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## Supplemental information

# Establishing risk of vision loss in Leber hereditary optic neuropathy

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# Supplemental Data

**Figure S1. Confirmation of heteroplasmic mutation in individuals from LHON pedigrees NZ10, VIC02 and VIC30 by PCR and Sanger sequencing.**

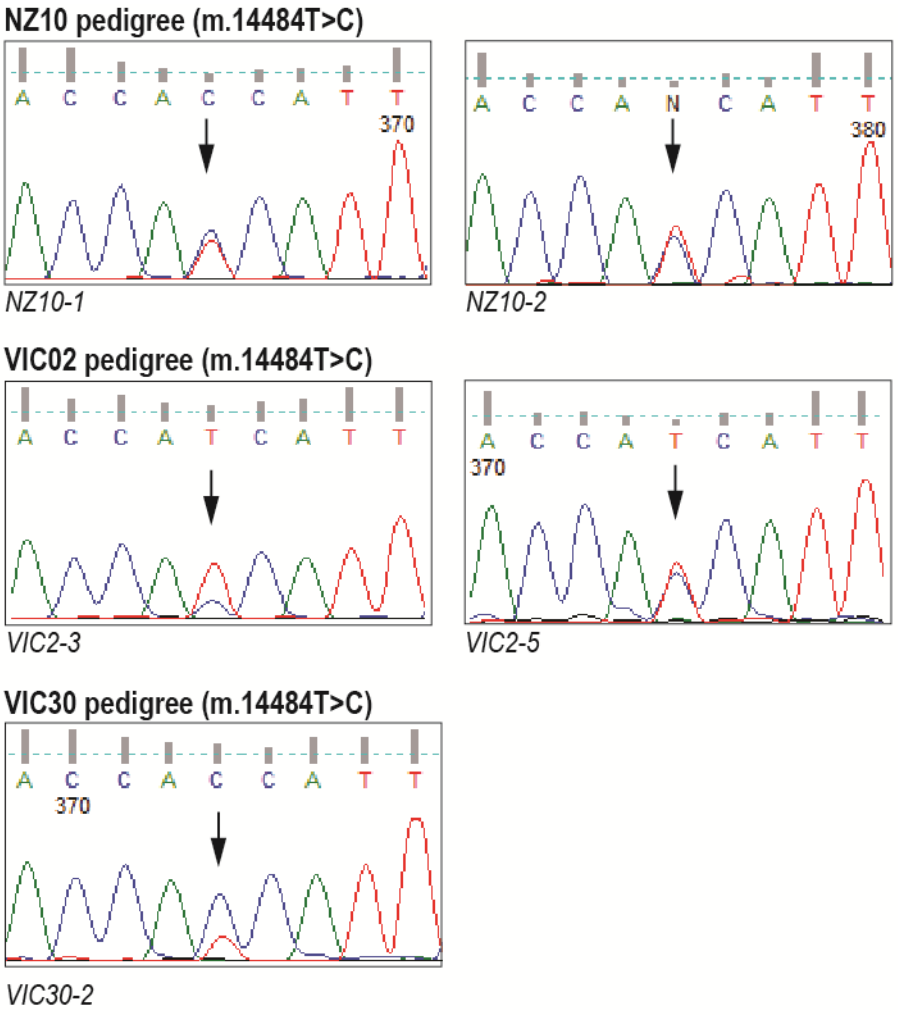

**Table S1. Primer sequences of primers used for PCR**

| Primer | Sequence |
|---|---|
| 11778_Fwd | CCC ACC TTG GCT ATC ATC |
| 11778_Rev | GGT AAG GCG AGG TTA GCG |
| 14484_Fwd | GCA TAA TTA AAC TTT ACT TC |
| 14484_ Rev | AGA ATA TTG AGG CGC CAT TG |
| 3460_Fwd | TTC AAA TTC CTC CCT GTA CG |
| 3460_Rev | GGC TAC TGC TCG CAG TG |
| DloopHV1_Fwd | TGG GGA AGC AGA TTT GGG TA |
| DloopHV1_Rev | ACG TGT GGG CTA TTT AGG CT |
| DloopHV2_Fwd | ATG GGC GGG GGT TGT ATT G |
| DloopHV2_Rev | CAC AGG TCT ATC ACC CTA TTA ACC |

**Table S2. Complete mtDNA Sequences of LHON Pedigrees**

Sequences are presented as differences from the mtDNA revised Cambridge Reference Sequence (NC_012920.1). Expansions or contractions of simple repeat sequences in the mitochondrial genome are not shown. In addition to the pedigree, we specify the pathogenic LHON mutation and the mtDNA haplogroup according to PhyloTree[1].

| Pedigree (mutation) | Haplogroup | mtDNA control region | mtDNA coding region |
|---|---|---|---|
| NSW01 (m.11778G>A) | H1n | 146 T:C; 263 A:G; 16468 T:C; 16519 T:C | 750 A:G; 1438 A:G; 2098 G:A; 3010 G:A; 4769 A:G; 8860 A:G; 14199 T:C; 15326 A:G; 15742 C:A; 15924 A:G |
| NSW03 (m.11778G>A) | U5a1 | 73 A:G; 263 A:G; 16256 C:T; 16270 C:T; 16293 A:G; 16399 A:G | 750 A:G; 1438 A:G; 2706 A:G; 3197 T:C; 4769 A:G; 7028 C:T; 7792 C:T; 8860 A:G; 9477 G:A; 11467 A:G; 11719 G:A; 11914 G:A; 12308 A:G; 12372 G:A; 13617 T:C; 14766 C:T; 14793 A:G; 15218 A:G; 15317 G:A; 15326 A:G |
| NSW04 (m.11778G>A) | J1c1 | 73 A:G; 185 G:A; 228 G:A; 263 A:G; 295 C:T; 462 C:T; 482 T:C; 489 T:C; 16069 C:T; 16126 T:C | 750 A:G; 1438 A:G; 2706 A:G; 3010 G:A; 3394 T:C; 4216 T:C; 4769 A:G; 7028 C:T; 8020 G:A; 8860 A:G; 10398 A:G; 11251 A:G; 11287 T:C; 11719 G:A; 12612 A:G; 13708 G:A; 14766 C:T; 14798 T:C; 15326 A:G; 15452 C:A |
| NSW06 (m.11778G>A) | H4a1 | 263 A:G | 750 A:G; 1438 A:G; 3992 C:T; 4024 A:G; 4769 A:G; 5004 T:C; 8269 G:A; 8860 A:G; 9123 G:A; 10124 T:C; 14365 C:T; 14582 A:G; 14956 T:C; 15326 A:G |
| NSW09 (m.11778G>A) | J1c4 | 73 A:G; 185 G:A; 228 G:A; 263 A:G; 295 C:T; 462 C:T; 489 T:C; 16069 C:T; 16126 T:C | 750 A:G; 1438 A:G; 2706 A:G; 3010 G:A; 4216 T:C; 4769 A:G; 7028 C:T; 7853 G:A; 8860 G:A; 9120 A:G; 9632 A:G; 9701 T:C; 10398 A:G; 11251 A:G; 11719 G:A; 12083 T:G; 12612 A:G; 13708 G:A; 14766 C:T; 14798 T:C; 15326 A:G; 15452 C:A |
| NSW11 (m.11778G>A) | Y2a | 73 A:G; 263 A:G; 482 T:C; 16126 T:C; 16231 T:C; 16305 A:G; 16311 T:C; 16362 T:C | 750 A:G; 1438 A:G; 2706 A:G; 4769 A:G; 5147 G:A; 5417 G:A; 6941 T:C; 7028 C:T; 7632 T:C; 7859 G:A; 8392 G:A; 8860 A:G; 10398 A:G; 11299 T:C; 11719 G:A; 12161 T:C; 12705 C:T; 14178 T:C; 14693 A:G; 14766 C:T; 14914 A:G; 15244 A:G; 15326 A:G |
| NSW17 (m.11778G>A) | T2f1 | 73 A:G; 195 T:C; 263 A:G; 16126 T:C; 16189 T:C; 16294 C:T; 16296 C:T; 16298 T:C; 16519 T:C | 709 G:A; 750 A:G; 1438 A:G; 1888 G:A; 2706 A:G; 4216 T:C; 4769 A:G; 4917 A:G; 5277 T:C; 5426 T:C; 6489 C:A; 7028 C:T; 8270 C:T; 8697 G:A; 8860 A:G; 10463 T:C; 11251 A:G; 11719 G:A; 11812 A:G; 13368 G:A; 14233 A:G; 14323 G:A; 14766 C:T; 14905 G:A; 15043 G:A; 15326 A:G; 15452 C:A; 15607 A:G; 15928 G:A |
| NSW18 (m.11778G>A) | J1c1 | 73 A:G; 263 A:G; 295 C:T; 462 C:T; 482 T:C; 489 T:C; 16069 C:T; 16126 T:C | 750 A:G; 1438 A:G; 2706 A:G; 3010 G:A; 3394 T:C; 4216 T:C; 4769 A:G; 7028 C:T; 8860 A:G; 10398 A:G; 11251 A:G; 11719 G:A; 12612 A:G; 13194 G:A; |

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|---|---|---|---|
| | | | 13708 G:A; 14766 C:T; 14798 T:C; 15326 A:G; 15452 C:A |
| NZ02 (m.11778G>A) | U5b2a1 | 73 A:G; 150 C:T; 152 T:C; 263 A:G; 16189 T:C; 16325 T:C | 750 A:G; 1438 A:G; 1721 C:T; 2706 A:G; 3197T:C; 4732 A:G; 4769 A:G; 6158 A:G; 7028 C:T; 7768 A:G; 8860 A:G; 9477 G:A; 11467 A:G; 11719 G:A; 12308 A:G; 12372 G:A; 13617 T:C; 13637 A:G; 14182 T:C; 14323 G:A; 14766 C:T; 15326 A:G |
| QLD02 (m.11778G>A) | J2b1 | 73 A:G; 150 C:T; 152 T:C; 263 A:G; 295 C:T; 489 T:C; 16069 C:T; 16126 T:C; 16193 C:T | 750 A:G; 1438 A:G; 2706 A:G; 2789 C:T; 4216 T:C; 4769 A:G; 5633 C:T; 7028 C:T; 7476 C:T; 8860 A:G; 9872 A:G; 10172 G:A; 10398 A:G; 11251 A:G; 11719 G:A; 12612 A:G; 13708 G:A; 13821 C:T; 14766 C:T; 15257 G:A; 15326 A:G; 15452 C:A; 15812 G:A |
| QLD03 (m.11778G>A) | J1c2 | 73 A:G; 185 G:A; 188 A:G; 228 G:A; 263 A:G; 295 C:T; 462 C:T; 489 T:C; 16069 C:T; 16126T:C | 750 A:G; 1438 A:G; 2706 A:G; 3010 G:A; 4216 T:C; 4769 A:G; 6269 A:C; 7028 C:T; 8860 A:G; 10398 A:G; 11251 A:G; 11719 G:A; 12612 A:G; 13708 G:A; 14766 C:T; 14798 T:C; 15326 A:G; 15452 C:A |
| QLD04 (m.11778G>A) | T2b4 | 73 A:G; 263 A:G; 16126 T:C; 16294 C:T; 16304 T:C; 16519 T:C | 709 G:A; 750 A:G; 930 G:A; 1438 A:G; 1888 G:A; 2706 A:G; 4216 T:C; 4769 A:G; 4917 A:G; 7028 C:T; 8697 G:A; 8860 A:G; 9254 A:G; 10463 T:C; 11251 A:G; 11719 G:A; 11812 A:G; 13368 G:A; 14233 A:G; 14766 C:T; 14905 G:A; 15326 A:G; 15452 C:A; 15607 A:G; 15928 G:A |
| TAS01[a] (m.11778G>A) | H | 152 T:C; 263 A:G; 16093 T:C | 750 A:G; 1438 A:G; 4626 A:G; 4769 A:G; 8860 A:G; 11788 C:T; 15317 G:A; 15326 A:G |
| TAS05 (m.11778G>A) | H3f | 93 A:G; 263 A:G; 16153 G:A; 16311 T:C; 16519 T:C | 750 A:G; 1438 A:G; 4769 A:G; 6776 T:C; 8860 A:G; 12811 T:C; 15326 A:G |
| VIC04 (m.11778G>A) | H1c3 | 195 T:C; 257 A:G; 263 A:G; 477 T:C; 16290 C:T; 16519 T:C | 750 A:G; 1438 A:G; 3010 G:A; 4769 A:G; 8473 T:C; 8860 A:G; 15326 A:G |
| VIC05 (m.11778G>A) | K2a4 | 73 A:G; 146 T:C; 152 T:C; 263 A:G; 16129 G:A; 16224 T:C; 16311 T:C; 16519 T:C | 709 G:A; 750 A:G; 1438 A:G; 1811 A:G; 2706 A:G; 3480 A:G; 4561 T:C; 4769 A:G; 7028 C:T; 8860 A:G; 9055 G:A; 9698 T:C; 9716 T:C; 10550 A:G; 11299 T:C; 11467 A:G; 11549 C:T; 11719 G:A; 12308 A:G; 12372 G:A; 14167 C:T; 14766 C:T; 14798 T:C; 15326 A:G |
| VIC06 (m.11778G>A) | H1 | 152 T:C; 263 A:G; 16189 T:C; 16239 C:T; 16519 T:C | 750 A:G; 1438 A:G; 3010 G:A; 4769 A:G; 8860 A:G; 11596 A:G; 13230 C:T; 13768 T:C; 15326 A:G |
| VIC07 (m.11778G>A) | I2a | 73 A:G; 152 T:C; 199 T:C; 204 T:C; 207 G:A; 250 T:C; 263 A:G; 16129 G:A; 16145 G:A; 16223 C:T; 16391 G:A; 16519 T:C | 750 A:G; 1438 A:G; 1719 G:A; 2706 A:G; 4529 A:T; 4769 A:G; 7028 C:T; 7813 C:T; 8251 G:A; 8860 A:G; 9266 G:A; 10034 T:C; 10238 T:C; 10398 A:G; 11065 A:G; 11719 G:A; 12501 G:A; 12705 C:T; 13780 A:G; 14766 C:T; 15043 G:A; 15326 A:G; 15758 A:G; 15924 A:G; 15937 A:G |
| VIC10 (m.11778G>A) | J2a1a | 73 A:G; 150 C:T; 152 T:C; 195 T:C 198 C:T; 222 C:T; 263 A:G; 295 | 750 A:G; 1438 A:G; 1587 T:C; 2706 A:G; 4216 T:C; 4769 A:G; 7028 C:T; 7476 C:T; 7789 G:A; 8860 A:G; 10398 |

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|---|---|---|---|
| | | C:T; 319 T:C; 489 T:C; 513 G:A; 16069 C:T; 16126 T:C; 16145 G:A; 16189 T:C; 16231 T:C; 16261 C:T | A:G; 10499 A:G; 11251 A:G; 11377 G:A; 11581 A:T; 11719 G:A; 12279 A:G[c]; 12612 A:G; 13708 A:G; 13722 A:G; 14133 A:G; 14766 C:T; 15257 G:A; 15326 A:G; 15452 C:A |
| VIC17 (m.11778G>A) | J1c5a | 73 A:G; 150 C:T; 185 G:A; 228 G:A; 263 A:G; 295 C:T; 462 C:T; 489 T:C; 16069 C:T; 16126 T:C; 16519 T:C | 750 A:G; 1438 A:G; 2387 T:C; 2706 A:G; 3010 G:A; 4216 T:C; 4769 A:G; 5198 A:G; 7028 C:T; 8860 A:G; 10192 C:T; 10398 A:G; 11251 A:G; 11719 G:A; 12612 A:G; 13708 G:A; 14766 C:T; 14798 T:C; 15326 A:G; 15452 C:A |
| VIC18 (m.11778G>A) | U4c1 | 73 A:G; 195 T:C; 263 A:G; 489 T:C; 499 G:A; 16169 C:T; 16179 C:T; 16234 C:T; 16356 T:C; 16519 T:C | 750 A:G; 1438 A:G; 1811 A:G; 2706 A:G; 4646 T:C; 4769 A:G; 4811 A:G; 5999 T:C; 6047 A:G; 6146 A:G; 7028 C:T; 8860 A:G; 9070 T:G; 10907 T:C; 11009 T:C; 11332 C:T; 11467 A:G; 11719 G:A; 12308 A:G; 12372 G:A; 14620 C:T; 14766 C:T; 14866 C:T; 15326 A:G; 15693 T:C |
| VIC19 (m.11778G>A) | B4b1a2 | 73 A:G; 207 G:A; 263 A:G; 499 G:A; 16136 T:C; 16153 G:A; 16189 T:C; 16217 T:C; 16235 A:G; 16519 T:C | 750 A:G; 827 A:G; 1438 A:G; 1664 G:A; 2706 A:G; 4769 A:G; 4820 G:A; 6023 G:A; 6216 T:C; 6413 T:C; 7028 C:T; 8860 A:G; 11719 G:A; 13590 G:A; 14766 C:T; 15326 A:G; 15535 C:T |
| VIC21 (m.11778G>A) | H13a1a | 152 T:C; 263 A:G; 16311 T:C | 750 A:G; 1438 A:G; 2259 A:G; 3591 G:T; 4745 A:G; 4769 A:G; 8860 A:G; 9233 T:C; 11410 T:C; 13680 C:T; 14872 C:T; 15326 A:G |
| VIC22 (m.11778G>A) | H13a1a | 263 A:G | 750 A:G; 1438 A:G; 2259 A:G; 4745 A:G; 4769 A:G; 8860 A:G; 13680 C:T; 14872 C:T; 15326 A:G; 15355 G:A |
| VIC25 (m.11778G>A) | T1a1 | 73 A:G; 152 T:C; 195 T:C; 263 A:G; 16126 T:C; 16163 A:G; 16172 T:C; 16186 C:T; 16189 T:C; 16294 C:T; 16304 T:C; 16519 T:C | 709 G:A; 750 A:G; 1438 A:G; 1888 G:A; 2706 A:G; 4216 T:C; 4769 A:G; 4917 A:G; 7028 C:T; 7269 G:A; 8967 G:A; 8860 A:G; 9443 T:C; 9899 T:C; 10463 T:C; 10646 G:A; 11251 A:G; 11719 G:A; 12432 C:T; 12633 C:A; 13368 G:A; 14766 C:T; 14905 G:A;15326 A:G; 15452 C:A; 15607 A:G; 15928 G:A |
| VIC29 (m.11778G>A) | U5a1a1 | 73 A:G; 263 A:G; 16256 C:T; 16270 C:T; 16399 A:G | 750 A:G; 1438 A:G; 1700 T:C; 2706 A:G; 3197 T:C; 4769 A:G; 5495 T:C; 6905 A:G; 7028 C:T; 8860 A:G; 9477 G:A; 11467 A:G; 11719 G:A; 12308 A:G; 12372 G:A; 13015 T:C; 13617 T:C; 14599 A:G; 14766 C:T; 14793 A:G; 15218 A:G; 15326 A:G; 15924 A:G |
| WAU03 (m.11778G>A) | I2a | 73 A:G; 152 T:C; 199 T:C; 204 T:C; 207 G:A; 250 T:C; 263 A:G; 16126 T:C; 16145 G:A; 16223 C:T; 16391 G:A; 16519 T:C | 750 A:G; 1438 A:G; 1719 G:A; 2706 A:G; 3398 T:C; 4529 A:T; 4769 A:G; 7028 C:T; 8251 G:A; 8860 A:G; 10034 T:C; 10238 T:C; 10398 A:G; 11065 A:G; 11719 G:A; 12501 G:A; 12705 C:T; 13780 A:G; 14766 C:T; 15043 G:A; 15326 A:G; 15758 A:G; 15924 A:G |
| WAU04 (m.11778G>A) | H3 | 263 A:G; 16189 T:C; 16519 T:C | 750 A:G; 1438 A:G; 4769 A:G; 5087 T:C; 6776 T:C; 8860 A:G; 10325 G:A; 15326 A:G |
| NSW12 (m.14484T>C) | K1c2 | 73 A:G; 146 T:C; 152 T:C; 263 A:G; 16224 T:C; 16311 T:C; 16320 | 750 A:G; 1189 T:C; 1438 A:G; 1811 A:G; 2706 A:G; 3480 A:G; 4769 A:G; 7028 C:T; 8860 A:G; 9006 A:G; 9055 G:A; 9698 T:C; 10398 A:G; 10550 A:G; |

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|---|---|---|---|
| | | C:T; 16356 T:C; 16519 T:C | 11299 T:C; 11467 A:G; 11719 G:A; 12308 A:G; 12372 G:A; 14002 A:G; 14040 G:A; 14167 C:T; 14766 C:T; 14798 T:C; 15326 A:G |
| NSW15 (m.14484T>C) | U5a1a1 | 73 A:G; 263 A:G; 16256 C:T; 16270 C:T; 16399 A:G | 750 A:G; 979 C:T; 1438 A:G; 1700 T:C; 2706 A:G; 3197 T:C; 4769 A:G; 5495 T:C; 6164 C:T; 7028 C:T; 8860 A:G; 9477 G:A; 11467 A:G; 11719 G:A; 12308 A:G; 12372 G:A; 13617 T:C; 14766 C:T; 14793 A:G; 15218 A:G; 15326 A:G; 15924 A:G |
| NSW19 (m.14484T>C) | L1b1a1 | 73 A:G; 152 T:C; 182 C:T; 185 G:T; 195 T:C; 247 G:A; 263 A:G; 264 C:T; 357 A:G; 16114 C:T; 16126 T:C; 16187 C:T; 16189 T:C; 16215 A:C; 16223 C:T; 16264 C:T; 16270 C:T; 16278 C:T; 16293 A:G; 16311 T:C; 16519 T:C | 709 G:A; 710 T:C; 750 A:G; 769 G:A; 825 T:A; 1018 G:A; 1738 T:C; 2352 T:C; 2706 A:G; 2758 G:A; 2768 A:G; 2885 T:C; 3308 T:C; 3396 T:C; 3594 C:T; 3666 G:A; 3693 G:A; 4104 A:G; 4769 A:G; 5036 A:G; 5046 G:A; 5393 T:C; 5655 T:C; 6548 C:T; 6827 T:C; 6989 A:G; 7028 C:T; 7055 A:G; 7146 A:G; 7256 C:T; 7389 T:C; 7521 G:A; 7867 C:T; 8248 A:G; 8468 C:T; 8655 C:T; 8701 A:G; 8860 A:G; 9540 T:C; 10398 A:G; 10688 G:A; 10810 T:C; 10873 T:C; 11719 G:A; 12519 T:C; 12705 C:T; 13105 A:G; 13506 C:T; 13650 C:T; 13789 T:C; 13880 C:A; 14178 T:C; 14203 A:G; 14560 G:A; 14766 C:T; 14769 A:G; 15115 T:C; 15326 A:G |
| TAS02 (m.14484T>C) | J1c2c | 73 A:G; 146 T:C; 185 G:A; 188 A:G; 222 C:T; 228 G:A; 263 A:G; 295 C:T; 462 C:T; 489 T:C; 16069 C:T; 16126 T:C; 16261 C:T; 16519 T:C | 750 A:G; 1438 A:G; 2706 A:G; 3010 G:A; 4216 T:C; 4769 A:G; 7028 C:T; 8610 T:C; 8860 A:G; 10398 A:G; 10685 G:A; 11251 A:G; 11719 A:G; 12612 A:G; 13281 T:C; 13708 G:A; 13933 A:G; 14766 C:T; 14798 T:C; 15326 A:G; 15452 C:A |
| VIC02[b] (m.14484T>C) | J1b1a | 73 A:G; 185 G:A; 242 C:T; 263 A:G; 295 C:T; 462 C:T; 489 T:C; 16069 C:T; 16126 T:C; 16145 G:A; 16172 T:C; 16222 C:T; 16261 C:T | 750 A:G; 1438 A:G; 1462 G:A; 2158 A:G; 2706 A:G; 3010 G:A; 4216T:C; 4659 G:A; 4769 A:G; 5460 C:T; 6345 T:C; 7028 G:A; 7299 A:G; 8269 G:A; 8557 G:A; 8860 A:G;10398 A:G; 11251 A:G; 11719 A:G; 12007 G:A; 12612 A:G; 13708 G:A; 13879 T:C; 14766 C:T; 15326 T:C; 15452 C:A |
| VIC08 (m.14484T>C) | J1c1 | 73 A:G; 152 T:C; 263 A:G; 295 C:T; 462 C:T; 489 T:C; 16069 C:T; 16126 T:C; 16193 C:T; 16519 T:C | 750 A:G; 1438 A:G; 2706 A:G; 3010 G:A; 4216 T:C; 4769 A:G; 7028 C:T; 7789 G:A; 7963 A:G; 8779 C:T; 8860 A:G; 9041 A:G; 10398 A:G; 11251 A:G; 11719 G:A; 12612 A:G; 12681 T:C; 13708 G:A; 14766 C:T; 15326 A:G; 15452 C:A |
| VIC11 (m.14484T>C) | J1c1 | 73 A:G; 185 G:A; 189 A:G; 228 G:A; 263 A:G; 295 C:T; 462 C:T; 489 T:C; 16069 C:T; 16126 T:C; 16293 A:G | 750 A:G; 1438 A:G; 2706 A:G; 3010 G:A; 3394 T:C; 4216 T:C; 4769 A:G; 7028 C:T; 8860 A:G; 10398 A:G; 11251 A:G; 11719 G:A; 12612 A:G; 13708 G:A; 14766 C:T; 14798 T:C; 15184 T:C; 15326 A:G; 15452 C:A |
| VIC14 (m.14484T>C) | H3c | 195 T:C; 263 A:G; 16176 C:T | 750 A:G; 1211 G:A; 1438 A:G; 4769 A:G; 6261 G:A; 6776 T:C; 7444 G:A; 8347 A:G; 8860 A:G; 12957 T:C; 14305 G:A15326 A:G |

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|---|---|---|---|
| TAS03 (m.3460G>A) | H5a1 | 263 A:G; 456 C:T; 16304 T:C | 750 A:G; 1438 A:G; 4336 T:C; 4769 A:G; 8860 A:G; 12696 T:C; 15326 A:G; 15833 C:T |
| VIC01 (m.3460G>A) | H | 93 A:G; 207 G:A; 263 A:G; 16519 T:C | 750 A:G; 1438 A:G; 4769 A:G; 8860 A:G; 9612 G:A; 11560 A:G; 15058 C:T; 15326 A:G |
| WAU06 (m.3460G>A) | M53 | 73 A:G; 240 A:G; 263 A:G; 390 A:T; 438 C:T; 489 T:C; 16051 A:G; 16093 T:C; 16223 C:T; 16316 A:G; 16400 C:T; 16519 T:C | 593 T:C; 750 A:G; 2010 T:C; 2706 A:G; 4769 A:G; 5493 T:C; 5821 G:A; 6216 T:C; 6719 T:C; 7028 C:T; 7805 G:A; 8701 A:G; 8860 A:G; 9302 C:T; 9540 T:C; 10084 T:C; 10398 A:G; 10400 C:T; 10873 T:C; 11167 A:G; 11560 A:G; 11719 G:A; 12630 G:A; 12705 C:T; 14766 C:T; 14783 T:C; 15043 G:A; 15301 G:A; 15315 C:T; 15326 A:G |
| NSW08 (m.14482C>G) | I1a | 73 A:G; 199 T:C; 204 T:C; 250 T:C; 263 A:G; 16129 G:A; 16172 T:C; 16223 C:T; 16311 T:C; 16391 G:A; 16519 T:C | 750 A:G; 1438 A:G; 1531 C:T; 1719 G:A; 2706 A:G; 3447 A:G; 4529 A:T; 4769 A:G; 6734 G:A; 7028 C:T; 8248 A:G; 8251 G:A; 8616 G:T; 8860 A:G; 9966 G:A; 10034 T:C; 10238 T:C; 10398 A:G; 10550 A:G; 11719 G:A; 12501 G:A; 12705 C:T; 12864 T:C; 13780 A:G; 14766 C:T; 15043 G:A; 15326 A:G; 15589 C:T |
| VIC20 (m.11778G>A/ m.14484T>C) | U5a1a1 | 73 A:G; 152 T:C; 263 A:G; 16231 T:C; 16256 C:T; 16270 C:T; 16399 A:G | 750 A:G; 1438 A:G; 1700 T:C; 2706 A:G; 3197 T:C; 4769 A:G; 5495 T:C; 7028 C:T; 8860 A:G; 9477 G:A; 11467 A:G; 11719 G:A; 12308 A:G; 12372 G:A; 12771 G:A;13617 T:C; 14766 C:T; 14793 A:G; 15218 A:G; 15326 A:G; 15924 A:G |
| QLD01 (m.14484T>C/ m.4160T>C) | U4a1a | 73 A:G; 152 T:C; 263 A:G; 499 G:A; 16134 C:T; 16356 T:C; 16519 T:C | 750 A:G; 961 T:C; 1438 A:G; 1811 A:G; 2706 A:G; 4646 T:C; 4769 A:G; 5999 T:C; 6047 A:G; 6845 C:T; 7028 C:T; 8818 C:T; 8860 A:G; 11332 C:T; 11467 A:G; 11719 G:A; 12308 A:G; 12372 G:A; 12937 A:G; 14620 C:T; 14766 C:T; 15326 A:G; 15693 T:C |

[a] Nine members of the TAS01 pedigree were used for sequencing; five of them were sequenced in triplicate. Within the limits of MitoChip-based sequencing, all sequences matched those obtained previously by both manual and automated sequencing procedures.

[b] Sequence change is heteroplasmic in the sample analyzed.

**Table S3. Partial mtDNA Sequences of LHON Pedigrees.**

Sequences are presented as differences from the mtDNA revised Cambridge Reference Sequence (NC_012920.1). Expansions or contractions of simple repeat sequences in the mitochondrial genome are not shown. In addition to the pedigree, we specify the pathogenic LHON mutation and the mtDNA haplogroup according to MitoMaster[2].

| Pedigree (mutation) | Haplogroup | mtDNA control region | mtDNA coding region |
|---|---|---|---|
| NSW02 (m.11778G>A) | H | 152 T:C; 263 A:G; 16189 T:C; 16239 C:T; 16519 T:C | 4769 A:G; 13768 T:C |
| NSW23 (m.11778G>A) | J | 73 A:G; 150 C:T; 152 T:C; 195 T:C; 215 A:G; 263 A:G; 295 C:T; 319 T:C; 489 T:C; 513 G:A; 16069 C:T; 16126 T:C; 16145 G:A; 16231 T:C; 16261 C:T | 3447 A:G; 4216 T:C; 4769 A:G; 7419 G:A; 7476 C:T; 11251 A:G; 11719 G:A; 12612 A:G; 13708 G:A; 13722 A:G; 15257 G:A |
| NSW26 (m.11778G>A) | K | 73 A:G; 146 T:C; 152 T:C; 263 A:G; 16224 T:C; 16259 C:T; 16311 T:C; 16320 C:T; 16519 T:C | 3480 A:G; 11299 T:C; 11467 A:G; 11719 G:A |
| NZ01 (m.11778G>A) | U | 73 A:G; 152 T:C; 217 T:C; 263 A:G; 508 A:G; 16051 A:G; 16092 T:C; 16129 G:C; 16189 T:C; 16362 T:C; 16519 T:C | 11719 G:A |
| NZ03 (m.11778G>A) | J | 73 A:G; 185 G:A; 188 A:G; 228 G:A; 263 A:G; 295 C:T; 462 C:T; 489 T:C; 16069 C:T; 16126 T:C; 16325 T:C; 16519 T:C | 4216 T:C; 4769 A:G; 11719 G:A; 11911 T:C; 12612 A:G; 13708 G:A; 14798 T:C |
| NZ12 (m.11778G>A) | H | 74 T:A; 263 A:G; 315 C:CC; 16337 C:A; 16519 T:C | |
| QLD05 (m.11778G>A) | HV | 263 A:G; 16111 C:T; 16519 T:C | |
| QLD10 (m.11778G>A) | N | 73 A:G; 204 T:C; 263 A:G; 16223 C:T | |
| QLD11 (m.11778G>A) | W | 73 A:G; 195 T:C; 204 T:C; 207 G:A; 263 A:G; 16223 C:T; 16292 C:T | 3505 A:G; 11719 G:A |
| QLD12 (m.11778G>A) | U | 195 T:C; 263 A:G; 16192 C:T; 16256 C:T; 16270 C:T; 16320 C:T; 16399 A:G | 11467 A:G |
| VIC03 (m.11778G>A) | U | 16192 C:T; 16249 T:C; 16270 C:T; 16311 T:C; 16411 C:G; 16412 G:T | 11440 G:A; 11467 A:G; 11719 G:A |
| VIC31 (m.11778G>A) | J | 16069 C:T; 16126 T:C; 16311 T:C; 16411 C:G; 16412 G:T | |
| VIC41 (m.11778G>A) | H | 152 T:C; 263 A:G; 16093 T:C | 11719 G:A |
| VIC43 (m.11778G>A) | K | 73 A:G; 114 C:T; 263 A:G; 315 C:CC; 16224 T:C; 16234 C:T; 16311 T:C | 11299 T:C; 11467 A:G; 11470 A:G; 11719 G:A |
| WAU01 (m.11778G>A) | J | 73 A:G; 228 G:A; 263 A:G; 295 C:T; 462 C:T; 482 T:C; 489 T:C; 16069 C:T | 3394 T:C; 4216 T:C; 4769 A:G; 11251 A:G; 11719 G:A; 12612 A:G; 13708 G:A; 13899 T:C; 14798 T:C |

| | | | |
|---|---|---|---|
| WAU02 (m.11778G>A) | K | 73 A:G; 150 C:T; 263 A:G; 315 C:CC; 16224 T:C; 16311 T:C; 16519 T:C | T11299C, A11467G, T11485C, G11719A, C11840T |
| ACT01 (m.14484T>C) | J | 73 A:G; 185 G:A; 228 G:A; 263 A:G; 295 C:T; 462 C:T; 482 T:C; 489 T:C; 16069 C:T; 16126 T:C; 16213 T:C | 3394 T:C; 4216 T:C; 4769 A:G; 9682 T:C; 11251 A:G; 11719 G:A; 12612 A:G; 13708 G:A |
| NZ10[a] (m.14484T>C) | J | 150 C:T; 152 T:C; 195 T:C; 215 A:G; 295 C:T; 319 T:C; 16126 T:C; 16145 G:A; 16231 T:C; 16261 C:T | 11251 A:G; 11377 G:A |
| NZ11 (m.14484T>C) | J | 150 C:T; 185 G:A; 228 G:A; 295 C:T; 462 C:T; 16126 T:C; 16311 T:C | |
| SAU05 (m.14484T>C) | H | 195 T:C; 263 A:G; 310T:C; 366 G:A; 16448 T:C | 11719 G:A |
| VIC30[a] (m.14484T>C) | H | 153 A:G; 195 T:C; 263 A:G | 14299 T:A; 14487 T:G; 14488 T:G |
| VIC42 (m.14484T>C) | J | 73 A:G; 185 G:A; 228 G:A; 263 A:G 295 C:T; 309 C:CCT; 310 T:C; 462 C:T; 482 T:C; 16126 T:C; 16213 G:A | 14484 T:C; 14766 C:T; 14798 T:C |
| NSW07 (m.3460G>A) | T | 73 A:G; 263 A:G; 331 A:G; 16126 T:C; 16234 T:C; 16294 C:T; 16296 C:T; 16519 T:C | 4216 T:C; 4769 A:G; 4917 A:G; 11251 A:G; 11719 G:A; 11812 A:G; 13965 T:C; 13966 A:G; 14687 A:G; 15928 G:A |
| VIC28 (m.3460G>A) | H | 114 C:T; 146 T:C; 195 T:C; 16288 T:C; 16302 A:G; 16362 T:C | |
| SAU04 (m.4171C>A) | HV0 | 72 T:C; 263 A:G; 195 T:C; 16497 A:G | |

[a] Sequence change is heteroplasmic in the sample analysed.

**Table S4. Updated Assignments of Australian LHON Matrilineal Pedigrees**

| Previous Assignment | Updated Assignment | Reference |
|---|---|---|
| NSW13 (m.14484T>C) | NSW19[a] | |
| NSW21(m.11778G>A) | VIC29[a, b] | |
| QLD08 (m.14484T>C) | TAS02[b] | |
| SAU01 (m.11778G>A) | NSW23[b] | Chan *et al*.[3] |
| TAS04 | None *OPA1*[c] | Mackey and Buttery[4] |
| VIC12 | None[d] | |
| VIC13 (m.11778G>A) | VIC04[b] | |
| VIC16 (m.11778G>A) | TAS01[a, b] | |
| VIC23 (m.11778G>A) | TAS01[a, b] | |
| VIC26 (m.11778G>A) | TAS01[a, b] | |
| VIC27 (m.11778G>A) | TAS01[b] | |
| VIC44 (m.14484T>C) | TAS02[b] | |

[a] Reassignment was made on the basis of mtDNA sequence analysis.
[b] Confirmed or determined by further genealogical analysis.
[c] Updated diagnosis of autosomal dominant optic atrophy
[d] Determination of the complete mtDNA sequence from one family member failed to reveal a LHON mutation. As a result, no assignment is made pending further investigation.

**Table S5. mtDNA haplogroup distribution amongst asymptomatic and affected individuals**

| | Mutation, number (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| mtDNA Haplotype | 11778 | 14484 | 3460 | 14484/ 4160 | 14482 | 14484/ 11778 | 4171 | Total |
| | n=3,986 | n=1,215 | n=176 | n=84 | n=54 | n=41 | n=12 | n=5,568 |
| H | 2,699 (67.7) | 98 (8.1) | 128 (72.7) | | | | 12 (100) | 2,937 (52.7) |
| J | 495 (12.4) | 934 (76.9) | | | | | | 1,429 (25.7) |
| U | 241 (6.0) | 26 (2.1) | | 84 (100) | | 41 (100) | | 392 (7.0) |
| I | 126 (3.2) | | | | 54 (100) | | | 180 (3.2) |
| K | 97 (2.4) | 67 (5.5) | | | | | | 164 (2.9) |
| L | | 54 (4.4) | | | | | | 54 (1.0) |
| T | 29 (0.7) | | 10 (5.7) | | | | | 39 (0.7) |
| B | 23 (0.6) | | | | | | | 23 (0.4) |
| M | | | 16 (9.1) | | | | | 16 (0.3) |
| N | 16 (0.4) | | | | | | | 16 (0.3) |
| Y | 14 (0.4) | | | | | | | 14 (0.3) |
| W | 7 (0.2) | | | | | | | 7 (0.1) |
| Unknown | 239 (6.0) | 36 (3.0) | 22 (12.5) | | | | | 297 (5.3) |
| Vision loss | | | | | | | | |
| Carrier | 3,586 (90.0) | 1,089 (89.6) | 155 (88.1) | 23 (27.4) | 47 (87.0) | 38 (92.7) | 10 (83.3) | 4,948 (88.9) |
| Affected | 400 (10.0) | 126 (10.4) | 21 (11.9) | 61 (72.6) | 7 (13.0) | 3 (7.3) | 2 (16.7) | 620 (11.1) |

**Table S6. Vision loss in offspring of affected women**

| | Pedigree_Mother ID | Individuals with vision loss/ Total offspring over 25 years old; [penetrance] | |
|---|---|---|---|
| | m.11778G>A | Male | Female |
| 1 | ACT02_210411 | 0/1 | 0/1 |
| 2 | ACT02_210414 | 1/1 | 0/0 |
| 3 | NSW01_177394 | 0/0 | 0/2 |
| 4 | NSW02_173447 | 0/0 | 0/2 |
| 5 | NSW03_107116 | 0/1 | 1/2 |
| 6 | NSW03_107118 | 0/0 | 0/2 |
| 7 | NSW04_177055 | 1/2 | 1/1 |
| 8 | NSW04_177163 | 0/1 | 0/1 |
| 9 | NSW04_177157 | 1/2 | 0/0 |
| 10 | NSW04_177052 | 1/3 | 0/0 |
| 11 | NSW04_177060 | 2/2 | 0/1 |
| 12 | NSW04_177117 | 0/1 | 0/2 |
| 13 | NSW04_210438 | 2/4 | 0/6 |
| 14 | NSW05_177864 | 1/3 | 0/1 |
| 15 | NSW06_177316 | 0/2 | 0/1 |
| 16 | NSW06_177330 | 0/0 | 0/1 |
| 17 | NSW06_177338 | 0/1 | 0/1 |
| 18 | NSW09_107204 | 0/3 | 1/2 |
| 19 | NSW09_107215 | 1/3 | 0/2 |
| 20 | NSW09_107201 | 1/4 | 0/2 |
| 21 | NSW09_107232 | 0/1 | 0/0 |
| 22 | NSW09_107254 | 1/1 | 0/0 |
| 23 | NSW11_177475 | 1/2 | 0/1 |
| 24 | NSW20_107993 | 2/2 | 1/1 |
| 25 | NSW20_107997 | 1/1 | 0/0 |
| 26 | NZ02_178125 | 1/2 | 0/0 |
| 27 | NZ02_178126 | 1/2 | 0/1 |
| 28 | QLD02_108797 | 0/0 | 0/1 |
| 29 | QLD02_108510 | 0/2 | 0/7 |
| 30 | VIC21_108837 | 0/1 | 0/3 |
| 31 | VIC21_107370 | 0/3 | 0/2 |
| 32 | QLD12_197430 | 0/0 | 0/1 |
| 33 | TAS01_105409 | 1/1 | 1/1 |
| 34 | TAS01_104842 | 0/2 | 0/0 |
| 35 | TAS01_105041 | 1/1 | 0/4 |
| 36 | TAS01_105245 | 0/1 | 2/2 |
| 37 | TAS01_104467 | 1/3 | 0/7 |
| 38 | TAS01_105011 | 2/2 | 0/2 |
| 39 | TAS01_105194 | 0/2 | 0/1 |
| 40 | TAS01_105223 | 0/2 | 0/2 |
| 41 | TAS01_105255 | 0/0 | 0/3 |
| 42 | TAS01_174915 | 3/3 | 0/1 |
| 43 | TAS01_174813 | 0/0 | 0/2 |
| 44 | TAS01_174490 | 0/0 | 0/2 |
| 45 | TAS01_174090 | 0/1 | 0/1 |
| 46 | TAS01_174449 | 1/3 | 0/4 |
| 47 | TAS01_174824 | 0/2 | 0/0 |
| 48 | VIC06_109398 | 1/4 | 1/5 |
| 49 | VIC06_109401 | 0/1 | 0/1 |
| 50 | VIC10_156049 | 0/1 | 0/0 |
| 51 | VIC40_178503 | 1/2 | 0/1 |
| 52 | WA01_107453 | 1/2 | 0/0 |
| 53 | WA01_107435 | 0/0 | 1/1 |

| | | | |
|---|---|---|---|
| 54 | WA01_107426 | 0/0 | 1/3 |
| 55 | WA02_195793 | 0/2 | 0/0 |
| 56 | WA04_109455 | 0/1 | 0/1 |
| | m.14484T>C | | |
| 57 | NSW19_107852 | 0/2 | 0/1 |
| 58 | SA02_178275 | 1/2 | 0/0 |
| 59 | TAS02_175792 | 0/0 | 0/3 |
| 60 | TAS02_175621 | 0/1 | 0/0 |
| 61 | TAS02_175743 | 0/1 | 0/2 |
| 62 | TAS02_175324 | 0/0 | 0/2 |
| 63 | TAS02_172941 | 1/2 | 0/1 |
| 64 | TAS02_206147 | 0/0 | 0/1 |
| 65 | TAS02_173057 | 0/6 | 0/3 |
| 66 | VIC02_109179 | 0/0 | 3/3 |
| 67 | VIC02_109183 | 0/1 | 0/0 |
| 68 | VIC11_109070 | 0/1 | 0/2 |
| 69 | VIC11_109069 | 0/0 | 1/2 |
| 70 | VIC11_108996 | 1/3 | 1/1 |
| | m.3460G>A | | |
| 71 | VIC01_108975 | 0/0 | 1/2 |
| 72 | NSW07_171660 | 0/1 | 0/1 |
| | m.14484T>C + m.4160T>C | | |
| 73 | QLD01_108448 | 0/0 | 1/1 |
| 74 | QLD01_108424 | 2/2 | 1/2 |
| 75 | QLD01_108446 | 2/2 | 1/1 |
| 76 | QLD01_108491 | 1/3 | 1/1 |
| 77 | QLD01_108444 | 0/3 | 0/1 |
| 78 | QLD01_108437 | 1/1 | 1/1 |
| 79 | QLD01_108463 | 1/1 | 2/2 |
| 80 | QLD01_108495 | 0/0 | 1/1 |
| 81 | QLD01_108474 | 1/1 | 0/0 |
| 82 | QLD01_108469 | 1/1 | 4/4 |
| 83 | QLD01_108473 | 0/0 | 2/2 |
| 84 | QLD01_108421 | 0/1 | 1/1 |
| 85 | QLD01_108439 | 1/1 | 0/0 |
| 86 | QLD01_108412 | 3/4 | 4/6 |
| 87 | QLD01_108441 | 0/0 | 2/2 |
| 88 | QLD01_108451 | 0/0 | 1/1 |
| 89 | QLD01_108454 | 0/0 | 1/1 |
| 90 | QLD01_108456 | 1/3 | 0/0 |
| 91 | QLD01_108466 | 1/1 | 2/2 |
| 92 | QLD01_108488 | 0/0 | 1/1 |
| 93 | QLD01_108493 | 0/0 | 1/2 |
| | m.14482C>G | | |
| 94 | NSW08_108088 | 1/1 | 1/2 |
| | Total | 49/132 [37.1%] | 44/149 [29.5%] |

**Supplemental Method**

**Participant recruitment**

In 1990, Professor David Mackey (DM) contacted all ophthalmologists in Tasmania and all organisations for the blind in Australia asking to be put in contact with any patient affected by LHON. In addition, DM contacted all clinicians and researchers who had published on LHON pedigrees in Australia. LHON family members were asked to provide their matrilineal family tree as far back as possible, often with assistance of other family members. A professional genealogist then expanded each pedigree using national genealogical resources such as the digitised and microfilmed births deaths and marriage records, published family trees and histories available at genealogical society libraries, as well as legal documents such as wills that name living descendants. Many smaller families were subsequently linked into the main pedigrees [4].

Subsequently, DM contacted every ophthalmologist in Australia and offered DNA testing for patients suspected to be affected by LHON. This identified some new branches of the main families and provided additional updated pedigree information as well as new mainly small families[3]. Since 1995, LHON patients and families have been referred to our clinics in Melbourne, Tasmania and Western Australia by ophthalmologists across Australia, and new patients have also self-referred to our research team or clinics. In addition to genealogical linkage investigations, we use mtDNA sequencing to identify related pedigrees and conduct more exhaustive genealogical searches to confirm potential linkages. We provide national genetic counselling advice to LHON families.

**Supplemental References**

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