

| Filter | Value | Description |
|------------------|--------------------------------------|--|
| LowQD | QD<1.5 | Variant Quality by Depth threshold |
| LowCoverage | DP < 5 | Coverage threshold |
| VeryLowQual | QUAL < 30.0 | Phred quality threshold |
| HARD_TO_VALIDATE | MQ0 >= 4 && ((MQ0 / (1.0*DP)) > 0.1) | Ambiguous alignments - potential artefacts |
| SnpcCluster | clusterWindowSize=10 | More than 3 SNP in 10 bp region |

Table S1. GATK filters used for WES analysis.

| Score | Categorical prediction | Deleterious cutoff | Type | Source |
|------------------|---|--------------------|------------------------|------------------|
| GERP | higher scores are more deleterious | ≥ 4.4 | Conservation scores | dbNSFP (annovar) |
| SIPHY | higher scores are more deleterious | ≥ 12.17 | | |
| CADD | Phred-like scaled C-score | ≥ 20 | Ensemble scores | |
| DANN | 0-1. higher scores indicate a higher probability to be damaging | ≥ 0.98 | | |
| METASVM | D: Deleterious; T: Tolerated | D | | |
| METALR | D: Deleterious; T: Tolerated | D | | |
| MCAP | | ≥ 0.025 | | |
| REVEL | 0-1. higher scores indicate a higher probability to be damaging | ≥ 0.5 | Functional predictions | |
| SIFT | D: Deleterious (sift ≤ 0.05); T: tolerated (sift > 0.05) | D | | |
| Polyphen2-Hdiv | D: Probably damaging (≥ 0.957) P: possibly damaging ($0.453 \leq \text{pp2_hdiv} \leq 0.956$) B: benign ($\text{pp2_hdiv} \leq 0.452$) | D | | |
| Polyphen2-Hvar | D: Probably damaging (≥ 0.909) P: possibly damaging ($0.447 \leq \text{pp2_hdiv} \leq 0.909$) B: benign ($\text{pp2_hdiv} \leq 0.446$) | D | | |
| LRT | D: Deleterious; N: Neutral; U: Unknown | D | | |
| MutationTaster | A: disease_causing_automatic D: disease_causing N: polymorphism P: polymorphism_automatic | D/A | | |
| MutationAssessor | H: high; M: medium; L: low; N: neutral | H/M | | |
| FATHMM | D: Deleterious; T: Tolerated | D | | |
| PROVEAN | D: damaging, N: neutral | D | | |
| VEST3 | 0-1. higher scores indicate a higher probability to be damaging | ≥ 0.5 | | |
| FATHMM_MKL | D: Deleterious; N: neutral | D | | |
| GENOCANYON | 0-1. higher scores indicate a higher probability to be damaging | ≥ 0.5 | Splicing predictions | |
| ADA | 0-1. higher scores indicate a higher probability to be damaging | ≥ 0.8 | | |
| RF | 0-1. higher scores indicate a higher probability to be damaging | ≥ 0.8 | | |

Table S2. Bioinformatics prediction algorithms

| HPO terms |
|--|
| "holoprosencephaly » |
| "ethmocephaly » |
| "choanal stenosis » |
| "cyclopia » |
| "proboscis » |
| "hydrocephalus » |
| "neural tube defect » |
| "microcephaly » |
| "schizencephaly » |
| "trigonocephaly » |
| "anencephaly » |
| "aprosencephaly » |
| "atelencephaly » |
| "abnormality of forebrain morphology » |
| "agenesis of corpus callosum » |
| "partial agenesis of the corpus callosum » |
| "cleft palate » |
| "cleft upper lip » |
| "coloboma » |
| "retinal dysplasia » |
| "absent nasal bridge » |
| "narrow nasal bridge » |
| "hypotelorism » |
| "anophthalmia" |

| MGI terms | Phenotypes |
|------------|---|
| MP:0005157 | holoprosencephaly |
| MP:0005163 | cyclopia |
| MP:0006290 | proboscis |
| MP:0000433 | microcephaly |
| MP:0005170 | cleft upper lip |
| MP:0000783 | abnormal forebrain morphology |
| MP:0000822 | abnormal brain ventricle morphology |
| MP:0000823 | abnormal lateral ventricle morphology |
| MP:0000913 | abnormal brain development |
| MP:0006291 | aprosencephaly |
| MP:0000798 | abnormal frontal lobe morphology |
| MP:0000108 | midline facial cleft |
| MP:0012136 | absent forebrain |
| MP:0003425 | abnormal optic vesicle formation |
| MP:0000428 | abnormal craniofacial morphology |
| MP:0001299 | abnormal eye distance/ position |
| MP:0005382 | craniofacial phenotype |
| MP:0012757 | abnormal cranial neural crest cell migration |
| MP:0006204 | embryonic lethality (Mus: E0 to less than E4.5) |
| MP:0006205 | embryonic lethality (Mus: E4.5 to less than E8) |
| MP:0006206 | embryonic lethality (Mus: E8 to less than E9) |
| MP:0006294 | absent optic vesicle |
| MP:0000784 | forebrain hypoplasia |
| MP:0000780 | abnormal corpus callosum morphology |
| MP:0000781 | decreased corpus callosum size |
| MP:0000784 | forebrain hypoplasia |
| MP:0000929 | open neural tube |
| MP:0000897 | abnormal midbrain morphology |
| MP:0005657 | abnormal neural plate morphology |
| MP:0004871 | premaxilla hypoplasia |
| MP:0005262 | coloboma |
| MP:0012559 | decreased forebrain volume |

Table S3. Phenotypic terms used for clinically-driven strategy.

Table S4. Genes identified by clinically-driven prioritization strategy

| Symbol |
|----------|
| TGIF1 |
| RBP4 |
| MYCN |
| PAX2 |
| PTEN |
| PIGL |
| C5ORF42 |
| ZEB2 |
| DIAPH1 |
| SMOC1 |
| P4HB |
| CEP152 |
| MBTPS2 |
| SALL2 |
| COX7B |
| IFT140 |
| SHH |
| HOXA2 |
| MIR204 |
| VSX2 |
| QARS |
| ASPM |
| STIL |
| CRIP1 |
| GPSM2 |
| BMP4 |
| PRRX1 |
| ZNF335 |
| ACTB |
| CC2D2A |
| RPGRIP1L |
| TMEM67 |
| TENM3 |
| SASS6 |
| VANGL2 |
| FUZ |
| UBB |
| TUBGCP4 |
| KIF11 |
| STAMBP |
| CCDC88C |
| MIR17HG |
| MED17 |
| PIK3R2 |
| CENPJ |
| DDX59 |
| ASXL1 |
| TP63 |
| WDR62 |
| PNKP |
| MFRP |
| IER3IP1 |
| KRAS |
| CDH1 |
| MPDZ |
| FOXO1 |
| XRCC4 |
| SIX3 |
| SLC9A6 |
| KATNB1 |
| L1CAM |
| TRMT10A |
| KNL1 |
| CDK5RAP2 |
| CCND2 |
| ANKLE2 |
| CD96 |
| CLDN19 |
| RAD50 |
| YAP1 |
| CDON |
| AKT3 |
| NDE1 |
| FREM1 |
| CEP135 |

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|----------|
| MSX1 |
| TUBGCP6 |
| ABCB6 |
| ESCO2 |
| HMX1 |
| CASK |
| PHC1 |
| GLI2 |
| PTCH1 |
| GDF3 |
| GDF6 |
| SLC1A4 |
| MED12 |
| THOC6 |
| EMX2 |
| SRD5A3 |
| NECTIN1 |
| ZIC2 |
| PCLO |
| IGBP1 |
| DCX |
| STAC3 |
| CDK6 |
| ARX |
| MFSD2A |
| FANCB |
| ZIC3 |
| SLC12A6 |
| EPG5 |
| CHD7 |
| SEMA3E |
| SUMO1 |
| PAX6 |
| RBBP8 |
| TBX22 |
| FLVCR2 |
| HMGB3 |
| ARFGEF2 |
| CENPE |
| PLK4 |
| MCPH1 |
| CKAP2L |
| FGFR1 |
| SLC25A19 |
| C12ORF57 |
| FOXH1 |
| NODAL |
| CCL2 |
| MTHFD1 |
| MTHFR |
| MTR |
| MTRR |
| T |
| VANGL1 |
| ARCN1 |
| CIT |
| EFTUD2 |
| MECP2 |
| MSMO1 |
| NBN |
| NHEJ1 |
| PLEKHG2 |
| PPP1R15B |
| RTTN |
| FRMD4A |
| KDM1A |
| MITF |
| CEP290 |
| IQCB1 |
| NPHP1 |
| NPHP4 |
| SDCCAG8 |
| TRAF3IP1 |
| WDR19 |
| BCOR |
| C21orf33 |
| CRYBA4 |

| |
|----------|
| DACH1 |
| HESX1 |
| IKBKG |
| NHS |
| OTX2 |
| PITX2 |
| PITX3 |
| PORCN |
| RAX |
| SIX6 |
| SOX2 |
| TFAP2A |
| VAX1 |
| C12orf57 |
| C5orf42 |
| IL1B |
| IL1RN |
| HPE1 |
| missing |
| STRA6 |
| COL4A1 |
| DISC1 |
| EOMES |
| CEP63 |
| IRF6 |
| DLX4 |
| GRHL3 |
| DPP6 |
| ZIC1 |
| ZIC4 |
| TDGF1 |
| FGF8 |
| DISP1 |
| DLL1 |
| GAS1 |
| ALDH1A3 |
| CTCF |
| ASXL3 |
| JAM3 |
| MED25 |
| PPP2R1A |
| SPATA5 |
| POGZ |
| CRIM1 |
| ASNS |
| TAF2 |
| IQSEC2 |
| RPL10 |
| MAB21L2 |
| VRK1 |
| PRSS56 |
| TMEM98 |
| LTC4S |
| FZD5 |
| CELSR1 |
| DACT1 |
| SCRIB |
| TMEM17 |
| ALX1 |
| ALX4 |
| PAX3 |
| GSC |
| FOXA2 |
| ERBB3 |
| HES1 |
| HES5 |
| ALX3 |
| PDGFRA |
| APAF1 |
| CDK5R1 |
| CREBBP |
| CRKL |
| EN1 |
| MARCKS |
| ITGAV |
| HSPG2 |
| ITGA4 |

| |
|---------|
| LHX1 |
| LHX2 |
| TTC21B |
| LRP8 |
| SMAD2 |
| NPR2 |
| SMAD5 |
| MESP1 |
| KITLG |
| SPTBN1 |
| IDUA |
| DLG4 |
| PTPRJ |
| NR1H3 |
| NR1H2 |
| SKI |
| DLX5 |
| AXL |
| TYRO3 |
| ZEB1 |
| TULP3 |
| POU3F2 |
| POU3F3 |
| FAT1 |
| CHRD |
| NOG |
| XRCC2 |
| WASF1 |
| WNT9B |
| FASN |
| RYK |
| MGAT2 |
| GLI3 |
| ENG |
| NKX2-1 |
| WASF2 |
| CENPA |
| HIC1 |
| MED1 |
| RAD23B |
| CTNNB1 |
| EYA1 |
| PDPK1 |
| FOXJ1 |
| FBLN5 |
| EXT1 |
| SP8 |
| CASP3 |
| JMJD6 |
| LPAR1 |
| RERE |
| SS18L1 |
| SMARCC1 |
| TCOF1 |
| RGMA |
| ACVRL1 |
| NAPA |
| PLP1 |
| LMO4 |
| TACC3 |
| SOX3 |
| SHROOM3 |
| FOXD1 |
| SEMA6A |
| FBXW7 |
| NF1 |
| RASA1 |
| TBR1 |
| PEX2 |
| CTSA |
| KCNA1 |
| AGA |
| CDK5 |
| TCF7L1 |
| TWSG1 |
| NCOA6 |
| OTX1 |

| |
|----------|
| HHAT |
| LMX1B |
| TTN |
| SOX11 |
| LAMP2 |
| LAMP1 |
| PCSK6 |
| HOXA1 |
| PDGFC |
| PDGFA |
| EFNB1 |
| MTOR |
| IGF2R |
| CDH2 |
| HES3 |
| MAPK8IP3 |
| DLC1 |
| RB1 |
| ZIC5 |
| MAP3K3 |
| ID4 |
| DST |
| GALC |
| KIFAP3 |
| EMX1 |
| NUMBL |
| NUMB |
| YBX1 |
| LDB1 |
| IPMK |
| PAH |
| NSDHL |
| NDST1 |
| GDF7 |
| MAN2B1 |
| FGFR2 |
| CASP9 |
| SFN |
| HSF1 |
| G3BP1 |
| UBR5 |
| NPM1 |
| APC |
| FOXQ1 |
| CASP2 |
| S1PR1 |
| DHCR7 |
| DYRK1A |
| FOLR1 |
| MANBA |
| PSEN1 |
| PSEN2 |
| DKK1 |
| MAPK8 |
| MAPK9 |
| PIGA |
| SFRP1 |
| SFRP2 |
| MAP3K7 |
| JUN |
| APBB2 |
| APBB1 |
| NEUROG2 |
| RAD51B |
| TP53 |
| KIF2A |
| MAPK7 |
| LAMA5 |
| GDF1 |
| ACVR1B |
| EP300 |
| KAT6A |
| NCSTN |
| SNX2 |
| VPS26A |
| RNF111 |
| WNT1 |

| |
|------------|
| SOD2 |
| KLF2 |
| ATOH7 |
| MMP14 |
| AXIN1 |
| FGF2 |
| SSBP3 |
| TBX1 |
| MECOM |
| ERBB4 |
| FBXO11 |
| FOXC1 |
| CDC42 |
| PDGFRB |
| SATB2 |
| ACVR2A |
| ACVR2B |
| HTT |
| DDB1 |
| SPRY4 |
| SPRY2 |
| AP3B1 |
| SMAD1 |
| ITGB1 |
| DLX6 |
| BAG6 |
| EDN1 |
| HHEX |
| HECTD1 |
| VLDLR |
| CYP26A1 |
| CYP26C1 |
| DRD1 |
| AKAP6 |
| PSAP |
| HIRA |
| PLXNB2 |
| SUMF1 |
| COMMD1 |
| SLC27A4 |
| EPB41L5 |
| SLC39A2 |
| PLEKHA1 |
| TCTN1 |
| LYNX1 |
| FRS2 |
| SOX9 |
| SMO |
| CTNNA1 |
| PDS5B |
| LTBP3 |
| SMAD3 |
| EDNRB |
| LAMC1 |
| ST8SIA4 |
| ST8SIA2 |
| CYP26B1 |
| TBX15 |
| PHGDH |
| DSCAM |
| CSNK2A1 |
| HPRT1 |
| HOXB1 |
| ATOH1 |
| TCF4 |
| CCKAR |
| TOM1L2 |
| LRP2 |
| ATP7B |
| MSX2 |
| SLC4A10 |
| MLST8 |
| MTA2 |
| RPL38 |
| THUMP3-AS1 |
| NDST3 |
| FOXD3 |

| |
|----------|
| FLVCR1 |
| SCUBE1 |
| GJA1 |
| FOXC1 |
| HSD17B7 |
| SULF2 |
| SULF1 |
| KAT5 |
| DLG1 |
| ISL1 |
| POU4F1 |
| NR6A1 |
| SOX4 |
| IFT88 |
| TBX10 |
| IFT172 |
| EFNB2 |
| LRIG3 |
| LIG4 |
| NEK1 |
| FGFR3 |
| GTF2IRD1 |
| GTF2I |
| ATMIN |
| IKBKAP |
| TRIP11 |
| RSPO2 |
| KMT2A |
| FGF9 |
| FES |
| GBX2 |
| CISD2 |
| PDS5A |
| ELAVL1 |
| BMP7 |
| EDNRA |
| PTPN11 |
| NFKB2 |
| NFKB1 |
| RFX4 |
| ATR |
| PGAP1 |
| TRIM71 |
| PKD1 |
| TRPM6 |
| NIPBL |
| GSX2 |
| LRP6 |
| KCNH2 |
| HGS |
| BNC2 |
| VEGFA |
| DRD2 |
| TGIF2 |
| MID1 |
| RDH10 |
| PKDCC |
| SH3PXD2B |
| LMNB2 |
| AURKA |
| HUWE1 |
| BRWD3 |
| KDM6A |
| RPS6KA6 |
| MAGOH |
| OPA1 |
| CECR2 |
| OTULIN |
| COL2A1 |
| BMPR1A |
| LIAS |
| TRIM33 |
| MACF1 |
| CTGF |
| RAPGEF2 |
| HAND1 |
| DICER1 |

| |
|----------|
| UCHL5 |
| ZNF423 |
| WLS |
| MKS1 |
| KIF20B |
| RHEB |
| LHX3 |
| GREM1 |
| TWIST2 |
| LIG3 |
| ADGRA2 |
| BOC |
| SOS1 |
| PDCD10 |
| ANP32B |
| CSF1 |
| RHOA |
| BTAF1 |
| TTBK2 |
| GRHL2 |
| ESPL1 |
| CCDC174 |
| CCT3 |
| GTF3C1 |
| INTS1 |
| NARFL |
| NDUFV2 |
| PHF5A |
| SF3A1 |
| TAF6 |
| DCAF1 |
| WEE1 |
| PRICKLE1 |
| IGF2BP1 |
| B9D1 |
| LMNB1 |
| POMT2 |
| INSC |
| PBX2 |
| PBX1 |
| PBX3 |
| BECN1 |
| DYNC2H1 |
| DCTN5 |
| SUFU |
| SMARCA4 |
| PTPN6 |
| STK36 |
| SPTAN1 |
| TIAM1 |
| FOXP4 |
| REST |
| HLA-DOA |
| BRD2 |
| MTHFD1L |
| OLIG2 |
| HOXB2 |
| GPR161 |
| KIF14 |
| XPNPEP1 |
| PAX7 |
| KIF7 |
| NABP2 |
| TBC1D32 |
| HAND2 |
| HAT1 |
| USP7 |
| SMC3 |
| PSAT1 |
| PRMT5 |
| PAK1IP1 |
| DHRS3 |
| MYH10 |
| FIG4 |
| CLP1 |
| TRAPPC10 |
| GLDC |

| |
|----------|
| RSG1 |
| CABLES1 |
| PTBP1 |
| WNT5A |
| ERMP1 |
| BLOC1S2 |
| CGN |
| ASIP |
| EML1 |
| MAP2K1 |
| MAP2K2 |
| MAPK1 |
| MAPK3 |
| CHRNA7 |
| SLK |
| FKBP10 |
| B3GAT3 |
| EVC2 |
| TSC1 |
| PCNT |
| ESRP1 |
| ESRP2 |
| LOXL3 |
| NRAS |
| ANAPC15 |
| BBOX1 |
| CDCA5 |
| CYB561 |
| DIAPH3 |
| MTF1 |
| NXN |
| PSPH |
| RAB34 |
| SMURF2 |
| TMEM132A |
| DPF2 |
| KARS |
| DDX3X |
| GORAB |
| ARID1A |
| CSF1R |
| MMACHC |
| RBM8A |
| CCP110 |
| GPT2 |

Table S5. Genes identified by transcriptomic prioritization strategy

| ENSG_ID | Symbol | Connected_genes |
|-----------------|-------------|-----------------|
| ENSG00000036530 | CYP46A1 | SHH |
| ENSG00000071073 | MGAT4A | SHH |
| ENSG00000108176 | DNAJC12 | SHH |
| ENSG00000112320 | SOBP | SHH |
| ENSG00000112619 | PRPH2 | SHH |
| ENSG00000117152 | RGS4 | SHH |
| ENSG00000117461 | PIK3R3 | SHH |
| ENSG00000122778 | KIAA1549 | SHH |
| ENSG00000123213 | NLN | SHH |
| ENSG00000123411 | IKZF4 | SHH |
| ENSG00000125827 | TMX4 | SHH |
| ENSG00000136546 | SCN7A | SHH |
| ENSG00000151812 | SLC35F4 | SHH |
| ENSG00000152910 | CNTNAP4 | SHH |
| ENSG00000162849 | KIF26B | SHH |
| ENSG00000164690 | SHH | SHH |
| ENSG00000165868 | HSPA12A | SHH |
| ENSG00000169302 | STK32A | SHH |
| ENSG00000171951 | SCG2 | SHH |
| ENSG00000176406 | RIMS2 | SHH |
| ENSG00000177511 | ST8SIA3 | SHH |
| ENSG00000179083 | FAM133A | SHH |
| ENSG00000183454 | GRIN2A | SHH |
| ENSG00000185736 | ADARB2 | SHH |
| ENSG00000187398 | LUZP2 | SHH |
| ENSG00000232224 | LINC00202-1 | SHH |
| ENSG00000240280 | TCAM1P | SHH |
| ENSG00000119977 | TCTN3 | SHH |
| ENSG00000041353 | RAB27B | SHH, SIX3 |
| ENSG00000060709 | RIMBP2 | SHH, SIX3 |
| ENSG00000065320 | NTN1 | SHH, SIX3 |
| ENSG00000077616 | NAALAD2 | SHH, SIX3 |
| ENSG00000103528 | SYT17 | SHH, SIX3 |
| ENSG00000105650 | PDE4C | SHH, SIX3 |
| ENSG00000109944 | C11orf63 | SHH, SIX3 |
| ENSG00000132334 | PTPRE | SHH, SIX3 |
| ENSG00000133460 | SLC2A11 | SHH, SIX3 |
| ENSG00000134324 | LPIN1 | SHH, SIX3 |
| ENSG00000135074 | ADAM19 | SHH, SIX3 |
| ENSG00000138162 | TACC2 | SHH, SIX3 |
| ENSG00000138650 | PCDH10 | SHH, SIX3 |
| ENSG00000148053 | NTRK2 | SHH, SIX3 |
| ENSG00000149403 | GRIK4 | SHH, SIX3 |
| ENSG00000155897 | ADCY8 | SHH, SIX3 |
| ENSG00000158806 | NPM2 | SHH, SIX3 |
| ENSG00000166455 | C16orf46 | SHH, SIX3 |
| ENSG00000169851 | PCDH7 | SHH, SIX3 |
| ENSG00000171189 | GRIK1 | SHH, SIX3 |
| ENSG00000171435 | KSR2 | SHH, SIX3 |
| ENSG00000185920 | PTCH1 | SHH, SIX3 |
| ENSG00000196090 | PTPRT | SHH, SIX3 |
| ENSG00000196104 | SPOCK3 | SHH, SIX3 |
| ENSG00000196277 | GRM7 | SHH, SIX3 |
| ENSG00000198879 | SFMBT2 | SHH, SIX3 |
| ENSG00000215217 | C5orf49 | SHH, SIX3 |
| ENSG00000248008 | DYNLL1-AS1 | SHH, SIX3 |
| ENSG00000175356 | SCUBE2 | SHH, SIX3 |
| ENSG00000009694 | TENM1 | SHH, ZIC2 |
| ENSG00000092421 | SEMA6A | SHH, ZIC2 |
| ENSG00000152578 | GRIA4 | SHH, ZIC2 |
| ENSG00000171533 | MAP6 | SHH, ZIC2 |
| ENSG00000175352 | NRIP3 | SHH, ZIC2 |
| ENSG00000001460 | STPG1 | SHH,ZIC2,SIX3 |
| ENSG00000005381 | MPO | SHH,ZIC2,SIX3 |
| ENSG00000006047 | YBX2 | SHH,ZIC2,SIX3 |

| | | |
|-----------------|----------|---------------|
| ENSG00000006128 | TAC1 | SHH,ZIC2,SIX3 |
| ENSG00000006283 | CACNA1G | SHH,ZIC2,SIX3 |
| ENSG00000007402 | CACNA2D2 | SHH,ZIC2,SIX3 |
| ENSG00000008118 | CAMK1G | SHH,ZIC2,SIX3 |
| ENSG00000010626 | LRRC23 | SHH,ZIC2,SIX3 |
| ENSG00000029153 | ARNTL2 | SHH,ZIC2,SIX3 |
| ENSG00000053108 | FSTL4 | SHH,ZIC2,SIX3 |
| ENSG00000063180 | CA11 | SHH,ZIC2,SIX3 |
| ENSG00000072182 | ASIC4 | SHH,ZIC2,SIX3 |
| ENSG00000081479 | LRP2 | SHH,ZIC2,SIX3 |
| ENSG00000091513 | TF | SHH,ZIC2,SIX3 |
| ENSG00000091622 | PITPNM3 | SHH,ZIC2,SIX3 |
| ENSG00000095203 | EPB41L4B | SHH,ZIC2,SIX3 |
| ENSG00000095587 | TLL2 | SHH,ZIC2,SIX3 |
| ENSG00000095713 | CRTAC1 | SHH,ZIC2,SIX3 |
| ENSG00000099204 | ABLIM1 | SHH,ZIC2,SIX3 |
| ENSG00000101180 | HRH3 | SHH,ZIC2,SIX3 |
| ENSG00000101282 | RSPO4 | SHH,ZIC2,SIX3 |
| ENSG00000101605 | MYOM1 | SHH,ZIC2,SIX3 |
| ENSG00000102900 | NUP93 | SHH,ZIC2,SIX3 |
| ENSG00000103154 | NECAB2 | SHH,ZIC2,SIX3 |
| ENSG00000104327 | CALB1 | SHH,ZIC2,SIX3 |
| ENSG00000104722 | NEFM | SHH,ZIC2,SIX3 |
| ENSG00000104814 | MAP4K1 | SHH,ZIC2,SIX3 |
| ENSG00000105251 | SHD | SHH,ZIC2,SIX3 |
| ENSG00000105379 | ETFB | SHH,ZIC2,SIX3 |
| ENSG00000106069 | CHN2 | SHH,ZIC2,SIX3 |
| ENSG00000106633 | GCK | SHH,ZIC2,SIX3 |
| ENSG00000108684 | ASIC2 | SHH,ZIC2,SIX3 |
| ENSG00000108830 | RND2 | SHH,ZIC2,SIX3 |
| ENSG00000108947 | EFNB3 | SHH,ZIC2,SIX3 |
| ENSG00000110906 | KCTD10 | SHH,ZIC2,SIX3 |
| ENSG00000112679 | DUSP22 | SHH,ZIC2,SIX3 |
| ENSG00000114654 | EFCC1 | SHH,ZIC2,SIX3 |
| ENSG00000117245 | KIF17 | SHH,ZIC2,SIX3 |
| ENSG00000118898 | PPL | SHH,ZIC2,SIX3 |
| ENSG00000120053 | GOT1 | SHH,ZIC2,SIX3 |
| ENSG00000123360 | PDE1B | SHH,ZIC2,SIX3 |
| ENSG00000124191 | TOX2 | SHH,ZIC2,SIX3 |
| ENSG00000124493 | GRM4 | SHH,ZIC2,SIX3 |
| ENSG00000124588 | NQO2 | SHH,ZIC2,SIX3 |
| ENSG00000125354 | 38961 | SHH,ZIC2,SIX3 |
| ENSG00000125895 | TMEM74B | SHH,ZIC2,SIX3 |
| ENSG00000128285 | MCHR1 | SHH,ZIC2,SIX3 |
| ENSG00000128596 | CCDC136 | SHH,ZIC2,SIX3 |
| ENSG00000128739 | SNRPN | SHH,ZIC2,SIX3 |
| ENSG00000129757 | CDKN1C | SHH,ZIC2,SIX3 |
| ENSG00000131019 | ULBP3 | SHH,ZIC2,SIX3 |
| ENSG00000131378 | RFTN1 | SHH,ZIC2,SIX3 |
| ENSG00000131480 | AOC2 | SHH,ZIC2,SIX3 |
| ENSG00000132434 | LANCL2 | SHH,ZIC2,SIX3 |
| ENSG00000133019 | CHRM3 | SHH,ZIC2,SIX3 |
| ENSG00000134115 | CNTN6 | SHH,ZIC2,SIX3 |
| ENSG00000135299 | ANKRD6 | SHH,ZIC2,SIX3 |
| ENSG00000135447 | PPP1R1A | SHH,ZIC2,SIX3 |
| ENSG00000135824 | RGS8 | SHH,ZIC2,SIX3 |
| ENSG00000138622 | HCN4 | SHH,ZIC2,SIX3 |
| ENSG00000139438 | FAM222A | SHH,ZIC2,SIX3 |
| ENSG00000139531 | SUOX | SHH,ZIC2,SIX3 |
| ENSG00000139890 | REM2 | SHH,ZIC2,SIX3 |
| ENSG00000140836 | ZFX3 | SHH,ZIC2,SIX3 |
| ENSG00000141449 | GREB1L | SHH,ZIC2,SIX3 |
| ENSG00000141668 | CBLN2 | SHH,ZIC2,SIX3 |
| ENSG00000142192 | APP | SHH,ZIC2,SIX3 |
| ENSG00000143842 | SOX13 | SHH,ZIC2,SIX3 |
| ENSG00000143850 | PLEKHA6 | SHH,ZIC2,SIX3 |
| ENSG00000144339 | TMEFF2 | SHH,ZIC2,SIX3 |

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| ENSG00000144619 | CNTN4 | SHH,ZIC2,SIX3 |
| ENSG00000145911 | N4BP3 | SHH,ZIC2,SIX3 |
| ENSG00000145934 | TENM2 | SHH,ZIC2,SIX3 |
| ENSG00000146950 | SHROOM2 | SHH,ZIC2,SIX3 |
| ENSG00000147465 | STAR | SHH,ZIC2,SIX3 |
| ENSG00000148358 | GPR107 | SHH,ZIC2,SIX3 |
| ENSG00000148948 | LRRC4C | SHH,ZIC2,SIX3 |
| ENSG00000150394 | CDH8 | SHH,ZIC2,SIX3 |
| ENSG00000150455 | TIRAP | SHH,ZIC2,SIX3 |
| ENSG00000150471 | LPHN3 | SHH,ZIC2,SIX3 |
| ENSG00000150551 | LYPD1 | SHH,ZIC2,SIX3 |
| ENSG00000151067 | CACNA1C | SHH,ZIC2,SIX3 |
| ENSG00000151136 | BTBD11 | SHH,ZIC2,SIX3 |
| ENSG00000151474 | FRMD4A | SHH,ZIC2,SIX3 |
| ENSG00000151892 | GFRA1 | SHH,ZIC2,SIX3 |
| ENSG00000151948 | GLT1D1 | SHH,ZIC2,SIX3 |
| ENSG00000153012 | LGI2 | SHH,ZIC2,SIX3 |
| ENSG00000153902 | LGI4 | SHH,ZIC2,SIX3 |
| ENSG00000155093 | PTPRN2 | SHH,ZIC2,SIX3 |
| ENSG00000155367 | PPM1J | SHH,ZIC2,SIX3 |
| ENSG00000157514 | TSC22D3 | SHH,ZIC2,SIX3 |
| ENSG00000157557 | ETS2 | SHH,ZIC2,SIX3 |
| ENSG00000159450 | TCHH | SHH,ZIC2,SIX3 |
| ENSG00000160179 | ABCG1 | SHH,ZIC2,SIX3 |
| ENSG00000161243 | FBXO27 | SHH,ZIC2,SIX3 |
| ENSG00000162188 | GNG3 | SHH,ZIC2,SIX3 |
| ENSG00000162552 | WNT4 | SHH,ZIC2,SIX3 |
| ENSG00000162755 | KLHDC9 | SHH,ZIC2,SIX3 |
| ENSG00000162981 | FAM84A | SHH,ZIC2,SIX3 |
| ENSG00000163377 | FAM19A4 | SHH,ZIC2,SIX3 |
| ENSG00000164484 | TMEM200A | SHH,ZIC2,SIX3 |
| ENSG00000164708 | PGAM2 | SHH,ZIC2,SIX3 |
| ENSG00000165152 | TMEM246 | SHH,ZIC2,SIX3 |
| ENSG00000165186 | PTCHD1 | SHH,ZIC2,SIX3 |
| ENSG00000165406 | MARCH8 | SHH,ZIC2,SIX3 |
| ENSG00000165821 | SALL2 | SHH,ZIC2,SIX3 |
| ENSG00000165966 | PDZRN4 | SHH,ZIC2,SIX3 |
| ENSG00000166073 | GPR176 | SHH,ZIC2,SIX3 |
| ENSG00000166452 | AKIP1 | SHH,ZIC2,SIX3 |
| ENSG00000166619 | BLCAP | SHH,ZIC2,SIX3 |
| ENSG00000168610 | STAT3 | SHH,ZIC2,SIX3 |
| ENSG00000168781 | PPIP5K1 | SHH,ZIC2,SIX3 |
| ENSG00000169758 | C15orf27 | SHH,ZIC2,SIX3 |
| ENSG00000170145 | SIK2 | SHH,ZIC2,SIX3 |
| ENSG00000170549 | IRX1 | SHH,ZIC2,SIX3 |
| ENSG00000171094 | ALK | SHH,ZIC2,SIX3 |
| ENSG00000171224 | C10orf35 | SHH,ZIC2,SIX3 |
| ENSG00000171956 | FOXB1 | SHH,ZIC2,SIX3 |
| ENSG00000172348 | RCAN2 | SHH,ZIC2,SIX3 |
| ENSG00000173065 | FAM222B | SHH,ZIC2,SIX3 |
| ENSG00000173114 | LRRN3 | SHH,ZIC2,SIX3 |
| ENSG00000173805 | HAP1 | SHH,ZIC2,SIX3 |
| ENSG00000174951 | FUT1 | SHH,ZIC2,SIX3 |
| ENSG00000175040 | CHST2 | SHH,ZIC2,SIX3 |
| ENSG00000176092 | AIM1L | SHH,ZIC2,SIX3 |
| ENSG00000176387 | HSD11B2 | SHH,ZIC2,SIX3 |
| ENSG00000176641 | RNF152 | SHH,ZIC2,SIX3 |
| ENSG00000176723 | ZNF843 | SHH,ZIC2,SIX3 |
| ENSG00000181274 | FRAT2 | SHH,ZIC2,SIX3 |
| ENSG00000182013 | PNMAL1 | SHH,ZIC2,SIX3 |
| ENSG00000182168 | UNC5C | SHH,ZIC2,SIX3 |
| ENSG00000182183 | FAM159A | SHH,ZIC2,SIX3 |
| ENSG00000182541 | LIMK2 | SHH,ZIC2,SIX3 |
| ENSG00000183111 | ARHGEF37 | SHH,ZIC2,SIX3 |
| ENSG00000183696 | UPP1 | SHH,ZIC2,SIX3 |
| ENSG00000184384 | MAML2 | SHH,ZIC2,SIX3 |
| ENSG00000184985 | SORCS2 | SHH,ZIC2,SIX3 |

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| ENSG00000185442 | FAM174B | SHH,ZIC2,SIX3 |
| ENSG00000186806 | VSIG10L | SHH,ZIC2,SIX3 |
| ENSG00000187634 | SAMD11 | SHH,ZIC2,SIX3 |
| ENSG00000188042 | ARL4C | SHH,ZIC2,SIX3 |
| ENSG00000189410 | SH2D5 | SHH,ZIC2,SIX3 |
| ENSG00000196141 | SPATS2L | SHH,ZIC2,SIX3 |
| ENSG00000196208 | GREB1 | SHH,ZIC2,SIX3 |
| ENSG00000197380 | DACT3 | SHH,ZIC2,SIX3 |
| ENSG00000197971 | MBP | SHH,ZIC2,SIX3 |
| ENSG00000198785 | GRIN3A | SHH,ZIC2,SIX3 |
| ENSG00000198795 | ZNF521 | SHH,ZIC2,SIX3 |
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| ENSG00000205744 | DENND1C | SHH,ZIC2,SIX3 |
| ENSG00000205929 | C21orf62 | SHH,ZIC2,SIX3 |
| ENSG00000214548 | MEG3 | SHH,ZIC2,SIX3 |
| ENSG00000223573 | TINCR | SHH,ZIC2,SIX3 |
| ENSG00000224165 | DNAJC27-AS1 | SHH,ZIC2,SIX3 |
| ENSG00000233930 | KRTAP5-AS1 | SHH,ZIC2,SIX3 |
| ENSG00000250366 | TUNAR | SHH,ZIC2,SIX3 |
| ENSG00000254245 | PCDHGA3 | SHH,ZIC2,SIX3 |
| ENSG00000254585 | MAGEL2 | SHH,ZIC2,SIX3 |
| ENSG00000259736 | CRTC3-AS1 | SHH,ZIC2,SIX3 |
| ENSG00000268089 | GABRQ | SHH,ZIC2,SIX3 |
| ENSG00000277586 | NEFL | SHH,ZIC2,SIX3 |
| ENSG00000280870 | MIR325HG | SHH,ZIC2,SIX3 |
| ENSG00000136250 | AOAH | SIX3 |
| ENSG00000138083 | SIX3 | SIX3 |
| ENSG00000169902 | TPST1 | SIX3 |
| ENSG00000170961 | HAS2 | SIX3 |
| ENSG00000184205 | TSPYL2 | SIX3 |
| ENSG00000050767 | COL23A1 | SIX3, ZIC2 |
| ENSG00000065357 | DGKA | SIX3, ZIC2 |
| ENSG00000082556 | OPRK1 | SIX3, ZIC2 |
| ENSG00000089116 | LHX5 | SIX3, ZIC2 |
| ENSG00000089472 | HEPH | SIX3, ZIC2 |
| ENSG00000103599 | IQCH | SIX3, ZIC2 |
| ENSG00000113296 | THBS4 | SIX3, ZIC2 |
| ENSG00000130055 | GDPD2 | SIX3, ZIC2 |
| ENSG00000130940 | CASZ1 | SIX3, ZIC2 |
| ENSG00000140807 | NKD1 | SIX3, ZIC2 |
| ENSG00000143032 | BARHL2 | SIX3, ZIC2 |
| ENSG00000143367 | TUFT1 | SIX3, ZIC2 |
| ENSG00000143409 | FAM63A | SIX3, ZIC2 |
| ENSG00000157657 | ZNF618 | SIX3, ZIC2 |
| ENSG00000169991 | IFFO2 | SIX3, ZIC2 |
| ENSG00000170571 | EMB | SIX3, ZIC2 |
| ENSG00000170743 | SYT9 | SIX3, ZIC2 |
| ENSG00000174963 | ZIC4 | SIX3, ZIC2 |
| ENSG00000179761 | PIPOX | SIX3, ZIC2 |
| ENSG00000183722 | LHFP | SIX3, ZIC2 |
| ENSG00000183780 | SLC35F3 | SIX3, ZIC2 |
| ENSG00000184185 | KCNJ12 | SIX3, ZIC2 |
| ENSG00000203952 | CCDC160 | SIX3, ZIC2 |
| ENSG00000204335 | SP5 | SIX3, ZIC2 |
| ENSG00000242866 | STRC | SIX3, ZIC2 |
| ENSG00000250208 | FZD10-AS1 | SIX3, ZIC2 |
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| ENSG00000013810 | TACC3 | TGIF1 |
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| ENSG00000074219 | TEAD2 | TGIF1 |
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| ENSG00000075218 | GTSE1 | TGIF1 |
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| ENSG00000106263 | EIF3B | TGIF1 |
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| ENSG00000107438 | PDLIM1 | TGIF1 |
| ENSG00000108179 | PPIF | TGIF1 |
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| ENSG00000114738 | MAPKAPK3 | TGIF1 |
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| ENSG00000137193 | PIM1 | TGIF1 |
| ENSG00000137337 | MDC1 | TGIF1 |
| ENSG00000137413 | TAF8 | TGIF1 |
| ENSG00000138092 | CENPO | TGIF1 |

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| ENSG00000139835 | GRTP1 | TGIF1 |
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| ENSG00000141401 | IMPA2 | TGIF1 |
| ENSG00000141510 | TP53 | TGIF1 |
| ENSG00000141756 | FKBP10 | TGIF1 |
| ENSG00000142632 | ARHGEF19 | TGIF1 |
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| ENSG00000148229 | POLE3 | TGIF1 |
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| ENSG00000157978 | LDLRAP1 | TGIF1 |
| ENSG00000158195 | WASF2 | TGIF1 |
| ENSG00000159217 | IGF2BP1 | TGIF1 |
| ENSG00000159259 | CHAF1B | TGIF1 |
| ENSG00000159958 | TNFRSF13C | TGIF1 |
| ENSG00000160447 | PKN3 | TGIF1 |
| ENSG00000161888 | SPC24 | TGIF1 |
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| ENSG00000163820 | FYCO1 | TGIF1 |
| ENSG00000163933 | RFT1 | TGIF1 |
| ENSG00000164032 | H2AFZ | TGIF1 |
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| ENSG00000164818 | DNAAF5 | TGIF1 |
| ENSG00000165060 | FXN | TGIF1 |
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| ENSG00000166813 | KIF7 | TGIF1 |
| ENSG00000166851 | PLK1 | TGIF1 |
| ENSG00000166965 | RCCD1 | TGIF1 |
| ENSG00000167107 | ACSF2 | TGIF1 |
| ENSG00000167513 | CDT1 | TGIF1 |
| ENSG00000167565 | SERTAD3 | TGIF1 |
| ENSG00000167601 | AXL | TGIF1 |
| ENSG00000167670 | CHAF1A | TGIF1 |
| ENSG00000167747 | C19orf48 | TGIF1 |
| ENSG00000167881 | SRP68 | TGIF1 |
| ENSG00000167900 | TK1 | TGIF1 |
| ENSG00000168077 | SCARA3 | TGIF1 |
| ENSG00000168393 | DTYMK | TGIF1 |
| ENSG00000168476 | REEP4 | TGIF1 |
| ENSG00000168496 | FEN1 | TGIF1 |
| ENSG00000168765 | GSTM4 | TGIF1 |
| ENSG00000168883 | USP39 | TGIF1 |

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| ENSG00000169105 | CHST14 | TGIF1 |
| ENSG00000169188 | APEX2 | TGIF1 |
| ENSG00000169813 | HNRNPF | TGIF1 |
| ENSG00000169871 | TRIM56 | TGIF1 |
| ENSG00000170779 | CDCA4 | TGIF1 |
| ENSG00000171960 | PPIH | TGIF1 |
| ENSG00000173040 | EVC2 | TGIF1 |
| ENSG00000173207 | CKS1B | TGIF1 |
| ENSG00000173530 | TNFRSF10D | TGIF1 |
| ENSG00000175063 | UBE2C | TGIF1 |
| ENSG00000175215 | CTDSP2 | TGIF1 |
| ENSG00000175970 | UNC119B | TGIF1 |
| ENSG00000176783 | RUFY1 | TGIF1 |
| ENSG00000176974 | SHMT1 | TGIF1 |
| ENSG00000177084 | POLE | TGIF1 |
| ENSG00000177426 | TGIF1 | TGIF1 |
| ENSG00000177602 | GSG2 | TGIF1 |
| ENSG00000178035 | IMPDH2 | TGIF1 |
| ENSG00000178999 | AURKB | TGIF1 |
| ENSG00000179051 | RCC2 | TGIF1 |
| ENSG00000180198 | RCC1 | TGIF1 |
| ENSG00000180340 | FZD2 | TGIF1 |
| ENSG00000181481 | RNF135 | TGIF1 |
| ENSG00000181924 | COA4 | TGIF1 |
| ENSG00000181938 | GIN53 | TGIF1 |
| ENSG00000182197 | EXT1 | TGIF1 |
| ENSG00000182199 | SHMT2 | TGIF1 |
| ENSG00000183763 | TRAP | TGIF1 |
| ENSG00000183798 | EMILIN3 | TGIF1 |
| ENSG00000183856 | IQGAP3 | TGIF1 |
| ENSG00000184232 | OAF | TGIF1 |
| ENSG00000186185 | KIF18B | TGIF1 |
| ENSG00000186638 | KIF24 | TGIF1 |
| ENSG00000186918 | ZNF395 | TGIF1 |
| ENSG00000187741 | FANCA | TGIF1 |
| ENSG00000188051 | TMEM221 | TGIF1 |
| ENSG00000188312 | CENPP | TGIF1 |
| ENSG00000188486 | H2AFX | TGIF1 |
| ENSG00000189091 | SF3B3 | TGIF1 |
| ENSG00000196411 | EPHB4 | TGIF1 |
| ENSG00000197905 | TEAD4 | TGIF1 |
| ENSG00000198176 | TFDP1 | TGIF1 |
| ENSG00000198805 | PNP | TGIF1 |
| ENSG00000203760 | CENPW | TGIF1 |
| ENSG00000203999 | LINC01270 | TGIF1 |
| ENSG00000213719 | CLIC1 | TGIF1 |
| ENSG00000213853 | EMP2 | TGIF1 |
| ENSG00000223773 | CD99P1 | TGIF1 |
| ENSG00000237649 | KIFC1 | TGIF1 |
| ENSG00000243364 | EFNA4 | TGIF1 |
| ENSG00000256269 | HMBS | TGIF1 |
| ENSG00000276043 | UHRF1 | TGIF1 |
| ENSG0000043355 | ZIC2 | ZIC2 |
| ENSG0000069020 | MAST4 | ZIC2 |
| ENSG00000103591 | AAGAB | ZIC2 |
| ENSG00000108375 | RNF43 | ZIC2 |
| ENSG00000109851 | DBX1 | ZIC2 |
| ENSG00000111432 | FZD10 | ZIC2 |
| ENSG00000116729 | WLS | ZIC2 |
| ENSG00000116990 | MYCL | ZIC2 |
| ENSG00000122644 | ARL4A | ZIC2 |
| ENSG00000128573 | FOXP2 | ZIC2 |
| ENSG00000131400 | NAPSA | ZIC2 |
| ENSG00000132938 | MTUS2 | ZIC2 |
| ENSG00000134215 | VAV3 | ZIC2 |
| ENSG00000144550 | CPNE9 | ZIC2 |
| ENSG00000152977 | ZIC1 | ZIC2 |

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|-----------------|------------|------|
| ENSG00000162631 | NTNG1 | ZIC2 |
| ENSG00000165588 | OTX2 | ZIC2 |
| ENSG00000168779 | SHOX2 | ZIC2 |
| ENSG00000170703 | TTL6 | ZIC2 |
| ENSG00000175147 | TMEM51-AS1 | ZIC2 |
| ENSG00000176454 | LPCAT4 | ZIC2 |
| ENSG00000176842 | IRX5 | ZIC2 |
| ENSG00000177508 | IRX3 | ZIC2 |
| ENSG00000182247 | UBE2E2 | ZIC2 |
| ENSG00000186493 | C5orf38 | ZIC2 |
| ENSG00000205221 | VIT | ZIC2 |
| ENSG00000243710 | CFAP57 | ZIC2 |
| ENSG00000274588 | DGKK | ZIC2 |

Table S6. Candidate variants

| Family | Gene | Type | Zyg | newChange | Frequency | CANDIDATE | KO_HPE |
|--------|---------|-----------|-----|--------------|-------------|----------------|--------|
| F1 | SHH | missense | HET | p.Cys102Tyr | | Clinical;WGCNA | Yes |
| F1 | FYCO1 | missense | HET | p.Pro144Thr | | WGCNA | No |
| F1 | GRHL3 | missense | HET | p.Met531Lys | 0,0000129 | Clinical | No |
| F1 | KARS | missense | HET | p.Arg421Gln | 0,0015 | Clinical | No |
| F1 | MYH10 | missense | HET | p.Ala996Val | 0,0094 | Clinical | No |
| F1 | PLXNB2 | missense | HET | p.Arg1248Cys | | Clinical | No |
| F10 | SIX3 | missense | HET | p.Arg107Trp | | Clinical;WGCNA | Yes |
| F10 | CAMK1G | missense | HET | p.Thr116Ile | 0,0000323 | WGCNA | No |
| F10 | PARP1 | missense | HET | p.Gly530Arg | 0,000505 | WGCNA | No |
| F10 | DAPK2 | missense | HET | p.Arg68Gln | 0,0064 | WGCNA | No |
| F10 | GREB1L | missense | HET | p.Phe1732Leu | | WGCNA | No |
| F10 | ABCG1 | missense | HET | p.Ala206Thr | | WGCNA | No |
| F10 | WDR19 | missense | HET | p.Arg464Cys | 0,000504 | Clinical | No |
| F10 | CEP135 | missense | HET | p.Arg454Gly | 0,0008 | Clinical | No |
| F10 | GLI3 | missense | HET | p.Gly727Arg | 0,006546 | Clinical | No |
| F10 | TRPM6 | missense | HET | p.Gly171Arg | 0,0038 | Clinical | No |
| F11 | LRP2 | missense | HET | p.Glu3089Lys | 0,00003229 | Clinical;WGCNA | Yes |
| F11 | CELSR1 | missense | HET | p.Tyr2820Cys | 0,00002247 | Clinical;WGCNA | No |
| F11 | SHH | missense | HET | p.Pro347Arg | | Clinical;WGCNA | Yes |
| F11 | LRP4 | missense | HET | p.Glu1691Lys | 0,0004 | WGCNA | No |
| F11 | FOXN4 | missense | HET | p.His187Tyr | 0,00001345 | WGCNA | No |
| F11 | NCAPD2 | missense | HET | p.Ser721Cys | 0,00239617 | WGCNA | No |
| F11 | TICRR | missense | HET | p.Ser1453Phe | 0,000599042 | WGCNA | No |
| F11 | HRH3 | missense | HET | p.Thr149Arg | | WGCNA | No |
| F11 | CHAF1B | missense | HET | p.Val16Ala | 0,006546 | WGCNA | No |
| F11 | HSD17B7 | missense | HET | p.Cys19Gly | 0,0002 | Clinical | No |
| F11 | LRP8 | missense | HET | p.Val832Met | 0,000077 | Clinical | No |
| F11 | AKAP6 | missense | HET | p.Ser1667Phe | 0,000798722 | Clinical | No |
| F11 | PCSK6 | synonymou | HET | c.2253G>A | | Clinical | No |
| F11 | CCP110 | missense | HET | p.Arg908Gln | 0,000004094 | Clinical | No |
| F11 | MKS1 | missense | HET | p.Gly255Arg | 0,0002 | Clinical | Yes |
| F11 | RBBP8 | stopgain | HET | p.Trp852Ter | | Clinical | No |
| F12 | PLEKHA6 | missense | HET | p.Ser373Asn | 0,00003544 | WGCNA | No |
| F12 | IQCH | missense | HET | p.Arg898His | 0,0003 | WGCNA | No |
| F12 | SPAG5 | missense | HET | p.Met1Val | 0,0064 | WGCNA | No |
| F12 | TOX2 | missense | HET | p.Pro349Leu | 0,00003731 | WGCNA | No |
| F12 | MAN2B1 | missense | HET | p.Pro248Leu | 0,0031 | Clinical | No |
| F12 | ASNS | missense | HET | p.Arg519His | 0,00003229 | Clinical | No |
| F13 | WASF2 | missense | HET | p.Glu122Gln | 0,0035 | Clinical;WGCNA | No |
| F13 | ASAP3 | missense | HET | p.Gly767Arg | 0,0017 | WGCNA | No |
| F13 | CFAP57 | missense | HET | p.Arg619Cys | 0,0028 | WGCNA | No |
| F13 | CRTAC1 | missense | HET | p.Arg153Cys | 0,0035 | WGCNA | No |
| F13 | TTC23 | missense | HET | p.Asp289Asn | 0,0001 | WGCNA | No |
| F13 | ETFB | missense | HET | p.Ala63Thr | 0,000077 | WGCNA | No |
| F13 | UMPS | missense | HET | p.Phe315Leu | | WGCNA | No |
| F13 | MCM2 | missense | HET | p.Thr39Ile | 0,00009927 | WGCNA | No |
| F13 | KIF20A | missense | HET | p.Trp346Arg | | WGCNA | No |
| F13 | LRRN3 | missense | HET | p.Ser427Asn | 0,004028 | WGCNA | No |
| F13 | APBB1 | missense | HET | p.Asn214Ser | | Clinical | No |
| F13 | SLC12A6 | missense | HET | p.Ile636Val | 0,000504 | Clinical | No |
| F14 | DLG1 | missense | HET | p.Asp267Gly | 0,0004 | Clinical | No |
| F14 | FOXC1 | missense | HET | p.Gly103Arg | | Clinical | No |
| F14 | ADGRA2 | missense | HET | p.Thr348Ile | 0,00504 | Clinical | No |
| F15 | SRP68 | missense | HET | p.Asp120Asn | 0,0019 | WGCNA | No |
| F15 | MCM5 | missense | HET | p.Asp81Gly | | WGCNA | No |
| F15 | NPHP4 | missense | HET | p.Arg1192Trp | 0,00303 | Clinical | No |
| F15 | IFT88 | missense | HET | p.Asp819Tyr | | Clinical | No |
| F15 | RB1 | missense | HET | p.Gly310Glu | 0,001523 | Clinical | No |
| F15 | ATP7B | missense | HET | p.Gly889Arg | 0,00009419 | Clinical | No |

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|-----|----------|------------|-----|--------------------|-------------|----------------|-----|
| F15 | SULF1 | missense | HET | p.Glu549Lys | 0,000199681 | Clinical | No |
| F16 | CNTN4 | missense | HET | p.Thr176Ala | 0,000399361 | WGCNA | No |
| F16 | ANKRD6 | missense | HET | p.Ala182Val | 0,00002031 | WGCNA | No |
| F16 | TRIP6 | frameshift | HET | p.Val174NA | | WGCNA | No |
| F16 | TRIP6 | frameshift | HET | p.Ala175NA | | WGCNA | No |
| F16 | PLEKHA1 | missense | HET | p.Arg302Trp | 0,0004 | Clinical | No |
| F16 | CIT | missense | HET | p.Arg976Cys | | Clinical | No |
| F16 | COL2A1 | missense | HET | p.Arg68His | 0,0001 | Clinical | Yes |
| F16 | MLST8 | missense | HET | p.Pro12Leu | 0,00002057 | Clinical | No |
| F16 | ZNF423 | missense | HET | p.Lys748Asn | 0,0002 | Clinical | No |
| F16 | CECR2 | missense | HET | p.Arg581Gly | | Clinical | No |
| F16 | RYK | missense | HET | R184H | 0,0008 | Clinical | No |
| F16 | FAT1 | missense | HET | p.Val3459Met | 0,0006 | Clinical | Yes |
| F16 | SHROOM3 | missense | HET | p.Gly186Arg | 0,0097 | Clinical | No |
| F16 | NDST1 | missense | HET | p.Arg132Cys | 0,0002 | Clinical | Yes |
| F17 | CRTAC1 | missense | HET | p.Arg153Cys | 0,0035 | WGCNA | No |
| F17 | MGAT4A | missense | HET | p.Thr236Ala | 0,008 | WGCNA | No |
| F17 | CENPW | stopgain | HET | p.Arg51Ter | 0,0031436 | WGCNA | No |
| F17 | TEAD3 | missense | HET | p.Gly33Ser | 0,0003 | WGCNA | No |
| F17 | C7orf49 | missense | HET | p.Arg11Lys | | WGCNA | No |
| F17 | MCM7 | missense | HET | p.Cys566Ser | 0,00003331 | WGCNA | No |
| F17 | CEP290 | missense | HET | p.Ala1735Val | | Clinical | No |
| F17 | TRAPPC10 | missense | HET | p.Gln857Arg | | Clinical | Yes |
| F17 | ZIC2 | nonframesh | HET | p.Ala461_Ala470dup | | Clinical;WGCNA | Yes |
| F18 | TK1 | missense | HET | p.Ala467_Ala471 | 0,00002225 | WGCNA | No |
| F18 | CCNJL | missense | HET | p.Val151Ile | 0,009567 | WGCNA | No |
| F18 | KIFAP3 | missense | HET | p.Phe356Cys | 0,0018 | Clinical | No |
| F18 | DHCR7 | splicing | HET | c.964-1G>C | 0,0054 | Clinical | No |
| F18 | PRICKLE1 | missense | HET | p.Ser739Phe | 0,0012 | Clinical | No |
| F18 | HGS | missense | HET | p.Pro241Arg | | Clinical | No |
| F18 | ABCB6 | missense | HET | p.Arg723Gln | 0,001007 | Clinical | No |
| F18 | IFT172 | missense | HET | p.Ala961Val | 0,000008126 | Clinical | Yes |
| F18 | CTNNB1 | missense | HET | p.Ala525Val | | Clinical | No |
| F19 | GLI2 | missense | HET | p.Phe323Ser | 0,00002437 | Clinical;WGCNA | Yes |
| F19 | CALHM2 | missense | HET | p.Ala158Gly | | WGCNA | No |
| F19 | SYT9 | missense | HET | p.Leu353Val | 0,008 | WGCNA | No |
| F19 | DNAAF5 | missense | HET | p.Val261Ile | 0,0006 | WGCNA | No |
| F19 | RBBP8 | missense | HET | p.Thr812Met | 0,00008874 | Clinical | No |
| F19 | PDGFRA | missense | HET | p.Gly1006Asp | | Clinical | No |
| F19 | ADGRA2 | missense | HET | p.Ala355Thr | 0,006 | Clinical | No |
| F19 | GLDC | missense | HET | p.Val735Leu | 0,0079 | Clinical | No |
| F19 | ZIC2 | nonframesh | HET | p.Ala467_Ala470dup | | Clinical;WGCNA | Yes |
| F20 | KIF26B | missense | HET | p.Ala467_Ala471 | 0,00006458 | WGCNA | No |
| F20 | CDCA8 | missense | HET | p.Ala75Thr | 0,0002 | WGCNA | No |
| F20 | TCTN3 | missense | HET | p.Asn512Ser | 0,00003229 | WGCNA | No |
| F20 | DAPK2 | missense | HET | p.Thr190Met | 0,000077 | WGCNA | No |
| F20 | PTPRT | missense | HET | p.Arg1403His | 0,0075 | WGCNA | No |
| F20 | PTPRT | missense | HET | p.Ala793Val | 0,00003229 | WGCNA | No |
| F20 | CNTN6 | missense | HET | p.Gly310Ser | 0,0012 | WGCNA | No |
| F20 | CGN | missense | HET | p.Arg807Gln | 0,0051 | Clinical | No |
| F20 | GORAB | missense | HET | p.Arg234Trp | 0,0005 | Clinical | No |
| F20 | HSPG2 | missense | HET | p.Arg1919Cys | 0,0082 | Clinical | No |
| F20 | TULP3 | missense | HET | p.Ser437Thr | 0,0005 | Clinical | No |
| F20 | AKAP6 | missense | HET | p.Gly2107Ala | | Clinical | No |
| F20 | FLVCR2 | missense | HET | p.Thr393Met | 0,00008825 | Clinical | No |
| F20 | FASN | missense | HET | p.Glu1958Lys | 0,005 | Clinical | No |
| F20 | NCOA6 | missense | HET | p.Pro576Leu | 0,000199681 | Clinical | No |
| F20 | ADGRA2 | missense | HET | p.Glu499Lys | 0,00002445 | Clinical | No |
| F20 | MPDZ | missense | HET | p.Ser298Thr | 0,0003 | Clinical | No |
| F20 | L1CAM | missense | HET | p.Thr38Met | 0,0004 | Clinical | No |
| F21 | CELSR1 | missense | HET | p.Arg954Cys | 0,00001121 | Clinical;WGCNA | No |

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|-----|---------|-----------|-----|--------------|-------------|----------------|-----|
| F21 | RNF135 | missense | HET | p.Trp415Cys | 0,0074 | WGCNA | No |
| F21 | AKAP6 | missense | HET | p.Ser1653Arg | 0,0005 | Clinical | No |
| F21 | PKD1 | missense | HET | p.Val4009Gly | | Clinical | No |
| F21 | B9D1 | missense | HET | p.Arg141Gln | 0,00001106 | Clinical | Yes |
| F21 | CTNNB1 | missense | HET | p.Ala525Val | | Clinical | No |
| F22 | SCUBE2 | stopgain | HET | p.Arg525Ter | 0,00004061 | WGCNA | No |
| F22 | BCL2L12 | missense | HET | p.Ser195Asn | | WGCNA | No |
| F22 | NUP210 | missense | HET | p.Arg1178Trp | 0,0004 | WGCNA | No |
| F22 | MACF1 | missense | HET | p.Lys5084Arg | | Clinical | No |
| F22 | NPHP4 | missense | HET | p.Ser972Gly | 0,0036 | Clinical | No |
| F22 | POMT2 | missense | HET | p.Arg578Cys | 0,00009439 | Clinical | No |
| F22 | PKD1 | missense | HET | p.Arg4276Trp | 0,0069 | Clinical | No |
| F22 | HIC1 | missense | HET | p.Trp511Cys | | Clinical | Yes |
| F22 | EP300 | missense | HET | p.Lys1427Arg | | Clinical | No |
| F22 | BOC | missense | HET | p.Ala311Val | 0,00001897 | Clinical | Yes |
| F22 | TBC1D32 | missense | HET | p.Ala739Thr | 0,0026 | Clinical | No |
| F23 | LRP2 | missense | HET | p.Asn3205Asp | 0,0054 | Clinical;WGCNA | Yes |
| F23 | GRIK4 | missense | HET | p.Ser622Asn | 0,0007 | WGCNA | No |
| F23 | INPPL1 | missense | HET | p.Gln104Arg | 0,00006476 | WGCNA | No |
| F23 | CHAF1B | missense | HET | p.Val16Ala | 0,006546 | WGCNA | No |
| F23 | TBX15 | missense | HET | p.Glu5Gly | | Clinical | No |
| F23 | ALX1 | missense | HET | p.Ala320Val | | Clinical | No |
| F23 | COL4A1 | missense | HET | p.Pro530Ser | 0,0008 | Clinical | No |
| F23 | ATP7B | missense | HET | p.Ile1119Val | 0,000504 | Clinical | No |
| F23 | FAT1 | missense | HET | p.Gly855Arg | 0,004028 | Clinical | Yes |
| F23 | TFAP2A | synonymou | HET | p.Arg255Arg | 0,00003254 | Clinical | No |
| F23 | NSDHL | missense | HET | p.Arg281His | 0,001376 | Clinical | No |
| F24 | UNG | missense | HET | p.Trp241Arg | 0,0004 | WGCNA | No |
| F24 | FYCO1 | missense | HET | p.Glu1383Lys | 0,0025 | WGCNA | No |
| F24 | CCT3 | missense | HET | p.Glu271Gln | | Clinical | No |
| F24 | NPHP4 | missense | HET | p.Leu260Pro | | Clinical | No |
| F24 | ATP7B | missense | HET | p.Met33Thr | 0,000998403 | Clinical | No |
| F24 | MED1 | missense | HET | p.Arg41His | 0,000399361 | Clinical | No |
| F24 | EPG5 | missense | HET | p.Arg1686His | 0,000081 | Clinical | No |
| F24 | TIAM1 | missense | HET | p.Glu204Lys | 0,0013 | Clinical | No |
| F25 | KIF7 | missense | HET | p.Ser1281Ile | 0,00199681 | Clinical;WGCNA | No |
| F25 | KIF7 | missense | HET | p.Arg850Leu | 0,00199681 | Clinical;WGCNA | No |
| F25 | MCM2 | missense | HET | p.Ile858Thr | 0,00399361 | WGCNA | No |
| F25 | HILPDA | missense | HET | p.Tyr8Cys | 0,00003233 | WGCNA | No |
| F25 | GORAB | missense | HET | p.Pro111Leu | 0,00009691 | Clinical | No |
| F25 | HSPG2 | missense | HET | p.Gly4194Arg | 0,0013 | Clinical | No |
| F25 | NPHP1 | missense | HET | p.Leu89Ser | | Clinical | No |
| F25 | PAX3 | missense | HET | p.Lys175Asn | 0,00359425 | Clinical | No |
| F25 | PAK1IP1 | missense | HET | p.Lys164Glu | | Clinical | No |
| F25 | DLC1 | missense | HET | p.Arg351Gln | 0,00419329 | Clinical | No |
| F25 | L1CAM | missense | HET | p.Val47Phe | 0,000688 | Clinical | No |
| F26 | PTCH1 | missense | HET | p.Pro1211Ser | 0,000508 | Clinical;WGCNA | Yes |
| F26 | SYDE1 | missense | HET | p.Arg537His | 0,000199681 | WGCNA | No |
| F26 | PABPC1L | missense | HET | p.Ala185Val | 0,0049 | WGCNA | No |
| F26 | KIF20A | missense | HET | p.Ser44Phe | 0,0035 | WGCNA | No |
| F26 | PRPH2 | missense | HET | p.Ser27Phe | 0,00001102 | WGCNA | No |
| F26 | COL2A1 | missense | HET | p.Pro365Ser | 0,001511 | Clinical | Yes |
| F26 | GSC | missense | HET | p.Leu38Met | 0,002092 | Clinical | No |
| F26 | MED1 | missense | HET | p.Asn295Ser | 0,0001 | Clinical | No |
| F26 | FAT1 | missense | HET | p.Val3629Leu | | Clinical | Yes |
| F27 | PTPRT | missense | HET | p.Arg1403His | 0,0075 | WGCNA | No |
| F27 | NPHP4 | missense | HET | p.Arg961His | 0,0032 | Clinical | No |
| F27 | MED17 | missense | HET | p.Leu243Phe | 0,0001 | Clinical | No |
| F27 | CRIP1 | missense | HET | p.Gly30Ala | 0,0001 | Clinical | No |
| F27 | DLG1 | missense | HET | p.Asp267Gly | 0,0004 | Clinical | No |
| F27 | KIF2A | missense | HET | p.Gly562Cys | | Clinical | No |

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|----|----------|--------------|-----|-------------------------|-------------|----------------|-----|
| F3 | SHH | missense | HET | p.Asp171His | | Clinical;WGCNA | Yes |
| F3 | VCL | missense | HET | p.Glu950Lys | 0,0000323 | WGCNA | No |
| F3 | MCM3 | stopgain | HET | p.Glu17Ter | 0,0016 | WGCNA | No |
| F3 | APAF1 | missense | HET | p.Glu777Lys | 0,0036869 | Clinical | No |
| F3 | FOXJ1 | missense | HET | p.Arg204Gln | 0,0002 | Clinical | No |
| F3 | MAN2B1 | splicing | HET | c.1416+5G>T | 0,0002 | Clinical | No |
| F3 | FAT1 | missense | HET | p.Tyr1770Cys | 0,0001 | Clinical | Yes |
| F3 | NDST1 | missense | HET | p.Arg80His | 0,0025 | Clinical | Yes |
| F4 | SHH | missense | HET | p.Phe241Val | | Clinical;WGCNA | Yes |
| F4 | WNT4 | missense | HET | p.Val204Met | 0,000004148 | WGCNA | No |
| F4 | SFMBT2 | missense | HET | p.Arg782His | 0,0074 | WGCNA | No |
| F4 | SCUBE2 | missense | HET | p.Thr285Met | 0,00815 | WGCNA | No |
| F4 | MACF1 | missense | HET | p.Arg2266Gly | 0,0004 | Clinical | No |
| F4 | STK36 | missense | HET | p.Arg497Gly | 0,002518 | Clinical | No |
| F4 | BOC | missense | HET | p.Val861Ile | 0,0002 | Clinical | Yes |
| F5 | SIX3 | missense | HET | p.Thr202Ile | | Clinical;WGCNA | Yes |
| F5 | DST | missense | HET | p.Pro2488His | 0,0099 | Clinical | No |
| F6 | FRMD4A | missense | HET | p.Thr846Met | 0,0004 | Clinical;WGCNA | No |
| F6 | KIF7 | missense | HET | p.Arg851His | 0,00005879 | Clinical;WGCNA | No |
| F6 | SIX3 | frameshift c | HET | p.Lys209NA | | Clinical;WGCNA | Yes |
| F6 | TMEM138 | missense | HET | p.Leu116Phe | 0,000008121 | WGCNA | No |
| F6 | GLT1D1 | missense | HET | p.Leu70Phe | 0,000199681 | WGCNA | No |
| F6 | CNTNAP4 | missense | HET | p.Ile337Val | 0,000504 | WGCNA | No |
| F6 | EPG5 | missense | HET | p.Gly1094Ser | 0,000399361 | Clinical | No |
| F6 | MECOM | missense | HET | p.Phe823Leu | 0,00003346 | Clinical | No |
| F6 | CTNNB1 | missense | HET | p.Thr418Ile | | Clinical | No |
| F6 | FIG4 | missense | HET | p.Arg88Gln | | Clinical | No |
| F6 | HOXA1 | frameshift c | HET | p.Gly324NA | | Clinical | No |
| F6 | NR6A1 | missense | HET | p.Lys479Gln | | Clinical | No |
| F7 | SIX3 | missense | HET | p.Phe254Val | | Clinical;WGCNA | Yes |
| F7 | ADARB2 | missense | HET | p.Gly418Ser | 0,0075 | WGCNA | No |
| F7 | FOXN4 | missense | HET | p.Arg316His | 0,0086 | WGCNA | No |
| F7 | CTCF | missense | HET | p.Pro643Ser | 0,0044 | Clinical | No |
| F7 | ACVR2A | missense | HET | p.Phe117Ile | 0,0014 | Clinical | No |
| F7 | SPRY4 | missense | HET | p.Ser241Tyr | 0,005 | Clinical | Yes |
| F8 | TGIF1 | missense | HET | p.Ala190Val | | Clinical;WGCNA | Yes |
| F8 | TTI1 | missense | HET | p.Ala162Thr | 0,0032 | WGCNA | No |
| F8 | ASPM | missense | HET | p.Met1983Leu | 0,0013454 | Clinical | No |
| F8 | SLK | missense | HET | p.Lys1176Thr | 0,0005 | Clinical | No |
| F8 | KMT2A | missense | HET | p.Tyr1205His | 0,000004063 | Clinical | No |
| F8 | PAH | missense | HET | p.Asp143Gly | 0,0000065 | Clinical | No |
| F8 | PRICKLE1 | missense | HET | p.Cys126Tyr | | Clinical | No |
| F8 | TRIP11 | frameshift s | HET | c.2692_2698GTATCTTATCTC | | Clinical | No |
| F8 | FGFR3 | missense | HET | p.Arg86His | 0,000008392 | Clinical | No |
| F8 | GLDC | missense | HET | p.Cys291Gly | 0,007583 | Clinical | No |
| F9 | TGIF1 | stopgain | HET | p.Tyr188Ter | | Clinical;WGCNA | Yes |
| F9 | TIMELESS | missense | HET | p.Asp1174Asn | 0,00002204 | WGCNA | No |
| F9 | ZNF521 | missense | HOM | p.Arg937Gly | 0,001007 | WGCNA | No |
| F9 | MRPS9 | missense | HET | p.Glu264Lys | 0,0047 | WGCNA | No |
| F9 | NFKB1 | missense | HET | p.Arg579Lys | 0,008056 | Clinical | No |
| F9 | ENG | missense | HET | p.Pro443Thr | | Clinical | No |

Table S7. Pathways enriched in candidate variants

For GeneOntology (GO), only the biological processes (BP) with minimum term depth of 5 are reported.

| p-value | term ID | term name | term depth |
|-------------------|---------------------|--|------------|
| 4,62E-13 | GO:0007224 | smoothened signaling pathway | 6 |
| 6,05E-12 | GO:0048706 | embryonic skeletal system development | 6 |
| 5,77E-11 | GO:0048705 | skeletal system morphogenesis | 6 |
| 4,6E-10 | GO:0072175 | epithelial tube formation | 6 |
| 6,39E-10 | GO:0060831 | smoothened signaling pathway involved in dorsal/ventral neural tube patterning | 6 |
| 2,93E-09 | GO:0001838 | embryonic epithelial tube formation | 7 |
| 8,29E-09 | GO:0001843 | neural tube closure | 7 |
| 9,61E-09 | GO:0060606 | tube closure | 6 |
| 1,48E-08 | GO:0048704 | embryonic skeletal system morphogenesis | 6 |
| 2,25E-08 | GO:0014020 | primary neural tube formation | 6 |
| 6,44E-08 | GO:0030326 | embryonic limb morphogenesis | 6 |
| 1,21E-07 | GO:0008589 | regulation of smoothened signaling pathway | 6 |
| 2,05E-07 | GO:0043010 | camera-type eye development | 7 |
| 3,34E-07 | GO:0001654 | eye development | 6 |
| 0,00000148 | REAC:5617833 | Assembly of the primary cilium | 2 |
| 0,00000212 | GO:0060271 | cilium assembly | 6 |
| 0,0000055 | GO:0043583 | ear development | 6 |
| 0,0000173 | GO:0016055 | Wnt signaling pathway | 7 |
| 0,0000239 | GO:0072006 | nephron development | 6 |
| 0,0000279 | REAC:5358351 | Signaling by Hedgehog | 1 |
| 0,000028 | GO:1905114 | cell surface receptor signaling pathway involved in cell-cell signaling | 6 |
| 0,0000528 | GO:2000027 | regulation of organ morphogenesis | 6 |
| 0,0000816 | GO:0048699 | generation of neurons | 6 |
| 0,0000912 | GO:0048839 | inner ear development | 7 |
| 0,000107 | KEGG:04340 | Hedgehog signaling pathway | 1 |
| 0,000119 | GO:0072163 | mesonephric epithelium development | 7 |
| 0,000146 | REAC:1852241 | Organelle biogenesis and maintenance | 1 |
| 0,000175 | GO:0001823 | mesonephros development | 6 |
| 0,000263 | GO:0030111 | regulation of Wnt signaling pathway | 6 |
| 0,000278 | GO:0072009 | nephron epithelium development | 7 |
| 0,000307 | GO:0030182 | neuron differentiation | 7 |
| 0,000322 | REAC:5635851 | GLI proteins bind promoters of Hh responsive genes to promote transcription | 1 |
| 0,000543 | GO:0001656 | metanephros development | 6 |
| 0,000819 | KEGG:05217 | Basal cell carcinoma | 1 |
| 0,000859 | GO:0048701 | embryonic cranial skeleton morphogenesis | 7 |
| 0,000884 | GO:0060993 | kidney morphogenesis | 6 |
| 0,00118 | REAC:5610787 | Hedgehog 'off' state | 2 |
| 0,00181 | GO:0072078 | nephron tubule morphogenesis | 6 |
| 0,00223 | GO:0072088 | nephron epithelium morphogenesis | 8 |
| 0,00274 | GO:0072028 | nephron morphogenesis | 7 |
| 0,00286 | GO:0072073 | kidney epithelium development | 6 |
| 0,00306 | GO:0060041 | retina development in camera-type eye | 8 |
| 0,00313 | GO:0007405 | neuroblast proliferation | 7 |
| 0,00329 | KEGG:05200 | Pathways in cancer | 1 |
| 0,0041 | GO:0090596 | sensory organ morphogenesis | 6 |
| 0,00436 | REAC:176974 | Unwinding of DNA | 1 |
| 0,00538 | GO:0060840 | artery development | 6 |
| 0,00742 | GO:0042471 | ear morphogenesis | 6 |
| 0,00864 | REAC:5620912 | Anchoring of the basal body to the plasma membrane | 3 |
| 0,0101 | GO:0030900 | forebrain development | 6 |
| 0,0102 | GO:0060675 | ureteric bud morphogenesis | 6 |
| 0,0148 | GO:0045879 | negative regulation of smoothened signaling pathway | 6 |
| 0,0198 | GO:0021517 | ventral spinal cord development | 6 |
| 0,0267 | GO:0045880 | positive regulation of smoothened signaling pathway | 7 |
| 0,046 | REAC:5632681 | Ligand-receptor interactions | 1 |
| 0,0461 | GO:0061005 | cell differentiation involved in kidney development | 6 |
| 0,0461 | GO:0021515 | cell differentiation in spinal cord | 6 |

| Gene | N candidate variants | Families | Variants |
|----------|----------------------|--------------------|--|
| B9D1 | 1 | F21 | NM_015681:exon6:c.422G>A:p.R141Q |
| BOC | 2 | F4; F22 | NM_033254:exon16:c.2581G>A:p.V861I NM_033254:exon7:c.932C>T:p.A311V |
| COL2A1 | 2 | F16;F26 | NM_033150:exon5:c.203G>A:p.R68H NM_033150:exon20:c.1093C>T:p.P365S |
| FAT1 | 4 | F3; F16; F23 ; F26 | NM_005245:exon10:c.5309A>G:p.Y1770C NM_005245:exon2:c.2563G>A:p.G855R NM_005245:exon18:c.10375G>A:p.V3459M NM_005245:exon19:c.10885G>T:p.V3629L |
| GLI2 | 1 | F19 | NM_005270:exon6:c.968T>C:p.F323S |
| HIC1 | 1 | F22 | NM_006497:exon2:c.1533G>C:p.W511C |
| IFT172 | 1 | F18 | NM_015662:exon27:c.2882C>T:p.A961V |
| LRP2 | 2 | F11 ; F23 | NM_004525:exon49:c.9265G>A:p.E3089K NM_004525:exon50:c.9613A>G:p.N3205D |
| MKS1 | 1 | F11 | NM_017777:exon8:c.763G>C:p.G255R |
| NDST1 | 2 | F3;F16 | NM_001543:exon2:c.239G>A:p.R80H NM_001543:exon2:c.394C>T:p.R132C |
| PTCH1 | 1 | F26 | NM_000264:exon22:c.3631C>T:p.P1211S |
| SHH | 4 | F1; F3;F4;F11 | NM_000193:exon3:c.1040C>G:p.P347R NM_000193:exon2:c.305G>A:p.C102Y NM_000193:exon3:c.721T>G:p.F241V NM_000193:exon2:c.511G>C:p.D171H |
| SIX3 | 4 | F5;F6;F7:F10 | NM_005413:exon1:c.605C>T:p.T202I NM_005413:exon1:c.626delA:p.K209fs NM_005413:exon1:c.760T>G:p.F254V NM_005413:exon1:c.319C>T:p.R107W |
| SPRY4 | 1 | F7 | NM_030964:exon3:c.722C>A:p.S241Y |
| TGIF1 | 2 | F8;F9 | NM_170695:exon2:c.569C>T:p.A190V NM_170695:exon2:c.564C>G:p.Y188X |
| ZIC2 | 2 | F17;F19 | NM_007129.3:exon3:c.1382_1411dup:p.Ala461_Ala470dup NM_007129.3:exon3:c.1392_1403dup:p.Ala467_Ala470dup |
| TRAPPC10 | 1 | F17 | NM_003274:exon17:c.2570A>G:p.Q857R |

Table S8. Exonic variants in KO HPE genes

Table S9. Oligogenic events found in GoNL control cohort

| Family | Gene | Variant | Type | Inheritance | Frequency |
|--------|--------|----------|----------|-------------|------------|
| GoNL1 | B9D1 | p.S51P | missense | Maternal | 0,0000906 |
| | FAT1 | p.Y1250C | missense | Paternal | 0,0024 |
| GoNL2 | SCUBE2 | p.T661N | missense | Paternal | 0,0001229 |
| | PTCH1 | p.G891S | missense | Maternal | 0,00815 |
| GoNL3 | SCUBE2 | p.T285M | missense | Maternal | 0,00815 |
| | LRP2 | p.R2617Q | missense | Maternal | 0,00002204 |
| | CELSR1 | p.R2367W | missense | Paternal | 0,00019968 |
| | PTCH1 | p.Y373F | missense | Paternal | 0,0000065 |