Inherited mitochondrial optic neurpathies

P Yu-Wai-Man, G Griffiths, G Hudson, P F Chinnery

ABSTRACT

Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (DOA) are the two most common inherited optic neurpathies and they result in significant visual morbidity among young adults. Both disorders are the result of mitochondrial dysfunction: LHON from primary mitochondrial DNA (mtDNA) mutations affecting the respiratory chain complexes; and the majority of DOA families have mutations in the OPA1 gene, which codes for an inner mitochondrial membrane protein critical for mtDNA maintenance and oxidative phosphorylation. Additional genetic and environmental factors modulate the penetrance of LHON, and the same is likely to be the case for DOA which has a markedly variable clinical phenotype. The selective vulnerability of retinal ganglion cells (RGCs) is a key pathological feature and understanding the fundamental mechanisms that underlie RGC loss in these disorders is a prerequisite for the development of effective therapeutic strategies which are currently limited.

Mitochondrial disorders are a major cause of chronic human disease with an estimated prevalence of 1 in 10 000 in the UK and a further 1 in 200 individuals being at-risk mutational carriers. Ocular involvement is a prominent feature in this group and often points towards the underlying mitochondrial aetiology, which allows for a more targeted diagnostic approach. Optic nerve dysfunction can be the presenting and only ophthalmological manifestation causing the two most common inherited optic neurpathies encountered in clinical practice, Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (DOA), which are the focus of this review. In the majority of cases, the pathology in LHON and DOA is limited to a highly specialised group of cells within the eye, the retinal ganglion cells (RGCs), but the phenotype associated with these two conditions is expanding, providing important insights into possible disease pathways leading to optic nerve degeneration and visual failure.

LEBER HEREDITARY OPTIC NEUROPATHY

LHON mutations

LHON (OMIM 545000) was first described as a distinctive clinical entity in 1871 by the German ophthalmologist Theodore Leber (1840–1917). He reported a characteristic pattern of visual loss among members of four families and his observations were subsequently confirmed in pedigrees from different populations. These early studies highlighted several of the salient features of LHON including the maternal transmission of the disease, the predilection of males to lose vision, and the almost exclusive involvement of the optic nerve. The non-Mendelian pattern of inheritance was only fully explained in 1988 when LHON became the first human disease proven to be caused by a point mutation (m.11778G>A) within the mitochondrial genome. Over 95% of LHON pedigrees are now known to harbour one of three mitochondrial DNA (mtDNA) point mutations: m.3460G>A, m.11778G>A and m.14484T>C, which all involve genes encoding complex I subunits of the mitochondrial respiratory chain. In a meta-analysis of 159 pedigrees from Northern Europe and Australia, m.11778G>A was the most prevalent mutation but there is considerable variation in the relative frequency of these three primary LHON mutations worldwide (table 1). The predominance of m.11778G>A is even more pronounced in the Far East where it accounts for ~90% of all cases, and although m.14484T>C is relatively rare, it is the most common mutation found among French Canadians (87%) as a result of founder event. Primary mutations have not been identified in a small minority of clinically diagnosed LHON patients, the most likely explanation being that rare pathogenic mtDNA variants are segregating in these families. Disease causing mutations have been identified in a proportion of these cases, while other putative LHON mutations require further confirmation as they have only been found in singletons or a single family (table 1).

Epidemiology

LHON is the most common of the primary mtDNA diseases, with a minimum prevalence of 1 in 31 000 affected individuals in the North East of England and 1 in 8500 carriers being at-risk of visual loss. Fairly similar figures have been reported in other Caucasian populations, with an LHON prevalence of 1 in 39 000 in the Netherlands and 1 in 50 000 in Finland. About 2% of visually impaired people on the blind register in Australia are also reported to suffer from LHON. The peak age of onset in LHON is between the age of 15–30 years and 95% of carriers who will experience visual failure will do so before the age of 50 years (table 2). However, visual deterioration can occur anytime during the first to the seventh decade of life and LHON should be part of the differential diagnosis for all cases of bilateral, simultaneous or visual field loss.

Correspondence to: Professor P F Chinnery, Mitochondrial Research Group, The Medical School, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK; P.F. Chinnery@ncl.ac.uk

Received 8 September 2008
Revised 8 September 2008
Accepted 7 October 2008
Published Online First
17 November 2008
where family history is difficult to trace back, given that de novo mutations are rare in LHON.\textsuperscript{14, 24}

### Clinical features

#### Pre-symptomatic phase

Fundal abnormalities such as telangiectatic vessels around the optic discs and variable degrees of retinal nerve fibre layer oedema have been documented in some asymptomatic carriers, and these can fluctuate with time. Using optical coherence tomography imaging, thickening of the temporal retinal nerve fibre layer was found in a proportion of unaffected LHON carriers, which provides further evidence that the papillomacular bundle is particularly vulnerable in this disorder.\textsuperscript{25, 26} On more detailed psychophysical testing, some individuals also exhibited subtle impairment of optic nerve function including loss of colour vision affecting mostly the red–green system, reduced contrast sensitivity, and subnormal visual electrophysiological parameters.\textsuperscript{27}

### Acute phase

LHON carriers remain asymptomatic until they experience blurring or clouding of vision in one eye. In the vast majority of cases, visual dysfunction is bilateral, the fellow eye becoming affected either simultaneously (25%) or sequentially (75%), with a median inter-eye delay of 6–8 weeks.\textsuperscript{20} Rare cases of unilateral optic neuropathy in LHON have been reported, with the fellow eye remaining unaffected over a follow-up period of up to 16 years.\textsuperscript{22, 29} Visual acuity reaches a nadir 4–6 weeks after disease onset and it is severely reduced to 6/60 or less. The characteristic field defect is a steep-sided central or centrocaecal scotoma and this can be formally documented using Goldmann or kinetic perimetry. Other clinical features include the early impairment of colour perception but, importantly, pupillary reflexes are preserved and patients usually report no pain on eye movement. Ocular examination during the acute stage provides other diagnostic clues and in classical cases the following abnormalities can be observed: vascular tortuosity of the central retinal vessels, swelling of the retinal nerve fibre layer, and a circumpapillary telangiectatic microangiopathy (fig 1). However, it must be stressed that in ~20% of LHON cases, the optic disc looks entirely normal in the acute phase.\textsuperscript{30, 31}

### Chronic phase

The retinal nerve fibre layer gradually degenerates and after 6 months, optic atrophy is a universal feature. If a patient is only seen at this stage, it can be difficult to exclude other compressive, infiltrative and inflammatory causes of a bilateral optic neuropathy, especially if there is no clear maternal family history. In these cases, neuroimaging of the anterior visual pathways is mandatory while awaiting the results of molecular genetic testing.

### Visual recovery

Visual recovery is observed in some patients even several years following disease onset. but the chances of improvement are influenced by the patient’s mutational status, being least with the m.11778G>A mutation, highest with the m.14484T>C mutation, and the m.3460G>A mutation having an intermediate visual prognosis (table 2). The recovery in visual parameters is not only restricted to visual acuity, but can also include the development of small islands of normal field (fenestrations) within the central scotoma or a reversal of dyschromatopsia.\textsuperscript{32, 33} Positive prognostic factors for visual improvement are

### Table 1 Pathogenic mtDNA mutations associated with Leber hereditary optic neuropathy

| Mutation | Gene         | Prevalence (%) | Reference |
|----------|--------------|----------------|-----------|
| m.3460G>A | MT-ND1       | >95            | (n)       |
| m.11778G>A | MT-ND4      | 13             | 220, 221  |
| m.14484T>C | MT-ND6       | 14             | 32, 222   |

#### Table 2 Lifetime risk of visual failure for Leber hereditary optic neuropathy carriers and recovery rates

| Pedigrees | Median onset | Male:female ratio | Visual recovery (%) | Reference |
|-----------|--------------|-------------------|---------------------|-----------|
| m.3460G>A | 9            | 29 years          | 2.3:1               | 22        |
|           |              |                   |                     | 22        |
| m.11778G>A | 8            | 20 years          | 4.3:1               | 25        |
|           |              |                   |                     | 20        |
| m.14484T>C | 49           | 28 years          | 4.5:1               | 4         |
|           |              |                   |                     | 21        |
| m.14484T>C | 66           | 24 years          | 3.7:1               | 25        |
|           |              |                   |                     | 20        |
| m.14484T>C | 10           | 29 years          | 5.3:1               | 25        |
|           |              |                   |                     | 28        |
| m.14484T>C | 17           | 27 years          | 2.1:1               | 37        |
|           |              |                   |                     | 23        |
| m.14484T>C | 23           | 19 years          | 7.7:1               | 58        |
|           |              |                   |                     | 11        |
an early age of onset (<20 years), subacute presentation with slow progression of the visual deficits, and large optic nerve head surface area.\textsuperscript{25–28} However, LHON is a devastating disorder with the majority of patients showing no functional improvement and remaining within the legal requirement for blind registration.

**Associated features**

Although visual failure is the defining feature in this mitochondrial disorder, cardiac arrhythmias and neurological abnormalities such as postural tremor, peripheral neuropathy, non-specific myopathy and movement disorders have been reported to be more common in LHON compared to controls.\textsuperscript{35–38} These are rarely clinically significant but a small number of LHON pedigrees do have severe neurological deficits (spastic dystonia, ataxia and juvenile onset encephalopathy) in addition to the optic neuropathy. These “LHON plus” syndromes have been linked to various mtDNA mutations in isolated pedigrees from Holland, Australia and North America: A11696G and/or A4520G and m.14459A, 42–44 respectively. Two mutations are rarely clinically significant but a small number of LHON pedigrees do have severe neurological deficits (spastic dystonia, ataxia and juvenile onset encephalopathy) in addition to the optic neuropathy. These “LHON plus” syndromes have been linked to various mtDNA mutations in isolated pedigrees from Holland, Australia and North America: A11696G and/or A4520G and m.14459A, 42–44 respectively. Two mtDNA complex I mutations point mutations, m.3376G>A and m.3697G>A, have also recently been identified in individuals with overlap clinical features of both LHON and MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). Interestingly, a significant minority of Caucasian LHON carriers, predominantly females with the m.11778G>A mutation, develop clinical and neuroimaging features indistinguishable from multiple sclerosis (MS), including unmatched oligoclonal bands in the cerebrospinal fluid (Harding’s disease).\textsuperscript{47–50} It is currently not known whether the prevalence of this MS-like illness in LHON is higher than expected due to the chance occurrence of these two disorders, and although controversial, some investigators have argued for a potential role of autoimmunity in the pathophysiology of this mitochondrial disorder.\textsuperscript{51–55}

**Diagnosis**

A tentative diagnosis of LHON can usually be made on clinical grounds, especially if classical ophthalmological features are present and a clear maternal history is elicited. Molecular genetic testing on a blood DNA sample, however, remains the gold standard and will confirm that the patient harbours one of the three primary mtDNA LHON mutations, with implications for future genetic counselling. If indicated, electrophysiological studies, including pattern electroretinograms (PERGs) and visual evoked potentials (VEPs), can be carried out to exclude retinal pathology and confirm optic nerve dysfunction.\textsuperscript{56} An electrocardiogram is also recommended to exclude a pre-excitation syndrome which has been documented in LHON, although such a finding is rare and does not require any intervention in the absence of cardiac symptoms.\textsuperscript{50–52}

**Biochemical features**

Oxidative phosphorylation (OXPHOS) provides for most of the cell’s adenosine triphosphate (ATP) requirements and this is achieved by a chain of five respiratory complexes situated on the inner mitochondrial membrane. Since all three primary LHON mutations involve complex I subunits, one would expect respiratory chain function to be compromised, leading to a deficit in ATP synthesis and RGC degeneration as a consequence of energy failure. However, both in vitro and in vivo biochemical studies have produced conflicting results regarding the extent of respiratory chain dysfunction in LHON (table 3). In a small number of in vivo studies using phosphorous magnetic resonance spectroscopy (\(^{31}\text{P}-\text{MRS}\), the most consistent defect of mitochondrial function was identified in persons with the m.11778G>A mutation and none among those with the m.3460G>A mutation.\textsuperscript{63–65} A striking conclusion from all these biochemical studies is that no significant difference between affected and unaffected individuals with a disease causing LHON mutation could be demonstrated. But as none of these studies have been performed directly on RGCs and the causative biochemical mechanisms could be highly tissue-specific, further studies are warranted.

**Neuropathology**

These functional studies also raise important issues regarding the cell specific ocular pathology in LHON which is limited to the RGC layer, with sparing of the retinal pigment epithelium and photoreceptors. There is pronounced cell body and axonal degeneration, with associated demyelination and atrophy observed from the optic nerves to the lateral geniculate bodies. Experimental data indicate impaired glutamate transport,\textsuperscript{66} oxidative stress\textsuperscript{67,70} and increased mitochondrial reactive oxygen species (ROS)\textsuperscript{71} within RGCs and support an apoptotic mechanism of cell death.\textsuperscript{72–75} LHON patients also have reduced \(\alpha\)-tocopherol/lipid ratios and high levels of \(8\)-hydroxy-2-deoxy-guanosine in blood leucocytes, both biological markers of oxidative stress\textsuperscript{69,70} and increased mitochondrial reactive oxygen species (ROS)\textsuperscript{71} within RGCs and support an apoptotic mechanism of cell death.\textsuperscript{72–75} LHON patients also have reduced \(\alpha\)-tocopherol/lipid ratios and high levels of \(8\)-hydroxy-2-deoxy-guanosine in blood leucocytes, both biological markers of increased free radical production.\textsuperscript{74–75} However, the selective vulnerability of RGCs in LHON still remains unexplained, and this area of research has been greatly hampered by the lack of access to diseased human tissues, the retina and optic nerve not being amenable to biopsies.

**Animal models**

The development of faithful animal models in LHON is therefore critical but there is still no murine model where the primary LHON mutations have been successfully introduced within the mitochondrial genome. In spite of these technical challenges, significant advances have been made over the past decade and there are currently three experimental paradigms, all of which disrupt OXPHOS and recapitulate the optic nerve degeneration seen in LHON: (1) intravitreal injection of a respiratory chain poison such as rotenone\textsuperscript{76}; (2) downregulation of nuclear encoded complex I subunits (for example, NFUFA1) with specific mRNA-degrading ribozymes\textsuperscript{77}; and (3) allotypic expression of mutant subunits (for example, MTND4) which are then imported into the mitochondria.\textsuperscript{78}

**Table 3** Respiratory chain dysfunction in Leber hereditary optic neuropathy

| MtDNA mutation | In vitro\textsuperscript{33–34} | In vivo\textsuperscript{35–37} |
|----------------|----------------------------------|-----------------------------|
|                | Complex I activity (%) | Respiratory rate (%) | ATP synthesis | \(^{31}\text{P}-\text{MRS}\) (%) |
| m.3460G>A      | 60–80 | 30–35 | 90 | 0–40 |
| m.11778G>A     | 0–50 | 30–50 | 35 | 75 |
| m.14484T>C     | 0–65 | 10–20 | 90 | 50 |

ATP, adenosine triphosphate; \(^{31}\text{P}-\text{MRS}\), phosphorous magnetic resonance spectroscopy.

\% decrease relative to controls.
Incomplete penetrance
An intriguing feature of LHON is that only ~50% of males and ~10% of females who harbour one of the three primary mutations actually develop the optic neuropathy. This incomplete penetrance and predilection for males to lose vision imply that additional genetic and/or environmental factors must modulate the phenotypic expression of LHON (fig 2). Alternatively, the gender bias could also result from a combination of subtle anatomical, hormonal and physiological variations between males and females.

Mitochondrial genetic factors
Heteroplasmy
Depending on their metabolic demands, cells can contain anywhere between 100–100 000 mitochondria, and with 2–10 mtDNA molecules in each mitochondrion, this results in a very high copy number per cell. In most LHON pedigrees, the primary mutation is homoplasmic—that is, every mtDNA molecule harbours the mutant allele. By contrast, 10–15% of LHON carriers are thought to be heteroplasmic, with one mtDNA sub-population carrying the wild type allele. Although limited and retrospective, the available data suggest that heteroplasmy contributes to incomplete penetrance, with the risk of blindness being minimal if the mutational load is <60%. However, quantifying the level of heteroplasmy for the purpose of pre-symptomatic testing is limited as the majority of individuals with a LHON mutation are homoplasmic.

MtDNA haplogroups
MtDNA accumulates mutations ~10 times faster than nuclear genome, resulting in a high degree of polymorphism. Because human mtDNA is strictly maternally inherited and does not recombine, polymorphisms have accumulated sequentially along radiating female lineages as women migrated out of Africa into the different continents ~150 000 years ago. Reflecting its evolution, a number of stable polymorphic variants cluster together in specific combinations referred to as haplogroups, with individuals of European ancestry belonging to one of nine haplogroups: H, I, J, K, T, U, V, W and X.

A recent meta-analysis of 159 European LHON pedigrees indicated that the risk of visual loss for the three primary LHON mutations is influenced by the mtDNA background. The risk of visual failure was greater when the m.11778G>A and m.14484T>C mutations arose on haplogroup J, whereas individuals with the m.3460G>A mutation were more likely to experience visual loss if they belonged to haplogroup K. On the other hand, individuals with the m.11778G>A mutation had a lower risk of visual loss when the mutation arose on haplogroup H. Haplogroups H, J and K are all defined by non-synonymous, polymorphic substitutions in the MT-CYB gene which codes for cytochrome b, the only mitochondrially encoded subunit of complex III. Recent experimental data support the existence of stable respiratory chain supercomplexes, one of which consists of a complex I monomer physically interacting with a complex III dimer. Although speculative, the haplogroup associated amino acid substitutions within cytochrome b could therefore influence the risk of visual failure by modulating the biochemical consequences of the primary LHON mutations through an effect on the stability of these putative I-III supercomplexes.

In support of this hypothesis, hybrid cell lines carrying the m.11778AG>A mutation on a haplogroup J background had a lower oxygen consumption and a longer doubling time compared to non-haplogroup J cell lines. However, haplogroup J was not found to further impair mitochondrial OXPHOS in the brain and skeletal muscle of patients harbouring the m.11778G>A mutation with 31P-MRS measurements and a study of South-East Asian LHON pedigrees found no association between specific mtDNA haplogroups and the risk of visual loss. These contradictory findings reflect the need for additional studies to clarify the significance of the mtDNA background on LHON penetrance.

Nuclear genetic factors
The predominance of affected males in LHON cannot be explained by mitochondrial inheritance and segregation analysis suggests the existence of a recessive X-linked susceptibility gene acting in synergy with the mtDNA mutation to precipitate the optic neuropathy. In the Bu and Rotter model, the...
development of blindness in males is consistent with the simultaneous inheritance of an X-linked visual loss allele and the primary LHON mutation, whereas females are affected either if they are homozygous at the susceptibility locus (40%) or heterozygous with skewed X chromosome inactivation of the wild-type allele (60%). Several studies have, however, failed to demonstrate any skewed X chromosome inactivation in affected female carriers, albeit in blood leucocytes and not in RGCs which are the affected tissues in LHON. Initial attempts to identify this X-linked susceptibility locus by standard linkage analysis were unsuccessful, but two recent studies using a larger number of more extensively defined LHON pedigrees found two overlapping disease loci with highly significant LOD scores at Xp21–Xq21 and Xq25–27. Although the actual causative gene in this region of interest has not yet been identified, a high risk haplotype [DXS8090(166)-DXS1068(268)] at Xp21 was defined which increased the risk of visual failure 35-fold for the m.11778G>A and m14484T>C mutations but not for m.8460G>A. The possibility of other autosomal modifier genes in LHON has not been excluded and the genetic aetiology of LHON might prove even more complex, with epistatic interaction of these multiple nuclear susceptibility loci and genetic heterogeneity.

Environmental factors

Five pairs of monozygotic twins harbouring a primary LHON mutation have been reported in the literature, and in two cases the twins have remained discordant. Although there is always the possibility that the unaffected sibling will lose vision later on in life, the existence of discordant monozygotic twins strongly suggests that environmental factors also contribute to penetrance. There are several reports of an increased risk of visual loss among LHON carriers with high tobacco and alcohol consumption, but the largest case-control study to date has failed to confirm this association.

There are also anecdotal reports of nutritional deprivation, exposure to industrial toxins, antiretroviral drugs, psychological stress or acute illness precipitating the onset of blindness in LHON. Of note, in some pedigrees the penetrance of LHON seems to be decreasing, falling to 1% and 9% in younger generations of two large, multi-generational pedigrees from Australia and Brazil, respectively. Both carry homoplasmic levels of the m.11778G>A mutation and this phenomenon has been ascribed to improved environmental and socio-economic factors. However, a much larger epidemiological study of 3613 LHON carriers from multi-generational pedigrees failed to detect a change in the penetrance of the three primary LHON mutations. The role of environmental triggers in LHON remains largely unanswered and more robust epidemiological data are needed, which will necessitate a multicentre collaborative effort in order to collect sufficient number of subjects for analysis.

Treatment

No generally accepted measures have been shown to either prevent or delay the onset of blindness in LHON, but for general health reasons LHON carriers should be advised to moderate their alcohol intake and stop smoking. In two small case series, oral administration of idebenone, a synthetic analogue of cobenzyme Q10, and vitamin B12 and C supplementation led to faster and greater visual recovery among affected individuals. However, a recent study has not found any improved visual prognosis from idebenone and multivitamin supplementation, and properly conducted treatment trials are needed before such a regimen can be advocated. The use of brimonidine eye drops, which is thought to have anti-apoptotic properties, was also unsuccessful in preventing second eye involvement in recently affected patients with unilateral optic neuropathy. The long term management of visually impaired patients remains supportive, with provision of visual aids and registration with the relevant social services.

Genetic counselling

It is important to stress to LHON carriers that it is not possible to predict accurately whether or when they will become affected. Despite these caveats, the two main predictive factors for visual failure remain age and gender, with males having about a 50% lifetime risk of blindness compared to only 10% for females, and these approximate figures can be further refined based upon the patient’s age. From published age dependent penetrance data, most patients experience visual loss in their late teens and 20s and the probability of becoming affected decreases with increasing age, being minimal once past the age of 50 years (table 2). Once a primary LHON mutation has been identified in a proband, other maternally related family members can be offered molecular genetic testing to exclude the possibility of a de novo mutation, which is rare. Since LHON shows strict maternal inheritance, male carriers can be reassured that none of their children will inherit the mtDNA mutation whereas female carriers will transmit the pathogenic mutation to all of their offspring. Since most mothers are homoplasmic, their children will only harbour the mutant species, but the situation is more complex for a heteroplasmic mother as she could transmit a higher or a lower level of the mutation to a particular offspring, which will impact on the latter’s risk of visual failure. Although the mutant level can be determined and there is evidence that a mutational threshold of 60% in blood is necessary for disease expression, genetic counselling for these unaffected heteroplasmic carriers remains difficult. For similar reasons, the prenatal genetic testing of heteroplasmic women with amniocentesis or chorionic villus sampling (CVS) would be difficult to interpret.

DOMINANT OPTIC ATROPHY

Clinical features

The clinical features of DOA (OMIM 165500) were first described in one British family by Batten in 1896; the phenotype was further clarified by Kjer in his extensive study of Dutch families in the 1950s, distinguishing it from LHON with which the disease was often confused. The prevalence of DOA is not well established and robust estimates based on molecular confirmation are not available, although a historical figure of 1 in 50 000 among Caucasians is often quoted in the literature. It is thought to be the most common inherited optic neuropathy in the Netherlands, with a population frequency of 1 in 12 000, and this much higher prevalence has been linked to a mutational founder event.

The onset of symptoms in DOA is relatively insidious. In pre-molecular case series, 13–29% of patients with optic atrophy were visually asymptomatic and were only identified through contact tracing via other affected family members. Classically, the visual decline starts in the first two decades of life, but there is a pronounced inter- and intra-familial variability in the severity of visual symptoms, which makes genetic counselling difficult. Visual acuity can range from 6/6 to the detection of hand movement only, and the rate of
progression of visual loss is not easy to predict, with 19–50% of patients experiencing further, albeit slow, deterioration on long term follow up.\textsuperscript{125–127} Although the overall visual prognosis is better when compared to LHON, with a mean visual acuity of 6/24–6/36, DOA results in significant visual impairment with about half of all affected individuals failing the driving standards and 13–46% registered as legally blind.\textsuperscript{130–132}

The predominant colour defect in DOA is a generalised dyschromatopsia, involving both the blue–yellow and red–green axes, with a minority of patients having pure tritanopia (<10%), which was once considered to be a pathognomonic feature of DOA.\textsuperscript{133} Central, centrocaecal and paracentral scotomas are the most common field abnormalities with sparing of the periphery, findings consistent with the primary involvement of the papillomacular bundle in this condition. Interestingly, as in LHON, there is usually no afferent pupillary defect, suggesting that the retino-tectal fibres sub-serving the pupillary light reflex are less susceptible to the downstream effects of both the LHON mtDNA mutations and the causative nuclear genetic defects in DOA.\textsuperscript{134} However, both magnocellular and parvocellular RGC pathways seem to be similarly affected, although this requires further investigation.\textsuperscript{127, 135}

The optic disc pallor in DOA falls into two main categories: diffuse pallor involving the entire neuro-retinal rim in about half of all cases, and a temporal wedge in the remainder (fig 3).\textsuperscript{123, 135} However, disc pallor can be subtle and 29% of affected patients had normal looking optic discs in one case series, highlighting the need to look carefully for other features of optic nerve dysfunction when assessing patients with a possible diagnosis of DOA.\textsuperscript{125} Other common optic disc findings include saucering (79%), peripapillary atrophy (69%) and a cup to disc ratio >0.5 (48%).\textsuperscript{131, 135, 136} The measurement of circumpapillary retinal nerve fibre layer thickness using optical coherence tomography (OCT) could also prove a useful adjunct in the diagnostic work-up of DOA, with recent studies showing a typical profile with bilateral symmetrical thinning around the optic disc, most pronounced in the temporal quadrant.\textsuperscript{137, 138}

**Ocular pathology**

Postmortem studies of two patients with DOA identified similar histopathological changes, with diffuse atrophy of the RGC layer, loss of myelin and fibrillary gliosis along the anterior visual pathways extending to the lateral geniculate body.\textsuperscript{139, 140} More recent MRI data from patients with DOA have also confirmed significant tissue loss and thinning of the optic nerve along its entire length.\textsuperscript{141} Although less pronounced, the underlying ocular pathology in DOA is therefore remarkably similar to LHON, with the primary loss of RGCs leading to ascending optic atrophy.

Visual electrophysiological findings are well documented in DOA and provide additional evidence for the primary loss of RGCs and the sparing of the outer retinal layers.\textsuperscript{133, 142, 143} It can therefore be a useful ancillary test when determining affected status in borderline DOA cases and also in excluding a primary retinal process such as early cone dystrophy, VEPs are either absent or, if traces are recordable, they are of low amplitudes with abnormal latencies. PERGs can be within the normal range in up to 40% of clinically affected individuals but usually demonstrate an abnormal P50:N95 ratio, with selective depression of the N95 negative wave amplitude confirming a primary optic nerve pathology. Additional involvement of the P50 component correlates with the severity of visual loss, but PERGs are not extinguished even in cases where visual acuity is reduced to detection of hand movements or worse.

**Molecular genetics**

The majority of DOA families show linkage to the \textit{OPA1} locus at 3q28–q29, and in 2000 two independent research groups identified pathogenic mutations in the \textit{OPA1} gene.\textsuperscript{144, 145} The proportion of \textit{OPA1} positive families is ~60% (range 32–89%), the lower detection rates in some of these case series reflecting the inclusion of singleton cases, a heterogeneous group that is more likely to include non-inherited forms of optic neuropathy, and the use of less sensitive mutation screening protocols such as single strand conformational polymorphism (SSCP) analysis.\textsuperscript{146, 147} Interestingly, a recent report suggested that large scale rearrangements of entire \textit{OPA1} coding regions could account for up to 20% of all \textit{OPA1} negative cases.\textsuperscript{148}

The causative nuclear defects in the remaining families with DOA have not yet been identified, but a small number of families have been mapped to other chromosomal loci—\textit{OPA3}, \textit{OPA4}, \textit{OPA5} and \textit{OPA7}, of which only the \textit{OPA3} gene has been characterised (table 4). The \textit{OPA3} gene was originally identified in eight Iraqi Jewish families with an autosomal recessive form of optic atrophy, associated with neurocognitive deficits, elevated urinary excretion of 3-methyl glutaconic acid, and increased plasma 3-methylglutaric acid levels (type III 3-methylglutaconic aciduria or Costeff syndrome).\textsuperscript{149–151} However, pathogenic mutations in the \textit{OPA3} gene have also been identified in two French families segregating both DOA and premature cataract in an autosomal dominant mode of inheritance (ADOAC).\textsuperscript{152, 153} The Opal3 protein is located in the
mitochondrial inner membrane but its exact function remains to be clarified. Preliminary findings in cultured fibroblasts from a patient with ADOA indicate an increased susceptibility to apoptosis, and one can speculate that a similar mechanism is leading to RGC dysfunction via disruption of the mitochondrial respiratory chain.152 154 155

OPA1 mutations

The OPA1 gene consists of 30 exons spanning over 100 Kb of genomic DNA and it codes for a 960 amino acid, dynamin related GTPase protein located within the inner mitochondrial membrane. Alternative splicing of exons 4, 4b and 5b result in eight different mRNA isoforms, and both their functional relevance and subcellular localisation are currently being investigated.156 Over 140 pathogenic mutations have been identified and these cluster in two specific regions: the GTPase region (exons 8–15) and the C-terminus which is the proposed site of the GTPase effector domain. The majority of OPA1 mutations (~50%) lead to premature termination codons (PTCs) as a result of nonsense mutations or frameshifts from small insertions, deletions or splice site mutations (eOPA1 database at http://lbbma.univ-angers.fr/lbbma.php?id = 9).157 These truncated mRNAs are unstable and get degraded by specific pathways (nonsense mediated mRNA decay), which are in-built protective cellular mechanisms against mutant proteins with possible dominant negative effects.158–160 The reduced Opa1 protein expression levels observed in these cases support the role of haploinsufficiency in DOA and this is further substantiated by one family with a microdeletion resulting in complete loss of one copy of the OPA1 gene.161 However, ~30% of OPA1 mutations are missense mutations within or close to the GTPase domain and these could exert their pathogenic effect via a deleterious, gain of function mechanism.162–164

Gene expression

The spatial localisation and expression pattern of the Opa1 protein have been examined in a wide range of post-mitotic human and murine tissues. The Opa1 protein is ubiquitous and abundant in the outer Plexiform retinal layers.165 166 In the human optic nerve, Opa1 was detected along the axonal tracts both in the pre- and post-lamina cribrina regions.167 168 The Opa1 protein is ubiquitous and abundant levels have been identified in non-ocular tissues such as the inner ear and various areas of the human brain, with a similar distribution pattern of the different isoforms.169 170 Overall, these immunohistochemical studies indicate that differential tissue expression of the OPA1 gene or its isoforms do not seem to underlie the selective vulnerability of RGCs in DOA.

Protein function

The Opa1 protein is part of the large, dynamin GTPase family of mechanoenzymes and it was first identified in a screen for nuclear genes required for mtDNA maintenance in the budding yeast Saccharomyces cerevisiae. Both the human and yeast (Mgm1+) homologues show a high degree of evolutionary conservation and functional studies in DOA have revealed several other important cellular roles in addition to mtDNA maintenance.171 172

Mitochondrial maintenance

Opa1 is an important pro-fusion protein and works in tandem with other members of the dynamin related mitofusin family (mfn-1 and mfn-2) to balance the pro-fusion effects of other GTPases such as Drp1 and Fis-1.173 174 It is therefore not surprising that mitochondrial network disruption is a key pathological feature seen in fibroblasts from DOA patients and other tissue cultures, including RGCs, where the expression of the Opa1 protein has been disrupted—for example, by small interfering RNAs.162 175 176 Instead of a typical elongated, filamentous mitochondrial network, the latter becomes highly fragmented, with isolated mitochondria showing aberrant balloon-like enlargements. Transmission electron microscopy (TEM) also confirms altered mitochondrial ultrastructure with abnormal mitochondrial cristae organisation and paracrystalline inclusion bodies.162

Fusion is postulated to subserve a protective biological function by allowing the exchange and complementation of mitochondrial contents.177 178 In this respect, neuronal cells with deficient mitochondrial fusion show a loss of mtDNA nucleoids and this important finding provides a possible disease mechanism, with the reduced expression of essential, mtDNA encoded, respiratory chain subunits resulting in a bioenergetic deficit, increased ROS levels and a greater susceptibility to undergo apoptosis.179 180 These deleterious consequences could also contribute to the formation and clonal expansion of secondary mtDNA abnormalities such as mtDNA deletions, which have recently been identified in a subgroup of DOA families with a more complex multi-system involvement in addition to the optic neuropathy.162–164

Oxidative phosphorylation

Impaired mitochondrial biogenesis is central to the pathophysiology in DOA and there is good experimental evidence to support a predominant complex I defect. There is reduced mitochondrial membrane potential and ATP synthesis in fibroblast cultures carrying pathogenic OPA1 mutations,181 182 and in vivo disturbance of oxidative metabolism was evident in the calf muscle of patients with DOA using 31P-MRS.183

Immuno precipitation studies also suggest that the Opa1 protein, in conjunction with other structural proteins such as the apoptosis inducing factor (AIF), interacts directly with complexes I, II and III and plays an important role in the assembly and stabilisation of their various component subunits.176 This provides another causal link between OPA1 mutations and the resulting mitochondrial respiratory chain defect in DOA.

**Table 4** Dominant optic atrophy loci reported in OPA1 negative families

| OMIM | Reported locus | Causative gene | Families (n) | Clinical features | Reference |
|------|----------------|----------------|-------------|-----------------|-----------|
| 605293 | 19q13.2-q13.3 | OPA3 | 2 | Optic atrophy + premature cataract | 152 |
| 605293 | 19q13.2-q13.3 | Unknown | 1 | Optic atrophy* | 250 |
| 610708 | 22q12.1-q13.1 | Unknown | 2 | Optic atrophy* | 251 |
| – | 19q21-q22 | Unknown | 1 | Optic atrophy + deafness | 252 |

*Similar clinical phenotype to OPA1 positive families.
Apoptosis
Apoptosis is the final common pathway leading to RGC loss in DOA and cell death is likely to be complex, being triggered by a combination of several interacting factors. Opa1 is processed by various, inner membrane proteases which include the presenilin associated rhomboid-like protein (Parl) and paraplegin, and this proteolytic cleavage results in a soluble, intermembrane form in addition to the integral, membrane bound form. These two proteins combine into oligomers which modulate the morphology of the inner mitochondrial membrane and the tightness of the cristae junctions, a process independent of the role of Opa1 in controlling fusion. Downregulation of Opa1 leads to aberrant cristae remodelling and the release of cytochrome c which is normally sequestered in the narrow junctions within the cristae. This will either be sufficient on its own to induce the apoptotic cascade or will sensitize the cell to other pro-apoptotic stimuli such as AIF, increased ROS or the dissipation of the mitochondrial membrane potential.

Animal models
There are now two established mouse models of DOA, with heterozygous mutations in exon 8 (c.1051C>T) and intron 10 (c.1065+5g>a) of the Opa1 gene. These two mutations are truncative, resulting in a 50% reduction in the expression of the Opa1 protein, and therefore represent a haploinsufficiency disease mechanism. In both models, homozygous mutant mice (Opa1−/−) died in utero during embryogenesis, highlighting the central role played by the Opa1 protein in early development. Heterozygous Opa1+/− mice faithfully replicated the human phenotype exhibiting a slowly progressive optic neuropathy and demonstrating objective reduction in visual function on psychophysical testing. There was a gradual loss of RGCs, leading to thinning of the retinal nerve fibre layer, and the surviving optic nerve axons had an abnormal morphology with swelling, distorted shapes, irregular areas of demyelination and myelin aggregates. Mitochondria within these axons showed disorganised cristae structures on TEM and cultured fibroblasts showed fragmentation of the mitochondrial network. These two Opa1 mouse models represent powerful tools for dissecting the pathways mediating the preferential loss of RGCs in DOA, by allowing functional studies to be performed directly on these specialised cells, something which is not possible in humans given the lack of ocular tissues. These mutant mice will also prove useful when investigating the potential therapeutic benefit of future biological agents which could be injected into the vitreous cavity, allowing direct access with the RGC layer.

Expanding phenotype
The hallmark of DOA is bilateral visual failure, but sensorineural deafness is a well reported association which is more commonly observed with some pathogenic mutations such as the p.R445H mutation. In his original description, Kjer also documented neurodevelopmental abnormalities in 10% of his Dutch cohort, although this has not been reported in other populations. More recently, DOA families have been described where the optic atrophy was segregating with additional ocular and extraocular features such as progressive external ophthalmoplegia, ptosis, myopathy, ataxia, neuropathy, and an MS-like disorder. These syndromal variants of DOA, so-called “DOA plus”, have been linked with the accumulation of multiple mtDNA deletions, a finding consistent with the presence of cytochrome c oxidase (COX) deficient fibres in limb muscle biopsies from affected individuals. All of the causative OPA1 mutations in these families were missense mutations with most, but not all of them, within the catalytic GTPase site of the protein. Although the actual proportion of families with these “DOA plus” phenotypes is as yet unknown, clinicians need to be aware of these additional clinical features as these can be subtle and therefore easily missed if not looked for specifically.

Genetic counselling
There is currently no treatment to influence the disease process in DOA and clinical management, as for LHON, is supportive. Despite DOA being an autosomal dominant Mendelian disorder, genetic counselling for mutational carriers is difficult because of the pronounced inter- and intra-familial variability in the visual phenotype. There are no definite genotype–phenotype correlations but missense mutations within the GTPase domain of the protein are more likely to result in a complex, multi-systemic involvement, although it must be stressed that this observation requires further investigation in a larger cohort of DOA families.

With the availability of molecular testing for OPA1 becoming more accessible, an increasing number of individuals with pathogenic mutations are being identified who are otherwise visually unaffected. The penetrance is >80% in well characterised, multi-generational families but figures as low as 43% have been reported, probably reflecting the different assessment criteria used (range 43–100%). This incomplete penetrance together with the variable clinical expressivity in both pure DOA and “DOA plus” families clearly imply that other, as yet unidentified, secondary factors are potentiating the deleterious effects of the OPA1 mutations.

MITOCHONDRIAL OPTIC NEUROPATHIES
The concept of inherited mitochondrial optic neuropathies is expanding with evidence of impaired mitochondrial function in other genetic diseases where optic nerve dysfunction is a recognised clinical feature (table 5). These include: (1) Friedreich’s ataxia where up to a third of cases have an optic neuropathy; (2) hereditary motor and sensory neuropathy type 6 (HMSN-6), a variant of Charcot–Marie–Tooth (CMT) disease defined by the presence of both optic atrophy and peripheral neuropathy; and (3) the hereditary spastic paraplegias (HSP).

Table 5 Other inherited optic neuropathies linked to mitochondrial dysfunction

| Disease                  | OMIM      | Inheritance | Gene (protein) | Protein function                                                                 | References |
|--------------------------|-----------|-------------|----------------|---------------------------------------------------------------------------------|------------|
| Friedreich’s ataxia      | 229300    | Ar          | FXN (frataxin) | Component of iron-sulfur clusters: regulation of mitochondrial respiratory chain activity and anti-oxidant properties | 253, 254   |
| HMSN-6                  | 601152    | Ad          | MFN2 (mitofusin-2) | Mitochondrial outer membrane GTPase: pro-fusion protein involved in maintenance of the mitochondrial network and mtDNA nucleoids (cif Opa1) | 216, 217, 255 |
| HSP-7                   | 607259    | Ar          | SPG7 (paraplegin) | Mitochondrial inner membrane protease: cleavage of Opa-1, control of mitochondrial ribosomal assembly and degradation of misfolded proteins | 219, 256   |

Ar, autosomal recessive; Ad, autosomal dominant.
Glucoma is the second most common cause of blindness in developed countries and accounts for about 10% of all blind registration in the UK. It is a primary, acquired optic neuropathy with a strong genetic component and OPA1 mutations have been identified in a number of patients initially diagnosed with normal tension glaucoma, highlighting the similarities in optic disc features shared with DOA. With other investigators reporting mtDNA abnormalities in their glaucoma cohorts, such as an increased mtDNA copy number and reduced respiratory chain activities in peripheral blood lymphocytes. Although further studies are needed, these findings suggest a possible mitochondrial influence on the pathogenesis of glaucoma.

UNIFYING HYPOTHESIS

The common theme in the various optic neuropathies described in this review is the vulnerability of RGCs to mitochondrial dysfunction. Although there is a high level of mitochondrial enzyme activity in RGCs, this phenomenon cannot be explained by a simple energetic deficit since photoreceptors have a much higher oxidative demand than RGCs and other mitochondrial disorders characterised by more severe complex I defects do not universally cause optic atrophy. It is possible that RGCs are preferentially involved because they are more sensitive to subtle imbalances in cellular redox state or increased ROS levels, but an attractive hypothesis implicates the differential mitochondrial concentration observed at the lamina cribosa. The lamina cribosa is a perforated collagen plate that marks the anatomical transition from the unmyelinated (pre-laminar) to the myelinated (post-laminar) segment of the human optic nerve. The pre-laminar section has a much higher concentration of mitochondria to support the higher energy demands of unmyelinated nerve conduction and it is likely that active processes involving the cytoskeletal architecture are needed to maintain this sharp mitochondrial gradient. Pathological mechanisms which disrupt this unique structural feature would lead to impaired axonal transport, as seen in CMT and HSP, and set up a vicious circle with fragmentation of the mitochondrial network at the lamina cribosa exacerbating even subtle mitochondrial energy deficits and eventually precipitating apoptotic cell death.

CONCLUSION

LHON and DOA show an intriguing degree of clinical and mechanistic overlap, with both disorders caused by the selective degeneration of the RGC layer. They are the two most common inherited optic neuropathies and they provide strong evidence that the maintenance of RGCs is heavily dependent upon normal mitochondrial function. This is further substantiated by recent studies pointing towards a mitochondrial link in sporadic glaucoma and other genetic disorders where optic nerve dysfunction is a prominent clinical feature. Although major advances have been achieved in the two decades since the primary LHON mutations were identified, several key questions remain unanswered. What secondary factors account for the notable incomplete penetrance and male bias in LHON? What explains the variable disease expression in DOA, and why is there no gender bias in this disorder, given the similarity to LHON? What are the causative nuclear genes in OPA1-negative families and will they also involve mitochondrial dysfunction? What mechanisms underpin the preferential loss of RGCs in these mitochondrial optic neuropathies? The characterisation of recently developed animal models and future genetic and functional studies will hopefully reveal important pathophysiological pathways amenable to therapeutic interventions.

Acknowledgements: PFC is a Wellcome Trust Senior Fellow in Clinical Science and PWWM is an MRC Clinical Research Fellow.

Competing interests: None.

REFERENCES

1. Schaefer AM, McFarland R, Blakely EL, He L, Whitaker RG, Taylor RW, Chinnery PF, Turnbull DM. Prevalence of mitochondrial DNA disease in adults. Ann Neurol 2008;63:35–9.
2. Elliott HI, Samuels DC, Eden JA, Relton CL, Chinnery PF. Pathogenic mitochondrial DNA mutations are common in the general population. Am J Hum Genet 2008;83:254–60.
3. Leber T. Ueber hereditare und congenital angelegte sehnervenleiden. Graefes Arch Ophthalmol 1871;17:249–91.
4. Bell J. Hereditary optic atrophy (Leber’s disease). In: Pearson K, ed. The treasury of human inheritance. Cambridge: Cambridge University Press, 1931:345–423.
5. Imai Y, Moriwaki D. A probable case of cytolytic inheritance in man: a critique of Leber’s disease. J Genet 1936;33:163–7.
6. Lundsgaard R. A genealogic, genetic and clinical study of 101 cases of retrolubar optic neuritis in 20 Danish families. Acta Ophthalmol 1944;21:1–306.
7. Wallace DC, Singh G, Lott MT, Hodges JA, Schurr TG, Lezza AM, Elas S, Nikoskelainen EK. Mitochondrial DNA mutation associated with Leber’s hereditary optic neuropathy. Science 1998;242:1427–30.
8. Mackey DA, Oostra RJ, Rosenberg T, Nikoskelainen E, Bronte-Stewart J, Poulet J, Harding AE, Guven G, Bulhuis PA, Norby S. Primary pathogenic mtDNA mutations in multigeneration pedigrees with Leber’s hereditary optic neuropathy. Am J Hum Genet 1996;59:481–5.
9. Mashima Y, Yamada K, Wakaikura M, Kigasaki K, Kudoh J, Shimizu N, Oguchi Y. Spectrum of pathogenic mitochondrial DNA mutations and clinical features in Japanese families with Leber’s hereditary optic neuropathy. Curr Eye Res 1998;19:403–8.
10. Yan MY, Wang AG, Chang WL, Hsu WM, Liu JH, Wei YH. Leber’s hereditary optic neuropathy-the spectrum of mitochondrial DNA mutations in Chinese patients. Am J Ophthalmol 2005;140:419–26.
11. Macmillan C, Kirkham T, Fu K, Allison V, Andermann D, Chitayat D, Forget D, Gans M, Hare H, Ducrea N, Zacchin D, Shoubridge EA. Pedigree analysis of French Canadian families with T14484C Leber’s hereditary optic neuropathy. Neurology 1998;50:417–22.
12. Macmillan C, Johns TA, Fu K, Shoubridge EA. Predominance of the T14484C mutation in French-Canadian families with Leber hereditary optic neuropathy is due to a founder effect [letter]. Am J Hum Genet 2000;66:332–5.
13. Taylor RW, Jobling MS, Turnbull DM, Chinnery PF. Frequency of rare mitochondrial DNA mutations in patients with suspected Leber’s hereditary optic neuropathy. J Med Genet 2005;42:676–82.
14. Man PY, Griffiths PG, Brown DT, Howell N, Turnbull DM, Chinnery PF. The epidemiology of Leber hereditary optic neuropathy in the North East of England. Am J Hum Genet 2003;72:333–9.
15. Spruill L, Kolbach DN, de Coo RF, Plomp AS, Bauw NJ, Smeets HJ, de Die-Smulders CEM. Influence of mutation type on clinical expression of Leber hereditary optic neuropathy. Am J Ophthalmol 2006;141:676–82.
16. Puomia A, Hamalainen P, Kivioja S, Savontaus ML, Koskimaki S, Huponen K, Nikoskelainen E. Epidemiology and penetrance of Leber hereditary optic neuropathy in Finland. Eur J Hum Genet 2007;15:1079–9.
17. Mackey DA, Burtrey RG. Leber hereditary optic neuropathy in Australia. Aust N Z J Ophthalmol 1992;20:177–84.
18. Yu-Wai-Man P, Bateman DE, Hudson G, Griffiths PG, Chinnery PF. Leber hereditary optic neuropathy presenting in a 75-year-old man. J Neuroophthalmol 2001;21:155.
19. Elodi LM, Rizzo JF, 3rd, Cestari DM. Leber’s hereditary optic neuropathy in an adult patient. Aust N Z J Ophthalmol 2000;28:676–82.
20. Newman NJ, Lott MT, Wallace DC. The clinical characteristics of pedigrees of Leber hereditary optic neuropathy with the 11178 mutation. Am J Ophthalmol 1991;111:750–62.
21. Johns DR, Smith KH, Miller NR. Leber’s hereditary optic neuropathy. Clinical manifestations of the 3460 mutation. Arch Ophthalmol 1992;110:1577–81.
22. Johns DR, Heher KL, Miller NR, Smith KH. Leber’s hereditary optic neuropathy. Clinical manifestations of the 14484 mutation. Arch Ophthalmol 1993;111:495–8.
23. Bioussé V, Brown MD, Newman NJ, Allen JC, Rosenfeld J, Meola G, Wallace DC. De novo 14484 mitochondrial DNA mutation in nonsyntogenic twins discordant for Leber’s hereditary optic neuropathy. Neurology 1997;49:1316–8.
24. Singh G, Barboni P, Benito ML, Montopoli P, Cortelli P, De Negri AM, Sadun A, Bianchi S, Longanesi L, Zanini M, Carelli V. Retinal nerve fiber layer evaluation by optical coherence tomography in unaffected carriers with Leber’s hereditary optic neuropathy. Ophthalmology 2005;112:127–31.

J Med Genet 2009;46:145–158. doi:10.1136/jmg.2007.054270 on 10 November 2008. Downloaded from http://jmg.bmj.com/ on October 19, 2022 by guest. Protected by copyright.
Review

26. Quiros PA, Torres RJ, Salomao S, Berezovsky A, Carelli V, Sherman J, Sadun F, De Negri A, Belfort R, Sadun AA. Colour vision defects in asymptomatic carriers of the Leber’s hereditary optic neuropathy (LHON) mtDNA 11778 mutation from a large Brazilian LHON pedigree: a case-control study. Br J Ophthalmol 2006;90:150–3.

27. Sadun AA, Salomao SR, Berezovsky A, Sadun F, Denegri AM, Quiros PA, Chianci F, Ventura D, Barbour P, Sherman J, Sutter E, Belfort RJ Jr, Carelli V, Patji S, Kevinsen M, Finel M, Hassinen IE. Subclinical carriers and conversions in Leber hereditary optic neuropathy: a prospective psychophysical study. Trans Am Ophthalmol Soc 2006;104:51–61.

28. Nikoskelainen EK, Huoponen K, Juvonen V, Lammintie T, Nummelin K, Savontaus ML. Ophthalmologic findings in Leber hereditary optic neuropathy, with special reference to mtDNA mutations. Ophthalmology 1996;103:504–14.

29. Sugitsuka E, Okabe H, Shindo K, Masahara Y. Woman with avascular unilateral Leber’s hereditary optic neuropathy with visual improvement. Clin Exp Ophthalmol 2007;35:688–70.

30. Nikoskelainen EK. Clinical picture of LHON. Clin Neurosci 1994;2:115–20.

31. Riordan-Eva P, Harding AE. Leber’s hereditary optic neuropathy: the clinical relevance of different mitochondrial DNA mutations. J Med Genet 1995;32:1–7.

32. Mackey D, Howell N. A variant of Leber hereditary optic neuropathy characterized by recovery of vision and by an unusual mitochondrial genetic etiology. Am J Hum Genet 1992;51:1218–28.

33. Howell NW, Kubacak i, Xu M, McCullough DA. Leber hereditary optic neuropathy: involvement of the mitochondrial ND1 gene and evidence for an intragenic suppressor mutation. Am J Hum Genet 1991;48:935–42.

34. Den DD, White NT, Bynon GW, Sahle TR, Hofstra RM, Bolhuis PA, van Oost BA. Genetic and biochemical impairment of mitochondrial complex I activity in a family with Leber hereditary optic neuropathy and hereditary spastic dystonia. Am J Hum Genet 1996;58:703–11.

35. Howell NW, Kubacak i, Xu M, McCullough DA. Leber hereditary optic neuropathy: involvement of the mitochondrial ND1 gene and evidence for an intragenic suppressor mutation. Eur J Hum Genet 2005;13:624–7.

36. Spruit JT, Smeets HJ, Hendrickx A, Bettink-Remeijer MW, Maat-Kievit AJ. A compound heterozygote for Leber’s hereditary optic neuropathy and Leigh disease. Neurol Genet 2005;12:47–20.

37. Harding AE. Leber’s hereditary optic neuropathy: the clinical relevance of different mitochondrial DNA mutations. J Med Genet 1995;32:1–7.

38. Blakely EL, de Silva R, King A, Schwarzer V, Harrer T, Dawidé G, Turnbull DM, Taylor RW. LHON/MELAS overlap syndrome associated with a mitochondrial ND1 gene mutation. Eur J Hum Genet 2005;13:624–7.

39. Spruit JT, Smeets HJ, Hendrickx A, Bettink-Remeijer MW, Maat-Kievit AJ. A compound heterozygote for Leber’s hereditary optic neuropathy and Leigh disease. Neurol Genet 2005;12:47–20.

40. Kellar-Wood JS, Wood JA, Meyers WA, Schapira AH, Mayeux R, Trope M, Bejjani BA. Genetic and biochemical impairment of mitochondrial complex I activity in a family with Leber hereditary optic neuropathy and hereditary spastic dystonia. Am J Hum Genet 1996;58:703–11.

41. Blakely EL, de Silva R, King A, Schwarzer V, Harrer T, Dawidé G, Turnbull DM, Taylor RW. LHON/MELAS overlap syndrome associated with a mitochondrial ND1 gene mutation. Eur J Hum Genet 2005;13:624–7.

42. Skowron JS, Smeets HJ, Hendrickx A, Bettink-Remeijer MW, Maat-Kievit AJ. A compound heterozygote for Leber’s hereditary optic neuropathy and Leigh disease. Neurol Genet 2005;12:47–20.

43. Kellar-Wood JS, Wood JA, Meyers WA, Schapira AH, Mayeux R, Trope M, Bejjani BA. Genetic and biochemical impairment of mitochondrial complex I activity in a family with Leber hereditary optic neuropathy and hereditary spastic dystonia. Am J Hum Genet 1996;58:703–11.

44. Blakely EL, de Silva R, King A, Schwarzer V, Harrer T, Dawidé G, Turnbull DM, Taylor RW. LHON/MELAS overlap syndrome associated with a mitochondrial ND1 gene mutation. Eur J Hum Genet 2005;13:624–7.

45. Spruit JT, Smeets HJ, Hendrickx A, Bettink-Remeijer MW, Maat-Kievit AJ. A compound heterozygote for Leber’s hereditary optic neuropathy and Leigh disease. Neurol Genet 2005;12:47–20.

46. Kellar-Wood JS, Wood JA, Meyers WA, Schapira AH, Mayeux R, Trope M, Bejjani BA. Genetic and biochemical impairment of mitochondrial complex I activity in a family with Leber hereditary optic neuropathy and hereditary spastic dystonia. Am J Hum Genet 1996;58:703–11.

47. Blakely EL, de Silva R, King A, Schwarzer V, Harrer T, Dawidé G, Turnbull DM, Taylor RW. LHON/MELAS overlap syndrome associated with a mitochondrial ND1 gene mutation. Eur J Hum Genet 2005;13:624–7.
83. Smith KH, Johns DR, Heeler KL, Miller NR. Heteroplasmia in Leber's hereditary optic neuropathy. Arch Ophthalmo 1993;111:1486–90.

84. Chinnery PF, Andrews RM, Turnbull DM, Howells NW. Leber hereditary optic neuropathy: does heteroplasmy influence the inheritance and expression of the G11778A mitochondrial DNA mutation? J Am Med Genet 2001;98:235–43.

85. Brown WM, George M Jr, Wilson AC. Rapid evolution of animal mitochondrial DNA. Proc Natl Acad Sci USA 1979;76:1867–71.

86. Wallace DC, Brown MD, Lott MT. Mitochondrial DNA variation in human evolution and disease. Gene 1989;83:211–30.

87. Torroni A, Huoponen K, Francalacci P, Petracca M, Morelli L, Scacchi R, Obinu D, Savontaus ML, Wallace DC. Classification of European mtDNAs from an analysis of three European populations. Genetics 1994;138:1835–30.

88. Hofmann S, Jakisch M, Bozdag R, Mertens S, Aholt S, Poppotta A, Gehrke KD. Population genetics and disease susceptibility: characterization of central European haplogroups by mtDNA gene mutations, correlation with D loop variants and association with disease. Hum Mol Genet 1997;6:1835–46.

89. Hudson G, Carelli V, Spruit J, Gerards M, Mowbray C, Achilli A, Pyle A, Elston J, Howell N, La Morgia C, Valentino ML, Huoponen K, Savontaus ML, Nikoskelainen E, Sadun AA, Salomao SR, Belfort R, Griffth P, Man PWY, de Coo RMJ, Horvath R, Zeviani M, Smeets HJT, Torroni A, Chinnery PF. Clinical expression of Leber hereditary optic neuropathy is affected by the mitochondrial DNA-haplogroup background. Am J Hum Genet 2007;81:228–33.

90. Dutkina NV, Eubeil H, Keegstra W, Bokema E, Braun HP. Structure of a mitochondrial supercomplex formed by respiratory-chain complexes I and III. Proc Natl Acad Sci USA 2005;102:3225–9.

91. Carelli V, Achilli A, Valentino ML, Rengo C, Semino O, Pala M, Oliveri A, Mattiazzi M, Palotti F, Carrara F, Zeviani M, Leuzzi C, Carducci M, Simonetti B, Mendiola L, Salomao S, Belfort R, Scuderi P, Man PWY, de Coo RMJ, Horvath R, Zeviani M, Smeets HJT, Torroni A, Chinnery PF. Mitochondrial mutations associated with Leber's hereditary optic neuropathy: studies on cytoplasmic hybrid (cybrid) cells. Biochim Biophys Acta 2000;1500:218–28.

92. Tharapahan PW, Kuentseewang KL, Laungtrakool K, Sanpachudtay T, Sukiptit B, Suphavilai R, Sirisawat C, Sura T, Lertrit P. Mitochondrial DNA haplogroup distribution in pedigrees of Southeast Asian G11778A Leber hereditary optic neuropathy. J Neurol Sci 2006;249:284–9.

93. Bu XD, Rotter J. X chromosome-linked and mitochondrial gene control of Leber hereditary optic neuropathy: evidence for segregation dependence on X chromosome inactivation. Proc Natl Acad Sci USA 1991;88:8198–202.

94. Bu X, Rotter J. Leber hereditary optic neuropathy: estimation of number of embryonic precursor cells and disease threshold in heterogeneous affected females at the X-linked locus. Clin Genet 1992;42:143–8.

95. Nakamura M, Fujiyawa Y, Yamamoto M. The two locus control of Leber hereditary optic neuropathy and a high penetrance in Japanese pedigrees. Hum Genet 1993;91:339–41.

96. Pegoraro E, Carelli V, Zeviani M, Cortelli P, Montagna P, Barboni P, Angelini C, Chinnery PF. X-inactivation patterns in female Leber's hereditary optic neuropathy patients do not support a strong X-linked determinant. Am J Med Genet 1996;61:356–62.

97. Oostra RJ, Kemp S, Bolhuis PA. Bleeker-Wagemakers EA. No evidence for ‘skewed’ inactivation of the X-chromosome in Leber's hereditary optic neuropathy in female carriers. Hum Genet 1996;97:503–7.

98. Hudson G, Carelli V, Horvath R, Zeviani M, Smeets HJ, Chinnery PF. X-inactivation patterns in females harboring mtDNA mutations that cause Leber hereditary optic neuropathy. Mol Vis 2007;13:2393–43.

99. Chen JD, Cox I, Denton MJ. Preliminary exclusion of an X-linked gene in Leber hereditary optic neuropathy by linkage analysis. Hum Genet 1989;82:203–7.

100. Carvalho MM, Muller B, Rotter E, Bieringer T, Kommereil G, Blankenberg A, Savontaus ML, Meltinger T, Lorenc M. Leber's hereditary optic neuropathy: the X-chromosomal susceptibility factor: no linkage to DXS7. Hum Hered 1992;42:216–21.

101. Sweeney MG, Davis MB, Lashworth A, Brockington M, Toscano A, Harding AE. Evidence against an X-linked locus close to DXS7 determining visual loss susceptibility in British and Italian families with Leber hereditary optic neuropathy. Am J Hum Genet 1992;51:741–8.

102. Handoko HY, Wirapat J, Sudoyo HA, Stipeau M, Marzuki S. Meiotic breakpoint mapping of a proposed linked visual loss locus provides evidence for a novel X-linked modifier locus for Leber hereditary optic neuropathy. J Med Genet 1998;35:688–71.

103. Hudson G, Keers S, Man PWY, Griffiths P, Huoponen K, Savontaus ML, Nikoskelainen E, Zeviani M, Carrara F, Horvath R, Karcagi V, Spruit J, de Coo RMJ, Smeets HJ, Chinnery PF. Identification of an X-chromosomal locus and haplotype modulating the phenotype of a mitochondrial DNA disorder. Am J Hum Genet 2005;77:1086–91.

104. Shankar SP, Fingert JH, Carelli V, Valentino ML, King TM, Dager SP, Salomao SR, Berezovsky A, Belfort R, Braun TA, Sheffield VC, Sadun AA, Stone EM. Evidence for a novel X-linked modifier locus for Leber hereditary optic neuropathy. Ophthalmol. Am J Ophthalmol. 2008;146:21–24.

105. Nickoskelainen EK, Savontaus ML, Wanpe OP, Kasila MJ,Nummelin KJ. Leber's hereditary optic neuropathy, a maternally inherited disease. A genealogic study in four pedigrees. Arch Ophthalmo 1987;105:665–71.
156. Schimpf S, Fuhrmann N, Schiach S, Wissinger B. Comprehensive cDNA study and quantitative transcript analysis of mutant OPA1 transcripts containing premature termination codons. J Med Genet 2008;2009:45:656–62.

160. Marchbank NJ, Craig JE, Leek JP, Tooyee M, Churchill AJ, Markham AF, Mackay DA, Toomes C, Inglehearn CF. Deletion of the OPA1 gene in a dominant optic atrophy family: evidence that haploinsufficiency is the cause of disease. J Med Genet 2002;39:487.

161. Votruba M, Johnston PB, Bremner FD, Berninger TA, Cohn AC, Newman NJ, Davies V, Alexander C, Anikster Y, Schimpf S, Schwanzbachfischer B, Martin MA, Avenos J, Ayuso C, Garasses R, Lenars G, Bonneau D, Carelli V. OPA1 mutations induce mitochondrial DNA instability and optic atrophy plus phenotypes. Brain 2008;131:338–51.

162. Ferrarin S, Lill C, Best G. Mitochondrial DNA depletion in isolated liver tissue from patient with MERRF. J Med Genet 2001;38:751–5.

163. Adachi-Usami E, Leary S, Losseff N, Bhattacharya SS, Moore AT, Miller DH, Moseley IF. Effects of OPA1 mutations on mitochondrial morphology and apoptosis: relevance to ADOA pathogenesis. J Cell Mol Med 2005;9:827–35.

164. Nunnari J. The intramitochondrial dynamin-related GTPase, Mgm1p, is a component of a protein complex that mediates mitochondrial fusion. Mol Biol Cell 1999;10:253–62.

165. Prat KM, Wetmore JL. OPA1 is a critical determinant of mitochondrial morphology and function. Cell 2001;105:511–22.

166. Chinnery PF, Ahlqvist K, Suomalainen A, Reynolds P, McFarland R, Turnbull DM, Chinnery PF. OPA1 mutations are associated with autism spectrum disorders, ataxia, and hearing loss. Brain 2004;127:569–77.

167. Huntly B, Patel A, Alimohammadi M, Fazeli SS, Boulton ME, Votruba M. A novel 19q13 region deletion in a family with progressive optic atrophy. J Med Genet 2002;39:407–86.

168. Marsden DB, De María A, Toomes C, Inglehearn CF. Deletion of the OPA1 gene in a dominant optic atrophy family: evidence that haploinsufficiency is the cause of disease. J Med Genet 2002;39:487.

169. Votruba M, Johnston PB, Bremner FD, Berninger TA, Cohn AC, Newman NJ, Davies V, Alexander C, Anikster Y, Schimpf S, Schwanzbachfischer B, Martin MA, Avenos J, Ayuso C, Garasses R, Lenars G, Bonneau D, Carelli V. OPA1 mutations induce mitochondrial DNA instability and optic atrophy plus phenotypes. Brain 2008;131:338–51.

170. Ferrarin S, Lill C, Best G. Mitochondrial DNA depletion in isolated liver tissue from patient with MERRF. J Med Genet 2001;38:751–5.

171. Adachi-Usami E, Leary S, Losseff N, Bhattacharya SS, Moore AT, Miller DH, Moseley IF. Effects of OPA1 mutations on mitochondrial morphology and apoptosis: relevance to ADOA pathogenesis. J Cell Mol Med 2005;9:827–35.

172. Nunnari J. The intramitochondrial dynamin-related GTPase, Mgm1p, is a component of a protein complex that mediates mitochondrial fusion. Mol Biol Cell 1999;10:253–62.

173. Prat KM, Wetmore JL. OPA1 is a critical determinant of mitochondrial morphology and function. Cell 2001;105:511–22.

174. Chinnery PF, Ahlqvist K, Suomalainen A, Reynolds P, McFarland R, Turnbull DM, Chinnery PF. OPA1 mutations are associated with autism spectrum disorders, ataxia, and hearing loss. Brain 2004;127:569–77.

175. Huntly B, Patel A, Alimohammadi M, Fazeli SS, Boulton ME, Votruba M. A novel 19q13 region deletion in a family with progressive optic atrophy. J Med Genet 2002;39:407–86.

176. Marsden DB, De María A, Toomes C, Inglehearn CF. Deletion of the OPA1 gene in a dominant optic atrophy family: evidence that haploinsufficiency is the cause of disease. J Med Genet 2002;39:487.

177. Votruba M, Johnston PB, Bremner FD, Berninger TA, Cohn AC, Newman NJ, Davies V, Alexander C, Anikster Y, Schimpf S, Schwanzbachfischer B, Martin MA, Avenos J, Ayuso C, Garasses R, Lenars G, Bonneau D, Carelli V. OPA1 mutations induce mitochondrial DNA instability and optic atrophy plus phenotypes. Brain 2008;131:338–51.

178. Ferrarin S, Lill C, Best G. Mitochondrial DNA depletion in isolated liver tissue from patient with MERRF. J Med Genet 2001;38:751–5.

179. Adachi-Usami E, Leary S, Losseff N, Bhattacharya SS, Moore AT, Miller DH, Moseley IF. Effects of OPA1 mutations on mitochondrial morphology and apoptosis: relevance to ADOA pathogenesis. J Cell Mol Med 2005;9:827–35.

180. Nunnari J. The intramitochondrial dynamin-related GTPase, Mgm1p, is a component of a protein complex that mediates mitochondrial fusion. Mol Biol Cell 1999;10:253–62.

181. Prat KM, Wetmore JL. OPA1 is a critical determinant of mitochondrial morphology and function. Cell 2001;105:511–22.

182. Chinnery PF, Ahlqvist K, Suomalainen A, Reynolds P, McFarland R, Turnbull DM, Chinnery PF. OPA1 mutations are associated with autism spectrum disorders, ataxia, and hearing loss. Brain 2004;127:569–77.

183. Huntly B, Patel A, Alimohammadi M, Fazeli SS, Boulton ME, Votruba M. A novel 19q13 region deletion in a family with progressive optic atrophy. J Med Genet 2002;39:407–86.

184. Marsden DB, De María A, Toomes C, Inglehearn CF. Deletion of the OPA1 gene in a dominant optic atrophy family: evidence that haploinsufficiency is the cause of disease. J Med Genet 2002;39:487.

185. Votruba M, Johnston PB, Bremner FD, Berninger TA, Cohn AC, Newman NJ, Davies V, Alexander C, Anikster Y, Schimpf S, Schwanzbachfischer B, Martin MA, Avenos J, Ayuso C, Garasses R, Lenars G, Bonneau D, Carelli V. OPA1 mutations induce mitochondrial DNA instability and optic atrophy plus phenotypes. Brain 2008;131:338–51.

186. Ferrarin S, Lill C, Best G. Mitochondrial DNA depletion in isolated liver tissue from patient with MERRF. J Med Genet 2001;38:751–5.

187. Adachi-Usami E, Leary S, Losseff N, Bhattacharya SS, Moore AT, Miller DH, Moseley IF. Effects of OPA1 mutations on mitochondrial morphology and apoptosis: relevance to ADOA pathogenesis. J Cell Mol Med 2005;9:827–35.

188. Nunnari J. The intramitochondrial dynamin-related GTPase, Mgm1p, is a component of a protein complex that mediates mitochondrial fusion. Mol Biol Cell 1999;10:253–62.

189. Prat KM, Wetmore JL. OPA1 is a critical determinant of mitochondrial morphology and function. Cell 2001;105:511–22.

190. Chinnery PF, Ahlqvist K, Suomalainen A, Reynolds P, McFarland R, Turnbull DM, Chinnery PF. OPA1 mutations are associated with autism spectrum disorders, ataxia, and hearing loss. Brain 2004;127:569–77.

191. Huntly B, Patel A, Alimohammadi M, Fazeli SS, Boulton ME, Votruba M. A novel 19q13 region deletion in a family with progressive optic atrophy. J Med Genet 2002;39:407–86.
Review

239. Degli Esposti M, Carelli V, Ghelli A, Ratta M, Crimi M, Sangiorgi S, Montagna P, Lenaz G, Lugaresi E, Cortelli P. Functional alterations of the mitochondrially encoded ND4 subunit associated with Leber’s hereditary optic neuropathy. FEBS Lett 1999;352:375–9.

240. Cock HR, Cooper JM, Schapira AH. The 14484 ND6 mtDNA mutation in Leber hereditary optic neuropathy does not affect fibroblast complex I activity [letter]. Am J Hum Genet 1995;57:1501–2.

241. Oostra RJ, Van Galert MJ, Bolhuis PA, Bleeker-Wagemakers EM, Van den Bogert C. The mitochondrial DNA mutation ND4*14,484C associated with Leber hereditary optic neuropathy, leads to deficiency of complex I of the respiratory chain. Biochem Biophys Res Commun 1995;215:1001–5.

242. Montagna P, Plazzi G, Cortelli P, Carelli V, Lugaresi E, Barboni P, Flocchi M. Abnormal lactate after effort in healthy carriers of Leber’s hereditary optic neuropathy [letter]. J Neurol Neurosurg Psychiatry 1994;57:201–7.

243. Majander A, Finel M, Savontaus ML, Nikoskelainen E, Wikstrom M. Catalytic activity of complex I in cell lines that possess replacement mutations in the ND genes in Leber’s hereditary optic neuropathy. Eur J Biochem 1996;239:291–7.

244. Hofhaus G, Johns DR, Hurko O, Attardi G, Dhomyn A. Respiration and growth defects in transmittochondrial cell lines carrying the 11778 mutation associated with Leber’s hereditary optic neuropathy. J Biol Chem 1996;271:13155–61.

245. Carelli V, Ghelli A, Ratta M, Baechldeca E, Sangiorgi S, Mancini R, Leuzzi V, Cortelli P, Montagna P, Lugaresi E, Degli Esposti M. Leber’s hereditary optic neuropathy: biochemical effect of 11778/ND4 and 3460/ND1 mutations and correlation with the mitochondrial genotype. Neurology 1997;48:1623–32.

246. Cock HR, Tabrizi SJ, Cooper JM, Schapira AH. The influence of nuclear background on the biochemical expression of 3460 Leber’s hereditary optic neuropathy. Ann Neurol 1998;44:187–93.

247. Cock HR, Cooper JM, Schapira AH. Functional consequences of the 3460-bp mitochondrial DNA mutation associated with Leber’s hereditary optic neuropathy, J Neurol Sci 1998;165:10–7.

248. Brown MD, Troncoso, Jun AS, Allen JC, Wallace DC. Functional analysis of lymphoblast and cybrid mitochondria containing the 3460, 11778, or 14484 Leber’s hereditary optic neuropathy mitochondrial DNA mutation. J Biol Chem 2000;275:39831–6.

249. Baracca A, Solani G, Gargi G, Lenaz G, Baruzzi A, Schapira AH, Martirnuzi A, Carelli V. Severe impairment of complex I-driven adenosine triphosphate synthesis in Leber hereditary optic neuropathy cybrids. Arch Neurol 2005;62:730–6.

250. Kerrison JB, Arnold VLJ, Sallum JMF, Vageli MR, Barmada MM, Li YY, Zhu DP, Maumenee IH. Genetic heterogeneity of dominant optic atrophy. Kjer type - Identification of a second locus on chromosome 18q12.2–12.3. Arch Ophthalmol 1999;117:805–10.

251. Barbet F, Hakli S, Oussaud C, Gerber S, Periatt I, Hanein S, Ducrocq D, Dufier JL, Munnich A, Kaplan J, Rozet JM. A third locus for dominant optic atrophy on chromosome 22q. J Med Genet 2005;42:a1.

252. Carelli V, Schimpfl S, Valentino ML, Fuhrmann N, Papke M, Scharf S, Tippmann S, Baumann B, Barboni P, Ghelli A, Bucli L, Lodi R, Barbirol B, Lugouri R, Carocci R, Villanova M, Montagna P, Baruzzi A, Wilsinger B. Dominant optic atrophy (DOA) and sensorineural hearing loss: clinical, biochemical, spectroscopic and molecular genetic study of a large Italian pedigree linked to a new locus on chromosome 16. Neurology 2007;68:A42.

253. Puccio H, Koenig M. Friedreich ataxia: a paradigm for mitochondrial diseases. Curr Opin Neurol Dev 2002;12:272–7.

254. Rouault TA, Tong WH. Iron-sulphur cluster biogenesis and mitochondrial iron homeostasis. Nat Rev Mol Cell Biol 2005;6:345–51.

255. Zuchner S, Vance JM. Mechanisms of disease: a molecular genetic update on hereditary axonal neuropathies. Nat Clin Pract Neurol 2006;2:45–53.

256. Casari G, Rugarli E. Molecular basis of inherited spastic paraplegias. Curr Opin Genet Dev 2001;11:336–42.

Drug and Therapeutics Bulletin (DTB)

Your key source of unbiased, independent advice
For over 45 years DTB has been an independent, indispensable part of evidence-based clinical practice. DTB offers healthcare professionals detailed assessment of, and practical advice on, individual medicines and other treatments, groups of treatment and the overall management of disease.

DTB is now also available online at http://dtb.bmj.com:
► browse or search all DTB content from the latest issue back to 1994
► email alerting, sophisticated searching, RSS feeds and full text links from cited references
► interactive services such as My Folders for quick access to articles that you have viewed previously and My Searches to save and re-use useful searches
► comment online on any DTB article

To subscribe, or for further information, please visit http://dtb.bmj.com

Drug and Therapeutics Bulletin (DTB)

Your key source of unbiased, independent advice
For over 45 years DTB has been an independent, indispensable part of evidence-based clinical practice. DTB offers healthcare professionals detailed assessment of, and practical advice on, individual medicines and other treatments, groups of treatment and the overall management of disease.

DTB is now also available online at http://dtb.bmj.com:
► browse or search all DTB content from the latest issue back to 1994
► email alerting, sophisticated searching, RSS feeds and full text links from cited references
► interactive services such as My Folders for quick access to articles that you have viewed previously and My Searches to save and re-use useful searches
► comment online on any DTB article

To subscribe, or for further information, please visit http://dtb.bmj.com

Drug and Therapeutics Bulletin (DTB)

Your key source of unbiased, independent advice
For over 45 years DTB has been an independent, indispensable part of evidence-based clinical practice. DTB offers healthcare professionals detailed assessment of, and practical advice on, individual medicines and other treatments, groups of treatment and the overall management of disease.

DTB is now also available online at http://dtb.bmj.com:
► browse or search all DTB content from the latest issue back to 1994
► email alerting, sophisticated searching, RSS feeds and full text links from cited references
► interactive services such as My Folders for quick access to articles that you have viewed previously and My Searches to save and re-use useful searches
► comment online on any DTB article

To subscribe, or for further information, please visit http://dtb.bmj.com
Correction

P Yu-Wai-Man, P G Griffiths, G Hudson, et al. Inherited mitochondrial optic neuropathies. J Med Genet 2009;46:145−58. Errors appeared in the first paragraph of the ‘Clinical features’ section in this paper. The correct paragraph should read as follows:

‘The clinical features of DOA (OMIM 165500) were first described in one British family by Batten in 1896 [119, 120], the phenotype was further clarified by Kjer in his extensive study of Danish families in the 1950’s, [119, 120] distinguishing it from LHON with which the disease was often confused. The prevalence of DOA is not well established and robust estimates based on molecular confirmation are not available, although a historical figure of 1 in 50,000 among Caucasians is often quoted in the literature. [121] It is thought to be the most common inherited optic neuropathy in Denmark with a population frequency of 1 in 12,000, and this much higher prevalence has been linked to a mutational founder event. [122]

J Med Genet 2011;48:284. doi:10.1136/jmg.2007.054270corr1