

ELECTRONIC LETTER

Mitochondrial DNA haplogroup distribution within Leber hereditary optic neuropathy pedigrees

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Leber hereditary optic neuropathy (LHON; OMIM #535000) is a mitochondrial genetic disease that causes blindness in young adults, with an estimated minimum prevalence of 3.2 per 100 000 in the north east of England.¹ It classically presents as bilateral subacute loss of central vision due to the focal neurodegeneration of the retinal ganglion cell layer. Over 95% of cases are principally due to one of three "primary" mtDNA point mutations: 3460G→A, 11778G→A, and 14484T→C, all of which involve genes that encode complex I subunits of the mitochondrial respiratory chain. However, less than ~50% of male and ~10% of female LHON carriers will develop the optic neuropathy.^{2,3} This marked incomplete penetrance and gender bias clearly indicates that additional genetic and/or environmental factors are required for the phenotypic expression of the pathogenic mtDNA mutations in LHON. However, these secondary factors remain poorly defined at the present time.

There has recently been considerable interest in the possible role of the mtDNA background on the phenotypic expression of mitochondrial genetic disorders. The hypothesis is that on their own, some polymorphisms are selectively "neutral" but that in specific combinations, they act in a synergistic, deleterious manner with established pathogenic mtDNA mutations to increase the risk of disease expression or to produce a more severe clinical outcome.⁴ The following nucleotide substitutions are found at a higher frequency in LHON patients relative to controls:⁵⁻⁷ 4216T→C, 4917A→G, 9804G→A, 9438G→A, 13708G→A, 15257G→A, and 15812G→A. Phylogenetic analysis has shown that 4216T→C, 13708G→A, 15257G→A, and 15812G→A all cluster on a specific mtDNA background, haplogroup J, which is one of the nine haplogroups that define populations of European ancestry.^{8,9} Several studies have subsequently found that LHON pedigrees that harbour the 11778G→A and 14484T→C mutations are apparently not randomly distributed along the phylogenetic tree, but tend to show a preferential association with haplogroup J (table 1). It has therefore been argued that these polymorphic variants interact with the primary mtDNA mutations, increasing the risk of visual loss among LHON carriers. However, the potential pathogenic role of these so-called "secondary" mtDNA mutations in LHON is still controversial. All the association studies published so far involved a relatively small number of pedigrees collected over a wide geographical area by centres with a specialist interest in LHON, thereby raising the possibility of ascertainment bias. To investigate further the presumed association between primary LHON mutations and haplogroup J, we determined the haplogroup distribution of a rigorously defined, population based LHON cohort from the north east of England, and carried out a systematic statistical review of the literature.

Key points

- Over 95% of Leber hereditary optic neuropathy (LHON) pedigrees harbour one of three mitochondrial DNA (mtDNA) point mutations: 3460G→A, 11778G→A, or 14484T→C. However, additional genetic and/or environmental factors influence the penetrance of the primary mtDNA mutations that cause focal degeneration of the optic nerve in LHON.
- There is evidence that the mtDNA background could be relevant for the phenotypic expression of LHON.
- We carried out a meta-analysis of 297 published LHON pedigrees and confirmed the strength of the association between one specific mtDNA lineage, haplogroup J, and two of the primary LHON mutations: 11778G→A (odds ratio (OR)=3.48, 95% confidence interval (CI) 2.36 to 5.15) and 14484T→C (OR=27.53, 95% CI 14.53 to 52.13), and confirmed the absence of an association with the 3460G→A mutation (OR=1.29, 95% CI 0.57 to 2.90).
- The most compelling explanation is that the risk of visual loss in LHON carriers with the 11778G→A and 14484T→C mutations is increased by haplogroup J, and by extension, one or more of the mtDNA polymorphisms that define this haplogroup.

MATERIALS AND METHODS

Study population

Patients presenting with unexplained visual failure or suspected LHON within the north east of England were referred to the Northern Genetics Service based in Newcastle upon Tyne over the 12 year period from January 1990 to May 2002. Diagnostic mitochondrial genetic analysis was then carried out within the Mitochondrial Research Group of the Department of Neurology, University of Newcastle upon Tyne. This led to the identification of 15 genealogically distinct LHON pedigrees, confirmed by sequencing of the mtDNA D-loop region¹ (table 2).

Haplogroup determination

One member of each pedigree was analysed and the haplogroup was determined by restriction enzyme analysis of the relevant PCR amplified mtDNA fragment, as described previously.¹⁰ The haplogroup distribution of 179 normal

Abbreviations: LHON, Leber hereditary optic neuropathy; mtDNA, mitochondrial DNA

controls from the north east of England had also been determined previously using the same protocol.¹¹

Systematic review

Published studies that had analysed haplogroup distribution in LHON pedigrees were identified by searching the main electronic databases (MedLine and Web of Science) from 1988, when the first LHON mutation was reported.¹² The keywords used in the search strategy were “optic atrophy”, “mitochondrial DNA”, “haplogroup”, and “phylogeny”. The reference lists of relevant papers were also assessed for the presence of additional studies not listed in these databases. Finally, the main investigators in the field of mitochondrial genetics were also contacted personally to obtain any unpublished data that might clarify some of their published results, especially if the raw data were not provided in the original paper.

Study selection

For the purpose of this review, studies (published or unpublished) were included only if sufficient data had been collected by the investigators to allow the haplogroup to be clearly deduced for their LHON pedigrees. In some of these studies, haplogroup status was not reported directly. However, pedigrees could still be grouped as being either J or non-J, as long as the polymorphic status at nucleotide positions 4216 and 13708 had been determined.^{9, 10} As far as possible, we tried to ascertain that all included pedigrees were unrelated and of European extraction.

Statistical analysis

A meta-analysis was carried out using the Mantel-Haenszel method as implemented in the Cochrane Review ManagerTM software (version 4.1). A fixed effect model was adopted given the lack of significant heterogeneity between the included studies (<http://www.cochrane.de/cochrane/hbook.htm>).

RESULTS

In our population based LHON cohort from the north east of England, there was a trend towards haplogroup J being over-represented in 11778G→A and 14484T→C pedigrees compared with our control population, but this was not statistically significant because of the small number of pedigrees involved (table 2). A total of 10 other haplogroup J association studies were identified through our search strategy (table 1). The main findings of our statistical meta-analysis are summarised graphically by a forest plot (fig 1).

For the 3460G→A pedigrees, the prevalence of haplogroup J (7.8%) was not significantly different to that in normal controls (9.3%) (odds ratio (OR) = 1.29 (95% CI 0.57 to

2.90)). Haplogroup J was moderately over-represented for the 11778G→A pedigrees (26.8% v only 9.3% in controls; OR = 3.48; 95% CI 2.36 to 5.15). There was a strong association between the 14484T→C mutation and haplogroup J (OR = 27.53; 95% CI, 14.53 to 52.13). Over 75% of the 14484T→C LHON pedigrees belong to haplogroup J, as against only ~11% of the control mtDNAs.

DISCUSSION

This meta-analysis confirms the reported association between two of the primary LHON mutations, 11778G→A and 14484T→C, and haplogroup J. This was particularly marked for 14484T→C, with pedigrees harbouring this mutation being ~30 times more likely to belong to this particular haplogroup than controls. While it is important to consider the possibility that these results are influenced by the method of ascertainment, particularly through a publication bias following the identification of the so-called “secondary” LHON mtDNA mutations in 1991, the magnitude of the association is so great that it seems unlikely that this can be the sole explanation. Moreover, our epidemiological study of LHON in a defined geographical region revealed the same trend towards a haplogroup J association, adding weight to our conclusion.

How can we explain the association between mtDNA haplogroup J and the 11778G→A and 14484T→C mutations? It is conceivable that this could be due to an early founder effect, whereby the 11778G→A and 14484T→C mutations arose early in the evolution of haplogroup J, leading to its over-representation on that mitochondrial lineage. There is some evidence in support of this hypothesis in the Dutch population,¹³ but this cannot provide a complete explanation because all three primary LHON mutations have arisen multiple times on different mitochondrial backgrounds¹⁰ (see also the discussion in Howell *et al*¹³ and Brown *et al*¹⁴). Moreover, none of these mtDNA mutations has been found in the large sample of normal control mitochondrial genomes that belong to haplogroup J (for examples, see <http://www.genpat.uu.se/mtDB/index.html>). There are a number of other possible explanations for this haplogroup J association. This particular mtDNA haplogroup J appears to be associated with successful ageing,¹⁵ a high complex I activity in spermatozoa,¹⁶ and a lower risk of developing Parkinson's disease,¹⁷ although the latter is still contentious.¹⁸ These putative “protective” effects of haplogroup J could confer a competitive advantage, leading to persistence of LHON mutations in the population, as has already been suggested,¹⁹ but it is difficult to see why this should be specific for the 11778G→A and 14484T→C LHON mutations only. Although a point of great debate, the most compelling

Table 1 Summary of haplogroup association studies in LHON

Study	Year	Controls			3460G→A			11778G→A			14484T→C		
		n	J	Non-J	n	J	Non-J	n	J	Non-J	n	J	Non-J
⁵	1991	175	16	159	–	–	–	36	4	32	–	–	–
⁶	1991	175	16	159	9	2	7	–	–	–	–	–	–
²⁶	1992	179	25	174	3	0	3	14	7	7	5	3	2
²⁷	1993	175	16	159	–	–	–	–	–	–	15	12	3
²²	1994	160	16	144	8	0	8	16	2	14	9	8	1
⁸	1995	175	16	159	10	1	9	17	4	13	8	6	2
²⁸	1997	67	5	62	4	1	3	23	10	13	21	14	7
¹⁰	1997	99	7	92	7	0	7	28	11	17	2	2	0
²⁹	1997	529	33	496	3	0	3	13	4	9	–	–	–
³⁰	1999	78	9	69	2	0	2	27	4	23	2	1	1
Current study		179	25	174	5	0	5	9	3	6	1	1	0

In most of these studies, haplogroup distribution for a representative sample of normal controls from the local population was also reported. If the latter was not provided, this was sought either directly from the original investigators or from other published sources: Finland^{9, 25} and the Netherlands (Dr G Barbuji, personal communication).

Table 2 Haplogroup distribution in the north east of England

Group	n	Haplogroup					Others
		H	U	J	K	T	
3460G→A	5	3	1	–	1	–	–
11778G→A	9	3	1	3	2	–	–
14484T→C	1	–	–	1	–	–	–
Controls	179	74 (41)	32 (18)	25 (14)	21 (12)	18 (10)	9 (5)

% in brackets.

explanation is that the risk of visual loss is increased by haplogroup J.

If this mtDNA background does have a deleterious effect, it would be expected that haplogroup J should result in a more pronounced respiratory chain defect, and thus influence the phenotype of LHON. Cybrid cell lines carrying the 11778G→A

mutation and haplogroup J were shown to have a lower oxygen consumption and a longer doubling time compared with cell lines with the 11778G→A mutation alone.²⁰ However, a recently published study showed no difference in respiratory chain function between cybrid cell lines harbouring mtDNA from different haplogroups on the same

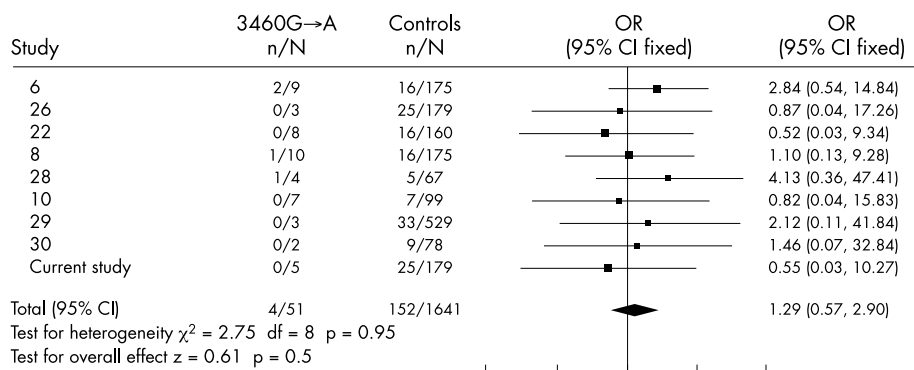
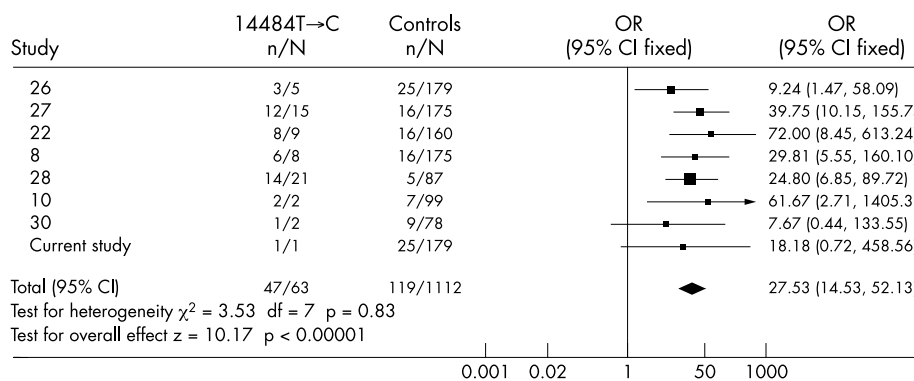
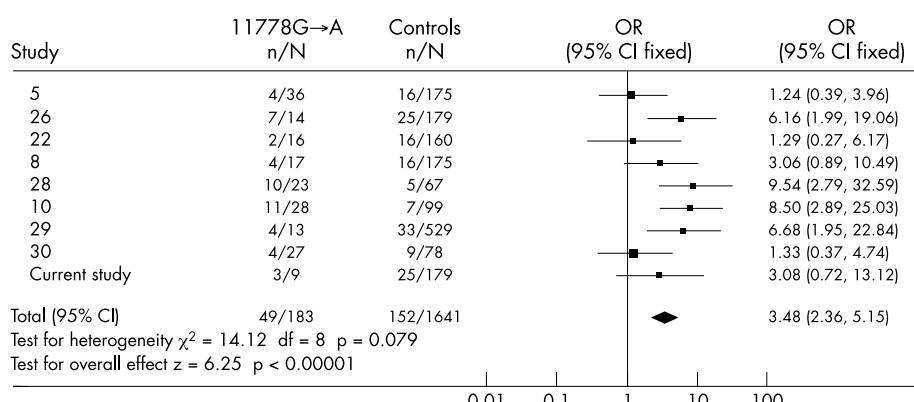


Figure 1 Meta-analysis of haplogroup J association studies. Comparison of (A) LHON 3460G→A v controls; (B) LHON 11778G→A v controls; (C) LHON 14484T→C v controls. OR, odds ratio. An OR of 1.0 indicates that the prevalence of haplogroup J is the same in both LHON and controls; OR < 1.0, under-represented; OR > 1.0, over-represented. The size of each square is proportional to the amount of information provided by the study. The diamond shaped figure denotes the combined results for all the included trials.



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nuclear genetic background.¹⁹ In vivo magnetic resonance spectroscopy in patients harbouring the 11778G→A mutation also failed to detect any deleterious effect in brain and skeletal muscle from haplogroup J.²¹ The influence of haplogroup J on the biochemical features of the 14484T→C mutation has not yet been determined. This result would be interesting in order to clarify the much stronger association of haplogroup J with 14484T→C compared with 11778G→A. However, these studies will require cautious interpretations, given that both in vitro and in vivo biochemical studies have produced conflicting results regarding the extent of respiratory chain dysfunction in LHON. There is currently no evidence that haplogroup J influences age of onset or final visual outcome in LHON, although this trend requires further confirmation in a larger LHON cohort.²² Haplogroup J is one of nine European specific haplogroups, and therefore it would also be expected that LHON should be more common in populations of European extraction. This hypothesis will be difficult to test, given the paucity of data regarding the prevalence of LHON in different ethnic groups, and potential confounding factors such as a population bottleneck.²³

The analysis presented here also provides strong statistically based evidence that there is no association between haplogroup J and the 3460G→A mtDNA mutation. This is a most intriguing finding, given the strong haplogroup affiliation for the two other primary LHON mutations. However, the 3460G→A mutation seems to behave differently in a number of ways. Firstly, 3460G→A is the LHON mutation most consistently associated with a significant biochemical complex I defect; secondly, compared with the 14484T→C mutation, it is associated with a poorer visual outcome; and thirdly, it is associated with a less prominent gender bias.²⁴ This evidence suggests that 3460G→A is perhaps a “stronger” mutation—that is, less susceptible to the epistatic and epigenetic factors influencing the expression of the 14484T→C mutation and possibly the 11778G→A mutation.

Based on our meta-analysis of all published and unpublished datasets, there seems to be little doubt that the 14484T→C mutation, and to a lesser extent the 11778G→A mutation, are over-represented in haplogroup J, but several additional questions remain unanswered. What is the combination of polymorphisms within haplogroup J that increases the risk of disease expression? Unfortunately, there are insufficient published data available to carry out haplogroup J sub-cluster analysis and explore further the differences reported in sub-clusters J1 and J2.¹⁰ Why should the 3460G→A mutation prove refractory to the mitochondrial genetic background? We have as yet no answer. Addressing these important issues will not only advance our understanding of LHON, but will also have broader relevance for other pathogenic mtDNA mutations.

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Correction

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The first author's name of all three papers has been corrected to Patrick Yu-Wai-Man.

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