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Genetics of Mitochondrial Cardiomyopathy

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Abstract

Purpose of Review Primary mitochondrial disorders (PMD) are a heterogeneous group of individual genetic multi-systemic diseases that are challenging to diagnose and manage; currently, there is no cure or FDA-approved therapies for these progressive genetic syndromes. Among the many organs that may be affected by mitochondrial disorders, the heart is one of the most common, given its high energy requirements, leading to mitochondrial cardiomyopathies.

Recent Findings Mitochondrial cardiomyopathies are due to underlying genetic defects in genes involved in mitochondrial functioning. These genes, which can be of nuclear or mitochondrial DNA, are either directly involved in the electron transport chain and oxidative phosphorylation or play a role in other mitochondrial pathways such as mitochondrial DNA (mtDNA) replication or maintenance of the inner mitochondrial membrane. Due to the high degree of variability and complexity, current therapeutic strategies are inadequately effective in treating mitochondrial cardiomyopathies. Further research, including longitudinal prospective natural history studies and large-scale randomized clinical trials, is warranted to determine the most effective therapeutic and pharmacologic strategies to address mitochondrial cardiomyopathies.

Summary In this review, we present our current understanding of mitochondrial cardiomyopathies, diagnostic tools, and management.

Keywords Primary mitochondrial disease · Mitochondrial cardiomyopathy · Management of mitochondrial cardiomyopathy

Introduction

Myocytes heavily rely on mitochondria for bioenergetic demands and energy consumption. Defects in mitochondrial function, therefore, impact the physiological functioning of myocytes. Primary mitochondrial disorders are due to pathogenic variants in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) and many of these have been known to involve cardiac function and/or structure. [1•, 2] While primary mitochondrial disorders may cause electrical disturbances, including Wolff-Parkinson-White, supraventricular tachycardia, bundle branch block, and other arrhythmias, this review will focus on mitochondrial cardiomyopathies. Disruption in bioenergetic mechanisms has recently been shown to contribute to several forms of heart failure. [3] While traditional cardiology focuses on general causes of pathologies causing heart conditions, the role of primary mitochondrial disorders and their impact on structure and function is recently becoming more apparent. We present a review of our current clinical understanding of cardiomyopathies known to be caused by primary mitochondrial disorders including clinical features, diagnosis, and management.

Primary Mitochondrial Disorders

Primary mitochondrial disorders (PMD) are a group of heterogeneous disorders often affecting multiple organ systems, especially those with the highest energy requirements including but not limited to the brain, skeletal muscle,

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endocrine, renal, ophthalmologic, sensorineural hearing, and cardiac conduction system and cardiac muscle. [4•] Disease manifestations may occur at any age and rarely can affect single rather than multiple organs, including isolated familial hypertrophic cardiomyopathy. [5] PMD, therefore, generally need coordinated multi-specialty consultations for thorough evaluation and management. Pathogenic variants in the genes that contribute to mitochondrial machinery cause insufficient energy production needed for the normal functioning of all cells, in addition to the creation of excess reactive oxygen species (ROS). The clinical course can be difficult to predict; some PMDs are progressive with high morbidity and mortality early in life, while others have a slowly progressive course with long periods of stability.

The prevalence of primary mitochondrial disorders is currently estimated to be about 1:6000, with an estimated carrier frequency of a pathogenic variant in mtDNA at 1:200. [6] Mitochondrial proteins are under the control of two genomes, nDNA and mtDNA. The maternally inherited mtDNA is present in hundreds to thousands of copies per mitochondrion, with numerous mitochondrion per cell; the absolute number varies from organ to organ based on unique energy requirements and demands The mtDNA encodes 37 genes in total; 13 essential polypeptides for the mitochondrial oxidative phosphorylation (OXPHOS) complexes: seven subunits of complex I (*ND1*, *ND2*, *ND3*, *ND4*, *ND4L*, *ND5*, and *ND6*) one subunit of complex III (cytochrome b, *cytb*), three subunits of complex IV (*COI*, *COII*, and *COIII*), and two subunits of complex V (*ATP6* and *ATP8*). The mtDNA-encoded hydrophobic polypeptides are translated in situ on mitochondrial ribosomes, which employ 22 tRNAs and 2 rRNAs also coded by the mtDNA. The remainder of genes necessary for mitochondrial function, estimated at > 1000, are nuclear-encoded, with pathogenic variants having an inheritance pattern that can be autosomal dominant, autosomal recessive, or X-linked.

Mitochondrial Involvement in Cardiomyopathies

Cardiomyopathies are a diverse group of pathologies characterized by structural and functional changes in the heart. Based on the American College of Cardiology/American Heart Association (ACC/AHA) stage and New York Heart Association (NYHA) functional class, MOGE(S) nosology encompasses these characteristics, which include morpho-functional phenotype (M), organ (s) involved (O), genetic inheritance pattern (G), etiological annotation (E), and functional status (S). [7] One of the essential first steps is to differentiate whether the origin of cardiomyopathy is mitochondrial. An instrumental identifying feature is the presence of isolated cardiomyopathy versus presentation as part of a multisystem disorder. Cardiomyopathy involving multiple systems with an unknown cause should raise concerns for mitochondrial cardiomyopathy (MCM). [8•, 9] Once the clinical examination and systematic screening of organs have established that cardiomyopathy is a part of a multi-system disorder, the patient should be referred to appropriate specialists, including a cardiac genetics clinic. [1•, 8•, 9–11] If the patient presents to a cardiologist, additional findings of central nervous system involvement (global developmental delay, regression, epilepsy), renal involvement, sensorineural hearing loss, diabetes, and/or skeletal myopathy (weakness, fatigue, exercise intolerance) would be a good indication to suspect an underlying primary mitochondrial disorder that requires a multidisciplinary approach.

Physiologic stressors such as infection, fever, fasting/starvation, dehydration, surgery, and anesthesia can trigger symptom onset or decline, sometimes referred to as a "mito crash." Certain cells, such as neurons, muscle cells (skeletal and cardiac), and the liver, have higher bioenergetic demands and are prominently impacted due to abnormal mitochondrial performance. Due to the high energy requirements of myocytes, cardiac manifestations are a key feature of mitochondrial diseases, with cardiomyopathies being one of the most common. [1•, 12] Twenty to forty percent of children and 30% of adults with mitochondrial disease have been reported to suffer from some form of cardiomyopathy. [13–17].

In a retrospective review of 113 pediatric patients with mitochondrial disease, the prevalence of cardiomyopathy was 40%. The mean presentation age was 33 months. In this cohort, 58% had hypertrophic cardiomyopathy, 29% had dilated cardiomyopathy, and 13% had left ventricular non-compaction. This report further highlighted that the patients with cardiomyopathy had an 18% survival rate to age 16 years as compared to 92% survival in children without cardiomyopathy. [18•].

Several studies on adult patients with mtDNA mutations have reported progressive cardiac disease. Wahbi et al. in 2015 in a retrospective study of 260 adults reported that 30% of the patients with primary mitochondrial disease had cardiac involvement at the time of diagnosis. [19] In another case series of 32 adult patients diagnosed with mitochondrial disease, 69% had mtDNA mutation, and 81% had evidence of cardiac involvement with EKG abnormalities and/or cardiomyopathy (19% hypertrophic; 3% restrictive and 3% left ventricular non-compaction). In the same study on future follow-up, two patients developed hypertrophic cardiomyopathy, and one with NARP developed peripartum dilated cardiomyopathy. [13] When a cardiac disease is present, morbidity and mortality may be increased. [18•].

Cardiac remodeling and subendocardial dysfunction can occur in MD patients without clinical cardiac manifestation. MCM and increased risk of cardiac involvement must be

considered in high-risk patients (with higher mutation load and disease burden) who might not have known mitochondrial disease, as cardiac presentation might be the first or even the only clinical manifestation. [5, 20–24] Advanced imaging techniques such as cardiac magnetic resonance (CMR) can be helpful in the early diagnosis of high-risk patients. Bates et al. (2013) in an MRI study of 22 mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) patients *(m.3243A > G)* without known cardiac involvement reported significant pathological cardiac findings, which included increased left ventricular mass index (LVMI), left ventricular mass to end-diastolic volume ratio (LVM/EDV), and wall thicknesses as compared to controls. [25].

Forms of Cardiomyopathy Associated with Mitochondrial Diseases (Table 1)

The presentation of cardiomyopathy in patients affected by mitochondrial diseases may vary significantly, ranging from being asymptomatic to manifestations such as heart failure, arrhythmias, and sudden cardiac death. [26] MCM most commonly includes hypertrophic cardiomyopathy, dilated cardiomyopathy, left ventricular non-compaction, or restrictive cardiomyopathy (RCM), generally in the absence of valvular disease, coronary artery disease, or hypertension. [1•, 4•, 27•, 28–30].

Hypertrophic Cardiomyopathy (HCM)

HCM is the most common form of cardiomyopathy caused due to genetic mutations with a prevalence of 1:500. [31] Due to the high energy demands, the cardiac cells undergo compensatory mitochondrial proliferation due to the mitochondrial defect. HCM has been reported in 40–50% of MCM cases. In addition to HCM being the most common primary cardiomyopathy, it is the most common presentation of MCM involving hypertrophic remodeling with the left ventricular wall thickness of ≥ 15 mm (in adults) in the absence of loading conditions (such as hypertension, valvular disease, etc.) contributing to wall thickening. [32–34] In the pediatric population, wall thickening of more than two standard deviations above the mean is a diagnosis of HCM. [32] Some mitochondrial disorders that feature HCM include mitochondrial DNA variants listed in Table 1.

Dilated Cardiomyopathy (DCM)

DCM is a major cause of heart failure, with a reported prevalence of 1:2500. [35, 36] DCM is also one of the major indications for cardiac transplants. It is characterized by dilatation and impaired functioning of one or both ventricles leading to heart failure. The clinical presentation includes signs of congestive heart failure, such as dyspnea, orthopnea, and congestive edema. Patients may also present with either atrial or ventricular arrhythmias and sometimes sudden cardiac death. [35–37] DCM accounts for up to 60% of cardiomyopathies among the pediatric population. [38, 39] Weintraub et al. have reported that 35% of DCM are caused due to genetic causes. [40] The exact percent of mitochondrial-related DCM is, however, not exactly known. [40–42] Mitochondrial diseases presenting with DCM include but not limited to are MELAS, Maternally inherited diabetes deafness (MIDD), LHON, and Barth syndrome (Table 1).

Restrictive Cardiomyopathy (RCM)

RCM is the least common of major cardiomyopathies and is characterized by stiff ventricular walls leading to diastolic dysfunction, dilated atria, and elevated end-diastolic pressure. [31, 34] Appearance of "granular" echoes on transthoracic echocardiography (TTE) is generally linked to cardiac amyloidosis when diagnosing RCM. However, RCM is also associated with mitochondrial disorders, including but not limited to MELAS, MIDD (Table 1). Specific imaging features on TTE can be a useful tool to screen amyloid deposits from secondary infiltrative cardiomyopathy. [43].

Left Ventricular Non-compaction (LVNC)

LVNC is also known as left ventricular hypertrabeculation or noncompaction cardiomyopathy (NCCM) and is characterized by left ventricular trabeculations, deep intertrabecular recesses along with a thin epicardial layer. LVNC is considered genetic cardiomyopathy by the American Heart Association and has been associated with several mitochondrial diseases (Table 1).

Histiocytoid Cardiomyopathy (HICMP)

HICMP is a rare genetic disorder of the pediatric population characterized by cardiac arrhythmias, Wolff-Parkinson-White (WPW) syndrome, or dilated cardiomyopathy. [44, 45] HICMP has been reported to also be associated with LVNC and MERF. [46] Key histological findings of HICMP include yellow-tan nodules on the epicardium, subendocardium, or cardiac valves consisting of histiocytoid-like cells with foamy granules. These cells have an increased number of normal or dysfunctional mitochondria, and many have called for classifying HICMP as a primary mitochondrial disease, including AHA [31, 44].

Table 1 Mitochondrial disorders which include cardiomyopathy as a key feature (table adapted from Mitochondrial Disease Genes Compendium: From Genes to Clinical Manifestations, 1st Edition—April 28, 2020, Editor: Marni Falk. eBook ISBN: 9,780,128,200,308)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
AARS2	Combined oxidative phosphorylation deficiency 8 (COXPD8); infantile cardiomyopathy; leukoencephalopathy, progressive, with ovarian failure (LKENP); adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP); lethal primary pulmonary hypoplasia; nonimmune hydrops fetalis	2011	Infantile CM	21549344	Nuclear (AR): MT-ARS alanine
ACAD9	Hypertrophic cardiomyopathy; exercise intolerance and lactic acidosis; mitochondrial complex I deficiency due to ACAD9 deficiency (MC1DN20)	2007	HCM DCM	17564966 30025539	Nuclear (AR): complex I and FAO
ACADL	Nonketotic hypoglycemia; Early-onset of severe cardiac and multiorgan failure; hepatic or hypoketotic hypoglycemic form; later-onset episodic myopathic form with intermittent rhabdomyolysis	1991 1995 (CM)	HCM DCM	7479827	Nuclear (AR): FAO
ACADVL	Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	1985 (disease identification) 1995 (first reported causal mutations)	HCM	4022672 7668252 7479827	Nuclear (AR): FAO
ACADS	Short-chain acyl-CoA dehydrogenase deficiency (ACADSD); lipid storage myopathy secondary to short-chain acyl-CoA dehydrogenase deficiency	1987	CM	3571488	Nuclear (AR): FAO
ACAT1	Alpha-methylacetoacetic aciduria; Beta-ketothiolase deficiency; ketone utilization disorder; 2-methyl-3-hydroxybutyric acidemia; mitochondrial acetoacetyl-CoA thiolase (MAT) deficiency; T2 deficiency; 3-oxothiolase deficiency; 3-ketothiolase deficiency; 3-KTD deficiency	1991	CM	1715688 30393371	Nuclear (AR): ketone body and isoleucine metabolism
AGK	*Sengers syndrome* (cataracts and cardiomyopathy)	2012	HCM	22284826 25208612	Nuclear (AR): IMM
ATPAF2 (ATP12)	Mitochondrial complex V (ATP synthase) deficiency, nuclear type 1 (MC5DN1)	2004	HCM	14757859	Nuclear (AR): complex V

Table 1 (continued)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
BAG3	Myopathy, myofibrillar, 6 (MFM6); cardiomyopathy, dilated, 1HH (CMD1HH)	2009 2011 (DCM)	isolated DCM	19085932 21353195	Nuclear (AD): co-chaperone/mito dynamics
BOLA3	Multiple mitochondrial dysfunctions syndrome 2 (MMDS2) hyperglycinemia	2011	HCM DCM	21944046	Nuclear (AR): Fe-S cluster
C1QBP	Combined oxidative phosphorylation deficiency	2017	CM (neonatal, childhood, later onset)	28942965	Nuclear (AR): protein synthesis
CA5A	Carbonic anhydrase VA deficiency	2014	HCM	24530203	Nuclear (AR): mitochondrial carbonic anhydrase
CHKB	Muscular dystrophy, congenital, megaconial type (MDCMC)	1998	DCM	9427222 1665002	Nuclear (AR): choline/ethanolamine kinase
COQ2	Primary CoQ10 deficiency; encephalopathy and multisystem disease; isolated steroid resistant nephrotic syndrome (SRNS)	2005	HCM	16116126 16400613	Nuclear (AR, AD): primary coenzymeQ10 synthesis
COQ4	Coenzyme Q10 deficiency, primary, type 7 (COQ10D7)	2012	HCM	22368301	Nuclear (AR): primary coenzymeQ10 synthesis
COQ8B (ADCK4)	Steroid-resistant nephrotic syndrome	2013	DCM	24270420	Nuclear (AR): primary coenzymeQ10 synthesis
COQ9	Coenzyme Q10 deficiency, primary, 5; Leigh syndrome; early neonatal demise	2009	HCM	19375058	Nuclear (AR): primary coenzymeQ10 synthesis
COX10	Mitochondrial complex IV deficiency; Leigh syndrome (LS)	2000	HCM	10767350 12928484 15455402 10767350	Nuclear (AR): complex IV assembly factor
COX14	Fatal neonatal lactic acidosis, mitochondrial complex IV deficiency	2012	HCM	22243966	Nuclear (AR): complex IV assembly
COX15	Leigh syndrome due to cytochrome c oxidase deficiency; cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency 2	2003	HCM (early-onset, fatal)	12474143	Nuclear (AR): complex IV assembly
COX6B1	Mitochondrial complex IV deficiency	2008	HCM LVH	18499082	Nuclear (AR): complex IV subunit
CPT2	CPT deficiency, hepatic, type II (CPT II); CPT II deficiency, lethal neonatal; myopathy due to CPT II deficiency, stress induced (autosomal dominant or recessive); encephalopathy, acute, infection-induced, 4, susceptibility to (IIAE4)	1992	DCM	1528846	Nuclear (AD/AR): FAO

Table 1 (continued)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
D2HGDH	D-2-hydroxyglutaric aciduria	1980 (biochemical) 2005 (genetic)	CM	6774165 15609246 9894884	Nuclear (AR): D-2-hydroxyglutarate dehydrogenase
DES	Muscular dystrophy, limb-girdle, type 2R; Myopathy, myofibrillar, 1; scapuloperoneal syndrome, neurogenic, Kaeser type; cardiomyopathy, dilated, 1I	1998	CM RVH	9697706	Nuclear (AD): desmin
DLD	Dihydrolipoamide dehydrogenase deficiency (E3 deficiency); maple syrup urine disease, type III (MSUD); Leigh syndrome; recurrent hepatitis; Infantile lactic acidosis with hypotonia	1986 (infantile LA) 1998 (hepatic) 2010 (myopathic)	CM	3769994 9764998 20652410	Dihydrolipoamide dehydrogenase/PDH pathway
DNAJC19	3-methylglutaconic aciduria, type V (MGCA5)	2006	DCM noncompaction cardiomyopathy	16055927	Nuclear (AR): IMM protein import
ECHS1	Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency; congenital lactic acidosis; Leigh syndrome; paroxysmal exercise dyskinesia	2015 (encephalopathy) 2016 (paroxysmal exercise associated dyskinesia	DCM HCM	26000322 27090768	Nuclear (AR): isoleucine and valine catabolism; short-chain fatty acid beta-oxidation
ELAC2	Mitochondrial hypertrophic cardiomyopathy; intellectual disability; prostate cancer	2013 2017 (CM)	Infantile onset HCM	23849775 28441660 31045291	Nuclear (AR): MT-tRNA 3'-processing endonuclease activity
ETFA	Glutaric acidemia IIA (multiple acyl-CoA dehydrogenase deficiency, MADD)	1991	CM	1882842	Nuclear (AR): electron transfer flavoprotein (FAO)
ETFB	Glutaric acidemia II (multiple acyl CoA dehydrogenase deficiency, MADD)	1990	CM	2246866	Nuclear (AR): electron transfer flavoprotein (FAO)
ETFDH	Glutaric acidemia IIA (MADD)	1982 (GA II neonatal onset) 2010 (GAII adult onset with cardiomyopathy/arrhythmia)	CM	7173260 20370797	Nuclear (AR): electron transfer flavoprotein (FAO)
FBXL4	Mitochondrial DNA depletion syndrome 13, encephalomyopathic type (MTDPS13)	2013	HCM	23993194 23993193	Nuclear (AR): involved in regulating mitochondrial bioenergetics, mitochondrial DNA (mtDNA) maintenance, and mitochondrial dynamics
FLAD1	Lipid storage myopathy due to flavin adenine dinucleotide synthetase deficiency	2014	CM	25058219	Nuclear (AR): flavin adenine dinucleotide synthetase
FXN	Friedreich ataxia with retained reflexes (FRDA, FRDA1, FA)	1996	HCM	8596916	Nuclear (AR/trinucleotide repeat disorder): biosynthesis of heme and assembly and repair of iron-sulfur clusters

Table 1 (continued)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
GTPBP3	Combined oxidative phosphorylation deficiency 23 (COXPD23)	2014	HCM	25434004	Nuclear (AR): mitochondrial translation (MT-tRNAs)
HADH (SCHAD)	3-Hydroxyacyl-CoA dehydrogenase deficiency (HADH deficiency); hyperinsulinemic hypoglycemia, familial, 4; sudden infant death syndrome (SIDS)	2000	DCM HCM	O'Brien LK et al. JIMD abstract	Nuclear (AR): FAO of short chain fatty acids
HADHA	Fatty liver, acute, of pregnancy; HELLP syndrome, maternal, of pregnancy; LCHAD deficiency; trifunctional protein deficiency	1994	CM	7811722	Nuclear (AD/AR): FAO
HADHB	Trifunctional protein deficiency with multisystem disease; hypoketotic hypoglycemia; dilated cardiomyopathy; rhabdomyolysis and myopathy; sudden infant death syndrome (SIDS); hydrops fetalis; maternal HELLP (hemolysis, elevated-liver enzymes, and low platelets) syndrome in pregnancy	1992 (TFP biochemical identification) 1996 (TFP caused by HADHB mutations)	DCM	1401059 8651282	Nuclear (AR): FAO
HSD17B10	17-Beta-hydroxysteroid dehydrogenase X deficiency; mental retardation, X-linked syndromic 10 (MRXS10)	2003	HCM	12696021	Nuclear (XL): maturation of tRNAs for MT-DNA translation
IDH2	D-2-hydroxyglutaric aciduria 2	2010	CM	20847235 10407777 9894884	Nuclear (AD): PDH pathway
LDB3	Cardiomyopathy, dilated, 1C, with or without LVNC (AD); Cardiomyopathy, hypertrophic, 24 (AD); Left ventricular noncompaction (AD); myopathy, myofibrillar (AD)	2005 (myofibrillar myopathy) 2003 (cardiomyopathy)	DCM LVNC HCM NCCM	15668942 14662268	Nuclear (AD, AR, XL): maintains the structural integrity of the striated muscle Z-disk
LIAS	Hyperglycinemia, lactic acidosis and seizures (HGCLAS); pyruvate dehydrogenase deficiency	2011	HCM	22152680	Nuclear (AR): catalyzes the synthesis of lipoic acid

Table 1 (continued)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
LMNA	Restrictive dermopathy, lethal; Emery-Dreifuss muscular dystrophy 3, AR (EDMD2); muscular dystrophy, congenital; mandibuloacral dysplasia (MADA); heart-hand syndrome, Slovenian type; lipodystrophy, familial partial, 2 (FPLD2); muscular dystrophy, limb-girdle, type 1B (LGMD1B); Hutchinson-Gilford progeria (HGPS); Charcot-Marie-Tooth disease, type 2B1, 605,588; CMT2B1; cardiomyopathy, dilated, 1A, 115,200; CMD1A; Malouf syndrome	1999–2000	DCM	10080180 10814726 10580070 10587585	Nuclear (AD, AR): lamins
MGME1 (C20orf72)	Mitochondrial DNA depletion syndrome 11 (MTDPS11); chronic progressive ophthalmoplegia (CPEO) plus; cerebellar ataxia	2013	DCM	23313956	Nuclear (AR): exonuclease involved in MT-DNA replication
MIPEP	Combined oxidative phosphorylation deficiency-31 (COXPD31)	2016	LVNC HCM	27799064	Nuclear (AR): protein cleavage post-mitochondrial import
MRPL3	Combined oxidative phosphorylation deficiency 9 (COXPD9)	2011	HCM (severe, infantile onset)	21786366	Nuclear (AR): MT ribosome subunit
MRPL44	Combined oxidative phosphorylation deficiency 16	2013 (infantile hypertrophic cardiomyopathy, hepatic steatosis, microvesicular fatty degeneration in muscle tissue, 2015 (Leigh syndrome, pigmentary retinopathy, hemiplegic migraine, exercise intolerance)	HCM (infantile, childhood-onset)	23315540 25797485	Nuclear (AR): MT ribosome subunit
MRPS22	Combined oxidative phosphorylation deficiency 5 (COXPD5); ovarian dysgenesis 7	2007	HCM	17873122	Nuclear (AR): MT ribosome subunit
MT-ATP6	Leigh syndrome; neuropathy, ataxia and retinitis pigmentosa (NARP); Charcot-Marie-Tooth (CMT); bilateral striatal necrosis	1996	DCM HCM	8644724	Mitochondrial: complex V subunit
MT-ATP8	Cardiomyopathy; neuropathy	2008	HCM	17954552	Mitochondrial: complex V subunit
MT-CO1	Sensorineural hearing loss, aminoglycoside exposure; sensorineural hearing loss, isolated; acquired idiopathic sideroblastic anemia; cytochrome C oxidase (complex IV) deficiency	1997	CM	9389715	Mitochondrial: complex IV subunit

Table 1 (continued)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
MT-CO2	Fatal infantile lactic acidosis; Alpers-Huttonlocher syndrome; encephalomyopathy; myopathy; optic neuropathy	1999	CM	10205264 10486321	Mitochondrial: complex IV subunit
MT-CYB	Leber hereditary optic neuropathy; Leber optic atrophy; mitochondrial encephalomyopathy; mitochondrial myopathy; cardiomyopathy	1999	CM	10502593	Mitochondrial: part of the electron transport chain
MT-ND1 LHON: m.3460G > A in MT-ND1	Leber hereditary optic neuropathy (LHON); Leber optic atrophy and dystonia; Leigh syndrome including maternally-inherited Leigh syndrome; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, childhood and juvenile onset; mitochondrial complex I deficiency	1991 (LHON) 2004 (MELAS) 2008 (Leigh syndrome and complex I deficiency) 2013 (Leigh syndrome)	CM	1928099 1674640 15466014 18504678 24063851	Mitochondrial: complex I subunit
MT-ND4 m.11778G > A (LHON), m.11777C > A (Leigh)	Leber hereditary optic neuropathy (LHON); LHON-plus; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome; Leigh syndrome; chronic progressive external ophthalmoplegia (CPEO)	1988	HCM	3201231	Mitochondrial: complex I subunit
MT-ND5	Leber's hereditary optic neuropathy; Leber optic atrophy; Leigh syndrome; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome; Parkinson disease modifier; cardiomyopathy; myoclonic epilepsy associated with ragged-red fibers (MERRF)	1993	CM	8213825 30587702	Mitochondrial: complex I subunit
MT-RNR1 m.1555A > G m.1494C > T m.827A > G	Deafness, aminoglycoside-induced; sensorineural hearing loss, nonsyndromic; cardiomyopathy (one report); Parkinsonism; neuropathy	1993 (aminoglycoside induced deafness 1993 (Parkinsons) 1999 Cardiomyopathy	Restrictive CM	7689389 8104867 9915970	Mitochondrial: MT-ribosome subunit (12S rRNA)
MT-RNR2	Myopathy; atypical presentation of MELAS including diabetes, hyperthyroidism, and cardiomyopathy	1981 2001	CM	72195481 7761147 11455195	Mitochondrial: MT-ribosome subunit (16S rRNA)

Table 1 (continued)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
MT-TG m.9997 T > C (hypertrophic cardiomyopathy)	Hypertrophic cardiomyopathy; Mitochondrial myopathy; mitochondrial encephalomyopathy; sudden infant death syndrome (SIDS)	1991	HCM	1709275 8079988	Mitochondrial: MT-tRNA-Glycine
MT-TH	Cardiomyopathy, idiopathic dilated, mitochondrial; pigmentary retinopathy and sensorineural deafness; mitochondrial encephalopathy and ragged red fibers (MERRF) and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) overlap syndrome; deafness, nonsyndromic sensorineural, mitochondrial	2000 (cardiomyopathy) 2003 (pigmentary retinopathy and sensorineural deafness) 2004 (MELAS/MERRF phenotype) 2011 (nonsyndromic sensorineural deafness)	HCM DCM	11038324 12682337 14967777 21931169	Mitochondrial: MT-tRNA-histidine
MT-TI	Cardiomyopathy, fatal infantile; cardiomyopathy, fatal; cardiomyopathy, familial hypertrophic; multisystem disorder; Leigh syndrome; encephalopathy, familial progressive necrotizing; hypertension, hypercholesterolemia, and hypomagnesemia; chronic progressive external ophthalmoplegia (CPEO); isolated exercise intolerance; myoclonic epilepsy ragged red fibers (MERRF)	1990	HCM	1978914 2014659	Mitochondrial: MT-tRNA-isoleucine
MT-TL1	Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome; myoclonic epilepsy and ragged red fibers (MERRF) syndrome; Leigh syndrome; progressive external ophthalmoplegia (PEO); Kearns-Sayre syndrome (KSS); maternally-inherited diabetes and deafness (MIDD) syndrome; Leigh syndrome; sudden cardiac death; cardiomyopathy	1990	CM	2268345 8151636 922976	Mitochondrial: MT-tRNA-leucine
MT-TR	Mitochondrial encephalomyopathy; isolated dilated cardiomyopathy	1997 (dilated cardiomyopathy) 2004 (primary mitochondrial disease)	DCM LVH	9344764	Mitochondrial: MT-tRNA-arginine

Table 1 (continued)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
MT-TS2	Mitochondrial diabetes; cerebellar ataxia, cataract, diabetes mellitus, retinitis pigmentosa, deafness syndrome; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome; myoclonic epilepsy and ragged red fiber (MERRF) syndrome and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome overlap; nonsyndromic hearing loss; progressive mitochondrial myopathy, deafness and sporadic seizures	1998 (mitochondrial diabetes)	HCM	9792552	Mitochondrial: MT-tRNA-serine
MT-TV	Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome; mitochondrial neurogastrointestinal encephalopathy (MNGIE) syndrome; Leigh syndrome	1996	HCM	8797538	Mitochondrial: MT-tRNA-valine
MT-TW	Leigh syndrome; encephalomyopathy; encephalocardiomyopathy; neurogastrointestinal syndrome; hypertrophic cardiomyopathy	1995	HCM	7695240	Mitochondrial: MT-tRNA-Trp
MTFMT	Combined oxidative phosphorylation deficiency 15 (COXPD15); mitochondrial complex I deficiency, nuclear type 27 (MC1DN27); Leigh syndrome	2011	HCM NCCM	21907147	Nuclear (AR): formylation of methionyl-tRNA for protein translation
MTO1	Combined oxidative phosphorylation deficiency 10 (COXPD10)	2012	HCM	22608499 29331171	Nuclear (AR): MT-tRNA modifier
NDUFA10	Leigh syndrome; mitochondrial complex I deficiency, nuclear type 22; mitochondrial complex I deficiency, nuclear type 22	2011	HCM	21150889	Nuclear (AR): complex I subunit
NDUFA11	Mitochondrial complex I deficiency; encephalocardiomyopathy; fatal infantile metabolic acidosis	2008	HCM	12381726	Nuclear (AR): complex I subunit
NDUFA2	Mitochondrial complex I deficiency nuclear type 13; Leigh syndrome (LS); mitochondrial leukoencephalopathy	2008	HCM	18513682	Nuclear (AR): complex I subunit

Table 1 (continued)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
NDUFAF1	Hypertrophic cardiomyopathy; mitochondrial complex I deficiency; leukodystrophy	2007	HCM	17557076	Nuclear (AR): complex I subunit
NDUFAF4	Fatal neonatal lactic acidosis; Leigh syndrome (LS)	2009	HCM	19463981	Nuclear (AR): complex I assembly factor
NDUFB10	Fatal infantile lactic acidosis; cardiomyopathy; complex I deficiency	2017	Early onset (prenatal) HCM	28040730	Nuclear (AR): complex I subunit
NDUFB11	Early-onset infantile multisystemic organ failure; linear skin defects with multiple congenital anomalies; chronic encephalopathy with severe developmental delay and intellectual disability; congenital sideroblastic anemia; histiocytoid cardiomyopathy	2015	DCM Histiocytoid CM HCM	25772934	Nuclear (AR): complex I subunit
NDUFS1	Leigh syndrome (LS); Leigh syndrome spectrum encephalopathy; leukoencephalopathy; mitochondrial complex I deficiency	2001	HCM	11349233	Nuclear (AR): complex I subunit
NDUFS2	Mitochondrial complex I deficiency; Leigh syndrome; isolated Leber's hereditary optic neuropathy (LHON)-like; neonatal lactic acidosis	2001	HCM	11220739	Nuclear (AR): complex I subunit
NDUFS4	Leigh syndrome (LS); mitochondrial complex I deficiency; late-onset Parkinsonism and dystonia	1998	HCM	9463323	Nuclear (AR): complex I subunit
NDUFS8	Leigh syndrome (LS); progressive external ophthalmoplegia-plus; mitochondrial complex I deficiency, nuclear type 2	1998	HCM	9837812	Nuclear (AR): complex I subunit
NDUFV2	Mitochondrial complex I deficiency; Leigh syndrome (LS); neonatal lactic acidosis	2003	HCM (early onset)	12754703	Nuclear (AR): complex I subunit
PARS2	EIEE75: early infantile epileptic encephalopathy-75	2015 2017 2018	CM	25629079 28077841 29410512	Nuclear (AR): MT-ARS proline
PDSS2	Coenzyme Q10 deficiency, primary, 3 (COQ10D3); Leigh syndrome (LS)	2006	CM	17186472	Nuclear (AR): coQ10 synthesis pathway

Table 1 (continued)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
POLG	Progressive external ophthalmoplegia, autosomal recessive; progressive external ophthalmoplegia, autosomal dominant (PEOA1); mitochondrial recessive ataxia syndrome (includes SANDO and SCAE); mitochondrial DNA depletion syndrome 4B (MNGIE type, MTDPS4B); mitochondrial DNA depletion syndrome 4A (Alpers type, MTDPS4A)	2001 (PEO) 2004 (Alpers-Huttenlocher syndrome)	CM	11431686 15122711	Nuclear (AR, AD): MT-DNA polymerase
RARS2	Pontocerebellar hypoplasia, type 6 (PCH6); progressive encephalopathy with edema, hypsarrhythmia and optic atrophy; hydrops fetalis	2007	CM	17847012	Nuclear (AR): MT-ARS arginine
RMND1	Combined oxidative phosphorylation deficiency 11	2012	CM	23022098 23022099 29071585	Nuclear (AR): MT-DNA translation
SCO1	Neonatal-onset hepatic failure and encephalopathy (+/− intrauterine growth retardation and hypertrophic cardiomyopathy); fatal infantile encephalopathy and lactic acidosis	2000	HCM	11013136	Nuclear (AR): copper homeostasis
SCO2	Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency 1, autosomal recessive; Leigh syndrome (LS); myopia 6, autosomal dominant	1999	HCM (early)	10545952	Nuclear (AR, AD): copper homeostasis
SDHA	Leigh syndrome (LS); leukodystrophy; mitochondrial respiratory chain complex II deficiency; mitochondrial dilated cardiomyopathy 1GG (MD1GG); hypertrophic cardiomyopathy; noncompaction cardiomyopathy; paragangliomas 5; gastrointestinal stromal tumor; pheochromocytoma	1995 (Leigh syndrome) 2012 (leukodystrophy)	DCM HCM NCCM LVNC	7550341 22972948	Nuclear (AR, AD): complex II subunit
SDHAF1	Succinate dehydrogenase complex assembly factor 1; mitochondrial respiratory chain complex II deficiency	2009 (infantile leukoencephalopathy)	CM	19465911	Nuclear (AR): complex II assembly factor, TCA cycle, and iron-sulfur cluster
SDHB	Complex II deficiency; paraganglioma and gastric stromal sarcoma; pheochromocytoma	2001(paragangliomatosis) 2012 (complex II deficiency)	HCM	22972948	Nuclear (AR): complex II subunit, TCA cycle, and iron-sulfur cluster

Table 1 (continued)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
SDHD	Complex II deficiency (PMID: 24,367,056); Leigh syndrome; Merkel cell carcinoma, somatic; carcinoid tumors, intestinal; paraganglioma and gastric stromal sarcoma; paragangliomas 1, with or without deafness; Cowden syndrome 3 (CWS3); pheochromocytoma, modifier	2012 (complex II deficiency)	CM	22972948	Nuclear (AR, AD): complex II subunit, TCA cycle
SLC22A5	Carnitine deficiency, systemic primary (CDSP)	1998 (biochemical description) 1998 (mutation identification)	HCM	9826541 10051646	Nuclear (AR): carnitine transporter
SLC25A20 (CACT)	Carnitine-acylcarnitine translocase deficiency (CACTD)	1992 (biochemical description) 2000 (mutation identification)	CM	1598097 10697964	Nuclear (AR): acylcarnitine transporter
SLC25A3	Mitochondrial phosphate carrier deficiency; neonatal lactic acidosis; hypertrophic cardiomyopathy; mitochondrial myopathy	2007	HCM	17273968	Nuclear (AR): mitochondrial copper transporter
SLC25A4 (ANT1)	Mitochondrial DNA depletion syndrome 12 (cardiomyopathic type, MTDPS12); progressive external ophthalmoplegia (PEO) with mitochondrial DNA deletions 3.; autosomal dominant PEO, often adult onset with cardiomyopathy, skeletal myopathy and ptosis; autosomal recessive mtDNA depletion, often pediatric-onset with hypertrophic cardiomyopathy, delayed motor milestones, exercise intolerance, lactic acidosis; de novo autosomal dominant variants with neonatal encephalopathy, severe hypotonia, lactic acidosis, respiratory insufficiency, and cardiomyopathy; de novo dominant variant presenting in childhood with isolated mild skeletal myopathy; severity of cardiomyopathy may be modulated by mtDNA haplogroup	2000 (dominant PEO) 2005 (recessive mtDNA depletion and cardiomyopathy)	HCM	10926541 16155110 27693233 23401503	Nuclear (AD, AR): ADP/ATP transporter
SURF1	Leigh syndrome (LS) due to complex IV deficiency; Charcot-Marie-Tooth disease, type 4 K (CMT4K)	1998	HCM	9843204 9837813	Nuclear (AR): complex IV assembly factor
TACO1	Mitochondrial complex IV deficiency; Leigh syndrome (LS)	2009	HCM	19503089	Nuclear (AR): complex IV subunit translation

Table 1 (continued)

Gene	Mitochondrial disease name	Year discovered	Cardiac phenotype	PMID	Gene inheritance and classification
TAZ	Barth syndrome (BTHS); dilated cardiomyopathy (DCM); hypertrophic cardiomyopathy (HCM); endocardial fibroelastosis; left ventricular noncompaction (LVNC)	1983 (Barth syndrome description) 1996 (genetic cause)	DCM (w/endocardial fibroelastosis) HCM LVNC Boys with neutropenia, CM and 3MG on UOA	6142097 8630491	Nuclear (XL): cardiolipin maturation
TMEM126B	Complex I deficiency	2016	HCM	27374773 27374774	Nuclear (AR): complex I assembly factor
TMEM70	Mitochondrial complex V (ATP synthase) deficiency, nuclear type 2	2008	HCM (nonprogressive) Neonatal HCM with 3MG on UOA seen in Romani ancestry	18953340 25326274	Nuclear (AR): complex V assembly factor
TRMT5	Complex hereditary spastic paraplegia	2015	HCM	26189817	Nuclear (AR): methylation of tRNAs
TSFM	Combined oxidative phosphorylation deficiency 3 (COXPD3); cardiomyopathy; Leigh syndrome (LS); infantile liver failure	2006 (encephalopathy or hypertrophic cardiomyopathy) 2012 (severe infantile liver failure) 2014 (Leigh syndrome)	DCM HCM	17033963	Nuclear (AR): translation elongation factor
TUFM	Combined oxidative phosphorylation deficiency 4 (COXPD4); Leigh syndrome (LS); infantile macrocystic leukodystrophy with micropolygyria; dilated cardiomyopathy	2007 (Infantile macrocystic leukodystrophy with micropolygyria) 2014 (dysplastic leukoencephalopathy) 2019 (dilated cardiomyopathy and lactic acidosis without encephalopathy)	DCM	30903008	Nuclear (AR): mitochondrial translation protein biosynthesis
VARS2	Central neurologic disease (PEO, ataxia, combined oxidative phosphorylation deficiency); myoclonic epilepsy with dysmorphic facial features; encephalopathy with cardiomyopathy; combined oxidative phosphorylation deficiency 20	2014 (facial dysmorphism, microcephaly, myoclonic seizures; PEO, ataxia, hypotonia, myopathy) 2018 (encephalopathy with cardiomyopathy); prognosis depends on severity of cardiomyopathy and myopathy	HCM	29314548	Nuclear (AR): MT-ARS valine
YARS2	Myopathy, lactic acidosis, and sideroblastic anemia type 2 (MLASA2); isolated sideroblastic anemia; myopathy	2002 (myopathy lactic acidosis and sideroblastic anemia, MLASA) 2018 (isolated sideroblastic anemia) 2018 (myopathy)	HCM	12075011 30026338	Nuclear (AR): MT-ARS tyrosine

Abbreviations: *CM*, cardiomyopathy; *HCM*, hypertrophic cardiomyopathy; *DCM*, dilated cardiomyopathy; *NCCM*, noncompaction cardiomyopathy; *LVNC*, left ventricular noncompaction; *MT*, mitochondrial; *AR*, autosomal recessive; *AD*, autosomal dominant; *XL*, X-linked; *tRNA*, transfer RNA; *MT-ARS*, mitochondrial aminoacyl-tRNA synthetase; *3MG*, 3 methylglutaconic acid; *UOA*, urine organic acids

Other Mitochondrial Diseases with Cardiomyopathies

Some other mitochondrial diseases with cardiac pathology include Barth syndrome (OMIM 302,060), Friedreich ataxia (OMIM 229,300), TMEM70-related mitochondrial complex V deficiency (OMIM 614,052), and Sengers syndrome (OMIM 212,350). [26, 47].

Mutations in the gene taffazzin (*TAZ*) cause Barth syndrome which is an X-linked recessive disorder, seen mainly in males. TAZ is an inner mitochondrial membrane protein that plays a role in the remodeling of cardiolipin. [48] DCM and LVNC are more commonly observed in Barth syndrome as compared to HCM. Boys with Barth syndrome commonly have neutropenia, facial dysmorphic features, and skeletal myopathy, and can have intellectual disability. 3-Methylglutaconic aciduria is a key abnormality on metabolic screening labs (urine organic acids). HCM is a cardiac manifestation of Friedreich ataxia (FA) which is an autosomal recessive disorder due to trinucleotide repeats in the frataxin (FXN) gene. TMEM70-related mitochondrial complex V deficiency, also known as neonatal mitochondrial encephalocardiomyopathy, has severe early onset HCM as one of the key features, and is common in the Romani population with a common founder splice site pathogenic variant. [49].

Sengers syndrome, also known as mitochondrial depletion syndrome 10 (MTDPS10), is an autosomal recessive disorder caused by pathogenic variants in acylglycerol kinase gene (AGK). AGK gene assists in the assembly of the mitochondrial adenosine nucleotide transporter ANT1. [50] Sengers syndrome is characterized by HCM, congenital cataracts, myopathy, and lactic acidosis.

Diagnosis of Mitochondrial Cardiomyopathies

An extensive integrated diagnostic strategy includes a thorough physical exam, patient history, family history, biochemical metabolic screening labs, histopathological studies, functional assays, molecular genetic analysis, and cardiac workup, including EKG and cardiac imaging. Although MCM can be manifested as various forms of cardiomyopathies, HCM is the most common cardiac phenotype in MD. Early stages of MCM include features of heart failure with preserved ejection fraction and worsening diastolic dysfunction. [51] In some cases, cardiac imaging, such as echocardiography and cardiac MRI, is essential for the diagnosis and monitoring of progressive MCM. [25] Some of the tests employed for diagnosing cardiomyopathies are discussed below.

Laboratory Tests and Histology

While development of cardiac manifestations could be due to the underlying primary mitochondrial disorder, the treating clinician should also be on alert for secondary causes of cardiac involvement. Depending on the systems involved, such as renal, endocrine, or gastrointestinal, various lab values could deviate from the normal, sometimes indicating the etiology of cardiomyopathy. Liver enzymes and creatine kinase levels could be elevated on lab investigation. Increased TSH level would indicate endocrinological involvement. Specific assays to interrogate infectious etiologies such as viral or parasitic could also be helpful. Drug abuse, such as alcohol, is one of the agents leading to cardiomyopathy. [40, 52] The thiamine level is an indicator of alcohol abuse. Prognostic stratification could also be determined by BNP and renal function levels. [53, 54].

Metabolic screening labs for mitochondrial dysfunction include lactate (caution: this may be elevated due to poor tissue perfusion), pyruvate, ammonia (to interrogate the urea cycle), acylcarnitine profile (to interrogate the fatty acid oxidation cycle), plasma amino acids, urine organic acids (which can show elevated 3-methlglutaconic acid or Krebs cycle intermediates), and urine amino acids (to check for renal tubular acidosis). Expanded testing can include glutathione (a marker of oxidative stress), coenzymeQ10 level, and newer growth factor-related biomarkers such as FGF-21 and GDF-15.

Functional assays interrogating the respiratory chain function of skeletal muscle (vastus lateralis) have historically been an integral part of diagnosing PMD. These assays include activities of mitochondrial respiratory chain complexes I–IV and citrate synthase. Muscle tissue can also undergo mitochondrial DNA sequencing and deletions, which may detect pathogenic variants not seen in noninvasive testing, such as blood or buccal swab due to tissue heteroplasmy or mutation load, which can differ from tissue to tissue. Histology may show ragged-red fibers, which may stain negative for cytochrome c oxidase (COX) and positive for succinate dehydrogenase (SDH) on skeletal muscle histology, which are classic findings of mitochondrial pathology in PMDs. [1•, 55–57].

Electron microscopy has been one of the most informative and direct observational tools in diagnosing mitochondrial proliferation, structure, size, mitochondrial cristae integrity, and foreign inclusions in muscle biopsies. [58, 59] Recent advances in imaging, such as real-time confocal imaging, although they have provided an immense understanding of mitochondrial dynamics, are yet to fully prove clinical utilities in the diagnostic process.

Electrocardiogram (EKG)

EKG is one of the first and most common tests for any suspicion of cardiac etiology. While the findings on EKG are generally non-specific, Limongelli et al. reported progressive changes in the EKG in cardiomyopathy. [13] Findings on the EKG could indicate ventricular hypertrophy, conduction changes such as PR elongation, AV blocks, left bundle branch blocks (LBBB), and pathological Q waves, to highlight a few. [37, 53, 60].

Echocardiography

Echocardiography is an essential tool to investigate the kinetic and structural changes of the ventricles. Most commonly, 2D echocardiography is used but the images can be challenging to obtain due to patient-to-patient variability. Specific findings on echocardiography can be useful for certain cardiomyopathies, such as left ventricular wall thickness > 15 mm is typical of HCM. However, to determine a more accurate size and function of cardiac chambers, an alternative 3D echocardiography might be more reproducible. [61]

Cardiovascular Magnetic Resonance (CMR)

Cardiac involvement is a frequent finding in MD patients. [62] Abnormal CMR findings could include an impaired left ventricular ejection-fraction (LV-EF < 60%), unexplained LV hypertrophy, late-gadolinium-enhancement (LGE)-positive features, higher maximal wall thickness, and concentricity (LV mass to end-diastolic volume). A study by Florian et al. in 2015 was aimed at characterizing the prevalence and pattern of cardiac abnormalities and testing the additional diagnostic value of CMR in mitochondrial disease patients. The cohort ($n = 64$) included CPEO/KSS ($n = 33$), MELAS/–like ($n = 11$), MERRF ($n = 3$), and other non-specific mitochondrial disease forms ($n = 17$). The results indicated that 53% of 64 prospectively studied mitochondrial myopathy adult subjects had cardiac MRI abnormalities. Notably, pathological CMR findings indicating cardiac involvement were detected significantly more often than pathological ECG results or elevated cardiac serum biomarkers. [63] CMR has also been reported to detect wall thickness with higher sensitivity than echocardiography. [64] Furthermore, CMR is indicated in the initial workup of DCM as it could provide information on etiology. Inflammation can be suspected based on the enhancement of gadolinium by necrotic or scar tissues, especially if associated with edema and hyperemia. [65, 66] Cardiac magnetic resonance spectroscopy (MRS) is a novel tool which allows assessment of cardiac bioenergetics in vivo and may shed light on abnormal mitochondrial dysfunction and cardiac remodeling.

Endomyocardial Biopsy

A cardiac biopsy is indicated when the treatment is dictated by the diagnosis, for example, in cases of hemochromatosis, sarcoidosis, and myocarditis. [40, 53, 67] Although not routine, biopsies of organs could sometimes reveal a diagnosis of mitochondrial disease. Electron microscopy may reveal abnormal cristae formation, gigantic mitochondria, abnormal inclusions, or onion peeling appearance of the mitochondria. Recently, a case report by Marua et al. reported a diagnosis of Leigh syndrome using an endomyocardial biopsy after skeletal muscle biopsy did not reveal any obvious findings of mitochondrial disorder. [68].

Molecular and Genetic Testing

Genetic testing and counseling are essential components of the diagnostic work-up for MCM, often including the patient's family members. Pedigree analysis and mode of inheritance pattern are some of the essential first steps in identifying the diagnosis. The maternal inheritance pattern strongly indicates that the presentation could be an MCM due to a pathogenic, maternally inherited mtDNA variant. [51] Advanced molecular workup involving not only nuclear DNA but also mitochondrial DNA may be useful to uncover an underlying mutation. Availability of testing may vary based on location, financial factors including insurance reimbursement, and type of testing. Some centers may offer panel-based testing, including nuclear and mitochondrial DNA genes, while others may offer whole exome or whole genome sequencing. The patient should receive proper counseling and review of the pros and cons of genetic testing. [40, 69, 70].

Clinical Case Presentations of Patients with Mitochondrial Disease and Cardiac Manifestations

Clinical Case #1: Biallelic Pathogenic *C1QBP* Variants [71]

A 29-year-old male presented four years after ICD placement for septal thickening and normal LVEF, with new onset dyspnea. His echocardiogram showed an LVEF of 15%. He was stabilized on heart failure therapy. One month later, he

presented with 20 lb weight loss, anorexia, and diarrhea. On exam, he had CPEO and skeletal muscle weakness. A repeat echocardiogram showed LVEF of 5–10% with concentric hypertrophy and LV thrombi. Despite CICU care, he required ECMO and eventually needed a cardiac transplant. Genetic analysis using whole-exome sequencing (WES) revealed biallelic pathogenic variants in *C1QBP (c.612C > G*, p.F204L) and a de novo deletion of *17p13.2*. Mitochondrial mtDNA analysis on heart explant showed multiple large-scale mtDNA deletions with 33% heteroplasmy. Only 12 patients exhibiting biallelic C1QBP variants have been reported with a high degree of clinical variability. Of the reported cases, skeletal and cardiac myopathies were common in addition to chronic progressive external ophthalmoplegia and lactic acidosis. Forty-one percent of the reported cases were diagnosed with cardiomyopathy in the first decade of life. [72–74].

Clinical Case #2: RMND1-Related Mitochondrial Disease [75, 76]

A 12-year-old male presents with a history of global developmental delay, hypotonia, sensorineural hearing loss status post cochlear implants, chronic kidney disease status post-renal transplant, and chronic systolic congestive heart failure. In the neonatal period, he developed respiratory distress; had multiple cardiac arrests, pulmonary hypertension, and pneumothorax; and required extracorporeal membrane oxygenation (ECMO) for 9 days and a ventilator for seventeen days. By 4 months, he had hypotonia and motor delays, and at 9 months, sensorineural hearing loss. Cochlear implants were placed at thirteen and fifteen months. At 18 months, he was diagnosed with failure to thrive, gastroesophageal reflux disease, and feeling aversion, which required the placement of a gastrostomy tube. By age four, he had developed hypertrophic cardiomyopathy from chronic hypertension versus underlying disease. At age six, his cardiomyopathy progressed while he was affected by influenza (ejection fraction decreased from 50 to 20%). At that time, cardiac catheterization was performed as part of the workup for renal transplant. His heart biopsy showed marked cardiomyocyte hypertrophy without fibrosis. However, the electron microscopy showed normal architecture of mitochondria. He received a renal transplant 6 months later. He demonstrated significant improvement after the renal transplant, with improved motor skills, resolution of hypertension, and improvement in cardiomyopathy. WES revealed a previously reported missense mutation *c.713A > G*, p.(Asn238Ser), and *c.1317 + 1G > T* splice mutation in gene *RMND1*. The patient presented several years later with acute on chronic systolic heart failure with worsening renal function and AKI in the setting of chronic kidney disease. He was admitted for treatment of fluid overload, needing diuresis, and milrinone. Shortly after admission, the echocardiography showed stable poor cardiac function with an ejection fraction of 20–25%. He became worse over the next few weeks and his kidneys made modest recovery. His parents elected for compassionate withdraw of care.

Clinical Case #3 (Unpublished): *ACAD9* Mutation

A 29-year-old female with concentric LVH of unclear etiology and reported a history of suspected mitochondrial disease in childhood presented with profound shock and lactic acidosis (peak 17), with an axillary Impella. Her hospital course was complicated by acute loss of pulses in the right hand requiring a right axillary cut-down and thrombectomy with the removal of Impella, VA-ECMO, ventilator-dependent respiratory failure requiring tracheostomy, hospital-acquired pneumonia, pulmonary embolism/DVT, and AKI needing intermittent hemodialysis. She showed recovery during her hospital course, her LVEF was 45–50%. She did not tolerate any neurohormonal blockade due to hypotension. Muscle biopsy was obtained and showed myopathy and atrophy with electron microscopy showing mitochondria with widened cristae and dense deposits with scattered mitochondria. Her electron transport chain testing, however, did not show a complex I deficiency. Molecular and genetic analysis using WES showed compound pathogenic/likely-pathogenic variants in *ACAD9* (*c.1594 C > T* (p.R532W) and *c.1646 G > A* (p.R549Q)), consistent with a diagnosis of *ACAD9*-related disease. No pathogenic variants were found on mtDNA sequencing. She was started on high-dose riboflavin in addition to dietary changes to reduce long-chain fat intake and consideration of medium-chain fat supplementation.

Clinical Case #4 (Unpublished): *MT-TL1 (m.3243A > G)*: MELAS

A 50-year-old male presented with fatigue and exercise intolerance, thin body habitus, and diabetes mellitus. His mother died 30 years ago of an unknown cause. She was very thin and had adult-onset diabetes and sensorineural hearing loss, fatigue, and exercise intolerance. His younger sister and brother, ages 48 and 46, also had diabetes and sensorineural hearing loss. Both siblings had a history of strokes and epilepsy. Genetic testing on his sister revealed that she harbored the common *MT-TL1* pathogenic variant, *m.3243A > G*, the cause of MELAS. Subsequently, both men were tested and tested positive for MELAS. Within several months, his fatigue progressed from exercise intolerance and needing daily naps to be unable to use stairs and developing dyspnea on any exertion. An echocardiogram revealed a left ventricular ejection fraction (LVEF) of 20%. One and a half years later, he underwent an orthotopic heart transplant.

Post-operative complications included nausea from immunosuppressives and weight loss, necessitating the placement of a gastrostomy tube for enteral nutrition. Two and a half years post-transplant, he is now doing well.

Clinical Case #5 (Unpublished): *NDUFB11* Mutation

A 3-month-old female presents with a brief resolved unexplained event (BRUE). She was riding in her infant car seat, and her mother heard her cry. The patient could not be woken up and was unresponsive, cyanotic, and with agonal breathing. The mother initiated cardiopulmonary resuscitation (CPR). On arrival of emergency medical services (EMS), the patient was defibrillated three times and ultimately admitted to the intensive care unit. A CMR showed LVNC with heavy trabeculations at the left ventricular apex. The anterior apical and mid-lateral walls were also trabeculated, with the ratio of compacted to non-compacted myocardium at end-diastole at 3.7:1 and 1.6:1, respectively. Moderate to severe left ventricular dilation with mild left ventricular systolic dysfunction (LVEF 45%) was noted. The ventricular septum showed delayed contraction. She underwent a cardiac catheterization complicated by ventricular fibrillation during the procedure requiring chest compressions and defibrillation. An electrophysiology study indicated Wolff-Parkinson-White (WPW) syndrome, and she underwent ablation. She then had an epicardial implantable cardioverter defibrillator (ICD) placed. She was hospitalized for a total of 3 weeks. On further evaluation at the Cardiomyopathy Genetics Clinic, a de novo likely pathogenic variant in *NDUFB11* (c.163_170dup; p. Glu57Asp fs*71) was detected using WES. The patient is now seven years old, attends school, and is active, although she has occasional leg pain and fatigue. *NDUFB11* is a complex I subunit of the electron transport chain. It is located on the X-chromosome. Pathogenic variants in *NDUFB11* have previously been reported with infantile-onset linear skin defects, potentially life-threatening cardiomyopathy, and/or arrhythmia. It has been seen mainly in females as an X-linked dominant disease and is thought to be embryonic lethal in males. Extra-cardiac manifestations include hypotonia, seizures, intellectual disability, brain malformations including agenesis of the corpus callosum and ventriculomegaly, seizures, optic atrophy, anemia, and lactic acidosis. [77–81].

Management of Mitochondrial Cardiomyopathies

Conventional treatment should be initiated if there is evidence of hypertrophic remodeling, even in absence of current symptoms. Beta-blockers or calcium channel blockers in hypertrophied hearts may be used to aid in diastolic filling and are not contraindicated in PMD. ACE inhibitors may prevent early hypertrophic remodeling. Medication management of left ventricular dysfunction may help prevent atrial fibrillation. Cardiac involvement may lead to fatigue, dyspnea on exertion, and exercise intolerance. Pacemaker placement is recommended based on AHA guidelines, and given the unknown natural history of some PMDs, should be done as soon as possible to prevent sudden progression and cardiac death.

The two pathologies of heart failure and arrhythmias are treated with diuretics and vasodilators in warm and wet type, whereas with inotropes in the cold and wet type. [82] Heart failures that are chronic are generally treated with pharmacological agents such as ACE inhibitors, ARBs, beta-blockers, furosemide, ivabradine, mineralocorticoid antagonists, digoxin, and angiotensin receptor neprilysin inhibitor (ARNI). [34, 40] The SGLT2 inhibitors have been established as a strongly recommended treatment for reduced ejection fraction heart failure. Their role, however, in preserved ejection fraction heart failures is yet to be established, and more information is needed to determine if this newer class of medications is efficacious in mitochondrial cardiomyopathies.

Additional interventions include implantable cardioverter defibrillators (ICD), biventricular pacing, mechanical support (ECMO), surgical correction for valvular insufficiency, and in some cases, cardiac transplantation. [34, 40] Cardiac transplantation has been reported in 14% of patients with Barth syndrome. [83] Patients with mitochondrial disease have been reported to generally tolerate solid-organ transplantation except for liver transplantation in POLG-related disease, which needs cautious evaluation. Knowledge of mitochondrial disease as a cause of organ failure during the transplantation procedure is helpful for appropriate consultations but is not an absolute contraindication: the risks and benefits need to be considered along with patient and family wishes and long-term prognostic factors. [76••].

One of the recent approaches to managing patients with DCM is using a combination of genetic and diagnostic testing to determine the positive genotype-negative phenotype and pre-treat patients with medications to avoid developing dilated cardiomyopathy symptoms. Two such drugs have been reported from clinical trials using carvedilol and eplerenone. [84, 85, 86•].

In a randomized, placebo-controlled trial of another drug, elamipretide, in patients with reduced ejection fraction heart failure (ejection fraction ≤ 35%), Daubert et al. (2017) reported a significant decrease in left ventricular end-diastolic volume (− 18 mL; $P = 0.009$) and end-systolic volume (− 14 mL; $P = 0.005$) in the highest dose cohort. This was the first study to evaluate the efficacy of elamipretide in heart failure with reduced ejection fraction and demonstrated

favorable changes in left ventricular volumes supporting a temporal association and dose–effect relationship. [87].

Furthermore, in 2018, Sabbah et al. performed a randomized control study on left ventricular tissue from dogs and humans with heart failure, comparing them to healthy tissues. The study revealed decreased levels of endothelial nitric oxide synthase, cyclic guanosine monophosphate (cGMP), and peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α, which is a transcription factor that drives mitochondrial biogenesis) in heart failure (both in dog and human tissues). In addition, changes were observed in the regulators of mitochondrial fission and fusion, including fission-1, dynamin-related protein-1, mitofusion-2, dominant optic atrophy-1, and mitofilin. In all instances, the maladaptation was normalized following long-term therapy with elamipretide. [88] Although these findings support the continued development of elamipretide as an innovative therapeutic target, further study of elamipretide is needed to determine long-term safety and efficacy in heart failure management.

Surveillance and Recommendations

As demonstrated in Table 1, there are various genetic causes of mitochondrial cardiomyopathy, and for each disease, there is marked variability. Therefore, surveillance is necessary, with annual cardiology evaluations with an electrocardiogram (for arrhythmias) and echocardiogram. Additional studies may be needed, with guidelines individualized to cardiac status and known genotype. To aid the clinician in management guidelines, there are several available guidelines for mitochondrial disorders, including those from the Mitochondrial Medicine Society. [62, 89••] These recommendations include patient care at a tertiary center with cardiology expertise in mitochondrial disease. For a list of clinics in the United States, please refer to https://www.mitonetwork.org/centers. Baseline assessments should include a standard 12-lead electrocardiogram (EKG) and echocardiogram. Additional monitoring may be needed based on patient symptoms, such as Holter monitoring, for palpitations or high-risk patients based on genetic etiology. Follow-up screening may be determined by the cardiologist while keeping the genetic etiology and risk of developing cardiac manifestations in mind. Follow-up of symptomatic patients (LVEF < 35%, paroxysmal events, LV systolic, or diastolic dysfunction) may require prolonged and more frequent monitoring.

For patients with arrhythmias (SVT, WPW), ablation should be considered. Pacemaker implantation may be indicated to prevent sudden cardiac death and may be combined with an implantable cardioverter defibrillator (ICD). Cardiac MRI may be utilized to obtain more precise imaging. CPET (cardiopulmonary exercise testing) can establish functional capacity, exercise fitness, and conditioning, and to measure response to therapies, caution needs to be taken and the risks vs benefits discussed with the individual patient. Physical therapy may benefit those impacted by PMD, and cardiology may need to dictate any restrictions based on cardiac limitations. Cardiac transplantation is an option based on the multisystemic picture, long-term expected prognosis, and known natural history of the individual mitochondrial disease.

In addition, we advocate that patients and families seek out support from the patient advocacy groups including the United Mitochondrial Disease Foundation (www.umdf.org) and MitoAction (www.mitoaction.org). Clinicians seeking further information may find additional resources through these organizations in addition to the Mitochondrial Medicine Society (www.mitosoc.org).

Conclusion

PMD presents with a highly variable clinical, biochemical, and genetic phenotype, and is extremely challenging to diagnose and manage. There have been consensus recommendations from the Mitochondrial Medicine Society for the diagnosis and management of mitochondrial diseases. [90, 91] According to Binder et al. (2021), given an increased risk of cardiac conduction disease and structural heart disease in PMD patients, a diagnosis of PMD should raise concerns, and patients screened for cardiac abnormalities. [92] As we learn and uncover the pathologies and presentations of MCM, a more updated and integrated recommendation focusing on MCM is warranted.

Various pathologies underlying mitochondrial cardiomyopathies have been reported, the most common of which include mitochondrial proliferation as an adaptive response to energy deficiency. Increased oxidative stress, uncoupled respiratory chain, and uneven mechanical contraction due to misaligned sarcomere are other causes affecting the functioning of myocytes, which could provide additional therapies aimed at these abnormalities specifically.

PMD commonly involves the heart and includes both conduction and/or structural abnormalities such as cardiomyopathy. In some of the PMDs, there is a known genotype–phenotype correlation, such as bundle branch block progressing to complete heart block in those with single large-scale mtDNA deletion syndromes (SLSMDS) including Kearns-Sayre syndrome. Patients with common mtDNA pathogenic variants causing disorders such as MELAS and MERRF (m.3243A > G and m.8344A > G) are at risk for hypertrophic cardiomyopathy and ventricular preexcitation, including asymptomatic family members who also harbor the familial pathogenic variant.

With ever-increasing detailed understanding of the underlying pathologies and diversifying features, MCM might need a categorization befitting its presentation. It remains to be seen whether MCM warrants its nosology akin to MOGE(S) nosology for cardiomyopathies.[7]

Recent advances in high throughput sequencing, such as next-generation sequencing (NGS) and WES with an additional focus on mtDNA sequencing and deletions, have transformed the diagnostic landscape of PMD. In addition to high-throughput sequencing, further advances in transcriptomics, such as RNA sequencing and proteomics, are expected to revolutionize diagnostic capabilities.

Mitochondrial cardiomyopathies are common in PMD. Initial testing of genetic etiology should include mitochondrial causes. Once diagnosed, patients should have a cardiologist familiar with primary mitochondrial disorders to evaluate and treat these cardiac manifestations.

Cardiac involvement in PMD is treatable, and more likely to be effective when started early, hence the need for cardiac screening in all patients with PMD. Symptoms may not appear until late in the course of cardiac manifestations, and the heart may be involved at any age and may progress slowly. Conversely, cardiac disease may suddenly arise, especially after a stressor such as infection or fasting. Since many patients with PMD are at risk for cardiac manifestations over time, and cardiac involvement may not have symptoms until late in the presentation, surveillance at periodic intervals is recommended. This includes a 12-lead EKG and trans-thoracic echocardiogram after initial diagnosis for baseline assessment and repeated annually unless otherwise specified by a cardiologist familiar with mitochondrial disease. Any further investigations (Holter monitoring, cardiac MRI, etc.) is determined by the cardiologist based on initial findings and the genetic etiology and cardiac risk associated with the patient's specific mitochondrial disease. PMD patients may derive benefit from addressing cardiac involvement which can improve long-term outcome and quality of life. Natural history studies are needed to determine if other management strategies will be helpful and to determine the overall morbidity and mortality of cardiac involvement in the PMD population.

Author Contribution A. T. and A. C. G. wrote and edited the manuscript.

Declarations

Ethics Statement A retrospective chart review of the clinical course and laboratory test results was performed for patients presented. Informed consent was provided, and all patients were enrolled in the Children's Hospital of Philadelphia (CHOP) Institutional Review Board (IRB) approved study #08–6177 (Marni J. Falk, PI) that allows for medical record reviews, medical photography, publication for educational purposes, and clinical cohort analyses.

Conflict of Interest Dr Atif Towheed declares no conflict of interest. Dr Amy Goldstein is a consultant for Reneo Pharmaceuticals and on the Speakers Bureau for United Mitochondrial Disease Foundation and MitoAction.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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