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Mitochondrial Disease Genetics Update Recent insights into the Molecular Diagnosis and Expanding Phenotype of Primary Mitochondrial Disease

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Abstract

Purpose of Review—Primary Mitochondrial Disease (PMD) are a genetically and phenotypically diverse group of inherited energy deficiency disorders caused by impaired mitochondrial oxidative phosphorylation (OXPHOS) capacity. Mutations in more than 350 genes in both mitochondrial and nuclear genomes are now recognized to cause primary mitochondrial disease following every inheritance pattern. Next-generation sequencing technologies have dramatically accelerated mitochondrial disease gene discovery and diagnostic yield. Here, we provide an up-to-date review of recently-identified, novel mitochondrial disease genes and/or pathogenic variants that directly impair mitochondrial structure, dynamics, and/or function.

Recent Findings—A review of PubMed publications was performed from the past 12 months that identified 16 new PMD genes and/or pathogenic variants, as well as expanded phenotype recognition for a wide variety of mitochondrial disease genes.

Summary—Broad-based exome sequencing has become the standard first-line diagnostic approach for PMD. This has facilitated more rapid and accurate disease identification, and greatly expanded understanding of the wide spectrum of distinct clinical phenotypes. A comprehensive dual-genome sequencing approach to PMD diagnosis continues to improve diagnostic yield, advance understanding of mitochondrial physiology, and provide strong potential to develop precision therapeutics targeted to diverse aspects of mitochondrial disease pathophysiology.

Keywords

Primary mitochondrial disease; nuclear genome; mitochondrial genome; phenotype expansion; novel gene discovery

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CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to declare.

INTRODUCTION

Mitochondria are ubiquitous intracellular organelles in which oxidative metabolism occurs to generate the majority of cellular energy in the chemical form of adenosine triphosphate (ATP)(1). Approximately 1,500 proteins exist within mitochondria, with origins from two distinct cellular genomes. The vast majority of mitochondrial proteins are encoded by the nuclear DNA (nDNA) genome, while only 13 mitochondrial proteins that are all core structural subunits of complexes I, III, IV and V in the oxidative phosphorylation (OXPHOS) pathway are encoded in the mitochondrial genome (mtDNA) (2). Primary mitochondrial disease (PMD) is a highly heterogeneous collection of inherited genetic-based disorders that share in common disrupted energy metabolism due to impaired oxidative phosphorylation (OXPHOS) capacity. The broad and highly variable but commonly progressive phenotypic spectrum ranges from adult-onset, isolated organ system involvement to infantile-onset, multi-systemic, lethal disease (2). Systemic involvement that may affect nearly every organ has been described, leading to immense variation of clinical phenotype that can pose a diagnostic challenge (3). In a recent survey of self-reported PMD individuals (n=270), both pediatric and adult PMD subjects reported a mean of 16 clinical symptoms, highlighting the substantial burden of this disease (4). While PMDs are individually rare, they have a collective minimal prevalence of 1 in 4,300 (5). To date, pathogenic variants in more than 350 genes have been associated with PMD (6, 7).

Since the early characterization of cellular energy production within mitochondria in the 1950s and the discovery of pathogenic mitochondrial DNA (mtDNA) variants only three decades ago (8–10), knowledge of the diverse molecular etiologies of PMD and deleterious effects of pathogenic variants has dramatically increased. This, in turn, has led to the elucidation of the underlying gene defects in individual patients with increasing potential to develop specific therapeutic strategies (2). Further, recent approval in the United Kingdom of novel reproductive technologies such as mitochondrial replacement technologies (MRT) holds potential to prevent the transmission of maternally inherited mtDNA disorders in families with known pathogenic mutations (11). Here, we summarize recent advances in PMD molecular etiologies, diagnostic approach, and emerging treatment approaches.

MOLECULAR ETIOLOGIES OF PRIMARY MITOCHONDRIAL DISEASE

Since the pioneering discoveries of pathogenic variants in mtDNA in 1988 (8, 9) and pathogenic variants in nuclear genes encoding proteins necessary for mitochondrial function in 2000–2001(12–14), pathogenic variants in more than 350 genes across both genomes have been recognized to cause PMD (6, 7, 10).

Mitochondrial DNA

The mitochondrial genome is comprised of 16,569 basepairs that encodes 37 genes, including 13 proteins, 22 transfer RNAs (tRNA), and 2 ribosomal RNAs (rRNA). mtDNA is exclusively maternally inherited through the oocyte, and replicates independently of the cell cycle. There are multiple copies of mtDNA in each mitochondrion, and multiple mitochondria per cell. mtDNA genome variants may exist in a state of homoplasmy, meaning in all mitochondrial genomes within a mitochondrion or cell, or in a state of

heteroplasmy, meaning the mutation is only present in a portion of the mitochondrial genomes. The portion of mitochondrial genomes with a specific variant may differ greatly between a given individual's tissues and among members of the same family. In general, the proportion of mitochondrial genomes that harbor a pathogenic variant directly correlates with disease severity (1). Many healthy individuals have low levels of pathogenic variants accumulate in some tissues with age, although if a pathogenic variant reaches a certain threshold heteroplasmy level that may vary greatly by tissue energy demand, phenotypic symptoms may develop over time.

While the basic concepts of heteroplasmy and threshold effect hold true for many pathogenic mtDNA variants, the correlation of precise heteroplasmy levels among various tissues with disease onset and tissue-specific manifestations remains poorly understood. Grady et al, 2018, recently characterized heteroplasmy levels in several tissues (blood, n=231; urine, n=235; skeletal muscle, n=77) over time in a cohort of individuals with the well-characterized pathogenic mtDNA variant m.3243A>G that may cause a range of clinical syndromes from Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-Like Episodes (MELAS) to Leigh Syndrome or Maternally Inherited Diabetes and Deafness (MIDD) (15). Many of the m.3243A>G carriers were clinically affected, with assessment made to correlate heteroplasmy level, disease burden, and disease progression (15). Results showed greatest correlation between heteroplasmy levels in blood and urine > muscle and blood > muscle and urine. Muscle heteroplasmy levels did not correlate with age, whereas both blood and urine heteroplasmy levels declined with age. Overall, blood heteroplasmy levels decreased at a rate of ~2.3% per year when adjusted for age. Males had 19.2% higher urine heteroplasmy levels than females. Urine heteroplasmy levels showed the greatest variability, up to 55%, compared to 15% in blood. Age-adjusted blood heteroplasmy levels showed greatest correlation with disease burden and progression. Muscle mtDNA copy number was associated with a decreased disease burden, providing valuable information about the role of mitochondrial biogenesis in m.3243A>G clinical phenotype penetrance.

Given that individuals who carry low heteroplasmy levels of pathogenic mtDNA variants may be asymptomatic, heteroplasmy shift therapy is a potential therapeutic strategy for PMD, with the goal to decrease the heteroplasmy level of a given pathogenic mtDNA mutation in affected individuals. Different approaches have been considered in the research setting, including use of mitoTALENS (mitochondrial targeted transcription activator-like effector nucleases) that utilize engineered nucleases to selectively degrade specific target mtDNA genomes(16, 17). Yang et al., 2018, showed that m.3243A>G pathogenic variant heteroplasmy levels in induced pluripotent stem cells (iPSCs) could be eliminated by mitoTALENs, with 'rescued' cells having normal energy production (18). When tested in porcine oocytes, mutant heteroplasmy levels were similarly decreased. Yahata et al., 2017, similarly showed that mitoTALENs could be used to decrease mutation heteroplasmy levels in iPSCs generated from individuals with the known pathogenic complex I *ND5* subunit m. 13513G>A mutation (19).

As mtDNA is maternally inherited through the oocyte, affected individuals with mtDNA-related disease may either inherit the variant from their mother or it may occur *de novo* in the oocyte or embryo that forms the affected individual. Whether the mother of an affected

individual is symptomatic depends on whether she carries the same mutation in her somatic cells and if so, at what level of heteroplasmy(20). Until recently, the only reliable reproductive options for women with mtDNA pathogenic variants to assure their offspring did not inherit a disease-causing mtDNA mutation were either adoption or utilizing an egg donor, with prenatal heteroplasmy testing largely considered unreliable. Vachin et al, 2018, sought to evaluate how informative placental heteroplasmy level testing was when compared to testing heteroplasmy levels in chorionic villi, amniotic fluid, cord blood, and fetal tissues (21). Enrolling individuals who carried several different pathogenic mtDNA variants, heteroplasmy levels were similar among all tissue samples tested when pathogenic variants were present at the extremes, either above 80% or below 20%. When heteroplasmy levels fell in an intermediate range, much greater variability between tissue heteroplasmy levels was seen. Significantly more variance was also seen in tissues obtained from full-term fetuses as compared to tissues obtained from pregnancies terminated between 12–18 weeks' gestation.

Preimplantation genetic diagnosis, or PGD, of embryos in the setting of in vitro fertilization (IVF) for mtDNA mutations has been a challenge due to both biological and technologic considerations (22). This option has been further refined in the past year, as Sallevelt et al., 2017 showed that assessing mtDNA heteroplasmy level in a single blastomere from an embryo carries a low diagnostic error rate and has improved outcomes on live birth delivery as compared to assessing two blastomeres (23).

MRT involves transplantation of the nuclear genome from the egg of an affected woman to an enucleated egg from an unaffected donor and has now been approved in the United Kingdom on a case-by-case basis (11, 24), however governmental and legal hurdles remain in place in many countries including the United States (25).

Nuclear DNA

Primary mitochondrial disease is commonly caused by pathogenic variants in nuclear genes, which can occur in any Mendelian pattern including autosomal dominant, autosomal recessive, or X-linked inheritance. Reproductive options for individuals with pathogenic variant(s) in a nuclear DNA gene exist to the same extent as for other Mendelian conditions. Nuclear DNA pathogenic variants are most commonly inherited in an autosomal recessive manner, particularly for childhood-onset diseases. mtDNA pathogenic variants are more commonly causative of adult-onset primary mitochondrial disease. However, improved diagnostic testing has demonstrated that mutations in both genomes can variably cause pediatric and adult onset disease.

Nuclear DNA genes in which mutations cause PMD encode proteins that have an array of roles within mitochondria, including as assembly factors or structural subunits of the electron transport chain (ETC) complexes; mtDNA maintenance; mtDNA replication, transcription, or translation; mitochondrial import and export; mitochondrial dynamics; and others.

NOVEL GENES AND EXPANDING PHENOTYPES

The advent of molecular technologies has accelerated the identification of PMD genes. Over the last 12 months alone, several novel PMD genes and/or pathogenic variant(s) have been discovered (Table 1). In addition, the delineation of previously well-recognized clinical syndromes has expanded in light of improved genomic diagnosis (Table 2). Several excellent PMD review articles have been written in the past year (Table 3).

DIAGNOSIS OF PRIMARY MITOCHONDRIAL DISEASE

While summarizing the diagnostic approach to PMD is outside the scope of this review, tremendous improvements in the diagnostic approach have been achieved in the molecular era of PMD(20, 75). Due to the challenges presented by significant clinical heterogeneity and lack of reliable biomarkers for all possible PMD, the genomic approach now tends to be the first-line investigation coupled to a specialist clinical assessment and biochemical screen. The genomic approach has several additional advantages, allowing the genetic diagnosis of other rare treatable diseases, more than one genetic disorder in a given patient, mitochondrial disease phenocopies and, even more importantly, ensuring that mitochondrial disorders are diagnosed when they may have been overlooked clinically (72).

Rapidly reducing costs have facilitated more wide-spread implementation of whole exome sequencing (WES) and whole genome sequencing (WGS) in large cohorts of PMD patients. The increasing application of next generation sequencing (NGS) in extended gene panels, WES, and WGS of both nuclear and mtDNA genomes to routine mitochondrial disease diagnostics has led to a dramatic increase in the PMD diagnostic yield (6). More invasive diagnostic tests such as the muscle biopsy are increasingly reserved for cases that cannot be solved by a first-line genomic approach in a more readily accessible tissue. Despite these substantial technologic advances, the diagnostic odyssey of patients with mitochondrial disease is often complex and burdensome. Grier et al., 2018 recently described the diagnostic odyssey in patients with self-reported mitochondrial disease and found that, on average, individuals saw eight different physicians and underwent many tests before receiving a diagnosis of PMD(76). More than half of the individuals surveyed received an incorrect clinical diagnosis prior to receiving their PMD diagnosis.

TOOLS AND RESOURCES FOR ASSESSING GENOMIC VARIANTS RELATED TO PRIMARY MITOCHONDRIAL DISEASE

With improving genomic sequencing technologies and increased global utilization of massively parallel diagnostic tests, the need for robust bioinformatics tools and data resources to accurately curate novel disease genes and variants for PMD has been well-recognized.

The Mitochondrial Disease Sequence Data Resource, MSeqDR, is an online, centralized Web portal that organizes both nuclear and mtDNA variants in all known and candidate genes for PMD(77–79). Available through this resource are tools both to provide comprehensive information on variants and genes, as well as tools to assist clinicians and

researchers in efficiently mining genomic data. MSeqDR has partnered with the Clinical Genome Resource, ClinGen, to form a mitochondrial disease expert panel to enable expert curation of variants and novel disease genes associated with PMD(80). MSeqDR also now provides mtDNA variant manually curated assertions from MITOMAP, the gold-standard resource for mtDNA variant curation(81). In addition, MSeqDR and MITOMAP incorporate data from an informatics tool recently developed to predict effects of novel mitochondrial tRNA variants (mitoTIP)(82), as well as HmtDB and HmtVAR, databases of mtDNA sequences, variants, and their predicted effects(83). MSeqDR custom tools are available to support PMD gene and variant submission by users or expert panels that are linked to ClinVar, as well as MSeqDR mvTool(77), which is a recently launched Web and API resource for comprehensive variant annotation, universal nomenclature collation, and reference genome conversion for mtDNA.

Lastly, there exists two tools that are regularly updated for variants in a common nuclear gene cause of PMD with a wide variety of phenotypes, *POLG*(84). *POLG* variants are expertly catalogued in the Human DNA Polymerase Gamma Mutation Database, https://tools.niehs.nih.gov/polg/. In addition, given recent recognition that there are distinct biochemical clusters within the POLG protein, variants falling within these clusters can have characteristic phenotypic effects that can be evaluated in an easily accessible online tool, the *POLG* variant server (85).

CLINICAL TRIALS FOR PRIMARY MITOCHONDRIAL DISEASES

While there are no cures or FDA approved drugs for PMD, several therapeutic PMD strategies are now being evaluated in clinical trials. The lack of validated biomarkers and outcome measures of PMD disease progression, limited natural history data, and inherent variable and fluctuations in PMD course impose intrinsic challenges to conducting PMD clinical trials. Several clinical trials are underway for treating PMD(75). In effort to improve trial enrollment in the mitochondrial disease patient community, a recent publication reported survey results of affected individuals and their family members performed to ascertain PMD patient motivations and barriers to clinical trial participation(4). Both adults and children with PMD prioritized weakness, exercise intolerance, fatigue, imbalance, and gastrointestinal involvement, along with developmental delay in children, as their predominant concerns they would most like to be evaluated in clinical trials.

CONCLUSION

Since the first discovery of a molecular etiology for primary mitochondrial disease 30 years ago (86), the field of mitochondrial genetics has advanced rapidly in the molecular era with at least 20 PMD genes discovered each year for the past decade(87). Genomic diagnosis has become the frontline testing modality, enabling increasingly broader spectrum of clinical phenotypes to be identified including atypical and less severe presentations. Nevertheless, many individuals with features highly concerning for PMD remain undiagnosed, highlighting that gaps still remain in our knowledge of the genetic basis of mitochondrial disease. Identifying the genetic basis of disease in each patient is particularly important, as

the development of effective, precision therapies requires improved understanding of underlying PMD etiology and mitochondrial pathophysiology.

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KEY POINTS:

- Primary mitochondrial disease is a heterogeneous group of energy deficiency disorders caused by pathogenic variants in nuclear or mitochondrial DNA, with more than 20 new genes discovered each year for the past decade.
- Bioinformatic tools and data resources for mitochondrial disease gene and variant curation are increasingly available and user-friendly, curated through a central portal at https://mseqdr.org.
- Precision therapies are emerging based on improved understanding of mitochondrial disease etiology and pathophysiology in PMD individuals.

Table 1:

Novel genes associated with primary mitochondrial disease reported in the past year

Component	Gene	Product	Phenotype	Relevance	Inheritance	Reference
Electron transport chain complex subunits	*COX4I1*	Complex IV subunit	Suspected Fanconi anemia (failure to thrive, short stature, macrocytosis, increased chromosome breakage)	One of only several nuclear-encoded complex IV subunits associated with disease	AR	(26)
	USMG5	Complex V subunit	Leigh syndrome	Identified Ashkenazi Jewish founder mutation with allele frequency of 0.57%.	AR	(27)
Iron sulfur cluster biogenesis	*FDXR*	Involved in iron-sulfur cluster biosynthesis and initiating electron transport chain (ETC) function by transferring electrons to mitochondrial cytochrome P450 from NADPH	Optic atrophy, neuropathy, hearing loss, ataxia	Expands understanding of iron sulfter cluster-related mitochondrial diseases	AR	(28, 29)
mtDNA translation	*WARS2*	Tryptophanyl-tRNA synthetase	Ranges from neonatal lactic acidosis to global developmental delay and intellectual disability, optic atrophy, and ataxia	Last mitochondrial aminoacyl tRNA synthetase to be associated with disease; identified severity range of phenotype, and lack of phenotype specificity	AR	(30, 31)
	MRPS34	A small mitoribosome subunit	Leigh syndrome	Additional insight into small mitoribosome subunit stability	AR	(32)
	MRPS2	A small mitoribosome subunit	Sensorineural hearing loss, developmental delay, hypoglycemia, lactic acidemia	Increased understanding of mtDNA translation defects	AR	(33)
	m.15927G>A (*tRNA-Thr*)	Mitochondrial tRNA for threonine	Leber hereditary optic neuropathy (LHON)	Identified first mitochondrial tRNA variant associated with LHON	Maternal	(34)
	C1QBP	Suspected to be involved in mitochondrial protein synthesis and mtDNA maintenance	Ranges from from infantile lactic acidosis and cardiomyopathy to adult onset progressive external ophthalmoplegia (PEO) and neuropathy	Associated with cardiomyopathy independent of age of onset, lack of central nervous system involvement	AR	(35)
	MRM2	2-O-ribose methyl-transferase in mitochondrial 16S rRNA, also functions in assembly and stability of large mitoribosome	MELAS-like syndrome	First report of defective mitochondrial ribosomal RNA nucleotide modification	AR	(36)

Component	Gene	Product	Phenotype	Relevance	Inheritance	Reference
				causing ETC deficiencies		
Mitochondrial membrane function and import	*MIEF2*	Regulates outer mitochondrial membrane fission	Proximal muscle weakness, exercise intolerance, elevated creatine kinase (CK), ragged red fibers and COX negative fibers on muscle biopsy	First mitochondrial fission/fusion defect resulting in myopathy	AR	(37)
	MSTO1	Regulates mitochondrial fusion	Myopathy, mood disorder	Localized to cytoplasm and interacts with mitochondrial fusion machinery	AD	(38, 39)
	SLC25A21	Mitochondrial inner membrane oxodicarboxylate carrier	Spinal muscular atrophy-like features, myopathy	Identified novel mitochondrial carrier defect leading to targeted therapy	AR	(40)
	SLC25A24	Mitochondrial inner membrane ATP-Mg/Pi carrier	Craniosynostosis, progeroid appearance, microphthalmia, increased sensitivity to oxidative stress	Increased sensitivity to oxidative stress leading to progeroid-like phenotype	AD	(41)
	MICU2	Mitochondrial calcium uniporter subunit	Intellectual disability, white matter involvement	Second gene encoding a subunit of the mitochondrial calcium uniporter, with distinct phenotype from first MCU subunit gene reported (*MICU1*)	AR	(42)
Mitochondrial proteostasis	*PITRM1*	Mitochondrial peptidase	Progressive spinocerebellar ataxia, cerebellar atrophy, intellectual disability, psychotic episodes	Expanded understanding of mitochondrial proteostasis defects	AR	(43)
Nuclear-encoded mitochondrial protein processing	*PMPCB*	Mitochondrial processing protease (MPP) catalytic subunit	Leigh-like syndrome, developmental regression, epilepsy	Expanded understanding of MPP defects	AR	(44)

Key: AR = autosomal recessive, AD = autosomal dominant

Table 2:

Expanded phenotypes associated with PMD reported in the past year

Component	Gene	Product/Function	Relevance	Reference
Electron transport chain enzyme subunits and assembly factors	*NDUFA2*	Complex I accessory subunit	Second and third reports of pathogenic variants in *NDUFA2*; first report of leukoencephalopathy with *NDUFA2* pathogenic variants	(45)
	NDUFA9	Complex I structural accessory subunit	Milder phenotype and correlation with effects on complex I assembly	(46)
	m.13094T>C (*mt-ND5*)	Complex I subunit	Summary of 20 affected and 4 asymptomatic individuals; range of heteroplasmy levels including undetectable in certain tissues even in those severely affected	(47)
	NDUFAF4	Complex I assembly factor	Report of second family with *NDUFAF4* pathogenic variant, expands phenotype to include Leigh syndrome, expands understanding of complex I assembly	(48)
	SCO2	Cytochrome c oxidase (Complex IV) assembly protein	First report of milder phenotype with neuropathy without cardiomyopathy	(49)
	m.8969G>A (*mt-ATP6*)	Complex V subunit	First report of stable phenotype with intellectual disability and short stature	(50)
	LYRM7	Chaperone protein for Rieske iron-sulfur protein important for Complex III assembly	Three additional probands reported (total now 11)	(51)
Iron sulfur cluster assembly	*ISCA1*	Iron-sulfur cluster (ISC) assembly machinery	Third proband reported, milder phenotype; further characterization of disease mechanism	(52)
	ISCA2	Iron-sulfur cluster (ISC) assembly machinery	Additional case reports, biochemical characterization, mitochondrial dysfunction characterization	(53–55)
mtDNA translation	*FARS2*	Phenylalanyl-tRNA synthetase	Review of cases reported to date, delineation of phenotypic spectrum (epileptic vs spastic paraplegia)	(56)
	GARS	Glycyl-tRNA synthetase	AR mode of inheritance, most prior cases were AD; implication of mitochondrial GARS rather than cytosolic GARS in prior case reports; loss of function in AR cases and gain of function in AD cases	(57)
Mitochondrial membrane function and import	*DNM1L*	Mitochondrial and peroxisomal fission	First report of milder phenotype (optic atrophy) and delineation of genotype-phenotype correlation	(58)
	MICU1	Mitochondrial calcium uniporter subunit	Review and summary of additional 13 cases, all reported cases with elevated CK and elevated liver transaminases, increased appreciation of intellectual disability and learning disability as phenotypic feature	(59)
Cofactor import	*SLC25A42*	Imports Coenzyme A into mitochondrial matrix	Thirteen additional probands (total 14) reported, further describing phenotypic spectrum (lactic acidosis to epilepsy and severe movement disorder)	(60, 61)

Component	Gene	Product/Function	Relevance	Reference
Other	*AIFM1*	NADH oxidoreductase, regulates apoptosis	Expands genotype-phenotype correlation; showed response to riboflavin in those with ataxia	(62, 63)
	FBXL4	mtDNA maintenance	Summary of all 87 affected individuals and pathogenic variants reported to date	(64)
	PNPLA8	Regulates oxidative stress	Second and third reports of pathogenic variants in PNPLA8 providing further evidence of progressive neurodegenerative phenotype	(65)
	SERAC1	Phosphatidylglycerol remodeling essential for mitochondrial function and intracellular cholesterol trafficking	Summary of 67 affected individuals with 41 different pathogenic variants	(66)
	TK2	Maintains mitochondrial deoxynucleotide pool	Summary of all 92 affected individuals reported to date	(67)

Table 3:

PMD review articles published during the past year

Topic	Highlights	Reference
mtDNA mechanisms		
mtDNA replication	Summary of mtDNA replication process	(68)
mtDNA replication defects	Overview of mtDNA maintenance and disorders arising from impaired mtDNA maintenance	(69)
mtDNA transcription and translation defects	Overview of genes important for mtDNA transcription and translation with pathogenic variants reported, organized by place in transcription or translation process in which gene product is involved, provides overview figure and summary tables organized by genetic mutations	(70)
mtDNA bottleneck	Summary of the mitochondrial genome bottleneck hypothesis	(1)
Biomarkers		
Biomarkers for primary mitochondrial disease	Overview of currently utilized biomarkers and summary of novel approaches	(71)
Natural History of PMD		
Review of PMD natural history studies	Summary of PMD natural history studies highlighting trends in phenotype, biochemical markers, genotype-phenotype correlation, and prognosis	(3)
Genomic Diagnosis		
Genomic diagnosis of PMD	Summarizes state of PMD diagnosis, proposes genomic sequencing as the first step	(72)
Approaches to diagnosis of PMD	Summary of different approaches to genomic sequencing for diagnosis of PMD and utility of databases and “–omics” to aid in variant interpretation	(7)
Treatment		
PMD treatment	Summary of existing therapies (mitochondrial supplemental medicines, exercise) and emerging therapies (both specific to the gene defect and universal)	(73)
Recent advances in understanding of mitochondrial pathophysiology and therapies	Overview of mitochondrial function, genomics, transcriptomics, proteomics, metabolomics, mitochondrial disease pathogenesis, and therapies	(6)
Genomic-based therapies for mtDNA-related PMD	Summary of technology for prevention of mtDNA transmission, mtDNA heteroplasmy shifting, and CRISPR	(74)