Genetic Basis of Mitochondrial Cardiomyopathy

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Elisa Mastantuono, Cordula Maria Wolf, and Holger Prokisch

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E. Mastantuono
Institute of Human Genetics, Technische Universität München, Munich, Germany

Institute of Human Genetics, Helmholtz Zentrum München, Munich, Germany

DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany

C. M. Wolf
Department of Pediatric Cardiology and Congenital Heart Defects, German Heart Center Munich, Technical University Munich, Munich, Germany

H. Prokisch (✉)
Institute of Human Genetics, Technische Universität München, Munich, Germany

Institute of Human Genetics, Helmholtz Zentrum München, Munich, Germany
e-mail: prokisch@helmholtz-muenchen.de

Abstract

Mitochondrial disorders are a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial energy metabolism, and they represent one of the largest groups of inborn errors of metabolism. Mitochondrial disorders can be caused by mutation of genes encoded by either nuclear DNA or mitochondrial DNA (mtDNA), with more than 300 disease-associated genes identified to date. Among these genes, around 100 have so far been associated with cardiac manifestations. Cardiomyopathy is estimated to occur in 20–40% of children with mitochondrial disorders. Genetic defects can affect a vast range of different mitochondrial functions including electron transport chain complex subunits and their assembly factors, mitochondrial transfer or ribosomal RNAs, factors involved in translation or mtDNA maintenance, and cofactor metabolism such as coenzyme Q10 synthesis. With collectively more than 1000 described cases, the most frequent mitochondrial cardiac diseases include Barth syndrome, Sengers syndrome, *ACAD9*- or *TMEM70*-related mitochondrial complex I or V deficiency, and Friedreich ataxia. Hypertrophic cardiomyopathy is the most common type of cardiomyopathy, but mitochondrial cardiomyopathies might also present as dilated, restrictive, left ventricular non-compaction, and histiocytoid cardiomyopathies. Mitochondrial cardiomyopathy can vary in severity from asymptomatic to severe manifestations including heart failure and sudden cardiac death. Congenital arrhythmias and congenital heart defects (CHDs) are also part of the clinical spectrum of mitochondrial disorders. In this chapter, we provide an overview of the constantly growing number of mitochondrial cardiac disorders and comment on the current practice in the diagnosis and treatment of patients with mitochondrial cardiomyopathy, including optimal therapeutic management and long-term monitoring.

3.1   Introduction

Mitochondrial disorders are a heterogeneous group of inborn errors of metabolism encompassing a wide range of clinical presentations, with > 300 disease-associated genes identified to date [1, 192]. Mitochondria are largely known as the powerhouse of the cell due to their crucial function in the generation of cellular energy. They exploit the energy stored in fats, carbohydrates, and proteins to produce ATP in a process called oxidative phosphorylation (OXPHOS). OXPHOS requires the transport of electrons to molecular oxygen via the mitochondrial respiratory chain, which involves four multi-subunit complexes (complex I–complex IV) and two mobile electron carriers, coenzyme Q10 (CoQ10) and cytochrome *c*. The respiratory chain generates a transmembrane proton gradient that is used by complex V (also known as ATP synthase) to synthesize ATP.

Major metabolic consequences of OXPHOS impairment include accumulation of intermediary metabolic products, increased generation of reactive oxygen species, and decreased energy production. As a consequence of energy deficiency, high-energy demand tissues such as muscle, brain, and liver can be impaired, with resulting multi-organ disease, often with a progression of symptoms developing over time. The variable and frequently systemic nature of mitochondrial disorders make molecular diagnosis difficult. Many different medical specialties are often involved in patient care (with individual physicians often becoming discouraged from solving such complex phenotypes). On the other hand, its very systemic nature aids in raising suspicion for the diagnosis of mitochondrial disorders. Specific combinations of the clinical features associated with mitochondrial disorders can subsequently be grouped into specific syndromes [2].

With an estimated prevalence of 1 in 5000 live births, mitochondrial disorders represent one of the largest groups of inborn errors of metabolism [3]. The onset of mitochondrial disorders has an apparent peak in early childhood (first 3 years of life) and a second broad peak beginning toward the second and the fourth decade of life (adult-onset diseases) [3]. Childhood-onset mitochondrial disorders are generally more severe, especially when clinical manifestation occurs in infancy (<1 year of age) or if they include cardiac involvement (mortality of 71% vs 26% without cardiac phenotype) [4].

Cardiac involvement, specifically cardiomyopathy and arrhythmias, are common features associated with both early- and late-onset forms of mitochondriopathy. Cardiomyopathy is estimated to occur in 20–40% of children with mitochondrial disorders [4, 5]. However, screening for cardiac involvement is not always performed, and this figure is therefore possibly underestimated. The most common form of cardiomyopathy is hypertrophic; however dilated cardiomyopathy and left ventricular (LV) non-compaction also occur relatively frequently [6, 7]. Conduction system and bradyarrhythmias, in addition to WPW syndrome and tachyarrhythmias, are the most commonly encountered arrhythmias in mitochondrial disorders [8, 9].

On the other hand, when a mitochondrial condition affects at the initial stage selectively the heart, the mitochondrial cardiomyopathy may be clinically indistinguishable from other genetic determined cardiomyopathies [147]. Hence, mitochondrial disorders should be suspected in idiopathic isolated forms of cardiomyopathies. Conventional cardiomyopathy gene panels often do not include all the mitochondrial cardiomyopathy-associated genes, and only the increasing use of whole-exome sequencing (WES) has led to unmasking of such cases. In general, the introduction of next-generation sequencing (NGS) has dramatically improved diagnostic yield for mitochondrial disorders and shifted the focus from mtDNA to the nuclear genome. Indeed, both mtDNA and nuclear genomes can be analyzed for pathogenic variants within a single experiment. Consequently, NGS has enabled the identification of a constantly growing list of new disease genes, thereby setting the foundation to uncover an increasing variety of pathophysiologic disease mechanisms [10–13].

Defects of the mitochondrial energy metabolism can be caused by mutations in a number of mitochondrial pathways and functions, including the ATP producing

chain from pyruvate dehydrogenase via Krebs cycle to OXPHOS by affecting replication of mtDNA or transcription and translation of mitochondrially encoded OXPHOS subunits. Furthermore, there are numerous additional functions involved in the mitochondrial energy metabolism, such as transport processes of proteins and substrates through the mitochondrial membranes, quality control systems, essential cofactors, motility of the organelle, and membrane integrity.

Mitochondrial genetics is complex, as the workhorse of mitochondria, the mitochondrial proteome (around 1500 proteins), is under the control of two genomes, the nuclear genome and the mitochondrial genome (mtDNA). Although only a small fraction of their proteins are encoded by mtDNA, abnormalities in mtDNA affect more than half of the adult cases, whereas nuclear DNA defects account for up to 80% of mitochondrial disorders in children [14]. Therefore, the most common mode of inheritance of mitochondrial disorders in children is autosomal recessive. For mtDNA variants, the number of wild-type copies is a key factor that determines whether a cell expresses a biochemical defect. This is usually determined by the proportion of mutated copies versus wild-type copies of mtDNA. Homoplasmy describes the setting in which all mtDNA copies have the same mutation, while heteroplasmy, on the other hand, occurs if a mixture of different genotypes, e.g., wild-type and mutant mtDNA, coexist. Variants in mtDNA causing mitochondrial disorders can be further classified into three types: (a) mutations in genes encoding structural proteins or in genes involved in protein synthesis, (b) single or multiple mtDNA deletions, and (c) mtDNA depletion. Multiple mtDNA deletions and mtDNA depletion are caused by nuclear gene defects. Screening the literature, we found an cassociated cardiac phenotype in around 100 genes ($n = 1855$ cases) among the 300 mitochondrial disease-associated genes described to date. However, concerning the number of patients per gene defect, a non-equal long tail distribution was observed. There are disorders like Friedreich ataxia for which more than 1200 patients have a reported cardiac involvement, Barth syndrome with more than 200 patients, and *ACAD9* with over 50 patients, while there are around 70 disease entities with less than 10 published cases with cardiac involvement (Table 3.1). Many individuals display a cluster of clinical features which fall into defined mitochondrial syndromes. Among them, MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and MERRF (myoclonic epilepsy with ragged red fibers) represent the syndromes most frequently associated with cardiac manifestations.

3.2   Cardiac Manifestation in Mitochondrial Disorders

Cardiomyopathies represent a significant clinical manifestation associated with mitochondrial disorders that can result in sudden cardiac death. Neonatal cardiomyopathies are often characterized by hypertrophy of one (mostly left) or both ventricles [147]. Ventricular dysfunction may be progressive in utero and after birth. Neonatal cardiomyopathy is often followed by fatal heart failure or, in other

Table 3.1 List of mitochondrial genes associated with cardiac manifestations

Gene	Inheritance	HCM	DCM	LVNC	RCM	HICM	Arrhythmias	CHD	SCD/CA	HT	Extra-cardiac manifestations	Patients with cardiac phenotype[a]
OXPHOS												
Complex I												
NDUFA2	AR	Yes							Yes		Leigh syndrome	1 pt. (Ref. [15])
NDUFA10	AR	Yes							Yes		Leigh syndrome	1 pt. (Ref. [16])
NDUFA11	AR	Yes	Yes						Yes	Yes	Encephalocardiomyopathy with brain atrophy	4 pts. (Ref. [17])
NDUFB11	XLR/de novo		Yes			Yes			Yes	Yes	Linear skin defects, hypotonia, eye abnormalities, microcephaly, DD, thyroid abnormalities	6 pts. (Refs. [18–21])
NDUFS2	AR	Yes									Leigh syndrome	6 pts. (Refs. [22–24])
NDUFS4	AR	Yes									Leigh syndrome	1 pt. (Ref. [25])
NDUFS8	AR	Yes									Leigh syndrome	2 pts. (Refs. [23, 26])
NDUFV2	AR	Yes							Yes		Early-onset encephalopathy	5 pts. (Refs. [27, 28])
MT-ND1	mt	Yes		Yes					Yes		LHON, Alzheimer's disease, cancer of colon, sudden infant death syndrome, adult-onset dystonia, MELAS	7 pts. (Refs. [7, 29])

(continued)

Table 3.1 (continued)

Gene	Inheritance	HCM	DCM	LVNC	RCM	HICM	Arrhythmias	CHD	SCD/CA	HT	Extra-cardiac manifestations	Patients with cardiac phenotype[a]
MT-ND2	mt	Yes									LHON, Leigh syndrome	1 pt. (Ref. [30])
Assembly												
NDUFAF1	AR	Yes		Yes			Yes		Yes		Cardioencephalomyopathy	2 pts. (Refs. [31, 32])
NDUFAF4	AR	Yes									Infantile mitochondrial encephalopathy	1 pt. (Ref. [33])
ACAD9	AR	Yes	yes	Yes			Yes	Yes	Yes	Yes	Cardiorespiratory depression, encephalopathy, and severe lactic acidosis	56 pts. (Ref. [34])
FOXRED1	AR	Yes									Leigh syndrome	1 pt. (Ref. [35])
TMEM126B	AR	Yes						Yes			Myopathy	1 pt. (Ref. [36])
Complex II												
SDHA	AR	Yes	Yes	Yes					Yes		Leigh syndrome, paragangliomas	5 pts. (Refs. [37–39])
SDHD	AR		Yes	Yes				Yes	Yes		Encephalomyopathy; carcinoid tumors, intestinal; Cowden-like syndrome; Merkel cell carcinoma, somatic; paraganglioma and gastric stromal sarcoma; paragangliomas 1, with our without deafness; pheocytochromocytoma	1 pt. (Ref. [40])

Gene	Inheritance						Clinical features	Points
Complex III								
BCS1L	AR	Yes					Gracile syndrome	2 pts. (Ref. [41])
MT-CYB	mt	Yes	Yes	Yes			Complex III deficiency, LHON, colorectal cancer, exercise intolerance, mitochondrial encephalomyopathy, multisystem disorder, infantile histiocytoid cardiomyopathy, exercise intolerance+cardiomyopathy +septooptic dysplasia, Parkinsonism/MELAS overlap syndrome	3 pts. (Ref. [42])
Complex IV								
COX6B1	AR	Yes				Yes	Encephalomyopathy, hydrocephalus	1 pt. (Ref. [43])
MT-CO2	AR	Yes	Yes				Complex IV deficiency; pigmentary retinopathy; colorectal cancer	3 pts. (Ref. [44])
MT-CO3	AR		Yes				Complex IV deficiency, LHON, seizures+lactic acidosis	5 pts. (Ref. [45])
COX7B	AD/de novo	Yes			Yes		Microphthalmia with linear skin lesions	2 pts. (Ref. [46])
Assembly								
SURF1	AR	Yes					Leigh syndrome	2 pts. (Refs. [47, 48])
COX14	AR	Yes					Severe congenital lactic acidosis and dysmorphic features associated with a	1 pt. (Ref. [49])

(continued)

Table 3.1 (continued)

Gene	Inheritance	HCM	DCM	LVNC	RCM	HICM	Arrhythmias	CHD	SCD/CA	HT	Extra-cardiac manifestations	Patients with cardiac phenotype[a]
											complex IV assembly defect and a specific decrease in the synthesis of COX I; brain hypertrophy, altered myelination, numerous cavities throughout the brain, hepatomegaly, renal hypoplasia, and adrenal hyperplasia	
COA5	AR	Yes			Yes						Lethal neonatal hypertrophic cardiomyopathy	2 pts. (Ref. [50])
Complex V												
TMEM70	AR	Yes	Yes				Yes	Yes	Yes		Complex V (ATP synthase) deficiency, nuclear type 2	49 pts. (Refs. [51–54])
MT-ATP6	mt	Yes									Leigh syndrome, LHON, infantile mitochondrial bilateral striatal necrosis, seizures+lactic acidosis, NARP	2 pts. (Ref. [55, 191])
MT-ATP8	mt	Yes						Yes			Susceptibility to reversible valproate-induced brain pseudoatrophy, neuropathy	5 pts. (Refs. [55–57])
Homeostasis												
TAZ	XLR	Yes	Yes	Yes			Yes	Yes	Yes	Yes	Barth syndrome, cardioskeletal myopathy with neutropenia and abnormal mitochondria,	200 pts. (Ref. [58])

Gene	Inheritance						Phenotype	Points (Refs.)
AGK	AR				Yes	Yes	3-methylglutaconic aciduria, type III; Sengers syndrome, cardioskeletal myopathy, cataracts, failure to thrive, marked respiratory fatigue, pulmonary distress, pulmonary hypertension, mitochondrial DNA depletion syndrome 10 (myopathic type)	25 pts. (Refs. [59–61])
DNAJC19	AR	Yes	Yes	Yes	Yes	Yes	3-Methylglutaconic aciduria, type V, ataxia	22 pts. (Refs. [62–65])
C1QBP	AR	Yes	Yes		Yes	Yes	Severe neonatal-, childhood-, or later-onset cardiomyopathy associated with combined respiratory chain deficiencies; severe neonatal-, childhood-, or later-onset cardiomyopathy associated with combined respiratory chain deficiencies Severe cardiomyopathy associated with combined respiratory chain deficiencies	4 pts. (Ref. [66])
AIFM1	XLR		Yes	Yes			Combined oxidative phosphorylation deficiency 6	1 pt. (Ref. [67])
XPNPEP3	AR	Yes					Nephronophthisis-like nephropathy 1	2 pts. (Ref. [68])
FBXL4	AR	Yes	Yes	Yes			Mitochondrial DNA depletion syndrome	7 pts. (Ref. [69])

(continued)

Table 3.1 (continued)

Gene	Inheritance	HCM	DCM	LVNC	RCM	HICM	Arrhythmias	CHD	SCD/CA	HT	Extra-cardiac manifestations	Patients with cardiac phenotype[a]
											13 (encephalomyopathic type)	
mtDNA replication, transcription and translation												
POLG	AR		Yes								Mitochondrial DNA depletion syndrome 4A (Alpers); mitochondrial depletion syndrome 4B (MNGIE type); mitochondrial recessive ataxia syndrome (includes SANDO and SCAE); progressive external ophthalmoplegia, autosomal dominant; progressive external ophthalmoplegia, autosomal recessive	5 pt. (Refs. [70–72])
TWNK	AR		Yes				Yes		Yes		Mitochondrial DNA depletion syndrome 7 (hepatocerebral type), progressive external ophthalmoplegia	8 pts. (Refs. [73, 74])
MGME1	AR		Yes				Yes				External ophthalmoplegia, emaciation, and respiratory failure	2 pts. (Ref. [75])
SLC25A4	AR	Yes	Yes						Yes		Progressive external ophthalmoplegia with mitochondrial DNA deletions	4 pts. (Refs. [76–78])

Gene	Inheritance								Phenotype	References
ELAC2	AR	Yes	Yes				Yes	Yes	Encephalopathy	8 pts. (Refs. [79–81])
HSD17B10	AR	Yes							17-Beta-hydroxysteroid dehydrogenase X deficiency; mental retardation, X-linked 17/31, microduplication; mental retardation, X-linked syndrome 10	1 pt. (Ref. [82])
LRPPRC	AR	Yes							Leigh syndrome, French-Canadian type	5 pts. (Ref. [83])
GTPBP3	AR	Yes	Yes			Yes	Yes		Lactic acidosis and encephalopathy	6 pts. (Ref. [84])
MTO1	AR	Yes				Yes	Yes	Yes	Cardiomyopathy, variable clinical symptoms depending on type of mutation	16 pts. (Refs. [85–87])
TRMT5	AR	Yes							Hypertrophic cardiomyopathy muscular hypotonia, psychomotor retardation	1 pt. (Ref. [88])
TRMT10C	AR	Yes							Congenital lactic acidosis, hypotonia, feeding difficulties, and deafness, death at 5 months	1 pt. (Ref. [89])
TRMU	AR	Yes							Acute infantile liver failure; deafness, mitochondrial	1 pt. (Ref. [81])
GFM1	AR	Yes							Combined oxidative phosphorylation deficiency 1; progressive hepatoencephalopathy, early-onset Leigh syndrome	2 pts. (Refs. [90, 91])

(continued)

Table 3.1 (continued)

Gene	Inheritance	HCM	DCM	LVNC	RCM	HICM	Arrhythmias	CHD	SCD/CA	HT	Extra-cardiac manifestations	Patients with cardiac phenotype[a]
TSFM	AR	Yes	Yes								Combined oxidative phosphorylation deficiency 3	3 pts. (Refs. [92, 93])
RMND1	AR	Yes	Yes				Yes	Yes	Yes		Encephaloneuromyopathy, multiple respiratory chain deficiency	14 pts. (Refs. [81, 94])
PARS2	AR		Yes								Alpers syndrome; infantile-onset neurodegenerative disorders	2 pts. (Ref. [95])
MRPS22	AR	Yes					Yes	Yes			Combined oxidative phosphorylation deficiency 5; edema, tubulopathy, and hypotonia	5 pts. (Refs. [96–98])
MRPL3	AR	Yes							Yes		Psychomotor retardation and multiple respiratory chain deficiency	5 pts. (Refs. [99, 100])
MRPL44	AR	Yes									Infantile cardiomyopathy	2 pts. (Refs. [101, 102])
MTFMT	AR	Yes		Yes			Yes	Yes			Leigh syndrome and combined OXPHOS deficiency	8 pts. (Refs. [81, 103, 104])
AARS2	AR	Yes	Yes								Combined oxidative phosphorylation deficiency 8; fatal infantile hypertrophic mitochondrial cardiomyopathy; brain and skeletal muscles also showed milder respiratory chain defects	7 pts. (Refs. [81, 105])

Gene	Inheritance					Disease	Score
GARS	AR	Yes				Charcot-Marie-Tooth disease 2D (CMT2D) and distal hereditary motor neuropathy type V	2 pts. (Refs. [81, 106])
KARS	AR	Yes				Charcot-Marie-Tooth disease, recessive intermediate, B	2 pts. (Refs. [107, 108])
LARS2	AR	Yes		Yes	Yes	Premature ovarian failure and hearing loss in Perrault syndrome	1 pt. (Ref. [109])
IARS2	AR	Yes				Cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal dysplasia	1 pt. (Ref. [110])
WARS2	AR	Yes				Mitochondrial encephalopathy	1 pt. (Ref. [13])
RRM2B	AR	Yes				Mitochondrial DNA depletion syndrome 8A and 8B	2 pts. (Ref. [111])
VARS2	AR	Yes	Yes		Yes	Neonatal encephalocardiomyopathy	9 pts. (Ref [112])
YARS2	AR	Yes				Myopathy, lactic acidosis, and sideroblastic anemia 2	4 pts. (Refs. [110, 113])
SUCLG1	AR	Yes				Mitochondrial DNA depletion syndrome 9 (encephalomyopathic type with methylmalonic aciduria)	3 pts. (Ref. [114])
MT-TA	mt	Yes				Myotonic dystrophy-like myopathy, mitochondrial myopathy	1 pt. (Ref. [115])

(continued)

Table 3.1 (continued)

Gene	Inheritance	HCM	DCM	LVNC	RCM	HICM	Arrhythmias	CHD	SCD/CA	HT	Extra-cardiac manifestations	Patients with cardiac phenotype[a]
MT-TG	mt	Yes									Exercise intolerance, sudden death	2 pts. (Ref [115])
MT-TL1	mt	Yes	Yes				Yes		Yes		MELAS syndrome, MERRF syndrome, cardiomyopathy with or without skeletal myopathy, mitochondrial encephalomyopathy, PEO	15 pts. (Ref. [116])
MT-TP	mt	Yes									Myopathy, susceptibility to Parkinson disease, MERRF syndrome	1 pt. (Ref. [115])
Cofactors												
COQ2	AR	Yes	Yes						Yes		Coenzyme Q10 deficiency; infantile encephalomyopathy, nephropathy	2 pts. (Refs. [117, 118])
COQ4	AR	Yes									Haploinsufficiency, mental retardation, encephalomyopathy, and dysmorphic features.	7 pts. (Refs. [119, 120])
BOLA3	AR	Yes									Combined deficiency of the 2-oxoacid dehydrogenases, associated with a defect in lipoate synthesis and accompanied by defects in complexes I, II, and III of the mitochondrial respiratory chain	3 pts. (Ref. [121])
FXN	AR	Yes	Yes	Yes			Yes		Yes		Friedreich ataxia, Friedreich ataxia with retained reflexes	1200 pts. (Ref. [190])

Gene	Inheritance				Disease	Points (Ref.)
COQ9	AR				Coenzyme Q10 deficiency	1 pt. (Ref. [122])
PDSS1	AR	Yes			Coenzyme Q10 deficiency; multisystem disease with early-onset deafness, mild mental retardation, optic atrophy, peripheral neuropathy, obesity, livedo reticularis, and cardiac valvulopathy	2 pts. (Ref. [123])
ISCU	AR	Yes			Myopathy with lactic acidosis, hereditary	2 pts. (Ref. [124])
NFU1	AR	Yes	Yes		Multiple mitochondrial dysfunctions syndrome 1	2 pts. (Refs. [121, 125])
LIAS	AR	Yes			Combined glycine cleavage and pyruvate dehydrogenase deficiency	3 pts. (Ref. [126])
COX10	AR	Yes			Complex IV deficiency; encephalopathy, progressive mitochondrial, with proximal renal tubulopathy	2 pts. (Ref. [127, 128])
COX15	AR	Yes			Complex IV deficiency; Leigh syndrome, early-onset fatal	1 pt. (Ref. [129])
SCO1	AR	Yes			Hepatic failure, early onset, and neurologic disorder	1 pt. (Ref. [130])
SCO2	AR	Yes		Yes	Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency	38 pts. (Refs. [117, 128, 131–131])
COA6	AR	Yes			Hypertrophic cardiomyopathy	1 pt. (Ref. [134])

(continued)

Table 3.1 (continued)

Gene	Inheritance	HCM	DCM	LVNC	RCM	HICM	Arrhythmias	CHD	SCD/CA	HT	Extra-cardiac manifestations	Patients with cardiac phenotype[a]
SLC25A26	AR	Yes									Neonatal mortality resulting from respiratory insufficiency and hydrops to childhood acute episodes of cardiopulmonary failure and slowly progressive muscle weakness	3 pts. (Ref. [135])
Inhibitors												
ECHS1	AR	Yes	Yes				Yes	Yes			Leigh-like, neonatal onset, cardiomyopathy	8 pts. (Ref. [136])
Substrates												
SLC25A3	AR	Yes						Yes			Mitochondrial phosphate carrier deficiency	7 pts. (Ref. [137])
ACADVL	AR	Yes	Yes						Yes		VLCAD deficiency	13 pts. (Refs. [138, 139])
CPT1A	AR	Yes									CPT deficiency, hepatic, type IA	1 pt. (Ref. [140])
CPT2	AR	Yes									Hepatic CPT deficiency type II, lethal neonatal CPT II deficiency, myopathy due to CPT II deficiency	1 pt. (Ref. [141])
HADH	AR	Yes									3-Hydroxyacyl-CoA dehydrogenase deficiency; hyperinsulinemic hypoglycemia, familial, 4	1 pt. (Ref. [142])
HADHA	AR	Yes									Fatty liver, acute, of pregnancy; HELLP syndrome, maternal, of	1 pt. (Ref. [143])

Gene	Inheritance					Clinical manifestations	Minimal no. of patients[a]
HADHB	AR	Yes				pregnancy; LCHAD deficiency; trifunctional protein deficiency Trifunctional protein deficiency	1 pt. (Ref. [143])
SLC22A5	AR	Yes			Yes	Cardiomyopathy, systemic carnitine deficiency	8 pts. (Refs. [132, 144])
SLC25A20	AR	Yes		Yes		Carnitine-acylcarnitine translocase deficiency	1 pt. (Ref. [145])
PPA2	AR	Yes			Yes	Early death, alcohol sensitivity	18 pts. (Ref. [146])

HCM hypertrophic cardiomyopathy, *DCM* dilated cardiomyopathy, *LVNC* left ventricular non-compaction, *RCM* restrictive cardiomyopathy, *HICM* histiocytoid cardiomyopathy, *CHD* congenital heart defect, *SCD/CA* sudden cardiac death/cardiac arrest, *HT* heart transplantation
[a]Minimal number of patients described in literature with cardiac manifestations

cases, can progress into a dilated form, non-compaction of the left ventricle, improve, or even regress completely [147].

Hypertrophic cardiomyopathy (HCM) is the most frequent manifestation in mitochondrial disorders. HCM is characterized by progressive myocardial thickening; diastolic and systolic ventricular dysfunction; histopathologic changes, such as myocyte disarray and fibrosis; and arrhythmias which may cause sudden cardiac death. In adulthood, hypertrophic cardiomyopathy has a prevalence of 1 in 500 and is typically caused by mutations in sarcomere genes [148]. Pediatric HCM is most frequently associated with Noonan syndrome (1 in 10,000), but it is also frequently found with inborn errors of metabolism, including mitochondrial disorder [149]. HCM was reported to be associated with about 90 mitochondrial disease genes out of 100 with a cardiac phenotype (Table 3.1).

Dilated cardiomyopathy (DCM) is characterized by progressive myocardial dilatation and thinning. Both diastolic and systolic ventricular dysfunctions can occur, and DCM is often associated with the occurrence of cardiac conduction system diseases, arrhythmias, and sudden arrhythmic death. DCM as a sequela of myocarditis is the most common cardiomyopathy in childhood, but it can also be inherited or part of systemic diseases, such as a mitochondrial disorder [150]. In mitochondrial disorders, DCM is often a consequence of a progressed HCM. It has been found in association with 30 disease genes, most frequently with Barth and DCMA syndromes [151].

Mitochondrial disorders can present with cardiac conduction defects typically involving sinus node dysfunction, atrioventricular block, ventricular conduction delay, or WPW syndrome. Progression in intraventricular conduction defect is unpredictable and responsible for sudden cardiac death. Overall, 17 mitochondrial disease genes were found in association with arrhythmias. Prevalence of Wolff-Parkinson-White syndrome among patients with mtDNA mutations is high (up to 15%), specifically in patients with MELAS and MERRF [152]. Also in the clinical presentation of Kearns-Sayre syndrome are cardiac conduction defects, together with progressive external ophthalmoplegia and pigmentary retinopathy [153].

Congenital heart defects (CHDs) are rarely recognized to be linked to mitochondrial disorders. CHDs have been identified in patients with mitochondrial disorders due to 16 different genetic defects; however the pathomechanism remains largely unknown (Table 3.1). The CHDs include patent ductus arteriosus (PDA), ventricular and septal defects (VSD and ASD), or more complex CHD defects (tetralogy of Fallot, transpositions of great arteries). Among them, if we consider three of the most frequent causes of cardiac disorder, we found CHDs to be reported in 30% of *TMEM70* cases and 10% of *ACAD9* and *TAZ* cases ([34, 53]; https://www.barthsyndrome.org;). This figure is clearly above the 1% of cases with CHDs identified in the general population. The observation of CHD is present in only a fraction of patients with the clinical presentation of mitochondrial disorders. Usually not all patients with a certain gene defect develop a cardiac phenotype, but the mitochondrial dysfunction predisposes patients to cardiac abnormalities [154]. Sengers syndrome or *ELAC2* patients seemed to be an exception, but for most gene defects which were tightly linked to cardiac manifestations, NGS

diagnostics extended the clinical spectrum to patients without cardiac phenotypes [59, 79, 80, 125].

Left ventricular non-compaction (LVNC) is a morphological abnormality of excessive trabeculation of the left ventricular myocardium, which is often complicated by ventricular dysfunction, arrhythmias, and cardioembolism. LVNC can be part of a structural heart disease. Additionally, mutations in a variety of genes, such as transcription factors, structural, nuclear, or ion channel genes, may cause LVNC. In general, the etiology of this disease entity is still poorly understood and object of current investigations. In mitochondrial disorders, Barth syndrome is most often associated with LVNC, but it is also typical for *DNAJC19* defects and reported in a total of 11 mitochondrial genes [62, 153, 155].

3.3 Genetic Causes of Mitochondrial Cardiac Manifestation

With about 300 gene defects reported in association with human mitochondrial disorders, the spectrum of respiratory chain defects is rather intricate. To break down the complexity, we have grouped the genes here into (1) disorders of oxidative phosphorylation (OXPHOS) subunits and their assembly factors; (2) defects of mitochondrial DNA, RNA, and protein synthesis; (3) defects in the substrate-generating upstream reactions of OXPHOS; (4) defects in cofactor metabolism; (5) defects in mitochondrial homeostasis; and (6) defects in relevant inhibitors (Fig. 3.1). In the following text, we will describe these groups in more details.

3.3.1 OXPHOS Subunits and Their Assembling Factors

Complex I deficiency is the most common biochemical phenotype observed in individuals with mitochondrial disorder and is responsible for approximately 30% of childhood-onset cases [156]. Complex I is composed of 44 subunits (7 encoded by mtDNA and 37 by nDNA), with genetic defects identified in 28 structural genes, in 11 assembly factors, and in a number of factors involved in mitochondrial translation (Fig. 3.1) [154].

Complex I deficiency is clinically heterogeneous, with a diverse spectrum of clinical presentations, such as Leigh syndrome, fatal infantile lactic acidosis (FILA), leukoencephalopathy, MELAS, or also hypertrophic cardiomyopathy. HCM, in particular, can be isolated or associated with multi-organ disease. Isolated HCM has been reported with mutations in nuclear-encoded subunits (*NDUFS2*, *NDUFV2*) and assembly factors (*ACAD9,* and less commonly *NDUFAF1*). Less frequently patients manifest with dilated cardiomyopathy, left ventricle non-compaction, or conduction defects (such as Wolff-Parkinson-White) [157]. Among 95 cases with complex I deficiency and cardiac manifestations described in the literature (Table 3.1), *ACAD9* deficiency, with 56 cases, represents the most frequent genetic cause observed [34]. Considering the number of *ACAD9* patients and the minor allele frequency of deleterious variants described so far, an
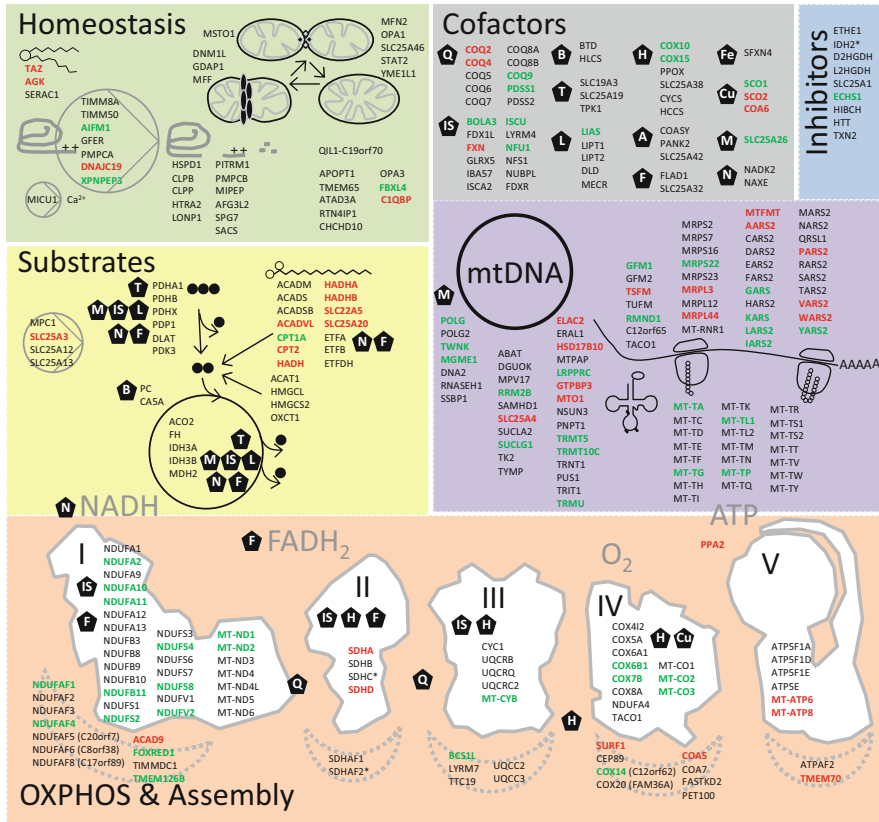
Fig. 3.1 Known disease genes ($n = 309$) in different parts of the mitochondrial energy metabolism. Q (coenzyme Q10), IS (iron-sulfur clusters), B (biotin), T (thiamine pyrophosphate), L (lipoic acid), H (heme), A (coenzyme A), F (riboflavin/FMN/FAD), Fe (iron), Cu (copper), M (s-adenosyl methionine), N (NADH/NADPH). Summary of mitochondrial genes with cardiac manifestations: in red are highlighted genes in which the cardiac involvement represents a major symptom among the other clinical features associated with the gene defect; in green are highlighted genes in which the cardiac involvement represents a minor symptom among the other clinical features associated with the gene defect

incidence of 59 new *ACAD9* patients born every year in Europe has been recently estimated [34]. The clinical spectrum of ACAD9 deficiency is characterized by predominant heart involvement. Other clinical recurrent symptoms include lactic acidosis and muscular weakness [158]. Age of onset, severity of the disease, and progression can vary significantly [34]. On a biochemical level, residual ACAD9 enzyme activity, and not complex I activity, seems to correlate with the severity of clinical symptoms in ACAD9-deficient patients [159]. Regarding the clinical presentation, the typical age of onset of patients with *ACAD9* deficiency is in the neonatal period or in early childhood, with the majority of the patients presenting in the first year of life. Looking at the survival data, for this subgroup with early

onset, the survival was poor (50% not surviving the first 2 years) and the outcome extremely severe compared to patients with a later presentation (more than 90% surviving 10 years) [34]. The patients with severe developmental delay or intellectual disability also showed an early disease onset; however neurological manifestations seem to be a rare presentation of the disease [34]. Furthermore, most patients currently alive are able to perform routine activities of daily living. This aspect could also influence the management of *ACAD9* patients, for example, for the decision of performing a cardiac transplant. Four patients with *ACAD9* defects underwent a cardiac transplant. Unfortunately, the two patients who presented within the first year died despite all efforts. In contrast, the two patients presenting after the age of 1 year developed normally, and their clinical status remains stable after years of follow-up (currently aged 15 and 35 years, respectively). However, additional longitudinal studies are warranted to better identify which patients with *ACAD9* deficiency are appropriate heart transplant candidates [160]. Supplementation with riboflavin showed improvement in complex I activity in the majority of patient-derived fibroblasts, and most patients similarly were reported to have clinical benefit with treatment. Most notably, patients presenting within the first year of life show a significantly better survival when treated with riboflavin [34]. However, detailed data about the starting point of riboflavin treatment, the dosage, etc. in large cohorts are needed [34, 161].

Isolated **complex II deficiency** is a rare cause of mitochondrial disorder. Complex II, or succinate dehydrogenase, is formed of four subunits, and it is the only respiratory chain complex entirely encoded by nDNA. Genetic defects were identified in four structural genes and two assembly factors. Clinically, neurological symptoms represent the most common presentation (especially Leigh syndrome or leukoencephalopathy), but hypertrophic and dilated cardiomyopathy, as well as left ventricular non-compaction, were identified in six of the reported cases [162]. In particular, early-onset hypertrophic cardiomyopathy with left ventricular non-compaction and severe complex II deficiency has been observed in association with SDHD defects [40]. Isolated and severe neonatal dilated cardiomyopathy has been associated with *SDHA* mutations [163]. Conduction abnormalities were present in the same patients and thus should be investigated in patients with complex II deficiency [162].

Complex III (coenzyme Q or cytochrome reductase) is a multi-subunit transmembrane protein encoded by both the mitochondrial (cytochrome *b*) and the nuclear genomes (ten subunits). Gene defects have been identified in five structural genes and five assembly factors [164]. Complex III or combined complex I and III deficiency typically manifests in infancy as a severe, multisystem disorder that includes features such as hypotonia, seizures, lactic acidosis, hypoglycemia, and intellectual disability. Variants in *BCS1L* can result in Björnstad syndrome and GRACILE syndrome, severe neonatal syndromes with multisystem and neurological manifestations. However, milder cases with survival into adulthood have also been described. In such cases, HCM has been reported in two patients [41]. In addition, different forms of cardiomyopathy (hypertrophic, dilated, and histiocytoid cardiomyopathy), either isolated or accompanied by multisystem mitochondrial disorder,

have been described in three patients with complex III deficiency associated with mutations in mitochondrial DNA-encoded cytochrome *b* (*MT-CYB*) [42, 165].

Complex IV—also called cytochrome *c* oxidase—is the terminal enzyme of the respiratory chain and consists of 14 subunits, 3 of which (named *COX1*, *COX2*, and *COX3*) are encoded by mitochondrial DNA. Complex IV deficiency has been associated with mutations in 11 structural genes and 8 assembly factors.

There are four types of complex IV deficiency differentiated by symptoms and age of onset: benign infantile mitochondrial type, French-Canadian type, infantile mitochondrial myopathy type, and Leigh syndrome. The clinical spectrum can vary among affected individuals, even within the same family. In mildly affected individuals can occur muscle weakness and hypotonia. Whereas in more severely affected individuals neurological dysfunction, heart and liver manifestations, lactic acidosis, and/or Leigh syndrome may also be present [166]. Cardiac involvement has been described in 16 published patients with complex IV deficiency (Table 3.1). Isolated dilated cardiomyopathy has been reported in individuals with complex IV deficiency and carrying *MT-CO2* and *MT-CO3* variants [167]. *SURF1*, a nuclear gene encoding a complex IV assembly factor, represents the most common cause of Leigh syndrome due to complex IV deficiency and is sometimes accompanied by cardiomyopathy [48]. In addition, there are a number of cofactor deficiencies which result in complex IV deficiency with cardiac manifestations (see Sect. 3.4 and Table 3.1).

Mitochondrial ATP synthase (**complex V**) synthesizes ATP from ADP and inorganic phosphate using the energy provided by the proton electrochemical gradient (proton-motive force) across the inner mitochondrial membrane. It consists of two functional domains, F1 and Fo. F1 comprises five different subunits, while the Fo region includes three main subunits a, b, and c, and six additional subunits. Gene defects have been identified in six structural genes and two assembly factors.

Most cases present with neonatal-onset hypotonia, lactic acidosis, hyperammonemia, hypertrophic cardiomyopathy, and 3-methylglutaconic aciduria. Among 55 cases with cardiac manifestations and complex V deficiency present in literature, 49 have been associated with variants in *TMEM70*. *TMEM70* deficiency is the most common genetic defect affecting the ATP synthase [51]. Frequent symptoms at onset are poor feeding, hypotonia, lethargy, and respiratory and heart failure, accompanied by lactic acidosis, 3-methylglutaconic aciduria, and hyperammonemia. In children with *TMEM70* deficiency, the most common heart problem is non-obstructive concentric HCM with preserved systolic function [52, 54]. With the exception of neonates with heart failure, the prognosis of cardiomyopathy in *TMEM70* patients is favorable, because HCM is mostly non-progressive or even regressive during long-term follow-up. Conduction defects (Wolff-Parkinson-White syndrome) have been found in 13% of *TMEM70* patients. Cardiomyopathy associated with systemic mitochondrial disorder has also been described with mutations in mitochondrial genes encoding complex V subunits, including *MT-ATP6* [191] and *MT-ATP8* [57, 168, 169].

3.3.2   Defects of Mitochondrial DNA, RNA, and Protein Synthesis

Mitochondrial protein translation defects typically cause multiple OXPHOS abnormalities and severe mitochondrial disorder. Gene defects have been identified in genes encoding elongation factors, aminoacyl-tRNA synthetases, tRNA-modifying enzymes, a mitochondrial peptide release factor, and an RNase that processes mitochondrial RNA. Mitochondrial disorders linked to protein translation defects manifest with neurological involvement and hypertrophic cardiomyopathy, as well as other multisystem abnormalities. Conditions with cardiac manifestations include defects in mitochondrial ribosomal proteins (*MRPS22*, *MRPL3*, *MRPL44*), mitochondrial tyrosine (*YARS2*) or alanine (*AARS2*) tRNA aminoacylation, and other enzymes involved in mitochondrial RNA metabolism [186, 188]. Cardiomyopathy resulting from mutations in *ELAC2* are usually associated with early severe forms of hypertrophic cardiomyopathy in the context of a multisystem disorder. However, isolated forms of hypertrophic and dilated cardiomyopathy may also be present.

Posttranscriptional modification of mitochondrial tRNAs is necessary for their stability and function. Abnormalities in these processes are illustrative of recently identified protein translation disorders that lead to cardiomyopathy. Hypertrophic cardiomyopathy and cardiac conduction defects in combination with psychomotor delay, encephalopathy, hypotonia, and lactic acidosis were found in children with variants in *MTO1* [86]. Mutations in *GTPBP3* have been described in association with neonatal hypertrophic or dilated cardiomyopathy and conduction defects. Again, most of the patients also showed extra-cardiac symptoms, such as encephalopathy, lactic acidemia, hypoglycemia, and hyperammonemia [84]. Another posttranscriptional modification defect of mitochondrial tRNAs was found in tRNA methyltransferase 5 (*TRMT5*) deficiency. Mutations in *TRMT5* have been described in association with hypertrophic cardiomyopathy, exercise intolerance, global developmental delay, hypotonia, peripheral neuropathy, renal tubulopathy, and lactic acidosis [88].

3.3.3   Defects in the Substrate-Generating Upstream Reactions of OXPHOS

Deficiencies of the mitochondrial phosphate carrier (*SLC25A3*) have been described in cases with hypertrophic cardiomyopathy accompanied by myopathy and lactic acidosis [137]. Lahrouchi et al. have recently reported a loss of function of the carnitine transport SLC22A5 in a family with history of pediatric cardiomyopathy and sudden cardiac death. The patients showed a reduction in the degree of cardiac hypertrophy, and her exercise tolerance improved markedly after L-carnitine supplementation [144]. Biallelic missense variants in the nuclear-encoded mitochondrial inorganic pyrophosphatase (PPA2) were identified in 17 individuals from 7 unrelated pedigrees presenting with seizures, lactic acidosis, cardiac arrhythmia, and exquisite sensitivity to alcohol, leading to sudden cardiac death [146].

3.3.4   Defects in Relevant Cofactors

Many cofactors have a key role in mitochondrial energy metabolism. Among them, some are required for the respiratory chain enzymes like coenzyme Q, iron-sulfur clusters, riboflavin, and heme. Their deficiency typically results in defects of more than one respiratory enzyme. Primary CoQ10 deficiency is a phenotypically and genetically heterogeneous condition, with various clinical presentations including encephalomyopathy, myopathy, cerebellar ataxia, nephrotic syndrome, and severe infantile multisystem mitochondrial disorder. Hypertrophic cardiomyopathy has been reported in cases with mutations in *COQ2*, *COQ4*, and *COQ9* [118, 119, 170, 187]. Fatal infantile cardioencephalomyopathy due to cytochrome c oxidase (COX) deficiency 1 is caused by biallelic variants in the *SCO2* gene. *SCO2* is a mitochondrial copper-binding protein involved in the biogenesis of the Cu(A) site in the cytochrome c oxidase (CcO) subunit Cox2 and in the maintenance of cellular copper homeostasis. Mutations in both *SCO1* and *SCO2* are associated with distinct clinical phenotypes in addition to tissue-specific cytochrome c oxidase deficiency. *SCO2* is highly expressed in the muscle, whereas *SCO1* is expressed at higher levels in the liver. This reflects the different clinical presentation of *SCO1*, mostly associated with hepatic liver failure, and *SCO2*, predominantly associated with severe early-onset cardiac failure. The onset of cardiomyopathy is either in utero or in the first days of life [132]. Copper-histidine supplementation in cell culture, and also the treatment in one patient, was reported to be beneficial for the cardiac phenotype [131].

3.3.5   Defects in Mitochondrial Homeostasis

Mitochondrial homeostasis involves several essential aspects of mitochondrial biogenesis, lipid synthesis, protein import, fission and fusion, quality control, and targeted degradation.

Barth syndrome is due to mutations in the X-linked *TAZ* gene, which codes for Tafazzin, a phospholipid transacylase involved in the remodelling of cardiolipin. Barth syndrome is characterized by cardiomyopathy, skeletal myopathy, distinctive facial features, developmental delay, neutropenia, and increased urinary levels of 3-methylglutaconic acid. Cardiomyopathy is the presenting manifestation in more than 70% of affected males and usually appears in infancy. Interestingly, in these patients, left ventricular non-compaction and dilated cardiomyopathies are more frequent cardiological findings than hypertrophic cardiomyopathy [171]. Patients can manifest with supraventricular and ventricular arrhythmias, sometimes related to sudden cardiac death [172]. Recently, a systematic mutation screening of *TAZ* in a large cohort of pediatric patients with primary cardiomyopathy identified pathogenic variants in 3.5% of the male patients [173]. In a mouse model of Barth syndrome, cardiac-specific loss of succinate dehydrogenase (complex II) activity has been described as a key event in the pathogenesis of cardiomyopathy [174]. Sengers syndrome is caused by the deficiency of the acylglycerol kinase (AGK) which is also

involved in the mitochondrial protein import. The clinical spectrum is characterized by the presence of hypertrophic cardiomyopathy, cataracts, myopathy, exercise intolerance, and lactic acidosis [60]. 3-Methylglutaconic aciduria associated with *DNAJC19* mutations (DCMA syndrome) is mainly associated with dilated cardiomyopathy or left ventricular non-compaction and non-progressive cerebellar ataxia [63]. Variants in *C1QBP*, encoding a complement component 1 Q subcomponent-binding protein, have been recently associated with severe forms of neonatal or later-onset cardiomyopathy associated with combined respiratory chain deficiencies [66].

3.3.6 Defects in Relevant Inhibitors

Mitochondrial short-chain enoyl-CoA hydratase-1 deficiency (ECHS1) is an autosomal recessive inborn error of metabolism caused by compound heterozygous mutations in the *ECHS1* gene and characterized by severely delayed psychomotor development, neurodegeneration, increased lactic acid, and cardiomyopathy due to the accumulation of toxic metabolites. Usually these patients are affected by hypertrophic cardiomyopathy and, more rarely, by the dilated form [136, 189].

3.3.7 Mitochondrial Syndromes

Mitochondrial syndromes represent a spectrum of symptoms typically associated with specific abnormalities of mitochondrial DNA (Table 3.2). They can be associated with cardiomyopathy, conduction abnormalities, or both. Kearns-Sayre syndrome is characterized by extra-cardiac manifestations such as pigmentary retinopathy, progressive external ophthalmoplegia, increased cerebrospinal fluid protein concentration, and cerebellar ataxia. Cardiac conduction block is one of the cardinal manifestations; however hypertrophic cardiomyopathy may also be observed. Sudden cardiac death occurs in up to 20% of cases [175].

Cardiomyopathy and/or conduction abnormalities may also accompany MELAS, MERRF, and mtDNA-associated Leigh syndrome/NARP (neuropathy, ataxia, and retinitis pigmentosa) syndromes. Cardiomyopathy occurs in 18–30% of individuals with MELAS syndrome [176]. Both dilated and hypertrophic cardiomyopathies have been observed in MELAS syndrome; however, more typical is non-obstructive concentric hypertrophy [177]. Cardiac conduction abnormalities including Wolff-Parkinson-White syndrome has been reported in 13–27% of individuals with MELAS syndrome [176]. Cardiomyopathy has been identified in 30% of MERRF cases and Wolff-Parkinson-White in 22% [178]. In NARP syndrome, the cardiological manifestations described thus far are hypertrophic cardiomyopathy and atrioventricular block [179].

Table 3.2 Genetic defects and clinical manifestations of mitochondrial syndromes

Mitochondrial syndrome	Genetic defect	Cardiac manifestation	Extra-cardiac manifestation
Kearns-Sayre	mtDNA deletion	A/C (heart block); DCM, HCM, PMVT	Progressive external ophthalmoplegia, pigmentary retinopathy, cerebellar ataxia, short stature, deafness, dementia, limb weakness, diabetes mellitus, renal tubulopathy
MELAS	mtDNA mut.: MT-TL1 enc. tRNALeu (m.3243A > G (80%), m.3271T > C (7.5%)), also MD-ND1 and others	HCM, DCM, LVNC, RCM; A/C (heart block, WPW syndrome)	Encephalomyopathy, lactic acidosis, stroke-like episodes, deafness, myopathy
MERRF	mtDNA mut.: MT-TK enc. tRNALys (m.8344A > G) also MT-TF, MT-TL1, MT-TI, MT-TP	HCM, DCM, HICM; A/C (WPW syndrome, others)	Myoclonic epilepsy, ataxia, myopathy, intellectual disability, deafness, short stature, optic atrophy
NARP/ mtDNA-associated LS	mtDNA mut.: LS, MT-ATP6, MT-TL1, MT-TK, MTTW, MT-TV, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-CO3; NARP, MT-ATP6(m.8993T > G, m.8993T > G)	HCM; A/C (heart block)	Leigh syndrome, neuropathy, ataxia, pigmentary retinopathy

DCM dilated cardiomyopathy, *HCM* hypertrophic cardiomyopathy, *HICM* histiocytoid cardiomyopathy, *LVNC* left ventricular non-compaction, *MELAS* mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, *MERRF* myoclonic epilepsy with ragged red fibers, *PMVT* polymorphic ventricular tachycardia, *RCM* restrictive cardiomyopathy, *WPW* Wolff-Parkinson-White syndrome

3.4   Characterization of the Cardiac Involvement

The clinical presentation in patients with cardiomyopathy varies from asymptomatic to severe heart failure with asphyxia. In some cases, a sudden cardiac death can even be the first manifestation of the underlying cardiac dysfunction in an apparently healthy individual. Therefore, the assessment of the cardiac status represents a fundamental step for the management, follow-up, and prognosis of these patients. History and physical examination might reveal multisystem involvement, such as failure to thrive, global developmental delay, muscle weakness, respiratory abnormalities, epilepsy, vision problems, and others [180]. Family history might be positive for the occurrence of multisystem disorders in ancestors (Fig. 3.2). If a significant ventricular dysfunction is present, the cardiac examination might show
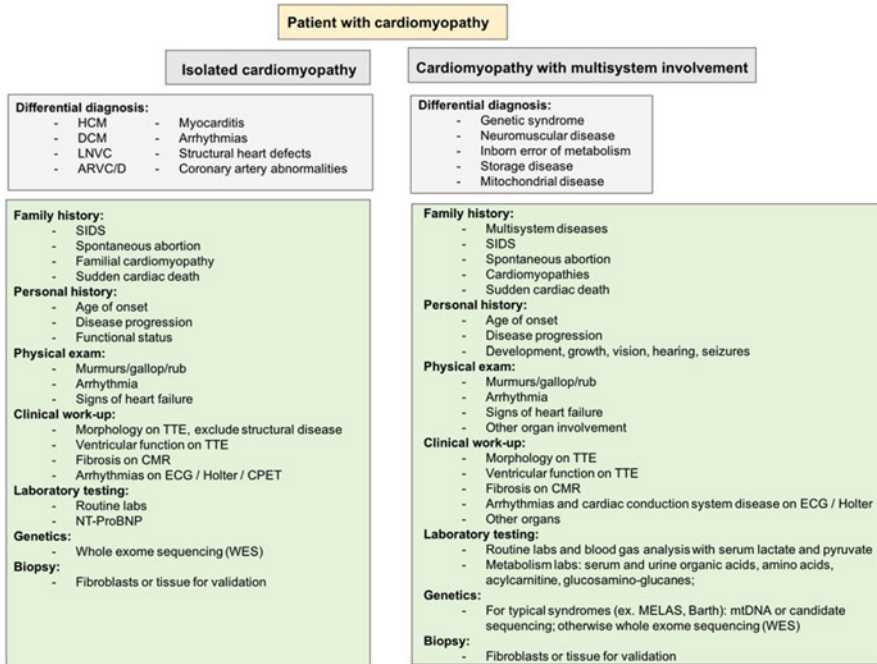
Patient with cardiomyopathy

Isolated cardiomyopathy	Cardiomyopathy with multisystem involvement
Differential diagnosis: - HCM - Myocarditis - DCM - Arrhythmias - LNVC - Structural heart defects - ARVC/D - Coronary artery abnormalities	**Differential diagnosis:** - Genetic syndrome - Neuromuscular disease - Inborn error of metabolism - Storage disease - Mitochondrial disease
Family history: - SIDS - Spontaneous abortion - Familial cardiomyopathy - Sudden cardiac death **Personal history:** - Age of onset - Disease progression - Functional status **Physical exam:** - Murmurs/gallop/rub - Arrhythmia - Signs of heart failure **Clinical work-up:** - Morphology on TTE, exclude structural disease - Ventricular function on TTE - Fibrosis on CMR - Arrhythmias on ECG / Holter / CPET **Laboratory testing:** - Routine labs - NT-ProBNP **Genetics:** - Whole exome sequencing (WES) **Biopsy:** - Fibroblasts or tissue for validation	**Family history:** - Multisystem diseases - SIDS - Spontaneous abortion - Cardiomyopathies - Sudden cardiac death **Personal history:** - Age of onset - Disease progression - Development, growth, vision, hearing, seizures **Physical exam:** - Murmurs/gallop/rub - Arrhythmia - Signs of heart failure - Other organ involvement **Clinical work-up:** - Morphology on TTE - Ventricular function on TTE - Fibrosis on CMR - Arrhythmias and cardiac conduction system disease on ECG / Holter - Other organs **Laboratory testing:** - Routine labs and blood gas analysis with serum lactate and pyruvate - Metabolism labs: serum and urine organic acids, amino acids, acylcarnitine, glucosamino-glucanes; **Genetics:** - For typical syndromes (ex. MELAS, Barth): mtDNA or candidate sequencing; otherwise whole exome sequencing (WES) **Biopsy:** - Fibroblasts or tissue for validation

Fig. 3.2 Clinical work-up of patient with suspected mitochondrial cardiomyopathy

signs of heart failure, such as dyspnea, sweating, failure to thrive, bilateral lung crackles, pitting edema, hepatomegaly, and signs of hypoperfusion. Severe cardiac manifestations including heart failure, ventricular tachyarrhythmias, and sudden cardiac death can occur during a metabolic crisis often precipitated by physiologic stressors such as febrile illness or surgery. The cardiac investigation should include chest X-ray, transthoracic echocardiography (TTE), electrocardiography (ECG), Holter ECG, cardiac magnetic resonance (CMR), and, in older children, cardiopulmonary exercise testing (CPET) (Fig. 3.2). TTE is performed to assess ventricular chamber sizes, myocardial thickness, and systolic and diastolic function [181]. If hypertrophy is present, it is mostly concentric [182] (Fig. 3.3), but asymmetric septal hypertrophy with or without left ventricular outflow obstruction has been described. ECG and Holter recordings are performed to screen for the presence of arrhythmias and cardiac conduction system disorders, such as sinus node dysfunction, atrioventricular block, WPW syndrome, or intraventricular conduction delay [181] (Fig. 3.3e-f). CPET is performed to assess exercise capacity as reflected by the maximum rate of oxygen consumption (peak VO2) [181] and to evaluate the risk for exercise-triggered arrhythmias or conduction system disease. CMR should be performed to fully evaluate cardiac morphology and ventricular function, to screen for storage diseases, and to assess the presence of interstitial or focal fibrosis. The indication for cardiac catheterization is on an individual basis and should be
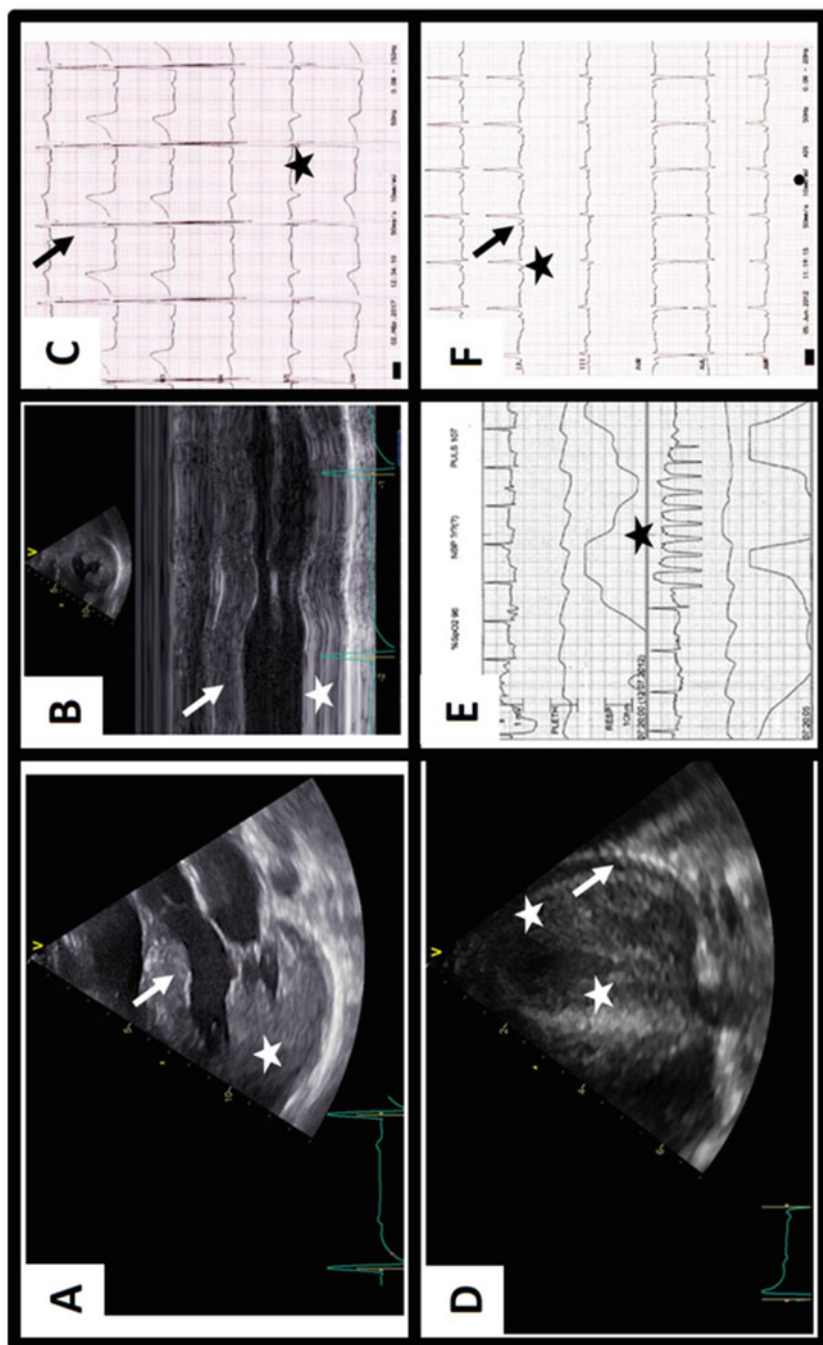
Fig. 3.3 Case presentation: cardiac manifestation of mitochondrial disorder. (**a**, **b**, **c**) A 15-year-old girl with complex I and IV deficiency and concentric hypertrophic cardiomyopathy presenting with metabolic crisis and seizures, but preserved cardiac function. Parasternal long axis (**a**) and parasternal short axis

(**b**) on transthoracic echocardiography show thickening of the left ventricular posterior wall (star) and of the interventricular septum (arrowhead); there is left ventricular hypertrophy on electrocardiography with deep S waves in the right (star) and tall R waves in the left (arrowhead) precordial leads. (**d**, **e**, **f**) A 2-month-old boy with complex I deficiency and severe concentric hypertrophic cardiomyopathy presenting with heart failure. Four-chamber view reveals massive thickening of the left ventricular myocardium (star) and pericardial effusion (arrowhead) on transthoracic echocardiography (**d**); telemetric monitoring shows brief runs of non-sustained self-limiting polymorphic ventricular tachycardia (star) (**e**); there is WPW syndrome with short PR interval (star) and delta-waves (arrowhead) on 12-lead surface electrocardiogram

performed if ventricular function is very poor in order to assess hemodynamics for possible heart transplantation or if the underlying diagnosis is not clear, so that endomyocardial biopsy results are made available. The conventional clinical approach of patients with mitochondrial cardiomyopathy includes detailed family and personal history and a clinical work-up to evaluate the cardiac defect, followed by histologic, enzymologic, molecular, and metabolic findings [153] (Fig. 3.2). If the cardiac phenotype is suspected to be based on a mitochondrial disorder, laboratory tests should include basic measurements, as well as detailed metabolic tests including ammonia, serum pyruvate, serum lactate, creatine kinase, quantitative amino acids, plasma acyl carnitine profile, and quantitative urine organic acids [153]. Care should be taken for proper processing of blood samples, as many metabolic tests require specific handling for accurate results. However, in clinical practice can frequently occur a mitochondrial cardiomyopathy without alteration of such classical metabolic findings.

3.5   Diagnosis of Potential Mitochondrial Cardiac Disease

The clinical spectrum of mitochondrial disorders often overlaps with common cardiological and extra-cardiac diseases. The diagnostic approach of these disorders is complex, time-consuming, and expensive. As mentioned above, although a positive biochemical result can substantiate a clinical diagnosis, the results are often inconclusive [11]. In this scenario, today's use of genetic testing represents a fundamental step in the diagnosis of mitochondrial disorders [12, 13] (Fig. 3.2). Whole-exome sequencing enables rapid, cost-effective, genome-wide screening and dramatically increases the diagnostic yield to greater than 60%, revealing a remarkable heterogeneity of underlying gene defects [11, 192]. With a genome-wide approach, missing genotype-phenotype correlations are revealed, and subsequently the list of new disease genes is ever growing. Indeed, in clinical practice, many mitochondrial cardiomyopathies would have been clinically misdiagnosed without the identification of the causal gene defects by NGS techniques. On the other hand, early-onset forms of hypertrophic cardiomyopathy related to specific disorders, such as Noonan syndrome, could also be erroneously suspected to be due to mitochondrial defects without a genetic confirmation. In case of identification of variants of uncertain significance (VUS), a further valuable diagnostic step to validate the genetic finding is represented by a targeted biochemical analysis in fibroblasts or tissue biopsies (endomyocardial biopsy) (Fig. 3.2). Fibroblasts should be stored in parallel to be available for functional confirmation without further delaying diagnosis [193].

3.6 Management of Patients with Mitochondrial Cardiomyopathy

During the past 6 years, more than 100 novel mitochondrial disorders have been identified, affecting diverse mitochondrial pathways. The application of NGS technologies facilitates our understanding of the pathophysiology of mitochondrial disorders in general and potentially treatable disease subgroups; but the clinical management of affected individuals is challenging, and diagnostic strategies are in flux [102]. Unfortunately, in current clinical practice, therapeutic options for the majority of classical mitochondrial syndromes are limited to supportive care. Nevertheless, there are several mitochondrial defects, especially related to cofactor metabolism, that can be corrected by specific treatment strategies [102]. If the patient is severely and progressively ill (e.g., neonatal lactic acidosis), a more rapid diagnostic procedure is important, and a muscle biopsy with functional investigations is necessitated in parallel with starting genetic testing. This holds true especially if the suspected diagnosis influences the disease management (e.g., PDHc deficiency: initiation of ketogenic diet) or if it can guide the end of life decisions (e.g., Leigh syndrome). In this regard, empirical therapy with thiamine (20 mg/kg/day), biotin (5 mg/kg/day), riboflavin (20 mg/kg/day), and coenzyme Q10 (15 mg/kg/day) might be considered in patients with rapidly progressive or potential life-threatening course of disease. The treatment effect depends on the underlying mitochondrial disorders, for example, L-carnitine supplementation is highly effective in patients who have dilated cardiomyopathy secondary to primary systemic carnitine deficiency and in Barth syndrome. On the other hand, it has low effect on other types of mitochondrial cardiomyopathy. L-Arginine is effective in MELAS syndrome. Riboflavin is highly effective in complex I deficiencies and in particular in *ACAD9* patients [34]. A low-fat, high-protein diet is important for long-chain fatty acid metabolism disorders [102]. Patients with mitochondrial disorders should avoid certain medications that interfere with mitochondrial function and can precipitate a crisis state, such as metformin, propofol, statins, valproic acid, macrolide antibiotics, or tetracyclines [153]. Regular clinical checkups of all organs affected are necessitated depending on the severity of multisystem involvement. Cardiac involvement is treated by conventional heart failure therapy which includes diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, and calcium antagonists. Oral anticoagulation may be indicated with poor systolic ventricular function according to the clinical guidelines. Implantation of a pacemaker might be necessary in severe cardiac conduction system disease. An implantable cardioverter-defibrillator device might be indicated if there is a significant risk for sudden arrhythmic death or for secondary prevention after survived sudden death. Prophylactic cardiac pacing device implantation is thus generally proposed to prevent cardiac death. In the absence of consistent data regarding the incidence of ventricular arrhythmia in patients with mitochondrial cardiomyopathy, an implantable cardiac defibrillator should be proposed according to current clinical guidelines. A metabolic crisis with acute or subacute multi-organ failure secondary to physiologic stressors, such as infection, toxic triggers, medications, psychological stress, heat, or dehydration, is an emergency and needs

to be managed appropriately. Cardiac complications during a crisis include cardiogenic shock, arrhythmias, and sudden cardiac death. Management should be focused to the underlying cause of the crisis and on treatment that can improve mitochondrial function. Fever needs to be treated and empiric antibiotics administered if an infection is suspected. Mechanical ventilation is required in case of respiratory failure and care needs to be taken with oxygenation, as it worsens the crisis by increasing free radical production. Correction of acid-base and electrolyte disturbances should be gradual. Continuous infusion of 10% arginine and dextrose-containing intravenous fluids should be best administered via central venous access given the risk for phlebitis and necrosis. Hemodialysis might be necessary for treatment-resistant hyperammonemia, hyperkalemia, or lactic acidosis [183, 184].

3.7   Conclusion and Perspectives

Cardiomyopathy and conduction defects are the most frequent manifestations of mitochondrial cardiac disease. Mitochondrial cardiomyopathy is associated with an ever-growing list of genes, currently around 100. This list outmatches the number of non-mitochondrial cardiomyopathy genes. Therefore, screening for cardiomyopathy should be a routine part of the management of individuals with known or suspected mitochondrial disorders. The diagnosis of mitochondrial disorders, however, remains challenging in many cases due to the myriad of different symptoms in overlap with other clinical conditions. NGS techniques of leukocyte-derived DNA are the state-of-the-art tool to diagnose mitochondrial disorders, enabling rapid, cost-effective, genome-wide screening with a diagnostic yield of greater than 60% [12, 13, 191]. During the past 6 years, more than 100 novel mitochondrial disorders have been identified and have facilitated our understanding of the pathophysiology of mitochondrial disorders. For the remaining undiagnosed cases, the role of complementary NGS approaches, such as genome sequencing and RNA sequencing, is gaining importance [185, 193]. These genomic approaches are still used on a research-oriented base, but we predict that in the future, they will become a valuable tool also in a diagnostic setting. Despite the scientific progress discussed thus far, it is important to underline the fact that most of these disorders do not have a treatment. This is with the exception of the group of cofactor metabolism deficiencies for which there are promising treatment options, highlighting the need for molecular diagnostics. There are still more than 70 diseases with less than 10 patients described. With the increasing number of patients, we will better understand the genotype-phenotype correlations which will help in counseling families. The better we understand the pathomechanism, the greater the chance we will identify new treatment options.

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