1056/NEJMoa021715
2. Nugent AW, Daubeney PE, Chondros P et al (2003) The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med 348:1639–1646. doi:10.1056/NEJMoa021737
3. Towbin JA, Lowe AM, Colan SD et al (2006) Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA 296:1867–1876. doi:10.1001/jama.296.15.1867

4. Colan SD, Lipshultz SE, Lowe AM et al (2007) Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. Circulation 115:773–781. doi:10.1161/CIRCULATIONAHA.106.621185
5. Schwartz ML, Cox GF, Lin AE et al (1996) Clinical approach to genetic cardiomyopathy in children. Circulation 94:2021–2038
6. Cox GF (2007) Diagnostic approaches to pediatric cardiomyopathy of metabolic genetic etiologies and their relation to therapy. Prog Pediatr Cardiol 24:15–25. doi:10.1016/j.ppedcard.2007.08.013

# Clinical Genetic Testing in Cardiomyopathies

11

Luisa Mestroni, Matthew R. G. Taylor, Enrico Fabris and Francesca Brun

## 11.1 The Challenges of Clinical Genetic Testing

The completion of the Human Genome Project was a landmark achievement that revealed the reference DNA sequence for our own genome. Almost immediately it became clear that there was no single "reference" DNA sequence, as even the approximately half-dozen human DNA samples used by the Human Genome Project contained tens of thousands of variations [1]. As clinical genetic testing becomes more mainstream, and various projects underway perform full DNA genome sequencing in thousands of individuals, the extent of this genetic variation is increasingly being appreciated. It is widely recognized that most of this variation is probably not relevant for determining health or risk of disease and it has been collectively referred to as "genetic noise". As in much of biology, separation of the "signal" from the "noise" can be challenging, and as molecular genetic sequencing expands in use and in the total length of DNA that can be sequenced in a single assay, problems in distinguishing a diagnostic genetic change from background genetic variation will remain a difficult task for researchers and clinicians to fulfill. Newer DNA sequencing technology can now complete the sequencing of an entire human genome several times in a matter of days, which is orders of magnitude faster than the nearly 13 years required for the initial first-pass done by the Human Genome Project consortium [2]. This technology, which will shortly be widely used in clinical genetic testing, will undoubtedly add new challenges to the difficulty of distinguishing signal from noise.

Two recent papers have clearly shown the breadth of genetic variation (the

L. Mestroni (✉)
Cardiovascular Institute, University of Colorado, Aurora, Colorado, USA
e-mail: luisa.mestroni@ucdenver.edu

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_11, © Springer-Verlag Italia 2013

"noise") in heart muscle diseases, arrhythmogenic right ventricular cardiomyopathy (ARVC) and long QT syndrome [3, 4]. Various authors had previously studied families with cardiomyopathy (CMP) to identify genes, and screen patient cohorts to determine the contribution of various genes. Although the screening of control populations for disease-causing mutations that have already been discovered is fairly standard in genetic studies, comprehensive DNA sequencing of large control cohorts to measure background genetic variation is not usually undertaken. The two studies provide compelling evidence that extensive evaluation in control populations should become standard for future genetic testing.

Kapplinger et al. [3] sequenced five genes causing ARVC (*PKP2*, *DSP*, *DSG2*, *DSC2* and *TMEM43*) and found that 16% of 427 healthy controls without disease also had genetic variations that could be classified as "mutations" by various criteria, illustrating the level of genetic noise and an overall frequency well beyond that predicted, assuming the low prevalence of ARVC. Another paper, on long QT syndrome, from Kapa et al. [4] investigated the background noise of long QT genes (*SCN5A*, *KCNQ1* and *KCNH2*). In over 1,300 normal controls, the "background noise" of mutations was again significant (10%).

Confirming that a suspected mutation is present in all affected relatives within a family can be critical to help assess the causal role of a putative mutation. In clinical circumstances, efforts to evaluate, recruit and test multiple patients in a given family are unlikely to be feasible. In some circumstances, investigators have taken additional steps to assess mutation pathogenicity using in vitro cellular or in vivo animal assays, but this approach is difficult to carry out when large numbers of mutations are identified. It is also not possible in clinical situations when working with clinical laboratories.

Therefore, the clinician should keep in mind that genetic testing continues to evolve, and in doing so it is being shown to be an imperfect tool and one that requires careful interpretation before and after testing is done. Interpretation should be done by trained physicians, often with the support of genetic counselors. Criteria for pathogenic mutations have not been definitely decided, and they are liable to undergo some changes as more knowledge is gained. Indeed, the pace of clinical testing seems at times to have moved faster and without circumspect consideration than research efforts would perhaps dictate. Stringent criteria ("radical" mutations, or missense mutations located in highly conserved and functionally important domains) and, whenever possible, analysis of genetic testing in multiple affected relatives can be used when applicable to help with genetic test interpretation. Furthermore, as underlined by several authors [3, 5–7], genetic tests must be integrated in the context of an expert clinical evaluation, together with a good family history and accurate clinical information, as for any other diagnostic test. Until the specificity of these types of molecular genetic tests is robust and understood, the clinical application of such tests is probably better performed in referral centers with expertise in cardiovascular genetics [5–7].

Furthermore, healthy individuals harboring a CMP mutation ("carriers") do

not inevitably develop cardiac disease. Thus, the identification of a mutation in a currently healthy individual should be interpreted as placing that person "at risk for" the condition, but not as a "diagnosis" of CMP. Ample evidence shows that the development of "disease" is age related, and usually manifests after puberty, in the third to fourth decade of life. Additionally, the penetrance of the disease gene (i.e., the proportion of carriers who eventually manifest the disease) is never 100%. Therefore, some carriers of CMP gene mutations may remain asymptomatic for their entire life. This important concept needs to be clearly explained to asymptomatic patients in the context of detailed genetic counseling, which should be ideally be provided whenever genetic testing is being considered within a family with CMP.

## 11.2 Following the Guidelines

Current guidelines provide important help to clinicians in selecting the appropriate genetic testing approach in CMPs.

In 2009, on behalf of the Heart Failure Society of America, a group of US experts published the "Practice Guideline" for the genetic evaluation of cardiomyopathy [6]. In 2010, a group of European experts published a position statement on genetic counseling and testing in CMPs on behalf of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases [8]. Finally, in 2011, two important statements were published. The Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) published an expert consensus statement on the state of genetic testing for the channelopathies and CMPs [9], and the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines published their report on hypertrophic cardiomyopathy (HCM) [10]. Therefore, a clinician can currently count on a number of international updated guidelines to provide appropriate management to patients with genetic heart muscle diseases, and below we summarize the most important principles of these guidelines [6, 8, 9].

Class I recommendation (according to the AHA/ACC definition: "is recommended") is applied to genetic testing in the following instances: (1) index cases with a sound clinical suspicion for the presence of a channelopathy or a CMP when the positive predictive value of a genetic test is high (likelihood of positive result >40% and signal/noise ratio <10%), (2) AND/OR when the genetic test result provides either diagnostic or prognostic information, (3) or when the genetic test result influences therapeutic choices. Another important point to keep in mind is that most of the available data are derived from registries that have followed patients and recorded outcome information, since randomized and/or blinded studies do not exist. All recommendations are therefore level of evidence C (i.e., based on expert opinions) [9]. Screening of family members for the mutation identified in the proband of the family is recommended as Class I when genetic testing leads to the adoption of

therapy/protective measures/lifestyle adaptations. Conversely, Class IIa recommendation is when results of genetic testing are not associated with the use of therapeutic or protective measures, but the results may be useful for reproductive counseling or instances in which genetic testing is requested by the patient who wants to know his/her mutation status. Limitations of the current guidelines are the lack of absolute evidence in many clinical genetic situations. Once again it is underlined that the final judgement regarding care of a particular patient must be made by the healthcare provider and patient based on all relevant circumstances [9]. Genetic counseling should be part of proper management of genetic CMPs and is recommended for all patients and relatives with familial heart disease, and it should include discussion of the risks, benefits and options available for clinical testing and/or genetic testing. Importantly, treatment decisions should not rely solely on the genetic test result, but should be based on an individual's comprehensive clinical evaluation. All guidelines agree that at the current status of knowledge, it is preferable for pre-genetic test counseling, genetic testing and the interpretation of genetic test results to be performed in centers experienced in genetic evaluation and family-based management of heritable CMPs [6, 8, 9].

For HCM, Class I recommendations include a comprehensive or targeted (*MYBPC3*, *MYH7*, *TNNI3*, *TNNT2*, *TPM1*) genetic testing for any patient in whom a cardiologist has established a clinical diagnosis of HCM based on examination of the patient's clinical history, family history and electrocardiographic/echocardiographic phenotype.

For DCM, Class I recommendations are a comprehensive or targeted (*LMNA* and *SCN5A*) DCM genetic testing for patients with DCM and significant cardiac conduction disease (i.e., first-, second- or third-degree heart block) and/or a family history of premature unexpected sudden death [9]. Genetic testing for patients with familial DCM is a Class IIa ("can be useful") recommendation, and used to confirm the diagnosis, recognize those who are at highest risk of arrhythmia and syndromic features, facilitate cascade screening within the family, and help with family planning [9]. Some authors also suggest the screening of sarcomeric genes in familial DCM, considering that the cumulative frequency is in the range of 4–8% [6]. The prognostic relevance of sarcomeric gene mutations in DCM is currently unknown, although unpublished data from our own registry suggest a worse outcome for sarcomeric gene mutation carriers.

In left ventricular non-compaction (LVNC), the consensus for genetic testing is a Class I recommendation [6, 9]. LVNC genetic testing can be useful for patients in whom a cardiologist has established a clinical diagnosis of LVNC based on examination of the patient's clinical history, family history and electrocardiographic/echocardiographic phenotype (Class IIa: can be useful).

Finally, genetic testing for restrictive cardiomyopathy (RCM) is recommended (Class I). Furthermore, RCM genetic testing can be considered (Class IIb) for patients in whom a cardiologist has established a clinical index of suspicion for RCM based on history and phenotype.

In all forms of CMP, the general principle is that mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of a disease-causative mutation in the index case. When genetic testing is non-diagnostic or unavailable, healthy at-risk family members should be clinically evaluated at regular intervals because of the reduced and age-related penetrance typical of CMPs. In these relatives, periodic clinical assessment should be performed until the age at which the probability of developing the phenotype drops below 5–10%, usually around the fourth decade of life [6, 8].

## 11.3 Conclusions

In conclusion, genetic testing is becoming an important tool for a personalized medical approach to CMPs. However, it must not be viewed as a simple blood test: a negative genetic test can never, by itself, rule out the presence of the CMP under consideration for the index case. Likewise, a positive genetic test must be carefully considered as one component of a comprehensive cardiogenetic evaluation, together with an accurate clinical diagnosis, understanding the probabilistic nature of genetic testing and an accurate family history. Clinical and genetic family screening remains of great importance, not only in the research setting but also for clinical testing and should be performed whenever possible. Finally, genetic counseling should be an integral part of a cardiogenetic evaluation, in order to inform and educate the patient of the intrinsic uncertainties of genetic testing.

## References

1. The 1000 Genomes Project Consortium (2010) A map of human genome variation from population-scale sequencing. Nature 467:1061–1073. doi:10.1038/nature09534
2. Metzker ML (2010) Sequencing technologies – the next generation. Nat Rev Genet 11:31–46. doi:10.1038/nrg2626
3. Kapplinger JD, Landstrom AP, Salisbury BA et al (2011) Distinguishing arrhythmogenic right ventricular cardiomyopathy/dysplasia-associated mutations from background genetic noise. J Am Coll Cardiol 57:2317–2327. doi:10.1016/j.jacc.2010.12.036
4. Kapa S, Tester DJ, Salisbury BA et al (2009) Genetic testing for long-QT syndrome: distinguishing pathogenic mutations from benign variants. Circulation 120:1752–1760. doi:10.1161/CIRCULATIONAHA.109.863076
5. MacRae CA (2009) Closer look at genetic testing in long-QT syndrome: will DNA diagnostics ever be enough? Circulation 120:1745–1748. doi:10.1161/CIRCULATIONAHA.109.900415
6. Hershberger RE, Lindenfeld J, Mestroni L et al (2009) Genetic evaluation of cardiomyopathy – a Heart Failure Society of America practice guideline. J Card Fail 15:83–97. doi:10.1016/j.cardfail.2009.01.006
7. GeneTests: Medical Genetics Information Resource (1993–2010) University of Washington, Seattle. http://www.genetests.org. Accessed Jan 2012

8. Charron P, Arad M, Arbustini E et al (2010) Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 31:2715–2726. doi:10.1093/eurheartj/ehq271
9. Ackerman MJ, Priori SG, Willems S et al (2011) HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm 8:1308–1339. doi:10.1016/j.hrthm.2011.05.020
10. Gersh BJ, Maron BJ, Bonow RO et al (2011) 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 124:e783–831. doi:10.1161/CIR.0b013e318223e2bd

# Concluding Remarks

# 12

Fulvio Camerini, Gianfranco Sinagra and Luisa Mestroni

Up to a few decades ago, the medical community was uncertain, vague and confused about cardiomyopathies (CMPs). By definition, the etiology was unknown [1] and the diagnostic approach was essentially based on the clinical phenotype. The classifications of these diseases, developed to provide order to a complex and rather confused matter, were appropriately considered to be a provisional "bridge between ignorance and knowledge" [2] that would change with the progress of science. The majority of CMP classifications [1, 3, 4] were based (and continue to be based) on the phenotype. However, the classical "hypertrophic-dilated-restrictive" approach has some limitations, considering that in this classification there is a mix of diagnostic criteria: anatomic-morphologic (hypertrophic cardiomyopathy [HCM], dilated cardiomyopathy [DCM]), functional (restrictive cardiomyopathy [RCM]) and anatomic-functional (arrhythmogenic right ventricular cardiomyopathy [ARVC]). In 2006 [5], the American Heart Association suggested an approach that was based mainly on etiology (genetic, mixed, acquired) and considered two groups: primary CMPs (the disease is solely or predominantly localized in the heart) and secondary CMPs (heart involvement is part of a multi-organ disorder).

In the last 20 years, remarkable progress has been made in the knowledge of etiology, pathogenesis, diagnosis and therapy. For example, a genetic background of DCM was considered rare (2%) in the 1980s, while we know now that a familial trait may be present in at least one-third of individuals [6, 7]. Right ventricular CMP (the adipositas cordis or the lipomatosis cordis of the classical pathologists [8]) was unknown as a CMP in the 1980s [1], then in 1982 it was considered to be a "dysplasia" (i.e., an abnormality of development) [9], in 1995 it was accepted as an arrhythmogenic CMP localized in the right ventricle, while in recent years it has been considered to be a disease that involves both ventricles [10–12].

G. Sinagra (✉)
Cardiovascular Department,
Ospedali Riuniti and University of Trieste, Italy
email: gianfranco.sinagra@aots.sanita.fvg.it

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2_12, © Springer-Verlag Italia 2013

In the past, our understanding of these disorders was essentially based on two sources: the correlation of clinical findings with morbid anatomy, and long-term follow-up data. However, more recently, genetics and molecular medicine have opened up new horizons, with potentially useful consequences for prevention and treatment of the disorders. The growth of molecular genetics in cardiology has been spectacular since the demonstration in 1989 [13] that HCM was caused by a mutation of the gene encoding cardiac myosin heavy chain. Since then, from a simplified theorem "one disease–one gene", we have been transported into an era characterized by high complexity, with a great number of genes involved. In HCM, for example, more than 15 sarcomere-related genes with hundreds different mutations have been identified. However, if we consider the presence of hypertrophic cardiomyopathy (defined as the presence of increased left ventricular wall thickness or mass in the absence of loading conditions sufficient to cause the observed abnormality [4]) in well-defined syndromes, metabolic diseases and mitochondrial disorders, then more than 70 genes are involved. The same phenomenon has been observed in other CMPs, especially DCM and ARVC, in which the number of causative genes will continue to increase in relation to ongoing research [14, 15].

Genotype–phenotype relationships are not always simple and clear, and the approach and possible interpretations may be complex. Different mutations in the same gene can cause apparently identical phenotypes, as well as be associated with phenotypes that are radically different one from the other. Moreover, apparently identical phenotypes may be the consequence of mutations in different genes (phenocopies). The comparative diagnosis between different forms is important, also from a prognostic and sometimes a therapeutic point of view. Some clinical features of CMPs can also vary within the same family, a phenomenon that indicates that sometimes there is not a clear-cut relationship between the mutation and its clinical consequences [16]. Finally, it should be reaffirmed that the association between the presence of a certain mutation (or mutations) and a cardiac abnormality (or complex of abnormalities) cannot always be considered a cause–effect phenomenon. With respect to genetic testing, the positive predictive value of a test will be the expression of the frequency with which a phenotype is observed in the presence of a specific genotype.

The clinical cardiologist must also be aware that many other factors of genetic and environmental origin may contribute to the variability of the phenotype, a variability that is sometimes very relevant within the same family. One factor causing variability is "incomplete penetrance", i.e., when an individual who carries a mutation does not manifest the disease phenotype, or develops the disease at a more advanced age (age-related penetrance). In CMPs, the penetrance (the proportion of carriers of a mutation affected by the disease) usually increases with the age, but almost never reaches 100%.

Another possible occurrence that may complicate the disease assessment is variable expressivity, i.e., only some aspects of the disease, sometimes minor, are present. In some CMPs, it is a common experience that early reports or

reports coming from referral centers frequently indicate the presence of severe forms of the disease, sometimes with an ominous prognosis, while subsequent findings frequently indicate that the disease is less severe, more common and often benign. For these reasons, the diagnostic criteria, which usually reflect the evident abnormalities of a severe disease, might be absent or less evident in some family members with early stages of the disease. Moreover, some CMPs can be associated with a peculiar symptomatology (e.g., supraventricular arrhythmias) or an involvement of other organs or systems (skeletal muscle, auditory system, etc.), or they might be a component of a syndrome involving multiple tissues and organs. Sometimes, traditional and neglected diagnostic techniques, such as electrocardiography, can be very useful for diagnosis. Electrocardiographic findings should be analyzed and interpreted considering the phenotype and the clinical context. Some electrocardiographic changes (e.g., negative T waves in V1–V3 in adults with ARVC [8], abnormal Q waves in HCM, and various abnormalities in the electrocardiograms of young patients with Duchenne muscular dystrophy [17]) may be the early manifestations of myocardial disease, signaling myocardial involvement well before the onset of clinical symptoms.

The role of the clinical cardiologist in this revolution of medical knowledge is clearly relevant, considering that in genetic studies the approach guided by the patient phenotype is extremely important: this involves a systematic, accurate, competent observation and study of the clinical characteristics of the phenotype of patients, the family history, and the correlation between the clinical findings and genetic data.

This book has been conceived from the perspective of the clinical cardiologist who takes care of his patients and their families, and is confronted with clinical problems that are sometimes difficult and complex. This book is also based on many years of experience, observations, studies and research in the field of CMPs, and on the Trieste Registry of Cardiomyopathies, which was started more than 30 years ago, and which contains data for more than 1,300 patients who have been systematically studied.

The aim of our book is to bring genetics closer to clinical practice, contribute to the construction of a bridge between clinical observation and molecular genetics, help in the identification of a possible specific genetic background, and finally to give support to clinicians in the study of some complex, usually rare syndromes that are frequently characterized by multi-organ involvement, in an attempt to link the experience of the past with the progress of the present.

## References

1. WHO/ISFC task force (1980) Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. Br Heart J 44:672–673
2. Goodwin JF (1982) The frontiers of cardiomyopathy. Br Heart J 48:1–18

3. Richardson P, McKenna W, Bristow M et al (1996) Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. Circulation 93:841–842
4. Elliott P, Andersson B, Arbustini E et al (2008) Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 29:270–276. doi:10.1093/eurheartj/ehm342
5. Maron BJ, Towbin JA, Thiene G et al (2006) Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 113:1807–1816. doi:10.1161/CIRCULATIONAHA.106.174287
6. Grunig E, Tasman JA, Kucherer H et al (1998) Frequency and phenotypes of familial dilated cardiomyopathy. J Am Coll Cardiol 31:186–194
7. Baig MK, Goldman JH, Caforio AL et al (1998) Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. J Am Coll Cardiol 31:195–201
8. Nava A, Rossi L, Thiene G (1997) Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Elsevier, Amsterdam
9. Marcus FI, Fontaine GH, Guiraudon G et al (1982) Right ventricular dysplasia: a report of 24 adult cases. Circulation 65:384–398
10. Pinamonti B, Sinagra G, Salvi A et al (1992) Left ventricular involvement in right ventricular dysplasia. Am Heart J 123:711–724
11. Sen-Chowdhry S, Syrris P, Ward D et al (2007) Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. Circulation 115:1710–1720. doi:10.1161/CIRCULATIONAHA.106.660241
12. Pinamonti B, Dragos AM, Pyxaras SA et al (2011) Prognostic predictors in arrhytmogenic right ventricular cardiomyopathy: results from a 10-year registry. Eur Heart J 32:1105-13
13. Jarcho JA, McKenna W, Pare JA et al (1989) Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. N Engl J Med 321:1372–1378. doi:10.1056/NEJM198911163212005
14. Herman DS, Lam L, Taylor MR et al (2012) Truncations of titin causing dilated cardiomyopathy. N Engl J Med 366:619-28
15. Taylor M, Graw S, Sinagra G et al (2011) Genetic variation in titin in arrhythmogenic right ventricular cardiomyopathy-overlap syndromes. Circulation 124:876-85
16. Watkins H, Ashrafian H, Redwood C (2011) Inherited cardiomyopathies. N Engl J Med 364:1643–1656. doi:10.1056/NEJMra0902923
17. James J, Kinnett K, Wang Y et al (2011) Electrocardiographic abnormalities in very young Duchenne muscular dystrophy patients precede the onset of cardiac dysfunction. Neuromuscul Disord 21:462–467. doi:10.1016/j.nmd.2011.04.005

# Appendix: Rare and Unusual Syndromes Characterized by the Presence of Cardiomyopathy

Cardiomyopathies are present in some rare and unusual complex syndromes that have been described in recent decades. Frequently, only one or a few cases or families have been studied, always from a clinical point of view, but later, in some cases, the identification of the gene and locus has also been possible. These syndromes are summarized in Table A.1. Cases with insufficient documentation have not been considered.

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2, © Springer-Verlag Italia 2013

**Table A1** Rare and unusual syndromes characterized by the presence of cardiomyopathy

| Syndrome | Gene locus | Cardiomyopathy | Age at observation | Clinical features | OMIM no.[a] | Reference |
|---|---|---|---|---|---|---|
| Aniridia (AN); catalase deficiency | PAX6 11p13; CAT11p13 | HCM | Months | Absence of the iris, frequent glaucoma and cataracts and corneal clouding.<br>Catalase activity of erythrocytes and leukocytes reduced | 106210; 614097 | [1] |
| Hypohidrotic ectodermal dysplasia: primary hypothyroidism and agenesis of the corpus callosum | ---- | CMP (not classified) | Months | Hypohidrotic ectodermal dysplasia. Hypothyroidism: absent normal thyroid and ectopic goiter. Agenesis of the corpus callosum; craniofacial dysmorphism, macrocephaly, hypertelorism, short and downward slanting eyelids, small nose and mouth, small, dysplastic and low-set ears, retrognathia. Severe mental delay, psychomotor development severely retarded | 225040 | [2] |
| Endocardial fibroelastosis (EFE): neurologic dysfunction, unusual facial appearance and inherited macrocephaly | ---- | Fibroelastosis | Neonatal period | Unusual facial appearance, mental retardation, macrocephaly: head size greater then two standard deviations above normal, dolichocephaly, low-set ears, small palpebral fissures, micrognathia, high arched palate, bifid uvula, cryptorchidism, seizures, possible hypothalamic dysfunction | 226000 | [3] |
| Familial dilated cardiomyopathy associated with cataracts and hip–spine disease | ---- | DCM | 30–79 years | Degenerative disease of the hips. Aseptic necrosis of femoral head, abnormalities of intervertebral discs of thoracolumbar spine, scoliosis, cataracts as early as age 25 years. | ---- | [4] |

(*cont.*) ↓

| | | | | | | |
|---|---|---|---|---|---|---|
| Ulnar agenesis and endocardial fibroelastosis | ---- | Endocardial fibroelastosis | Neonatal period | Bilateral ulnar agenesis, radial hypoplasia, oligodactyly, hydrops fetalis | 276822 | [5] |
| Cardiomyopathy with arrhythmias and ectodermal dysplasia | ---- | DCM (one case with prolonged QT) First-degree AV block, supraventricular tachycardia, ventricular ectopics, non-sustained VT and polymorphic VT | 18 months to 3 years | Partial or complete alopecia, dystrophic nails, dental abnormalities | ---- | [6] |
| Familial cardiomyopathy, hypogonadism, collagenoma (see also Malouf syndrome) | ---- | DCM (with predominant right ventricle involvement) | 21–48 years | Scalp tumors (collagenoma), hypogonadism: atrophic testicles, infertility, azoospermia | 212112; 115250 | [7, 8] |
| Familial progressive sinoatrial and AV conduction disease of adults onset; sudden death, DCM and brachydactyly; heart-hand syndrome Slovenian type | LMNA | DCM, progressive sinoatrial and AV conduction disease, sudden death due to ventricular arrhythmias | Fourth to fifth decade | Brachydactyly with mild hand involvement and more severe foot involvement; myopathy, latent skeletal muscle involvement | 610140 | [9, 10] |

(*cont.*) →

**Table A1** Rare and unusual syndromes characterized by the presence of cardiomyopathy (*continued*)

| Syndrome | Gene-locus | Cardiomyopathy | Age at observation | Clinical features | OMIM no.[a] | Reference |
|---|---|---|---|---|---|---|
| Leber's congenital amaurosis (and heart failure in infancy) (LCA1) | GUCY2D 17p13.1 | DCM | Months | Amaurosis, poor vision, reduced or absent electroretinogram; nistagmus; short obese habitus | 204000 | [11] |
| Oncocytic cardiomyopathy, microphthalmia, with linear skin defects (MCOPS7) | HCCS Xp22.2 | "Oncocytic CMP"; short PR with WPW; HCM | Weeks | Erythematous depressed lesions with a linear pattern on the left cheek, central face, ear, perioral area and neck. Microphthalmia, short palpebral fissures, mild micrognathia. Happle et al. proposed the term MIDAS for the association of microphthalmia, dermal aplasia, and sclerocornea | 309801 | [12, 13] |
| Simpson–Golabi–Behmel syndrome (macrosomia, coarse face and other congenital abnormalities) (SGBS1) | GPC3 Xq26.2 | HCM; DCM; first-degree AV block; bundle branch block; severe tachyarrhythmias; cardiovascular malformation | Few months to 18 years | Macrosomia, hepatosplenomegaly, nephromegaly; coarse face, macroglossia; specific orofacial anomalies: hypertelorism, cleft palate, midline groove in the tongue or lower lip, wide mouth with malocclusion; other anomalies: supernumerary nipples, hernias, renal dysplasia, cryptorchidism, broad hands and feet, hand abnormalities, vertebral or rib defects; developmental delay, mental retardation | 312870 | [14, 15] |
| Familial neurofibromatosis. HCM (NF1) | NF1 17q11.2 | HCM | 42–46 years | Inherited neurofibromatosis, skin nodules, severe kyphoscoliosis, cafè au lait skin patches | 162200 | [16] |

(*cont.*) ↓

| | | | | | | |
|---|---|---|---|---|---|---|
| Beckwith–Wiedemann syndrome (BWS) | NSD1 5q35.2-q35.3; H19 11p15.5 KCNQ10T1 11p15.5; CDKN1C 11p15.4 | HCM (potentially reversible) | Few weeks | Exomphalos, macroglossia and gigantism. Other features: hyperinsulinism, hypoglycemia, macroglossia, visceromegaly, renal anomalies | 130650 | [17] |
| Congenital deafmutism | ---- | HCM | Adults | Congenital deaf-mutism | ---- | [18] |
| Hypergonadotropic hypogonadism with DCM (Malouf syndrome) | LMNA 1q22 - | DCM | 18–19 years | Ovarian dysgenesis, hypergonadotropic hypogonadism. Associated features: collagenoma, mild mental retardation, broad nasal base, blepharoptosis, minor skeletal anomalies | 212112 | [19] |
| Microcephaly-cardiomyopathy | --- | DCM observed in infancy but later complete resolution | 3 years | Mental retardation, short forehead, down-slanting palpebral fissures, narrow palate, crowded teeth, large gap between first and second toes; behavioral problems | 251220 | [20] |
| HCM in total lipodystrophy (CGL1-CGL2) | AGPAT2 9q34.3; BSCL2 11q12.3 | HCM | 16–28 years | Marked paucity or absence of adipose tissue, severe or extreme insulin resistance, hepatic steatosis, glucose intolerance or diabetes mellitus, hyperlipidemia | 608594 269700 | [21] |
| Facio-cardio-renal syndrome, Eastman–Bixler syndrome | ---- | DCM (?); endocardial fibroelastosis; conduction defects | 1–5 years | Associated features: severe mental retardation, horseshoe kidneys. Characteristic facies: broad nasal bridge, large chin, open mouth | 227280 | [22] |

(*cont.*) →

**Table A1** Rare and unusual syndromes characterized by the presence of cardiomyopathy (*continued*)

| Syndrome | Gene-locus | Cardiomyopathy | Age at observation | Clinical features | OMIM no.[a] | Reference |
|---|---|---|---|---|---|---|
| Coffin–Lowry syndrome (CLS) | RPS6KA3 Xp22.12 | RCM; DCM (?) | Few months to 14 years | X-linked syndrome, skeletal and facial anomalies, growth retardation, mental retardation | 303600 | [23, 24] |
| Andersen–Tawil syndrome (Andersen cardiodysrhythmic periodic paralysis) | KCNJ2 17q24.3 | DCM (described later in 2006) | 18 years | Ventricular arrhythmias, periodic paralysis, dysmorphic features | 170390 | [25] |
| Oculopharyngodistal myopathy | ---- | DCM, LVNC | Adult | Eye and facial muscle weakness, distal muscle weakness and atrophy, dysphagia, dysarthria | 164310 | [26] |
| Prader–Willi syndrome | NDN 15q11.2 SNRPN 15q11.2 | DCM | 25 years | Obesity, muscular hypotonia, mental retardation, short stature, hypogonadotropic hypogonadism, small hands and feet, type 2 diabetes mellitus, dyslipidemia | 176270 | [27] |
| Cardiac disease in methylmalonic acidemia | MUT 6p12.3 | DCM, HCM | 2–22 years | Broad clinical spectrum ranging from a benign condition to fatal neonatal disease | 251000 | [28] |

(*cont.*) ↓

| | | | | | | |
|---|---|---|---|---|---|---|
| Right ventricular obstructive cardiomyopathy in primary myoadenylate deaminase deficiency | AMPD1 1p13.2 | Right ventricular obstructive hypertrophic cardiomyopathy | 61 years | Impaired bioenergetics production, exercise induced muscle pain, fatigue and/or rhabdomyolysis (rare) | 102770 | [29] |
| Cardiomyopathy in propionic aciduria | PCCB 3q.22.3; PCCA 13q32.3 | DCM | 5–11 years | Episodic vomiting, lethargy and ketosis, neutropenia, periodic thrombocytopenia, hypogammaglobulinemia, developmental retardation, intolerance to protein | 606054 | [30] |

[a]Online Mendelian inheritance in man [31].
*AV,* atrioventricular; *CMP,* cardiomyopathy; *DCM,* dilated cardiomyopathy; *HCM,* hypertrophic cardiomyopathy; *LVNC,* left ventricular non-compaction; *WPW*, Wolff–Parkinson–White.

## References


1. Gilgenkrantz S, Vigneron C, Gregoire MJ et al (1982) Association of del(11)(p15.1p12), aniridia, catalase deficiency, and cardiomyopathy. Am J Med Genet 13:39–49. doi:10.1002/ajmg.1320130108
2. Fryns JP, Chrzanowska K, Van den Berghe H (1989) Hypohidrotic ectodermal dysplasia, primary hypothyroidism, and agenesis of the corpus callosum. J Med Genet 26:520–521
3. Jennings MT, Hall JG, Kukolich M (1980) Endocardial fibroelastosis, neurologic dysfunction and unusual facial appearance in two brothers, coincidentally associated with dominantly inherited macrocephaly. Am J Med Genet 5:271–276. doi:10.1002/ajmg.1320050309
4. Krasnow N, Qazi QH, Yermakov V (1985) A familial dilated cardiomyopathy associated with cataracts and hip-spine disease. Chest 87:56–61
5. Marles SL, Chudley AE (1990) Ulnar agenesis and endocardial fibroelastosis. Am J Med Genet 37:258–260. doi:10.1002/ajmg.1320370219
6. Hammill WW, Fyfe DA, Gillette PC et al (1988) Cardiomyopathy with arrhythmias and ectodermal dysplasia: a previously unreported association. Am Heart J 115:373–377
7. Sacks HN, Crawley IS, Ward JA, Fine RM (1980) Familial cardiomyopathy, hypogonadism, and collagenoma. Ann Intern Med 93:813–817
8. Henderson RR, Wheeler CE, Jr, Abele DC (1968) Familial cutaneous collagenoma. Report of cases. Arch Dermatol 98:23–27
9. Sinkovec M, Petrovic D, Volk M, Peterlin B (2005) Familial progressive sinoatrial and atrioventricular conduction disease of adult onset with sudden death, dilated cardiomyopathy, and brachydactyly. A new type of heart–hand syndrome? Clin Genet 68:155–160. doi:10.1111/j.1399-0004.2005.00476.x
10. Renou L, Stora S, Yaou RB et al (2008) Heart–hand syndrome of Slovenian type: a new kind of laminopathy. J Med Genet 45:666–671. doi:10.1136/jmg.2008.060020
11. Russell-Eggitt IM, Taylor DS, Clayton PT et al (1989) Leber's congenital amaurosis–a new syndrome with a cardiomyopathy. Br J Ophthalmol 73:250–254
12. Bird LM, Krous HF, Eichenfield LF et al (1994) Female infant with oncocytic cardiomyopathy and microphthalmia with linear skin defects (MLS): a clue to the pathogenesis of oncocytic cardiomyopathy? Am J Med Genet 53:141–148. doi:10.1002/ajmg.1320530205
13. Happle R, Daniels O, Koopman RJ (1993) MIDAS syndrome (microphthalmia, dermal aplasia, and sclerocornea): an X-linked phenotype distinct from Goltz syndrome. Am J Med Genet 47:710–713. doi:10.1002/ajmg.1320470525
14. Lin AE, Neri G, Hughes-Benzie R, Weksberg R (1999) Cardiac anomalies in the Simpson–Golabi–Behmel syndrome. Am J Med Genet 83:378–381
15. Konig R, Fuchs S, Kern C, Langenbeck U (1991) Simpson–Golabi–Behmel syndrome with severe cardiac arrhythmias. Am J Med Genet 38:244–247
16. Fitzpatrick AP, Emanuel RW (1988) Familial neurofibromatosis and hypertrophic cardiomyopathy. Br Heart J 60:247–251
17. Ryan CA, Boyle MH, Burggraf GW (1989) Reversible obstructive hypertrophic cardiomyopathy in the Beckwith–Wiedemann syndrome. Pediatr Cardiol 10:225–228
18. Csanady M, Hogye M, Forster T (1987) Hypertrophic cardiomyopathy associated with congenital deaf-mutism. Eur Heart J 8:528–534
19. Malouf J, Alam S, Kanj H et al (1985) Hypergonadotropic hypogonadism with congestive cardiomyopathy: an autosomal-recessive disorder? Am J Med Genet 20:483–489. doi:10.1002/ajmg.1320200309
20. Winship IM, Viljoen DL, Leary PM, De Moor MM (1991) Microcephaly-cardiomyopathy: a new autosomal recessive phenotype? J Med Genet 28:619–621
21. Rheuban KS, Blizzard RM, Parker MA et al (1986) Hypertrophic cardiomyopathy in total lipodystrophy. J Pediatr 109:301–302
22. Eastman JR, Bixler D (1977) Facio-cardio-renal syndrome: a newly delineated recessive disorder. Clin Genet 11:424–430

23. Facher JJ, Regier EJ, Jacobs GH et al (2004) Cardiomyopathy in Coffin-Lowry syndrome. Am J Med Genet A 128A:176–178. doi:10.1002/ajmg.a.30056
24. Massin MM, Radermecker MA, Verloes A et al (1999) Cardiac involvement in Coffin–Lowry syndrome. Acta Paediatr 88:468–470
25. Schoonderwoerd BA, Wiesfeld AC, Wilde AA et al (2006) A family with Andersen–Tawil syndrome and dilated cardiomyopathy. Heart Rhythm 3:1346–1350. doi:10.1016/j.hrthm.2006.07.021
26. Thevathasan W, Squier W, MacIver DH et al (2011) Oculopharyngodistal myopathy–-a possible association with cardiomyopathy. Neuromuscul Disord 21:121–125. doi:10.1016/j.nmd.2010.10.002
27. Takaya J, Higashino H, Tsujimoto D et al (2010) Prader–Willi syndrome associated with dilated cardiomyopathy. Pediatr Int 52:503–504. doi:10.1111/j.1442-200X.2010.03149.x
28. Prada CE, Al Jasmi F, Kirk EP et al (2011) Cardiac disease in methylmalonic acidemia. J Pediatr 159:862–864. doi:10.1016/j.jpeds.2011.06.005
29. de Gregorio C, Morabito G, Musumeci O et al (2011) Right ventricular obstructive hypertrophic cardiomyopathy in primary myo-adenylate deaminase deficiency. Acta Myol 30:46–48
30. Romano S, Valayannopoulos V, Touati G et al (2010) Cardiomyopathies in propionic aciduria are reversible after liver transplantation. J Pediatr 156:128–134. doi:10.1016/j.jpeds.2009.07.002
31. Online Mendelian inheritance in man. http://www.omim.org/. Accessed 18 May 2012

# Glossary

***AARS2*; Alanyl-tRNA synthetase 2: OMIM 612035; locus 6p21.1**
The protein encoded by the *AARS2* gene belongs to the class II aminoacyl-tRNA synthetase family. Aminoacyl-tRNA synthetases play critical roles in mRNA translation. The encoded protein is a mitochondrial enzyme that specifically aminoacylates alanyl-tRNA.

***ABCC9*; ATP-binding cassette, subfamily C, member 9: OMIM 601439; locus 12p12.1**
Alternative name: sulfonylurea receptor 2 (*SUR2)*.
The protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. *ABCC9* encodes a subunit of ATP-sensitive potassium channels (K-ATP). It can form cardiac and smooth-muscle-type K-ATP channels with KIR6.2. KIR6.2 forms the channel pore while the regulatory *SUR2A* subunit is required for activation and regulation. Potassium movement through KIR6.2 does not require energy expenditure, yet ATP hydrolysis at *SUR2A* is integral in the transduction of metabolic signals from cellular energy pathways to the channel pore. In this way, K-ATP channels set membrane excitability in response to stress challenge and preserve cellular energy-dependent functions, a vital role in securing cellular homeostasis under stress.

***ACAD9*; Acyl-CoA dehydrogenase family, member 9: OMIM 611103; locus 3q21.3**
This gene encodes a member of the acyl-CoA dehydrogenase family. The encoded protein localizes to the mitochondria and catalyzes the rate-limiting step in the beta-oxidation of fatty acyl-CoA. It is specifically active toward palmitoyl-CoA and long-chain unsaturated substrates.

***ACADVL*; Acyl-CoA dehydrogenase, very long-chain: OMIM 609575; locus 17p13.1**
The *ACADVL* gene encodes the very long chain acyl-CoA dehydrogenase. The

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2, © Springer-Verlag Italia 2013

enzyme catalyzes the major part of mitochondrial palmitoyl-CoA dehydrogenation in liver, heart, skeletal muscle and skin fibroblasts.

***ACTA1*; Actin, alpha, skeletal muscle 1: OMIM 102610; locus 1q42.13**
The *ACTA1* gene provides instructions for making a protein called skeletal alpha-actin, which is part of the actin protein family. Skeletal alpha-actin plays an important role in skeletal muscles and it forms the core of sarcomeres, where it interacts with a variety of other proteins to facilitate muscle contraction.

***ACTC1*; Actin, alpha cardiac muscle: OMIM 102540; locus 15q14**
The *ACTC1* gene encodes a protein which belongs to the actin family which is composed of three main groups of actin isoforms: alpha, beta and gamma. Alpha actins are major component of the contractile apparatus.

***ACTN2*; Alpha-actinin 2: OMIM 102573; locus 1q43**
This gene encodes an actin-binding protein with multiple roles in different cells. In skeletal, cardiac and smooth muscle, cytoskeletal isoforms are localized to the Z-disk and analogous dense bodies. They help to anchor the myofibrillar actin filaments. Moreover alpha-actinin is implicated in the binding of cardiac ion channels, $K_v1.5$ in particular.

***AGL*; Amylo-1,6-glucosidase, 4-alpha-glucano transferase: OMIM 610860; locus 1p21.2**
The *AGL* gene encodes an enzyme that is involved in the breakdown of glycogen. It has two catalytic activities: amylo-1,6-glucosidase and 4-alpha-glucanotransferase, which may function independently of one another.

***AGXT*; Alanine-glyoxylate aminotransferase: OMIM 604285; locus 2q37.3**
The *AGXT* gene provides instructions for making a liver enzyme called alanine-glyoxylate aminotransferase. This gene is expressed only in the liver and the encoded protein is localized mostly in the peroxisomes, where it is involved in glyoxylate detoxification. Specifically in the peroxisome, alanine-glyoxylate aminotransferase converts a compound called glyoxylate to the amino acid glycine, which is later used for making enzymes and other proteins.

***ALMS1*; Alstrom syndrome protein 1 (or *AMLS1* gene): OMIM 606844; locus 2p13.1**
The *ALMS1* gene provides instructions for making a protein whose function was not clearly known until now. Alstrom syndrome protein 1 is present in most of the tissues of the body, usually at low levels. Within cells, this protein is located in structures called centrosomes and it has also been found at the base of cilia. Centrosomes play a role in cell division and in the assembly of microtubules. Cilia are involved in cell movement and many different chemi-

cal signaling pathways. Based on its location, researchers suggest that the Alstrom syndrome protein 1 might be involved in the organization of microtubules, the transport of various materials, and the normal function of cilia.

***ANKRD1*; Ankyrin repeat domain-containing protein 1: OMIM 609599; locus 10q23.31**
The ankyrin gene encodes for the protein ankyrin 1. This protein may play an important role in endothelial cells activation. Studies in rat cardiomyocytes suggest that this gene functions as a transcription factor. Interactions between this protein and the sarcomeric proteins myopalladin and titin suggest that it may also be involved in the myofibrillar stretch-sensor system.

***ARSB*; Arylsulfatase B: OMIM 611542; locus 5q14.1**
The *ARSB* gene encodes arylsulfatase B, which is a lysosomal enzyme that removes the C4 sulfate ester group from the *N*-acetylgalactosamine sugar residue at the non-reducing terminus of the glycosaminoglycans dermatan sulfate and chondroitin sulfate during lysosomal degradation.

***ATPAF2*; ATP synthase, mitochondrial F1 complex, assembly factor 2: OMIM 608918; locus 17p11.2**
This gene encodes an assembly factor for the F1 component of the mitochondrial ATP synthase. The protein binds to the F1 alpha-subunit to prevent this subunit from forming non-productive homo-oligomers during enzyme assembly. *ATPAF2* interacts strongly with the ATP synthase F1 alpha-subunit and weakly with the F1 beta-subunit.

***ATP7B*; ATPase, Cu++ -transporting, beta polypeptide: OMIM 606882; locus 13q14.3**
The *ATP7B* gene encodes a polypeptide that acts as a plasma membrane copper-transport protein. This protein is found primarily in the liver, with smaller amounts in the kidneys and brain. This protein functions as a monomer, exporting copper out of the cells, such as the efflux of hepatic copper into the bile.

***BAG3*; Bcl2-associated athanogene 3: OMIM 603883; locus 10q26.11**
The *BAG3* gene encodes Bcl2-associated athanogene 3 protein, a member of the Bcl2 family of apoptosis regulator proteins. This protein inhibits the chaperone activity of HSP70/HSC70 by promoting substrate release. It has anti-apoptotic activity.

***BRAF*; V-RAF murine sarcoma viral oncogene homolog B1: OMIM 164757; locus 7q34**
For the function of *BRAF*, see *RAF1*. It should be noted that chemical signaling through the RAS/MAPK pathway is essential for normal development before birth.

***BSCL2*; Seipin (or Bernardinelli–Seip congenital lipodystrophy type 2 protein): OMIM 606158; locus 11q12.3**
The *BSCL2* gene encodes seipin, a protein localized mainly in the endoplasmic reticulum membrane. The *BSCL2* gene is active in many cells throughout the body (particularly nerve and brain cells, and adipocytes) and probably has a critical role in the early development of these cells. However, the function of seipin is currently not known.

**Cadherins**
Cadherins, named for "calcium-dependent adhesion", are a family of calcium-dependent cell–cell adhesion molecules. They are localized on the surface of cells and help neighboring cells to attach to one another to form organized tissues. Different forms of cadherins (muscle, neural, placental and epithelial) have been identified.

***CALR3*; Calreticulin 3: OMIM 611414; locus 19p13.11**
Calreticulin is a protein involved in regulation of intracellular calcium homeostasis and endoplasmic reticulum calcium capacity. The protein affects on store-operated calcium influx and influences calcium-dependent transcriptional pathways during embryonic development. Calreticulin is also involved in the folding of newly synthesized proteins and glycoproteins.

***CAV3*; Caveolin 3: OMIM 601253; locus 3p25.3**
The *CAV3* gene encodes a protein called caveolin 3, the muscle-specific form of the caveolin protein family, localized in the membrane surrounding muscle cells. The protein is the main component of the caveolae ("little caves"), which are small pouches in the muscle cell membrane. The caveolin 3 protein acts as a scaffold to organize other molecules, and is important for the cell signaling and maintenance of cell structure.

***CNBP*** (HGNC approved gene symbol)**; Zinc finger protein 9 (*ZFN9*): OMIM 116955; locus 3q21.3**
Alternative name: cellular retroviral nucleic acid-binding protein 1; CNBP1.
The *CNBP* gene (also known as *ZNF9*) encodes a protein called zinc finger protein 9, which is a ubiquitous protein, but is most abundant in the heart and in skeletal muscles. This protein has seven regions called zinc finger domains, which are thought to bind to specific sites on DNA and RNA. The *CNBP* protein is necessary for normal embryonic development and appears to regulate the activity of other genes.

***COA5*** (HGNC approved gene symbol)**; Chromosome 2 open reading frame 64 (*C2ORF64*): OMIM 613920; locus 2q11.2**
The cytochrome c oxidase assembly factor 5 gene encodes an assembly factor for mitochondrial cytochrome c oxidase. Defects in *COA5* are the cause of mitochondrial complex IV deficiency.

***COX10*; Cytochrome c oxidase assembly protein COX10: OMIM 602125; locus 17p12**
The *COX10* gene encodes a cytochrome c oxidase (COX) assembly protein involved in the mitochondrial heme biosynthesis pathway. *COX10* catalyzes the farnesylation of a vinyl group at position C2, resulting in the conversion of protoheme (heme B) to heme O. The COX10 protein is required for the expression of functional COX.

***COX15*; Cytochrome c oxidase assembly protein COX15: OMIM 603646; locus 10q24.2**
Cytochrome c oxidase (COX) is the terminal component of the mitochondrial respiratory chain and catalyzes electron transfer from the reduced cytochrome c to oxygen.

***CRYAB*; Crystallin, Alpha-B: OMIM 123590; locus 11q23.1**
Crystallin, alpha, beta and gamma, are separated into two classes: taxon-specific or enzyme, and ubiquitous. The latter class constitutes major proteins of vertebrate eye lens, and maintains the transparency and refraction index of the lens.

***CSRP3*; Cysteine- and glycine-rich protein 3: OMIM 600824; locus 11p15.1**
The *CSRP3* gene encodes a member of the CSRP family of LIM domain proteins, which are probably involved in processes important for development and cellular differentiation. It is a regulator of myogenesis and plays a crucial role in the organization of cytosolic structure of cardiomyocytes. It could play a role in mechanical stretch sensing and may promote the assembly of interacting proteins at Z-line structures. It is also essential for calcineurin anchorage to the Z-line and is also required for stress-induced calcineurin-NFAT activation.

***DES*; Desmin: OMIM 125660; locus 2q35**
The *DES* gene encodes desmin, a muscle-specific cytoskeletal protein. Desmin proteins surround rod-like structures called Z-discs that are located within the sarcomere. Desmin connects the Z-discs to one another, linking neighboring sarcomeres and forming myofibrils. The connection of sarcomeres to each other is essential for muscle function.

***DMD*; Dystrophin: OMIM 300377; locus Xp21.2-p21.1; and DGC dystrophin glycoprotein complex**
*DMD*, the second largest human gene, encodes dystrophin, which acts as an anchor connecting the cytoskeleton of a muscle fiber to the surrounding extracellular matrix, and strengthens muscle fibers and protects them from injury as muscles contract and relax. Components of the DGC complex are sarcoglycans, dystroglycans, caveolin-3, syntrophins, dystrobrevins and nitric oxide synthetase.

***DMPK*; Dystrophia myotonica protein kinase: OMIM 605377; locus 19q13.32**
The *DMPK* gene encodes a protein called dystrophia myotonica protein kinase. This protein plays an important role in muscles, heart and brain, with involvement in communication within cells. It appears to regulate the production and function of important structures inside muscle cells by interacting with other proteins. Dystrophia myotonica protein kinase can inhibit a specific subunit (PPP1R12A) of the muscle protein myosin phosphatase, an enzyme that plays a role in contraction and relaxation of the muscle.

***DSC2*; Desmocollin 2: OMIM 125645; locus 18q12.1**
Desmocollin 2 is a calcium-dependent glycoprotein, and a member of the desmocollin subfamily of the cadherins superfamily. Desmocollin is found primarily in epithelial cells and constitutes the adhesive proteins for cell–cell junction.

***DSG2*; Desmoglein 2: OMIM 125671; locus 18q12.1**
The protein is a component of desmosomes, which are structures responsible for cell–cell junctions in epithelial, myocardial and other cell types. Desmoglein is a calcium-binding transmembrane glycoprotein component of desmosomes.

***DSP*; Desmoplakin: OMIM 125647; locus 6p24.3**
Other entities represented: *DSPI*, desmoplakin I; *DSPII*, desmoplakin II. Desmosomes are intercellular junctions that tightly link adjacent cells. Desmoplakin is a component of desmosomes that anchors intermediate filaments to desmosomal plaques. Desmoplakin interacts with the N-terminal region of plakophilin 1 and plakoglobin.

***DTNA*; Dystrobrevin, alpha: OMIM 601239; locus 18q12.1**
The protein encoded by the *DTNA* gene belongs to the dystrobrevin subfamily of the dystrophin family. It is a component of the dystrophin-associated protein complex (DPC), which consists of dystrophin and several integral and peripheral membrane proteins (e.g., dystroglycans, sarcoglycans, syntrophins, and alpha and beta dystrobrevin). The DPC localizes to the sarcolemma and its disruption is associated with various forms of muscular dystrophy.

***DUX4*; Double homeobox protein 4 and D4Z4 macrosatellite repeat: OMIM 606009 locus 4q35.2**
D4Z4 macrosatellite repeat is a region of DNA located in the proximal subtelomeric region of 4q35. The D4Z4 region normally consists of multiple copies of a 3.3-kb repeat. Each repeat contains a copy of *DUX4* that encodes a protein called double homeobox protein 4, which might be involved in transcriptional regulation. It appears that the D4Z4 region influences the activity of other genes located nearby on chromosome 4. An abnormally short D4Z4 may somehow disrupt the normal regulation of these genes.

***EMD*; Emerin: OMIM 300384; locus Xq28**
Alternative name: *STA*.
The emerin gene encodes a ubiquitous protein, emerin, localized along the nuclear envelope of many cell types and which is a member of the nuclear lamina-associated protein family. The nuclear envelope is a structure that surrounds the nucleus, acting as a barrier between the nucleus and the cytoplasm. Emerin together with other proteins is probably involved in the regulation of the activity of certain genes with control of cell division cycle and maintenance of structure and stability of the nucleus. Emerin is produced in many tissues but appears to be particularly important for the normal function of skeletal and cardiac muscles.

***EYA4*; Eyes absent 4: OMIM 603550; locus 6q23.2**
The *EYA4* gene belongs to a family of genes called PTP (protein tyrosine phosphatases). It encodes a protein that plays a role in regulating the activity of other genes. Considering its role, the EYA4 protein is called a transcription factor or transcription co-activator. Two regions of the EYA4 protein are important for interactions with other proteins. These interactions help to control gene activities that are important for heart function, development of the inner ear and maintenance of normal hearing.

***FHL1*; Four and a half LIM domains 1: OMIM 300163; locus Xq26.3**
This gene encodes a member of the four-and-a-half-LIM-only protein family. Family members contain two highly conserved, zinc finger domains with four highly conserved cysteine residues binding a zinc atom in each zinc finger. The protein is involved in many cellular processes, and may have an involvement in muscle development or hypertrophy.

***FKTN*; Fukutin: OMIM 607440; locus 9q31.2**
The *FKTN* gene provides instructions for making a protein called fukutin. The function of this protein is probably to modify a protein called alpha-dystroglycan. Specifically, fukutin probably adds chains of sugar molecules to alpha-dystroglycans (the process of glycosylation, which is critical for the normal function of alpha-dystroglycan). The alpha-dystroglycan protein helps to anchor the cytoskeleton with the extracellular matrix. In skeletal muscle, glycosylated alpha-dystroglycan helps to stabilize and protect muscle fibers. A shortage of fukutin and the consequent glycosylation defect are probably the cause of a destabilization of muscle cells with progressive damage of muscle fibers.

***FOXRED1*; FAD-dependent oxidoreductase domain-containing protein 1: OMIM 613622; locus 11q24.2**
The *FOXRED* gene encodes a protein that contains a FAD-dependent oxidoreductase domain. The protein is localized in the mitochondria and is considered a chaperone protein for the formation of the mitochondrial complex 1.

***FXN*; Frataxin: OMIM 606829; locus 9q21.11**
Frataxin is a mitochondrial protein with an important role in respiratory function and iron homeostasis. It appears to help assemble clusters of iron and sulfur molecules that are critical for the function of many proteins. Frataxin is found in many cells through the body, with the highest levels in the heart, spinal cord, liver, pancreas and skeletal muscle.

***GAA*; Glucosidase, alpha, acid: OMIM 606800; locus 17q25.3**
The enzyme acid alpha-glucosidase (also know as acid maltase) is encoded by the *GAA* gene, and is localized in lysosomes. It breaks down glycogen into glucose.

***GALNS*; Galactosamine-6-sulfate sulfatase: OMIM 612222; locus 16q24.3**
The *GALNS* gene encodes a lysosomal enzyme required for the degradation of mucopolysaccharides, keratan sulfate and chondroitin 6-sulfate. Specifically, this enzyme removes 6-sulfate groups from keratan sulfate (particularly abundant in cartilage and cornea) and chondroitin 6-sulfate.

***GBE1*; Glycogen branching enzyme: OMIM 607839; locus 3p12.2**
The *GBE1* gene provides instructions for making the glycogen branching enzyme. This enzyme is involved in the production of glycogen, which is the result of the assembly of many molecules of glucose. Some glucose molecules are linked together in a straight line, while others branch off and form side chains. The glycogen branching enzyme is involved in the formation of these side chains.

***GLA*; Galactosidase, Alpha: OMIM 300644; locus Xq22.1**
The *GLA* gene encodes the enzyme alpha-galactosidase. This enzyme is active in lysosomes, which are stuctures that are considered to be recycling centers within cells. Alpha-Galactosidase breaks down a substance called globotriaosylceramide (a fatty substance attached to three sugars). Mutations in the *GLA* gene alter the structure and function of the enzyme so that it is unable to break down globotriaosylceramide. As a consequence, there is a systemic accumulation of globotriaosylceramide in different cells of the body, particularly skin, kidneys, heart and nervous system. The progressive accumulation of this substance causes the different symptoms of Fabry disease.

***GLB1*; Galactosidase, beta-1: OMIM 611458; locus 3p22.3**
The *GLB1* gene provides instructions for producing an enzyme called beta-galactosidase. This enzyme is located in lysosomes, which are compartments within cells that break down and recycle different types of molecules, including substances called GM1 ganglioside (important for normal functioning of brain cells) and keratan sulfate (abundant in cartilage and cornea). Moreover the *GLB1* gene encodes for the elastin-binding protein important for the formation of elastic fibers.

***GNPTAB*; *N*-acetylglucosamine-1-phosphotransferase, alpha/beta subunits: OMIM 607840; locus 12q23.2**
This gene encodes two different parts, the alpha and beta subunits, of an enzyme called GlcNAc-1-phosphotransferase, a heterohexameric complex. *N*-acetylglucosamine-1-phosphotransferase is involved in the first step of making a molecule called mannose 6-phosphate (M6P). M6P acts as a tag that indicates that a hydrolase should be transported to the lysosome. These recognition markers are essential for appropriate trafficking of lysosomal enzymes.

***GUSB*; Beta-glucuronidase: OMIM 611499; locus 7q11.21**
The *GUSB* gene encodes beta-glucuronidase, a lysosomal hydrolase involved in the stepwise degradation of glucuronic-acid-containing glycosaminoglycans. Beta-Glucuronidase is involved in the breakdown of three types of glycosaminoglycans: dermatan sulfate, heparan sulfate and chondroitin sulfate.

***GYS1*; Glycogen synthase 1: OMIM 138570; locus 19q13.33**
The protein encoded by *GYS1* gene catalyzes the addition of glucose monomers to the growing glycogen molecule through the formation of alpha-1,4-glycoside linkages.

***HFE*; Hereditary hemochromatosis protein: OMIM 613609; locus 6p22.2;**
The *HFE* gene encodes a protein located on the surface of cells of different organs, mainly liver and intestinal cells, but also on some cells of the immunosystem. The HFE protein interacts with other proteins to detect the amount of iron in the body. The HFE protein regulates the production of the protein called hepcidin. Hepcidin is produced in the liver and is very important for the regulation of iron absorption. Moreover the HFE protein interacts with two proteins, the transferrin receptors.

***HRAS*; V-HA-RAS Harvey rat sarcoma viral oncogene homolog: OMIM 190020; locus 11p15.5**
The *HRAS* gene encodes a protein called V-HA-RAS Harvey rat sarcoma viral oncogene homolog, which is primarily involved in the regulation of cell division. See *KRAS*.

***IDS*; Iduronate-2-sulfatase: OMIM 300823; locus Xq28**
The *IDS* gene provides instructions for producing an enzyme called iduronate-2-sulfatase that removes sulfate from a molecule known as sulfated alpha-L-iduronic acid, which is present in two glycosaminoglycans: heparan sulfate and dermatan sulfate. Iduronate-2-sulfatase is required for the lysosomal degradation of heparan sulfate and dermatan sulfate.

***IDUA*; Alpha-L-iduronidase: OMIM 252800; locus 4p16.3**
The *IDUA* gene encodes an enzyme called alpha-L-iduronidase that removes

sulfate from a molecule known as sulfated alpha-L-iduronic acid, which is present in two glycosaminoglycans: heparan sulfate and dermatan sulfate.

***ILK*; Integrin-linked kinase: OMIM 602366; locus 11p15.4**
ILK is a serine-threonine protein kinase that associates with the cytoplasmic domain of beta-integrins and acts as a proximal receptor kinase regulating integrin-mediated signal transduction. It may act as a mediator of inside-out integrin signaling.

***JPH2*; Junctophilin 2: OMIM 605267; locus 20q13.12**
Junctional membrane complexes link the plasma membrane with endoplasmic/sarcoplasmic reticulum; they are common in all excitable cells and mediate cross-talk between cell surface and intracellular ion channels. The protein encoded by *JPH2* is a component of the junctional complexes, composed of a C-terminal hydrophobic segment spanning the endoplasmic/sarcoplasmic reticulum membrane and a remaining cytoplasmic domain that shows specific affinity for the plasma membrane. *JPH2* is necessary for proper intracellular calcium signaling in cardiac myocytes via its involvement in ryanodine-receptor-mediated calcium ion release.

***JUP*; Junction plakoglobin: OMIM 173325; locus 17q21.2**
Junction plakoglobin is a major cytoplasmic protein and a common constituent of submembranous plaques of desmosomes and intermediate junctions. The membrane-associated plaques influence the arrangement and function of both the cytoskeleton and the cells within the tissue. The presence of junction plakoglobin in the desmosomes and in the intermediate junction suggests it plays a central role in structure and function of submembranous plaques.

***KCNJ2*; Potassium channel, inwardly rectifying, subfamily J, member 2: OMIM 600681; locus 17q24.3**
The *KCNJ2* gene belongs to a large family of genes that produce potassium channels. The protein encoded by this gene is an integral membrane protein and inward-rectifier type potassium channel. The protein, which has a greater tendency to allow potassium to flow into a cell rather than out of a cell, probably participates in establishing action potential waveform and excitability of neuronal and muscle tissues.

***KRAS*; V-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog: OMIM 190070; locus 12p12.1**
The *KRAS* gene encodes a protein called K-Ras important for the regulation of cell division. The K-Ras protein is a GTPase, which converts GTP into GDP. The *KRAS* gene belongs to a class of genes known as oncogenes, which, when mutated, may cause normal cells to become cancerous. The *KRAS* gene is a member of the Ras family of oncogenes, which includes other two genes: *HRAS* and *NRAS*. The proteins produced by these three genes are GTPases important in the process of cell division, differentiation and apoptosis.

***LAMA4*; Laminin alpha 4: OMIM 600133; locus 6q21**
Laminin, a glycoprotein, is the major non-collagenous constituent of basement membranes. It is composed of three non-identical chains (A, B1 and B2). *LAMA4* encodes a variant of the A chain.

***LAMP2*; Lysosomal-associated membrane protein 2: OMIM 309060; locus Xq24**
The *LAMP2* gene provides instructions for making a protein called lysosomal-associated membrane protein 2, which is present in the membrane of lysosomes. Lysosomes are compartments in the cell that digest and recycle materials. The LAMP2 protein probably helps transport cellular materials and digestive enzymes into the lysosomes, with formation of cellular structures called autophagic vacuoles (or autophagosomes). Autophagic vacuoles transfer cellular material into the lysosome where it can be broken down. LAMP2 protein might be involved in the fusion between autophagic vacuoles and the lysosomes.

***LDB3*; LIM-domain binding 3: OMIM 605906; locus 10q23.2**
Alternative name**:** Z-Band alternatively spliced PDZ motif-containing protein (*ZASP*); cypher.
LIM domains are protein structural domains, composed of two contiguous zinc finger domains, separated by a two-amino acid residue hydrophobic linker. LIM-domain-containing proteins are important in organ development and oncogenesis and in cytoskeletal organization, with a role in maintaining the Z-disc stability in striated and cardiac muscle. Moreover LIM domains mediate protein–protein interactions critical to cellular processes.
Origin of names: The name LIM name derives from the initials of the three transcription factors in which the sequence was first seen (Lin-11, Isl-1, and Mec-3); ZASP is the acronym of Z-band alternatively spliced PDZ-motif containing protein; PDZ is an acronym combining the first letters of three proteins: post-synaptic density protein (PSD95), *Drosophila* disk large tumor suppressor (digA) and Zonula occludens-1 protein (Z0-1); CYPHER was named by Zhau et al. [1], who reported the cloning and characterization of a novel striated muscle-restricted LIM-domain-containing protein. They named the protein CYPHER because of its homology with another LIM-domain protein: Enigma.

***LMNA*; Lamin A/C: OMIM 150330; locus 1q22**
The proteins (lamin A and lamin C) encoded by *LMNA* are essential components of the nuclear lamina, a complex network that lies beneath and support the nuclear envelope. The lamina is considered to provide structural support to the nucleus as well as having a role in the organization of chromatin and in the process of DNA replication.

***MAP2K1*; Mitogen-activated protein kinase kinase 1: OMIM 176872; locus 15q22.31**
Alternative name: MAPK/ERK kinase 1; MEK1.

***MAP2K2*; Mitogen-activated protein kinase kinase 2: OMIM 601263; locus 19p13.3**
Alternative name: MAPK/ERK kinase 2; MEK2.
The *MAP2K1* gene provides instructions for making a protein known as MEK1 that is part of a signaling pathway called the RAS/MAPK pathway, which transmits chemical signals from outside the cell to the cell's nucleus. RAS/MAPK signaling helps to control the proliferation, differentiation and movement of cells, and apoptosis.
The *MAP2K2* gene is very similar to *MAP2K1*. It provides instructions for making a protein known as MEK2. Like MEK1, the MEK2 protein functions as part of the RAS/MAPK signaling pathway. Together they appear to be essential for normal development before birth and for survival after birth.

***MRPS22*; Mitochondrial ribosomal protein S22: OMIM 605810; locus 3q23**
Mitochondrial ribosomal proteins are encoded by nuclear genes and help in protein synthesis within the mitochondrion. Mitochondrial ribosomal protein S22 is a component of the mitochondrial ribosome small subunit (28S), which comprises a 12S rRNA and about 30 distinct proteins.

***MTATP6*; ATP synthase 6: OMIM 516060**
Alternative name: mitochondrially encoded ATP synthase 6.
***MTATP8*; ATP synthase 8: OMIM 516070**
The *MTATP6* and *MTATP8* genes belong to a family of genes called mitochondrial respiratory chain complex genes. ATP synthase 6 and ATP synthase 8 proteins are subunits of a large enzyme called mitochondrial ATP synthase. These enzymes are essential in the oxidative phosphorylation process.

***MTTG*; Transfer RNA, mitochondrial, glycine: OMIM 590035;**
***MTTH*; Transfer RNA, mitochondrial, histidine: OMIM 590040**
***MTTK*; Transfer RNA, mitochondrial, lysine: OMIM 590060**
***MTTI*; Transfer RNA, mitochondrial, isoleucine: OMIM 590045**
***MTTL1*; Transfer RNA, mitochondrial, leucine, 1: OMIM 590050**
Mitochondrial DNA contains 37 genes, all essential for normal mitochondrial function. Thirteen of these genes encode enzymes involved in oxidative phosphorylation, and the remaining genes provide instructions for making molecules called transfer RNA (tRNA) and ribosomal RNA. These types of RNA help assemble amino acids into functioning proteins. tRNA is involved in protein synthesis and brings the correct amino acid to the ribosomes, and a specific tRNA must form a covalent bond with a specific amino acid. There are many different types of tRNA in a cell, each transcribed from a different tRNA gene. It has been hypothesized that some clinical manifestations caused by mutations in mitochondrial tRNA may derive from defects in oxidative phosphorylation, resulting in marked mitochondrial energy deficiency with a compensatory mitochondrial proliferation. The *MTTG* gene provides instructions for a specific form of tRNA that trans-

fers the amino acid glycine to a growing polypeptide chain at the ribosome site of protein synthesis during translation.
The *MTTH* gene provides instructions for a specific form of tRNA: $tRNA^{his}$. The $tRNA^{his}$ molecule is present only in mitochondria; it attaches to the amino acid histidine and inserts it into the appropriate locations in different proteins. The $tRNA^{his}$ molecule is involved in the assembly of proteins that carry out the process of oxidative phosphorylation.
The *MTTK* gene provides instructions for a specific form of tRNA: $tRNA^{lys}$. The $tRNA^{lys}$ molecule is present only in mitochondria and attaches the amino acid lysine and inserts it into the appropriate locations in many different cells. The $tRNA^{lys}$ molecule is involved in the assembly of proteins that carry out the process of oxidative phosphorylation.
The *MTTL1* gene encodes a specific form of tRNA designated as $tRNA^{Leu}$ . During protein assembly the molecule attaches the amino acid leucine and inserts it into the appropriate locations in the protein.
The *MTTI* gene provides instructions for a specific form of tRNA that transfers the amino acid isoleucine to a growing polypeptide chain at the ribosome site of protein synthesis during translation.

***MYBPC3*; Myosin-binding protein C: OMIM 600958; locus 11p11.2**
Cardiac myosin binding protein C (arrayed transversely in sarcomere A-bands) binds myosin heavy chain in thick filaments and titin in elastic filaments. Phosphorylation of these proteins modulates contraction.

***MYH6*; Myosin heavy chain 6, alpha: OMIM 160710; locus 14q11.2**
***MYH7*; Myosin heavy chain 7, beta: OMIM 160760; locus 14q11.2**
Myosin converts chemical energy into mechanical force through hydrolysis of ATP. Myosin is organized within the cell as a pair of heavy chains and two pairs of light chains. Myosin heavy chain is a contractile protein which exists as a family of distinct isoforms. There are two myosin heavy chain genes expressed in the heart ventricles: alpha-myosin heavy chain, which is almost exclusively expressed in cardiac tissue, and beta-myosin heavy chain, which is expressed in cardiac and slow skeletal muscle.

***MYL2*; Myosin light chain 2, regulatory, cardiac, slow: OMIM 160781; locus 12q24.11**
***MYL3*; Myosin light chain 3, alkali, ventricular, skeletal, slow: OMIM 160790; locus 3p21.31**
The *MYL3* gene encodes myosin light chain 3, an alkali light chain. In the myosin molecule, there are two heavy chains and four associated light chains. Two of the light chains are regulatory light chains (encoded by the *MYL2* gene) and two are alkali light chains or essential light chains (encoded by the *MYL3* gene). The light chains stabilize the long alpha-helical neck of the myosin head. The function of light chains in striated muscle is only partially understood.

***MYLK2*; Myosin light chain kinase 2: OMIM 606566; locus 20q11.21**
This gene encodes a myosin light chain kinase implicated in global muscle contraction and cardiac function. The protein phosphorylates a specific serine in the N-terminus of the myosin light chain.

***MYO6*; Myosin VI: OMIM 600970; locus 6q14.1**
The *MYO6* gene encodes a protein called myosin VI, which is part of a group of proteins called "unconventional myosins". Each of these proteins plays a role in transporting molecules within cells. "Unconventional myosins" interact with actin, which is important for cell movement and shape. Myosin VI is active in many cells. In the inner ear, myosin VI plays a role in the development and maintenance of the stereocilia.

***MYOT*; Titin immunoglobulin domain protein: OMIM 604103; locus 5q31.2**
Alternative name: myotilin.
The *MYOT* gene encodes a protein called myotilin, which is present in myocardium and skeletal muscle. It is a component of a complex of multiple actin cross-linking proteins. It binds to other proteins to help form sarcomeres, and it is also involved in the control of myofibril assembly and stability at the Z-lines in muscle cells.

***MYOZ2*; Myozenin 2: OMIM 605602; locus 4q26**
The *MYOZ2* gene encodes a protein of the family of sarcomeric proteins that bind to calcineurin, a phosphatase involved in calcium-dependent signal transduction in different cell types. Members of this family tether calcineurin to alpha-actinin at the Z-line of the sarcomere and thus they play an important role in the modulation of calcineurin signaling.

***MYPN*; Myopalladin: OMIM 608517; locus 10q21.1**
Myopalladin is a component of the sarcomere that tethers nebulin (see Nebulin) in skeletal muscle and nebulette (see Nebulette) in cardiac muscle to alpha-actinin at the Z-lines. Nebulette binds to actin and plays an important role in the assembly of the Z-disc.

***NAGLU*; *N*-acetylglucosaminidase, alpha: OMIM 609701; locus 17q21.2**
This gene encodes an enzyme that is involved in the stepwise breakdown of glycosaminoglycans. Specifically, alpha-*N*-acetylglucosaminidase degrades heparan sulfate by hydrolysis of terminal *N*-acetyl-D-glucosamine residues in *N*-acetyl-alpha-D-glucosaminides.

***NDUFA2*; NADH-ubiquinone oxidoreductase 1 alpha subcomplex, 2: OMIM 602137; locus 5q31.3**
The encoded protein is a subunit of the hydrophobic protein fraction of the NADH ubiquinone oxidoreductase (complex 1), which is the first enzyme of

the mitochondrial electron transport chain located in the inner mitochondrial membrane. Complex 1 is composed of at least 41 subunits, of which seven are encoded by the mitochondrial genome and the remainder by nuclear genes. Complex 1 functions in the transfer of electrons from NADH to the respiratory chain. In particular, it catalyzes the NADH oxidation with concomitant ubiquinone reduction and proton ejection out of the mitochondria. The encoded protein may be involved in regulating complex 1 activity or its assembly via assistance in redox processes.

***NDUFA10*; NADH-ubiquinone oxidoreductase 1 alpha subcomplex, 10: OMIM 603835; locus 2q37.3**
The protein encoded by this gene is an accessory subunit of the NADH ubiquinone oxidoreductase (complex 1) (see *NDUFA2*).

***NDUFS2*; NADH-ubiquinone oxidoreductase Fe-S protein 2: OMIM 602985; locus 1q23.3**
The protein encoded by this gene is a core subunit of the NADH ubiquinone oxidoreductase (complex 1) (see *NDUFA2*).

***NDUFS4*; NADH-ubiquinone oxidoreductase Fe-S protein 4: OMIM 602694; locus 5q11.2**
This gene encodes an accessory subunit of the NADH ubiquinone oxidoreductase (complex 1) (see *NDUFA2*).

***NDUFS8*; NADH-ubiquinone oxidoreductase Fe-S protein 8: OMIM 602141; locus 11q13.2**
This gene encodes a subunit of the NADH ubiquinone oxidoreductase (complex 1) (see *NDUFA2*). The encoded protein is involved in the binding of two of the six to eight iron-sulfur clusters of complex 1 and, as such, is required in the electron transfer process.

***NEB*; Nebulin: OMIM 161650; locus 2q23.3**
Nebulin is a giant protein component of the cytoskeletal matrix that coexists with the thick and thin filaments within the sarcomeres of skeletal muscle.

***NEBL*; Nebulette: OMIM 605491; locus 10p12.31**
Nebulette is an isoform of the protein nebulin. While nebulin is expressed preferentially in skeletal muscle, nebulette is expressed in cardiac muscle. It binds to actin and plays an important role in the assembly of the Z-disc.

***NEXN*; Nexilin, rat, homolog of: OMIM 613121; locus 1p31.1**
The *NEXN* gene encodes a filamentous actin-binding protein that may function in cell adhesion and migration. It has an essential role in the maintenance of Z-line and sarcomere integrity.

***NKX2-5*; NK2 homeobox 5: OMIM 600584; locus 5q35.1**
Homeobox-containing genes play critical roles in regulating tissue-specific gene expression essential for tissue differentiation, as well as determining the temporal and spatial patterns of development.

***NRAS*; Neuroblastoma ras viral oncogene homolog: OMIM 164790; locus 1p13.2**
The *NRAS* gene encodes a protein called neuroblastoma ras viral oncogene homolog, which is primarily involved in the regulation of cell division (see *KRAS*).

***PDLIM3*; PDZ and LIM-domain protein 3: OMIM 605889; locus 4q35.1**
The protein encoded by the *PDZLIM3* gene contains a PDZ domain and a LIM domain, indicating that it might be involved in cytoskeletal assembly. It might also play a role in the organization of actin filament arrays.

***PKP2*; Plakophilin 2: OMIM 602861; locus 12p11.21**
The *PKP2* gene provides instructions for making a protein called plakophilin-2. In myocardial cells, plakophilin-2 is one of the several proteins present in the desmosomes. Desmosomes provide strength to the myocardium and are involved in signaling between neighboring cells.

***PLN*; Phospholamban: OMIM 172405; locus 6q22.31**
Phospholamban is expressed in the sarcoplasmic reticulum membrane as a 30 kDa homopentamer. Phospholamban has been postulated to regulate the activity of the calcium pump of the sarcoplasmic reticulum.

***PRKAG2*; Protein-kinase, AMP-activated, non-catalytic, gamma-2: OMIM 602743; locus 7q36.1**
The *PRKAG2* gene provides instructions for making one part (the gamma-2 subunit) of a larger enzyme, AMP-activated protein kinase (AMPK). This enzyme helps to sense and respond to energy demands within the cells of many different tissues, including cardiac and skeletal muscles. AMPK regulates chemical pathways involving the molecule adenosine triphosphatase (ATP), the main energy source of the cell. AMPK probably plays a role in controlling the activity of other genes and in regulating the activity of some ion channels in the heart. These channels play a critical role in maintaining the normal rhythm of the heart.

***PSEN-1*; Presenilin-1: OMIM 104311; locus 14q24.2**
***PSEN-2*; Presenilin-2: OMIM 600759; locus 1q42.13**
Presenilin 1 and 2 are similar in size and localized to intracellular compartments that are similar in location to those of endoplasmic reticulum and Golgi complex. The presenilins together with other proteins form the gamma-secretase complex, which acts on numerous protein substrates and is also responsible for

proteolytic cleavage of amyloid precursor protein. Moreover presenilins interact with more than 20 proteins that couple to diverse signaling pathways, and several of these proteins are potentially relevant for myocardial disease.

***PTPN11*; Protein-tyrosine phosphatase, nonreceptor-type 11: OMIM 176876; locus 12q24.13**
The *PTPN11* gene encodes a protein called SHP-2. The protein contributes to regulation of the activation of the RAS/MAPK signaling pathway, which helps to control important cell functions: proliferation, differentiation, cell movement and apoptosis. During embryonic development, the SHP-2 protein is critical for the development of the heart and several other tissues.

***RAF1*; V-RAF-1 murine leukemia viral oncogene homolog 1: OMIM 164760; locus 3p25.2**
The *RAF1* gene encodes a protein that is part of a signaling pathway, the RAS/MAPK pathway. This pathway transmits chemical signals from outside the cell to the nucleus. RAS/MAPK signaling is important for the control of proliferation, differentiation of cells, cell movement and apoptosis. The *RAF1* gene belongs to a class of genes known as oncogenes, which have the potential, when mutated, to cause the normal cells to become cancerous.

***RBM20*; RNA-binding motif protein 20: OMIM 613171; locus 10q25.2**
The gene encodes a protein that is expressed in the heart and skeletal muscle, and is likely to bind RNA.

***RYR2*; Ryanodine receptor 2: OMIM 180902; locus 1q43**
The *RYR2* gene provides instructions for making a protein called ryanodine receptor 2. This protein is part of a family of ryanodine receptors that form channels that transport calcium ions within myocytes. These channels are embedded in the outer membrane of the sarcoplasmic reticulum. The RYR2 channels control the flow of calcium ions out of the sarcoplasmic reticulum. The release and re-uptake of calcium ions is fundamental for the presence of a regular heart rhythm.

***SCN5A*; Sodium channel, type V alpha subunit: OMIM 600163; locus 3p22.2**
The *SCN5A* gene provides instructions for making a sodium channel. Sodium channels, abundant in the cardiac muscle, control the flow of sodium ions into cardiac muscle cells and are responsible for the generation and propagation of action potentials.

***SCO2*; SCO2, S. cerevisiae, homolog of: OMIM 604272; locus 22q13.33**
This gene encodes one of the cytochrome c oxidase (COX) assembly factors. Human COX is a multimeric protein complex that catalyzes the transfer of electrons from cytochrome c to molecular oxygen, and this helps to maintain

the proton gradient across the inner mitochondrial membrane that is necessary for aerobic ATP production. The encoded protein is a metallochaperone that is involved in the biogenesis of COX subunit II.

***SDHA*; Succinate dehydrogenase complex, subunit A, flavoprotein: OMIM 600857; locus 5p15.33**
The *SDHA* gene belongs to a family of genes called the mitochondrial respiratory chain complex. This gene encodes one of four subunits of the succinate dehydrogenase (SDH) enzyme. The SDH enzyme links two pathways in energy conversion: the citric acid cycle (Krebs cycle) and oxidative phosphorylation.

**Sarcoglycans**
***SGCA*; Sarcoglycan, alpha: OMIM 600119; locus 17q21.33**
***SGCB*; Sarcoglycan, beta: OMIM 600900; locus 4q12**
***SGCG*; Sarcoglycan, gamma: OMIM 608896; locus 13q12.12**
***SGCD*; Sarcoglycan, delta: OMIM 601411; locus 5q33.3**
Sarcoglycans are transmembrane components of the large dystrophin-associated glycoprotein complex and they are involved in the cytoarchitecture of the cardiac cells, providing structural linkage between the subsarcolemmal cytoskeleton and the extracellular matrix. Their function is not clearly elucidated. The sarcoglycan subcomplex is characterized by the presence of different proteins (the alpha, beta, gamma and delta sarcoglycans). Beta-Sarcoglycan is expressed ubiquitously, but mainly in skeletal and cardiac muscle, while the alpha, gamma and delta sarcoglycans are expressed in striated and smooth muscle. The four sarcoglycans are tightly bound to each other so that a mutation in one is usually associated with partial or total deficiency of all.

***SGSH*; *N*-sulfoglucosamine sulfohydrolase: OMIM 605270; locus 17q25.3**
The *SGSH* gene provides instructions for producing an enzyme called sulfamidase. Sulfamidase is involved in the stepwise breakdown of large molecules called glycosaminoglycans (GAGs). Sulfamidase removes a sulfate molecule from a sugar called glucosamine when it is at the end of the GAG chain.

***SLC22A5*; Solute carrier family 22 (organic cation transporter), member 5: OMIM 603377; locus 5q31.1**
The *SLC22A5* gene encodes a protein called OCTN2 that is present in heart muscle and liver, as well as in other tissues. The protein, positioned within the cell membrane, transports carnitine into the cell. Carnitine brings fatty acids, a major source of energy for the heart muscle, into the mitochondria.

***SLC25A4*; Solute carrier family 25 (mitochondrial carrier, adenine nucleotide translocator), member 4: OMIM 103220; locus 4q35.1**
The *SLC25A4* gene provides instructions for making the protein adenine nucleotide translocase type 1 (ANT1). ANT1 functions in mitochondria and

activates a process, called oxidative phosphorylation, which converts adenosine diphosphate (ADP) into adenosine triphosphate (ATP), the main energy source of the cells. Moreover, ANT1 might be a part of another structure localized in the inner membrane called the mitochondrial permeability transition pore. This structure allows various molecules to pass into the mitochondrion and probably has a role in the process of apoptosis of the cell.

***SOS1*; Son of sevenless, drosophila, homolog 1: OMIM 182530; locus 2p22.1**
The *SOS1* gene encodes a protein involved in a pathway within cells that controls growth and development. It is particularly important for embryonic development.

***TAZ*; Tafazzin: OMIM 300394; locus Xq28**
The *TAZ* gene provides instruction for producing a group of proteins called tafazzins. Tafazzins probably have two distinct functions in cells and tissues: (1) to play a role in the maintenance of the inner membrane of mitochondria, and (2) to promote the differentiation and maturation of osteoblasts, while preventing adipocytes from maturing.

***TCAP*; Titin-cap: OMIM 604488; locus 17q12**
Alternative name**:** telethonin
TCAP is a sarcomeric protein localized at the periphery of the Z-discs at the border of the sarcomere and it serves as a structural anchor and a signaling center. TCAP glues two parallel titin molecules within the same sarcomere, to provide titin with an increased mechanical resistance ability.

***TGFB3*; Transforming growth factor, beta-3: OMIM 190230; locus 14q24.3**
Transforming growth factor, beta3 is a member of the TGF-B family of proteins. It is involved in embryogenesis and cell differentiation.

***TMEM43*; Transmembrane protein 43: OMIM 612048; locus 3p25.1**
The protein belongs to the TMEM43 family and probably has an important role in maintaining nuclear envelope structure by organizing protein complexes at inner nuclear membrane. It is also required for retaining emerin at the inner nuclear membrane.

***TMPO*; Thymopoietin: OMIM 188380; locus 12q23.1**
Alternative name**:** lamina-associated polypeptide 2 (*LAP2*).
A single *TMPO* gene encodes three thymopoietins: alpha (present in the nucleus), beta and gamma (localized to the nuclear membrane). Harrys et al. [2] suggested that TMPO-beta appears to be the human homolog of the rat protein lamina-associated polypeptide-2 (LAP2), which probably has an important role in the regulation of nuclear architecture. It might help to direct the assem-

bly of the nuclear lamina, and as a consequence maintain the structural organization of the nuclear envelope.

**Troponin subunits**
Troponin is the central regulatory protein of striated muscle contraction and consists of three subunits: TnI, which is the inhibitor of actomyosin-ATPase; TnT, which contains the binding site for tropomyosin; and TnC, which abolishes the inhibitory action of TnI on actin filaments, thus allowing the interaction of actin with myosin.

***TNNC1*; Troponin C, slow: OMIM 191040; locus 3p21.1**
The binding of calcium to troponin C abolishes the inhibitory action of TnI on actin filaments, thus allowing the interaction of actin with myosin, the hydrolysis of ATP and the generation of tension.

***TNNI3*; Troponin I, cardiac: OMIM 191044; locus 19q13.42**
The *TNNI3* gene provides instructions for making a protein called troponin I cardiac isoform, which is found only in heart muscle. Troponin I cardiac isoform is one of the three subunits that form the troponin protein complex of the thin filaments. Troponin I cardiac isoform is responsible for relaxation of the heart muscle following contraction.

***TNNT2*; Troponin T2, cardiac: OMIM 191045; locus 1q32**
This protein is encoded by the *TNNT2* gene in humans. The protein encoded by this gene is the tropomyosin-binding subunit of the troponin complex, which is located on the thin filament of striated muscles. It regulates muscle contraction in response to alteration of intracellular calcium ion concentration. The troponin complex, along with tropomyosin, is responsible for the calcium-dependent regulation of striated muscle contraction.

***TPM1*; Tropomyosin 1: OMIM 191010; locus 15q22.2**
This gene encodes a protein that is a member of the tropomyosin family of widely distributed actin-binding proteins. Tropomyosin 1 is involved in the contractile system of striated and smooth muscles and in the cytoskeleton of non-muscle cells. It plays a central role, in association with the troponin complex, in the calcium-dependent regulation of vertebrate striated muscle contraction.

***TSFM*; Ts translation elongation factor, mitochondrial: OMIM 604723; locus 12q14.1**
This gene encodes a mitochondrial translation elongation factor. This factor is an enzyme that catalyzes the exchange of guanine nucleotides on the translation elongation factor Tu during the elongation step of mitchondrial protein translation.

***TTN*; Titin: OMIM 188840; locus 2q31.2**
Titin is a giant protein present in the cardiac and skeletal muscle. Individual titin molecules span half of the sarcomere and run between the Z-disc and the M-line. Titin interacts with many sarcomeric proteins at the Z-line region, and E-band and M-line regions, and it is considered to play a crucial role in striated muscle development, structure, elasticity and cell signaling. The main function of titin is to provide a passive mechanical tension in muscle, generating the force responsible for restoring the resting length of the sarcomere.

***VCL*; Vinculin: OMIM 193065; locus 10q22.2**
Vinculin is a protein of the cytoskeleton associated with the cytoplasmic face of cell–cell and cell–extracellular matrix adherence-type junctions. It is considered to be one of several proteins that interact in anchoring F-actin to the membrane.

## References

1. Zhou Q, Ruiz-Lozano P, Martone ME, Chen J (1999) Cypher, a striated muscle-restricted PDZ and LIM domain-containing protein, binds to alpha-actinin-2 and protein kinase C. J Biol Chem 274:19807–19813
2. Harris CA, Andryuk PJ, Cline SW et al (1995) Structure and mapping of the human thymopoietin (TMPO) gene and relationship of human TMPO beta to rat lamin-associated polypeptide 2. Genomics 28:198–205. doi:10.1006/geno.1995.1131

## Web Sites

OMIM: Online Mendelian Inheritance in Man. http://www.ncbi.nlm.nih.gov/omim. Accessed 18 May 2012
Genetics Home Reference. http://ghr.nlm.nih.gov/. Accessed 18 May 2012
National Center for Biotechnology Information: Entrez Gene. http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene. Accessed 18 May 2012
Weizmann Institute of Science: GeneCards. http://www.genecards.org/. Accessed 18 May 2012
UniProt. www.uniprot.org/. Accessed 18 May 2012

# Index





G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies,*
DOI: 10.1007/978-88-470-2757-2, © Springer-Verlag Italia 2013

**T**