**Supplementary Table S1. Genotyping methods applied in each proband**

| Case No. | Sample ID | Sequence analysis of all exons | | | | | | | | | | LCA APEX | *ABCA4* *APEX* | USH APEX | *CEP290* intronic mutation | Nijmegen screening |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *AIPL1* | *CEP290* | *CRB1* | *CRX* | *GUCY2D* | *LRAT* | *RDH12* | *RPE65* | *RPGRIP1* | *TULP1* | | | | | |
| 1 | 063070 | R | | | R | R(-)/N | | | R | | | | | | | N |
| 2 | 063071 | | | N/R | | | | | | | | | | | | N |
| 3 | 063072 | R | | | | R | R | | R | | | | | | | N |
| 4 | 063073 | R | N | R | R | R | R | | R | | R | | | | | N |
| 5 | 063074 | R | N | R | R | R | R | | R | | R | | | | | N |
| 6 | 063075 | R | | R | R | R | R | | R | | R | | | | | N |
| 7 | 063076 | | | | R | R | | | | | | R; 2006 | | | | N |
| 8 | 063077 | R | | R | R | R | R | | R | R | | | | | | N |
| 9 | 063078 | R | | | R | R | R | | R | | | | | | | N |
| 10 | 063079 | | | | | | | | | | | | | | | N |
| 11 | 063080 | R | | R | R | R | R | | R | | | | R | | | N |
| 12 | 063081 | | | | | | | | R | R | | | | | | N |
| 12 | 063082 | | | | | | | | | | | R; 2009 | | | | N |
| 13 | 063083 | R | | | R | R(-)/N | R | | R | R | | R; 2006 | | | | N |
| 14 | 063084 | | | | | | | | N | | | R; 2011 | | | | N |
| 15 | 063086 | R | | R | R | R | R | | R | R | | R; 2006 | | | R | N |
| 16 | 063087 | | | | | | | | | | | | | | | N |
| 17 | 063088 | | N | | R | R | R | | | | | R; 2006 | | | | N |
| 18 | 063089 | | | R | R | R | R | | R | | | R; 2006 | | | R | N |
| 19 | 063090 | R | | R | R | R | | | R | | | R; 2006 | | | | N |
| 20 | 063091 | R | | N | R | R | R | | R | | | | | | | N |
| 21 | 063092 | R | | | R | R | R | | R(-)/N | | | R; 2012 | | | | N |
| 22 | 063093 | R | | R | R | R | | | R | | R | | | | | N |
| 23 | 063094 | R | N | R | R | R | R | | R | | R | | | | | N |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 24 | 063095 | R | | R | R | R | R | | R | R | | | | | | N |
| 25 | 063096 | R | | | | R | R | | R | | R | | | | | N |
| 26 | 063097 | | | | | N | | | | | | R; 2006 | | | | N |
| 27 | 063098 | | N | | | | | | | | | R; 2006 | | | | N |
| 28 | 063099 | R/N | | R | R | R | R | | R | R | | | | | R | N |
| 29 | 063101 | | | | R | R | R | | R/N | | | R; 2006 | | | | N |
| 30 | 063103 | R | N | | | R | | | R | | | | | | | N |
| 31 | 063104 | R | | | R | R | | | R/N | | R | | | | | N |
| 32 | 063105 | | | | | | | | | | | R; 2009 | | | | N |
| 33 | 063106 | | | | | | | | N | | | R; 2012 | | | | N |
| 34 | 063107 | | | | | | | | | | | R; 2012 | | | | N |
| 35 | 063108 | | | | | | | | | | | R; 2012 | | | | N |
| 36 | 063109 | | | | | | | | | | | | | | | N |
| 37 | 063111 | | | | | | | | | | | | | | | N |
| 38 | 063112 | | | | | | | | N | | | | | | | N |
| 39 | 063113 | | | | | | | | | | | | | | | N |
| 40 | 063114 | | | | | | | | | | | | | | | N |
| 41 | 063115 | | | | | | | | | | | | | | | N |
| 42 | 063116 | | | | | | | | N | | | | | | | N |
| 43 | 063117 | N | | | | | | | | | | | | | | N |
| 44 | 063118 | | | | | | | | | | | | | | | N |
| 45 | 063119 | | | N | | | | | | | | | | | | N |
| 46 | 063120 | | | | | | | | N | | | R; 2012 | | | | N |
| 47 | 063121 | | | | | | | | | | | | | | | N |
| 48 | 063122 | | | | | | | | | | | | | | | N |
| 49 | 063123 | | | | | N | | | | | | | | | | N |
| 50 | 063124 | | | | | | | | | | | R; 2011 | | R | | N |
| 51 | 063126 | | | | | | | | N | | | R; 2008 | | | | N |
| 52 | 063127 | | | | | | | | N | | | | | | | N |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 53 | 063128 | | | | | | | | | | | | | | | N |
| 54 | 063129 | | | | | | | | | | | R; 2010 | | | | N |
| 55 | 063130 | | | | | | | | N | | | R; 2011 | | | | N |
| 56 | 063131 | | | | | | | | | | | R; 2010 | | | | N |
| 57 | 063132 | | | | | | | | | | | R; 2010 | | | | N |
| 58 | 063133 | | | | | N | | | | | | R; 2011 | | | | N |
| 59 | 063134 | N | | | | | | | | | | | | | | N |
| 60 | 063135 | | | | | | | | | | | | | | | N |
| 61 | 063136 | | | | | | | | | | | | | | | N |
| 62 | 064259 | | | | | | | | | | | R; 2007 | | | | |
| 63 | 064260 | R | | | R | R | R | | R | | | | | | | |
| 64 | 064261 | R | | R | R | R | R | | R | R | | | | | | |
| 65 | 064262 | | | | | | | | | | | R; 2010 | | | | |
| 66 | 064263 | R | | R | R | R | R | | R | R | | | | | | |
| 67 | 064264 | | | | | | | | | | | R; 2009 | | | R | |
| 68 | 064265 | | | | | R | | | | | | R; 2009 | | | | |
| 69 | 064266 | | | | | | | | | | | R; 2009 | | | | |
| 70 | 064267 | R | | R | R | R | R | R | R | | | | R | | | |
| 71 | 064268 | R | | | R | R | R | | | R | | R; 2006 | | | | |
| 72 | 064287 | | | | | R | | | R | | | | | | | |
| 73 | 064269 | R | | | | R | R | | R | | R | | | | | |
| 74 | 064270 | | | | R | R | | | R | | | | | | | |
| 75 | 064271 | R | | | | R | | | R | | | | | | | |
| 75 | 064272 | R | | | | R | | | R | | | | | | | |
| 76 | 064273 | R | | | | R | R | | R | | | | | | | |
| 77 | 064275 | | | | | | | | R | | | | | | | |
| 77 | 064276 | | | | | | | | R | | | | | | | |
| 78 | 064277 | R | | | | | | | R | R | | | | | | |
| 79 | 064278 | R | | R | R | R | R | | R | | | R; 2006 | | | | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 80 | 064279 | R | | | | R | R | | R | | | | R | | | |
| 81 | 064281 | R | | R | R | R | R | | R | R | | R; 2006 | | | | |
| 82 | 064282 | | | | | | | | | | | R; 2012 | | | | |
| 83 | 064283 | | | | | | | | | | | R; 2012 | | | | |
| 84 | 064284 | R | | | R | R | R | | R | | | R; 2012 | | | | |
| 85 | 064285 | R | | R | R | | R | | R | | | R; 2006 | | | | |
| 86 | 064286 | | | | | | | | R | R | | R; 2010 | | | | |

R: Genotyping analysis performed in Regensburg, Germany (former affiliation of MNP and BL)
N: Genotyping screening performed in Nijmegen, The Netherlands

**Supplementary Table S2. Primers used for mutation hotspot screening and second allele identification**

| *Gene* | Exon | Forward primer (5'-3') | Reverse primer (5'-3') |
|---|---|---|---|
| ***AIPL1*** | Exon 1 | TCTCAGCCGCCTAAGTGTCTTCC | TCCCTTTCTTCTCACTCAACATTTAGG |
| | Exon 2 | CGGGCCTTGAACAGTGTGTCTAG | CGCACCAGAACTCGGCCAC |
| | Exon 3 | GCCTGGCACACAGTTAACCACAG | GTCCCTCTCCAGTGCTGGCAC |
| | Exon 4-5 | AGGGAGATGTGCCACAGGGTC | TGGCAGGTGTCTCCGTGGC |
| | Exon 6 | TGCCTCTGAGGCTGGGAAGG | CACGATCCTGGTCAATCGAACC |
| ***CEP290*** | Exon 1 | AGCGCCTTACCTCCTCTTCT | GCCCTCAGGCTAAAGAACCT |
| | Exon 2-3 | AAAATGTAAGGTGCTAGAAAACCAA | CCAGGTATTTTCACAAAGATTACCTTA |
| | Exon 4 | TTGAGGACTTGAGGTAAAAAGGA | CCATAATAAACTTTTTCCAAGGTG |
| | Exon 5 | GGATCTGCCATATAATACTTTTTGTT | CCCTTTCGTCACTATTCCTCA |
| | Exon 6 | TGCTTGTTGTTGACTCATTTGAA | CCAATAATAATAAAAAGCCAGGTAA |
| | Exon 7 | CATTTTCTACTTTGTTAGAGAGGATTT | GAAGACTCCAGTCCTGGTTAAAA |
| | Exon 8-9 | AATATGCATCATTTTCCCAAA | AGGAACCATTGCTCTGAATTG |
| | Exon 10 | GGACACTTATGGCTGCGTTT | AAGACAGACAAAAATTCACATCC |
| | Exon 11 | TTCCAGGATGACTTCAATGAT | CCCTAATAAACGTGTTATAAACCAG |
| | Exon 12 | TGCCAGTAGTTGCTCATACTTTC | TTCCAACTGTAATAAAACTGGTTGATA |
| | Exon 13 | AAAAGGCATACTTGTACCCACA | GAAAATGCATCCATCATTTACAA |
| | Exon 14 | TGGGATCACTGATTTGAAGGA | CAGAATAGTCTGTGAATGGCAAG |
| | Exon 15 | GGATTTGGTTTATAAAAGCACAATAAA | CACTTCAATCAGGTTAGCTCCA |
| | Exon 16-17 | TGACATTTTTGCAGCTTATTTGA | TTCATATCCAGACAACTCACTTATCA |
| | Exon 18 | TGGAGGGATTTTGGAAACAA | TTTTCCTTTACTCTCTTTGCAATAC |
| | Exon 19 | TTTTTGTTTGCACTTTAACATCAG | CCCTTTTAGGCCCATGATTT |
| | Exon 20 | TGTGAAAAAGATCTGATCATCCA | TGGCTAAATCTTTCTTGTAGCAAT |
| | Exon 21 | TTATCATGCTTGGCAATGAA | ACATTCTTATGTTTAGCATTTTCTTTT |
| | Exon 22 | TGGCAGGGCATTCACATATC | TTGAGAAAAGTACTATCTGCATGCTT |
| | Exon 23 | TGTGTTGCTTACAGATTTGGTGA | TTCACAATTAACAAGAATATACTGCAA |
| | Exon 24 | GCTATGATACCTCTTGTGTTGAGAAA | TCAGAAAAAGCAAAATAAGAATCAGA |
| | Exons 25-26 | TCTTTCTCAAAAGTGGCTAGTGC | CCCCCAAACACAAAAATATTGA |
| | Exon 27 | TGGATTGTGAGTTTTAAGGAGATG | TTGGTGGGGTTAAGTACAGGA |
| | Exon 28 | TGGTACAGGCATCACACAGG | TTTCAGAGATCCAGACAAACCA |
| | Exon 29 | GGCCAAGTAAAGAGGATTGC | GAATTGTATACCTGTAATTGGGTTTC |
| | Exon 30 | TGAAAACGAATGGCTTTTTG | AACATATCCCACTCCCAACA |
| | Exon 31 | AACTTTCACTGGAAAAATTTGAAAC | GCCTGGGAAACAGATCAAGA |
| | Exon 32 | TCATCAATGGAGGAATGTTATTTG | GTCATTTGTGCAATATTCTTGTTT |
| | Exon 33 | TTTCTTCAATGTGTTGTGAGGA | TCTGTGAGTTAACACTCTAGACTATGC |
| | Exon 34 | AAGAGGGGTTTAATCTATGTTTTATCA | CATTCTATGCATTGCCCTCA |
| | Exon 35 | AAGCATGCAAATAACTGCTGTC | TCCAATCACATGCAAGTAACAA |
| | Exon 36 | GAGGGGACATGCATACCAGT | TTTTGGCAACAAAAAGGGTAA |
| | Exon 37 | TTTGATCATTTGAGGAACCAAA | GCCTGGCATAGCAAACACTT |
| | Exon 38 | TGAATTGCAGCAACCACTCT | AAAAGCAATCTACCACATATTTTTCC |
| | Exon 39 | TTTGTGAAATATGTTCCATTAAACTCA | CACCAACAGTGCATTATAAATTCC |
| | Exon 40 | TGGAAAAATATATGTAGTTTGTGGTT | TTTGAAAGTCAGTTTTAACAAATACCA |
| | Exon 41 | AAAATGCAGAAGCAGCTACCA | AGCCAGGTCATCAAATTAAGG |
| | Exon 42 | TCAACCTGTATAGCAAAATGAACA | CGAGATCACAGGAAAATCCA |
| | Exon 43 | TGGATTTTCCTGTGATCTCG | CCCAAGCTTAAGACAACACACA |
| | Exon 44 | CATTTAAAGGAGGCCTTCAGTG | TGCTTTTGGCCAGATTAAGAA |
| | Exon 45 | CCTTTTGACAGTATTTTCTTATCCA | AAAAGTAAACATAACAACTAAGGAAGG |
| | Exon 46 | TTTTCAATGGCTGTAGCTATGTT | CAGGGCACTTGTAGAGGCATA |

| | | | |
|---|---|---|---|
| | Exon 47 | AGAATTGTTTTAAGGATGAATTGAA | AACCCTTAGCCTTGCCTCTC |
| | Exon 48 | AACGTTGGGAACTTCGTTCT | CTTCCAGTTTTTCCAAGAGGT |
| | Exon 49 | GCATTTAGAGCCCCAGGTTA | CAGGAAGAAACCAGGTTATCCA |
| | Exon 50 | AGCTAAAACTTTGACTAGAAGAAACAG | GGTGCCCTTCAGTTAGATGG |
| | Exon 51 | ACGCTTTGTTAAAAATGTGTATCTT | TCTCTAGTTGTAGCAATTCGGAGT |
| | Exon 52 | CGATAAAGGCTAGCTTGTTCTGA | GATCAGAAATCTGAGCCAAAAA |
| | Exon 53 | CATCCAGTGTTTTCCAGGTTC | TTTTTAGGATACGTAGTTAAAGATGGT |
| | Exon 54 | TTGCTGTATTTGACCATTCAGG | TCACCAGAGCTCACTGCCTA |
| ***CRB1*** | Exon 1 | CGCTCCTCTCTGAGACAGAC | TTTTATAGAACATGCAACATTATCC |
| | Exon 2.1 | AATGAGTTTGGTTGAGGCAG | ATATCCAGCAGGGCAGATG |
| | Exon 2.2 | CAGTGGGACAATCTGTGAAAC | AATGTCACCTCTGCTTCTGC |
| | Exon 3.1 | GCTCTGGTAAACAAAGCATTG | GAATCCAGGGGCACAGTCG |
| | Exon 3.2 | GACGAATGTTGGTCCCAGC | CAGAGTGGTAAAATAGTTCATG |
| | Exon 4 | GAAACAGTATAAAGATATCTGATC | GCTATAAGCGATATGTGTATTC |
| | Exon 5 | AACCTCCTTTTAGGCAAATG | GGTTAAAGCCATGGTCTGC |
| | Exon 6.1 | GAGCTATTCATGCACTTCTGC | GCCTCTGCAAATATTACCTCC |
| | Exon 6.2 | GAAGCTGGAGCTGCTAAGTG | TTTGCTGTTTCTGCTCTGC |
| | Exon 7.1 | TCCATCCCTTCTGTCTTTTG | TCCTAGGTTTTGTGAAGACTGA |
| | Exon 7.2 | GCAATGCTGACTCCAAACTC | TGGTGGGTCAGTAACATCATC |
| | Exon 8 | CAACATTTTTCTATTTAGTTGCC | CTCAAATGTCGCAACTTAACTG |
| | Exon 9.1 | AATGATCATTACTATTAATAACGG | GTGTTTCGTTGTCCACTTCC |
| | Exon 9.2 | TTGCAGTCAGTGAATGATGG | GGGACAGGAGCAATGATAAG |
| | Exon 10 | CTTTTCTTGAATGAGATGAACAAG | GAACTTTGAGTAATCCCATCATTC |
| | Exon 11 | TTCACAACCAATGTATTCAACAG | TCATACGCAAAATGAGGTAAG |
| | Exons 12-13 | TTCCTGAGTAGTTCCATTGTCC | CCCAGTTGCAGATTAACATTG |
| | Exon 14 | GCTGTTCCAGAGAGATAAGGC | CTCAACAACTGGCTCGTCAT |
| ***GUCY2D*** | Exon 1 | TCAGCTTGGGGAGATTAAGG | GAGGGGCCTCTGACATTTAC |
| | Exon 2.1 | TACTCGGGCTTGGAGAAAC | CTTCTTCGGCGAGCAGC |
| | Exon 2.2 | GACCCCATCTTCTCTCGG | ATGATCACTGCTGCGGAC |
| | Exon 3 | AGGTAGGCTCCCTTGCAG | GGCTGTCCTCTCCCCTC |
| | Exon 4 | GAATCTGGTCTGTCTGTGGG | CTCTCTTTCATCACTTTGTGG |
| | Exons 5-6 | GAAGAGGCCTCCCCTGG | GGAAGGAACCAAATTTACGG |
| | Exon 7 | TCAACCCAGGACTCTGACAC | AGGGCCTGAGCATTCTTC |
| | Exon 8 | CCCATCGTGGGATTTTAAG | TACCCAGCTGCAAAGAGAAG |
| | Exons 9-10 | TCTTGATTAACAGCCCCTTC | GAGAAGCCCTTGAAATAATGG |
| | Exon 11 | AACCTGGGCTTTCTGGTG | CTTTTCTAACTGCAGGGTGC |
| | Exon 12 | AGAGGCAGCCTTTGTGTTC | AGCTGTCTCAGGTTGCTGAC |
| | Exons 13-14 | GGTTCAGAGTGAACAGCCC | AGATTGATTGGGCAGGTAGG |
| | Exon 15 | CGCTTCGTGTACTCGGG | CCTCTACAGGAAATCTGGGG |
| | Exons 16-17 | GGAGATAATGGGTGCGAAG | AGGTCAGAAGGGTGAGCTG |
| | Exons 18-19 | AGCTCACCCTTCTGACCTG | GACACCTGGCTTGGGTG |
| | Exon 20 | CTCTGTAGCTGGCAGAGCAG | AAAGCAGCACACACCACAAC |
| ***LRAT*** | Exon 1.2 | TTTGCCTTCCTCTCTCCTCAG | CTGGCCACTTTGACAATAACG |
| | Exon 1.2 | ATGCCCGACATCCTGTTG | AAGAGAAAAGGTCAGGGATGG |
| | Exon 2 | TCTTGGGTTTAGCCACCTTTC | GTAAGCACTTTGCGTGATTCC |
| ***RPE65*** | Exon 1 | CAACTTCTGTTCCCCCTCCCTCAG | CTCTTCAGGAGCCCTTGAAATAGC |
| | Exon 2 | TCTATCTCTGCGGACTTTGAGCAT | ATAGGAAGCCAGAGAAGAGAGACT |
| | Exon 3 | CCCAAGGCAGGGATAAGAAGCAAT | AAGCTAGGCCCTACTTTGAGGAGG |
| | Exon 4 | ACATGGGCTGTACGGATTGCTCCT | GAGAGAAAAAGGGCTAATATAAAA |
| | Exon 5 | ATGGCTTGAAAATTACTGGACTGA | TGGTGAATTAATTTTAAGTTCCAA |
| | Exon 6 | AGGTATAATGTATCTTCCTTCTCT | TTATCTTTCTCACAATACAGTAAC |

| | | |
|---|---|---|
| Exon 7 | CTGTTCTAAATGCTTTGTATTAAA | TAGGCCAAGCCAATCTTTAAACTT |
| Exon 8 | TGTGGCTTGAGAATCAGCCCTTTC | GTGTACATTATTAAACACATCTTC |
| Exon 9 | GTACACTTTTTTCCTTTTTAAATG | ACCCCGTAATTTCCAGGAACAATG |
| Exon 10 | AGAATCATCTCTCTAAAATTATTT | CTGAGAGAGATGAAACATTCTGGT |
| Exon 11 | GAATTCTTTCCTGCTCACTGAGGT | GAGCACATGCTTAGGAAAACTCTT |
| Exon 12 | ACTTCACACGGGAGTGAACAAATG | GTCAATATGCTTTACTTGACTAGC |
| Exon 13 | GCTAGTCAAGTAAAGCATATTGAC | CATACAGAGCTGCAGTAAGAAGAG |
| Exon 14 | TGACACTCAATCTATAGCTTCGGC | GATTGCAGACCTGAAGCTGATTTT |

**ARMS-primers used for screening *CEP290* c.2991+1655A>G mutation**

| **ARMS Primer** | **Sequence (5'-3')** |
|---|---|
| ARMS *CEP290* c.2991+1655A>G wild type - forward | ACCGCACCTGGCCCCAGTTGTAATTGTGGA |
| ARMS *CEP290* c.2991+1655A>G mutant - forward | ACCGCACCTGGCCCCAGTTGTAATTGTGGG |
| ARMS *CEP290* c.2991+1655A>G reverse | AGTAAGGAGGATGTAAGACTGGAGATAGAG |

**Supplementary Table S3. Estimated carrier frequencies of causative variants in LCA genes**

| Gene name | % | LCA | | arRP | |
|---|---|---|---|---|---|
| | | q2 | 2pq | q2 | 2pq |
| ***AIPL1*** | 5.3 | 1/943396 | 1/486 | | |
| ***CEP290*** | 15 | 1/333333 | 1/289 | | |
| ***CRB1*** | 9.9 | 1/5050501 | 1/356 | 1/175000 | 1/210 |
| ***GUCY2D*** | 11.7 | 1/427350 | 1/327 | | |
| ***LRAT*** | 0.5 | 1/10000000 | 1/1582 | 1/233333 | 1/242 |
| ***RPE65*** | 6 | 1/833333 | 1/457 | 1/175000 | 1/242 |
| | | **~1/103306** | **~1/70** | **~1/77** | **~1/37** |

The Hardy-Weinberg equilibrium ($p^2+ 2pq+ q^2=1$) was used to estimate the carrier frequencies for autosomal recessive traits. p, frequency of the wild type allele; q, frequency of the recessive mutant allele; $q^2$, prevalence of a homozygous recessive allele; 2pq, carrier frequency. Percentage of patients affected by mutations in the gene was calculated by assuming a prevalence LCA of 1:50,000.

**Supplementary Table S4. Allele frequencies of identified variants in this study**

| Gene | Nucleotide change | Amino acid change | Number of alleles | Reference |
|---|---|---|---|---|
| *AIPL1* | **c.815G>C** | **p.(R272P)** | **1** | **novel** |
| *AIPL1* | c.834G>A | p.(W278*) | 7 | 1 |
| *CEP290* | c.1219_1220delAT | p.(M407Efs*14) | 1 | 2 |
| *CEP290* | **c.2119_2123dupCAGCT** | **p.(Q709Sfs*11)** | **2** | **novel** |
| *CEP290* | c.2991+1655A>G | p.(C998*)/p.=# | 8 | 3 |
| *CEP290* | **c.5364+2T>G** | **p.(?)** | **2** | **novel** |
| *CRB1* | c.584G>T | p.(C195F) | 1 | 4 |
| *CRB1* | c.613_619delATAGGAA | p.(I205Dfs*13) | 3 | 5 |
| *CRB1* | c.2290C>T | p.(R764C) | 1 | 6 |
| *CRB1* | c.2401A>T | p.(K801*) | 2 | 6 |
| *CRB1* | **c.2549G>T** | **p.(G850V)** | **1** | **novel** |
| *CRB1* | c.2843G>A | p.(C948Y) | 1 | 6 |
| *CRB1* | **c.4006G>A** | **p.(V1336I)** | **1** | **novel** |
| *CRB1* | c.4121_4130del10 | p.(A1374Nfs*20) | 2 | 6 |
| *GUCY2D* | c.779T>C | p.(L260P) | 2 | 7 |
| *GUCY2D* | (c.380C>T) | p.(P127L) | 1 | **novel** |
| *GUCY2D* | **c.1561C>T** | **p.(R521*)** | **2** | **novel** |
| *GUCY2D* | c.1694T>C | p.(F565S) | 1 | 8 |
| *GUCY2D* | **c.1877T>C** | **p.(S626F)** | **2** | **novel** |
| *GUCY2D* | c.1957G>A | p.(G653R) | 1 | 7 |
| *GUCY2D* | c.2234delC | p.(P745Lfs*39) | 1 | 7 |
| *GUCY2D* | **c.2135_2136delinsTC** | **p.(E712V)** | **1** | **novel** |
| *GUCY2D* | c.2302C>T | p.(R768W) | 5 | 9 |
| *GUCY2D* | c.2513G>C | p.(R838P) | 1 | 10 |
| *GUCY2D* | c.2849C>T | p.(A950V) | 2 | 7 |
| *GUCY2D* | **c.3043+5G>A** | **p.(?)** | **1** | **novel** |
| *RDH12* | c.2T>C | p.(M1T) | 1 | 11 |
| *RDH12* | c.379G>T | p.(G127*) | 2 | 12 |
| *RDH12* | c.582C>G | p.(Y194*) | 1 | 11 |
| *RPE65* | c.11+5G>A | p.(?) | 4 | 13 |

| | | | | |
|---|---|---|---|---|
| *RPE65* | **c.94G>T** | **p.(G32C)** | **1** | **novel** |
| *RPE65* | **c.130C>T** | **p.(R44*)** | **4** | **novel** |
| *RPE65* | c.272G>A | p.(R91Q) | 1 | 14 |
| *RPE65* | c.271C>T | p.(R91W) | 2 | 15 |
| *RPE65* | **c.329A>G** | **p.(D110G)** | **7** | **novel** |
| *RPE65* | **495+1dup** | **p.(?)** | **2** | **novel** |
| *RPE65* | c.769T>G | p.(Y239D) | 1 | 16 |
| *RPE65* | c.963T>G | p.(N321K) | 2 | 17 |
| *RPE65* | **c.1088C>G** | **p.(P363R)** | **1** | **novel** |
| *RPE65* | c.1102T>C | p.(Y368H) | 4 | 18 |
| *RPE65* | c.1328T>C | p.(V443A) | 1 | 19 |
| *RPE65* | c.1374G>A | p.(W458*) | 1 | 7 |
| *RPE65* | c.1543C>T | p.(R515W) | 1 | 20 |
| *RPGRIP1* | **c.930+3A>G** | **p.(?)** | **1** | **novel** |
| *RPGRIP1* | **c.3618-5del** | **p.(?)** | **1** | **novel** |
| *TULP1* | **c.1495_1496dup** | **p.(D500Vfs*4)** | **1** | **novel** |

**Supplementary Table S5. *RPE65* variants registered in LOVD**

| Exon/Intron | cDNA Change | Protein Change | Allele Count | Coding Effect | Classification | Reference |
|---|---|---|---|---|---|---|
| 1 | c.-4G>A | p.(?) | 1 | Unknown | Variant of unknown significance | 21 |
| 1 | c.2T>C | p.(Met1?) | 5 | Start loss | Affects function | 15,22 |
| 2 | c.16G>T | p.(Glu6*) | 2 | Nonsense | Affects function | 23,24 |
| 2 | c.57_58del | p.(Glu20Glyfs*31) | 4 | Frameshift | Affects function | 21,25 |
| 2 | c.65T>C | p.(Leu22Pro) | 2 | Missense | Variant of unknown significance | 26,27 |
| 2 | c.74C>T | p.(Pro25Leu) | 2 | Missense | Affects function | 28 |
| 2 | c.89dup | p.(Thr31Asnfs*21) | 1 | Frameshift | Affects function | 13 |
| 2 | c.89T>C | p.(Val30Ala) | 1 | Missense | Variant of unknown significance | 29 |
| 2 | c.90_91insT | p.(Thr31Tyrfs*21) | 1 | Frameshift | Affects function | 22 |
| 3 | c.95G>T | p.(Gly32Val) | 1 | Missense | Affects function | 30 |
| 3 | c.97_116del | p.(Ile34Glnfs*11) | 2 | Frameshift | Affects function | 31 |
| 3 | c.106_114del | p.(Leu36_Leu38del) | 2 | In-frame deletion | Affects function | 30 |
| 3 | c.118G>A | p.(Gly40Ser) | 23 | Missense | Affects function | 15,19,23,24,31-40 |
| 3 | c.131G>A | p.(Arg44Gln) | 29 | Missense | Affects function | 14,19,31,32,34,37,39-43 |
| 3 | c.133T>C | p.(Cys45Arg) | 1 | Missense | Variant of unknown significance | 38 |
| 3 | c.138del | p.(Pro47Glnfs*47) | 4 | Frameshift | Affects function | 9,19,33,36 |
| 3 | c.144_145insT | p.(Leu49Serfs*3) | 1 | Frameshift | Affects function | 18 |
| 3 | c.177C>G | p.(His59Gln) | 1 | Missense | Affects function | 44 |
| 3 | c.179T>C | p.(Leu60Pro) | 10 | Missense | Affects function | 24,45 |
| 3 | c.183dup | p.(Asp62*) | 1 | Frameshift | Affects function | 44 |
| 3 | c.190C>T | p.(Gln64*) | 4 | Nonsense | Affects function | 43,46 |
| 3 | c.200T>G | p.(Leu67Arg) | 7 | Missense | Affects function | 25,47-49 |
| 3 | c.201_202delGCinsTT | p.(His68Tyr) | 1 | Missense | Affects function | 27 |
| 3 | c.208T>G | p.(Phe70Val) | 2 | Missense | Affects function | 26,50 |
| 3 | c.219dup | p.(Glu74Argfs*14) | 6 | Frameshift | Affects function | 51 |
| 3 | c.235T>C | p.(Tyr79His) | 1 | Missense | Affects function | 22 |
| 3 | c.289dup | p.(Arg97Lysfs*34) | 3 | Frameshift | Affects function | 19,52 |
| 4 | c.249C>G | p.(Phe83Leu) | 2 | Missense | Affects function | 25 |
| 4 | c.253C>T | p.(Arg85Cys) | 1 | Missense | Variant of unknown significance | 19 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 4 | c.254G>A | p.(Arg85His) | 1 | Missense | Affects function | 22 |
| 4 | c.271C>T | p.(Arg91Trp) | 100 | Missense | Affects function | 14,15,18,19,22,23,31,32,34-36,39,40,42,50,53-58 |
| 4 | c.272G>A | p.(Arg91Gln) | 17 | Missense | Variant of unknown significance | 19,22,25,31,35,37,39,40 |
| 4 | c.272G>C | p.(Arg91Pro) | 1 | Missense | Affects function | 26 |
| 4 | c.289_309del | p.(Arg97_Phe103del) | 6 | In-frame deletion | Affects function | 9,14,35 |
| 4 | c.292_311del | p.(Ile98Hisfs*26) | 20 | Frameshift | Affects function | 22,32,37 19,39,40,59 |
| 4 | c.295G>A | p.(Val99Ile) | 2 | Missense | Probably no functional effect | 60 |
| 4 | c.297_308del | p.(Ile100_Phe103del) | 1 | In-frame deletion | Affects function | 31 |
| 4 | c.297del | p.(Ile100*) | 1 | Nonsense | Affects function | 14 |
| 4 | c.302C>T | p.(Thr101Ile) | 3 | Missense | Affects function | 19,34 |
| 4 | c.304G>A | p.(Glu102Lys) | 3 | Missense | Affects function | 15,26 |
| 4 | c.304G>T | p.(Glu102*) | 21 | Nonsense | Affects function | 7,19,21,22,33,36,61 |
| 4 | c.310G>C | p.(Gly104Arg) | 2 | Missense | Affects function | 62 |
| 4 | c.311G>A | p.(Gly104Asp) | 1 | Missense | Affects function | 31 |
| 4 | c.329A>T | p.(Asp110Val) | 1 | Missense | Affects function | 24 |
| 4 | c.344T>C | p.(p.Ile115Thr) | 1 | Missense | Affects function | 63 |
| 5 | c.354G>T | p.(Arg118Ser) | 3 | Missense | Affects function | 19,64 |
| 5 | c.361del | p.(Ser121Leufs*6) | 12 | Frameshift | Affects function | 29,41,45,65 |
| 5 | c.361dup | p.(Ser121Phefs*10) | 2 | Frameshift | Affects function | 65 |
| 5 | c.370C>T | p.(Arg124*) | 11 | Nonsense | Affects function | 15,19,22,23,26,33,36,41,66 |
| 5 | c.382G>C | p.(Val128Leu) | 1 | Missense | Probably no functional effect | 22 |
| 5 | c.394G>A | p.(Ala132Thr) | 13 | Missense | Probably no functional effect | 15,19,22,55,65,67 |
| 5 | c.395C>A | p.(Ala132Asp) | 2 | Missense | Affects function | 31 |
| 5 | c.406G>T | p.(Val136Phe) | 1 | Missense | Probably no functional effect | 64 |
| 5 | c.427T>G | p.(Tyr143Asp) | 2 | Missense | Variant of unknown significance | 68 |
| 5 | c.430T>C | p.(Tyr144His) | 1 | Missense | Affects function | 47 |
| 5 | c.430T>G | p.(Tyr144Asp) | 13 | Missense | Affects function | 14,19,26,31,37,39,69 |
| 5 | c.434C>A | p.(Ala145Asp) | 2 | Missense | Affects function | 49 |
| 5 | c.440_441del | p.(Thr147Argfs*9) | 2 | Frameshift | Affects function | 26 |
| 5 | c.444G>T | p.(Glu148Asp) | 1 | Missense | Variant of unknown significance | 43 |
| 5 | c.484A>C | p.(Thr162Pro) | 1 | Missense | Affects function | 19 |

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|---|---|---|---|---|---|---|
| 6 | c.499G>T | p.(Asp167Tyr) | 6 | Missense | Affects function | 19,22-24,26,51 |
| 6 | c.500del | p.(Asp167Valfs*41) | 4 | Frameshift | Affects function | 31 |
| 6 | c.540C>A | p.(His180Gln) | 1 | Missense | Affects function | 53 |
| 6 | c.542C>T | p.(Pro181Leu) | 2 | Missense | Affects function | 41 |
| 6 | c.544C>A | p.(His182Asn) | 1 | Missense | Affects function | 43 |
| 6 | c.544C>T | p.(His182Tyr) | 9 | Missense | Affects function | 15,19,31-33,36,37 |
| 6 | c.545A>G | p.(His182Arg) | 8 | Missense | Affects function | 14,31,39,55 |
| 6 | c.565G>A | p.(Val189Ile) | 1 | Missense | Variant of unknown significance | 55 |
| 6 | c.615_616del | p.(Ile206Cysfs*27) | 2 | Frameshift | Affects function | 22,43 |
| 7 | c.668_669del | p.(Ser223*) | 1 | Nonsense | Affects function | 22 |
| 7 | c.700C>T | p.(Arg234*) | 11 | Nonsense | Affects function | 22,26,41,43,46,51,70 |
| 7 | c.715T>G | p.(Tyr239Asp) | 12 | Missense | Affects function | 19,31-34,36,50,71 |
| 8 | c.731G>T | p.(Gly244Val) | 2 | Missense | Affects function | 55 |
| 8 | c.746A>G | p.(Tyr249Cys) | 2 | Missense | Affects function | 24 |
| 8 | c.751G>T | p.(Val251Phe) | 2 | Missense | Affects function | 72 |
| 8 | c.778_785del | p.(Asn260Glnfs*18) | 4 | Frameshift | Affects function | 13,22,51 |
| 9 | c.859G>T | p.(Val287Phe) | 14 | Missense | Affects function | 9,19,31,32,39,40,55 |
| 9 | c.864G>T | p.(Trp288Cys) | 1 | Missense | Affects function | 55 |
| 9 | c.868C>T | p.(His290Tyr) | 3 | Missense | Affects function | 65 |
| 9 | c.871A>G | p.(Ile291Val) | 1 | Missense | Probably no functional effect | 55 |
| 9 | c.881A>C | p.(Lys294Thr) | 4 | Missense | Probably no functional effect | 22,34,73 |
| 9 | c.886dup | p.(Arg296Lysfs*7) | 1 | Frameshift | Affects function | 41 |
| 9 | c.893del | p.(Lys298Serfs*27) | 7 | Frameshift | Affects function | 9,19,24,37,39,74 |
| 9 | c.907A>T | p.(Lys303*) | 5 | Nonsense | Affects function | 14,19,31,39,75 |
| 9 | c.912C>A | p.(Tyr304*) | 1 | Nonsense | Affects function | 76 |
| 9 | c.917C>T | p.(Thr306Ile) | 1 | Missense | Variant of unknown significance | 76 |
| 9 | c.938A>G | p.(His313Arg) | 1 | Missense | Affects function | 26 |
| 9 | c.939T>A | p.(His313Gln) | 2 | Missense | Affects function | 65 |
| 9 | c.952T>A | p.(Tyr318Asn) | 3 | Missense | Affects function | 19,34 |
| 9 | c.962dup | p.(Asn321Lysfs*15) | 1 | Frameshift | Affects function | 15 |
| 9 | c.963_964insA | p.(Gly322Argfs*14) | 1 | Frameshift | Affects function | 36 |
| 9 | c.963T>G | p.(Asn321Lys) | 12 | Missense | Probably no functional effect | 22,24,29,34,37,52,55,77,78 |

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|---|---|---|---|---|---|---|
| 9 | c.989G>A | p.(Cys330Tyr) | 8 | Missense | Variant of unknown significance | 43,46,79 |
| 9 | c.991_993dup | p.(Trp331dup) | 5 | In-frame duplication | Affects function | 41,80 |
| 9 | c.993G>A | p.(Trp331*) | 2 | Nonsense | Affects function | 25 |
| 9 | c.997G>C | p.(Gly333Arg) | 1 | Missense | Affects function | 60 |
| 10 | c.1022T>C | p.(Leu341Ser) | 29 | Missense | Affects function | 14,15,19,25,31,32,39-41,64,81 |
| 10 | c.1028T>A | p.(Leu343*) | 1 | Nonsense | Affects function | 14 |
| 10 | c.1059dup | p.(Lys354Glufs*11) | 7 | Frameshift | Affects function | 32,33,35,39,40,60 |
| 10 | c.1067del | p.(Asn356Metfs*17) | 13 | Frameshift | Affects function | 18,19,22,43,46,51,70,82 |
| 10 | c.1067dup | p.(Asn356Lysfs*9) | 7 | Frameshift | Affects function | 19,31,32,36,53 |
| 10 | c.1069_1070insT | p.(Ala357Valfs*8) | 2 | Frameshift | Affects function | 9 |
| 10 | c.1078G>C | p.(Ala360Pro) | 3 | Missense | Variant of unknown significance | 29,34 |
| 10 | c.1087C>A | p.(Pro363Thr) | 16 | Missense | Affects function | 13,22,24,43,46,69 |
| 10 | c.1102T>C | p.(Tyr368His) | 69 | Missense | Affects function | 14,18,19,22-24,31,32,39,42,50,68,83-85 |
| 10 | c.1103A>G | p.(Tyr368Cys) | 4 | Missense | Affects function | 25,48 |
| 11 | c.1178C>A | p.(Ala393Glu) | 7 | Missense | Affects function | 9,19,33,36 |
| 11 | c.1205G>A | p.(Trp402*) | 2 | Nonsense | Affects function | 19,81 |
| 11 | c.1207_1210dup | p.(Glu404Alafs*4) | 4 | Frameshift | Affects function | 15 |
| 11 | c.1220T>C | p.(Val407Ala) | 1 | Missense | Variant of unknown significance | 15 |
| 11 | c.1223T>C | p.(Leu408Pro) | 10 | Missense | Affects function | 19,31,34,39,40 |
| 12 | c.1244_1338del | p.(Phe416Leufs*2) | 1 | Frameshift | Affects function | 34 |
| 12 | c.1249G>C | p.(Glu417Gln) | 12 | Missense | Affects function | 14,31,32,37,39,42 |
| 12 | c.1292A>G | p.(Tyr431Cys) | 5 | Missense | Affects function | 14,19,31,75 |
| 12 | c.1301C>T | p.(Ala434Val) | 11 | Missense | Probably no functional effect | 9,24,34,43,46,55 |
| 12 | c.1304A>G | p.(Tyr435Cys) | 1 | Missense | Affects function | 30 |
| 12 | c.1307G>T | p.(Gly436Val) | 2 | Missense | Affects function | 22,24 |
| 12 | c.1328T>C | p.(Val443Ala) | 3 | Missense | Affects function | 19,64 |
| 12 | c.1336dup | p.(Arg446Lysfs*4) | 1 | Frameshift | Affects function | 29 |
| 13 | c.1355T>G | p.(Val452Gly) | 1 | Missense | Affects function | 15 |
| 13 | c.1370C>A | p.(Thr457Asn) | 2 | Missense | Probably no functional effect | 18,22 |
| 13 | c.1379G>A | p.(Trp460*) | 1 | Nonsense | Affects function | 31 |
| 13 | c.1380G>A | p.(Trp460*) | 1 | Nonsense | Affects function | 19 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 13 | c.1380G>C | p.(Trp460Cys) | 1 | Missense | Affects function | 64 |
| 13 | c.1384G>T | p.(Glu462*) | 4 | Nonsense | Affects function | 9,19 |
| 13 | c.1409C>T | p.(Pro470Leu) | 2 | Missense | Affects function | 17 |
| 13 | c.1418T>A | p.(Val473Asp) | 5 | Missense | Affects function | 15,36,43,46 |
| 13 | c.1430A>G | p.(Asp477Gly) | 23 | Missense | Affects function | 86 |
| 14 | c.1451G>A | p.(Gly484Asp) | 1 | Missense | Affects function | 64 |
| 14 | c.1459_1460del | p.(Leu487Glufs*25) | 2 | Frameshift | Affects function | 62 |
| 14 | c.1501_1505del | p.(Tyr501Profs*10) | 5 | Frameshift | Affects function | 19,39 |
| 14 | c.1543C>T | p.(Arg515Trp) | 8 | Missense | Affects function | 19,20,38,44 |
| 14 | c.1583G>T | p.(Gly528Val) | 1 | Missense | Affects function | 22 |
| 14 | c.1590C>A | p.(Phe530Leu) | 1 | Missense | Affects function | 87 |
| 14 | c.1590del | p.(Phe530Leufs*40) | 7 | Frameshift | Affects function | 23,41,66 |
| 14 | c.1597T>A | p.(Ser533Thr) | 2 | Missense | Probably no functional effect | 19,29 |
| 1i | c.11+1G>T | p.(?) | 2 | Splice site variant | Affects function | 32 |
| 1i | c.11+5G>A | p.(?) | 62 | Splice site variant | Affects function | 9,13,14,18,19,22-24,31-33,36,37,39,41,43,46,63,64,83-85,88 |
| 1i | c.12-2A>G | p.(?) | 1 | Splice site variant | Affects function | 23 |
| 2i | c.94+10A>G | p.(?) | 1 | Splice site variant | Probably no functional effect | 24 |
| 2i | c.95-1G>A | p.(?) | 8 | Splice site variant | Affects function | 45 |
| 2i | c.95-2A>C | p.(?) | 4 | Splice site variant | Affects function | 31,40 |
| 2i | c.95-2A>T | p.(?) | 6 | Splice site variant | Affects function | 26,32,43 |
| 2i | c.95-3C>G | p.(?) | 6 | Splice site variant | Affects function | 89 |
| 6i | c.643+1G>C | p.(?) | 10 | Splice site variant | Affects function | 54 |
| 6i | c.643+4A>G | p.(?) | 1 | Splice site variant | Affects function | 22 |
| 6i | c.644-2A>T | p.(?) | 3 | Splice site variant | Affects function | 15,43 |
| 7i | c.725+4A>G | p.(?) | 5 | Splice site variant | Affects function | 19,31,37,39 |
| 7i | c.726-3C>A | p.(?) | 1 | Splice site variant | Affects function | 90 |
| 7i | c.858+1G>A | p.(?) | 4 | Splice site variant | Affects function | 43,46 |
| 8i | c.858+1G>T | p.(?) | 10 | Splice site variant | Affects function | 13,56 |
| 11i | c.1243+2T>A | p.(?) | 1 | Splice site variant | Affects function | 87 |
| | | Total alleles | 914 | | | |
| | | Probably no functional effect | 50 | | | |

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|---|---|
| Heterozygous Cases | 140 |
| Dominant Cases | 23 |
| Homozygous Cases | 231 |
| Compound Heterozygous Cases | 144 |
| Uniparental Isodisomy | 1 |
| Total Cases | 539 |

## Supplementary Table S6. In silico analysis *RPE65* missense variants

| Exon | cDNA Change | Protein Change | AC | PhyloP | PolyPhen -2 score | PolyPhen-2 Prediction | SIFT Score | SIFT Prediction | ExAC (AC, TA, HZ, AF) | Classification | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | c.65T>C | p.(Leu22Pro) | 2 | 4.48 | 0.089 | Probably no functional effect | 0.23 | TOLERATED | 6, 118912, 0, 5.046e-05 | Variant of unknown significance | 7,8 |
| 2 | c.74C>T | p.(Pro25Leu) | 2 | 5.33 | 0.988 | Probably damaging | 0.05 | DAMAGING | 3, 118980, 0, 2.521e-05 | Affects function | 9 |
| 2 | c.89T>C | p.(Val30Ala) | 1 | 1.06 | 0.655 | Possibly damaging | 0.42 | TOLERATED | - | Variant of unknown significance | 11 |
| 3 | c.95G>T | p.(Gly32Val) | 1 | 5.77 | 1 | Probably damaging | 0 | DAMAGING | - | Affects function | 12 |
| 3 | c.118G>A | p.(Gly40Ser) | 23 | 5.77 | 1 | Probably damaging | 0 | DAMAGING | - | Affects function | 3-5,13-23 |
| 3 | c.131G>A | p.(Arg44Gln) | 29 | 5.77 | 1 | Probably damaging | 0 | DAMAGING | 7, 121406, 0, 5.766e-05 | Affects function | 13,14,16,19,21-27 |
| 3 | c.133T>C | p.(Cys45Arg) | 1 | 1.06 | 0.536 | Possibly damaging | 0.26 | TOLERATED | - | Variant of unknown significance | 20 |
| 3 | c.177C>G | p.(His59Gln) | 1 | 1.58 | 1 | Probably damaging | 0 | DAMAGING | - | Affects function | 30 |
| 3 | c.179T>C | p.(Leu60Pro) | 10 | 4.73 | 1 | Probably damaging | 0.26 | TOLERATED | - | Affects function | 5,31 |
| 3 | c.200T>G | p.(Leu67Arg) | 7 | 4.73 | - | - | 0 | DAMAGING | - | Affects function | 6,33-35 |
| 3 | c.201_202delGCinsTT | p.(His68Tyr) | 1 | -0.36/5.77 | 1 | Probably damaging | 0.28 | TOLERATED | - | Affects function | 8 |
| 3 | c.208T>G | p.(Phe70Val) | 2 | 4.73 | 1 | Probably damaging | 0.22 | TOLERATED | - | Affects function | 7,36 |
| 3 | c.235T>C | p.(Tyr79His) | 1 | 4.73 | 0.97 | Probably damaging | 0.07 | TOLERATED | - | Affects function | 2 |
| 4 | c.249C>G | p.(Phe83Leu) | 2 | 0.77 | 0.776 | Possibly damaging | 0.04 | DAMAGING | - | Affects function | 6 |
| 4 | c.253C>T | p.(Arg85Cys) | 1 | 2.63 | 1 | Probably damaging | 0.06 | TOLERATED | 14, 120410, 0, 0.0001163 | Variant of unknown significance | 21 |
| 4 | c.254G>A | p.(Arg85His) | 1 | 3.19 | 0.887 | Possibly damaging | 0.04 | DAMAGING | 2, 120484, 0, 1.66e-05 | Affects function | 2 |
| 4 | c.271C>T | p.(Arg91Trp) | 100 | 1.09 | 0.999 | Probably damaging | 0.01 | DAMAGING | 10, 120738, 0, 8.282e-05 | Affects function | 2-4,13,14,16-18,21-23,25,26,29,36,39-44 |
| 4 | c.272G>A | p.(Arg91Gln) | 17 | 5.86 | 0.283 | Probably no functional effect | 0.52 | TOLERATED | 4, 120746, 0, 3.313e-05 | Variant of unknown significance | 2,6,13,17,19,21-23 |
| 4 | c.272G>C | p.(Arg91Pro) | 1 | 5.86 | 0.926 | Possibly damaging | 0.2 | TOLERATED | - | Affects function | 7 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | c.295G>A | p.(Val99Ile) | 2 | 5.77 | 0.077 | Probably no functional effect | 0.12 | TOLERATED | 36, 120964, 1, 0.0002976 | Probably no functional effect | 46 |
| 4 | c.302C>T | p.(Thr101Ile) | 3 | 5.77 | 0.982 | Probably damaging | 0.25 | TOLERATED | - | Affects function | 16,21 |
| 4 | c.304G>A | p.(Glu102Lys) | 3 | 5.77 | 1 | Probably damaging | 0.19 | TOLERATED | - | Affects function | 3,7 |
| 4 | c.310G>C | p.(Gly104Arg) | 2 | 0.86 | 1 | Probably damaging | 0.01 | DAMAGING | - | Affects function | 49 |
| 4 | c.311G>A | p.(Gly104Asp) | 1 | 5.77 | 1 | Probably damaging | 0.01 | DAMAGING | - | Affects function | 13 |
| 4 | c.329A>T | p.(Asp110Val) | 1 | 4.73 | 0.991 | Probably damaging | 0 | DAMAGING | - | Affects function | 5 |
| 4 | c.344T>C | p.(p.Ile115Thr) | 1 | 4.73 | 0.989 | Probably damaging | 0.07 | TOLERATED | - | Affects function | 50 |
| 5 | c.354G>T | p.(Arg118Ser) | 3 | 1.17 | 0.969 | Probably damaging | 0.04 | DAMAGING | - | Affects function | 21,51 |
| 5 | c.382G>C | p.(Val128Leu) | 1 | 1.25 | 0 | Probably no functional effect | 1 | TOLERATED | - | Probably no functional effect | 2 |
| 5 | c.394G>A | p.(Ala132Thr) | 13 | 3.6 | 0.012 | Probably no functional effect | 0.24 | TOLERATED | 348, 121220, 4, 0.002871 | Probably no functional effect | 2,3,21,41,52,54 |
| 5 | c.395C>A | p.(Ala132Asp) | 2 | 3.84 | 0.159 | Probably no functional effect | 0.03 | DAMAGING | - | Affects function | 13 |
| 5 | c.406G>T | p.(Val136Phe) | 1 | 0.21 | 0 | Probably no functional effect | 0.19 | TOLERATED | 1, 121256, 0, 8.247e-06 | Probably no functional effect | 51 |
| 5 | c.427T>G | p.(Tyr143Asp) | 2 | 1.06 | 0.995 | Probably damaging | 0.13 | TOLERATED | - | Variant of unknown significance | 55 |
| 5 | c.430T>C | p.(Tyr144His) | 1 | 4.81 | 1 | Probably damaging | 0.09 | TOLERATED | - | Affects function | 33 |
| 5 | c.430T>G | p.(Tyr144Asp) | 13 | 1.06 | 1 | Probably damaging | 0.01 | DAMAGING | - | Affects function | 7,13,19,21,22,26,56 |
| 5 | c.434C>A | p.(Ala145Asp) | 2 | 0.91 | 0.944 | Possibly damaging | 0.05 | DAMAGING | - | Affects function | 35 |
| 5 | c.444G>T | p.(Glu148Asp) | 1 | 2.47 | 0.028 | Probably no functional effect | 0.24 | TOLERATED | - | Variant of unknown significance | 27 |
| 5 | c.484A>C | p.(Thr162Pro) | 1 | 4.81 | 0.994 | Probably damaging | 0.25 | TOLERATED | 2, 121378, 0, 1.648e-05 | Affects function | 21 |
| 6 | c.499G>T | p.(Asp167Tyr) | 6 | 5.69 | 1 | Probably damaging | 0.07 | TOLERATED | 1, 119408, 0, 8.375e-06 | Affects function | 2,4,5,7,21,37 |
| 6 | c.540C>A | p.(His180Gln) | 1 | 0.61 | 1 | Probably damaging | 0 | DAMAGING | - | Affects function | 39 |
| 6 | c.542C>T | p.(Pro181Leu) | 2 | 4 | 1 | Probably damaging | 0.03 | DAMAGING | - | Affects function | 24 |
| 6 | c.544C>A | p.(His182Asn) | 1 | 5.69 | 0.995 | Probably damaging | 0.1 | TOLERATED | - | Affects function | 27 |
| 6 | c.544C>T | p.(His182Tyr) | 9 | 5.69 | 0.995 | Probably damaging | 0.34 | TOLERATED | 1, 120778, 0, 8.28e-06 | Affects function | 3,13-15,18,19,21 |
| 6 | c.545A>G | p.(His182Arg) | 8 | 4.73 | 0.993 | Probably damaging | 0.32 | TOLERATED | | Affects function | 13,22,26,41 |
| 6 | c.565G>A | p.(Val189Ile) | 1 | 5.69 | 0.46 | Possibly damaging | 0.49 | TOLERATED | 11, 120912, 0, 9.098e-05 | Variant of unknown significance | 41 |
| 7 | c.715T>G | p.(Tyr239Asp) | 12 | 4.73 | 1 | Probably damaging | 0 | DAMAGING | - | Affects | 13-16,18,21,36,58 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | function | |
| 8 | c.731G>T | p.(Gly244Val) | 2 | 6.26 | 1 | Probably damaging | 0.38 | TOLERATED | - | Affects function | 41 |
| 8 | c.746A>G | p.(Tyr249Cys) | 2 | 3.51 | 1 | Probably damaging | 0 | DAMAGING | 5, 120826, 1, 4.138e-05 | Affects function | 5 |
| 8 | c.751G>T | p.(Val251Phe) | 2 | 6.26 | 1 | Probably damaging | 0 | DAMAGING | - | Affects function | 59 |
| 9 | c.859G>T | p.(Val287Phe) | 14 | 3.51 | 0.989 | Probably damaging | 0.02 | DAMAGING | - | Affects function | 13,14,21-23,28,41 |
| 9 | c.864G>T | p.(Trp288Cys) | 1 | 5.45 | 0.994 | Probably damaging | 0.16 | TOLERATED | - | Affects function | 41 |
| 9 | c.868C>T | p.(His290Tyr) | 3 | 5.45 | 1 | Probably damaging | 0.93 | TOLERATED | - | Affects function | 52 |
| 9 | c.871A>G | p.(Ile291Val) | 1 | 0.45 | 0 | Probably no functional effect | 1 | TOLERATED | 2, 121084, 0, 1.652e-05 | Probably no functional effect | 41 |
| 9 | c.881A>C | p.(Lys294Thr) | 4 | 4.56 | 1 | Probably damaging | 0.01 | DAMAGING | 486, 121148, 8, 0.004012 | Probably no functional effect | 2,16,60 |
| 9 | c.917C>T | p.(Thr306Ile) | 1 | 0.89 | 0.999 | Probably damaging | 0.29 | TOLERATED | - | Variant of unknown significance | 63 |
| 9 | c.938A>G | p.(His313Arg) | 1 | 4.4 | 1 | Probably damaging | 0.01 | DAMAGING | - | Affects function | 7 |
| 9 | c.939T>A | p.(His313Gln) | 2 | -0.12 | 1 | Probably damaging | 0 | DAMAGING | 1, 121400, 0, 8.237e-06 | Affects function | 52 |
| 9 | c.952T>A | p.(Tyr318Asn) | 3 | 4.4 | 1 | Probably damaging | 0 | DAMAGING | 1, 121392, 0, 8.238e-06 | Affects function | 16,21 |
| 9 | c.963T>G | p.(Asn321Lys) | 12 | 0.12 | 0.013 | Probably no functional effect | 0.27 | TOLERATED | 651, 121402, 18, 0.005362 | Probably no functional effect | 2,5,11,16,19,38,41,64,65 |
| 9 | c.989G>A | p.(Cys330Tyr) | 8 | 2.47 | 0.998 | Probably damaging | 0.72 | TOLERATED | 1, 121412, 0, 8.236e-06 | Variant of unknown significance | 27,32,66 |
| 9 | c.997G>C | p.(Gly333Arg) | 1 | 5.29 | 1 | Probably damaging | 0.01 | DAMAGING | - | Affects function | 46 |
| 10 | c.1022T>C | p.(Leu341Ser) | 29 | 4.436 | 1 | Probably damaging | 0.02 | DAMAGING | - | Affects function | 3,6,13,14,21-24,26,51,68 |
| 10 | c.1078G>C | p.(Ala360Pro) | 3 | 5.77 | 0.047 | Probably no functional effect | 0.24 | TOLERATED | - | Variant of unknown significance | 11,16 |
| 10 | c.1087C>A | p.(Pro363Thr) | 16 | 5.77 | 0.64 | Possibly damaging | 0.41 | TOLERATED | 2, 121120, 0, 1.651e-05 | Affects function | 2,5,10,27,32,56 |
| 10 | c.1102T>C | p.(Tyr368His) | 69 | 4.73 | 1 | Probably damaging | 0 | DAMAGING | 8, 121144, 0, 6.604e-05 | Affects function | 2,4,5,13,14,21,22,25,26,29,36 ,55,70-72 |
| 10 | c.1103A>G | p.(Tyr368Cys) | 4 | 4.73 | 1 | Probably damaging | 0.1 | TOLERATED | - | Affects function | 6,34 |
| 11 | c.1178C>A | p.(Ala393Glu) | 7 | 5.45 | 1 | Probably damaging | 0.03 | DAMAGING | - | Affects function | 15,18,21,28 |
| 11 | c.1220T>C | p.(Val407Ala) | 1 | 4.48 | 0.426 | Probably no functional effect | 0.88 | TOLERATED | 1, 120798, 0, 8.278e-06 | Variant of unknown significance | 3 |
| 11 | c.1223T>C | p.(Leu408Pro) | 10 | 4.48 | 1 | Probably damaging | 0.01 | DAMAGING | - | Affects function | 13,16,21-23 |
| 12 | c.1249G>C | p.(Glu417Gln) | 12 | 545 | 1 | Probably damaging | 0.01 | DAMAGING | - | Affects function | 13,14,19,22,25,26 |
| 12 | c.1292A>G | p.(Tyr431Cys) | 5 | 4.48 | 1 | Probably damaging | 0.05 | DAMAGING | 1, 120968, 0, 8.267e-06 | Affects function | 13,21,26,62 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 12 | c.1301C>T | p.(Ala434Val) | 11 | 5.45 | 0.026 | Probably no functional effect | 1 | TOLERATED | 846, 120978, 25, 0.006993 | Probably no functional effect | 5,16,27,28,32,41 |
| 12 | c.1304A>G | p.(Tyr435Cys) | 1 | 2.87 | 1 | Probably damaging | 0 | DAMAGING | - | Affects function | 12 |
| 12 | c.1307G>T | p.(Gly436Val) | 2 | 5.45 | 1 | Probably damaging | 0.07 | TOLERATED | - | Affects function | 2,5 |
| 12 | c.1328T>C | p.(Val443Ala) | 3 | 4.48 | 0.871 | Possibly damaging | 0.38 | TOLERATED | - | Affects function | 21,51 |
| 13 | c.1355T>G | p.(Val452Gly) | 1 | 4.89 | 0.996 | Probably damaging | 0.1 | TOLERATED | - | Affects function | 3 |
| 13 | c.1370C>A | p.(Thr457Asn) | 2 | 0.85 | 0 | Probably no functional effect | 0.36 | TOLERATED | 1, 120960, 0, 8.267e-06 | Probably no functional effect | 2,29 |
| 13 | c.1380G>C | p.(Trp460Cys) | 1 | 0.86 | 1 | Probably damaging | 0.03 | DAMAGING | - | Affects function | 51 |
| 13 | c.1409C>T | p.(Pro470Leu) | 2 | 5.94 | 1 | Probably damaging | 0.01 | DAMAGING | - | Affects function | 73 |
| 13 | c.1418T>A | p.(Val473Asp) | 5 | 4.97 | 1 | Probably damaging | 0 | DAMAGING | - | Affects function | 3,18,27,32 |
| 13 | c.1430A>G | p.(Asp477Gly) | 23 | 2.3 | 0 | Probably no functional effect | 1 | TOLERATED | - | Affects function* | 74 |
| 14 | c.1451G>A | p.(Gly484Asp) | 1 | 5.94 | 1 | Probably damaging | 0 | DAMAGING | 2, 120516, 0, 1.66e-05 | Affects function | 51 |
| 14 | c.1543C>T | p.(Arg515Trp) | 8 | 0.53 | 1 | Probably damaging | 0 | DAMAGING | 2, 120986, 0, 1.653e-05 | Affects function | 20,21,30,75 |
| 14 | c.1583G>T | p.(Gly528Val) | 1 | 6.02 | 1 | Probably damaging | 0 | DAMAGING | - | Affects function | 2 |
| 14 | c.1590C>A | p.(Phe530Leu) | 1 | 4.24 | 0.929 | Possibly damaging | 0.01 | DAMAGING | - | Affects function | 76 |
| 14 | c.1597T>A | p.(Ser533Thr) | 2 | 0.37 | 0 | Probably no functional effect | 0.43 | TOLERATED | 2, 120712, 0, 1.657e-05 | Probably no functional effect | 11,21 |
| | | Total alleles | 573 | | | | | | | | |

AC, allele count; AF, allele frequency; ExAC, exome aggregation consortium; HZ, homozygous individuals; TA, total alleles

*Variant c.1430A>G; p.(Asp477Gly) is considered as Affects function due to its different mutational mechanism in an autosomal dominant manner

## Supplementary Table S7. Splice prediction non-canonical splice site variants in *RPE65*

| Exon | cDNA Change | Protein Change | Allele Count | Splice Site Finder-like (0-100) ≥70 | MaxEntScan (0-12) ≥0 | NNSPLICE (0-1) >0.4 | GeneSplicer (0-15) ≥0 | HSF (0-100) ≥60 | ExAC (AC, TA, HZ, AF) | Classification | Reference No. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1i | c.11+5G>A | p.(?) | 62 | 78.95 ⇒ — | 9.09 ⇒ 1.53 **(-83.2%)** | 0.96 ⇒ 0.61 **(-36.4%)** | 6.82 ⇒ — | 84.67 ⇒ 72.51 **(-14.4%)** | 11, 120956, 0, 9.094e-05 | Affects function | 2,4,5,10,13-15,18,19,21,22,24,26-29,32,50,51,70-72,77 |
| 2i | c.94+10A>G | p.(?) | 1 | = 80.04 | = 8.08 | = 0.88 | 4.89 ⇒ 3.15 **(-35.6%)** | = 86.63 | - | Probably no functional effect | 5 |
| 2i | c.95-3C>G | p.(?) | 6 | 84.15 ⇒ 73.33 **(-12.9%)** | 9.37 ⇒ 0.62 **(-93.3%)** | 0.97 ⇒ — | 8.64 ⇒ — | 91.38 ⇒ 81.08 **(-11.3%)** | - | Affects function | 78 |
| 6i | c.643+4A>G | p.(?) | 1 | 95.64 ⇒ 85.56 **(-10.5%)** | 10.67 ⇒ 8.56 **(-19.8%)** | 0.98 ⇒ 0.83 **(-15.4%)** | - | 98.84 ⇒ 90.50 **(-8.4%)** | - | Affects function | 2 |
| 7i | c.725+4A>G | p.(?) | 5 | 83.18 ⇒ 73.10 **(-12.1%)** | 6.43 ⇒ 3.16 **(-50.8%)** | - | 0.70 ⇒ — | 86.00 ⇒ 77.66 **(-9.7%)** | - | Affects function | 13,19,21,22 |
| 7i | c.726-3C>A | p.(?) | 1 | 78.75 ⇒ — | 9.36 ⇒ 6.22 **(-33.6%)** | 0.60 ⇒ — | - | 84.53 ⇒ 75.14 **(-11.1%)** | 2, 120388, 0, 1.661e-05 | Affects function | 79 |

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