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Review

Molecular genetic and clinical aspects of mitochondrial disorders in childhood

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Abstract

Mitochondrial OXPHOS disorders are caused by mutations in mitochondrial or nuclear genes, which directly or indirectly affect mitochondrial oxidative phosphorylation (OXPHOS). Primary mtDNA abnormalities in children are due to rearrangements (deletions or duplications) and point mutations or insertions. Mutations in the nuclear-encoded polypeptide subunits of OXPHOS result in complex I and II deficiency, whereas mutations in the nuclear proteins involved in the assembly of OXPHOS subunits cause defects in complexes I, III, IV, and V. Here, we review recent progress in the identification of mitochondrial and nuclear gene defects and the associated clinical manifestations of these disorders in childhood.

Keywords: mtDNA; OXPHOS; Mitochondrial disorders; Mutation

1. Introduction

The discovery, in 1988, that mitochondrial DNA (mtDNA) mutations cause disease in humans (Holt et al., 1988; Lestienne and Ponsot, 1988; Zeviani et al., 1988) opened a new research field involving these disorders. Since then, more than 100 pathogenic mtDNA point mutations and numerous mtDNA rearrangements have been discovered, but important questions concerning the relationship between these mutations and their phenotypic expression remain to be resolved.

Mutations in mtDNA only explain about 20% of mitochondrial OXPHOS disorders in childhood (Darin et al., 2001). The list of nuclear gene mutations involved in OXPHOS diseases are increasing continuously and may for example involve structural subunits of the respiratory chain, assembly factors, translation factors as well proteins important for the maintenance of mtDNA.

The mitochondrial OXPHOS disorders probably constitute the most common group of neurometabolic diseases in childhood (Darin et al., 2001). The clinical features of these disorders are sometimes characteristic but never specific for any genetic defect. The most commonly affected organs are those with a high energy demand such as skeletal muscle and/or the central nervous system, which explain why the term "mitochondrial encephalomyopathies" (DiMauro et al., 1999) has been applied. However, virtually any organ and tissue can be affected. Heterogeneity in the distribution of mutated mtDNA and the tissue-specific expression of nuclear genes are two plausible explanations for the widely varying clinical phenotypes (Larsson and Clayton, 1995).

The major function performed by mitochondria in aerobically active cells is the synthesis of ATP (Fang et al., 1994). The process of ATP synthesis is mediated by the OXPHOS system. The OXPHOS system, located in the mitochondrial inner membrane, is composed of five multisubunit enzyme complexes (Fig. 1). Four of them are NADH-dehydrogenase (NADH–ubiquinone oxidoreductase, complex I), succinate dehydrogenase

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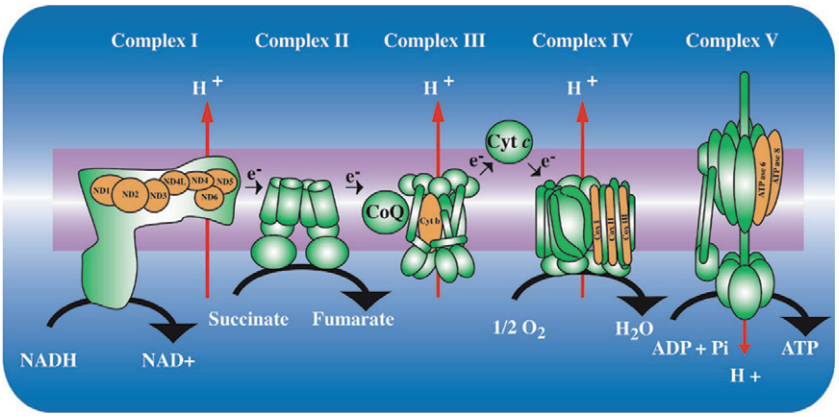

Fig. 1. Schematic illustration of the mitochondrial oxidative phosphorylation system showing the electron transport chain enzyme complexes (complexes I–IV) and ATP synthase (complex V). mtDNA-encoded subunits are indicated in orange and nuclear encoded subunits in green. Complex I is composed of 43 subunits, of which 7 are encoded by mtDNA. Nuclear DNA encodes all subunits of complex II. Complex III is made up of 11 subunits, of which all but one (cytochrome b) are encoded by nuclear DNA. Complex IV, the terminal step of the respiratory chain, is composed of 13 structural subunits, three of which are encoded by genes of the mtDNA and form the catalytic core of the enzyme. Complex V couples proton flow from the intermembrane space back to the matrix by the conversion of ADP and inorganic phosphate to ATP. Two subunits in complex V (ATPase 6 and 8 genes) are encoded by mtDNA.

(succinate–ubiquinone oxidoreductase, complex II), cytochrome *bc1* complex (ubiquinol–cytochrome *c* oxidoreductase, complex III), and cytochrome *c* oxidase (complex IV). Substrates feed reducing equivalents to the respiratory chain at different points. Electrons are passed down the chain and protons are pumped across the inner mitochondrial membrane, buliding up a gradient, which is used to drive ATP production through the reentry of protons via ATP synthase (complex V) (Janssen et al., 2004). Mitochondria also participate in the generation of reactive oxygen species, and the initiation of apoptosis may be an additional mechanism for pathology (Wallace et al., 1998).

Human mtDNA is a 16.6 kb double-stranded circular molecule encoding for 13 enzyme subunits involved in the respiratory chain (Fig. 2) (Anderson et al., 1981). They include seven subunits of complex I, cytochrome *b* of complex III, three subunits of complex IV, and two subunits of complex V. The mtDNA also encodes for two rRNAs and 22 tRNAs necessary for mitochondrial protein synthesis. The replication of mtDNA requires several nuclear-encoded factors such as mtRNA polymerase, mitochondrial transcription factor A (mtTFA), DNA polymerase gamma (POLG), deoxyguanosine kinase (DGUOK), and thymidine kinase 2 (TK2) (Larsson and Clayton, 1995; Larsson and Luft, 1999; Kollberg et al., 2005). mtDNA is more vulnerable to mutation than nuclear DNA and the mutation rate is much higher in mtDNA. This can be explained by the lack of histones in mtDNA and the continuous exposure of the molecule to reactive oxygen species. In pathological conditions, there is often a mixture of wild-type and mutated mtDNA, so-called heteroplasmy. mtDNA mutations are functionally recessive and the proportion of mtDNA with a pathogenic mutation must reach a certain level (threshold level) for the phenotypic expression of the mutation. mtDNA is almost exclusively maternally inherited and many mtDNA disorders therefore display a maternal mode of inheritance.

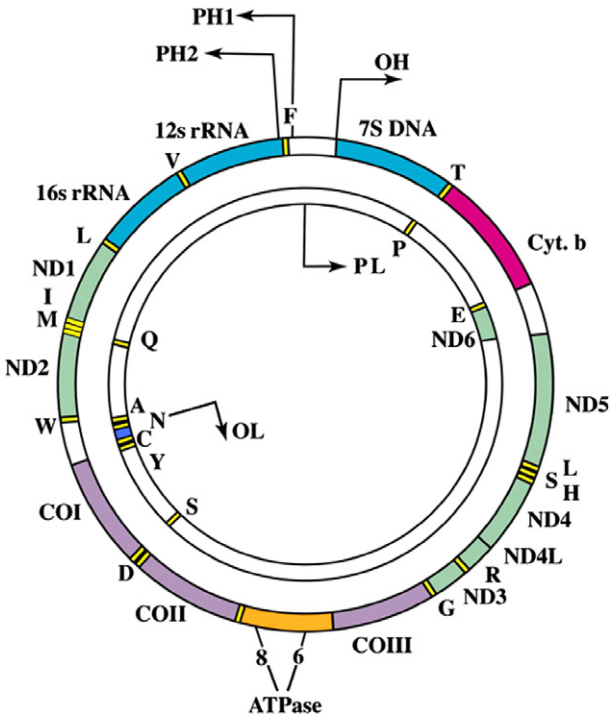

Fig. 2. Circular map of mtDNA showing the genes for NADH-dehydrogenase (ND) subunits 1–6 and ND4L, cytochrome *b* (Cyt b), cytochrome *c* oxidase subunits (COI, II, and III), ATPase 6 and 8 genes and 12S and 16S rRNA. The yellow filled boxes represent 22 tRNA genes. Arrows indicate the origin of replication for the heavy (OH) and the light (OL) strands and the promoters of transcription for the heavy (PH) and light (PL) strands.

In this article, we review recent progress in the identification of mitochondrial and nuclear gene defects in association with OXPHOS disorders. The genetics and the clinical manifestations of these disorders will be discussed.