**Additional Table 6**: Top 5 candidate genes for each of the 65 leaf nodes showed in the additional file 8. See the main manuscript for more details about the selection of the candidate genes for each HPO leaf term.

| HPO ID | HPO term | Entrez Gene ID | Gene Symbol |
|---|---|---|---|
| HP:0004942 | Aortic aneurysm | 72 | ACTG2 |
| HP:0100760 | Clubbing of toes | 7516 | XRCC2 |
| HP:0000114 | Proximal tubulopathy | 1892 | ECHS1 |
| HP:0003557 | Increased variability in muscle fiber diameter | 8516 | ITGA8 |
| | | 3694 | ITGB6 |
| HP:0002040 | Esophageal varix | 85440 | DOCK7 |
| | | 7049 | TGFBR3 |
| HP:0002913 | Myoglobinuria | 1962 | EHHADH |
| | | 1892 | ECHS1 |
| HP:0003642 | Type I transferrin isoform profile | 201595 | STT3B |
| | | 1109 | AKR1C4 |
| | | 199857 | ALG14 |
| HP:0006965 | Acute necrotizing encephalopathy | 4697 | NDUFA4 |
| | | 4539 | MT-ND4L |
| HP:0008316 | Abnormal mitochondria in muscle tissue | 4697 | NDUFA4 |
| | | 51204 | TACO1 |
| | | 1352 | COX10 |
| | | 4539 | MT-ND4L |
| | | 4538 | MT-ND4 |
| HP:0004339 | Abnormality of sulfur amino acid metabolism | 1757 | SARDH |
| | | 55811 | ADCY10 |
| | | 1137 | CHRNA4 |
| | | 271 | AMPD2 |
| | | 272 | AMPD3 |
| HP:0004944 | Cerebral aneurysm | 1757 | SARDH |
| | | 55811 | ADCY10 |
| | | 91137 | SLC25A46 |
| | | 271 | AMPD2 |
| | | 272 | AMPD3 |
| HP:0002725 | Systemic lupus erythematosus | 629 | CFB |
| HP:0001659 | Aortic regurgitation | 27229 | TUBGCP4 |
| | | 2239 | GPC4 |
| | | 3340 | NDST1 |
| | | 57822 | GRHL3 |
| | | 5378 | PMS1 |
| HP:0004353 | Abnormality of pyrimidine metabolism | 790 | CAD |
| | | 7516 | XRCC2 |
| | | 580 | BARD1 |
| | | 10747 | MASP2 |
| | | 58484 | NLRC4 |
| HP:0000831 | Insulin-resistant diabetes mellitus | 3991 | LIPE |
| | | 3764 | KCNJ8 |
| | | 5260 | PHKG1 |
| HP:0001019 | Erythroderma | 3149 | HMGB3 |
| | | 7516 | XRCC2 |
| | | 5657 | PRTN3 |
| | | 28952 | CCDC22 |
| | | 2224 | FDPS |

| HPO ID | HPO term | Entrez Gene ID | Gene Symbol |
|---|---|---|---|
| HP:0002223 | Absent eyebrow | 9463 | PICK1 |
| | | 389549 | FEZF1 |
| HP:0004481 | Progressive macrocephaly | 4697 | NDUFA4 |
| | | 4538 | MT-ND4 |
| | | 54539 | NDUFB11 |
| | | 4539 | MT-ND4L |
| HP:0010459 | True hermaphroditism | 54585 | LZTFL1 |
| | | 9786 | KIAA0586 |
| | | 11020 | IFT27 |
| | | 57822 | GRHL3 |
| | | 26281 | FGF20 |
| HP:0003521 | Disproportionate short-trunk short stature | 54567 | DLL4 |
| | | 3371 | TNC |
| | | 9096 | TBX18 |
| HP:0010996 | Abnormality of monocarboxylic acid metabolism | 790 | CAD |
| HP:0000991 | Xanthomatosis | 9971 | NR1H4 |
| | | 4047 | LSS |
| | | 3991 | LIPE |
| | | 80347 | COASY |
| | | 4744 | NEFH |
| HP:0003645 | Prolonged partial thromboplastin time | 2266 | FGG |
| | | 3026 | HABP2 |
| | | 10747 | MASP2 |
| | | 733 | C8G |
| | | 199857 | ALG14 |
| HP:0009161 | Aplasia/Hypoplasia of the middle phalanx of the 5th finger | 26585 | GREM1 |
| | | 2535 | FZD2 |
| | | 57216 | VANGL2 |
| HP:0003076 | Glycosuria | 140628 | GATA5 |
| | | 388753 | COA6 |
| HP:0002304 | Akinesia | 1139 | CHRNA7 |
| | | 9037 | SEMA5A |
| | | 54567 | DLL4 |
| | | 8506 | CNTNAP1 |
| | | 3763 | KCNJ6 |
| HP:0003974 | Absent radius | 6909 | TBX2 |
| | | 26585 | GREM1 |
| | | 7468 | WHSC1 |
| | | 23129 | PLXND1 |
| | | 6997 | TDGF1 |
| HP:0003215 | Dicarboxylic aciduria | 1962 | EHHADH |
| | | 1892 | ECHS1 |
| | | 3417 | IDH1 |
| | | 4329 | ALDH6A1 |
| | | 126129 | CPT1C |
| HP:0002085 | Occipital encephalocele | 284217 | LAMA1 |
| | | 1109 | AKR1C4 |
| | | 85301 | COL27A1 |
| | | 8516 | ITGA8 |
| | | 3694 | ITGB6 |
| HP:0000677 | Oligodontia | 25885 | POLR1A |
| | | 2535 | FZD2 |
| | | 7161 | TP73 |
| | | 7049 | TGFBR3 |

| HPO ID | HPO term | Entrez Gene ID | Gene Symbol |
|---|---|---|---|
| | | 28952 | CCDC22 |
| HP:0001218 | Autoamputation | 4916 | NTRK3 |
| | | 51164 | DCTN4 |
| | | 10715 | CERS1 |
| | | 127833 | SYT2 |
| | | 10087 | COL4A3BP |
| HP:0003254 | Abnormality of DNA repair | 7516 | XRCC2 |
| | | 4437 | MSH3 |
| | | 7469 | NELFA |
| | | 580 | BARD1 |
| | | 79991 | STN1 |
| HP:0100864 | Short femoral neck | 11020 | IFT27 |
| | | 2239 | GPC4 |
| | | 283375 | SLC39A5 |
| | | 2817 | GPC1 |
| | | 22978 | NT5C2 |
| HP:0009027 | Foot dorsiflexor weakness | 56776 | FMN2 |
| | | 4744 | NEFH |
| | | 5859 | QARS |
| HP:0002905 | Hyperphosphatemia | 844 | CASQ1 |
| | | 26281 | FGF20 |
| | | 6809 | STX3 |
| | | 80055 | PGAP1 |
| HP:0002839 | Urinary bladder sphincter dysfunction | 25894 | PLEKHG4 |
| | | 81570 | CLPB |
| | | 6327 | SCN2B |
| | | 23025 | UNC13A |
| | | 27445 | PCLO |
| HP:0009617 | Abnormality of the distal phalanx of the thumb | 2619 | GAS1 |
| | | 26585 | GREM1 |
| | | 57216 | VANGL2 |
| | | 22978 | NT5C2 |
| | | 84976 | DISP1 |
| HP:0002097 | Emphysema | 5450 | POU2AF1 |
| | | 3105 | HLA-A |
| | | 7049 | TGFBR3 |
| HP:0100631 | Neoplasm of the adrenal gland | 1021 | CDK6 |
| | | 7468 | WHSC1 |
| | | 3481 | IGF2 |
| HP:0000073 | Ureteral duplication | 9091 | PIGQ |
| | | 7161 | TP73 |
| | | 126129 | CPT1C |
| | | 1962 | EHHADH |
| | | 284098 | PIGW |
| HP:0002181 | Cerebral edema | 790 | CAD |
| | | 4697 | NDUFA4 |
| | | 4538 | MT-ND4 |
| | | 4539 | MT-ND4L |
| | | 1892 | ECHS1 |
| HP:0002557 | Hypoplastic nipples | 9091 | PIGQ |
| | | 6909 | TBX2 |
| | | 4040 | LRP6 |
| | | 284098 | PIGW |
| | | 120 | ADD3 |

| HPO ID | HPO term | Entrez Gene ID | Gene Symbol |
|---|---|---|---|
| HP:0004359 | Abnormality of fatty-acid metabolism | 1962 | EHHADH |
| | | 1892 | ECHS1 |
| | | 126129 | CPT1C |
| | | 4329 | CPT1C |
| | | 57468 | SLC12A5 |
| HP:0009720 | Adenoma sebaceum | 2475 | MTOR |
| | | 4437 | MSH3 |
| | | 2272 | FHIT |
| | | 5293 | PIK3CD |
| | | 5378 | PMS1 |
| HP:0003233 | Hypoalphalipoproteinemia | 9971 | NR1H4 |
| | | 3991 | LIPE |
| | | 5260 | PHKG1 |
| | | 27229 | TUBGCP4 |
| | | 5446 | PON3 |
| HP:0010980 | Hyperlipoproteinemia | 9971 | NR1H4 |
| | | 5446 | PON3 |
| | | 8694 | DGAT1 |
| | | 5445 | PON2 |
| HP:0003002 | Breast carcinoma | 4437 | MSH3 |
| HP:0001480 | Freckling | 4437 | MSH3 |
| | | 5378 | PMS1 |
| | | 7161 | TP73 |
| | | 1021 | CDK6 |
| | | 1031 | CDKN2C |
| HP:0005293 | Venous insufficiency | 54567 | DLL4 |
| | | 1303 | COL12A1 |
| | | 1399 | CRKL |
| | | 3371 | TNC |
| | | 6678 | SPARC |
| HP:0006443 | Patellar aplasia | 7994 | KAT6A |
| HP:0002025 | Anal stenosis | 6909 | TBX2 |
| | | 80055 | PGAP1 |
| HP:0009888 | Abnormality of secondary sexual hair | 6909 | TBX2 |
| | | 7161 | TP73 |
| | | 4744 | NEFH |
| | | 4047 | LSS |
| | | 6862 | T |
| HP:0003311 | Hypoplasia of the odontoid process | 3371 | TNC |
| | | 4774 | NFIA |
| | | 22926 | ATF6 |
| | | 8239 | USP9X |
| | | 26137 | ZBTB20 |
| HP:0004311 | Abnormality of macrophages | 2214 | FCGR3A |
| | | 330 | BIRC3 |
| | | 4671 | NAIP |
| | | 58484 | NLRC4 |
| | | 6809 | STX3 |
| HP:0001974 | Leukocytosis | 3551 | IKBKB |
| | | 3932 | LCK |
| | | 5657 | PRTN3 |
| | | 58484 | NLRC4 |
| | | 330 | BIRC3 |

| HPO ID | HPO term | Entrez Gene ID | Gene Symbol |
|---|---|---|---|
| HP:0100578 | Lipoatrophy | 3991 | LIPE |
| | | 23022 | PALLD |
| | | 844 | CASQ1 |
| | | 29119 | CTNNA3 |
| | | 6006 | RHCE |
| HP:0000625 | Cleft eyelid | 23129 | PLXND1 |
| | | 246243 | RNASEH1 |
| | | 9463 | PICK1 |
| | | 25885 | POLR1A |
| | | 10512 | SEMA3C |
| HP:0007361 | Abnormality of the pons | 5297 | PI4KA |
| | | 9091 | PIGQ |
| | | 284098 | PIGW |
| | | 80055 | PGAP1 |
| | | 163786 | SASS6 |
| HP:0002667 | Nephroblastoma (Wilms tumor) | 580 | BARD1 |
| HP:0002612 | Congenital hepatic fibrosis | 11020 | CYP4B1 |
| | | 54585 | LZTFL1 |
| | | 85440 | 85440 |
| | | 51164 | DCTN4 |
| | | 55690 | PACS1 |
| HP:0002967 | Cubitus valgus | 26585 | GREM1 |
| | | 26281 | FGF20 |
| HP:0010286 | Abnormality of the salivary glands | 4437 | MSH3 |
| | | 7161 | TP73 |
| | | 5378 | PMS1 |
| | | 2272 | FHIT |
| | | 3417 | IDH1 |
| HP:0010675 | Abnormal foot bone ossification | 4047 | LSS |
| | | 3149 | HMGB3 |
| | | 440275 | EIF2AK4 |
| | | 389549 | FEZF1 |
| | | 22926 | ATF6 |
| HP:0010899 | Abnormality of aspartate family amino acid metabolism | 1757 | SARDH |
| | | 55811 | ADCY10 |
| | | 271 | AMPD2 |
| | | 272 | AMPD3 |
| | | 91137 | SLC25A46 |
| HP:0002922 | Increased CSF protein | 57468 | SLC12A5 |
| | | 3106 | HLA-B |
| | | 3105 | HLA-A |
| | | 4179 | CD46 |
| | | 283375 | SLC39A5 |