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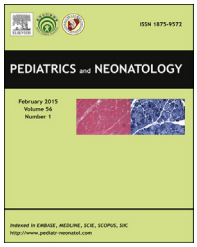

INVITED REVIEW ARTICLE

# Diagnostic Approach in Infants and Children with Mitochondrial Diseases

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Mitochondrial diseases are a heterogeneous group of disorders affecting energy production in the human body. The diagnosis of mitochondrial diseases represents a challenge to clinicians, especially for pediatric cases, which show enormous variation in clinical presentations, as well as biochemical and genetic complexity.

Different consensus diagnostic criteria for mitochondrial diseases in infants and children are available. The lack of standardized diagnostic criteria poses difficulties in evaluating diagnostic methodologies. Even though there are many diagnostic tools, none of them are sensitive enough to make a confirmative diagnosis without being used in combination with other tools. The current approach to diagnosing and classifying mitochondrial diseases incorporates clinical, biochemical, neuroradiological findings, and histological criteria, as well as DNA-based molecular diagnostic testing. The confirmation or exclusion of mitochondrial diseases remains a challenge in clinical practice, especially in cases with nonspecific clinical phenotypes. Therefore, follow-up evolution of clinical symptoms/signs and biochemical data is crucial.

The purpose of this study is to review the molecular classification scheme and associated phenotypes in infants and children with mitochondrial diseases, in addition to providing an overview of the basic biochemical reactions and genetic characteristics in the mitochondrion, clinical manifestations, and diagnostic methods. A diagnostic algorithm for identifying mitochondrial disorders in pediatric neurology patients is proposed.


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## 1. Introduction

Mitochondrial disease (MD) was first introduced in 1962, when a group of investigators, Luft et al[1], described a young Swedish woman with severe nonthyroid origin hypermetabolism. In 1963, Engel and Cunningham[2] used a modification of the Gomori trichrome stain that allowed for the detection of abnormal mitochondrial proliferation in muscle as irregular purplish patches in fibers that were dubbed "ragged red fibers (RRFs)". Since then, there has been great interest in the diagnosis of mitochondrial diseases (MDs). The diagnosis of MD can be traced back to the premolecular era, 1962–1988, when MDs were defined on the basis of clinical examination, muscle biopsy, and biochemical criteria. In the molecular era, the full complexity of these disorders became evident.

MDs are a heterogeneous group of disorders affecting energy production in the human body, which can occur with a probable frequency in preschool children (age < 6 years) of approximately 1 in 11,000,[3] and the minimum birth prevalence for respiratory chain disorders with onset at any age was estimated at 1 in 7634.[4] MDs may present at any age with a spectrum of symptoms and signs spanning a number of medical specialties. As cells with high energy requirements, such as neurons, skeletal and cardiac muscle, are particularly vulnerable to limited adenosine triphosphate (ATP) supply, encephalopathy and myopathy are often prominent features in various mitochondrial phenotypes. Enzymes involved in mitochondrial energy production are coded by two genomes (mitochondrial and nuclear) in the organism. Due to their clinical, biochemical, and genetic complexity, MDs represent a challenge to clinicians, especially for pediatric cases, which show enormous variation in clinical presentations and course.

In Taiwan, the first clinical MD was reported in 1988,[5] and the first mitochondrial DNA (mtDNA) mutation was identified in 1992.[6] Many cases have since been reported in pediatric groups.[7–47] Although MDs are being diagnosed more frequently, clinical physicians still find diagnosis a challenge because clinical symptoms/signs evolve over time and the number of genes known to be involved in mitochondrial energy production continues to increase.

The purpose of this study is to review the molecular classification scheme and associated phenotypes in infants and children with MDs, in addition to providing an overview of the basic biochemical reactions and genetic characteristics in the mitochondrion, clinical manifestations, and diagnostic methods. A diagnostic algorithm for identifying MDs in pediatric neurology patients is proposed.

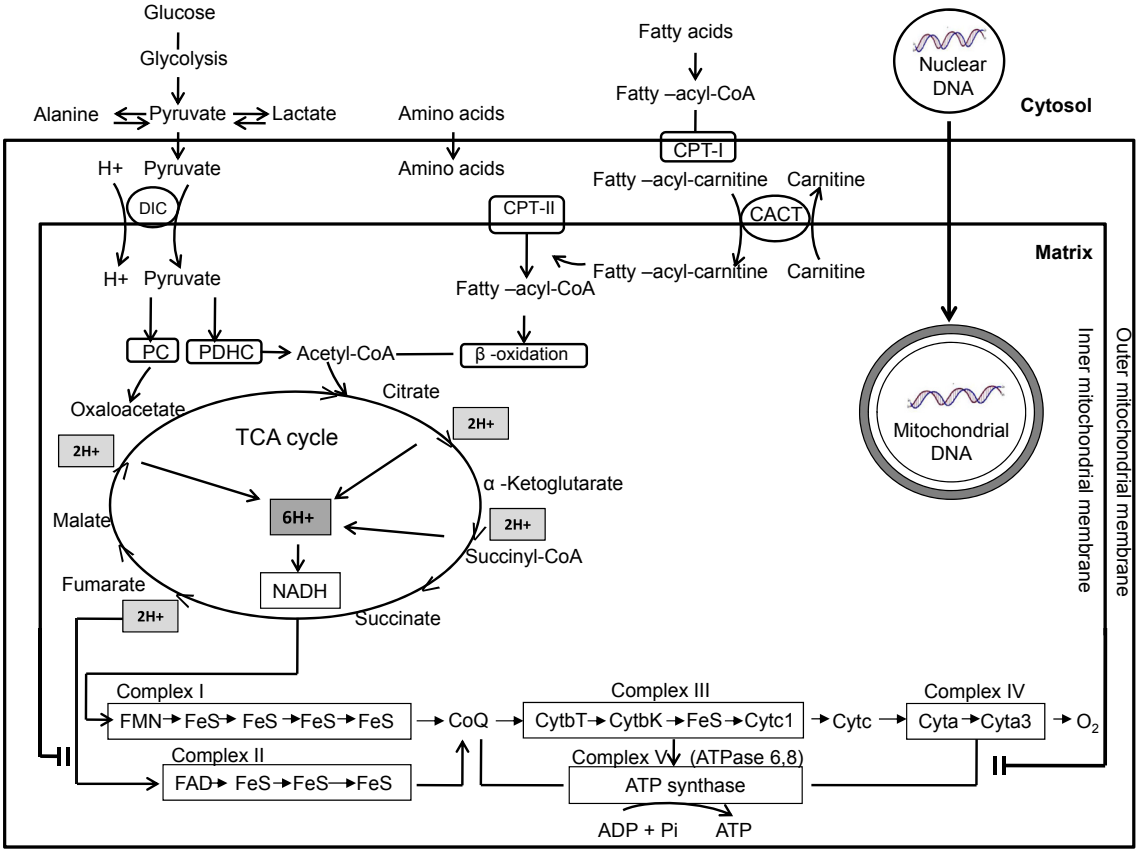


**Figure 1** Metabolic pathways in mitochondrion. ADP = adenosine diphosphate; ATP = adenosine triphosphate; CACT = carnitine–acylcarnitine translocase; CoQ = coenzyme Q; CPT = carnitine palmitoyltransferase; Cyta = cytochrome *a*; Cytb = cytochrome *b*; Cytc = cytochrome *c*; DIC = dicarboxylate carrier; FAD = flavin adenine dinucleotide; FeS = iron sulfur protein; FMN = flavin mononucleotide; NADH = nicotinamide adenine dinucleotide; PC = pyruvate carboxylase; PDHC = pyruvate dehydrogenase complex; TCA = tricarboxylic acid.