

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/99560/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Majander, Anna, Bowman, Richard, Poulton, Joanna, Antcliff, Richard J, Reddy, M Ashwin, Michaelides, Michel, Webster, Andrew R, Chinnery, Patrick F, Votruba, Marcela, Moore, Anthony T and Yu-Wai-Man, Patrick 2017. Childhood-onset Leber hereditary optic neuropathy. *British Journal of Ophthalmology* 101 (11), pp. 1505-1509. 10.1136/bjophthalmol-2016-310072

Publishers page: <http://dx.doi.org/10.1136/bjophthalmol-2016-310072>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <http://orca.cf.ac.uk/100416/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Majander, Anna, Bowman, Richard, Poulton, Joanna, Antcliff, Richard J., Reddy, M. Ashwin, Michaelides, Michel, Webster, Andrew R., Chinnery, Patrick F., Votruba, Marcela, Moore, Anthony T. and Yu-Wai-Man, Patrick 2017. Childhood-onset Leber hereditary optic neuropathy. *British Journal of Ophthalmology* 10.1136/bjophthalmol-2016-310072 filefile

Publishers page: <http://dx.doi.org/10.1136/bjophthalmol-2016-310072>
<<http://dx.doi.org/10.1136/bjophthalmol-2016-310072>>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Supplementary Table 1. Data summary of previously published LHON patients with onset of visual loss ≤ 12 years of age.

Mutation	Patients	Sex			Age at onset (y)	BCVA [#]		
	n	f	m	m:f	Mean Median	Mean Median	≥ 0.5 (%)	< 0.05 (%)
11778	47	18	29	1.6 (3.9)*	8.3 8.0	0.15 0.10	4/59 (7)	18/59 (31)
3460	11	4	7	1.8	8.6 8.0	0.74 0.10	4/6 (67)	0/6 (0)
14484	11	6	5	0.8	9.2 9.0	0.82 0.80	10/14 (71)	0/14 (0)
All	69	28	41	1.5 (2.3)*	8.5 8.0	0.30 0.12	18/79 (23)	18/79 (23)

*Ratio after excluding two atypical families carrying the m.11778A>G mutation, one German and one Chinese, with a high proportion of affected female carriers.

Number of eyes with best-corrected visual acuity (BCVA) ≥ 0.5 or < 0.05 in Snellen decimal. One eye of a child carrying the m.11778G>A mutation was excluded from analysis due to unilateral anterior persistent faetal vasculature and pre-existing dense amblyopia.

Abbreviations: BCVA, best corrected visual acuity; f, female; m, male.

Supplementary Table 2. Meta-analysis of childhood-onset LHON patients.

Mutation	Patients	Sex			Age at onset (y)	BCVA [#]		
	n	f	m	m:f	Mean Median	Mean Median	≥ 0.5 (%)	< 0.05 (%)
11778	60	21	39	1.9	8.0 8.0	0.16 0.10	9/85 (11)	27/85 (32)
3460	18	6	12	2.0	8.17.7	0.63 0.73	12/20 (60)	2/20 (10)
14484	18	8	10	1.3	8.18.0	0.67 0.80	17/28 (61)	0/28 (0)
All	96	34	62	1.8	8.08.0	0.34 0.17	38/133 (29)	29/133 (22)

Number of eyes with best-corrected visual acuity (BCVA) ≥ 0.5 or < 0.05 in Snellen decimal.

Abbreviations: BCVA, best corrected visual acuity; f, female; m, male.

Supplementary appendix

- 1 Newman NJ, Lott MT, Wallace DC. The clinical characteristics of pedigrees of Leber's hereditary optic neuropathy with the 11778 mutation. *Am J Ophthalmol* 1991;111:750-62.
- 2 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*. Dec 1992; 51:1218–1228
- 3 Johns DR, Smith KH, Miller NR. Leber's hereditary optic neuropathy: clinical manifestations of the 3460 mutation. *Arch Ophthalmol* 1992;110:1577-81.
- 4 Johns DR, Heher KL, Miller NR, et al. Leber's hereditary optic neuropathy: clinical manifestations of the 14484 mutation. *Arch Ophthalmol* 1993;111:495-8.
- 5 Moorman CM, Elston JS, Matthews P. Leber's hereditary optic neuropathy as a cause of severe visual loss in childhood. *Pediatrics* 1993;91:988-9.
- 6 Riordan-Eva P, Sanders MD, Govan GG, et al. The clinical features of Leber's hereditary optic neuropathy defined by the presence of a pathogenic mitochondrial DNA mutation. *Brain* 1995;118:319-37.
- 7 Nikoskelainen EK, Huoponen K, Juvonen V, et al. Ophthalmologic findings in Leber Hereditary Optic Neuropathy, with special reference to mtDNA mutations. *Ophthalmology* 1996;103:504-14.
- 8 Pezzi PP, De Negri AM, Sadun F, et al. Childhood Leber's hereditary optic neuropathy (ND1/3460) with visual recovery. *Pediatr Neurol* 1998;19:308-12.
- 9 Thieme H, Wissinger B, Jandek C, et al. A pedigree of Leber's hereditary optic neuropathy with visual loss in childhood, primarily in girls. *Graefes Arch Clin Exp Ophthalmol* 1999;237:714-9.
- 10 Leo-Kottler B, Christ-Adler M. Lebersche optikusneuropathie (LHON) bei frauen und kindern. *Ophthalmologe* 1999;96:698-701.

- 11 Balayre S, Gicquel JJ, Mercie M, et al. Childhood Leber hereditary optic neuropathy. A case of a 6-year-old girl with loss of vision. *J Fr Ophthalmol* 2003;26:1063-6.
- 12 Sadun F, De Negri AM, Carelli V, et al. Ophthalmologic findings in a large pedigree of 11778/Haplogroup J Leber hereditary optic neuropathy. *Am J Ophthalmol* 2004;137:271-7.
- 13 Kawasaki A, Borruat FX. Rapid onset of visual recovery following acute visual loss due to Leber's hereditary optic neuropathy. *Rev Neurol (Paris)* 2005;161:599-601.
- 14 Barboni P, Savini G, Valentino ML, et al. Leber's hereditary optic neuropathy with childhood onset. *Invest Ophthalmol Vis Sci* 2006;47:5303-9.
- 15 Yu-Wai-Man P, Elliott C, Griffiths PG, et al. Investigation of auditory dysfunction in Leber hereditary optic neuropathy. *Acta Ophthalmol* 2008;86:630-3.
- 16 Bosley TM, Brodsky MC, Glasier CM, et al. Sporadic bilateral optic neuropathy in children: the role of mitochondrial abnormalities. *Invest Ophthalmol Vis Sci* 2008;49:5250-6.
- 17 Zhou X, Zhang H, Zhao F, et al. Very high penetrance and occurrence of Leber's hereditary optic neuropathy in a large Han Chinese pedigree carrying the ND4 G11778A mutation. *Mol Genet Metab* 2010;100:379-84.
- 18 Liang M, Jiang P, Li F, Zhang J, et al. Frequency and spectrum of mitochondrial ND6 mutations in 1218 Han Chinese subjects with Leber's hereditary optic neuropathy. *Invest Ophthalmol Vis Sci* 2014;55:1321-31.
- 19 Romero P, Fernández V, Slabaugh M, et al. Pan-American mtDNA haplogroups in Chilean patients with Leber's hereditary optic neuropathy. *Mol Vis* 2014;20:334-40.
- 20 Jiang P, Liang M, Zhang J, et al. Prevalence of Mitochondrial ND4 Mutations in 1281 Han Chinese Subjects With Leber's Hereditary Optic Neuropathy. *Invest Ophthalmol Vis Sci* 2015;56:4778-88.