Presentation and Diagnostic Evaluation of Mitochondrial Disease

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KEYWORDS

• Mitochondrial • Myopathy • Metabolic • Electron transport chain • mtDNA
• Diagnosis

KEY POINTS

- Mitochondrial diseases (MD) are a heterogeneous group of disorders with symptoms of organ dysfunction across multiple body systems.
- The unifying feature in MD is the dysfunction of mitochondrial respiratory chain complex function caused by genetic mutations.
- Diagnosis of MD is complicated by the lack of gold standard diagnostic testing strategies and the potential for false-negative test results caused by sampling issues.
- By integrating data obtained from clinical, imaging, pathologic, molecular, and enzymatic assessments, it is often possible to identify MD despite these issues.

FEATURES OF MITOCHONDRIAL DISEASE

Mitochondrial disease (MD) occurs when alteration of mitochondrial respiratory chain (RC) complex function caused by genetic mutation produces a detectable disease state. Activities of complexes I to V can be altered (**Fig. 1**), and physiologic consequences of

Disclosure Statement: Dr D.P. Dimmock is a member of advisory boards for Audentes Therapeutics and Biomarin. He has been funded for work performed for Biomarin, Shire, Alexion, Genzyme/Sanofi, and Cytonet. He has worked as a paid consultant for Illumina and Complete Genomics. He has also participated in a sponsored research agreement with Demeter Therapeutics. Dr M.W. Lawlor is a member of advisory boards for Audentes Therapeutics, and has been supported by sponsored research agreements by Audentes Therapeutics and Solid Biosciences. He is a scientific collaborator with Acceleron Pharma and Pfizer. He has recently been a consultant for Sarepta Therapeutics.
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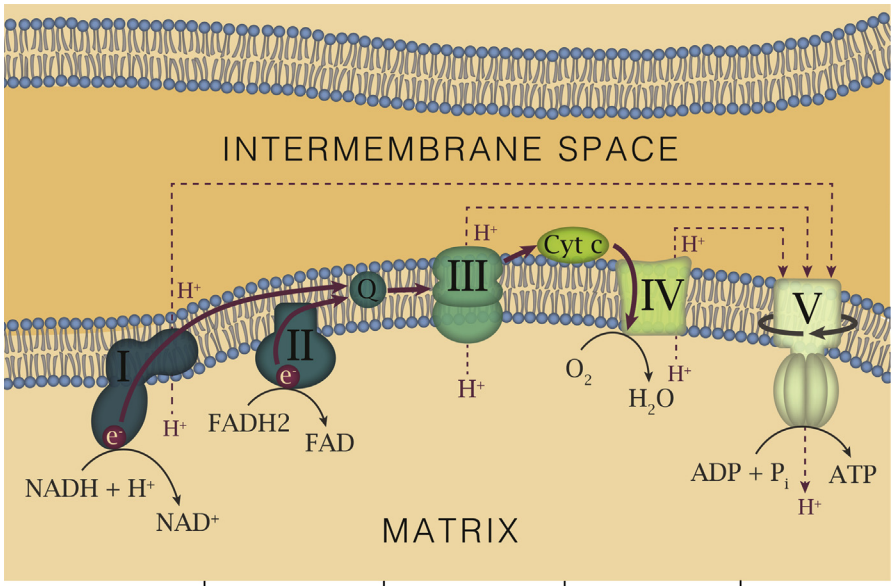
Pediatr Clin N Am 64 (2017) 161–171
http://dx.doi.org/10.1016/j.pcl.2016.08.011
pediatric.theclinics.com



Complex I	Complex II	Complex III	Complex IV	Complex V
NADH dehydrogenase	**Succinate dehydrogenase**	**Ubiquinol cytochrome C oxidoreductase**	**Cytochrome C oxidase**	**ATP synthase**
47 Subunits (7 mtDNA, 40 nDNA)	4 Subunits (0 mtDNA, 4 nDNA)	11 Subunits (1 mtDNA, 10 nDNA)	13 Subunits (3 mtDNA, 10 nDNA)	17 Subunits (2 mtDNA, 15 nDNA)

Fig. 1. Diagram of mitochondrial RC components. Each mitochondrial RC complex is depicted and named, as are the critical cofactors, coenzyme Q (CoQ) and cytochrome c (Cyt C). For each complex, the proportion of subunits encoded by the mtDNA and nDNA are shown. The flow of electrons (*solid red lines/arrows*) and protons (*dashed red lines/arrows*) in the RC are also displayed. The solid line encircling complex V depicts its rotation as it produces ATP. NADH, nicotinamide adenine dinucleotide.

mitochondrial RC defects include reduced metabolic capacity, reduced ATP synthesis, and increased oxidative and nitrosative stress.[1,2] Mutations in nuclear DNA (nDNA) or mitochondrial DNA (mtDNA) can lead to defects in the complexes essential for RC function or for the transport and assembly of mitochondrial proteins (**Box 1**). Additionally, because mtDNA mutations can impair mitochondrial function, mutations that affect

Box 1
Nuclear and mitochondrial genomes in mitochondrial disease

- The mitochondrial genome encodes 37 genes, encoding two ribosomal RNAs, 22 transfer RNAs, and 13 subunits of RCs.
- There are at least 1000 nuclear genes associated with mitochondrial function.
- Some pathologic patterns (cytochrome oxidase–negative/succinate dehydrogenase–overexpressing fibers) specifically suggest mutations in the mitochondrial genome.
- Gene diagnostic panels are available for disease subsets, along with sequencing of the mitochondrial and nuclear genomes separately.