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SCIENCE DIRECT

Gene 354 (2005) 162 – 168

GENE
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FUNCTIONAL GENOMICS

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Review

# Disorders of nuclear-mitochondrial intergenomic signaling

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Received 25 January 2005; accepted 25 March 2005
Available online 25 May 2005
Received by K. Wolf

**Abstract**

Depletion and multiple deletions of mitochondrial DNA (mtDNA) have been associated with a number of autosomal disorders classified as defects of nuclear-mitochondrial intergenomic signaling. The mendelian forms of progressive external ophthalmoplegia (PEO) are clinically and genetically heterogeneous disorders characterized by the accumulation of multiple deletions of mtDNA in postmitotic patient's tissues.

Most of the autosomal dominant PEO (adPEO) families carry heterozygous mutations in either one of three genes: *ANT1*, *Twinkle*, and *POLG1*. Mutations in *POLG1* can also cause autosomal recessive PEO (arPEO) and apparently sporadic cases. In addition, recessive *POLG1* mutations are responsible for sensory-atactic neuropathy, dysarthria and ophthalmoplegia (SANDO), juvenile spino-cerebellar ataxia–epilepsy syndrome (SCAE) and Alpers–Huttenlocher hepatopathic poliodystrophy.

Mutations in thymidine phosphorylase gene (*TP*) are linked to mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), an autosomal recessive disorder in which PEO is associated with gastrointestinal dysmotility and leukodystrophy.

Finally, mitochondrial DNA depletion syndromes (MDS), defined by tissue-reduction in mtDNA copy number, have been linked to mutations in two genes involved in deoxyribonucleotide (dNTP) metabolism: thymidine kinase 2 (*TK2*) and deoxyguanosine kinase (*DGUOK*).


*Keywords:* Mitochondrial DNA; Multiple deletions; Depletion; Autosomal

## 1. Introduction

Mitochondrial respiratory chain is the result of the interplay of two physically and functionally separated genomes, the nuclear DNA and the mtDNA. Human mtDNA is a 16.6 kb circular double-stranded DNA containing only 37 genes. A total of 24 mtDNA genes encode the RNA apparatus, including 2 ribosomal RNAs and 22 tRNAs, which are involved in the in situ translation of 13 respiratory chain proteins, encoded by the remaining mtDNA genes. The mtDNA encoded proteins are all subunits of respiratory complexes I, III, IV and V, while the subunits of complex II are entirely nucleus-encoded. Since the factors responsible for mtDNA maintenance and replication are all encoded by nuclear DNA genes, mutations in any of these factors may in principle affect the integrity of mtDNA, causing either qualitative or quantitative mtDNA molecular lesions. The latter are not transmitted per se, i.e. via maternal inheritance, but, being secondary to nuclear gene mutations, segregate with mendelian traits.

The first example of these disorders was an Italian family in which an adult-onset, autosomal dominant mitochondrial myopathy was characterized by the presence of progressive external ophthalmoplegia (PEO), and associated with the

*Abbreviations:* mtDNA, mitochondrial DNA; PEO, progressive external ophthalmoplegia; ad, autosomal dominant; ar, autosomal recessive; SANDO, sensory-atactic neuropathy, dysarthria and ophthalmoplegia; SCAE, spino-cerebellar ataxia–epilepsy; TP, thymidine phosphorylase; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; MDS, mitochondrial DNA depletion syndrome; dNTP, deoxyribonucleotide; TK2, thymidine kinase 2; dGK, deoxyguanosine kinase; *POLG1*, gene encoding mitochondrial DNA polymerase gamma; ANT, adenine nucleotide translocator; MPTP, mitochondrial permeability transition pore.

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0378-1119/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.gene.2005.03.025

accumulation of multiple rather than single mtDNA deletions in muscle (sporadic PEO is typically due to single mtDNA deletions) (Zeviani et al., 1988, 1989). This disease was attributed to a specific defect in a (nuclear) gene controlling the nuclear-mitochondrial intergenomic signaling. Thirteen years later, this prediction turned out to be true, since this very family was found to carry a prevalent mutation in *POLG1*, the gene encoding the catalytic subunit of mtDNA polymerase γ (Pol γ). Two years after the identification of multiple mtDNA deletions in adPEO, a second group of mendelian syndromes, characterized by infantile myopathy or hepatopathy, was associated with depletion of mtDNA in affected tissues (Moraes et al., 1991).

Since then, a number of syndromes associated with multiple deletions or tissue-specific depletions of mtDNA have been reported, including MNGIE, which is characterized by a combination of both multiple mtDNA deletions and depletion in affected tissues (Hirano et al., 1994). Very recently, the list has further expanded to encompass a spectrum of severe infantile or juvenile encephalopathies including SCAE, SANDO, and Alpers' syndrome. The latter is a multisystem disorder of infancy or childhood characterized by a combination of liver and neurological failure. SCAE, SANDO and Alpers' syndrome have all been associated with recessive mutations in POLG1, the master gene of mtDNA replication (Van Goethem et al., 2003; Van Goethem et al., 2004; Winterthun et al., 2005).

## 2. Clinical manifestations

### 2.1. mtDNA breakage syndromes

Chronic external ophthalmoplegia is a common sign in mitochondrial disorder and often occurs with other variable features. One form is associated with multiple deletions of mtDNA in skeletal muscle and can be inherited as a dominant or a recessive trait.

#### 2.1.1. Autosomal dominant PEO

By definition, autosomal dominant PEO families include progressive weakness of the extraocular muscles as a cardinal feature; patients have ptosis and limitation of their eye movements. The onset of the disease is in adulthood; the first symptoms typically arise when patients are 20–40 years old. Generalized muscle weakness is frequently present. Additional features vary among families: they may include sensory ataxia, motor peripheral neuropathy, sensorineural hearing loss, cataracts, hypogonadism, parkinsonism, psychiatric abnormalities consisting of severe depression and avoidant personality and rhabdomyolysis. Dysphagia, dysphonia, weakness of facial muscles, and peripheral neuropathy may be prominent symptoms in selected families (Zeviani et al., 1989; Servidei et al., 1991; Melberg et al., 1996; Suomalainen et al., 1997). At rest, elevated levels of plasma lactate are detected only occasionally, and in severely affected patients. Symptoms seem to progress along with the age of the patients. Examination of muscle biopsies shows the presence of ragged-red fibers due to the subsarcolemmal accumulation of abnormal mitochondria. In addition, the histochemical reaction to cytochrome *c* oxidase is decreased or absent in scattered fibers, and neurogenic changes are frequently observed. Biochemically, the activities of mtDNA-related respiratory complexes in muscle homogenate can range from normal to about 50% of the normal mean (Servidei et al., 1991). Presymptomatic patients appear normal at the clinical examination, but often have laboratory, electrophysiological, morphological, and biochemical features of a subclinical mitochondrial encephalomyopathy.

#### 2.1.2. Autosomal recessive PEO

In 1989 the presence of multiple mtDNA deletions was reported in muscle specimens from two siblings with PEO, optic atrophy, muscle weakness, and peripheral neuropathy (Yuzaki et al., 1989). However, in contrast to autosomal dominant PEO families, the two siblings were the only affected members of the pedigree and were born from consanguineous, apparently healthy parents. The suggested mode of transmission was autosomal recessive (Mizusawa et al., 1988). Since then, multiple deletions of mtDNA have been reported in numerous sporadic PEO cases (Fig. 1, Panel A) or in other families in which, as in the family described by Yuzaki and colleagues, PEO was clearly transmitted as a recessive trait (up to 11% in our series) (Lamantea et al., 2002). In addition, a peculiar autosomal recessive syndrome associated with multiple mtDNA deletions in muscle was found in six patients from two unrelated families from eastern Arabia. The patients presented with childhood-onset, autosomal recessive PEO, mild facial and proximal limb weakness, and severe cardiomyopathy, requiring cardiac transplantation (Bohlega et al., 1996).

#### 2.1.3. Mitochondrial neurogastrointestinal encephalomyopathy

MNGIE is an autosomal recessive disease characterized by the unusual combination of 6 features: (1) progressive external ophthalmoplegia, (2) severe gastrointestinal dysmotility, (3) cachexia, (4) peripheral neuropathy, (5) diffuse leukoencephalopathy on brain MRI, and (6) evidence of mitochondrial dysfunction (histological, biochemical, or genetic abnormalities of mitochondria). The disorder is described in the companion article by Hirano and colleagues.

#### 2.1.4. Alpers–Huttenlocher hepatopathic poliodystrophy, SANDO, and SCAE syndrome

These syndromes are all characterized by an association with recessive mutations of *POLG1*, the master gene of mtDNA replication. However, it is still unclear which is the specific damage on mtDNA caused by these mutations. Alpers–Huttenlocher's hepatopathic poliodystrophy