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## Mitochondrial Disorders and The Eye

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### Abstract

**Purpose of Review**—Mitochondrial disease is a heterogeneous group of energy metabolism disorders that present across all ages with a wide range of ocular or multi-systemic manifestations. This review focuses on recent progress made toward understanding the various ophthalmologic manifestations of primary mitochondrial diseases and discusses the implications of mitochondrial dysfunction, placing particular emphasis on recent investigations into the pathogenesis and emerging therapies for mitochondrial-based ophthalmologic disorders.

**Recent Findings**—Novel pathogenic mitochondrial DNA mutations continue to be detected in diverse ethnic populations for primary mitochondrial ophthalmologic disorders that common affect the optic nerve, retina, and extraocular muscles. Promising antioxidant and gene therapy approaches are being actively investigated to treat these ophthalmologic manifestations, as in Leber Hereditary Optic Neuropathy. Mitochondrial dysfunction is also increasingly implicated in common ophthalmologic disorders of aging, including diabetic retinopathy, age-related macular degeneration, and glaucoma. Several proteins recently recognized to play a role in the mitochondrial oxidative stress response within retinal cells, such as prohibitin and MMP2, may serve as novel biomarkers and therapeutic targets for common ophthalmologic disorders. Therapies that inhibit mitochondrial function and induce apoptosis within tumor cells, such as EDL-155 and curcumin, may offer novel therapeutic agents for ocular neoplasms such as retinoblastoma and uveal melanoma.

**Summary**—Primary mitochondrial genetic disease manifestations can involve almost all aspects of the eye. Mitochondrial dysfunction is increasingly recognized as playing a causative role in the common ophthalmologic disorders in aging. This understanding has unleashed a range of emerging therapeutic approaches for mitochondrial-based ophthalmologic disorders directed at optimizing mitochondrial function.

### Keywords

Mitochondria; oxidative stress; antioxidant; apoptosis; diabetic retinopathy; ocular neoplasm

## INTRODUCTION

Mitochondria are the major site of cellular energy production, for which they are notoriously recognized to function as “the powerhouse of the cell”. In addition, mitochondria play a range of other basic roles critical to cell integrity and survival such as reactive species generation and scavenging, calcium regulation, steroid biosynthesis, nucleotide metabolism,

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regulation of intermediary metabolism, and initiation of apoptosis [1]. The eye is one of the most commonly affected organs in mitochondrial disease, with devastating effects that may variably involve the extraocular eye muscles, levator muscle, lens, retina, or optic nerve [2].

Mitochondrial diseases are categorized as either primary or secondary to indicate their underlying etiology. Primary mitochondrial diseases result from direct impairment of mitochondrial functions by genes located in either mitochondrial DNA (mtDNA) or nuclear DNA (nDNA). Indeed, all but 13 of the more than 1,000 proteins necessary to mitochondrial composition and function are encoded by nuclear genes [3]. Secondary mitochondrial dysfunction results either from environmental factors and/or other genetic disorders [1]. The etiology of many common ocular disorders is increasingly recognized to involve either an accumulation of mitochondrial DNA mutations and/or secondary mitochondrial damage. In this review, we explore recent investigations into the genetic basis and therapeutic advances for the varied ophthalmologic manifestations of both primary and secondary mitochondrial disorders.

### Ocular sequelae of primary mitochondrial diseases

Many primary mitochondrial diseases have ophthalmologic involvement, commonly with significant phenotypic overlap that may prohibit ready distinction of a specific genetic etiology based on clinical parameters alone [2]. To further complicate matters, mutations in a given mitochondrial disease gene may be associated with a spectrum of different clinical phenotypes [4].

**Dominant Optic Atrophy (DOA)**—DOA is a genetic disease that primarily affects the retinal ganglion cells (RGC) and nerve fiber layer of the retina. The prevalence of DOA is estimated at 1 in 35,000 individuals in northern Europe [5]. Visual acuity typically decreases over the first two decades of life to a mean of 20/80 to 20/120. Thinning of the neuroretinal rim appears to be a universal finding in DOA, with occasional findings including “saucerization” of the disc, a cup to disc ratio exceeding 0.5, and peripapillary atrophy [6, 7]. The early optic nerve appearance is often characterized by sectoral pallor of the optic nerve.

Mutations in the nuclear-encoded dynamin-like GTPase nuclear gene, *OPA1*, which is involved in mitochondrial fusion, are responsible for the majority of DOA cases [8]. In contrast, mutations in a mitochondrial-localized gene of unknown function, *OPA3*, have been identified in only two kindreds with familial optic atrophy, premature cataracts, and 3-methylglutaconic aciduria [9–11]. *OPA1* disease may also involve neuromuscular manifestations [12] in up to 20% of patients due to secondary impairment of mitochondrial respiratory chain complex IV [13]. *OPA1* expression pattern is not exclusive to RGCs. It is expressed within other retinal cell layers, including the inner and outer plexiform and photoreceptor layers, as well as in non-ocular organs such as the cochlea and brain. *OPA1* mutations can cause mitochondrial disease even in the absence of optic atrophy [14].

A recent retrospective study that evaluated the efficacy of genetic diagnostic testing among 38 individuals with an autosomal dominant family history of optic atrophy and 150 sporadic cases of bilateral optic atrophy identified *OPA1* mutations in approximately 14% of the patient cohort, whereas *OPA3* mutations were not found in any cases of isolated optic atrophy [15]. The rate of detecting *OPA1* mutations was 50% among individuals with a family history of visual failure compared to 5.3% of sporadic cases. This was similar to another study by the same group that identified *OPA1* mutations in 57.6% of individuals with a family history but only 14% of sporadic cases [5]. These studies highlight the particular utility of testing for *OPA1* mutations in individuals with a family history of optic atrophy.

The mechanism by which *OPA1* causes ophthalmologic disease was explored in a heterozygous *OPA1* mutant mouse model that develops visual dysfunction and structural changes in the retina and optic nerve. From 10 months old, affected mice were found to develop dendritic pruning in RGCs that preceded the onset of clinical visual loss and structural changes. This role of *OPA1* in maintaining the dendritic morphology of retinal cells underscores the importance of a normal balance of mitochondrial fusion and fission in retinal and optic nerve function [16].

**Leber Hereditary Optic Neuropathy (LHON)**—Characterized by acute and painless central vision loss of both eyes in a sequential fashion over a period of days to months, LHON was the first maternally-inherited ophthalmologic disorder to be linked to a point mutation in mitochondrial DNA [17]. LHON has a recognized disease prevalence estimated at 1 in 25,000 in England and other areas of Europe [18]. Three mtDNA point mutations within mitochondrial respiratory chain complex I subunit genes (G11778A in *ND4*, G3460A in *ND1*, and T14484C in *ND6*) collectively cause 95% of LHON cases. Other pathogenic mtDNA mutations continue to be identified, particularly among non-Caucasian ethnic groups, such as the recently identified mtDNA T12338C mutation in *ND5* that appears to be common in Han Chinese [19].

The pathogenesis of LHON involves initial thickening of the retinal nerve fiber layers with disc pseudoedema and RGC loss within the optic nerve [6, 7]. A recent genome-wide expression profiling study in LHON patient leukocytes found that the G11778A mutation downregulates *OPA1* expression, which the authors postulated might result in a fragmented mitochondrial network, dissipation of the mitochondrial membrane potential, and disorganization of the cristae structure of optic nerve mitochondria [20]. Nuclear gene, mtDNA gene, and environmental modifiers that affect the penetrance of the classic LHON mtDNA mutations continue to be recognized. It has been known for some time that the T14484C mutation in *ND6* is associated with a more favorable prognosis and spontaneous recovery of vision in some individuals [18]. In the Han Chinese population, a mtDNA T14502C variant in *ND6* increases the clinical penetrance of LHON in patients who have the classic mtDNA G11778A mutation in *ND4* [21]. A recent epidemiological study of 196 affected and 206 unaffected carriers from 125 LHON pedigrees that carry one of the three LHON primary mtDNA mutations, found a strong association between visual loss and smoking that was independent of gender and alcohol intake, with a clinical penetrance of LHON in 93% of men who smoked [22]. A trend was also found for visual failure with heavy alcohol intake. Based on these findings, the authors suggested that asymptomatic carriers of a LHON mtDNA mutation should be strongly advised not to smoke and to moderate their alcohol intake.

Although no cure currently exists for LHON, promising clinical trials are underway. Use of the coenzyme Q10 derivative, idebanone, continues to be investigated as a possible treatment for LHON patients [23]. The Rescue of Hereditary Optic Disease Outpatient Study evaluated visual acuity outcomes of LHON individuals orally treated with placebo versus idebanone, where those treated with idebanone showed significantly improved visual acuity compared to controls [24]. During the first year of clinical trial recruitment for gene therapy in LHON, affected individuals were characterized to determine their potential candidacy for intraocular injections of a viral vector that encodes a normal *ND4* gene [25]. Patients having low retinal nerve fiber layer thickness or low photoreceptor cell amplitudes on pattern electroretinogram appeared to be prime candidates to receive targeted gene therapy. These emerging therapies hold the potential to improve visual outcome in LHON.

**Chronic Progressive External Ophthalmoplegia (CPEO)**—CPEO is a complex disorder that impairs extraocular muscle mobility and in association with ptosis but rarely

diplopia. Visual acuity is typically spared, although some patients may develop optic atrophy or retinal involvement. The disease is most commonly caused by a single mtDNA deletion that is typically only detectable in skeletal muscle. The disease may be “sporadic” in that the mtDNA deletion occurs *de novo* in the affected individual and is unlikely to be transmitted to an affected individual’s progeny. Other structural rearrangements or point mutations in mtDNA that may also result in CPEO that can be transmitted in a maternal fashion. In addition, multiple mtDNA deletions or duplications can be the cause of disease, which typically result from mutations in any of a number of nuclear genes that are involved in mitochondrial DNA maintenance. Such nuclear gene mutations are largely inherited in an autosomal dominant fashion. Six nuclear genes have been implicated, including *TYMP*, *ANT1*, *PEO1*, *POLG*, *POLG2*, and even *OPA1* [26]. Genetic diagnostic testing is available on a clinical basis ([www.genetests.org](http://www.genetests.org)).

A clinical diagnosis of CPEO is typically confirmed by the finding of mtDNA deletion(s) on skeletal muscle biopsy, with muscle histology revealing classic “ragged red fibers”, that are characteristic of secondary mitochondrial proliferation, as well as cytochrome oxidase-negative fibers, that are consistent with secondary deficiency of mitochondrial complex IV. While extraocular muscles have been used previously as a tissue source for diagnostic purposes, a retrospective cases series found that biopsy of the orbicularis muscle at the time of blepharoplasty or ptosis surgery in patients with CPEO. was an equally effective means of obtaining muscle tissue in which to diagnose a mitochondrial myopathy, while avoiding the need for a subsequent muscle biopsy of the proximal limb that inflicts increased morbidity and cost [27].

CPEO may also occur as part of a generalized mitochondrial myopathy. A recent study found that 51 of 59 individuals with definite mitochondrial disease had involvement of the extraocular muscles, including strabismus, ptosis, and progressive external ophthalmoplegia [28]. A retrospective review of 40 patients with late-onset CPEO found that multi-system involvement was common, as 60% of patients had gastrointestinal dysfunction, 40% had migraines, 5% had cardiac conduction defects, and 2.5% had pigmentary retinopathy [29]. These studies highlight the need to view mitochondrial disease manifestations as a spectrum, where ophthalmologic manifestations of CPEO may well be only one facet of the clinical picture [1].

**Pigmentary retinopathy and other ophthalmologic problems—**Pigmentary retinopathy is a non-specific finding that may be found in several mitochondrial diseases. The best described primary mtDNA disease in which pigmentary retinopathy may be seen is Neurogenic weakness, Ataxia, and Retinitis Pigmentosa (NARP), which results from a T8993C mtDNA mutation in the mitochondrial complex V subunit gene, *ATPase 6*. Pigmentary retinopathy can also occur in a range of other mtDNA cytopathies including Leigh syndrome (degenerative disorder involving the basal ganglia and brainstem), Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke (MELAS), Myoclonic Epilepsy and Ragged Red Fibers (MERRF), LHON, Kearns-Sayre Syndrome (KSS), and mitochondrial myopathy [28]. A recent retrospective study identified retinal pigmentary changes in 16 of 59 children and adolescents with definite mitochondrial disease [28]. At least one or more other ophthalmologic finding was also present in 81% of these patients, including ptosis (n = 16), reduced eye motility (n = 22) including severe external ophthalmoplegia (n = 9), strabismus (n = 4), nystagmus (n = 9), low visual acuity (n = 21), refractive error (n = 26), photophobia (n = 4), and partial or total optic atrophy (n = 25) [28]. These data provide strong support for obtaining a dilated ophthalmological examination, including electroretinogram, in individuals of all ages with suspected mitochondrial disease.

## Secondary mitochondrial dysfunction in classic ophthalmologic diseases

Ophthalmologic diseases that have not traditionally been considered to have obvious mitochondrial origins are increasingly recognized to result in part from impaired mitochondrial function, increased oxidative stress, and increased apoptosis.

**Common mitochondrial pathophysiology**—As a high energy demand organ, the eye is particularly susceptible to the consequences of mitochondrial damage. Mitochondria are a major site of oxidative stress generation and scavenging. In addition, mitochondria are the mediators of cellular apoptosis that is initiated by the release of cytochrome c from the mitochondrial intermembrane space, where it plays an integral role in energy generation within the respiratory chain. Oxidative damage that results over time from mtDNA instability leads to cumulative mitochondrial damage, which is recognized to be an important pathogenic factor in age-related ophthalmologic disorders such as diabetic retinopathy, age-related macular degeneration, and glaucoma [30].

**Diabetic retinopathy**—Diabetic retinopathy is the leading cause of blindness in young adults. The pathogenesis of diabetic retinopathy involves progressive dysfunction of retinal mitochondria in the setting of hyperglycemia, with mtDNA damage and accelerated apoptosis occurring in retinal capillary cells [31]. Matrix metalloproteinase-2 (MMP2) now appears to be a central protein that mediates this process, as it becomes activated and pro-apoptotic in diabetic retinal cells [31]. Activated MMP2 causes mitochondrial membrane degradation through modulation of Hsp60 (heat shock protein 60) and damage to connexin 43, which activates the apoptotic machinery [32]. Antioxidant therapy, such as overexpression of the main mitochondrial superoxide scavenging enzyme, manganese superoxide dismutase (MnSOD), reduces MMP2-mediated mitochondrial damage and inhibits the development of diabetic retinopathy [31]. Targeted therapies to inhibit MMP2 activation may offer plausible new candidates for the treatment of diabetic retinopathy.

Other biomarkers of oxidative stress have been identified that may contribute to diabetic retinopathy. Proteomic analysis of *in vivo* mouse models exposed to constant light and *in vitro* models of increased oxidative stress led to the identification of prohibitin as a novel biomarker for oxidative stress in the retina and retinal pigment epithelium (RPE) [33]. Prohibitin regulation was found to be an early signaling event in the retina and RPE under conditions of oxidative stress, including in the settings of aging or diabetes mellitus.

Antioxidant scavenging of diabetes-induced oxidant stress has been the subject of several recent investigations. Overexpression of MnSOD in bovine RPE protected these cells from mtDNA damage and respiratory chain dysfunction that otherwise occurred due to glucose-induced oxidative damage [34]. In another study, a novel antioxidant agent, SS31, was found to attenuate glucose-induced injury in human diabetic retinal cells, where significantly decreased mitochondrial oxidant species generation, decreased cell destruction, and reduced cytochrome c release was seen following treatment of cells in high glucose media with SS31 [35]. These exciting findings underscore the potential reversibility of oxidative-stress mediated retinal damage in diabetes mellitus.

**Age-related macular degeneration (AMD)**—Retinal degeneration, particularly including AMD, is responsible for a large proportion of blindness in the elderly population. Light appears to have a deleterious effect on retinal cells that already have compromised mitochondrial function. Wavelengths of light ranging from 400 to 760 nm appear to specifically affect tissues that are replete with mitochondria by reducing the activity of mitochondrial dehydrogenases and increasing the release of reactive oxygen species [36]. Since retinal ganglion cells are not protected by macular pigments from short wavelengths



of light, they are particularly vulnerable to light-induced damage. Therefore, diseases of the retinal ganglion cells, such as AMD, may be exacerbated by light-induced mitochondrial dysfunction [36]. To determine whether pathogenic mtDNA variants also occur in patients with AMD, retinal and blood mtDNA were compared between AMD patients and age-matched controls [37]. The authors found that retinal cells had more mtDNA rearrangements and deletions than did blood, with a greater number of non-synonymous gene variants of potential pathogenic significance occurring in AMD patients. These mtDNA genome alterations seem to accumulate over time in the diseased retinal ganglion cells both as a consequence from, and likely ongoing cause of, oxidative stress that exacerbates mitochondrial dysfunction in the retina.

**Glaucoma**—Glaucoma is the second-leading cause of blindness worldwide. It is an optic neuropathy that manifests with optic nerve cupping and atrophy similar to what is observed in primary mitochondrial optic neuropathies [38]. The optic nerve is packed with mitochondria, making it particularly susceptible to impairment of mitochondrial respiratory capacity that can selectively damage RGCs [39]. Mitochondrial function may be impaired by mutations in either nuclear or mtDNA genes, mechanical stress or chronic hypoperfusion caused by increased intraocular pressure, toxic xenobiotics, or even light-induced oxidative stress [38]. A recent study found *OPA1* overexpression to have a protective affect on RGCs in a mouse model of glaucoma, decreasing the rate of apoptosis and possibly leading to decreased glaucomatous changes in the optic nerve [40]. Normal tension glaucoma has been shown to associate with cumulative sequence variants in several nuclear genes that encode mitochondrial proteins, including those involved in mitochondrial fusion [41].

A mitochondrial role in the development of primary congenital glaucoma, which is characterized by trabecular dysgenesis, has also been the subject of recent investigation. Developing trabecular meshwork is thought to have particular sensitivity to oxidative stress induced damage [42]. A recent study found an increased burden of potentially pathogenic mtDNA mutations among 35 congenital glaucoma patients relative to controls, which the authors postulated may impair mitochondrial function within the trabecular meshwork [42]. Such mitochondrial-mediated trabecular damage may conceivably be amenable to early initiation of antioxidant therapy, although additional studies will be needed to conclusively implicate mitochondrial dysfunction in the etiology of primary congenital glaucoma.

## Ocular Neoplasms

Ocular cancers, although rare, can be particularly aggressive, with significant morbidity and mortality. While the origin of these cancers is not typically considered to be mitochondrial, some recent investigational therapies have been targeted at disruption of mitochondrial function in tumor cells to specifically induce their apoptosis. Two such cancers studied in the past year were retinoblastoma and uveal melanoma.

**Retinoblastoma**—Retinoblastoma is the most common form of ocular cancer in children, with most cases diagnosed by 1–2 years old. Although potentially metastatic if left untreated, retinoblastoma is the most curable form of childhood cancer in the United States, with a 95% estimated cure rate [43]. A novel isoquinoline derivative, EDL-155, was recently evaluated as a potential agent to selectively destroy retinoblastoma cells [44]. *In vitro* treatment resulted in mitochondrial disruption and induction of autophagy. Additionally, the authors demonstrated *in vivo* treatment efficacy using a rat retinoblastoma model in which EDL-155 suggested localized tumor cell destruction after four periocular injections [44].

**Uveal melanoma**—Uveal melanoma, the most common primary intraocular tumor in adults, is a very rare and aggressive cancer associated with a poor prognosis, where up to half of patients develop liver metastases within 15 years of diagnosis [45]. A recent *in vitro* study of the effects of curcumin on uveal melanoma cells demonstrated induction of apoptosis [45]. Curcumin is a plant-derived polyphenol antioxidant and anti-inflammatory compound found in the spice turmeric, which prior studies have suggested has an *in vitro* apoptotic effect on cancers ranging from leukemia to solid tumors such as prostate and ovarian cancers [45, 46]. The viability of uveal melanoma cells was significantly decreased in a dose- and time-dependent manner following curcumin administration, where mitochondrial-induced apoptosis and cell destruction was progressively increased with greater curcumin concentrations. Therapies directed at inhibiting tumor-specific mitochondrial function thus hold promise as a novel means to treat ocular cancers.

## SUMMARY

Mitochondrial function is intimately linked to many aspects of ophthalmologic health. Primary mitochondrial diseases that are caused by mutations in either the nuclear genome or mitochondrial genome frequently involve clinically significant ophthalmologic disease that most commonly involves the optic nerve, retina, extraocular eye muscles, and eyelids. Recent work suggests that all individuals with primary mitochondrial disorders should be carefully evaluated for ophthalmologic involvement. Similarly, patients with “classic” mitochondrial disorders that primarily affect the eye should undergo evaluation for multi-systemic involvement, in particular affecting the brain, heart, hearing, and gastrointestinal tract. In recent years, it has become evident that mitochondrial dysfunction, perhaps through alterations in oxidative stress balance, contribute to a wide range of common and complex ophthalmologic diseases of aging, such as diabetic retinopathy, AMD, and glaucoma. Finally, even ocular cancers that are not known to result from primary mitochondrial causes may be treatable with agents that selectively induce mitochondrial toxicity within tumor cells. Such findings hold promise for improved diagnosis, management, and treatments of the mitochondrial causes and consequences of ophthalmologic disease across the age spectrum.

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## Abbreviations

<b>mtDNA</b>	mitochondrial DNA
<b>nDNA</b>	nuclear DNA
<b>CPEO</b>	chronic progressive ophthalmoplegia
<b>LHON</b>	Leber hereditary optic neuropathy
<b>DOA</b>	dominant optic atrophy
<b>MELAS</b>	mitochondrial encephalomyopathy lactic acidosis and stroke
<b>MERRF</b>	myoclonic epilepsy and ragged red fibers
<b>RGC</b>	retinal ganglion cells
<b>RPE</b>	retinal pigmented epithelium
<b>AMD</b>	age related macular degeneration

<b>MMP2</b>	matrix metalloproteinase
<b>MnSOD</b>	manganese superoxide dismutase

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**Table 1**  
**Major ophthalmologic manifestations of primary mitochondrial diseases**

DISEASE NAME	GENETIC DEFECT	OCULAR FINDINGS	INHERITANCE PATTERN
DOA	<i>OPA1</i>	Optic atrophy	Autosomal Dominant, Autosomal Recessive
LHON	mtDNA 11778G>A, 1448T>C, and 3460G>A mutations	Optic Neuropathy	Maternal
CPEO	<i>TYMP, ANT1, PEO1, POLG, POLG2</i>	Ptois, Ophthalmoplegia	Sporadic, Autosomal Dominant, Maternal
NARP	mtDNA 8993T>C mutation	Optic Atrophy, Retinopathy	Maternal
MELAS	mtDNA 3243A>G mutation	Retinopathy, Ophthalmoplegia	Maternal
MERRF	mtDNA 8344A>G mutation	Retinopathy	Maternal
KSS	Large-scale mtDNA deletions	Pigmentary Retinopathy, Ophthalmoplegia	Maternal
Leigh Syndrome	Multiple nuclear and mitochondrial genes	Retinopathy	Maternal

DOA=Dominant Optic Atrophy; LHON=Leber's Hereditary Optic Neuropathy; CPEO=Chronic Progressive External Ophthalmoplegia; NARP=Neurogenic weakness, Ataxia, Retinitis Pigmentosa; MELAS=Mitochondrial encephalomyopathy, Lactic acidosis, and stroke-like episodes; MERRF=Myoclonic epilepsy and Ragged Red Fibers; KSS=Kearns-Sayre Syndrome

**Table 2**  
**Additional mitochondrial diseases with ophthalmologic sequelae**

These diverse nuclear gene causes of mitochondrial disorders were not discussed in this review but also commonly involve ocular manifestations.

DISEASE	GENE	OCULAR FINDING	INHERITANCE PATTERN
Wolfram Syndrome	<i>WFS1</i>	Optic Atrophy	Autosomal recessive <sup>*</sup>
Friedrich's Ataxia	<i>FXN</i>	Optic Atrophy	Autosomal recessive
MNGIE	<i>TYMP</i>	Ptosis, Ophthalmoplegia	Autosomal recessive
HSP	<i>SPG7</i>	Optic Atrophy	Autosomal recessive, Autosomal dominant, X-linked

<sup>\*</sup> Wolfram-like syndrome and low-frequency sensorineural hearing loss are reported to be autosomal recessive disorders.

MNGIE=mitochondrial neurogastrointestinal encephalomyopathy; HMSN= hereditary motor sensory neuropathy; HSP = hereditary sensory paraplegia