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Minireview

Diagnosis of mitochondrial myopathies

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ABSTRACT

Mitochondria are ubiquitous organelles and play crucial roles in vital functions, most importantly, the oxidative phosphorylation and energy metabolism. Therefore, mitochondrial dysfunction can affect multiple tissues, with muscle and nerve preferentially affected. Mitochondrial myopathy is a common clinical phenotype, which is characterized by early fatigue and/or fixed muscle weakness; rhabdomyolysis can seldom occur. Muscle biopsy often identifies signs of diseased mitochondria by morphological studies, while biochemical analysis may identify respiratory chain deficiencies. The clinical, morphological and biochemical data guide molecular analysis. Being the mitochondrial function under the control of both mitochondrial DNA and nuclear DNA, the search for mitochondrial DNA mutations and mitochondrial DNA quantitation, may not be sufficient for the molecular diagnosis of mitochondrial myopathies. Approximately 1500 nuclear genes can affect mitochondrial structure and function and the targeting of such genes may be necessary to reach the diagnosis. The identification of causative molecular defects in nuclear or mitochondrial genome leads to the definite diagnosis of mitochondrial myopathy.

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Abbreviations: ATP, adenosine triphosphate; CoQ10, coenzyme Q10; CK, creatine kinase; EMG, Electromyography; Pi, inorganic phosphate; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; (PCr), phosphocreatine; ^{31}P-MRS, ^{31}-phosphorous magnetic resonance spectroscopy; PEO, progressive external ophthalmoplegia; RRF, ragged-red fibers.

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1. Introduction

Muscle contraction and relaxation depend on energy derived from the hydrolysis of adenosine triphosphate (ATP). Several biochemical processes provide ATP, including oxidative phosphorylation, glycogen and glucose metabolism, lipid metabolism, purine nucleotide cycle, and creatine kinase (CK)-dependent reaction of phosphocreatine with adenosine diphosphate [1]. Glycogen, glucose and free fatty acids provide fuel for muscle energy metabolism [2] and oxidative phosphorylation is the principal method for the synthesis of ATP. Oxidative phosphorylation occurs within the mitochondria, which, therefore, plays a crucial role in energy metabolism.

Oxidative phosphorylation is accomplished through 5 multi-subunit transmembrane complexes and 2 electron carriers, coenzyme Q10 and cytochrome *c*, which transport electrons between complexes [3]. Thirteen subunits only of the complexes are encoded by mitochondrial DNA (mtDNA), while the other subunits and the assembly factors are nuclear DNA (nDNA)-encoded. Indeed, mtDNA contains only 37 genes, 24 encoding for the RNA apparatus (22 tRNA and 2 rRNA) and 13 for the subunits of the respiratory chain complexes I, III, IV and V. Complex II is entirely encoded by nDNA. In addition to oxidative phosphorylation, mitochondria play essential roles in other vital functions, such as the modulation of calcium signaling, cellular redox balance and apoptosis [4]. Several hundreds of nuclear genes are required for the correct mitochondrial function. Through fusion and fission, mitochondria preserve their quality, efficiency and cellular distribution, warranting muscle cell integrity [5]. Failure to maintain mitochondrial function results in failure to generate energy and increased free-radical production, leading to disease [6]. Being the mitochondrial function under the control of a dual genome, the maternally inherited mtDNA and the Mendelian inherited nDNA, mitochondrial diseases are potentially inherited with maternal, autosomal dominant or recessive or X-linked modality.

2. Clinical features of mitochondrial myopathies

Mitochondria are ubiquitous organelles and therefore mitochondrial dysfunction can affect multiple tissues. Mitochondrial myopathy is a well-recognized feature of mitochondrial dysfunction. Mitochondrial myopathy commonly manifests with exercise intolerance and premature fatigue. Muscle weakness occurs, but early fatigue is often out of proportion to the degree of weakness. The myopathy may selectively affect the extraocular muscles (progressive external ophthalmoplegia, PEO), and/or extend to bulbar, limb and axial muscles. Limb muscle weakness is usually proximal but occasionally distal muscles are selectively involved and the clinical phenotype consists of distal myopathy [7]. Recurrent rhabdomyolysis and myoglobinuria are rare in mitochondrial myopathy but have been described in sporadic cases of isolated myopathy with mutations in mtDNA genes encoding cytochrome b (*MTCYB*) of complex III [8,9], cytochrome *c* oxidase subunits I (*MT-CO1*) [10], II (MT-CO2) [11] and III (MT-CO-III) of complex [12], and tRNA [13] (Table 1). Resting lactic acidosis is often present in these cases. The pathogenesis of rhabdomyolysis in mitochondrial myopathies has remained indeterminate and there has been no correlation between the severity of the oxidative defect and the rhabdomyolysis [13]. Exercise-induced muscle contractures, typical of glycolytic disorders, are not features of mitochondrial myopathies. The myopathy can be the sole manifestation of mitochondrial dysfunction or a facet of a multisystem disease (encephalopathy, peripheral neuropathy, epilepsy, stroke-like events, gastrointestinal dysmotility, diabetes, etc.) which increases the clinical suspicion for a mitochondrial disease. For example, the complete clinical spectrum of mitochondrial encephalomyopathy, lactic acidosis and stroke-like events (MELAS) is often highly suggestive of a mitochondrial cytopathy, although matrilineal relatives of MELAS patients may be oligosymptomatic and may lack the myopathy as well as other clinical features. The clinical phenotypes are often genetically heterogeneous, therefore, a MELAS-like presentation can be the result of a mtDNA point mutation or of *POLG* mutations, or others. Occasionally, unique phenotypes are highly suggestive of the causative gene, as in the case of the combined myopathy, lactic acidosis and sideroblastic anemia due to *YARS2* mutations [14].

Among the mitochondrial myopathies, it is of relevance to mention the myopathic form of primary coenzyme Q10 (CoQ10) deficiency because patients improve with CoQ10 supplementation. CoQ10 is an essential electron carrier from complexes I and II to complex III of the mitochondrial respiratory chain and an antioxidant; mutations in genes involved in its biosynthesis can result in a pure myopathy that manifests with myalgia, muscle weakness, myoglobinuria, and hyperCKemia or multisystem disease [15–17].

Table 1
Mitochondrial genes that can result in isolated mitochondrial myopathy.

mtDNA genes	Protein	Respiratory chain complex	Phenotype	Reference
MTCYB	Cytochrome b	Complex III	Limb myopathy, rhabdomyolysis	[8,9]
MT-CO1	Cytochrome *c* oxidase subunit I	Complex IV	Limb myopathy, rhabdomyolysis	[10]
MT-CO2	Cytochrome *c* oxidase subunit II	Complex IV	Limb myopathy, rhabdomyolysis	[11]
MT-CO3	Cytochrome *c* oxidase subunit III	Complex IV	Limb myopathy, rhabdomyolysis	[12]
tRNAs	–	–	Limb myopathy, rhabdomyolysis	[13]

Table 2
Nuclear genes resulting in mitochondrial myopathy, in isolation or as part of multisystem disease.

nDNA genes	Protein	mtDNA	Reference
POLG	mtDNA Polγ, catalytic subunit	Multiple deletions or depletion	[73,77,78]
POLG2	mtDNA Polγ, accessory subunit	Multiple deletions	[19,90]
C10ORF2	Mitochondrial helicase TWINKLE	Multiple deletions	[21]
ANT1	Adenine nucleotide translocase 1	Multiple deletions	[18]
OPA1	Optic atrophy 1	Multiple deletions	[20,91,92]
RRM2B	Ribonucleotide reductase p53R2	Multiple deletions	[23,93]
TK2	Thymidine kinase 2	Multiple deletions or depletion	[22,24–26]
DNA2	Nuclease/helicase	Multiple deletions	[27]
SUCLA2	Succinate-CoA ligase, β subunit	Depletion	[94]
EARS2	Mitochondrial glutamyl-tRNA synthetase	Normal	[95]
YARS2	Mitochondrial tyrosyl-tRNA		[14]
ETFDH	Electron transfer flavoprotein dehydrogenase	Normal	[96]
BCORL1[a]	BCL-6 corepressor-like protein 1	Depletion	

Polγ, polymerase gamma.
[a] Reported at the 2013 Mitochondrial Medicine meeting by A. Suomalainen.