*Supplementary materials*

**Functional characterization of rare RAB12 variants and their role in musician's and other dystonias**

Eva Hebert et al.

**Figure S1.** Photograph of Individual L-10289 (mildly affected mother of the index patient from Family D) showing a 15-degree tilt of the trunk to the right as well as dystonic posturing of the right hand (involuntary flexion of the third to fifth finger and thumb and extension of the index finger).

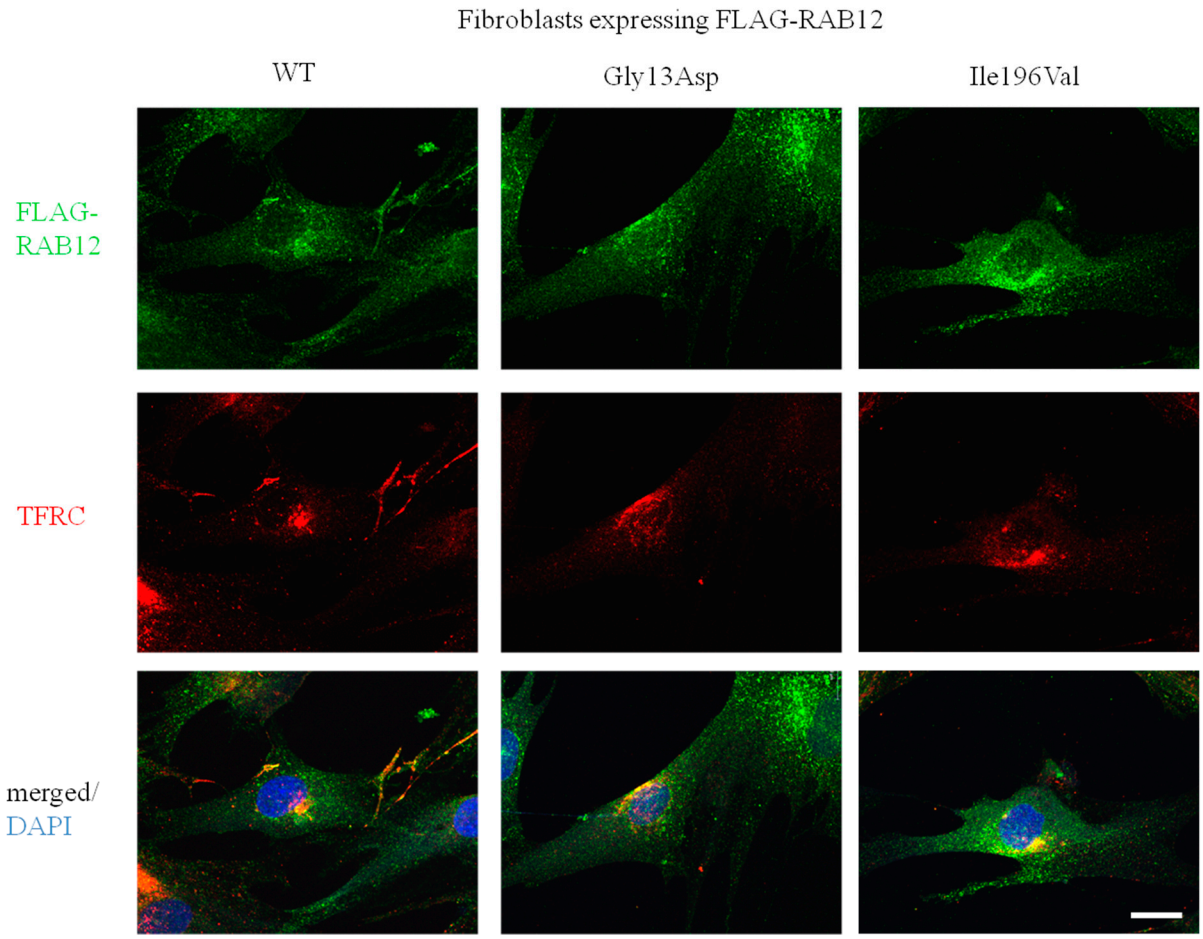


**Figure S2.** TFRC colocalized with wildtype and mutant FLAG-RAB12. Immunofluorescent staining of fibroblasts expressing FLAG-RAB12 WT, p.Gly13Asp, or p.Ile196Val revealed predominant perinuclear localization of TFRC (red) which overlaps with the localization of FLAG-RAB12 (green) in all three cell lines (WT, p.Gly13Asp, p.Ile196Val). The nucleus was stained with DAPI (blue). Scale bar: 20µm.

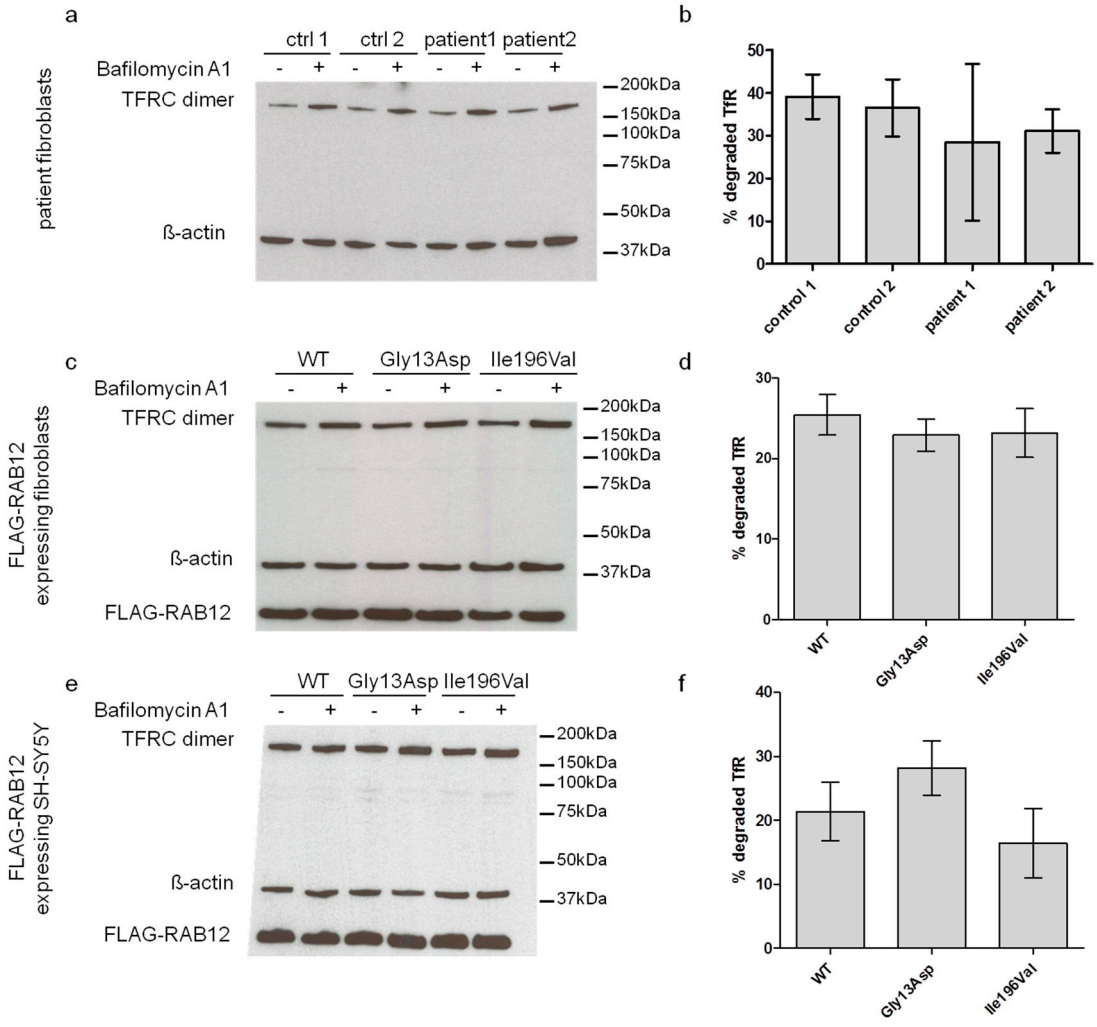


**Figure S3.** Lysosomal degradation of the physiological dimeric TFRC was not affected by the RAB12 mutations. Western Blot analysis revealed the degradation of TFRC in patient fibroblasts with endogenous expression of RAB12 (a, b) in fibroblasts ectopically expressing FLAG-RAB12 (c, d), and in SH-SY5Y cells ectopically expressing FLAG-RAB12 (e, f). Cells were treated with Bafilomycin A1 for 24h. ß-actin served as loading control and for normalization. Bars in B, D, and F indicate means of three independent experiments ± SEM. ctrl control, WT wildtype

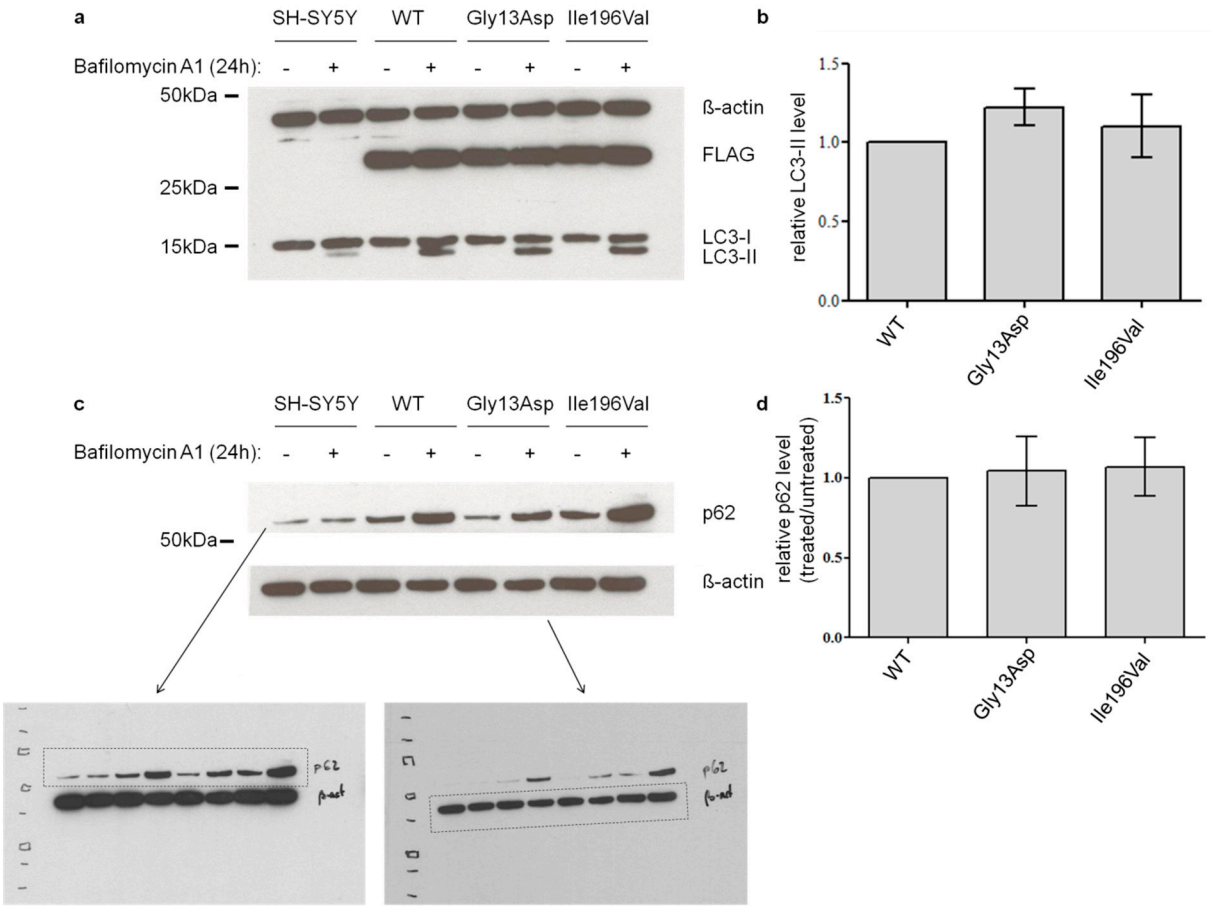


**Figure S4.** Relative LC3-II protein levels are marginally increased in SH-SY5Y cells overexpressing RAB12 Gly13Asp protein and p62 levels remained constant. a) Western Blot of proteins extracted from stably transfected SH-SY5Y cells. Expression of FLAG-tagged RAB12 WT equals the expression of mutated RAB12 proteins (Gly13Asp, I196Val) (lane 3, 5, 7). Bafilomycin treatment (3nM, 24h) increased the level of active LC3-II proteins whereas the protein levels of RAB12 and ß-actin remained constant. b) Relative LC3-II protein levels are not significantly increased in Bafilomycin-treated RAB12 mutant SH-SY5Y cells (p.Gly13Asp, p.Ile196Val) compared to RAB12 WT expressing cells. n=3 c) Western blot of the same proteins of A) shows that inhibition of autophagy with Bafilomycin A1 causes an elevation of p62 protein levels in the transfected SH-SY5Y cells but not in untransfected SH-SY5Y cells. Protein bands of cropped images (indicated by boxes in the lower blots) were subjected to quantification. Both blots represent the same membrane with same proteins and antibodies, only exposure times differ. D) The ratio of relative p62 in treated vs. untreated cells was not changed in the RAB12 mutants, n=3. Bars indicate means ± SEM.

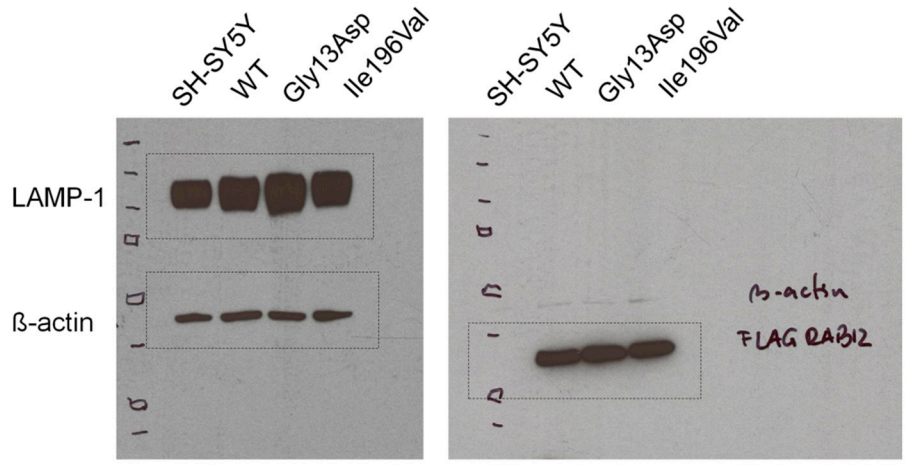


**Figure S5.** Original Blots of Figure 3A. Boxes around the protein bands indicate cropping lines. The two images were generated from the same membrane. Probing with the FLAG antibody was performed subsequent to LAMP-1 and ß-actin.

**Table S1.** Demographic data of 604 other dystonia patients tested for mutations in the *RAB12* gene.

| | | |
|---|---|---|
| Sex | Male | 250 |
| | Female | 354 |
| Age at onset | Known for | 457 |
| | Mean±SD (years) | 41±16 |
| | Range | 1-82 |
| Family history | Positive | 60 |
| | Negative | 278 |
| | Unknown | 266 |
| Phenotype | Generalized dystonia | 59 |
| | Segmental dystonia | 123 |
| | Hemidystonia | 1 |
| | Multifocal dystonia | 3 |
| | Focal dystonia | |
| | Cranial dystonia | 5 |
| | Cervical dystonia | 254 |
| | Blepharospasm | 56 |
| | Spasmodic dysphonia | 6 |
| | Other focal dystonia | 92 |
| | Myoclonus-dystonia | 5 |

SD Standard deviation.

**Table S2.** Initial NGS variant calls. Detected Variants in MD families were filtered to be (1) exonic or splicing, (2) to affect protein function (synonymous variants were disregarded), (3) rare, with a known frequency <1% in the database for single nucleotide polymorphisms (dbSNP132) and (4) shared within definitely affected members within a family.

| Family | Code | Variants detected by NGS | Exonic/ splicing variants | Non-synonymous variants | Rare heterozygous variants (frequency <1%) | Same gene locus within one family |
|---|---|---|---|---|---|---|
| A | L-2381 | n.a. | 28 208 | 23 753 | 1 632[a)] | 83 |
| | L-2276 | n.a. | 28 102 | 23 658 | 1 498[a)] | |
| | L-2283 | n.a. | 27 737 | 23 357 | 1 459[a)] | |
| B | L-2286 | 3 434 750 | 20 718 | 11 000 | 1 388 | 509 |
| | L-2322 | 3 808 124 | 20 898 | 10 340 | 1 044 | |
| C | L-2332 | 3 815 968 | 20 583 | 10 116 | 1 023 | n.a. |

[a)] At the time when these exome data were generated and annotated, frequencies from ExAC or 1000g were not yet available and frequencies in the exome variant server at http://evs.gs.washington.edu/EVS/ were not included in the annotated files. Therefore, we initially excluded all variants with an rs number in dbSNP132. Of the remaining variants, 94 variants did overlap between the three affected family members and their frequency was manually looked up in ExAC which identified another 11 variants as common polymorphisms (minor allele frequency >1%).

n.a.: not applicable

**Table S3.** Filter steps of variants generated with recent exome sequencing (Centogene) in Families A, B, and D.

| Variants | Family A | Family B | Family D |
|---|---|---|---|
| all | 105480 | 103152 | 109082 |
| Found only in affected members, exonic and splice site variants, frequency in ExAC, 1000G, ESP6500 $\leq$ 1% | 844 | 4279 | 412 |
| Y Chromosome and mitochondrial DNA excluded | 833 | 4223 | 412 |
| NGS quality criteria: Frequency $\geq$ 25, read number $\geq$ 20, quality score $\geq$ 100 | 631 | 1134 | 234 |
| All affected members heterozygous | 533 | 477 | 216 |
| In-house WES: max. 10 homozygous/20 heterozygous carriers in ca. 4500 in-house controls | 97 | 74 | 131 |
| Synonymous variants excluded | 60 | 46 | 80 |

In-house WES: Whole exome sequencing results of 4542 controls were generated at Centogene (Rostock, Germany)

**Table S4.** Primer sequences for Sanger sequencing of RAB12 on DNA level (Exons 1-6), cDNA level, and used for side-directed mutagenesis.

| | | **Primer sequence (5' -> 3')** | **Fragment length [bp]** |
|---|---|---|---|
| **Exon 1** | F | GATGCTGCTGCCGCTACT | 623 |
| | R | CCCATCCCCGAAAGACTC | |
| **Exon 2** | F | TAGACCGATCACTCAGGATAAG | 463 |
| | R | CTCTCTCTTGATGGAAACACTG | |
| **Exon 3** | F | TCAGGTCAAAGGGAAATAGGG | 552 |
| | R | GCAGCTGGATGTAGTGGAATG | |
| **Exon 4** | F | AACAGCCAAGAGCATTGT | 493 |
| | R | TAAAGGAGCACGAAGTCA | |
| **Exon 5** | F | GAGCGTCAGTGGGACTTTC | 351 |
| | R | GCGCCTGAGCACAACTAC | |
| **Exon 6** | F | AAAGGTCTTCATCTGTGTCA | 563 |
| | R | TTGGAGGGAAATAGGTAACT | |
| **cDNA** | F | CTGCTTCCCTTCCTCCTCT | 764 |
| | R | GCCTGGTGATTTCTCTGTCC | |
| **Mutagenesis** | | | |
| c.38G>A p.Gly13Asp | F | CCGCCGCCGTCCCCGGCCC | |
| | R | GGGCCGGGGACGGCGGCGG | |
| c.586A>G p.Ile196Val | F | GGATAACTTCAATGTGGACGAGGTATTTTTGAAACTTGTCGATGA | |
| | R | TCATCGACAAGTTTCAAAAATACCTCGTCCACATTGAAGTTATCC | |

**Table S5.** Variants detected by recent exome sequencing (Centogene) in Families A, B, and D after filtering.

| Overlap | Family | Gene | Chrom | Position | Allele | Transcript | coding DNA change | Protein Change | hom/het carriers of total ExAC individuals[a)] | C-scaled CADD score |
|---|---|---|---|---|---|---|---|---|---|---|
| B+D | B | MUC4 | 3 | 195510913 | -/AGAGGGG TGGTGTGA CCTGTGG ATACTGAG GAAGCATCGG TGACATGA | NM_018406.6 | c.7538_7539ins AGAGGGG TGGTGTGA CCTGTGG ATACTGAG GAAGCATCGG TGACATGA | in-frame | novel | 0,018 |
| | D | MUC4 | 3 | 195506809 | G/T | NM_018406.6 | c.11642C>A | p.A3881D | 1/10 of 4186 [b)] | 0,895 |
| A | | KIF17 | 1 | 20998598 | C/T | NM_020816.2 | c.2555G>A (rs139517726) | p.R852H | 0/79 of 33343 | 34 |
| | | SYTL1 | 1 | 27671939 | -/A | NM_001193308.1 | c.114dupA | frameshift | novel | 31 |
| | | HFM1 | 1 | 91784888 | G/T | NM_001017975.3 | c.2642C>A (rs369341064) | p.T881N | 0/5 of 33333 | 21,8 |
| | | EML6 | 2 | 55189686 | G/A | NM_001039753.2 | c.4996G>A (rs202192837) | p.G1666R | 0/30 of 4653 [b)] | 33 |
| | | CFAP65 | 2 | 219900226 | A/G | NM_194302.3 | c.518T>C | p.L173S | 0/1 of 33365 | 13,31 |
| | | COPS7B | 2 | 232672281 | C/A | NM_022730.1 | c.721C>A | p.P241T | 0/1 of 652 [b)] | 23 |
| | | GRIP2 | 3 | 14581790 | G/A | NM_001080423.2 | c.317C>T (rs188992337) | p.T106I | 1/222 of 32704 | 15,57 |
| | | SLC15A2 | 3 | 121641638 | G/A | NM_021082.3 | c.797G>A | p.R266H | 0/2 of 33007 | 34 |
| | | CP | 3 | 148925345 | C/T | NM_000096.3 | c.841G>A | p.V281I | novel | 18,38 |
| | | FRYL | 4 | 48581258 | T/C | NM_015030.1 | c.2260A>G (rs188966880) | p.T754A | 1/208 of 32542 | 4,087 |
| | | ANK2 | 4 | 114278701 | C/G | NM_001148.4 | c.8927C>G (rs371343942) | p.S2976C | 0/9 of 33361 | 23,7 |
| | | FAT4 | 4 | 126373018 | C/T | NM_024582.4 | c.10847C>T (rs111423173) | p.T3616M | 3/388 33343 | 24,8 |
| | | DNAH5 | 5 | 13865895 | G/A | NM_001369.2 | c.4237C>T | p.Q1413* | 0/1 of 33194 | 42 |
| | | FNIP1 | 5 | 131008129 | A/T | NM_133372.2 | c.2008T>A | p.L670I | 0/1 of 33349 | 14,76 |
| | | ERMARD | 6 | 170155517 | A/G | NM_018341.2 | c.314A>G (rs542068627) | p.E105G | 0/2 of 33320 | 26,8 |
| | | PXDNL | 8 | 52366157 | G/A | NM_144651.4 | c.1171C>T (rs141730527) | p.R391W | 0/111 of 33368 | 21,6 |
| | | CHD7 | 8 | 61655009 | A/G | NM_017780.3 | c.1018A>G (rs41305525) | p.M340V | 3/416 of 33358 | 2,014 |
| | | PKHD1L1 | 8 | 110477058 | G/T | NM_177531.4 | c.7997G>T (rs200190153) | p.G2666V | 0/37 of 33358 | 27,6 |
| | | PKHD1L1 | 8 | 110498978 | G/A | NM_177531.4 | c.9808G>A (rs200880307) | p.G3270S | 0/197 of 33351 | 19,9 |
| | | SLC52A2 | 8 | 145583505 | C/A | NM_001253815.1 | c.353C>A (rs117500243) | p.A118D | 1/301 of 33200 | 21,4 |
| | | C8ORF33 | 8 | 146278000 | C/T | NM_023080.2 | c.35C>T (rs139779460) | p.A12V | 2/323 of 32872 | 17,09 |
| | | ECM2 | 9 | 95277059 | C/T | NM_001393.3 | c.908G>A (rs143789386) | p.R303Q | 2/180 of 66640 | 11,66 |
| | | CARD19 | 9 | 95874559 | T/C | NM_032310.3 | c.424T>C (rs147126180) | p.C142R | 1/37 of 4252 [b)] | 23,6 |
| | | PLAU | 10 | 75672059 | G/A | NM_002658.3 | c.172G>A (rs55744193) | p.G58R | 2/582 of 33121 | 9,936 |
| | | LCOR | 10 | 98715216 | T/C | NM_001170765.1 | c.839T>C (rs200583240) | p.M280T | 0/3 of 33336 | 7,413 |
| | | COL17A1 | 10 | 105816892 | C/T | NM_000494.3 | c.1306G>A (rs805697) | p.G436R | 2/571 of 33079 | 10,63 |
| | | MUC2 | 11 | 1093643 | C/T | NM_002457.2 | c.5459C>T (rs202186340) | p.T1820M | 0/22 of 33085 | 8,046 |
| | | MUC5B | 11 | 1254407 | G/A | NM_002458.2 | c.2230G>A (rs199581050) | p.G744S | 0/122 of 25186 | 15,04 |
| | | MUC5B | 11 | 1268923 | G/A | NM_002458.2 | c.10813G>A (rs200676815) | p.G3605R | 1/100 of 25794 | 20,1 |
| | | MMP26 | 11 | 5010915 | C/T | NM_021801.3 | c.137C>T (rs35365239) | p.S46L | 5/579 of 31950 | 0,657 |
| | | MYO7A | 11 | 76870496 | G/A | NM_000260.3 | c.1007G>A | p.R336H | 1/123 of | 22,3 |

| Overlap | Family | Gene | Chrom | Position | Allele | Transcript | coding DNA change | Protein Change | hom/het carriers of total ExAC individuals[a)] | C-scaled CADD score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | (rs45629132) | | 33219 | |
| | | PRCP | 11 | 82560132 | C/G | NM_199418.2 | c.943G>C (rs143734237) | p.A315P | 0/57 of 33357 | 7,56 |
| | | MMP20 | 11 | 102449808 | C/G | NM_004771.3 | c.1313G>C (rs61753770) | p.G438A | 1/367 of 33348 | 27,7 |
| | | ATM | 11 | 108196837 | G/C | NM_000051.3 | c.6860G>C (rs1800061) | p.G2287A | 0/22 of 33342 | 10,23 |
| | | DLAT | 11 | 111930748 | A/G | NM_001931.4 | c.1636A>G (rs143152014) | p.T546A | 0/33 of 33366 | 0,003 |
| | | ZBTB39 | 12 | 57397612 | G/C | NM_014830.2 | c.1090C>G (rs143767392) | p.R364G | 0/24 of 33369 | 23,4 |
| | | MARS | 12 | 57908753 | C/T | NM_004990.3 | c.2116C>T (rs148501787) | p.R706C | 0/27 of 33357 | 35 |
| | | COCH | 14 | 31355389 | A/G | NM_001135058.1 | c.1348A>G (rs139503327) | p.I450V | 0/69 of 33285 | 22 |
| | | SYNE2 | 14 | 64593458 | C/T | NM_182914.2 | c.13850C>T (rs148582250) | p.T4617I | 0/63 of 33255 | 10,88 |
| | | PROX2 | 14 | 75321867 | C/G | NM_001243007.1 | c.1747G>C | p.E583Q | novel | 28,9 |
| | | MLH3 | 14 | 75483796 | C/T | NM_001040108.1 | c.4351G>A (rs28939071) | p.E1451K | 0/87 of 33370 | 23,6 |
| | | C14ORF159 | 14 | 91639726 | C/T | NM_001102368.1 | c.550C>T | p.R184W | n.a. | 26 |
| | | TRIP11 | 14 | 92477355 | T/C | NM_004239.3 | c.1289A>G (rs142579179) | p.E430G | 0/25 of 33356 | 26,6 |
| | | ATXN3 | 14 | 92537380 | -/GCTGCTG CTGCTGCTGC TGCTGCTGC | NM_004993.5 | c.890_891ins GCTGCTG CTGCTGCTGC TGCTGCTGC | frameshift | novel | 25,7 |
| | | ATG2B | 14 | 96772059 | T/A | NM_018036.5 | c.4600A>T (rs72704878) | p.T1534S | 0/301 of 33359 | 0,004 |
| | | TRPM1 | 15 | 31294573 | G/A | NM_001252020.1 | c.4381C>T (rs3784587) | p.R1461C | 1/529 of 33369 | 17,22 |
| | | PLA2G4F | 15 | 42437975 | C/T | NM_213600.3 | c.1661G>A (rs148529696) | p.C554Y | 0/203 of 33162 | 25,7 |
| | | GCNT3 | 15 | 59911403 | A/- | NM_004751.2 | c.966del | frameshift | novel | 26,6 |
| | | FEM1B[c)] | 15 | 68583172 | CAAT/GAAC | NM_015322.3 | c.1476CAAT>GAAC (rs143637660,rs6494729) | in-frame | 2/500 of 33369, 33370/0 of 33370 | 0,956 |
| | | SLC28A1 | 15 | 85467271 | T/C | NM_004213.3 | c.1013T>C (rs139484056) | p.V338A | 0/80 of 33365 | 22,1 |
| | | CHSY1 | 15 | 101718402 | T/A | NM_014918.4 | c.1600A>T (rs141305214) | p.I534L | 0/16 of 33370 | 19,03 |
| | | TSC2 | 16 | 2104355 | C/G | NM_000548.3 | c.395C>G | p.S132C | novel | 14,25 |
| | | TSC2 | 16 | 2104389 | C/G | NM_000548.3 | c.429C>G | p.F143L | novel | 11,19 |
| | | CDH13 | 16 | 83378467 | C/G | NM_001220488.1 | c.778C>G (rs200608482) | p.L260V | 0/12 of 33161 | 23,6 |
| | | ZNF469 | 16 | 88499661 | C/G | NM_001127464.1 | c.5699C>G | p.A1900G | novel | 12,54 |
| | | ABHD15 | 17 | 27893566 | A/- | NM_198147.2 | c.419del | frameshift | 1/501 of 30896 | 29,3 |
| | | MTMR4 | 17 | 56569151 | A/G | NM_004687.4 | c.3461T>C | p.I1154T | novel | 28,2 |
| | | RAB12 | 18 | 8636320 | A/G | NM_001025300.2 | c.586A>G (rs143888944) | p.I196V | 0/55 of 32868 | 16,52 |
| | | LAMA5 | 20 | 60893686 | G/A | NM_005560.4 | c.7063C>T | p.Q2355* | novel | 38 |
| | | VCX | X | 7811854 | G/A | NM_013452.2 | c.418G>A | p.V140M | novel | 3,939 |
| Family B | | MROH7 | 1 | 55119410 | A/G | NM_001039464.2 | c.811A>G (rs199971430) | p.S271G | 0/40 of 33349 | 4,847 |
| | | MYT1L | 2 | 1891354 | C/T | NM_015025.2 | c.2542G>A | p.A848T | novel | 14,78 |
| | | EFCAB12 | 3 | 129127565 | T/C | NM_207307.1 | c.1172A>G | p.N391S | 0/1 of 9093 [b)] | 0,001 |
| | | KIF15 | 3 | 44816753 | G/A | NM_020242.2 | c.70G>A (rs146639559) | p.G24S | 0/1 of 33280 | 24,7 |
| | | MFN1 | 3 | 179080209 | C/T | NM_033540.2 | c.475C>T (rs575310683) | p.R159C | 0/3 of 33363 | 24,5 |
| | | OXNAD1 | 3 | 16312496 | C/T | NM_138381.3 | c.37C>T (rs146704754) | p.R13W | 0/14 of 33369 | 24,9 |

| Overlap | Family | Gene | Chrom | Position | Allele | Transcript | coding DNA change | Protein Change | hom/het carriers of total ExAC individuals[a)] | C-scaled CADD score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | PCCB | 3 | 136019898 | C/T | NM_001178014.1 | c.971C>T (rs147538201) | p.T324I | 0/54 of 33366 | 24,9 |
| | | PPM1M | 3 | 52283798 | C/T | NM_144641.3 | c.1348C>T (rs142217810) | p.H450Y | 0/43 of 32121 | 9,789 |
| | | TRAK1 | 3 | 42261019 | A/G | NM_001042646.2 | c.1997A>G | p.N666S | 0/1 of 33370 | 12,16 |
| | | BST1 | 4 | 15704847 | C/T | NM_004334.2 | c.80C>T | p.A27V | 0/1 of 2053 [b)] | 0,919 |
| | | EPHA5 | 4 | 66467556 | C/T | NM_004439.5 | c.713G>A (rs147719164) | p.R238Q | 0/10 of 33345 | 20,9 |
| | | RASSF6 | 4 | 74477500 | C/T | NM_201431.2 | c.109G>A | p.A37T | 0/1 of 33358 | 10,88 |
| | | ZFYVE16 | 5 | 79733022 | C/T | NM_001105251.1 | c.518C>T | p.P173L | novel | 0,067 |
| | | ROS1 | 6 | 117700302 | G/T | NM_002944.2 | c.2517C>A (rs199731317) | p.D839E | 0/15 of 33231 | 25,4 |
| | | SERINC1 | 6 | 122773101 | C/A | NM_020755.2 | c.691G>T (rs138235986) | p.A231S | 0/37 of 33248 | 25 |
| | | PRPS1L1 | 7 | 18067266 | C/G | NM_175886.2 | c.140G>C (rs138696713) | p.S47T | 0/5 of 33368 | 24,1 |
| | | SAMD9 | 7 | 92731677 | T/C | NM_001193307.1 | c.3734A>G | p.E1245G | 0/4 of 33138 | 19,51 |
| | | SLC29A4 | 7 | 5336629 | C/G | NM_001040661.1 | c.682C>G | p.R228G | novel | 32 |
| | | FAM83A | 8 | 124204212 | T/A | NM_032899.4 | c.648+2T>A | splice site | novel | 25,3 |
| | | IKBKAP | 9 | 111673437 | G/A | NM_003640.3 | c.1213C>T (rs139703788) | p.R405W | 0/58 of 33153 | 32 |
| | | CAPN1 | 11 | 64976845 | T/C | NM_001198868.1 | c.1781T>C (rs148743672) | p.V594A | 2/170 of 30235 | 24,4 |
| | | NAALADL1 | 11 | 64815499 | T/G | NM_005468.2 | c.1370A>C (rs139760307) | p.Q457P | 0/21 of 31186 | 23,3 |
| | | NARS2 | 11 | 78147859 | A/G | NM_024678.5 | c.1291T>C (rs370150532) | p.Y431H | 0/5 of 33334 | 28,4 |
| | | NUP37 | 12 | 102494834 | A/C | NM_024057.2 | c.330T>G | p.D110E | novel | 25,1 |
| | | LRR1 | 14 | 50080993 | A/G | NM_152329.3 | c.1024A>G (rs186223942) | p.I342V | 0/14 of 33079 | 6,095 |
| | | ADAMTSL3 | 15 | 84651321 | C/T | NM_207517.2 | c.2941C>T (rs140552733) | p.R981W | 0/230 of 33353 | 31 |
| | | C15ORF41 | 15 | 36937461 | C/T | NM_001130010.1 | c.185C>T (rs139465273) | p.S62L | 0/44 of 4549 [b)] | 9,025 |
| | | DIS3L | 15 | 66618536 | G/A | NM_001143688.1 | c.2035G>A | p.E679K | 0/0 of 33345 | 23,3 |
| | | MAN2A2 | 15 | 91454701 | C/T | NM_006122.2 | c.2030C>T | p.S677L | 0/9 of 33295 | 23,7 |
| | | MYO5C [c)] | 15 | 52556426 | CACA/TACG | NM_018728.3 | c.1008TGTG>CGTA (rs180901348, rs4776032) | in-frame | 0/346 of 33301, 33354/9 of 33363 | 13,97 |
| | | RPAP1 | 15 | 41822094 | A/T | NM_015540.2 | c.1027T>A (rs139677678) | p.L343M | 0/128 of 32568 | 24,2 |
| | | AMFR | 16 | 56398010 | C/T | NM_001144.5 | c.1607G>A (rs144358339) | p.R536H | 0/36 of 31589 | 23,5 |
| | | DNASE1L2 | 16 | 2287265 | C/T | NM_001374.2 | c.280C>T (rs200934792) | p.R94W | 0/58 of 7865 [b)] | 31 |
| | | SCNN1B | 16 | 23383160 | G/A | NM_000336.2 | c.1108G>A | p.V370I | 0/2 of 33370 | 0,002 |
| | | SLC9A3R2 | 16 | 2086440 | G/A | NM_001130012.2 | c.530G>A | p.R177H | 0/11 of 19395 [b)] | 26,6 |
| | | VWA3A | 16 | 22134476 | A/G | NM_173615.3 | c.1427A>G (rs200794387) | p.Y476C | 0/17 of 16297 [b)] | 23,2 |
| | | AOC2 | 17 | 40997761 | C/T | NM_009590.2 | c.1118C>T (rs143214815) | p.T373M | 0/0 of33370 | 12,77 |
| | | ETV4 | 17 | 41606946 | C/A | NM_001079675.2 | c.1054G>T | p.D352Y | novel | 28,8 |
| | | ITPKC | 19 | 41223528 | C/T | NM_025194.2 | c.488C>T | p.P163L | 0/8 of 33303 | 7,44 |
| | | MIDN | 19 | 1257143 | A/C | NM_177401.4 | c.1279A>C | p.S427R | novel | 24,4 |
| | | RYR1 | 19 | 39016132 | G/A | NM_000540.2 | c.10616G>A (rs143987857) | p.R3539H | 1/179 of 32162 | 26,1 |
| | | SBSN | 19 | 36018570 | C/A | NM_001166034.1 | c.614G>T | p.R205I | novel | 10,25 |

| Overlap | Family | Gene | Chrom | Position | Allele | Transcript | coding DNA change | Protein Change | hom/het carriers of total ExAC individuals[a)] | C-scaled CADD score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | TCF3 | 19 | 1627375 | C/T | NM_003200.3 | c.349G>A (rs368163858) | p.V117M | 0/2 of 25284 [b)] | 22 |
| | | CCDC116 | 22 | 21991307 | A/G | NM_152612.2 | c.1790A>G (rs150451119) | p.D597G | 0/120 of 32008 | 6,712 |
| | | DEPDC5 | 22 | 32206512 | G/A | NM_001242896.1 | c.1330G>A (rs201394709) | p.G444R | 0/68 of 33330 | 23 |
| Family D | | PLCH2 [c)] | 1 | 2431099 | AGAA/GGAG | NM_014638.2 | c.2601AGAA>GGAG (rs145549953, rs138167803) | in-frame | 0/316 of 16001 [b)], 0/313 of 15956 [b)] | 2,662 |
| | | LUZP1 | 1 | 23419368 | C/T | NM_001142546.1 | c.1387G>A (rs200208053) | p.E463K | 0/78 of 33328 | 25,6 |
| | | UBXN11 | 1 | 26620735 | C/T | NM_183008.2 | c.520G>A (rs201526751) | p.E174K | 2/155 of 33363 | 7,387 |
| | | MACF1 | 1 | 39854002 | G/A | NM_012090.5 | c.9302G>A (rs185233667) | p.R3101Q | 0/43 of 33351 | 4,803 |
| | | SLC44A3 | 1 | 95286518 | G/C | NM_001114106.2 | c.41G>C (rs200690456) | p.G14A | 0/6 of 4355 [b)] | 0,019 |
| | | FAM63A | 1 | 150974740 | C/T | NM_001163258.1 | c.498G>A (rs142215084) | p.W166* | 0/43 of 33361 | 39 |
| | | SCAMP3 | 1 | 155230432 | G/A | NM_005698.3 | c.163C>T (rs11557757) | p.P55S | 2/402 of 32949 | 0,573 |
| | | IGSF9 | 1 | 159899485 | C/T | NM_001135050.1 | c.2269G>A (rs200969104) | p.G757S | 0/12 of 16661 [b)] | 25,2 |
| | | IGFN1 | 1 | 201166349 | A/T | NM_001164586.1 | c.271A>T | p.N91Y | novel | 20,9 |
| | | PQLC3 | 2 | 11312136 | C/T | NM_152391.3 | c.440C>T (rs141308570) | p.A147V | 0/2 of 33361 | 18,66 |
| | | TTC7A | 2 | 47238530 | G/A | NM_020458.2 | c.1348G>A (rs114276698) | p.V450M | 2/169 of 32796 | 25,9 |
| | | MYO7B | 2 | 128347710 | T/C | NM_001080527.1 | c.1898T>C (rs61743282) | p.F633S | 0/94 of 17894 [b)] | 26,1 |
| | | POTEF | 2 | 130832545 | C/T | NM_001099771.2 | c.2500G>A | p.V834M | novel | 25,3 |
| | | ANKAR | 2 | 190593470 | T/C | NM_144708.3 | c.3116T>C (rs150498189) | p.V1039A | 0/312 of 33340 | 21,4 |
| | | RAPH1 | 2 | 204304816 | A/G | NM_213589.1 | c.3097T>C | p.S1033P | novel | 18,84 |
| | | NRP2 | 2 | 206590654 | C/T | NM_201266.1 | c.838C>T (rs79750907) | p.P280S | 0/210 of 33364 | 28,2 |
| | | ATIC | 2 | 216182923 | C/T | NM_004044.6 | c.190C>T | p.R64C | 0/1 of 33369 | 34 |
| | | SPHKAP | 2 | 228858308 | G/T | NM_001142644.1 | c.4663C>A (rs192502309) | p.L1555I | 1/227 of 14862 [b)] | 20,9 |
| | | GAL3ST2 | 2 | 242742812 | C/T | NM_022134.2 | c.428C>T (rs141828605) | p.P143L | 0/266 of 30020 | 32 |
| | | RFTN1 | 3 | 16411695 | C/A | NM_015150.1 | c.918G>T (rs199584688) | p.K306N | 0/23 of 33370 | 14,62 |
| | | MYH15 | 3 | 108174612 | G/C | NM_014981.1 | c.2293C>G (rs144221103) | p.H765D | 0/76 of 33361 | 24,2 |
| | | ZNF639 | 3 | 179051533 | A/C | NM_016331.1 | c.781A>C (rs147750542) | p.I261L | 1/113 of 33367 | 8,338 |
| | | SLC2A9 | 4 | 9943614 | A/G | NM_020041.2 | c.737T>C | p.L246P | novel | 26,8 |
| | | CNOT6L | 4 | 78740530 | -/CGCG | NM_144571.2 | c.-68_-71dup | 5'UTR | novel | 5,559 |
| | | GPRIN3 | 4 | 90171113 | G/A | NM_198281.2 | c.149C>T (rs147824548) | p.A50V | 0/139 of 33359 | 0,704 |
| | | SLC9B2 | 4 | 103971435 | T/C | NM_178833.4 | c.547A>G | p.I183V | 0/3 of 33238 | 0,032 |
| | | PDE5A | 4 | 120427058 | C/T | NM_001083.3 | c.2219G>A (rs139979143) | p.R740K | 0/408 of 32595 | 16,22 |
| | | TMEM184C | 4 | 148539204 | T/C | NM_018241.2 | c.97T>C | p.C33R | novel | 21,5 |
| | | THBS4 | 5 | 79373995 | T/- | NM_003248.4 | c.2210del | frameshift | novel | 35 |
| | | NRG2 | 5 | 139251390 | C/T | NM_013982.2 | c.1028G>A (rs545628035) | p.R343Q | 0/5 of 33350 | 28,7 |
| | | SQSTM1 | 5 | 179250873 | G/A | NM_003900.4 | c.317G>A | p.R106Q | 0/2 of 32188 | 23,2 |
| | | OR2B6 | 6 | 27925059 | T/C | NM_012367.1 | c.41T>C | p.L14P | novel | 23 |
| | | HLA-G | 6 | 29795822 | A/G | NM_002127.5 | c.74-2A>G (rs535773328) | splice site | 0/45 of 28699 | 13,77 |

| Overlap | Family | Gene | Chrom | Position | Allele | Transcript | coding DNA change | Protein Change | hom/het carriers of total ExAC individuals[a)] | C-scaled CADD score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | ABHD16A | 6 | 31660879 | C/A | NM_021160.2 | c.551G>T (rs139667935) | p.R184L | 1/154 of 33154 | 26,3 |
| | | HLA-DRB1 | 6 | 32549565 | G/A | NM_002124.3 | c.421C>T | p.H141Y | novel | 24,9 |
| | | ASCC3 | 6 | 101215065 | G/A | NM_006828.2 | c.1552C>T | p.R518C | 0/4 of 33362 | 29,1 |
| | | NFE2L3 | 7 | 26224760 | G/A | NM_004289.6 | c.1442G>A (rs148159120) | p.S481N | 1/447 of 33366 | 0,051 |
| | | GLI3 | 7 | 42004307 | G/A | NM_000168.5 | c.4364C>T | p.T1455M | novel | 0,006 |
| | | SND1 | 7 | 127343283 | A/G | NM_014390.2 | c.746A>G (rs140863632) | p.K249R | 0/8 of 33366 | 16,84 |
| | | CSPP1 | 8 | 68028252 | C/G | NM_024790.6 | c.1376C>G (rs146431326) | p.S459C | 4/531 of 33369 | 26,3 |
| | | XPA | 9 | 100437758 | GTACAA GTCTTACG/- | NM_000380.3 | c.772_785del | frameshift | novel | 35 |
| | | PPRC1 | 10 | 103900396 | G/T | NM_015062.3 | c.2131G>T | p.V711L | novel | 0,005 |
| | | SYT8 | 11 | 1856615 | C/T | NM_138567.3 | c.226C>T (rs143638495) | p.R76C | 0/270 of 29629 | 11,54 |
| | | NADSYN1 | 11 | 71196598 | G/A | NM_018161.4 | c.1466G>A | p.R489Q | novel | 33 |
| | | WNT11 | 11 | 75898191 | C/T | NM_004626.2 | c.983G>A (rs559115261) | p.R328Q | 0/0 of 33039 | 33 |
| | | AAMDC | 11 | 77553582 | A/T | NM_024684.2 | c.40A>T | p.M14L | novel | 18,7 |
| | | DDX25 | 11 | 125775489 | G/A | NM_013264.4 | c.172G>A (rs559195926) | p.V58I | 0/0 of4514 [b)] | 16,52 |
| | | FAM90A1 | 12 | 8374993 | C/T | NM_018088.3 | c.820G>A (rs200459059) | p.A274T | 0/40 of 32028 | 0,685 |
| | | APOLD1 | 12 | 12939898 | T/G | NM_001130415.1 | c.152T>G | p.F51C | 0/0 of 375 [b)] | 26,7 |
| | | TEP1 | 14 | 20869194 | G/A | NM_007110.4 | c.1498C>T (rs138962979) | p.R500W | 0/344 of 33369 | 34 |
| | | NID2 | 14 | 52472479 | C/T | NM_007361.3 | c.4093G>A (rs201207693) | p.A1365T | 0/3 of 33332 | 23,8 |
| | | ENTPD5 | 14 | 74442714 | G/A | NM_001249.2 | c.647C>T (rs138322972) | p.T216I | 0/96 of 33229 | 29,6 |
| | | NRDE2 | 14 | 90756819 | G/C | NM_017970.3 | c.1975C>G (rs147436404) | p.L659V | 0/13 of 33251 | 16,52 |
| | | CHGA | 14 | 93396098 | G/A | NM_001275.3 | c.293G>A (rs77938104) | p.S98N | 3/537 of 33068 | 17,17 |
| | | HERC2 | 15 | 28491031 | T/C | NM_004667.5 | c.3573A>G | p.I1191M | novel | 24,8 |
| | | EIF3J | 15 | 44829395 | -/GGCGGCGGC | NM_003758.2 | c.2_3insGGCGGCGGC | in-frame | novel | 12,47 |
| | | CCDC154 | 16 | 1487862 | G/A | NM_001143980.1 | c.1246C>T (rs571439720) | p.R416W | 0/1 of 2226 [b)] | 25,2 |
| | | NKD1 | 16 | 50666241 | G/A | NM_033119.4 | c.745G>A (rs375061540) | p.V249I | 0/20 of 33350 | 28,4 |
| | | P2RX5 | 17 | 3594990 | G/A | NM_002561.3 | c.236C>T (rs142264131) | p.S79L | 0/67 of 33293 | 33 |
| | | ALOX15B | 17 | 7950265 | A/G | NM_001141.2 | c.1328A>G (rs146833910) | p.Q443R | 1/292 of 33359 | 1,021 |
| | | TOM1L2 | 17 | 17788003 | A/G | NM_001082968.1 | c.446T>C (rs143220830) | p.V149A | 0/106 of 33369 | 24,7 |
| | | CSHL1 | 17 | 61987575 | C/T | NM_022579.1 | c.418G>A | p.D140N | 0/1 of 33369 | 0,334 |
| | | AZI1 | 17 | 79171966 | CA/TG | NM_001009811 | c.1418TG>CA | p.V473A | novel[d)] | 7,409 |
| | | PYCR1 | 17 | 79893008 | G/A | NM_006907.2 | c.334C>T (rs147653673) | p.R112W | 1/77 of 29920 | 23,3 |
| | | STARD6 | 18 | 51851090 | C/T | NM_139171.1 | c.635G>A (rs147831274) | p.R212H | 0/218 of 33335 | 12,19 |
| | | SERPINB3 | 18 | 61322980 | C/T | NM_006919.2 | c.1084G>A (rs12953909) | p.E362K | 2/636 of33351 | 14,12 |
| | | DNMT1 | 19 | 10252846 | T/C | NM_001130823.1 | c.3167A>G | p.N1056S | 0/3 of 33267 | 26,1 |
| | | GATAD2A | 19 | 19616186 | C/T | NM_017660.3 | c.1805C>T | p.A602V | 0/7 of 33183 | 23,4 |
| | | FFAR3 | 19 | 35850139 | G/A | NM_005304.3 | c.347G>A | p.S116N | novel | 23,4 |
| | | HSPB6 | 19 | 36247851 | G/A | NM_144617.2 | c.59C>T (rs11549029) | p.P20L | 0/6 of 1816[b)] | 19,83 |

| Overlap | Family | Gene | Chrom | Position | Allele | Transcript | coding DNA change | Protein Change | hom/het carriers of total ExAC individuals[a)] | C-scaled CADD score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | BCL3 | 19 | 45260434 | G/A | NM_005178.4 | c.680G>A (rs546909663) | p.S227N | 0/5 of 7931[b)] | 12,58 |
| | | FASTKD5 | 20 | 3127441 | A/G | NM_021826.4 | c.2276T>C (rs147125058) | p.V759A | 1/48 of 33099 | 25,7 |
| | | RIN2 | 20 | 19955688 | A/G | NM_001242581.1 | c.1166A>G | p.H389R | 0/4 of 32862 | 7,523 |
| | | CST1 | 20 | 23731400 | T/C | NM_001898.2 | c.104A>G | p.Y35C | 0/0 of 33360 | 10,82 |
| | | CASS4 | 20 | 55028075 | C/A | NM_001164116.1 | c.1843C>A | p.P615T | novel | 24,4 |
| | | IL10RB | 21 | 34652167 | G/A | NM_000628.4 | c.442G>A (rs45545138) | p.V148M | 0/128 of 33369 | 15,82 |
| | | UMODL1 | 21 | 43519254 | G/A | NM_173568.3 | c.1150G>A (rs200027906) | p.G384R | 0/1 of 33262 | 21,3 |
| | | CRYBB3 | 22 | 25597401 | C/G | NM_004076.3 | c.38C>G (rs147831812) | p.A13G | 2/393 of 33214 | 23,8 |
| | | NPTXR | 22 | 39222627 | G/A | NM_014293.3 | c.976C>T (rs34637063) | p.R326W | 2/367 of 33340 | 34 |

a) ExAC frequencies were calculated from non-Finnish European individuals.

b) Site is covered in fewer than 80% of the individuals in ExAC, which may indicate a low-quality site.

c) Two synonymous SNVs are reported instead of the listed variant.

d) A synonymous (rs117891655, 0 homozygous and 224 heterozygous carriers among 8415 non-Finnish Europeans) and a missense (rs2659016, 15430 homozygot and 18 heterozygots of 15448 non-Finnish Europeans) SNV are listed in ExAC

n.a. not available