Biochimica et Biophysica Acta 1787 (2009) 518–528

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

Review

# Retinal ganglion cell neurodegeneration in mitochondrial inherited disorders

Valerio Carelli [a,*], Chiara La Morgia [a], Maria Lucia Valentino [a], Piero Barboni [a], Fred N. Ross-Cisneros [b], Alfredo A. Sadun [b]

[a] Department of Neurological Sciences, University of Bologna, Via Ugo Foscolo 7, 40123, Bologna, Italy
[b] Doheny Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

ARTICLE INFO

*Article history:*
Received 28 December 2008
Received in revised form 24 February 2009
Accepted 26 February 2009
Available online 5 March 2009

*Keywords:*
Optic nerve
Optic neuropathy
Retinal ganglion cell
LHON
Complex I
DOA
OPA1
Mitochondrial DNA
Neurodegeneration

ABSTRACT

Since the early days of mitochondrial medicine, it has been clear that optic atrophy is a very common and sometimes the singular pathological feature in mitochondrial disorders. The first point mutation of mitochondrial DNA (mtDNA) associated with the maternally inherited blinding disorder, Leber's hereditary optic neuropathy (LHON), was recognized in 1988. In 2000, the other blinding disorder, dominant optic atrophy (DOA) Kjer type, was found associated with mutations in the nuclear gene *OPA1* that encodes a mitochondrial protein. Besides these two non-syndromic optic neuropathies, optic atrophy is a prominent feature in many other neurodegenerative diseases that are now recognized as due to primary mitochondrial dysfunction. We will consider mtDNA based syndromes such as LHON/dystonia/Mitochondrial Encephalomyopahty Lactic Acidosis Stroke-like (MELAS)/Leigh overlapping syndrome, or nuclear based diseases such as Friedreich ataxia (mutations in *FXN* gene), deafness–dystonia–optic atrophy (Mohr–Tranebjerg) syndrome (mutations in *TIMM8A*), complicated hereditary spastic paraplegia (mutations in *SPG7*), *DOA* "plus" syndromes (mutations in *OPA1*), Charcot–Marie–Tooth type 2A (CMT2A) with optic atrophy or hereditary motor and sensory neuropathy type VI (HMSN VI) (mutations in *MFN2*), and Costeff syndrome and DOA with cataract (mutations in *OPA3*). Thus, genetic errors in both nuclear and mitochondrial genomes often lead to retinal ganglion cell death, a specific target for mitochondrial mediated neurodegeneration. Many mechanisms have been studied and proposed as the bases for the pathogenesis of mitochondrial optic neuropathies including bioenergetic failure, oxidative stress, glutamate toxicity, abnormal mitochondrial dynamics and axonal transport, and susceptibility to apoptosis.



## 1. Introduction

Retinal ganglion cells (RGCs) are the final output of the retina. They project their long axons to form the optic nerve and relate the visual information to the brain [1]. The RGCs somata resides in the inner retina and the axons, having emerged from the cell body, enter the retinal nerve fiber layer (RNFL), turn into the optic nerve head, cross the lamina cribrosa and, emerging posterior to the ocular globe, become myelinated and organized in bundles, giving form to the optic nerve. For the long intraocular length these axons remain unmyelinated and thus very energy dependent in order to transmit the action potential. Once they achieve myelination posterior to globe, their energy dependence decreases drastically, as they now "enjoy" the efficiency of saltatory action potential conduction [2,3].

This physiological dichotomy is reflected in the need to distribute the mitochondria asymmetrically, such that they are very abundant in the intraocular unmyelinated portion, and remarkably fewer posterior to the lamina cribrosa, where they remain in clusters under the nodes of Ranvier or travelling towards the synaptic terminal. This functionally skewed system is probably at the basis of the extreme vulnerability of this cell type to respiratory chain dysfunction, oxidative stress and ultimately apoptosis [2–4]. Thus, RGCs degeneration, optic nerve atrophy, and consequent blindness are very frequent clinical features of mitochondrial disorders [5].

We here review the most relevant phenotypes, distinguishing non-syndromic and syndromic optic neuropathies.

## 2. Syndromic or non-syndromic?

Leber's hereditary optic neuropathy (LHON) [6,7] and dominant optic atrophy (DOA) [8–10] are the two most frequent mitochondrial hereditary optic neuropathies with monosymptomatic expression [2,11]. In contradistinction, optic neuropathy, as a part of a more complex syndrome, is frequent in other multi-systemic mitochondrial disorders such as the LHON/dystonia/Mitochondrial Encephalomyopathy Lactic Acidosis Stroke-like (MELAS)/Leigh overlapping syndrome [2,12–16], or mitochondrial diseases due to genetic errors in nuclear genes encoding mitochondrial proteins such as Friedreich ataxia (FRDA) [17], deafness–dystonia–optic atrophy (Mohr–Tranebjerg) syndrome (MTS) [18], complicated hereditary spastic parapaplegia (HSP) associated with mutations in the *SPG7* gene [19], DOA "plus"

* Corresponding author. Tel.: +39 051 209 2747; fax: +39 051 209 2751.
*E-mail address:* valerio.carelli@unibo.it (V. Carelli).

0005-2728/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbabio.2009.02.024

**Table 1**

| Disease | Genetic defect | Protein | Function | Visual defect | References |
|---|---|---|---|---|---|
| *Non-syndromic* | | | | | |
| Leber's hereditary optic neuropathy (LHON, OMIM #535000) | mtDNA genes: -11778/*ND4* -3460/*ND1* -14484/*ND6* -Others | ND subunits of Complex I | Respiratory chain Complex I | Optic atrophy, central scotoma (papillomacular bundle), colour vision defects, acute/subacute, visual recovery | [2,7,11,29,30,39] |
| Dominant optic atrophy (DOA, OMIM #165500) | Nuclear genes: -*OPA1* (3q28-q29) -others | Optic atrophy 1 (OPA1, dynamin-like GTPase) | Mitochondrial fusion, control of cristae morphology and apoptosis, maintenance of membrane potential and OXPHOS, stability and maintenance of mtDNA | Optic atrophy, central scotoma (papillomacular bundle), colour vision defects, congenital/slowly progressive, no visual recovery | [2,9–11,58,66,69] |
| *Syndromic* | | | | | |
| LHON/dystonia/MELAS/Leigh overlapping syndrome (OMIM #500001, 540000, 256000) | mtDNA genes: missense point mutations in *ND* subunit genes | ND subunits of Complex I | Respiratory chain Complex I | LHON-like optic atrophy, retinal pigmentary changes | [2,12–16,79–83] |
| Friedreich ataxia (FRDA, #229300) | Nuclear gene: *FXN* (9q13) | Frataxin | Handling of iron, chaperoning iron–sulphur clusters; antioxidant protection | Optic atrophy and optic radiations involvement, concentric restriction, slowly progressive or occasionally LHON-like subacute optic neuropathy | [7,88,89, 92–94] |
| Mohr–Tranebjaerg syndrome (MTS, OMIM #304700) | Nuclear gene: *TIMM8A*/*DDP* (Xq22) | TIMM8A (translocase of the inner membrane, TIM) | Co-assembles with TIMM13, necessary for the import of TIMM23, other unknown functions | Late optic atrophy, early visual cortex and optic radiations involvement | [18,96–98] |
| Hereditary spastic paraplegia 7 (HSP7, OMIM #607259) | Nuclear gene: *SPG7* (16q24.3) | Paraplegin (mitochondrial metalloprotease of the AAA family) | Quality control of mitochondria including stability of complex I (?) and maturation of proteins involved in ribosomal assembly, proteolitic processing of OPA1 (?) | Optic atrophy, no detailed descriptions | [19,111–113] |
| Optic atrophy, deafness, ophthalmoplegia and myopathy (DOA plus, OMIM #125250, 165500) | Nuclear genes: -OPA1 (3q28–q29) missense mutations in the GTPase domain (R445H and others) | Optic atrophy 1 (OPA1, dynamin-like GTPase) | Mitochondrial fusion, control of cristae morphology and apoptosis, maintenance of membrane potential and OXPHOS, stability and maintenance of mtDNA | Profound congenital/childhood onset optic atrophy | [2,20,21,124–127] |
| Hereditary motor and sensory neuropathy type VI (HMSN VI, OMIM #601152) or Charcot–Marie–Tooth type 2A (CMT2A, OMIM #609260) with optic atrophy | Nuclear gene: *MFN2* (1p36.2) | Mitofusin 2 (Mfn2, dynamin-like GTPase) | Mitochondrial fusion, control of apoptosis, modulation of cellular energy balance (?) | Optic atrophy, central scotoma (papillomacular bundle), colour vision defects, subacute, visual recovery over years in cases with late-onset, OPA1-like optic neuropathy in early-onset cases | [23,24] |
| Infantile encephalopathy (OMIM +603850.0001) | Nuclear gene: *DLP1*/*DRP1* (12p11.21) | Dynamin-like protein 1 (DLP1, dynamin-like GTPase) | Mitochondrial fission, control of apoptosis | Optic atrophy and optic nerve hypoplasia | [116] |
| Optic atrophy plus Costeff syndrome (OMIM #258501) and Optic atrophy with cataract (OMIM #165300) | Nuclear gene: *OPA3* (19q13.2–q13.3) | Optic atrophy 3 (OPA3) | Function unknown | Optic atrophy, cataract | [25–28] |

syndromes [20,21], Charcot–Marie–Tooth type 2A (CMT2A) with optic atrophy or hereditary motor and sensory neuropathy type VI (HMSN VI) [22–24], and Costeff syndrome [25,26] and DOA with cataract [27,28]. For all of these mitochondrial disorders (summarized in Table 1), we briefly review the optic nerve pathology to uncover common motifs, or to emphasize differences in the clinical expression and in the possible mechanisms leading to optic neuropathy.

## 3. Non-syndromic optic neuropathies: LHON and DOA

The non-syndromic optic neuropathies, LHON and DOA, are by definition limited to a single cellular target, i.e. the RGCs that originate the optic nerve. Both diseases share the hallmark of early and preferential involvement of the small axons that form the papillomacular bundle, the anatomical substrate for central and colour vision [2,11].

### 3.1.1. LHON clinical features

Theodor Leber first described LHON as a hereditary optic atrophy affecting mostly young males [6]. It is now well established that LHON is maternally inherited, being due to the three frequent pathogenic mtDNA point mutations at positions 11778/ND4, 3460/ND1, and 14484/ND6 [7,29,30]. Epidemiological studies demonstrated that LHON is the most frequent mitochondrial disease [31]. LHON patients present with rapid and painless loss of central vision in one or both

eyes accompanied by the fading of colours (dyschromatopsia). The second eye is usually involved within weeks. The loss of visual acuity is profound and levels off below 20/400 within a few months; the visual field defects show large centro-coecal absolute scotomas. At fundus examination the characteristic signs include circumpapillary telangiectatic microangiopathy, swelling of the RNFL around the disc (pseudoedema), and lack of leakage on fluorescein angiography (in contrast to true disc edema) [32–34]. The optic disc appears hyperemic initially, though the axonal loss in the papillomacular bundle leads to severe temporal pallor of the optic disc. In time, the optic disc turns completely atrophic. Microangiopathy and fundus changes such as RNFL swelling may be present in asymptomatic maternal family members [35]. The endpoint of LHON is usually optic atrophy associated with permanent loss of central vision and very poor general visual function although there is relative sparing of pupillary light responses [36,37]. Spontaneous recovery of visual acuity may infrequently occur even years after onset, and the most favourable prognostic factors are young age of onset and the 14484/ND6 mutation [38–40].

The few LHON patients that have been studied with histopathology showed a drastic loss of RGCs and RNFL in the retina. The postlaminar optic nerve cross-sections display a variable loss of temporal and central fibers with different degrees of axonal sparing in the nasal periphery and absence of inflammatory signs. Larger axon profiles are selectively spared and found within the reactive gliotic tissue replacing the fiber loss [2,41,42]. Electron microscopy reveals ultrastructural changes in the few spared axons, such as patchy accumulations of mitochondria and wide variability in myelin thickness. Remarkably, there is also the persistence of degenerating axons, long after the clinical onset of LHON [2,41]. Hence, it can be concluded that the degenerative process continues for decades. The retinal and optic nerve head anatomy can now be also explored *in vivo* by optical coherence tomography (OCT) [5]. This technique was recently applied to re-defining with objective measures the natural history of LHON. The acute phase (first six months) was characterized by loss of the papillomacular bundle temporal fibers and swelling of the adjacent RNFL in the superior/inferior quadrants [43]. The chronic phase (after the first six months) was characterized by severe loss of fibers in all quadrants, the nasal being the most spared [43]. OCT evaluation of RNFL thickness also clearly distinguished patients that experienced some degrees of visual recovery, who had a significant relative preservation of RNFL, from those who did not [43]. Furthermore, OCT evaluation of unaffected carriers has documented early swelling of the papillomacular bundle in the temporal/inferior quadrants [44].

### 3.1.2. LHON genetics and pathophysiology

Incomplete penetrance in homoplasmic LHON maternal lineages and male prevalence among the affected individuals are two features of LHON that remain a mystery and are currently matters of intense investigation. In this regard the genetic basis of LHON is very complex. There are three frequent pathogenic point mutations (11778/ND4, 3460/ND1, and 14484/ND6), and a handful of other rarer but truly pathogenic mtDNA point mutations, all affecting subunits of complex I [2,11]. Recently, the importance of mtDNA variation in LHON has been fully recognized. There is now solid evidence that two subclades of haplogroup J (J1c and J2b) are relevant to increase penetrance of the 11778/ND4 and 14484/ND6 mutations [45,46]. Furthermore, specific "private" non-synonymous variants in mtDNA may also modify the clinical expression of LHON, as recently shown for the recurrence of myoclonus in two LHON pedigrees [47]. However, mtDNA pathogenic mutations and modifying background are a necessary but still not sufficient condition to determine the phenotypic expression. The role of nuclear modifying genes has been postulated and debated [48]. The X chromosome has been under enquiry for a long time as a good candidate for modifying genes, which would also explain the male prevalence. This two-locus model was formally compatible with segregation studies in LHON pedigrees [49] and recent linkage analysis documented two loci on X chromosome [50,51]. However, to date no significant genetic variants associated with LHON were reported by the direct sequencing of candidate genes in the X-linked loci, as well as studies on the X-inactivation pattern in affected females failed to observe the predicted excess of skewed inactivation [52].

The real contribution of various environmental factors proposed to trigger LHON also remains ambiguous. Tobacco smoking and alcohol consumption are the most likely risk factors both by analogy with toxic and nutritional optic neuropathies and through direct investigation [2,53]. Exposures to less common toxic agents such as solvent vapours [54], as well as head trauma, uncontrolled diabetes, or pharmaceutical agents that interfere with mitochondrial metabolism, such as ethambutol and antiretroviral drugs have also been reported [2,5].

The biochemical effects of LHON mutations and the possible pathogenic mechanisms remain areas of continuous investigation. Every model of LHON pathophysiology assumes a defective complex I function. Loss of energetic efficiency, increased oxidative stress, and propensity to apoptotic cell death have all been variably documented in patient's tissues and cell models of the disease [2,3]. As a consequence, altered axonal transport of organelles and axoplasmic stasis with swelling of axons has been proposed as key features leading to the threshold for the acute phase of the disease [3]. The latter is characterized by a remarkably synchronous wave of RGCs degeneration, most likely involving apoptotic cell death [55,56]. At this stage, the commitment to cell death might be already irreversible, as suggested by the recent failure of therapeutic trials designed to save the second eye by drug administration in the small window of time separating the optic neuropathy in the first from the second eye [57].

### 3.2.1. DOA clinical features

DOA, also known as Kjer's optic neuropathy [8], can be considered as the companion disease to LHON. DOA is characterized by a slowly progressive bilateral loss of central vision starting in childhood and variably progressing in adult life [2,11,58,59]. Patient examination demonstrates centrocecal scotomas and impairment of colours vision (tritanopia) and temporal pallor of the optic disc. The end-stage fundus appearance of DOA is characterized by complete optic atrophy and frequent optic disc excavation [60]. Overall, despite a remarkably different natural history, LHON and DOA share a similar endpoint and begin with the predominant involvement of the papillomacular bundle [2]. Both diseases also share a remarkable variability in penetrance [61].

The histopathology of DOA is limited to just two old studies [62,63]. Selective loss of RGCs was reported, particularly in the macular area, with a substantially normal appearance of the rest of the retina. The optic nerve showed axonal loss and swelling, demyelination, and an increased content of collagen especially in the temporal aspect (suggesting specific vulnerability of the papillomacular bundle fibers), without signs of inflammation.

### 3.2.2. DOA genetics and pathophysiology

About 60% of DOA cases are now linked to mutations in the *OPA1* gene identified in 2000 [9,10]. Two further loci have been reported (*OPA4* and *OPA5*), but the genes involved have not yet been identified [64,65]. The screening of numerous cohorts of DOA families of different ethnic origin led to the identification of a large number (over 100) of different mutations in the *OPA1* gene, including missense, nonsense, deletion/insertion, and splicing mutations,

mostly clustered in the GTPase domain and the 3′ end of the coding region [66, see http://lbbma.univ-angers.fr]. The large majority of *OPA1* mutations are predicted to produce a premature truncated protein and haploinsufficiency is the mechanism assumed to underlay DOA in these cases, whereas missense mutations, mostly affecting the GTPase domain, are predicted to exert a dominant-negative effect. In general, the genotype–phenotype correlation is weak, with great variability in both penetrance and clinical severity. As is the case for LHON, other as yet unknown genetic or epigenetic/environmental factors may play a role in the phenotypic expression of DOA.

The *OPA1* gene encodes a 960 amino acid residue protein targeted to mitochondria by a leader sequence, and belonging to a family of highly conserved GTPases related to dynamin [67,68]. OPA1 has eight mRNA isoforms resulting from alternative splicing. These are expressed in a variety of tissues, with the highest levels found in retina, brain, testis, heart, and muscle [69]. OPA1 is anchored to the mitochondrial inner membrane facing the inter-membrane space and has an important role in the mitochondrial fusion process and also in protection from apoptosis by dealing with cytochrome *c* storage and release [69–71]. Down-regulation of OPA1 using specific small interference RNA leads to fragmentation of the mitochondrial network concomitantly to dissipation of the mitochondrial membrane potential and to a drastic disorganization of the cristae [70]. Recent studies provide mounting evidence that OPA1 is also involved in OXPHOS efficiency [72–74]. In particular OPA1 mutations inducing haploinsufficiency were shown to impair ATP synthesis in patient-derived fibroblasts when oxidative phosphorylation was driven by complex I substrates, thus converging DOA to a final biochemical pathway with LHON. A similar convergence was shown by another study demonstrating that LHON and DOA cells suffer a similar coupling defect in respiration [74].

## 4. Syndromic optic neuropathies

### 4.1. Mitochondrial DNA-based disorders

#### 4.1.1. LHON/dystonia/MELAS/Leigh overlapping syndrome

Optic atrophy may occur in mitochondrial encephalomyopathies such as Myoclonic Epilepsy, Ragged-Red-Fibers (MERRF) [75] and MELAS [76]. Furthermore, although the visual system is not usually

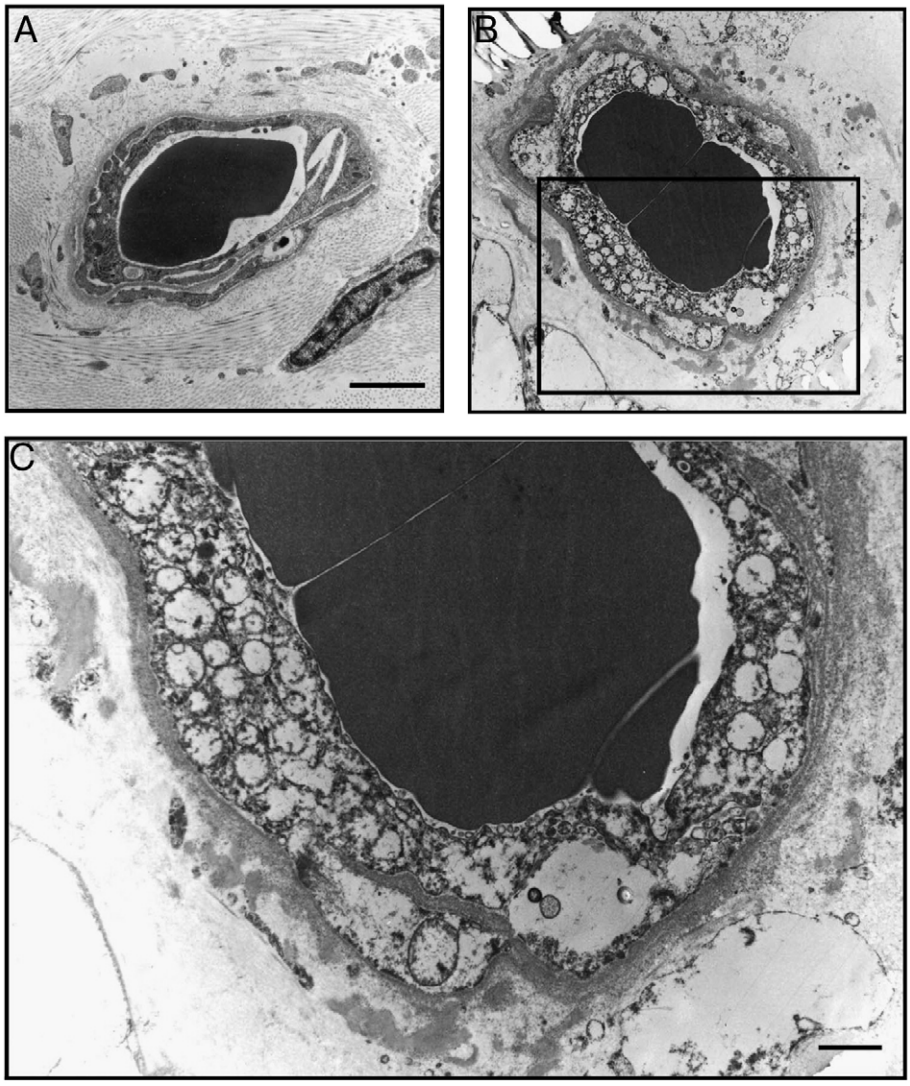


**Fig. 1.** Human capillaries in the optic nerve head from post-mortem tissue; transmission electro microscopy (TEM) [unpublished data, Ross-Cisneros, Sadun, Carelli; partially presented at ARVO 2001 — Ross-Cisneros FN, Win PH, Carelli V, Sadun AA, Invest Ophthalmol Vis Sci 42 (2001) S625]. (A) Capillary from a normal age-matched control and (B) a capillary from a LHON patient with the 11778/ND4 mutation. Note the abnormal accumulation of mitochondria in the cytoplasm of the capillary's endothelium in (B). The highlighted (boxed) area in (B) is represented in (C) and is enlarged to allow closer examination of the numerous mitochondria circumscribing the entire extent of this capillary's endothelium. Note the cristae in the periphery of these mitochondria which appear "swollen" and display various diameters (sizes). Bar (A) 3 μm, and (C) 1 μm.

emphasized, optic atrophy is a frequent clinical feature in Leigh syndrome as documented by histopathological reports [77]. MERRF and MELAS are usually due to mtDNA point mutations affecting tRNAs [78]. The underlying genetic defect in Leigh syndrome is very broad, including both nuclear genes and mtDNA mutations, the latter most often affecting complex I subunit genes [78]. The 14459/ND6 mutation is the first mutation that showed an overlapping clinical expression, which ranged from LHON to dystonia with bilateral striatal necrosis to full blown Leigh syndrome [79,80]. A few years later another mutation at position 13513 in the ND5 subunit gene of complex I was found associated with MELAS and later in cases with LHON-like severe optic neuropathy [13,81,82].

A great deal of interest is now focused on this growing group of mtDNA point mutations affecting the ND genes, mainly ND5, ND6, and ND1, which are associated with a syndromic overlapping LHON/Dystonia/MELAS/Leigh syndrome [12–16,79–82]. It should be noted that a few "LHON-plus" cases of adult-onset Leigh syndrome were also reported in association with the "classical" 11778/ND4, 3460/ND1, or 14484/ND6 LHON mutations [83]. These observations point to a possible common pathogenic mechanism with different degrees of central nervous system involvement, where the LHON-like optic neuropathy represents only the tip of the iceberg. We previously hypothesized that the link between LHON, MELAS, and Leigh syndromes may relate to mitochondrial angiopathy, as a shared common feature, which implies a possible vascular involvement in the pathophysiology of these phenotypes [2] [unpublished data, Ross-Cisneros, Sadun, Carelli; Fig. 1].

Vascular changes in LHON are well known and their role in the pathophysiology of the disease has been debated [2,84]. The microangiopathy often seen in LHON may persist as a subclinical sign over a number of years in asymptomatic family members without the development of optic neuropathy [35,84]. During the active phase of LHON, these vascular abnormalities may become more pronounced as evidenced by arteriovenous shunting in the telangiectatic vascular bed, with dilatation of retinal artery branches, tortuosity of peripapillary arterioles and occasional peripapillar haemorrhages [5,33,34]. Once vision loss stabilizes, the vascular abnormalities disappear. Our histopathologic investigations show accumulations of mitochondria within smooth musculature and endothelium, similarly to what has been described in mitochondrial angiopathy in MELAS patients [85,86] [unpublished data, Ross-Cisneros, Sadun, Carelli; Fig. 1]. In MELAS, a pathogenic role for such vascular changes has been hypothesized, with particular reference to the stroke-like episodes. Furthermore, Leigh syndrome is also characterized by vascular changes and by small vessel proliferation in the anatomical areas surrounding the necrotizing lesions, which are the histological hallmark [77]. Thus, the mitochondrial angiopathy seems to link LHON, MELAS and Leigh syndromes, suggesting the need to further investigate the role of vascular pathology. LHON might be considered a small scale stroke-like (MELAS) or Leigh syndrome acute/subacute episode that specifically targets the optic nerve head [2].

### 4.2. Nuclear DNA-based disorders

#### 4.2.1. Friedreich ataxia (FRDA) and Mohr–Tranebjaerg syndrome (MTS)

Friedreich ataxia (FRDA) is the most common autosomal recessive hereditary ataxia characterized by spinocerebellar ataxia with absence of deep tendon reflexes, dysarthria, hypertrophic cardiomyopathy and scoliosis, and as possible additional features diabetes mellitus, pes cavus, deafness and optic atrophy [87]. The genetic defect is a GAA triplet expansion in the first intron of the *FXN* gene on chromosome 9, which may reach over 1000 repeats in both alleles, the normal range being 27–36 repeats [88]. A minority of FRDA patients are compound heterozygotes for the GAA triplet expansion and a point mutation [89].

The *FXN* gene encodes frataxin, a 210 amino acid long protein targeted to mitochondria and directed to the inner mitochondrial membrane, whose amount is greatly reduced by the triplet expansion. Deficient mitochondrial respiration in the heart and muscle of FRDA patients has been documented, with a specific impairment of iron–sulphur containing proteins such as complexes I, II and III and aconitase [90,91]. Frataxin has also been variously implicated in iron homeostasis, oxidative stress and the biosynthetic pathways related to iron–sulphur containing enzymes [87].

Optic neuropathy in FRDA patients has been described in only a few studies [92–94]. Recently, a systematic investigation of the visual pathway involvement has been undertaken in twenty-six molecularly confirmed FRDA patients, by the integrated use of different techniques including OCT, diffusion weighted imaging (DWI), visual fields (VF) and pattern evoked potentials (P-VEPs) [17]. All FRDA patients presented some degree of visual pathway involvement, but in only a small subset was this apparent clinically. Most patients with FRDA presented with a slowly progressive degenerative process involving both the optic nerve and the optic radiations, as documented by the DWI investigation [17]. In a few cases, all with severe disease and large triplet expansion, a subacute/acute visual failure mimicking LHON overlapped the slow progression of optic neuropathy. Thus, the conclusion of this study was that FRDA is a mitochondrial multisystemic disorder for which involvement of visual pathway is common and the pattern of visual loss and the underlying pathological mechanism clearly differs from the classical non-syndromic mitochondrial optic neuropathies, such as LHON and OPA1-related DOA. In FRDA there is an apparently independent involvement of the optic radiations, which is in addition to the optic nerve/anterior pathway [17].

A different example of a nuclear-encoded mitochondrial disease is represented by the deafness–dystonia–optic atrophy syndrome (Mohr–Tranebjaerg syndrome; MTS) described by Mohr [95] and Tranebjaerg [96], which is an X-linked recessive trait due to mutations in the deafness/dystonia peptide (DDP)/TIMM8A [97,98]. Most mitochondrial proteins are encoded by the nuclear genome and need to be transported through the double membranes of mitochondria to reach their final destination and be activated to their function [99]. This process is mediated by the coordinated action of a complex set of translocation systems of the outer (translocase of the outer membrane or TOM) and inner (translocase of the inner membrane or TIM) mitochondrial membranes. MTS is to date the only human disorder affecting a TIM protein and most mutations in the *TIMM8A* gene lead to a truncated protein or are large deletions with complete loss of the protein [97,100].

TIMM8A is a small Tim protein that co-assembles with the partner protein TIMM13 in a soluble inter-membrane space complex involved in chaperoning the mitochondrial import of nuclear-encoded precursors proteins [99]. There is evidence that lack of TIMM8A abolishes the assembly with TIMM13, possibly leading to a decreased rate of TIMM23 import [101]. This latter protein is essential for import of proteins to the matrix and may, at least hypothetically, lead in turn to defective oxidative phosphorylation and energy production or to other still unidentified mitochondrial dysfunctions.

Affected males with MTS have a consistent clinical expression with childhood onset deafness, followed by progressive dystonia, blindness, and other variable neurological features including ataxia, spasticity, mental deterioration and behavioural disorder. However, even within the same family with the same mutation, the timing and the prevalence of such clinical features may vary. Females carriers are usually unaffected, but may occasionally express a late-onset oligosymptomatic version of MTS, suffering torticollis and writer's cramp, or mild deafness [102]. Pathological investigations revealed neuronal cell loss in the striate cortex, basal ganglia, and dorsal roots of the spinal cord and posterior columns, as well as loss of RGCs and resultant depletion of axons in the optic nerve; in the retina there is

also a reduction of cells in the inner nuclear layer [18]. Although visual loss is mainly due to neurodegeneration of the visual cortex, degeneration of the retina and the optic nerve also contribute to visual impairment [103,104].

In this regard, MTS shows some similarity with FRDA, having a clear involvement of the entire visual pathway, including optic nerves, optic radiations and visual cortex. In FRDA the degenerative process of the posterior visual pathways (optic radiations) is probably independent and possibly asynchronous from that of the anterior visual pathways (optic nerve). In the case of MTS, there is a dearth of systematic investigations in a sufficient number of patients by the same integrated use of different techniques that was recently applied to FRDA [17], and hence for MTS little is understood. In particular, we cannot exclude that in the case of MTS the degenerative process may start from the visual cortex (atrophy of the visual cortex), and progress in a retrograde way (including gliosis of the occipital poles and optic radiations), affecting only in the late stages the retina with RGCs loss and subsequent optic nerve atrophy [18,103].

*4.2.2. Complicated hereditary spastic paraparaplegia*

Hereditary spastic paraplegias (HSPs), previously known as Strumpell–Lorrein disease, are a group of similar neurodegenerative disorders with a clinical presentation of weakness and spasticity in the lower limbs [105,106]. Seventeen genes, out of 41 spastic paraplegia gene (SPG) loci mapped, have been identified, reflecting the large genetic heterogeneity underlying HSPs and the blurred boundaries with other similar disorders. HSPs are also distinguished in pure forms and complicated variants characterized by other neurological signs including optic atrophy [106,107]. Among the genes associated with HSPs a few have been reported to be mitochondrial proteins, such as paraplegin (*SPG7*) [18], heat shock protein 60 (*SPG13*) [108] and REEP1 (*SPG31*) [109].

Optic atrophy may complicate the clinical picture of families with autosomal recessive spastic paraplegia due to mutations in the *SPG7* gene encoding for paraplegin [19]. Unfortunately, description of the ophthalmological features in these patients remains elusive. It is interesting to note that paraplegin, a mitochondrial metalloprotease of the AAA family, has been reported to co-assemble with a homologous protein, AFG3L2, to form a complex in the mitochondrial inner membrane [110]. The lack of this paralegin/AFG3L2 complex impairs complex I activity in mitochondria and increases sensitivity to oxidative stress, a general paradigm of mitochondrial optic neuropathies [2,3]. This is bolstered by studies of paraplegin-deficient mice, which show axonal swellings due to massive accumulation of organelles and neurofilaments, suggestive of impaired axonal transport [111]. Similar changes were also seen in the axons of the optic nerve from this animal model and closely resemble the ultrastructural abnormalities described in LHON [2]. More recent studies indicated a role of paraplegin in the quality control of mitochondria, including the maturation of proteins involved in ribosome assembly and translation within mitochondria [112]. Finally, paraplegin has also been involved in the proteolytic cleavage of OPA1, although its exact role is still questioned [113–115]. Clear-cut ultrastructural abnormalities of mitochondria are reported in the paraplegin-deficient mice, including aberrant cristae, which are also seen in the OPA1 mutant cells from patients with DOA, in association with the hyperfragmentation of the mitochondrial network [70,73]. There is consensus that axonal transport and trafficking are the key features to be affected by various mechanisms in HSPs and that long axons of the corticospinal tracts slowly degenerate with a retrograde, “dying-back” paradigm [105,106,112]. This raises the question as to whether for HSPs, as in FRDA and MTS, there is an involvement of both anterior and posterior parts of the visual pathway. Specific ophthalmologic investigations are warranted to clarify how the optic neuropathy and visual loss develop in HSPs.

*4.2.3. Disorders related to fission/fusion genes: DOA plus (OPA1), CMT2A with optic atrophy or HMSN VI (Mfn2) and DLP1-related encephalopathy*

After discovering that most DOA patients had mutations in the *OPA1* gene, several other neurodegenerative diseases have been further associated with genetic defects affecting the mitochondrial fission/fusion machinery. These include syndromic forms of DOA in combination with chronic progressive external ophthalmoplegia (CPEO) with specific missense mutations in the GTPase domain of the *OPA1* gene (DOA plus syndrome) [20,21], CMT2A with optic atrophy or HMSN VI associated with mutations in the *MFN2* gene encoding mitofusin 2 (Mfn 2) [23,24], and, just recently, a first case of infantile encephalopathy described in association with mutant *DLP1* gene [116].

CPEO, isolated or in a syndromic combination with other clinical features, is the most frequent manifestation of mitochondrial myopathy and has a heterogeneous genetic basis. It can be associated with either mtDNA single deletions and point mutations, or with mutations in nuclear genes resulting in mtDNA multiple deletions [78]. At least five nuclear genes are now known to be involved in CPEO associated with mtDNA multiple deletions and autosomal recessive or dominant inheritance. These are both subunits of *POLG* [117,118], which is the enzyme replicating mtDNA, the mitochondrial replicative DNA helicase Twinkle (*PEO1*) [119], the heart/muscle specific adenine nucleotide translocator ANT1 [120] (*SLC25A4*), and finally the thymidine phosphorylase (*TP*) which is involved in nucleoside pool maintenance [121]. Among these genes, mutations in at least two of them, i.e. *POLG1* and *TP*, may present with a combination of deletions and depletion of mtDNA in skeletal muscle [122,123].

The association of CPEO and mitochondrial myopathy with optic atrophy is rare [124,125], and never reported as due to mutations in the above mentioned genes. Thus, the recent identification of the same peculiar *OPA1*/R445H mutation in two large families described by Treft et al. [124] and Meire et al. [125] combining the clinical phenotype of autosomal dominant CPEO and DOA was of particular interest [126]. Unfortunately the authors of this latter study did not perform any muscle biopsy or mtDNA investigation on these patients to better characterize the myopathy. A further set of seven families with this CPEO/DOA plus phenotype were subsequently reported by two independent studies carrying different OPA1 missense mutations in the GTPase domain [20,21]. Among them, the *OPA1*/R445H mutation was also found, and they were all associated with classic mitochondrial myopathy with cytochrome *c* oxidase-negative fibers and mtDNA multiple deletions [20,21]. These two reports, documenting independently the molecular basis of this overlapping CPEO/DOA plus phenotype, placed unexpectedly OPA1 as another gene implicated in mtDNA maintenance and stability [127]. The patients belonging to this group suffer severe sensorineural deafness, cerebellar ataxia, axonal sensory–motor polyneuropathy, in addition to severe early-onset optic atrophy and late CPEO/mitochondrial myopathy. A further study recently reported that patients with CPEO/DOA plus phenotype and mtDNA multiple deletions carried missense mutations in the GTPase domain of the *OPA1* gene in 14.2% of a series of 21 probands investigated, being mutations in *OPA1* more common than mutations in *POLG2, SLC25A4,* and *PEO1* [128]. How these *OPA1* missense mutations generate mtDNA multiple deletions and how this produces the clinical phenotype, remains to be fully understood.

Another recent remarkable and closely related finding was the association of axonal CMT2A with mutations in the *MFN2* gene [23]. Shortly after this report, a number of CMT2A cases with optic atrophy, fulfilling the diagnostic criteria for HMSN VI, were also described as due to mutations in the *MFN2* gene [24]. In some of the latter cases, the optic neuropathy was reported in full details and closely resembled a benign LHON variant, similar to the cases with the 14484/ND6 mutation that are prone to recover visual acuity after an initial acute decline of vision [2,11]. These HMSNVI/CMT2A

patients mostly presented with subacute visual loss, central scotomas, colour vision defects and pale optic discs. They experienced, over years, variable degrees of recovery of visual acuity, colour vision and reduction of the central scotoma, reverting back to near normal visual function. However, in contrast with recovery of visual acuity in LHON, a late age of onset was a favourable predictive factor in these HMSNVI/CMT2A patients, whereas those cases with childhood onset of visual loss had a slowly progressive course without visual recovery, similarly to DOA patients. Thus, a remarkable link bridges LHON and DOA to HMSNVI/CMT2A with optic neuropathy, suggesting a continuum of optic nerve involvement in all these clinical phenotypes. On the other hand, the axonal peripheral neuropathy characterizing CMT2A has also recently been recognized in a family with mutations in POLG1 gene and mtDNA multiple deletions [129]. Furthermore, at least two studies on the functional consequences of mutant Mfn2 protein point to mechanisms already considered in the previous sections of this review for both LHON and DOA [2,3]. The first study documents an impaired mitochondrial coupling and reduced membrane potential in fibroblasts from CMT2A patients with missense mutations in the *MFN2* gene [130]. However, a more recent study with a similar design investigating mitochondrial phenotype of fibroblasts from CMT patients with mutant *MFN2* failed to document a defective respiratory function [131]. The second study documents impaired axonal transport of mitochondria not related to a bioenergetic deficiency [132]. These authors propose that an impairment of mitochondrial trafficking would affect the longest axonal systems, possibly underlying the pathogenesis of peripheral neuropathy. This argument is similar to what has been discussed for the HSPs.

Finally, after having described mutations in genes coding for the mitochondrial fusion machinery, there is now reported a case of a disease associated with a heterozygous dominant-negative mutation in the dynamin-like protein 1 (DLP1), the protein involved in mitochondrial fission [116]. Interestingly, the clinical phenotype of this patient was a severe infantile encephalopathy, with evidence of optic atrophy and hypoplasia, dysmyelination and abnormal gyral pattern of cerebral cortex, and a severe respiratory dysfunction with lactic acidosis. This patient died at the age of 37 days. Cell studies overexpressing the DLP1 mutation clearly demonstrated a hypertubulated mitochondrial network [116].

#### *4.2.4. OPA3 gene: Costeff syndrome and DOA with cataract*

Costeff syndrome is characterized by optic atrophy associated with increased urinary excretion of 3-methylglutaconic and 3-methylglutaric acids [25]. In addition to optic atrophy, these patients may display extrapyramidal signs, spasticity, ataxia, dysarthria, and cognitive deficits. Costeff syndrome has been associated with mutations in *OPA3*, a gene that encodes a poorly characterized mitochondrial protein [26]. After the initial definition of the syndrome in an Iraqi Jew genetic isolate, mutations in *OPA3* have been reported in other populations [133]. Furthermore, at variance with the autosomal recessive Costeff syndrome, allelic mutations in *OPA3* have also been reported in families with DOA with cataract [27,28]. Recently, a mouse model of OPA3-related disease was created recapitulating most of the clinical features observed in the patients, but function of the OPA3 protein remains elusive [134].

## 5. Pathogenic mechanisms: some insights

Understanding the multiple layers of how the molecular defects described in this review converge to tissue/cell specific neurodegeneration, i.e. the RGCs for optic neuropathies, has been a great challenge and a subject of inquiry [extensively reviewed in Refs. 2–5,11]. This review has been focused on a genotype–phenotype correlation attempting to link and compare the optic neuropathy in many mitochondrial disorders sharing this clinical feature. Thus, it is beyond our scope to examine in details all the experimental findings and the proposed biochemical pathways that would translate each molecular defect of the disorders reviewed into cell dysfunction and ultimately the death that is remarkably specific for these neurons in the retina. However, we would like to delineate some common themes, and the first point we make is that there is increasing evidence that complex I dysfunction is part of the pathophysiology of many mitochondrial diseases other than LHON or the mtDNA related LHON/dystonia/MELAS/Leigh overlapping syndrome [2,3], obviously playing a major role in their pathophysiology. Fibroblasts from DOA patients carrying frame shift/stop codon/splicing (haploinsufficiency) mutations in the *OPA1* gene have recently been shown to display a defective ATP synthesis mainly when driven through complex I substrates [73]. The pathophysiology of FRDA also implicates a defective complex I, in addition to other enzymatic components sharing the iron–sulphur clusters such as complex II and III, and aconitase [90]. Furthermore, a complex I defect has been reported in association with mutations in the paraplegin gene, implicating this respiratory complex in the pathogenesis of HSP with mutations in *SPG7* [110]. Thus, it seems a common theme that the optic nerve is more frequently involved in mitochondrial disorders when complex I is affected, even if the claim that optic neuropathies are exclusively due to complex I dysfunction cannot be a general paradigm. In fact, we can mention cases contradicting this paradigm, where optic atrophy is a major clinical feature in patients with either mutations in a nuclear-encoded complex II subunit or a mutation in an mtDNA encoded subunit of complex IV [135,136]. The opposite is also true as many severe Leigh cases, due to nuclear defects of complex I, reported no apparent involvement of the optic nerve.

The consequences of complex I dysfunction may go beyond the immediate effects on energy conservation and ROS production; there is mounting evidence tightly linking complex I dysfunction with predisposition to apoptosis [55,56,137]. There is also a tight connection between fission/fusion, mitochondrial network dynamics, control and regulation of apoptosis [70,71,138]. There are many intricacies of how different genetic defects, in the nuclear and in the mitochondrial genomes, affect different biochemical systems and cell functions implicated in mitochondrial homeostasis. However, in many cases these may converge towards common final pathways, one of which may link complex I dysfunction and RGCs neurodegeneration [3].

There is another overarching common theme that seems to link some of the disorders considered in this review. The machinery driving to mitochondrial biogenesis and mtDNA maintenance can be either a source of pathology or provide a compensatory mechanism for the cell. In fact, the regulation of mtDNA copy number and amount of mitochondria remains a poorly explored issue in mitochondrial optic neuropathies, despite some evidence that compensatory mitochondrial biogenesis is activated by the LHON mutations, whereas a partial reduction of mtDNA copy number has been reported in DOA patients with OPA1 mutations [139,140]. Concerning mtDNA maintenance, accumulation of mtDNA multiple deletions links different phenotypes of CPEO, including the CPEO/DOA plus phenotype [20,21,128], as well as the involvement of peripheral nervous system [129]. The fission/fusion dynamics and how it relates to the accumulation of mtDNA multiple deletions is an exciting new field to be explored, and it promises to deliver further surprises. However, it has also been argued that mtDNA instability in CPEO/DOA plus patients has more to do with the late development of mitochondrial myopathy and central nervous system involvement than with the early onset of severe optic atrophy and deafness [127]. Unfortunately, we still have a very poor understanding of how mitochondrial fission/fusion is carried out and regulated in post-mitotic highly specialized cells such as skeletal muscle and neurons [141,142]. In this regard, the other common theme of axonal transport and trafficking with particular reference on mitochondria has been considered as a key

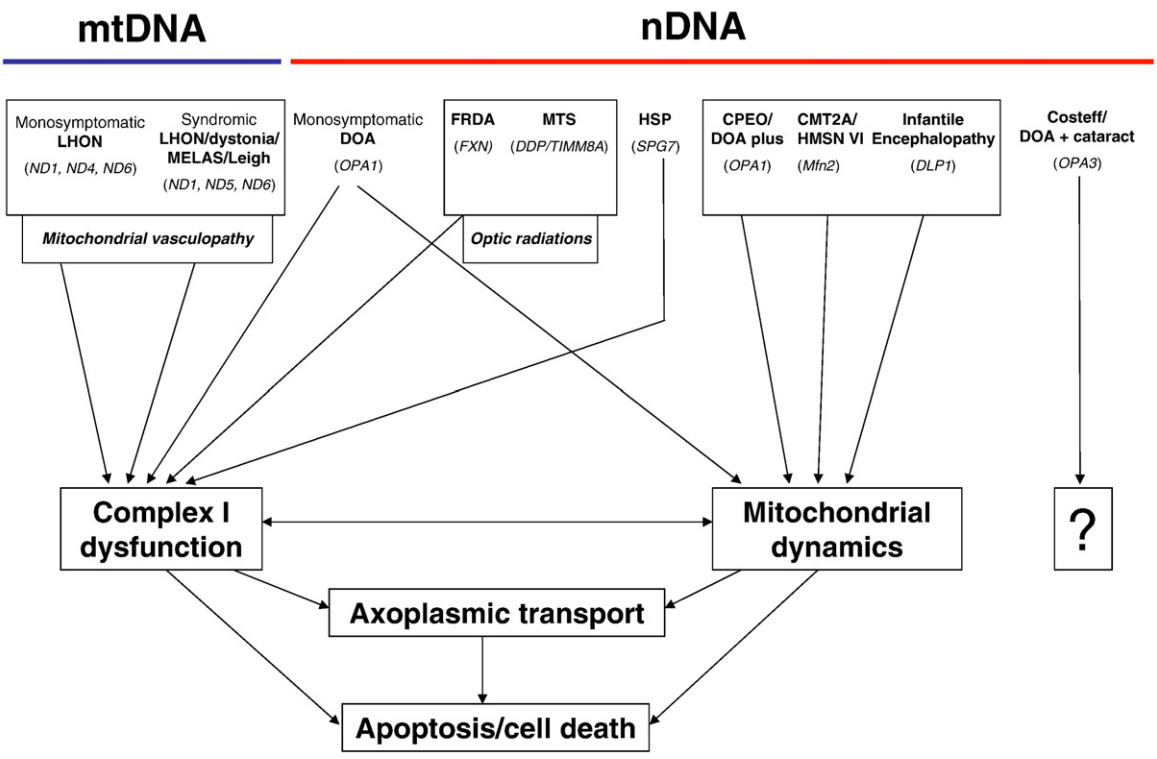


**Fig. 2.** Schematic summary of the common themes linking mitochondrial optic neuropathies.

point in the pathophysiology of LHON and DOA [2,3], HSPs [106,111,112] and CMT2A/HMSNVI [132]. In summary, the control of mitochondrial biogenesis by cells as compensation of respiratory chain dysfunction probably involves feed-back loops and nuclear-mitochondrial cross-talk. These systems and their messengers are far from being understood, yet manipulations of these mechanisms hold promise for therapeutic purposes and represent a new challenge for the field of mitochondrial medicine [143].

Finally, we must recognize that our current understanding is based on many assumptions and simplifications. We anticipate many new insights from current investigations on the genetic basis and pathogenic mechanisms of these disorders. For example, we already must revise the paradigm that all mitochondrial optic neuropathies look alike. To date, the hallmark of a mitochondrial optic neuropathy has been the preferential involvement of the small fibers of the papillomacular bundle, which characterizes both LHON and DOA. The reason for this super-selectivity on the fibers serving central vision has been variously hypothesized, and the most supported explanation is that the majority of these RGCs are small, with thinly myelinated fibers and a high firing rate [42]. Thus, these axons present the most disadvantageous conditions in terms of energy requirements as related to their capability of accommodating mitochondria (surface area/volume) [42]. Moreover, the recent OCT studies on LHON patients indicate that during the acute phase the RNFL is swollen in the superior and inferior arcades, possibly because of stasis of axonal transport and perhaps of compensatory increase in mitochondrial numbers in the prelaminar area [43,44]. This may produce some mechanical constrain to the thin fibers of the papillomacular bundle contributing to their early involvement and sparing the most nasal fibers. However, now the new descriptions of FRDA optic neuropathy and visual pathology in MTS show different scenarios, with specific patterns of neurodegeneration and involvement of the visual pathway, in particular including optic radiations and not limited to just optic atrophy. As we gain more details on the nature of visual loss in CMT2A patients with *MFN2* mutations or in HSPs with mutations in *SPG7* gene (paraplegin), we may anticipate greater understanding of optic nerve and visual pathway involvement in mitochondrial diseases. Understanding of the fundamental pathogenic mechanisms of mitochondrial optic neuropathies will hopefully open an avenue to cure and prevent blindness in these patients.

## 6. Conclusions

The intriguing fact that RGCs are the most common target tissue for mitochondrial dysfunction has brought much focus on optic neuropathies as a model for neurodegeneration. Mitochondrial neuro-ophthalmology has been a fruitful playground to understand some specific mechanisms of disease, which may trigger and drive the solution of broader questions in neurology and mitochondrial medicine. In particular, the common themes delineated in the present review (Fig. 2), such as the respiratory defect and increased ROS production associated with complex I, strictly connected with mitochondrial dynamics, both related to the axoplasmic transport in neurons, may all converge to the final outcome of apoptotic death of RGCs. Furthermore, investigations of mitochondrial biogenesis and mtDNA maintenance will be instrumental to understand cell strategies for compensation and survival, as well as the role played in modifying the pathogenic mechanisms. The great effort currently invested in research in this field is worthwhile and promising. The eye is the only part of the central nervous system readily accessible to both measurement and certain therapeutic strategies aimed to protect against RGCs neurodegeneration. The eye will likely provide a window that will lead to major breakthroughs for neurodegenerative diseases in general.

## Acknowledgements

Our research is funded by Telethon-Italy (grant #GGP06233 to VC), Fondazione Gino Galletti (support to VC), IFOND (support to AAS and VC), Research to Prevent Blindness (support to AAS), The Cleveland Foundation (support to AAS), Oakley Alzeheimer's Research Foundation (support to AAS), and NIH grant #EY03040 (support to AAS).

## References


[1] A.A. Sadun, J.S. Glaser, Chapter 4, anatomy of the visual sensory system, in: J.S. Glaser (Ed.), Neuro-ophthalmology, 3rd Ed, Lippincott Williams and Wilkins, Philadelphia, 1999, pp. 75–94.

[2] V. Carelli, F.N. Ross-Cisneros, A.A. Sadun, Mitochondrial dysfunction as a cause of optic neuropathies, Prog. Retin. Eye Res. 23 (2004) 53–89.

[3] V. Carelli, C. La Morgia, L. Iommarini, R. Carroccia, M. Mattiazzi, S. Sangiorgi, S. Farne', A. Maresca, B. Foscarini, L. Lanzi, M. Amadori, M. Bellan, M.L. Valentino, Mitochondrial optic neuropathies: how two genomes may kill the same cell type? Biosci. Rep. 27 (2007) 173–184.

[4] P. Yu-Wai-Man, P.F. Chinnery, P.G. Griffiths, Optic neuropathies—importance of spatial distribution of mitochondria as well as function, Med. Hypotheses 65 (2005) 1038–1042.

[5] V. Carelli, P. Barboni, A.A. Sadun, Chapter 5. Mitochondrial ophthalmology, in: S. Di Mauro, M. Hirano, E. Schon (Eds.), Mitochondrial medicine, Informa Healthcare Abingdon, Oxon, UK, 2006, pp. 105–142.

[6] T. Leber, Uber hereditare und congenital-angelegte Sehnervenleiden, Arch. Ophthalmol. 17 (1871) 249–291.

[7] D.C. Wallace, G. Singh, M.T. Lott, J.A. Hodge, T.G. Schurr, A.M. Lezza, L.J. Elsas, E.K. Nikoskelainen, Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy, Science 242 (1988) 1427–1430.

[8] P. Kjer, Infantile optic atrophy with dominant mode of inheritance: a clinical and genetic study of 19 Danish families, Acta Ophthalmol. Scand. 37 (1959) 1–146.

[9] C. Alexander, M. Votruba, U.E.A. Pesch, D.L. Thiselton, S. Mayer, A. Moore, M. Rodriguez, U. Kellner, B. Leo-Kottler, G. Auburger, S.S. Bhattacharya, B. Wissinger, OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28, Nat. Genet. 26 (2000) 211–215.

[10] C. Delettre, G. Lenaers, J-M. Griffoin, N. Gigarel, C. Lorenzo, P. Belenguer, L. Pelloquin, J. Grosgeorge, C. Turc-Carel, E. Perret, C. Astarie-Dequeker, L. Lasquellec, B. Arnaud, B. Ducommun, J. Kaplan, C.P. Hamel, Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy, Nat. Genet. 26 (2000) 207–210.

[11] P. Yu-Wai-Man, P.G. Griffiths, G. Hudson, P.F. Chinnery, Inherited mitochondrial optic neuropathies, J. Med. Genet. 46 (3) (2009) 145–158.

[12] E.M. Ruiter, M.H. Siers, C. van den Elzen, B.G. van Engelen, J.A. Smeitink, R.J. Rodenburg, F.A. Hol, The mitochondrial 13513G>A mutation is most frequent in Leigh syndrome combined with reduced complex I activity, optic atrophy and/or Wolff–Parkinson–White, Eur. J. Hum. Genet. 15 (2007) 155–161.

[13] T. Pulkes, L. Eunson, V. Patterson, A. Siddiqui, N.W. Wood, I.P. Nelson, J.A. Morgan-Hughes, M.G. Hanna, The mitochondrial DNA G13513A transition in ND5 is associated with a LHON/MELAS overlap syndrome and may be a frequent cause of MELAS, Ann. Neurol. 46 (1999) 916–919.

[14] L. Spruijt, H.J. Smeets, A. Hendrickx, M.W. Bettink-Remeijer, A. Maat-Kievit, K.C. Schoonderwoerd, W. Sluiter, I.F. de Coo, R.Q. Hintzen, A MELAS-associated ND1 mutation causing Leber hereditary optic neuropathy and spastic dystonia, Arch. Neurol. 64 (2007) 890–893.

[15] E.L. Blakely, R. de Silva, A. King, V. Schwarzer, T. Harrower, G. Dawidek, D.M. Turnbull, R.W. Taylor, LHON/MELAS overlap syndrome associated with a mitochondrial MTND1 gene mutation, Eur. J. Hum. Genet. 13 (2005) 623–627.

[16] M.L. Valentino, P. Barboni, C. Rengo, A. Achilli, A. Torroni, R. Lodi, C. Tonon, B. Barbiroli, F. Fortuna, P. Montagna, A. Baruzzi, V. Carelli, The 13042G → A/ND5 mutation in mtDNA is pathogenic and can be associated also with a prevalent ocular phenotype, J. Med. Genet. 43 (2006) e38.

[17] F. Fortuna, P. Barboni, R. Liguori, M.L. Valentino, G. Savini, C. Gellera, C. Mariotti, G. Rizzo, C. Tonon, D. Manners, R. Lodi, A.A. Sadun, V. Carelli, Visual system involvement in patients with Friedreich's ataxia, Brain 132 (2009) 116–123.

[18] L. Tranebjaerg, P.K. Jensen, M. Van Ghelue, C.L. Vnencak-Jones, S. Sund, K. Elgjo, J. Jakobsen, S. Lindal, M. Warburg, A. Fuglsang-Frederiksen, K. Skullerud, Neuronal cell death in the visual cortex is a prominent feature of the X-linked recessive mitochondrial deafness-dystonia syndrome caused by mutations in the TIMM8a gene, Ophthalmic Genet. 22 (2001) 207–223.

[19] G. Casari, M. De Fusco, S. Ciarmatori, M. Zeviani, M. Mora, P. Fernandez, G. De Michele, A. Filla, S. Cocozza, R. Marconi, A. Dürr, B. Fontaine, A. Ballabio, Spastic paraplegia and OXPHOS impairment caused by mutations in paraplegin, a nuclear-encoded mitochondrial metalloprotease, Cell 93 (1998) 973–983.

[20] P. Amati-Bonneau, M.L. Valentino, P. Reynier, M.E. Gallardo, B. Bornstein, A. Boissière, Y. Campos, H. Rivera, J.G. de la Aleja, R. Carroccia, L. Iommarini, P. Labauge, D. Figarella-Branger, P. Marcorelles, A. Furby, K. Beauvais, F. Letournel, R. Liguori, C. La Morgia, P. Montagna, M. Liguori, C. Zanna, M. Rugolo, A. Cossarizza, B. Wissinger, C. Verny, R. Schwarzenbacher, M.A. Martín, J. Arenas, C. Ayuso, R. Garesse, G. Lenaers, D. Bonneau, V. Carelli, OPA1 mutations induce mitochondrial DNA instability and optic atrophy 'plus' phenotypes, Brain 131 (2008) 338–351.

[21] G. Hudson, P. Amati-Bonneau, E.L. Blakely, J.D. Stewart, L. He, A.M. Schaefer, P.G. Griffiths, K. Ahlqvist, A. Suomalainen, P. Reynier, R. McFarland, D.M. Turnbull, P.F. Chinnery, R.W. Taylor, Mutation of OPA1 causes dominant optic atrophy with external ophthalmoplegia, ataxia, deafness and multiple mitochondrial DNA deletions: a novel disorder of mtDNA maintenance, Brain 131 (2008) 329–337.

[22] I. Voo, B.E. Allf, N. Udar, R. Silva-Garcia, J. Vance, K.W. Small, Hereditary motor and sensory neuropathy type VI with optic atrophy, Am. J. Ophthalmol. 136 (2003) 670–677.

[23] S. Züchner, I.V. Mersiyanova, M. Muglia, N. Bissar-Tadmouri, J. Rochelle, E.L. Dadali, M. Zappia, E. Nelis, A. Patitucci, J. Senderek, Y. Parman, O. Evgrafov, P.D. Jonghe, Y. Takahashi, S. Tsuji, M.A. Pericak-Vance, A. Quattrone, E. Battaloglu, A.V. Polyakov, V. Timmerman, J.M. Schröder, J.M. Vance, Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot–Marie–Tooth neuropathy type 2A, Nat. Genet. 36 (2004) 449–451.

[24] S. Züchner, P. De Jonghe, A. Jordanova, K.G. Claeys, V. Guergueltcheva, S. Cherninkova, S.R. Hamilton, G. Van Stavern, K.M. Krajewski, J. Stajich, I. Tournev, K. Verhoeven, C.T. Langerhorst, M. de Visser, F. Baas, T. Bird, V. Timmerman, M. Shy, J.M. Vance, Axonal neuropathy with optic atrophy is caused by mutations in mitofusin 2, Ann. Neurol. 59 (2006) 276–281.

[25] H. Costeff, N. Gadoth, N. Apter, M. Prialnic, H. Savir, A familial syndrome of infantile optic atrophy, movement disorder, and spastic paraplegia, Neurology 39 (1989) 595–597.

[26] Y. Anikster, R. Kleta, A. Shaag, W.A. Gahl, O. Elpeleg, Type III 3-methylglutaconic aciduria (optic atrophy plus syndrome, or Costeff optic atrophy syndrome): identification of the OPA3 gene and its founder mutation in Iraqi Jews, Am. J. Hum. Genet. 69 (2001) 1218–1224.

[27] P. Reynier, P. Amati-Bonneau, C. Verny, A. Olichon, G. Simard, A. Guichet, C. Bonnemains, F. Malecaze, M.C. Malinge, J.B. Pelletier, P. Calvas, H. Dollfus, P. Belenguer, Y. Malthièry, G. Lenaers, D. Bonneau, OPA3 gene mutations responsible for autosomal dominant optic atrophy and cataract, J. Med. Genet. 41 (2004) e110.

[28] C. Verny, P. Amati-Bonneau, F. Dubas, Y. Malthiéry, P. Reynier, D. Bonneau, An OPA3 gene mutation is responsible for the disease associating optic atrophy and cataract with extrapyramidal signs, Rev. Neurol. (Paris) 161 (2005) 451–454.

[29] N. Howell, L.A. Bindoff, D.A. McCullough, I. Kubacka, J. Poulton, D. Mackey, L. Taylor, D.M. Turnbull, Leber hereditary optic neuropathy: identification of the same mitochondrial ND1 mutation in six pedigrees, Am. J. Hum. Genet. 49 (1991) 939–950.

[30] D.R. Johns, M.J. Neufeld, R.D. Park, An ND-6 mitochondrial DNA mutation associated with Leber hereditary optic neuropathy, Biochem. Biophys. Res. Comm. 187 (1992) 1551–1557.

[31] P.Y. Man, P.G. Griffiths, D.T. Brown, N. Howell, D.M. Turnbull, P.F. Chinnery, The epidemiology of Leber hereditary optic neuropathy in the North East of England, Am. J. Hum. Genet. 72 (2003) 333–339.

[32] J.L. Smith, W.F. Hoyt, J.O. Susac, Ocular fundus in acute Leber optic neuropathy, Arch. Ophthalmol. 90 (1973) 349–354.

[33] E. Nikoskelainen, W.F. Hoyt, K. Nummelin, Ophthalmoscopic findings in Leber's hereditary optic neuropathy. II. The fundus findings in affected family members, Arch. Ophthalmol. 101 (1983) 1059–1068.

[34] E. Nikoskelainen, W.F. Hoyt, K. Nummelin, H. Schatz, Fundus findings in Leber's hereditary optic neuropathy. III. Fluorescein angiographic studies, Arch. Ophthalmol. 102 (1984) 981–989.

[35] E. Nikoskelainen, W.F. Hoyt, K. Nummelin, Ophthalmoscopic findings in Leber's hereditary optic neuropathy. I. Fundus findings in asymptomatic family members, Arch. Ophthalmol. 100 (1982) 1597–1602.

[36] H. Lüdtke, C. Kriegbaum, B. Leo-Kottler, H. Wilhelm, Pupillary light reflexes in patients with Leber's hereditary optic neuropathy, Graefes Arch. Clin. Exp. Ophthalmol. 237 (1999) 207–211.

[37] S. Bose, N. Dhillon, F.N. Ross-Cisneros, V. Carelli, Relative post-mortem sparing of afferent pupil fibers in a patient with 3460 Leber's hereditary optic neuropathy, Graefes Arch. Clin. Exp. Ophthalmol. 243 (2005) 1175–1179.

[38] E.M. Stone, N.J. Newman, N.R. Miller, D.R. Johns, M.T. Lott, D.C. Wallace, Visual recovery in patients with Leber's hereditary optic neuropathy and the 11778 mutation, J. Clin. Neuroophthalmol. 12 (1992) 10–14.

[39] D. Mackey, N. Howell, A variant of Leber hereditary optic neuropathy characterized by recovery of vision and by an unusual mitochondrial genetic etiology, Am. J. Hum. Genet. 51 (1992) 1218–1228.

[40] P.P. Pezzi, A.M. De Negri, F. Sadun, V. Carelli, V. Leuzzi, Childhood Leber's hereditary optic neuropathy (ND1/3460) with visual recovery, Pediatr. Neurol. 19 (1998) 308–312.

[41] A.A. Sadun, Y. Kashima, A.E. Wurdeman, J. Dao, K. Heller, J. Sherman, Morphological findings in the visual system in a case of Leber's hereditary optic neuropathy, Clin. Neurosci. 2 (1994) 165–172.

[42] A.A. Sadun, P.H. Win, F.N. Ross-Cisneros, S.O. Walker, V. Carelli, Leber's hereditary optic neuropathy differentially affects smaller axons in the optic nerve, Trans. Am. Ophthalmol. Soc. 98 (2000) 223–232.

[43] P. Barboni, G. Savini, M.L. Valentino, P. Montagna, P. Cortelli, A.M. De Negri, F. Sadun, S. Bianchi, L. Longanesi, M. Zanini, A. De Vivo, V. Carelli, Retinal nerve fiber layer evaluation by optical coherence tomography in Leber's hereditary optic neuropathy, Ophthalmology 112 (2005) 120–126.

[44] G. Savini, M. Zanini, V. Carelli, A.A. Sadun, F.N. Ross-Cisneros, P. Barboni, Correlation between retinal nerve fibre layer thickness and optic nerve head size: an optical coherence tomography study, Br. J. Ophthalmol. 89 (2005) 489–492.

[45] V. Carelli, A. Achilli, M.L. Valentino, C. Rengo, O. Semino, M. Pala, A. Olivieri, M. Mattiazzi, F. Pallotti, F. Carrara, M. Zeviani, V. Leuzzi, C. Carducci, G. Valle, B. Simionati, L. Mendieta, S. Salomao, R. Belfort Jr, A.A. Sadun, A. Torroni, Haplogroup effects and recombination of mitochondrial DNA: novel clues from the analysis of Leber hereditary optic neuropathy pedigrees, Am. J. Hum. Genet. 78 (2006) 564–574.

[46] G. Hudson, V. Carelli, L. Spruijt, M. Gerards, C. Mowbray, A. Achilli, A. Pyle, J. Elson, N. Howell, C. La Morgia, M.L. Valentino, K. Huoponen, M.L. Savontaus, E. Nikoskelainen, A.A. Sadun, S.R. Salomao, R. Belfort Jr, P. Griffiths, P.Y. Man, R.F. de Coo, R. Horvath, M. Zeviani, H.J. Smeets, A. Torroni, P.F. Chinnery, Clinical expression of Leber hereditary optic neuropathy is affected by the mitochondrial DNA-haplogroup background, Am. J. Hum. Genet. 81 (2007) 228–233.

[47] C. La Morgia, A. Achilli, L. Iommarini, P. Barboni, M. Pala, A. Olivieri, C. Zanna, S. Vidoni, C. Tonon, R. Lodi, R. Vetrugno, B. Mostacci, R. Liguori, R. Carroccia, P. Montagna, M. Rugolo, A. Torroni, V. Carelli, Rare mtDNA variants in Leber

hereditary optic neuropathy families with recurrence of myoclonus, Neurology 70 (2008) 762–770.
[48] V. Carelli, C. Giordano, G. d'Amati, Pathogenic expression of homoplasmic mtDNA mutations needs a complex nuclear–mitochondrial interaction, Trends Genet. 19 (2003) 257–262.
[49] X.D. Bu, J.I. Rotter, X chromosome-linked and mitochondrial gene control of Leber hereditary optic neuropathy: evidence from segregation analysis for dependence on X chromosome inactivation, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 8198–8202.
[50] G. Hudson, S. Keers, W.M.P. Yu, P. Griffiths, K. Huoponen, M.L. Savontaus, E. Nikoskelainen, M. Zeviani, F. Carrara, R. Horvath, V. Karcagi, L. Spruijt, I.F. de Coo, H.J. Smeets, P.F. Chinnery, Identification of an X-chromosomal locus and haplotype modulating the phenotype of a mitochondrial DNA disorder, Am. J. Hum. Genet. 77 (2005) 1086–1091.
[51] S.P. Shankar, J.H. Fingert, V. Carelli, M.L. Valentino, T.M. King, S.P. Daiger, S.R. Salomao, A. Berezovsky, R. Belfort Jr., T.A. Braun, V.C. Sheffield, A.A. Sadun, E.M. Stone, Evidence for a novel x-linked modifier locus for leber hereditary optic neuropathy, Ophthalmic Genet. 29 (2008) 17–24.
[52] G. Hudson, V. Carelli, R. Horvath, M. Zeviani, H.J. Smeets, P.F. Chinnery, X-Inactivation patterns in females harboring mtDNA mutations that cause Leber hereditary optic neuropathy, Mol. Vis. 13 (2007) 2339–2343.
[53] A.A. Sadun, V. Carelli, S.R. Salomao, A. Berezovsky, P.A. Quiros, F. Sadun, A.M. DeNegri, R. Andrade, M. Moraes, A. Passos, P. Kjaer, J. Pereira, M.L. Valentino, S. Schein, R. Belfort, Extensive investigation of a large Brazilian pedigree of 11778/haplogroup J Leber hereditary optic neuropathy, Am. J. Ophthalmol. 136 (2003) 231–238.
[54] V. Carelli, F. Franceschini, S. Venturi, P. Barboni, G. Savini, G. Barbieri, E. Pirro, C. La Morgia, M.L. Valentino, F. Zanardi, F.S. Violante, S. Mattioli, Grand rounds: could occupational exposure to n-hexane and other solvents precipitate visual failure in leber hereditary optic neuropathy? Environ. Health Perspect. 115 (2007) 113–115.
[55] A. Ghelli, C. Zanna, A.M. Porcelli, A.H. Schapira, A. Martinuzzi, V. Carelli, M. Rugolo, Leber's hereditary optic neuropathy (LHON) pathogenic mutations induce mitochondrial-dependent apoptotic death in transmitochondrial cells incubated with galactose medium, J. Biol. Chem. 278 (2003) 4145–4150.
[56] C. Zanna, A. Ghelli, A.M. Porcelli, A. Martinuzzi, V. Carelli, M. Rugolo, Caspase-independent death of Leber's hereditary optic neuropathy cybrids is driven by energetic failure and mediated by AIF and endonuclease G, Apoptosis 10 (2005) 997–1007.
[57] N.J. Newman, V. Biousse, R. David, M.T. Bhatti, S.R. Hamilton, B.K. Farris, R.L. Lesser, S.A. Newman, R.E. Turbin, K. Chen, R.P. Keaney, Prophylaxis for second eye involvement in Leber hereditary optic neuropathy: an open-labeled, nonrandomized multicenter trial of topical brimonidine purite, Am. J. Ophthalmol. 140 (2005) 407–415.
[58] C. Delettre, G. Lenaers, L. Pelloquin, P. Belenguer, C.P. Hamel, OPA1 (Kjer type) dominant optic atrophy: a novel mitochondrial disease, Mol. Genet. Metab. 75 (2002) 97–107.
[59] A.C. Cohn, C. Toomes, A.W. Hewitt, L.S. Kearns, C.F. Inglehearn, J.E. Craig, D.A. Mackey, The natural history of OPA1-related autosomal dominant optic atrophy, Br. J. Ophthalmol. 92 (2008) 1333–1336.
[60] M. Votruba, D. Thiselton, S.S. Bhattacharya, Optic disc morphology of patients with OPA1 autosomal dominant optic atrophy, Br. J. Ophthalmol. 87 (2003) 48–53.
[61] A.C. Cohn, C. Toomes, C. Potter, K.V. Towns, A.W. Hewitt, C.F. Inglehearn, J.E. Craig, D.A. Mackey, Autosomal dominant optic atrophy: penetrance and expressivity in patients with OPA1 mutations, Am. J. Ophthalmol. 143 (2007) 656–662.
[62] P. Kjer, O.A. Jensen, L. Klinken, Histopathology of eye, optic nerve and brain in a case of dominant optic atrophy, Acta Ophthalmol. (Copenh) 61 (1983) 300–312.
[63] P.B. Johnston, R.N. Gaster, V.C. Smith, R.C. Tripathi, A clinicopathologic study of autosomal dominant optic atrophy, Am. J. Ophthalmol. 88 (1979) 868–875.
[64] J.B. Kerrison, V.J. Arnould, J.M. Ferraz Sallum, M.R. Vagefi, M.M. Barmada, Y. Li, D. Zhu, I.H. Maumenee, Genetic heterogeneity of dominant optic atrophy, Kjer type: identification of a second locus on chromosome 18q12.2–12.3, Arch. Ophthalmol. 117 (1999) 805–810.
[65] F. Barbet, S. Hakiki, C. Orssaud, S. Gerber, I. Perrault, S. Hanein, D. Ducroq, J.L. Dufier, A. Munnich, J. Kaplan, J.M. Rozet, A third locus for dominant optic atrophy on chromosome 22q, J. Med. Genet. 42 (2005) e1.
[66] M. Ferre, P. Amati-Bonneau, Y. Tourmen, Y. Malthiery, P. Reynier, eOPA1: an online database for OPA1 mutations, Hum. Mutat. 25 (2005) 423–428.
[67] G.J.K. Praefcke, H.T. McMahon, The dynamin superfamily: universal membrane tubulation and fission molecules? Nat. Rev. 5 (2004) 133–147.
[68] S. Hoppins, L. Lackner, J. Nunnari, The machine that divide and fuse mitochondria, Ann. Rev. Biochem. 76 (2007) 751–780.
[69] A. Olichon, E. Guillou, C. Delettre, T. Landes, L. Arnauné-Pelloquin, L.J. Emorine, V. Mils, M. Daloyau, C. Hamel, P. Amati-Bonneau, D. Bonneau, P. Reynier, G. Lenaers, P. Belenguer, Mitochondrial dynamics and disease, OPA1, Biochim. Biophys. Acta 1763 (2006) 500–509.
[70] A. Olichon, L. Baricault, N. Gas, E. Guillou, A. Valette, P. Belenguer, G. Lenaers, Loss of OPA1 perturbates the mitochondrial inner membrane structure and integrity, leading to cytochrome *c* release and apoptosis, J. Biol. Chem. 278 (2003) 7743–7746.
[71] C. Frezza, S. Cipolat, O. Martins de Brito, M. Micaroni, G.V. Beznoussenko, T. Rudka, D. Bartoli, R.S. Polishuck, N.N. Danial, B. De Strooper, L. Scorrano, OPA1 controls apoptotic cristae remodeling independently from mitochondrial fusion, Cell 126 (2006) 177–189.
[72] R. Lodi, C. Tonon, M.L. Valentino, S. Iotti, V. Clementi, E. Malucelli, P. Barboni, L. Longanesi, S. Schimpf, B. Wissinger, A. Baruzzi, B. Barbiroli, V. Carelli, Deficit of in vivo mitochondrial ATP production in OPA1-related dominant optic atrophy, Ann. Neurol. 56 (2004) 719–723.
[73] C. Zanna, A. Ghelli, A.M. Porcelli, M. Karbowski, R.J. Youle, S. Schimpf, B. Wissinger, M. Pinti, A. Cossarizza, S. Vidoni, M.L. Valentino, M. Rugolo, V. Carelli, OPA1 mutations associated with dominant optic atrophy impair oxidative phosphorylation and mitochondrial fusion, Brain 131 (2008) 352–367.
[74] A. Chevrollier, V. Guillet, D. Loiseau, N. Gueguen, M.A. de Crescenzo, C. Verny, M. Ferre, H. Dollfus, S. Odent, D. Milea, C. Goizet, P. Amati-Bonneau, V. Procaccio, D. Bonneau, P. Reynier, Hereditary optic neuropathies share a common mitochondrial coupling defect, Ann. Neurol. 63 (2008) 794–798.
[75] P.F. Chinnery, N. Howell, R.N. Lightowlers, D.M. Turnbull, Molecular pathology of MELAS and MERRF. The relationship between mutation load and clinical phenotypes, Brain 120 (1997) 1713–1721.
[76] J.M. Hwang, H.W. Park, S.J. Kim, Optic neuropathy associated with mitochondrial $tRNA^{[Leu(UUR)]\ A3243G}$ mutation, Ophthalmic Genet. 18 (1997) 101–105.
[77] J.B. Cavanagh, B.N. Harding, Pathogenic factors underlying the lesions in Leigh's disease. Tissue responses to cellular energy deprivation and their clinico-pathological consequences, Brain 117 (1994) 1357–1376.
[78] S. DiMauro, E.A. Schon, Mitochondrial disorders in the nervous system, Annu. Rev. Neurosci. 31 (2008) 91–123.
[79] A.S. Jun, M.D. Brown, D.C. Wallace, A mitochondrial DNA mutation at nucleotide pair 14459 of the NADH dehydrogenase subunit 6 gene associated with maternally inherited Leber hereditary optic neuropathy and dystonia, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 6206–6210.
[80] D.M. Kirby, S.G. Kahler, M.-L. Freckmann, D. Reddihough, D.R. Thorburn, Leigh disease caused by the mitochondrial DNA G14459A mutation in unrelated families, Ann. Neurol. 48 (2000) 102–104.
[81] F.M. Santorelli, K. Tanji, R. Kulikova, S. Shanske, L. Vilarinho, A.P. Hays, S. DiMauro, Identification of a novel mutation in the mtDNA ND5 gene associated with MELAS, Biochem. Biophys. Res. Commun. 238 (1997) 326–328.
[82] P. Corona, C. Antozzi, F. Carrara, L. D'Incerti, E. Lamantea, V. Tiranti, M. Zeviani, A novel mtDNA mutation in the ND5 subunit of complex I in two MELAS patients, Ann. Neurol. 49 (2001) 106–110.
[83] B. Funalot, P. Reynier, A. Vighetto, D. Ranoux, J.P. Bonnefont, C. Godinot, Y. Malthiery, J.L. Mas, Leigh-like encephalopathy complicating Leber's hereditary optic neuropathy, Ann. Neurol. 52 (2002) 374–377.
[84] E.K. Nikoskelainen, Clinical picture of LHON, Clin. Neurosci. 2 (1994) 115–120.
[85] R. Sakuta, I. Nonaka, Vascular involvement in mitochondrial myopathy, Ann. Neurol. 25 (1989) 594–601.
[86] H. Hasegawa, T. Matsuoka, Y. Goto, I. Nonaka, Strongly succinate dehydrogenase reactive blood vessels in muscles from patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Ann. Neurol. 29 (1991) 601–605.
[87] M. Pandolfo, Friedreich ataxia, Arch. Neurol. 65 (2008) 1296–1303.
[88] V. Campuzano, L. Montermini, M.D. Moltò, L. Pianese, M. Cossée, F. Cavalcanti, E. Monros, F. Rodius, F. Duclos, A. Monticelli, F. Zara, J. Cañizares, H. Koutnikova, S.I. Bidichandani, C. Gellera, A. Brice, P. Trouillas, G. De Michele, A. Filla, R. De Frutos, F. Palau, P.I. Patel, S. Di Donato, J.L. Mandel, S. Cocozza, M. Koenig, M. Pandolfo, Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion, Science 271 (1996) 1423–1427.
[89] M. Cossée, A. Dürr, M. Schmitt, N. Dahl, P. Trouillas, P. Allinson, M. Kostrzewa, A. Nivelon Chevallier, K.H. Gustavson, A. Kohlschütter, U. Müller, J.L. Mandel, A. Brice, M. Koenig, F. Cavalcanti, A. Tammaro, G. De Michele, A. Filla, S. Cocozza, M. Labuda, L. Montermini, J. Poirier, M. Pandolfo, Friedreich's ataxia: point mutations and clinical presentation of compound Heterozygotes, Ann. Neurol. 45 (1999) 200–206.
[90] A. Rötig, P. de Lonlay, D. Chretien, F. Foury, M. Koenig, D. Sidi, A. Munnich, P. Rustin, Aconitase and mitochondrial iron–sulphur protein deficiency in Friedreich ataxia, Nat. Genet. 17 (1997) 215–217.
[91] R. Lodi, J.M. Cooper, J.L. Bradley, D. Manners, P. Styles, D.J. Taylor, A.H. Schapira, Deficit of in vivo mitochondrial ATP production in patients with Friedreich ataxia, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 11492–11495.
[92] W.M. Carroll, A. Kriss, M. Baraitser, G. Barrett, A.M. Halliday, The incidence and nature of visual pathway involvement in Friedreich's ataxia, a clinical and visual evoked potential study of 22 patients, Brain 103 (1980) 413–434.
[93] S.J. Givre, M. Wall, R.H. Kardon, Visual loss and recovery in a patient with Friedreich ataxia, J. Neuro-Ophthalmol. 20 (2000) 229–233.
[94] N. Porter, S.M. Downes, C. Fratter, P. Anslow, A.H. Nemeth, Catastrophic visual loss in a patient with Friedreich ataxia, Arch. Ophthalmol. 125 (2007) 273–274.
[95] J. Mohr, K. Mageroy, Sex-linked deafness of a possibly new type, Acta Genet. Stat. Med. 10 (1960) 54–62.
[96] L. Tranebjaerg, C. Schwartz, H. Eriksen, S. Andreasson, V. Ponjavic, A. Dahl, R.E. Stevenson, M. May, F. Arena, D. Barker, et al., A new X linked recessive deafness syndrome with blindness, dystonia, fractures and mental deficiency is linked to Xq22, J. Med. Genet. 32 (1995) 257–263.
[97] H. Jin, M. May, L. Tranebjaerg, E. Kendall, G. Fontán, J. Jackson, S.H. Subramony, F. Arena, H. Lubs, S. Smith, R. Stevenson, C. Schwartz, D. Vetrie, A novel X-linked gene, DDP, shows mutations in families with deafness (DFN-1), dystonia, mental deficiency and blindness, Nat. Genet. 14 (1996) 177–180.
[98] C.M. Koehler, D. Leuenberger, S. Merchant, A. Renold, T. Junne, G. Schatz, Human deafness dystonia syndrome is a mitochondrial disease, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 2141–2146.
[99] W. Neupert, J.M. Herrmann, Translocation of proteins into mitochondria, Annu. Rev. Biochem. 76 (2007) 723–749.

[100] A. Pizzuti, G. Fabbrini, L. Salehi, L. Vacca, M. Inghilleri, B. Dallapiccola, A. Berardelli, Focal dystonia caused by Mohr–Tranebjaerg syndrome with complete deletion of the DDP1 gene, Neurology 62 (2004) 1021–1022.
[101] K. Roesch, S.P. Curran, L. Tranebjaerg, C.M. Koehler, Human deafness dystonia syndrome is caused by a defect in assembly of the DDP1/TIMM8a–TIMM13 complex, Hum. Mol. Genet. 11 (2002) 477–486.
[102] R.H. Swerdlow, G.F. Wooten, A novel deafness/dystonia peptide gene mutation that causes dystonia in female carriers of Mohr–Tranebjaerg syndrome, Ann. Neurol. 50 (2001) 537–540.
[103] J. Binder, S. Hofmann, S. Kreisel, J.C. Wöhrle, H. Bäzner, J.K. Krauss, M.G. Hennerici, M.F. Bauer, Clinical and molecular findings in a patient with a novel mutation in the deafness dystonia peptide (DDP1) gene, Brain 126 (2003) 1814–1820.
[104] V. Ponjavic, S. Andreasson, L. Tranebjaerg, H.A. Lubs, Full-field electroretinograms in a family with Mohr–Tranebjaerg syndrome, Acta Ophthalmol. Scand. 74 (1996) 632–635.
[105] G. Stevanin, M. Ruberg, A. Brice, Recent advances in the genetics of spastic paraplegias, Curr. Neurol. Neurosci. Rep. 8 (2008) 198–210.
[106] S. Salinas, C. Proukakis, A. Crosby, T.T. Warner, Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms, Lancet Neurol. 7 (2008) 1127–1138.
[107] J. Makhoul, M. Cordonnier, C. Van Nechel, Optic neuropathy in Strumpell–Lorrain disease: presentation of a clinical case and literature review, Bull. Soc. Belge. Ophtalmol. 286 (2002) 9–14.
[108] J.J. Hansen, A. Dürr, I. Cournu-Rebeix, C. Georgopoulos, D. Ang, M.N. Nielsen, C.S. Davoine, A. Brice, B. Fontaine, N. Gregersen, P. Bross, Hereditary spastic paraplegia SPG13 is associated with a mutation in the gene encoding the mitochondrial chaperonin Hsp60, Am. J. Hum. Genet. 70 (2002) 1328–1332.
[109] S. Züchner, G. Wang, K.N. Tran-Viet, M.A. Nance, P.C. Gaskell, J.M. Vance, A.E. Ashley-Koch, M.A. Pericak-Vance, Mutations in the novel mitochondrial protein REEP1 cause hereditary spastic paraplegia type 31, Am. J. Hum. Genet. 79 (2006) 365–369.
[110] L. Atorino, L. Silvestri, M. Koppen, L. Cassina, A. Ballabio, R. Marconi, T. Langer, G. Casari, Loss of m-AAA protease in mitochondria causes complex I deficiency and increased sensitivity to oxidative stress in hereditary spastic paraplegia, J. Cell. Biol. 163 (2003) 777–787.
[111] F. Ferreirinha, A. Quattrini, M. Pirozzi, V. Valsecchi, G. Dina, V. Broccoli, A. Auricchio, F. Piemonte, G. Tozzi, L. Gaeta, G. Casari, A. Ballabio, E.I. Rugarli, Axonal degeneration in paraplegin-deficient mice is associated with abnormal mitochondria and impairment of axonal transport, J. Clin. Invest. 113 (2004) 231–242.
[112] E.I. Rugarli, T. Langer, Translating m-AAA protease function in mitochondria to hereditary spastic paraplegia, Trends Mol. Med. 12 (2006) 262–269.
[113] N. Ishihara, Y. Fujita, T. Oka, K. Mihara, Regulation of mitochondrial morphology through proteolytic cleavage of OPA1, EMBO J. 25 (2006) 2966–2977.
[114] S. Duvezin-Caubet, M. Koppen, J. Wagener, M. Zick, L. Israel, A. Bernacchia, R. Jagasia, E.I. Rugarli, A. Imhof, W. Neupert, T. Langer, A.S. Reichert, OPA1 processing reconstituted in yeast depends on the subunit composition of the m-AAA protease in mitochondria, Mol. Biol. Cell. 18 (2007) 3582–3590.
[115] O. Guillery, F. Malka, T. Landes, E. Guillou, C. Blackstone, A. Lombès, P. Belenguer, D. Arnoult, M. Rojo, Metalloprotease-mediated OPA1 processing is modulated by the mitochondrial membrane potential, Biol. Cell. 100 (2008) 315–325.
[116] H.R. Waterham, J. Koster, C.W. van Roermund, P.A. Mooyer, R.J. Wanders, J.V. Leonard, A lethal defect of mitochondrial and peroxisomal fission, N. Engl. J. Med. 356 (2007) 1736–1741.
[117] G. Van Goethem, B. Dermaut, A. Lofgren, J.J. Martin, C. Van Broeckhoven, Mutation of POLG is associated with progressive external ophthalmoplegia characterized by mtDNA Deletions, Nat. Genet. 28 (2001) 211–212.
[118] M.J. Longley, S. Clark, C. Yu Wai Man, G. Hudson, S.E. Durham, R.W. Taylor, S. Nightingale, D.M. Turnbull, W.C. Copeland, P.F. Chinnery, Mutant POLG2 disrupts DNA polymerase gamma subunits and causes progressive external ophthalmoplegia, Am. J. Hum. Genet. 78 (2006) 1026–1034.
[119] J.N. Spelbrink, F.Y. Li, V. Tiranti, K. Nikali, Q.P. Yuan, M. Tariq, S. Wanrooij, N. Garrido, G. Comi, L. Morandi, L. Santoro, A. Toscano, G.M. Fabrizi, H. Somer, R. Croxen, D. Beeson, J. Poulton, A. Suomalainen, H.T. Jacobs, M. Zeviani, C. Larsson, Human mitochondrial DNA deletions associated with mutations in the gene encoding Twinkle, a phage T7 gene 4-like protein localized in mitochondria, Nat. Genet. 28 (2001) 223–231.
[120] J. Kaukonen, J.K. Juselius, V. Tiranti, A. Kyttälä, M. Zeviani, G.P. Comi, S. Keränen, L. Peltonen, A. Suomalainen, Role of adenine nucleotide translocator 1 in mtDNA maintenance, Science 289 (2000) 782–785.
[121] I. Nishino, A. Spinazzola, M. Hirano, Thymidine phosphorylase gene mutations in MNGIE, a human mitochondrial disorder, Science 283 (1999) 689–692.
[122] G. Hudson, P.F. Chinnery, Mitochondrial DNA polymerase-gamma and human disease, Hum. Mol. Genet. 15 (Spec No 2) (2006) R244–R252.
[123] M. Hirano, C. Lagier-Tourenne, M.L. Valentino, R. Martí, Y. Nishigaki, Thymidine phosphorylase mutations cause instability of mitochondrial DNA, Gene 354 (2005) 152–156.
[124] R.L. Treft, G.E. Sanborn, J. Carey, M. Swartz, D. Crisp, D.C. Wester, D. Creel, Dominant optic atrophy, deafness, ptosis, ophthalmoplegia, dystaxia, and myopathy. A new syndrome, Ophthalmology 91 (1984) 908–915.
[125] F. Meire, J.J. De Laey, S. de Bie, M. van Staey, M.T. Matton, Dominant optic nerve atrophy with progressive hearing loss and chronic progressive external ophthalmoplegia (CPEO), Ophthalmic. Paediatr. Genet. 5 (1985) 91–97.
[126] M. Payne, Z. Yang, B.J. Katz, J.E. Warner, C.J. Weight, Y. Zhao, E.D. Pearson, R.L. Treft, T. Hillman, R.J. Kennedy, F.M. Meire, K. Zhang, Dominant optic atrophy, sensorineural hearing loss, ptosis, and ophthalmoplegia: a syndrome caused by a missense mutation in OPA1, Am. J. Ophthalmol. 138 (2004) 749–755.
[127] M. Zeviani, OPA1 mutations and mitochondrial DNA damage: keeping the magic circle in shape, Brain 131 (2008) 314–317.
[128] J.D. Stewart, G. Hudson, P. Yu-Wai-Man, E.L. Blakeley, L. He, R. Horvath, P. Maddison, A. Wright, P.G. Griffiths, D.M. Turnbull, R.W. Taylor, P.F. Chinnery, OPA1 in multiple mitochondrial DNA deletion disorders, Neurology 71 (2008) 1829–1831.
[129] T. Harrower, J.D. Stewart, G. Hudson, H. Houlden, G. Warner, D.G. O'Donovan, L.J. Findlay, R.W. Taylor, R. De Silva, P.F. Chinnery, POLG1 mutations manifesting as autosomal recessive axonal Charcot–Marie–Tooth disease, Arch. Neurol. 65 (2008) 133–136.
[130] D. Loiseau, A. Chevrollier, C. Verny, V. Guillet, N. Gueguen, M.A. Pou de Crescenzo, M. Ferré, M.C. Malinge, A. Guichet, G. Nicolas, P. Amati-Bonneau, Y. Malthièry, D. Bonneau, P. Reynier, Mitochondrial coupling defect in Charcot–Marie–Tooth type 2A disease, Ann. Neurol. 61 (2007) 315–323.
[131] E.A. Amiott, P. Lott, J. Soto, P.B. Kang, J.M. McCaffery, S. DiMauro, E.D. Abel, K.M. Flanigan, V.H. Lawson, J.M. Shaw, Mitochondrial fusion and function in Charcot–Marie–Tooth type 2A patient fibroblasts with mitofusin 2 mutations, Exp. Neurol. 211 (2008) 115–127.
[132] R.H. Baloh, R.E. Schmidt, A. Pestronk, J. Milbrandt, Altered axonal mitochondrial transport in the pathogenesis of Charcot–Marie–Tooth disease from mitofusin 2 mutations, J. Neurosci. 27 (2007) 422–430.
[133] R. Kleta, F. Skovby, E. Christensen, T. Rosenberg, W.A. Gahl, Y. Anikster, 3-Methylglutaconic aciduria type III in a non-Iraqi-Jewish kindred: clinical and molecular findings, Mol. Genet. Metab. 76 (2002) 201–206.
[134] V.J. Davies, K.A. Powell, K.E. White, W. Yip, V. Hogan, A.J. Hollins, J.R. Davies, M. Piechota, D.G. Brownstein, S.J. Moat, P.P. Nichols, M.A. Wride, M.E. Boulton, M. Votruba, A missense mutation in the murine Opa3 gene models human Costeff syndrome, Brain 131 (2008) 368–380.
[135] M.A. Birch-Machin, R.W. Taylor, B. Cochran, B.A. Ackrell, D.M. Turnbull, Late-onset optic atrophy, ataxia, and myopathy associated with a mutation of a complex II gene, Ann. Neurol. 48 (2000) 330–335.
[136] C. Bruno, A. Martinuzzi, Y. Tang, A.L. Andreu, F. Pallotti, E. Bonilla, S. Shanske, J. Fu, C.M. Sue, C. Angelini, S. DiMauro, G. Manfredi, A stop-codon mutation in the human mtDNA cytochrome *c* oxidase I gene disrupts the functional structure of complex IV, Am. J. Hum. Genet. 65 (1999) 611–620.
[137] A.M. Porcelli, A. Angelin, A. Ghelli, E. Mariani, A. Martinuzzi, V. Carelli, V. Petronilli, P. Bernardi, M. Rugolo, Respiratory complex I dysfunction due to mitochondrial DNA mutations shifts the voltage threshold for opening of the permeability transition pore toward resting levels, J. Biol. Chem. 284 (2009) 2045–2052.
[138] D.F. Suen, K.L. Norris, R.J. Youle, Mitochondrial dynamics and apoptosis, Genes Dev. 22 (2008) 1577–1590.
[139] M.Y. Yen, C.S. Chen, A.G. Wang, Y.H. Wei, Increase of mitochondrial DNA in blood cells of patients with Leber's hereditary optic neuropathy with 11778 mutation, Br. J. Ophthalmol. 86 (2002) 1027–1030.
[140] J.Y. Kim, J.M. Hwang, H.S. Ko, M.W. Seong, B.J. Park, S.S. Park, Mitochondrial DNA content is decreased in autosomal dominant optic atrophy, Neurology 64 (2005) 966–972.
[141] H. Chen, D.C. Chan, Critical dependence of neurons on mitochondrial dynamics, Curr. Opin. Cell. Biol. 18 (2006) 453–459.
[142] Z. Li, K. Okamoto, Y. Hayashi, M. Sheng, The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses, Cell 119 (2004) 873–887.
[143] T. Wenz, F. Diaz, B.M. Spiegelman, C.T. Moraes. Activation of the PPAR/PGC-1alpha pathway prevents a bioenergetic deficit and effectively improves a mitochondrial myopathy phenotype, Cell. Metab. 8 (2008) 249–256.