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# Mitochondria, oxidative stress and neurodegeneration

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ABSTRACT

Mitochondria are involved in ATP supply to cells through oxidative phosphorylation (OXPHOS), synthesis of key molecules and response to oxidative stress, as well as in apoptosis. They contain many redox enzymes and naturally occurring inefficiencies of oxidative phosphorylation generate reactive oxygen species (ROS). CNS functions depend heavily on efficient mitochondrial function, since brain tissue has a high energy demand. Mutations in mitochondrial DNA (mtDNA), generation and presence of ROS and environmental factors may contribute to energy failure and lead to neurodegenerative diseases. Many rare metabolic disorders have been associated with mitochondrial dysfunction. More than 300 pathogenic mtDNA mutations involve proteins that regulate OXPHOS and mitochondrial structural integrity, and have also been described in neurodegenerative diseases with autosomal inheritance. Mitochondria may have an important role in ageing-related neurodegenerative disorders like Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). In primary mitochondrial and neurodegenerative disorders, there is strong evidence that mitochondrial dysfunction occurs early and has a primary role in pathogenesis. In the present review, we discuss several mitochondrial diseases as models of neurodegeneration.


## 1. Introduction

ATP production by mitochondria is essential for cell function, signalling pathways and overall cell activities. Mitochondria are involved in ATP supply to cells through oxidative phosphorylation (OXPHOS), synthesis of key molecules and response to oxidative stress (Fig. 1). They are also involved in apoptosis and in dynamic movements required for correct respiratory activity and metabolic efficiency through fusion/fission [1]. Mitochondria contain many redox enzymes and naturally occurring inefficiencies of oxidative phosphorylation generate reactive oxygen species (ROS).

CNS functions strongly depend on efficient mitochondrial function, because brain tissue has a high energy demand. Mutations in the mitochondrial genome, defects in mitochondrial dynamics, generation and presence of ROS, protein aggregate-associated dysfunctions and environmental factors may alter energy metabolism and in many cases are associated with neurodegenerative diseases (Fig. 2) [2].

## 2. Primary mitochondrial disorders and neurodegeneration

Human mitochondrial DNA (mtDNA) is well known as a circular, double-stranded molecule of 16569 base pairs. It contains 37 genes, including 13 protein-encoding genes, 22 transfer RNA genes and two ribosomal RNA genes. All 13 protein-encoding genes are components of the mitochondrial respiratory chain, which is located in the inner membrane [2].

By the 1980s, many rare metabolic disorders with mitochondrial dysfunctions had been recognized [3]. Since then more than 300 pathogenic mtDNA mutations have been associated with diseases [4]. Mitochondrial dysfunctions have also been described in neurodegenerative diseases with non-maternal inheritance, involving a number of other proteins, which regulate OXPHOS and mitochondrial dynamics, implicated in maintaining mitochondrial structural integrity [5].

Whatever the mechanism, the final common feature of mitochondrial disorders is impaired respiratory chain activity or failure of mitochondrial function, resulting in a wide range of clinical presentations (Table 1). Table 2 shows the genetic classification of neurodegenerative mitochondrial diseases: mutations in mtDNA may be sporadic or maternally transmitted, whereas nuclear gene mutations have Mendelian inheritance. In the present review, we discuss some mitochondrial diseases as models of neurodegeneration (Table 3).

## 3. Mitochondrial diseases as models of neurodegeneration

Leber's hereditary optic neuropathy (LHON, MIM #535000), the most common cause of maternally inherited blindness, highlights the link between energy production, oxidative stress and neurodegeneration. It is related to mutations in subunits of NADH-dehydrogenase in mtDNA and their impact on mitochondrial OXPHOS has been extensively investigated [17]. Eye pathology in LHON is limited to retinal ganglion cells

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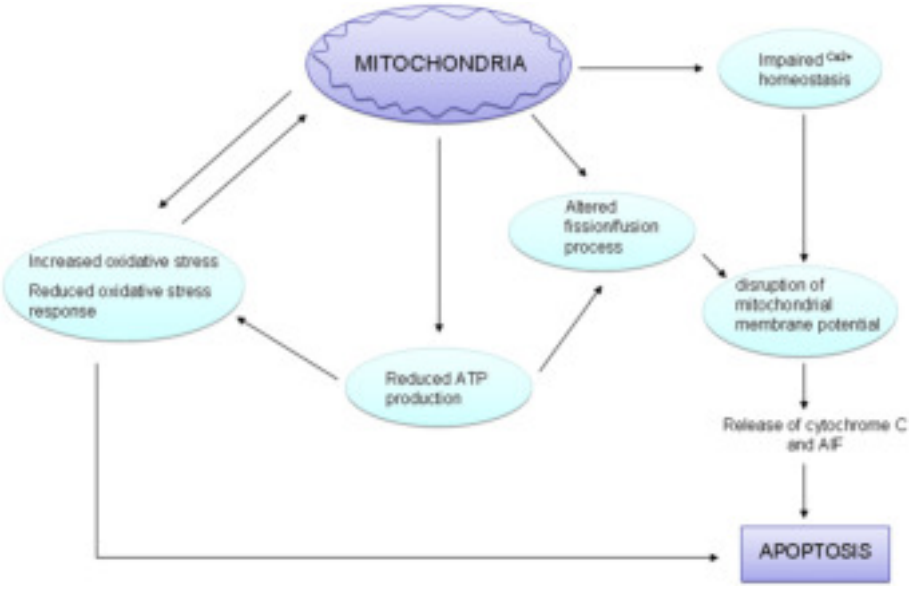


**Fig. 1.** Main interaction between mitochondria, oxidative stress and apoptosis.

(RGCs), sparing the retinal pigmented epithelium and photoreceptor layer. Pronounced atrophy of cell bodies and axons is associated with demyelination and degeneration from the optic nerve to the lateral geniculate body. Impaired activity of the EAAT1 glutamate transporter and increased mitochondrial reactive oxygen species (ROS) production trigger RCG death by apoptosis [18–20]. Calcium deregulation is another important factor involved in LHON pathogenesis: complex I mutations may shift the voltage threshold for permeability transition pore opening towards resting level, due to $Ca^{2+}$ deregulation and enhanced ROS generation. Impaired axonal distribution of mitochondria in RCG is also thought to contribute to local energy deprivation at sites where most ATP is needed [21]. In fact, it is presumed that this anatomic selectivity is partly a consequence of the high metabolic demand of target tissues, although the mitochondrial defect is not limited to neurons or the nervous system. In addition, incomplete penetrance and male predominance suggest that other genetic and environmental factors contribute to signs and symptoms. Smoking and other environmental factors (including hormones, head trauma, occupational exposure, chemical toxins, drugs or pharmacological substances) are known to trigger LHON, supporting the notion that excess ROS production may be an important pathogenetic factor [22–25].

Autosomal dominant optic atrophy (ADOA, MIM #165500) is a form of slowly progressive optic neuropathy, usually with onset in the first decade of life. ADOA has mainly been linked to the OPA1 gene, which encodes a mitochondrial dynamin-related GTP protein that plays a role in mitochondrial fusion, crista building, apoptosis and mtDNA maintenance [13]. The pathogenic mechanism of ADOA is not completely understood, but several studies suggest similarities with LHON (Fig. 3). Fibroblasts of ADOA patients carrying OPA1 mutations have shown defects in mitochondrial OXPHOS, mitochondrial membrane potential reduction and mitochondrial DNA instability (mainly in *ADOA plus* patients) [11,26]. Increased sensitivity to apoptotic signals and altered mitochondrial network, probably a primary consequence of loss of pro-fusion activity of OPA1, have also been reported [27]. The selective degeneration of RGCsin ADOA patients is directly correlated with their sensitivity to cell death. Mitochondrial dysfunction and reduced expression of OPA1 promote degeneration of these cells.

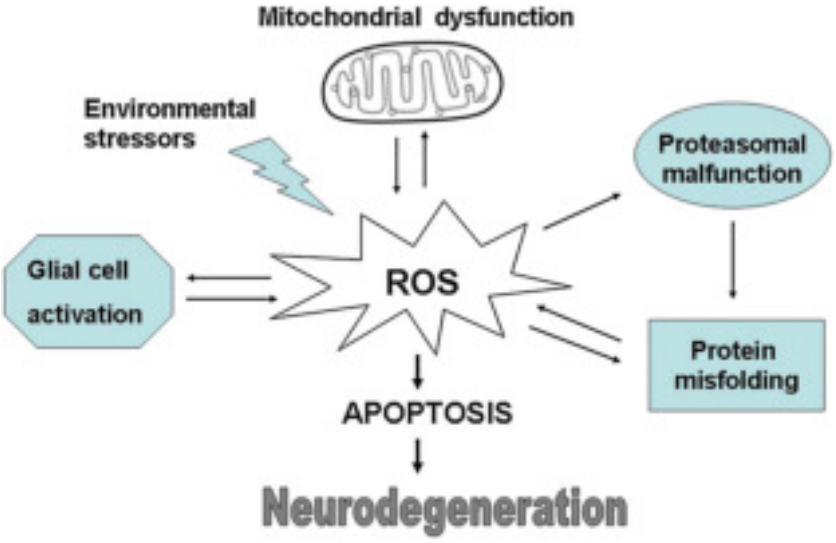


**Fig. 2.** Different pathogenetic mechanisms leading to neurodegeneration.

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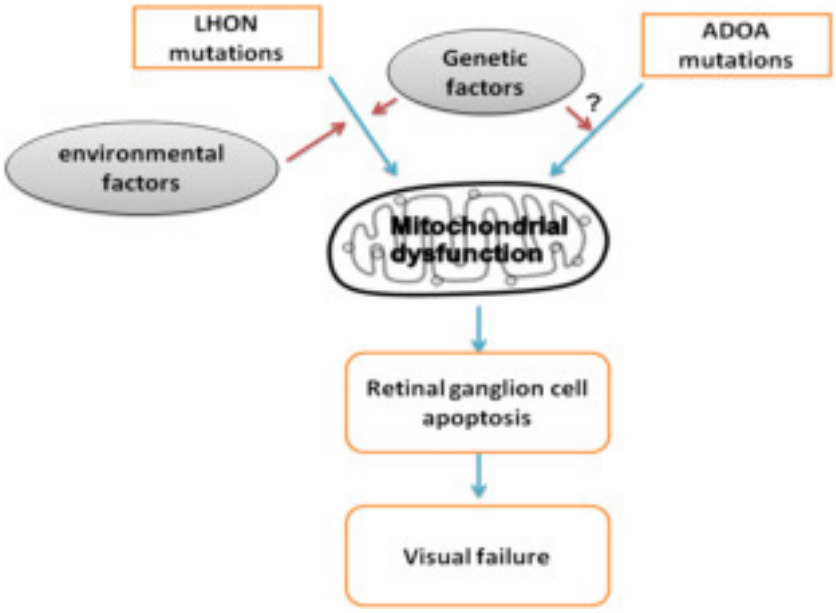


**Fig. 3.** Mitochondrial dysfunction in LHON and ADOA.

Charcot-Marie-Tooth hereditary neuropathy type 2A (CMT2A, MIM#609260) is an early onset peripheral neuropathy inherited in an autosomal dominant manner. Mutations in the CMT2A locus have been linked to mitofusin 2 (MFN2) genes [28] encoding an outer mitochondrial membrane protein that has an important role in regulating fusion of mitochondria, in cooperation with MFN1 and OPA1 [13]. MFN2 may exert a direct influence on mitochondrial biogenesis by regulating the expression of nuclear-encoded respiratory chain subunits [29]. MFN2 may also be involved in axonal transport of mitochondria by interaction with miro (Miro1/Miro2) and milton (OIP106/GRIF1) proteins, which link mitochondria to kinesin motors [30]. Neuropathological studies of CMT2 patients show degeneration of long peripheral axons and many small axonal mitochondria [31]. In cultured fibroblasts, Rouzier et al. [32] showed mitochondrial fusion deficiency and fragmented mitochondria, leading to respiratory chain and mitochondrial DNA repair defects. In line with this hypothesis, fibroblasts from CMT2A patients show a mitochondrial coupling defect, with impaired membrane potential and reduced OXPHOS capacity [33]. Brain mitochondrial dysfunction similar to that of primary mitochondrial disorders was recently demonstrated in an Italian family with a new MFN2 gene mutation [15].

Myoclonic epilepsy and ragged-red fibres (MERRF, MIM #545000) is usually related to an A to G transition at nucleotide 8344 in the *MT-TK* gene of mtDNA. Patients with this mutation often show degenerative features in the olivocerebellar pathway, with severe neuronal loss involving inferior olivary complex, Purkinje cells and dentate nucleus. Oversized mitochondria showing inclusions have been described in surviving neurons of the cerebellum [34]. Several biochemical studies show that the 8344 mutation hampers effective synthesis of mitochondrial proteins, leading to electron transport chain malfunction. This impaired activity decreases mitochondrial membrane potential and oxidative production of ATP and modifies calcium homeostasis and ROS production, evolving to increased apoptosis [35]. Wu et al. [36] found functional alterations of antioxidant enzymes in MERRF skin fibroblasts, suggesting that mtDNA mutation-elicited oxidative stress, oxidative damage, and altered gene expression are involved in the pathogenesis and progression of the syndrome.

**Table 1**
Typical symptoms and signs encountered in mitochondrial disorders.

| |
|---|
| Peripheral nervous system: myopathy, polineuropathy |
| Central nervous system: ataxia, retinal degeneration, mental retardation or deterioration, seizures, epilepsy, myoclonus, migraine, stroke-like episodes, dystonia, weakness, dyskinesia, cerebellar signs, psychosis |
| Sensoryneural deafness |
| Muscle: weakness, hypotonia, external ophtalmoplegia, exercise intolerance, wasting, fatigue, cramps, myotonia, stiffness, lactic acidosis |
| Heart: heart block, hypertrophic cardiomyopathy, myocardial thickening |
| Ear: Hypoacusia, peripheral vertigo |
| Eye: optic atrophy, retinopathy, glaucoma, cataract |
| Bowel: dysphagia, vomiting, diarrhoea, anorexia, malabsorption, intestinal pseudo-obstruction |
| Liver: hepatic failure, transaminase increase |
| Endocrine glands: infertility, delayed puberty, diabetes, thyroid dysfunction, hypogonadism, short stature, hypoglycaemia, osteoporosis, amenorrhoea |
| Kidney: renal tubulopathy, renal cysts |
| Bone marrow: sideroblastic anaemia |

### 3.1. Mitochondrial ataxias

Cerebellar or sensory ataxia is a frequent clinical feature of mitochondrial disorders. Purkinje and other cerebellar cells may be selectively vulnerable to mitochondrial respiratory chain dysfunction correlated with varying degrees of cell loss [37]. Many mtDNA mutations cause ataxia [4]. The most frequent and best clinically and genetically characterized are Kearns–Sayre syndrome (KSS), Mitochondrial Encephalopathy, Lactic acidosis and Stroke-like episodes (MELAS), MERRF and Neuropathy, Ataxia and Retinitis pigmentosa (NARP) [38]. Nuclear genes causing mitochondrial ataxia have attracted recent

**Table 2**
Genetic classification of neurodegenerative mitochondriopathies.

| |
|---|
| 1) Disorders due to mutations in mtDNA genes encoding for respiratory chain proteins, tRNAs or rRNAs (LHON, MELAS, MERRF, NARP, Leigh syndrome, KSS) |
| 2) Disorders due to mutations in nDNA genes encoding for: |
| • respiratory chain proteins (Leigh syndrome, leukodystrophy, paraganglioma, GRACILE syndrome, leukodystrophy and tubulopathy) |
| • proteins implicated in mitochondrial metabolism (Leigh syndrome, Alpers syndrome, infant encephalopathy, MNGIE, SANDO, Wolfram syndrome) |
| • proteins implicated in mitochondrial dynamics (ADOA, CMT type 2A, 4A, and 6) |
| • proteins correlated to mitochondrial functions (AD, PD, HD, ALS, Friedreich ataxia, Hereditary spastic paraplegia) |

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**Table 3**
Mitochondrial diseases as a model of neurodegeneration: gene, protein and disease. Inheritance: AD, autosomal dominant; S, sporadic; M, maternal.

| Disease | Gene affected | Inheritance | Protein | Function | Phenotype | Onset | Prevalence | References |
|---|---|---|---|---|---|---|---|---|
| Leber's hereditary optic neuropathy | mt-ND1 mt-ND4 mt-ND6 (90% of affected patients) | M, S | ND subunits of Complex I | Respiratory chain Complex I | Bilateral, painless subacute visual failure. | Late adolescence or early adulthood | 1:31,000 North of England; 1:39,000 Dutch population; 1:50,000 Finnish population | [6–8] |
| Autosomal dominant optic atrophy | OPA1 (almost all affected patients) | AD | OPA1 | Mitochondrial fusion, cristae structuration, apoptosis and mtDNA maintenance | Variable loss of visual acuity, temporal optic nerve pallor, tritanopia and development of central, paracentral or coecocentral scotomas. Additional neurological symptoms: visual failure, optic atrophy, PEO, ataxia, deafness and sensory-motor neuropathy | Childhood | 1:35,000 North of England; 1:12,000 Denmark; 1:8,375 south-eastern Sicily, Italy | [7,9–13] |
| Charcot-Marie-Tooth hereditary neuropathy type 2A | CMT2A (almost all affected patients) | AD | MFN2 | Mitochondrial fusion | Sensory-motor axonal polyneuropathy. Additional symptoms: optic atrophy, sensorineural hearing loss, spastic paraparesis | Childhood | Unknown | [14,15] |
| Myoclonic epilepsy with ragged red fibres | mt-TK (80% of affected patients) | M, S | tRNA lysine ($tRNA^{Lys}$) | Transfer RNA | Myoclonic epilepsy with photo-sensitive general tonic-clonic seizures, myopathy with ptosis and ophtalmoparesis, cerebellar ataxia, dementia and deafness. | Childhood | m.8344A>G 0.25:100,000 northern England; 0–0.25:100,000 western Sweden | [8,16] |

interest, particularly the group of genes encoding factors affecting mitochondrial DNA maintenance, including the major locus for mitochondrial disease, the *POLG1* gene. This gene encodes the catalytic subunit of human mtDNA polymerase gamma and is subject to various mutations associated with heterogeneous phenotypes having ataxia as the main symptom [39]. Likewise, combination of Sensory Ataxic Neuropathy, Dysarthria and Ophthalmoparesis (SANDO) [40] has been associated with *POLG1* mutations [41], as well as Mitochondrial Recessive Ataxia Syndrome (MIRAS) and Spinocerebellar Ataxia-Epilepsy Syndrome (SCAE).

### 3.2. Ataxia and coenzyme Q10 deficiency

Coenzyme Q10 (CoQ10) is an essential electron carrier in the mitochondrial respiratory chain and also acts as an antioxidant in various cell membranes. The most common neurological signs associated with CoQ10 deficiency are cerebellar ataxia, mild muscle involvement, mental retardation and hypogonadism (adults) with onset in childhood or adulthood [42]. It was suggested that oxidative phosphorylation dysfunction may occur in CoQ10 deficiency syndrome and *in vitro* studies showed that CoQ10 deficiency has different biochemical consequences leading to cell death [43]. Although there is no evidence of a specific gene directly involved in CoQ10 deficiency associated with ataxia, several mutations in different genes involved in the CoQ10 biosynthetic pathway have recently been reported [38].

### 3.3. Neurodegenerative POLG1-related disorders with extrapyramidal involvement

Mutations in the *POLG1* gene result in aberrant replication and impaired maintenance of mtDNA, leading to a significant decrease in mtDNA copy number, or multiple deletions in mtDNA, which translate into mitochondrial dysfunction. These mutations have been associated with heterogeneous dominant or recessive phenotypes. A significant association of variants of the *POLG1* CAG repeat, encoding a polyglutamine tract (poly-Q) with idiopathic sporadic PD, has been demonstrated in the Finnish [44], in the North American Caucasian [45] and in the Swedish [46] population. However, since controversial reports exist, further genetic studies in cohorts from other geographical regions as well as functional studies of POLG1 poly-Q variants are needed. In addition, Mancuso et al. [47] reported co-existence of parkinsonism and *POLG1* mutations with mtDNA multiple deletions in several families, suggesting a possible role of POLG1 in inherited parkinsonism. The role of *POLG1* gene mutations as cause of mitochondrial parkinsonism is discussed more extensively in a recent review [48]. *POLG1* mutations were recently reported in a patient with multiple system atrophy of the cerebellar subtype (MSA-C) [49].

## 4. Secondary mitochondrial dysfunctions in neurodegenerative diseases

There is much evidence that increased oxidative stress and altered apoptosis are linked to the pathogenesis of several ageing-related neurodegenerative diseases. Many studies have considered the role of mitochondria in the pathogenesis of neurodegenerative diseases, however it is unclear whether mitochondrial impairment and oxidative stress are actually involved in the onset and progression of neurodegenerative disorders like Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and Amyotrophic Lateral Sclerosis (ALS), or are consequences of neurodegeneration (Fig. 4). Finally, mitochondria interact with an impressive number of specific proteins implicated in genetic forms of neurodegenerative disease (Table 4).

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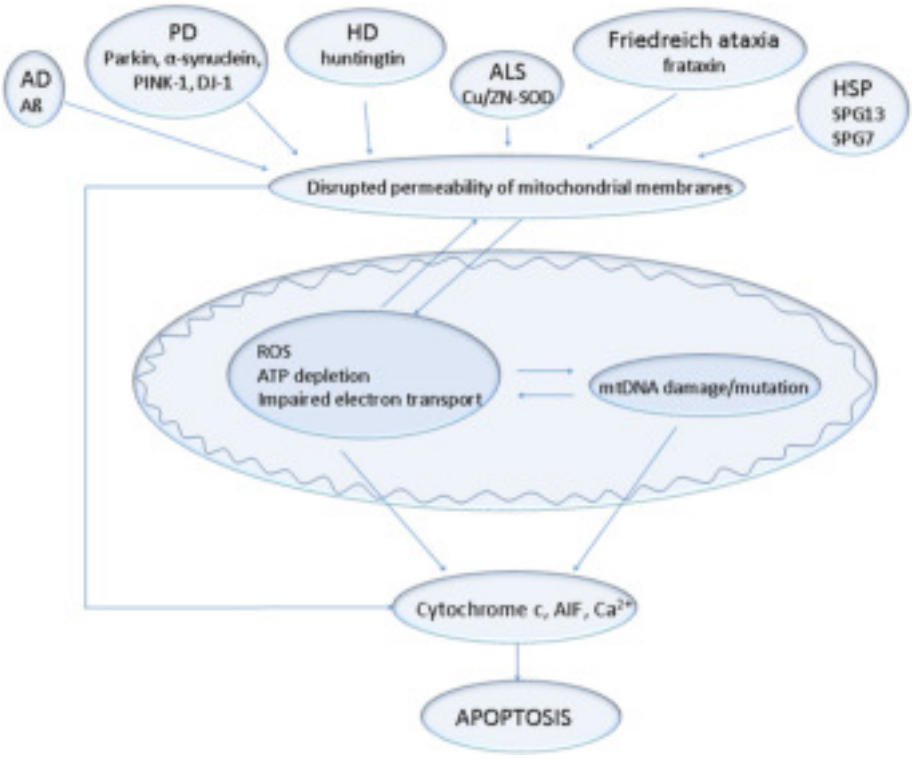


**Fig. 4.** Role of mitochondria in neurodegenerative disease.

*4.1. Mitochondria and Parkinson's disease*

Several observations suggest that mitochondrial dysfunction is involved in the pathogenesis of PD and the degeneration of dopaminergic neurons [50]. The substantia nigra of PD patients shows reduced activity of mitochondrial respiratory electron transport chain NADPH deydrogenase (complex I) and complex I inhibitors such as rotenone, MPTP and pesticides cause neurological changes similar to PD [51]. Point mutations and deletions accumulate in mtDNA of neurons in the brains of PD patients [52] and several mtDNA polymorphisms and haplotypes are associated with the risk of PD [53]. Mutations in mtDNA or nuclear genes involved in mitochondrial function, such as POLG, cause PD-like symptoms [54]. On the other hand, many genes associated with familial forms of PD are involved in mitochondrial function [51] (Fig. 5).

Recent studies reveal that α-synuclein contains an amino-terminal mitochondrial targeting sequence and can associate with the inner mitochondrial membrane, interacting with mitochondrial complex I function [55]. In transgenic mice, overexpression of α-synuclein impairs mitochondrial function, increases oxidative stress and enhances nigral pathology induced by MPTP [56]. It has also been suggested that mutant A53T α-synuclein might damage mitochondria directly [57]. Finally, *wt* alpha-synuclein and its mutant forms are reported to induce changes reminiscent of mammalian cell apoptosis [58].

**Table 4**
Proteins implicated in major neurodegenerative disease with mitochondrial involvement.

| Protein | Description | Disease |
|---|---|---|
| APP | Precursor of Aß | Alzheimer's disease |
| Aß | Major component of senile plaque | " " |
| PS1 and PS2 | Component of γ-secretase | " " |
| α-synuclein | Component of Lewy bodies | Parkinson's disease |
| Parkin | A ubiquitin E3 ligase | " " |
| DJ-1 | DJ-1 acts as a potential ROS scavenger/sensor | " " |
| PINK1 | PINK1 has protective effects against cell death | " " |
| LRRK2 | Kinase | " " |
| HTRA2 | Proapoptotic factor | " " |
| SOD1 | Cu/Zn superoxide dismutase | ALS |
| Huntingtin | Mutation are associated with expanded polyglutamine repeats | Huntington's disease |
| Frataxin | Mitochondrial iron chaperone involved in the biogenesis of iron-containing enzymes and iron detoxification | Friedreich's ataxia |
| SPG7 | Mitochondrial membrane metalloprotease | Hereditary spastic paraplegia |
| SPG13 | Mitochondrial chaperone | " " " |
| SOD1 | Cu/Zn superoxide dismutase | ALS |
| Huntingtin | Mutation are associated with expanded polyglutamine repeats | Huntington's disease |
| Frataxin | Mitochondrial iron chaperone involved in the biogenesis of iron-containing enzymes and iron detoxification | Friedreich's ataxia |
| SPG7 | Mitochondrial membrane metalloprotease | Hereditary spastic paraplegia |
| SPG13 | Mitochondrial chaperone | " " " |

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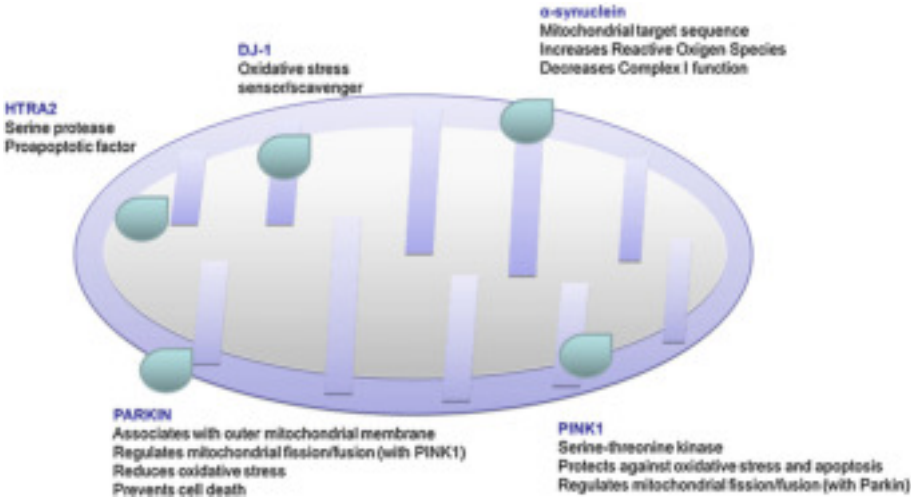


**Fig. 5.** Interaction between genes associated with familial forms of PD and mitochondrial function.

Our group studied PBLs from two siblings with PD associated with A53T α-synuclein mutation. We demonstrated a higher rate of apoptosis, which suggests that α-synuclein plays an important role in regulation of the mitochondrial apoptotic pathway [59].

The protein parkin is associated with the outer mitochondrial membrane and prevents cell death by inhibiting mitochondrial swelling, cytochrome c release and caspase activation [60]. Parkin deficiency causes oxidative stress and mitochondrial impairment, as demonstrated in leukocytes from patients with parkin mutations showing selective impairment in complex I activity [61]. Muscle alterations with severe depletion of subsarcolemmal and intermyofibrillar mitochondria have been found in a patient with parkin-related parkinsonism without mtDNA mutation [62].

Phosphatase and tensin homologue (PTEN)-induced kinase 1 (PINK1) is a mitochondrial kinase that seems to have protective effects against cell death by suppressing release of cytochrome c by mitochondria [63]. PINK1 deficiency causes a decrease in complex I activity and alters synaptic function in Drosophila neurons [64]. There is evidence that PINK1 and parkin may play a role in the same pathway, probably affecting the balance between mitochondrial fission and fusion [65].

DJ-1 is a negative regulator of PTEN tumour-suppressor protein, which promotes apoptosis by phosphorylating phosphatidylinositol-3,4,5-triphosphate, necessary for activation of the Akt pathway [66]. DJ-1 acts as a potential ROS scavenger/sensor and *DJ-1* mutations are associated with increased oxidative stress and apoptosis [67].

HTRA2 is a mitochondrial quality control agent which behaves as a proapoptotic factor when released into the cytosol [68]. Mutations in HTRA2 determine mitochondrial swelling and lower mitochondrial membrane potential [69].

Finally, although the exact role of leucine-rich-repeat kinase 2 (LRRK2) mutations in mitochondrial dysfunction still needs to be elucidated, association of about 10% of LRRK2 with mitochondria suggests that this protein has a role in mediating mitochondrial function [68].

A rare autosomal recessive juvenile parkinsonism, Kufor-Rakeb syndrome, was recently linked to mutations in *ATP13A2*, that encodes a lysosomal transmembrane protein of the P-type ATPase superfamily. Although no direct relation between *ATP13A2* and mitochondrial function has been demonstrated, our group showed high sensitivity to oxidative stress and an evident increase in apoptotic cell death in lymphocytes from patients with c.G2629A mutation in *ATP13A2* [70].

### 4.2. Mitochondria and Alzheimer's disease (AD)

Several evidences suggest that mitochondrial dysfunction and oxidative damage have a role in the pathogenesis of AD. In transfected cells and transgenic mice overexpressing precursor amyloid protein (APP), this protein clogged the mitochondrial protein import machinery, causing mitochondrial dysfunction and impaired energy metabolism [71]. In brains of AD patients and transgenic mouse models, ß-amyloid protein (Aß) interacts with binding alcohol dehydrogenase protein (ABAD), a mitochondrial-matrix protein, causing mitochondrial oxidative damage and impaired activity of respiratory complexes [72]. Aß also interacts with HtrA2/Omi, a proapoptotic serine protease released into the cytoplasm by mitochondria on apoptotic stimulation [73]. Aß inhibits ketoglutarate dehydrogenase complex, and reduced cytochrome-c-oxidase (COX) activity has persistently been found in brain and other tissue of AD patients [74]. Reduced cell energy due to complex I and COX inhibition promotes tau phosphorylation [75], suggesting that mitochondrial damage could play a role in the formation of tangles and neurodegeneration. Presenilin and other components of the γ-secretase complex have also been localized to mitochondria [76].

mtDNA haplogroups seem to influence the risk of AD, and in most cases, the demented parent of an AD patient is the mother [77]. Moreover, when AD mtDNA is transferred to cell lines devoid of mtDNA, a respiratory enzyme deficiency similar to that seen in AD tissues is found, suggesting that the deficit is carried at least in part by mtDNA abnormalities [78]. However, no causative mtDNA changes have been reported in AD patients [79].

An important role of Aß in modulating proteins involved in mitochondrial fission/fusion processes was recently suggested. In hippocampal tissues of AD patients, reduced levels of Drp-1, OPA1, Mfn1, Mfn2 and increased levels of Fis1 have been shown, suggesting impaired mitochondrial dynamics in favour of fission. Moreover, in hippocampal neurons overexpressing APP, mitochondria accumulated in the perinuclear area suggesting that Aß can impair mitochondrial transport and consequently contribute to synaptic dysfunction [80].

Impairment of mtDNA base excision repair (BER), the primary nuclear and mtDNA repair pathway for small base modifications, may also play a role in AD pathogenesis. A significant BER deficiency was found in affected and unaffected AD brain regions and has been correlated with severity in patients with MCI [81].

### 4.3. Mitochondrial and Huntington's disease (HD)

HD is an autosomal dominant disorder due to the expansion of a CAG trinucleotide repeat in the *huntingtin* (*HTT*) gene: repeat numbers greater than 40 are associated with onset of the disease. Mutant HTT might cause mitochondrial dysfunction by interacting directly with the organelle, modulating respiration, membrane potential and

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$Ca^{2+}$ buffering [82]. Respiratory transport chain activity, in particular complex II activity, is reduced in HD brains [83]. The complex-II inhibitor, 3-nitropropionic acid, induces striatal degeneration and movement disorders resembling those of HD in rodents and primates [82], while overexpression of complex-II subunits restores complex II activity and reduces cell death in striatal neurons expressing mutant HTT [84]. HTT is associated with the outer mitochondrial membrane and mutant HTT increases mitochondrial sensitivity to calcium-induced mitochondria permeabilization and cytochrome *c* release [68].

HTT may alter mitochondrial function by directly affecting transcription of nuclear-encoded proteins: mutant HTT may in fact translocate to the nucleus where it binds to p53, which in turn activates the pro-apoptotic Bcl-2 family proteins, BAX and PUMA [82]. Mice knockout for PGC-1α, a key transcriptional co-regulator of mitochondrial metabolic pathways, shows impaired mitochondrial function, hyperkinetic movements and striatal degeneration similar to HD [85].

Recent studies suggest that alterations in mitochondrial dynamics may be involved in the pathogenesis of HD: it is likely that normal HTT may regulate mitochondrial fission and fusion complexes and mutant HTT may alter the assembly and function of these complexes, which may in turn cause bioenergy failure, HD-linked neuronal dysfunction and cell death [82]. Finally, degeneration of medium spiny neurons, which are particularly affected in HD, may be due to selective impairment of mitochondrial $Ca^{2+}$ buffering, increased expression of cell death mediators and increased vulnerability of this cell type to trafficking and mitochondrial fission/fusion defects [86].

### *4.4. Mitochondria in amyotrophic lateral sclerosis (ALS)*

Approximately 10% of cases of ALS type 1, a fatal neurodegenerative disorder, are familial and about 20% of Mendelian cases are caused by mutations in the copper-zinc superoxide dismutase type 1 (*SOD1*) gene [87]. Postmortem and biopsy samples of ALS patients show impaired mitochondrial respiratory chain complex activity, while overexpression of mutant SOD1 in transgenic mice causes impaired electron transport chain activity, decreased mitochondrial calcium-loading capacity and aberrant ROS production [68]. Several studies have demonstrated that SOD1 and its mutant form localize to mitochondria in affected tissues [88]. SOD1 aggregates on the outer mitochondrial membrane may block protein importation and promote aberrant ROS production with consequent oxidative damage to mitochondrial proteins and lipids [89]. Mutant SOD1 mitochondrial aggregates may contribute to apoptotic cell death by causing release of cytochrome c [90] and sequestering the anti-apoptotic protein Bcl-2 [91].

### *4.5. Other common neurodegenerative diseases*

Friedreich ataxia is the most common hereditary ataxia, characterized by reduced levels of a mitochondrial protein called frataxin [92]. Frataxin deficiency is associated with abnormalities in iron metabolism leading to accumulation of iron in mitochondria and depletion in the cytosol [93]. Respiratory chain dysfunction enhances oxidative stress by increasing leakage of electrons and superoxide formation [92]. *In vitro* studies have demonstrated that frataxin deficient cells not only generate more free radicals, but also have a reduced capacity to mobilize antioxidant defences [94].

Hereditary spastic paraplegias belong to a genetically heterogeneous group of neurological disorders characterized by progressive weakness and spasticity of the lower extremities. Mitochondrial defects have been directly implicated in two forms of hereditary spastic paraplegias linked to mutations in the genes SPG13 and SPG7 [95]. SPG13 encodes the mitochondrial matrix chaperonin Hsp60, which plays a role in folding imported mitochondrial proteins. SPG7 encodes paraplegin, a subunit of mitochondrial metallopeptidase that localizes to the inner mitochondrial membrane and is implicated in the turnover of misfolded respiratory chain peptides [96]. Patients with paraplegin mutations show mitochondrial respiratory chain dysfunction, impaired complex I activity and increased sensitivity to oxidative stress [97].

## 5. Conclusion

Numerous evidences present in literature rise the possibility that mitochondria and oxidative stress play a crucial role in neurodegeneration, opening new perspectives for therapy. The investigation of mitochondrial diseases as a model of neurodegenerative disease, is useful for defining the role of these organelles in normal and pathological conditions.

## Conflict of interest

None.

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## References

[1] Karbowski M. Mitochondria on guard: role of mitochondrial fusion and fission in the regulation of apoptosis. Adv Exp Med Biol 2010;687:131–42.
[2] Filosto M, Scarpelli M, Cotelli MS, Vielmi V, Todeschini A, Gregorelli V, et al. The role of mitochondria in neurodegenerative diseases. J Neurol 2011;258:1763–74.
[3] Scholte HR. The biochemical basis of mitochondrial diseases. J Bioenerg Biomembr 1988;20:161–91.
[4] MITOMAP: a human mitochondrial genome database. http://www.mitomap.org2011.
[5] Morais VA, De Strooper B. Mitochondria dysfunction and neurodegenerative disorders: cause or consequence. J Alzheimer Dis 2010;20:255–63.
[6] Spruijt L, Kolbach DN, de Coo RF, Plomp AS, Bauer NJ, Smeets HJ, et al. Influence of mutation type on clinical expression of Leber hereditary optic neuropathy. Am J Ophthalmol 2006;141:676–82.
[7] Yu-Wai-Man P, Griffiths PG, Burke A, Sellar PW, Clarke MP, Gnanaraj L, et al. The prevalence and natural history of dominant optic atrophy due to OPA1 mutations. Ophthalmology 2010;117:1538–46.
[8] Chinnery PF, Johnson MA, Wardell TM, Singh-Kler R, Hayes C, Brown DT, et al. The epidemiology of pathogenic mitochondrial DNA mutations. Ann Neurol 2000;48:188–93.
[9] Kjer B, Eiberg H, Kjer P, Rosenberg T. Dominant optic atrophy mapped to chromosome 3q region. II. Clinical and epidemiological aspects. Acta Ophthalmol Scand 1996;74:3–7.
[10] Gallus GN, Cardaioli E, Rufa A, Collura M, Da Pozzo P, Pretegiani E, et al. High frequency of OPA1 mutations causing high ADOA prevalence in south-eastern Sicily, Italy. Clin Genet 2011, doi:10.1111/j.1399-0004.2011.01751.x.
[11] Hudson G, Amati-Bonneau P, Blakely EL, Stewart JD, He L, Schaefer AM, et al. Mutation of OPA1 causes dominant optic atrophy with external ophthalmoplegia, ataxia, deafness and multiple mitochondrial DNA deletions: a novel disorder of mtDNA maintenance. Brain 2008;131:329–37.
[12] Pretegiani E, Rufa A, Gallus GN, Cardaioli E, Malandrini A, Federico A. Spastic paraplegia in 'dominant optic atrophy plus' phenotype due to OPA1 mutation. Brain 2011;134:195.
[13] Chen H, Chan DC. Emerging functions of mammalian mitochondrial fusion and fission. Hum Mol Genet 2005;14:283–9.
[14] Chung KW, Kim SB, Park KD, Choi KG, Lee JH, Eun HW, et al. Early onset severe and late-onset mild Charcot-Marie-Tooth disease with mitofusin 2 (MFN2) mutations. Brain 2006;129:2103–18.
[15] Del Bo R, Moggio M, Rango M, Bonato S, D'Angelo MG, Ghezzi S, et al. Mutated mitofusin 2 presents with intrafamilial variability and brain mitochondrial dysfunction. Neurology 2008;71:1959–66.
[16] Darin N, Oldfors A, Moslemi AR, Holme E, Tulinius M. The incidence of mitochondrial encephalomyopathies in childhood: clinical features and morphological, biochemical, and DNA abnormalities. Ann Neurol 2001;49:377–83.
[17] Carelli V, Ross-Cisneros FN, Sadun AA. Mitochondrial dysfunction as a cause of optic neuropathies. Prog Retin Eye Res 2004;23:53–89.
[18] Beretta S, Mattavelli L, Sala G, Tremolizzo L, Schapira AH, Martinuzzi A, et al. Leber hereditary optic neuropathy mtDNA mutations disrupt glutamate transport in cybrid cell lines. Brain 2004;127:2183–92.
[19] Zanna C, Ghelli A, Porcelli AM, Martinuzzi A, Carelli V, Rugolo M. Caspase-independent death of Leber's hereditary optic neuropathy cybrids is driven by energetic failure and mediated by AIF and endonuclease G. Apoptosis 2005;10:997–1007.
[20] Battisti C, Formichi P, Cardaioli E, Bianchi S, Mangiavacchi P, Tripodi SA, et al. Cell response to oxidative stress induced apoptosis in patients with Leber's hereditary optic neuropathy. J Neurol Neurosurg Psychiatry 2004;75:1731–6.

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[21] Kirches E. LHON: mitochondrial mutations and more. Curr Genomics 2011;12:44–54.
[22] Dotti MT, Plewnia K, Cardaioli E, Manneschi L, Rufa A, Alemà G, et al. A case of ethambutol-induced optic neuropathy harbouring the primary mitochondrial LHON mutation at nt 11778. J Neurol 1998;245:302–3.
[23] Carelli V, Franceschini F, Venturi S, Barboni P, Savini G, Barbieri G, et al. Grand rounds: could occupational exposure to n-hexane and other solvents precipitate visual failure in Leber hereditary optic neuropathy? Environ Health Perspect 2007;115:113–5.
[24] Cardaioli E, Da Pozzo P, Gallus GN, Franceschini R, Rufa A, Dotti MT, et al. Leber's hereditary optic neuropathy associated with cocaine, ecstasy and telithromycin consumption. J Neurol 2007;254:255–6.
[25] Rufa A, Dotti MT, Cardaioli E, Da Pozzo P, Federico A. Leber hereditary optic neuropathy in 2 of 4 siblings with 11778 mtDNA mutation: clinical variability or effect of toxic environmental exposure? Eur Neurol 2005;53:32–4.
[26] Chevrollier A, Guillet V, Loiseau D, Gueguen N, de Crescenzo MA, Verny C, et al. Hereditary optic neuropathies share a common mitochondrial coupling defect. Ann Neurol 2008;63:794–8.
[27] Olichon A, Landes T, Arnauné-Pelloquin L, Emorine LJ, Mils V, Guichet A, et al. Effects of OPA1 mutations on mitochondrial morphology and apoptosis: relevance to ADOA pathogenesis. J Cell Physiol 2007;211:423–30.
[28] Züchner S, Mersiyanova IV, Muglia M, Bissar-Tadmouri N, Rochelle J, Dadali EL, et al. Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. Nat Genet 2004;36:449–51.
[29] Pich S, Bach D, Briones P, Liesa M, Camps M, Testar X, et al. The Charcot-Marie-Tooth type 2A gene product, Mfn2, up-regulates fuel oxidation through expression of OXPHOS system. Hum Mol Genet 2005;14:1405–15.
[30] Misko A, Jiang S, Wegorzewska I, Milbrandt J, Baloh RH. Mitofusin 2 is necessary for transport of axonal mitochondria and interacts with the Miro/Milton complex. J Neurosci 2010;30:4232–40.
[31] Funalot B, Magdelaine C, Sturtz F, Ouvrier R, Vallat JM. Ultrastructural lesions of axonal mitochondria in patients with childhood-onset Charcot-Marie-Tooth disease due to MFN2 mutations. Bull Acad Natl Med 2009;193:151–60.
[32] Rouzier C, Bannwarth S, Chaussenot A, Chevrollier A, Verschueren A, Bonello-Palot N, et al. The MFN2 gene is responsible for mitochondrial DNA instability and optic atrophy 'plus' phenotype. Brain 2012;135:23–34.
[33] Loiseau D, Chevrollier A, Verny C, Guillet V, Gueguen N, MA Pou de Crescenzo, et al. Mitochondrial coupling defect in Charcot-Marie-Tooth type 2A disease. Ann Neurol 2007;61:315–23.
[34] Greaves LC, Reeve AK, Taylor RW, Turnbull DM. Mitochondrial DNA and disease. J Pathol 2012;226:274–86.
[35] Rommelaere G, Michel S, Malaisse J, Charlier S, Arnould T, Renard P. Hypersensitivity of A8344G MERRF mutated cybrid cells to staurosporine-induced cell death is mediated by calcium-dependent activation of calpains. Int J Biochem Cell Biol 2012;44:139–49.
[36] Wu SB, Ma YS, Wu YT, Chen YC, Wei YH. Mitochondrial DNA mutation-elicited oxidative stress, oxidative damage, and altered gene expression in cultured cells of patients with MERRF syndrome. Mol Neurobiol 2010;41:256–66.
[37] Lax NZ, Hepplewhite PD, Reeve AK, Nesbitt V, McFarland R, Jaros E, et al. Cerebellar ataxia in patients with mitochondrial DNA disease: a molecular clinicopathological study. J Neuropathol Exp Neurol 2012;71:148–61.
[38] Zeviani M, Simonati A, Bindoff LA. Ataxia in mitochondrial disorders. Handb Clin Neurol 2012;103:359–72.
[39] Schicks J, Synofzik M, Schulte C, Schöls L. POLG, but not PEO1, is a frequent cause of cerebellar ataxia in Central Europe. Mov Disord 2010;25:2678–82.
[40] Fadic R, Russell JA, Vedanarayanan VV, Lehar M, Kuncl RW, Johns DR. Sensory ataxic neuropathy as the presenting feature of a novel mitochondrial disease. Neurology 1997;49:239–45.
[41] Van Goethem G, Martin JJ, Dermaut B, Löfgren A, Wibail A, Ververken D, et al. Recessive POLG mutations presenting with sensory and ataxic neuropathy in compound heterozygote patients with progressive external ophthalmoplegia. Neuromuscul Disord 2003;13:133–42.
[42] Montero R, Pineda M, Aracil A, Vilaseca MA, Briones P, Sánchez-Alcázar JA, et al. Clinical, biochemical and molecular aspects of cerebellar ataxia and coenzyme Q10 deficiency. Cerebellum 2007;6:118–22.
[43] Quinzii CM, Hirano M. Primary and secondary CoQ(10) deficiencies in humans. Biofactors 2011;37:361–5.
[44] Luoma PT, Eerola J, Ahola S, Hakonen AH, Hellström O, Kivistö KT, et al. Mitochondrial DNA polymerase gamma variants in idiopathic sporadic Parkinson disease. Neurology 2007;69:1152–9.
[45] Eerola J, Luoma PT, Peuralinna T, Scholz S, Paisan-Ruiz C, Suomalainen A, et al. POLG1 polyglutamine tract variants associated with Parkinson's disease. Neurosci Lett 2010;477:1–5.
[46] Anvret A, Westerlund M, Sydow O, Willows T, Lind C, Galter D, et al. Variations of the CAG trinucleotide repeat in DNA polymerase γ (POLG1) is associated with Parkinson's disease in Sweden. Neurosci Lett 2010;485:117–20.
[47] Mancuso M, Filosto M, Orsucci D, Siciliano G. Mitochondrial DNA sequence variation and neurodegeneration. Hum Genomics 2008;3:71–8.
[48] Orsucci D, Caldarazzo Ienco E, Mancuso M, Siciliano G. POLG1-related and other "mitochondrial Parkinsonisms": an overview. J Mol Neurosci 2011;44:17–24.
[49] Mehta AR, Fox SH, Tarnopolsky M, Yoon G. Mitochondrial mimicry of multiple system atrophy of the cerebellar subtype. Mov Disord 2011;26:753–5.
[50] Swerdlow RH. The neurodegenerative mitochondriopathies. J Alzheimers Dis 2009;17:737–51.
[51] Shapira AH. Mitochondria in the aetiology and pathogenesis of Parkinson's disease. Lancet Neurol 2008;7:97–109.
[52] Kraytsberg Y, Kudryavtseva E, McKee AC, Geula C, Kowall NW, Khrapko K. Mitochondrial DNA deletions are abundant and cause functional impairment in aged human substantia nigra neurons. Nat Genet 2006;38:518–20.
[53] Pyle A, Foltynie T, Tiangyou W, Lambert C, Keers SM, Allcock LM, et al. Mitochondrial DNA haplogroup cluster UKJT reduces the risk of PD. Ann Neurol 2005;57:564–7.
[54] Horvath R, Kley RA, Lochmuller H, Vorgerd M. Parkinson syndrome, neuropathy, and myopathy caused by the mutation A8344G (MERRF) in tRNALys. Neurology 2006;68:56–8.
[55] Chinta SJ, Mallajosyula JK, Rane A, Andersen JK. Mitochondrial alpha-synuclein accumulation impairs complex I function in the dopaminergic neurons and results in increased mitophagy in vitro. Neurosci Lett 2010;486:235–9.
[56] Song DD, Shults CW, Sisk A, Rockenstein E, Masliah E. Enhanced substantia nigra mitochondrial pathology in human α-synuclein transgenic mice after treatment with MPTP. Exp Neurol 2004;186:158–72.
[57] Martin LJ, Pan Y, Price AC, Sterling W, Copeland NG, Jenkins NA, et al. Parkinson's disease alpha-synuclein transgenic mice develop neuronal mitochondrial degeneration and cell death. J Neurosci 2006;26:41–50.
[58] Flower TR, Chesnokova LS, Froelich CA, Dixon C, Witt SN. Heat shock prevents alpha-synuclein-induced apoptosis in a yeast model of Parkinson's disease. J Mol Biol 2005;351:1081–100.
[59] Battisti C, Formichi P, Radi E, Federico A. Oxidative-stress-induced apoptosis in PBLs of two patients with Parkinson disease secondary to alpha-synuclein mutation. J Neurol Sci 2008;267:120–4.
[60] Darios F, Corti O, Lücking CB, Hampe C, Muriel MP, Abbas N, et al. Parkin prevents mitochondrial swelling and cytochrome c release in mitochondria-dependent cell death. Hum Mol Genet 2003;12:517–26.
[61] Müftüoglu M, Elibol B, Dalmizrak O, Ercan A, Kulaksiz G, Ogüs H, et al. Mitochondrial complex I and IV activities in leukocytes from patients with parkin mutations. Mov Disord 2004;19:544–8.
[62] Amboni M, Pellecchia MT, Cozzolino A, Picillo M, Vitale C, Barone P, et al. Cerebellar and pyramidal dysfunctions, palpebral ptosis and weakness as presenting symptoms of PARK-2. Mov Disord 2009;24:303–5.
[63] Chen H, Chan DC. Mitochondrial dynamics – fusion, fission, movement, and mitophagy – in neurodegenerative diseases. Hum Mol Genet 2009;18:169–76.
[64] Morais VA, Verstreken P, Roethig A, Smet J, Snellinx A, Vanbrabant M, et al. Parkinson's disease mutations in PINK1 result in decreased Complex I activity and deficient synaptic function. EMBO Mol Med 2009;1:99–111.
[65] Deng H, Dodson MW, Huang H, Guo M. The Parkinson's disease genes pink1 and parkin promote mitochondrial fission and/or inhibit fusion in Drosophila. Proc Natl Acad Sci U S A 2008;105:14503–8.
[66] Yang Y, Gehrke S, Haque ME, Imai Y, Kosek J, Yang L, et al. Inactivation of Drosophila DJ-1 leads to impairments of oxidative stress response and phosphatidylinositol 3-kinase/Akt signaling. Proc Natl Acad Sci U S A 2005;102:13670–5.
[67] Irrcher I, Aleyasin H, Seifert EL, Hewitt SJ, Chhabra S, Phillips M, et al. Loss of the Parkinson's disease-linked gene DJ-1 perturbs mitochondrial dynamics. Hum Mol Genet 2010;19:3734–46.
[68] Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative disease. Nature 2006;443:787–95.
[69] Strauss KM, Martins LM, Plun-Favreau H, Marx FP, Kautzmann S, Berg D, et al. Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson's disease. Hum Mol Genet 2005;14:2099–111.
[70] Radi E, Formichi P, Di Maio G, Battisti C, Federico A. Altered apoptosis regulation in kufor-rakeb syndrome patients with mutations in the atp13a2 gene. J Cell Mol Med 2011, doi:10.1111/j.1582-4934.2011.01488.x.
[71] Anandatheerthavarada HK, Biswas G, Robin MA, Avadhani NG. Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. J Cell Biol 2003;161:41–54.
[72] Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, Reddy PH. Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression. Hum Mol Genet 2006;15:1437–49.
[73] Lindholm D, Eriksson O, Korhonen L. Mitochondrial proteins in neuronal degeneration. Biochem Biophys Res Commun 2004;321:753–8.
[74] Casley CS, Canevari L, Land JM, Clark JB, Sharpe MA. Beta-amyloid inhibits integrated mitochondrial respiration and key enzyme activities. J Neurochem 2002;80:91–100.
[75] Melov S, Adlard PA, Morten K, Johnson F, Golden TR, Hinerfeld D, et al. Mitochondrial oxidative stress causes hyperphosphorylation of tau. PLoS One 2007;2:536.
[76] Hansson CA, Frykman S, Farmery MR, Tjernberg LO, Nilsberth C, Pursglove SE, et al. Nicastrin, presenilin, APH-1, and PEN-2 form active gamma-secretase complexes in mitochondria. J Biol Chem 2004;279:51654–60.
[77] Edland SD, Silverman JM, Peskid ER, Tsuang D, Wijsman E, Morris JC. Increased risk of dementia in mothers of Alzheimer's disease cases: evidence for maternal inheritance. Neurology 1996;47:254–6.
[78] Swerdlow RH, Parks JK, Cassarino DS, Maguire DJ, Maguire RS, Bennett Jr JP, et al. Cybrids in Alzheimer's disease: a cellular model of the disease? Neurology 1997;49:918–25.
[79] Tanaka N, Goto YI, Akanuma J, Kato M, Kinoshita T, Yamashita F, et al. Mitochondrial DNA variants in a Japanese population of patients with Alzheimer's disease. Mitochondrion 2010;10:32–7.
[80] Wang X, Su B, Zheng L, Perry G, Smith MA, Zhu X. The role of abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. J Neurochem 2009;109:153–9.

Please cite this article as: Federico A, et al, Mitochondria, oxidative stress and neurodegeneration, J Neurol Sci (2012), doi:10.1016/j.jns.2012.05.030

[81] Weissman L, Jo DG, Sørensen MM, de Souza-Pinto NC, Markesbery WR, Mattson MP, et al. Defective DNA base excision repair in brain from individuals with Alzheimer's disease and amnestic mild cognitive impairment. Nucleic Acids Res 2007;35:5545–55.
[82] Bossy-Wetzel E, Petrilli A, Knott AB. Mutant huntingtin and mitochondrial dysfunction. Trends Neurosci 2008;31:609–16.
[83] Kwong JQ, Beal MF, Manfredi G. The role of mitochondria in inherited neurodegenerative diseases. J Neurochem 2006;97:1659–75.
[84] Reddy PH, Mao P, Manczak M. Mitochondrial structural and functional dynamics in Huntington's disease. Brain Res Rev 2009;61:33–48.
[85] Lin J, Wu PH, Tarr PT, Lindenberg KS, St-Pierre J, Zhang CY, et al. Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1 alpha null mice. Cell 2004;119:121–35.
[86] Cui L, Jeong H, Borovecki F, Parkhurst CN, Tanese N, Krainc D. Transcriptional repression of PGC-1 alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. Cell 2006;127:59–69.
[87] Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature 1993;362:59–62.
[88] Vijayvergiya C, Beal MF, Buck J, Manfredi G. Mutant superoxide dismutase 1 forms aggregates in the brain mitochondrial matrix of amyotrophic lateral sclerosis mice. J Neurosci 2005;25:2463–70.
[89] Mattiazzi M, D'Aurelio M, Gajewski CD, Martushova K, Kiaei M, Beal MF, et al. Mutated human SOD1 causes dysfunction of oxidative phosphorylation in mitochondria of transgenic mice. J Biol Chem 2002;277:29626–33.
[90] Takeuchi H, Kobayashi Y, Ishigaki S, Doyu M, Sobue G. Mitochondrial localization of mutant superoxide dismutase 1 triggers caspase-dependent cell death in a cellular model of familial amyotrophic lateral sclerosis. J Biol Chem 2002;277:50966–72.
[91] Pasinelli P, Belford ME, Lennon N, Bacskai BJ, Hyman BT, Trotti D, et al. Amyotrophic lateral sclerosis-associated SOD1 mutant proteins bind and aggregate with Bcl-2 in spinal cord mitochondria. Neuron 2004;43:19–30.
[92] Marmolino D. Friedreich's ataxia: past, present and future. Brain Res Rev 2011;67:311–30.
[93] Bulteau AL, O'Neill HA, Kennedy MC, Ikeda-Saito M, Isaya G, Szweda LI. Frataxin acts as an iron chaperone protein to modulate mitochondrial aconitase activity. Science 2004;305:242–5.
[94] Busi MV, Maliandi MV, Valdez H, Clemente M, Zabaleta EJ, Araya A, et al. Deficiency of Arabidopsis thaliana frataxin alters activity of mitochondrial Fe-S proteins and induces oxidative stress. Plant J 2006;48:873–82.
[95] Hansen JJ, Dürr A, Cournu-Rebeix I, Georgopoulos C, Ang D, Nielsen MN, et al. Hereditary spastic paraplegia SPG13 is associated with a mutation in the gene encoding the mitochondrial chaperonin Hsp60. Am J Hum Genet 2002;70:1328–32.
[96] Arnold I, Langer T. Membrane protein degradation by AAA proteases in mitochondria. Biochim Biophys Acta 2002;1592:89–96.
[97] Atorino L, Silvestri L, Koppen M, Cassina L, Ballabio A, Marconi R, et al. Loss of m-AAA protease in mitochondria causes complex I deficiency and increased sensitivity to oxidative stress in hereditary spastic paraplegia. J Cell Biol 2003;163:777–87.

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