**Table S1. Clinical characteristics and hemodynamic parameters of child- vs adult-onset PAH cases\* at diagnosis.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Age at dx**  **(y)** | **F:M ratio** | **MPAP**  **(mm Hg)** | **MCWP**  **(mm Hg)** | **CO, Fisk (L/min)** | **PVR**  **(Woods units)** |
| Child (n=226) | 7.7 ± 5.4  (226) | 1.65:1 | 55.1 ± 18.6 (225) | 9.0 ± 3.0  (220) | 3.2 ± 1.6 (168) | 18.1 ± 11.7 (168) |
| Adult (n=2345) | 51.6 ± 14.7 (2345) | 4.02:1 | 49.6 ± 13.9 (2293) | 10.2 ± 4.2  (2231) | 4.6 ± 1.7 (1630) | 10.0 ± 5.9 (1630) |
| P-value | <0.0001\*\* | <0.0001\*\*\* | <0.0001\*\* | <0.0001\*\* | <0.0001\*\* | <0.0001\*\* |

\*Data are from the PAH Biobank (n=2,572 cases). Child-onset, <18 years of age at diagnosis.

Abbreviations: dx, diagnosis; F:M, female:male; MPAP, mean pulmonary artery pressure; MCWP, mean capillary wedge pressure; CO, cardiac output; PVR, pulmonary vascular resistance.

\*\*Student’s t-test, 2-tailed

\*\*\*Fisher’s exact test, 2-tailed

**Table S2. Similar frequency of rare synonymous variants among European PAH cases and controls.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Mutation type\*** | **PAH cases**  **(n = 2789)** | **Controls**  **(n = 18819)** | **Enrichment** | **P-value** |
| SYN, all | 116982 | 792028 | 1.0 | 0.28 |
| SYN, predicted cryptic splice site | 795 | 5652 | 0.95 | 0.18 |
| MIS | 236401 | 1598016 | 1.0 | 0.41 |
| Indel | 12898 | 88577 | 0.98 | 0.06 |

\*SYN, synonymous; MIS, missense; Indel, insertion/deletion.

**Table S3. Rare predicted deleterious *KDR* missense variants\* among 4,175 PAH cases\*\*.**

| **Case ID** | **Sex** | **Agedx** | **PAH subclass** | **Ancestry** | **Gene \*\*\*** | **Exon** | **Nucleotide change** | **Amino acid change** | **Variant type** | **MAF (gnomAD exomes)** | **CADD score** | **Revel** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 06-049 | F | 53 | APAH-CHD | EUR | *KDR* | 23 | c.3089C>G | p.(Ala1030Gly) | D-Mis | --- | 29.3 | 0.87 |
| 22-037 | F | 43 | IPAH | EUR | *KDR* | 23 | c.3175T>C | p.(Tyr1059His) | D-Mis | --- | 29.4 | 0.90 |
| E011155 | F | 74 | IPAH | EUR | *KDR* | 25 | c.3311C>A | p.(Ser1104Tyr) | D-Mis | 3.61E-05 | 29.5 | 0.86 |
| 15-032 | M | 25 | IPAH | EUR | *KDR* | 26 | c.3439C>T | p.(Pro1147Ser) | D-Mis | 9.16E-05 | 25.2 | 0.88 |
| E013241 | F | 73 | IPAH | EUR | *KDR* | 26 | c.3439C>T | p.(Pro1147Ser) | D-Mis | 9.16E-05 | 25.2 | 0.88 |
| W000314 | M | 75 | IPAH | EUR | *KDR* | 26 | c.3439C>T | p.(Pro1147Ser) | D-Mis | 9.16E-05 | 25.2 | 0.88 |

\*Rare, deleterious variants defined as gnomAD\_exome\_ALL AF ≤1.00E-04 and LGD or missense with variable REVEL cut-off (*KDR* 0.86).

\*\*Cases are heterozygous for the indicated variants.

\*\*\*Transcript: *KDR* NM\_002253.3

**Table S4. Characteristics of longest shared haplotypes among PAH cases with recurrent variants in new candidate risk genes shows that the haplotype lengths are small and therefore do not support a common ancestor.** Genomic position are data based on human assembly GRCh38/hg38.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Gene | Variant position | Haplotype position | Haplotype length | Variant carrier IDs | Frequency in EUR cases | Frequency in EUR controls |
| *KDR* | 4:55088939 | 4:55079914-55088939 | 9025 | 15-032 E013241 W000314 | 2767/2790 | 10996/11088 |
| *KDR* | 4:55092622 | 4:55080187-55092622 | 12435 | W000274 27-015 | 2247/2790 | 8958/11088 |
| *FBLN2* | 3:13630815 | 3:13630900-13613921 | 16979 | 23-001 29-031 34-005 W000210 | 1367/2790 | 5624/11088 |
| *PDGFD* | 11:103926920 | 11:103909727-104000027 | 90300 | E000820 E010173 | 1585/2790 | 5703/11088 |
| *PDGFD* | 11:103996172 | 11:103909727-104038007 | 128280 | E012465 E014342 | 129/2790 | 501/11088 |

**STable S5. Burden of *de novo* variants in pediatric-onset IPAH (n = 66 child-parent trios).**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Variant type\*** | **Observed** | **Expected by chance** | **Enrichment** | **P-value** | **Estimated # of risk variants** |
| All genes  (18939 genes) | SYN | 18 | 20.4 | 0.88 | 0.74 | N/A |
| LGD | 9 | 6.3 | 1.43 | 0.31 | N/A |
| MIS | 53 | 45.1 | 1.18 | 0.23 | N/A |
| D-Mis | 17 | 9.2 | 1.84 | 0.019 | N/A |
| LGD + D-Mis | 26 | 15.4 | 1.69 | 0.014 | 11 |
| HLE or HHE\*\*  (5756 genes) | SYN | 10 | 7.5 | 1.34 | 0.35 | N/A |
| LGD | 6 | 2.5 | **2.4** | **0.04** | N/A |
| MIS | 23 | 16.9 | 1.36 | 0.14 | N/A |
| D-Mis | 11 | 3.9 | **2.85** | **0.002** | **6** |
| LGD + D-Mis | 17 | 6.3 | **2.7** | **0.0003** | **11** |

\* SYN, synonymous; LGD, likely gene-disrupting; MIS, missense; D-Mis, deleterious missense based on REVEL >0.5.

\*\*HLE, high lung expression (murine E16.5 lung stromal cells); HHE, high heart expression (murine E14.5 heart).

**Table S6**. **Rare *de novo* LGD or D-Mis risk variants identified in 124 pediatric-onset PAH trios.**

| **Gene symbol** | **Gene name** | **Transcript** | **Variant type** | **Nucleotide change** | **Protein change** | **REVEL score** | **AF gnomAD exomes** | **pLI** | **Lung expression (% rank)** | **Heart expression**  **(% rank)** | **Gene-level associated medical condition(s)**  **(OMIM #, mode of inheritance)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *ACVRL1* | Activin A receptor, type II like 1 | NM\_001077401.2 | D-Mis | c.955G>C | p.(Gly319Arg) | 0.83 | . | 0.01 | 88.70 | 51.42 | Hereditary hemorrhagic telangiectasia  (600376, AD) |
| *ALDH9A1* | Aldehyde dehydrogenase family 9 subfamily A member 1 | NM\_000696.3 | D-Mis | c.545A>G | p.(Tyr182Cys) | 0.88 | 2.44E-05 | 0.00 | 57.11 | 59.25 |  |
| *AMOT* | Angiomotin | NM\_001113490.1 | LGD | c.957delC | p.(.Leu320Cysfs\*55) | . | . | 0.21 | 67.96 | 94.51 |  |
| *ATP6V0A2* | ATPase, H+ transporting, lysosomal, VO subunit A2 | NM\_012463.4 | D-Mis | c.1184A>G | p.(Asn395Ser) | 0.82 | . | 0.00 | 70.43 | 61.38 |  |
| *BMPR2* | Bone morphogenetic protein receptor, type II | NM\_001204.7 | D-Mis | c.1471C>T | p.(Arg491Trp) | . | . | 1.00 | 86.44 | 42.01 | PAH (178600, AD)  PVOD (265450, AD) |
| *BMPR2* | Bone morphogenetic protein receptor, type II | NM\_001204.7 | LGD | c.418+1G>A | p.(=) | 0.96 | . | 1.00 | 86.44 | 42.01 | PAH (178600, AD)  PVOD (265450, AD) |
| *BRWD3* | Bromodomain- and WD repeat-containing protein 3 | NM\_153252.5 | D-Mis | c.1087G>T | p.(Asp363Tyr) | 0.58 | . | 1.00 | 61.56 | 47.34 | Mental retardation (300659, XLR) |
| *CHRNA4* | Cholinergic receptor, neuronal nicotinic, alpha polypeptide 4 | NM\_000744.7 | D-Mis | c.721C>T | p.(Arg241Trp) | 0.92 | . | 0.02 | 29.90 | 18.42 | Epilepsy (600513, AD) |
| *CNTN4* | Contactin 4 | NM\_001206956.1 | D-Mis | c.722A>G | p.(His241Arg) | 0.66 | . | 1.00 | 42.65 | 23.58 |  |
| *CSNK2A2* | Casein kinase II, alpha 2 | NM\_001896.4 | D-Mis | c.551A>T | p.(His184Leu) | 0.50 | . | 1.00 | 54.88 | 77.13 |  |
| *DNMT3A* | DNA methyltransferase 3A | NM\_153759.3 | D-Mis | c.473T>C | p.(Leu158Pro) | 0.78 | . | 0.00 | 98.27 | 96.73 | Acute myeloid leukemia (601626)  Heyn-Sproul\_Jackson syndrome (618724, AD), Tatton-Brown-Rahman syndrome (615879, AD) |
| *EMC8* | Endoplasmic reticulum membrane protein complex subunit 8 | NM\_006067.5 | LGD | c.633G>C | p.(\*211Tyrext\*15) | . | 4.06E-06 | 0.26 | 72.18 | 66.27 |  |
| *EMID1* | Emi domain-containing protein 1 | NM\_001267895.2 | D-Mis | c.1114G>A | p.(Gly372Arg) | 0.77 | . | 0.04 | 55.13 | 36.41 |  |
| *GAMT* | Guanidinoacetate methyltransferase | NM\_000156.6 | D-Mis | c.490G>T | p.(Gly164Cys) | 0.92 | . | 0.00 | 42.58 | 65.43 | Cerebral creatinine deficiency syndrome 2 (612736, AR) |
| *GDPD4* | Glycerophosphodiester phosphodiesterase domain containing 4 | NM\_182833.3 | LGD | c.1561T>A | p.(\*521Lysext\*64) | . | . | 0.00 | 9.53 | 0.00 |  |
| *GRHL2* | Grainyhead-like transcription factor 2 | NM\_001330593.2 | D-Mis | c.749C>T | p.(Pro250Leu) | 0.62 | . | 1.00 | 35.55 | 28.19 | Corneal dystrophy (618031, AD)  Deafness (608641, AD)  Ectodermal dysplasia/short stature syndrome (616029, AR) |
| *HNRNPF* | Heterogeneous nuclear ribonucleoprotein F | NM\_001098208.1 | LGD | c.629delA | p.(Tyr210Leufs\*14) | . | . | 0.86 | 85.44 | 97.61 |  |
| *HSPA4* | Heat shock protein family A (HSP70) member 4 | NM\_002154.4 | D-Mis | c.2051C>G | p.(Pro684Arg) | 0.62 | 4.10E-06 | 0.03 | 42.59 | 95.61 |  |
| *ITPR1* | Inositol 1,4,5-triphosphate receptor type 1 | NM\_001168272.1 | D-Mis | c.3614C>T | p.(Ala1205Val) | 0.69 | 1.69E-05 | 1.00 | 94.57 | 78.37 | Gillespie syndrome (206700, AD, AR)  Spinocerebellar ataxia (606658, AD; 117360, AD) |
| *KDM3B* | Lysine demethylase 3B | NM\_016604.4 | D-Mis | c.3298C>T | p.(Pro1100Ser) | 0.66 | . | 1.00 | 89.37 | 86.59 |  |
| *KEAP1* | Kelch-like ECH-associated protein 1 | NM\_012289.4 | LGD | c.1752C>A | p.(Tyr584\*) | . | . | 0.25 | 79.29 | 82.09 |  |
| *MBTPS1* | Membrane-bound transcription factor protease, site 1 | NM\_003791.4 | D-Mis | c.1342G>A | p.(Ala448Thr) | 0.61 | 5.41E-06 | 0.13 | 97.85 | 95.59 | Spondyloepiphyseal dysplasia  (618392, AR, 1 patient only) |
| *MECOM* | MDS1 and EVI1 complex locus | NM\_001163999.1 | D-Mis | c.2285T>C | p.(Phe762Ser) | 0.76 | . | 1.00 | 81.79 | 59.65 | Radioulnar synostosis and amegakaryocytic thrombopenia (RUSAT2, 616738, AD) |
| *MFN2* | Mitofusin 2 | NM\_001127660.1 | D-Mis | c.311G>A | p.(Arg104Gln) | 0.94 | . | 1.00 | 76.46 | 96.94 | Charcot-Marie-Tooth disease (609260, AD; 617087, AR)  Hereditary motor and sensory neuropathy (601152, AD) |
| *MYOM1* | Myomesin 1 | NM\_019856.2 | LGD | c.3019C>T | p.(Arg1007\*) | . | 1.27E-05 | 0.00 | 57.08 | 99.42 |  |
| *NOTCH1* | Notch receptor 1 | NM\_017617.5 | D-Mis | c.1430T>A | p.(Ile477Asn) | 0.74 | . | 1.00 | 87.73 | 87.89 | Adams-Oliver syndrome (616028AD)  Aortic valve disease (109730, AD) |
| *NUCB1* | Nucleobindin 1 | NM\_006184.6 | LGD | c.568dupT | p.(Tyr190Leufs\*29) | . | . | 0.00 | 94.51 | 93.26 |  |
| *OLFML2B* | Olfactomedin-like 2B | NM\_001297713.1 | D-Mis | c.1694T>A | p.(Ile565Asn) | 0.69 | . | 0.00 | 74.96 | 75.85 |  |
| *PSMD12* | Proeasome 26S subunit, non-ATPase 12 | NM\_174871.4 | LGD | c.1207\_1209del | p.(Asn403del) | . | . | 1.00 | 84.88 | 89.07 | Stankiewicz-Isidor syndrome (617516, AD) |
| *PTPN11* | Protein tyrosine phosphatase non-receptor type 11 | NM\_002834.5 | D-Mis | c.182A>G | p.(Asp61Gly) | 0.92 | . | 1.00 | 92.32 | 94.20 | LEOPARD syndrome (151100, AD)  Leukemia (607785)  Metachondromatosis (156250, AD)  Noonan syndrome (163950, AD) |
| *PTPRK* | Protein tyrosine phosphatase receptor type K | NM\_001291984.2 | D-Mis | c.4202T>C | p.(Val1401Ala) | 0.54 | . | 0.98 | 93.06 | 90.50 |  |
| *RAF1* | Raf-1 proto-oncogene, serine/threonine kinase | NM\_002880.3 | D-Mis | c.781C>A | p.(Pro261Thr) | 0.87 | . | 1.00 | 26.87 | 91.43 | Cardiomyopathy (615916, AD)  LEOPARD syndrome (611554)  Noonan syndrome (611553, AD) |
| *RASA2* | RAS P21 protein activator 2 | NM\_001303245.2 | D-Mis | c.1916C>T | p.(Thr639Ile) | 0.56 | 1.63E-05 | 0.00 | 74.96 | 66.34 |  |
| *SLC25A24* | Solute carrier family 25 member 24 | NM\_013386.5 | D-Mis | c.649C>T | p.(Arg217Cys) | 0.81 | . | 0.00 | 77.16 | 73.97 | Fontaine progeroid syndrome (612289, AD) |
| *SLC38A6* | Solute carrier family 38 member 6 | NM\_153811 | LGD | c.364-1G>T | p.(=) | . | . | 0.00 | 44.38 | 33.57 |  |
| *SRPRA* | SPR receptor subunit alpha | NM\_001177842.1 | D-Mis | c.100C>A | p.(Arg34Ser) | 0.64 | . | NA | NA | NA |  |
| *TBX4* | T-box transcription factor 4 | NM\_018488.3 | LGD | c.293C>G | p.(Pro98Arg) | 0.97 | . | 0.41 | 98.98 | 24.64 | Ischiocoxopodopatellar syndrome with or without PAH (147891, AD)  Posterior amelia with pelvic and pulmonary hypoplasia syndrome (601360, AR) |
| *TBX4* | T-box transcription factor 4 | NM\_018488.3 | LGD | c.538\_547del | p.(Pro180Ilefs\*45) | . | . | 0.41 | 98.98 | 24.64 | Ischiocoxopodopatellar syndrome with or without PAH (147891, AD)  Posterior amelia with pelvic and pulmonary hypoplasia syndrome (601360, AR) |
| *TBX4* | T-box transcription factor 4 | NM\_018488.3 | D-Mis | c.985G>T | p.(Asp329Tyr) | 0.61 | . | 0.41 | 98.98 | 24.64 | Ischiocoxopodopatellar syndrome with or without PAH (147891, AD)  Posterior amelia with pelvic and pulmonary hypoplasia syndrome (601360, AR) |
| *TBX4* | T-box transcription factor 4 | NM\_018488.3 | LGD | c.1054C>T | p.(Arg352\*) | . | . | 0.41 | 98.98 | 24.64 | Ischiocoxopodopatellar syndrome with or without PAH (147891, AD)  Posterior amelia with pelvic and pulmonary hypoplasia syndrome (601360, AR)Posterior amelia with pelvic and pulmonary hypoplasia syndrome(601360) |
| *TRH* | Thyrotropin-releasing hormone | NM\_007117.5 | D-Mis | c.253C>A | p.(His85Asn) | 0.54 | . | 0.00 | 12.25 | 75.66 | Thyrotropin-releasing hormone deficiency (275120, AR) |
| *TUBB6* | Tubulin beta 6 class V | NM\_001303527.2 | DMis | c.40C>T | p.(Arg14Trp) | 0.68 | 8.13E-06 | 0.00 | 92.18 | 89.57 | Congenital facial palsy with ptosis and velopharyngeal dysfunction (617732, AD) |
| *ZMYM2* | Zinc finger MYM-type containing 2 | NM\_001190965.3 | LGD | c.1618C>T | p.(Arg540\*) | . | . | 0.97 | 93.10 | 77.22 |  |
| *ZNF620* | Zinc finger protein 620 | NM\_175888.4 | LGD | c.74G>A | p.(Trp25\*) | . | . | 0.00 | NA | NA |  |

\*Rare, deleterious variants defined as gnomAD AF ≤1.00E-04 and LGD or missense with REVEL <0.5.

**Table S7. Clinical characteristics of pediatric PAH cases with rare *de novo* LGD or D-Mis variants.**

| **Gene symbol** | **Variant type** | **Gene-level associated medical condition(s)** | **Case ID** | **Sex** | **Age of dx** | **Genetic ancestry** | **PAH**  **class** | **PAH subclass** | **Heart defect** | **Growth & development phenotype** | **Other medical condition(s)** | **MPAP (mmHg)** | **MPCWP (mmHg)** | **CO Fick**  **(L/min)** | **PVR**  **(Woods units)** | **Vital status** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *ACVRL1* | D-Mis | HHT | JM0057 | M | 6 | AFR | APAH | HHT |  |  | NA | 54 | 4 | 2.7 | 18.5 | Deceased |
| *ALDH9A1, TUBB6* | D-Mis | *TUBB6*: Congenital facial palsy with ptosis and velopharyngeal dysfunction | 15-002\* | F | 9 | AFR | IPAH |  |  |  |  | 75 | 8 | 5.8 | 11.55 | Transfer to adult care |
| *AMOT, ZNF620* | LGD |  | JM0004\* | M | 1 | EUR | IPAH |  |  |  |  | 36 | 11 | 3.6 | 6.94 | Alive 2016 |
| *ATP6V0A2* | D-Mis |  | JM1344 | M | 12.5 | EAS | IPAH |  |  | Autism |  | 54 | 9 | 2.4 | 12.08 | Alive 2020 |
| *BMPR2* | D-Mis | PAH; PVOD | JM625 | M | 3 | EUR | IPAH |  |  |  | Anemia, depression, renal failure | NA | NA | NA | NA | NA |
| *BMPR2*, *MECOM* | LGD | *BMPR2*: PAH; PVOD  *MECOM*: RUSAT2 | LP2001061\* | F | 3 | EUR | IPAH |  |  |  |  | NA | NA | NA | NA | NA |
| *BRWD3, GDPG4* | D-Mis,  LGD | *BRWD3*: Mental retardation | JM140\* | F | 3 | EUR | APAH | CHD | TOGV |  | Asthma, depression | 59 | 14 | 6.8 | 6.62 | Deceased (17 y) |
| *CHRNA4* | D-Mis | Epilepsy | JM187 | M | 0.75 | EUR | APAH | CHD | VSD, coarctation of the aorta | Multiple congenital anomalies |  | NA | NA | NA | NA | NA |
| *CNTN4* | D-Mis |  | JM0035 | F | 12 | EUR | IPAH |  |  |  |  | 29 | 5 | 3.8 | 6.32 | Deceased following tx |
| *CSNK2A2, SLC38A6,*  *TRH* | D-Mis,  LGD,  D-Mis | *TRH*: TRH deficiency | JM0028\* | F | 9 | EUR | IPAH |  |  |  |  | 37 | 8 | 2 | 14.5 | Deceased |
| *DNMT3A* | D-Mis | Heyn-Sproul\_Jackson syndrome, Tatton-Brown-Rahman syndrome, AML | JM217 | F | 15 | EUR | APAH | CHD | VSD, Eisenmenger syndrome | Down syndrome | Asthma, thyroid cancer | NA | NA | NA | NA | NA |
| *EMC8* | LGD |  | JM1307 | M | 3 | SAS | IPAH |  |  | NA | NA | NA | NA | NA | NA | NA |
| *EMID1* | D-Mis |  | 15-054 | M | 4 | AFR | IPAH |  |  |  |  | 34 | 9 | NA | NA | NA |
| *GAMT, MFN2* | D-Mis | *GAMT*: Cerebral creatinine deficiency syndrome 2  *MFN*: Charcot-Marie-Tooth disease,  Hereditary motor and sensory neuropathy | FPPH4004\* | M | 10 | EUR | FPAH |  |  | NA | NA | NA | NA | NA | NA | NA |
| *GRHL2* | D-Mis | Corneal dystrophy,  Deafness, Ectodermal dysplasia/short stature syndrome | LP2000991 | M | 2 | EUR | IPAH |  | secundum ASD |  |  | 69 | NA | NA | NA | NA |
| *HNRNPF* | LGD |  | FPPH5703 | F | 0.25 | EUR | FPAH |  |  | PPHN, myelodysplastic syndrome | Microangiopathic hemolytic anemia, thrombocytopenia | 56 | 3 | 1.4 | 37.86 | Deceased (1.25 y) |
| *HSPA4* | D-Mis |  | JM192 | F | 15 | EUR | APAH | CHD | ASD, PDA |  |  | NA | 6 | 12.9 | 0.93 | NA |
| *ITPR1* | D-Mis |  | 15-042 | M | 5 | EUR | IPAH |  |  |  |  | 106 | 5 | 5.6 | 18.04 | Alive 2018 |
| *KDM3B* | D-Mis |  | 15-006 | F | 8 | EUR | IPAH |  |  |  |  | 37 | 5 | NA | NA | Alive 2018 |
| *KEAP1* | LGD |  | JM852 | F | 2 | EUR | IPAH |  |  | Developmental delay, Incontinentia pigmenti, spastic diplegia |  | 63 | 11 | 1.5 | 34.67 | Deceased |
| *MBTPS1* | D-Mis | Spondyloepiphyseal dysplasia (1 patient) | JM0024 | F | 4 | EUR | APAH | CHD | ASD, dextrocardia | Small stature for age |  | 52 | 9 | 2.2 | 19.55 | Alive 2020 |
| *MYOM1* | LGD |  | JM1367 | F | 8 | EUR | IPAH |  | Secundum ASD | Chronic lung disease of prematurity |  | NA | 7 | NA | NA | Alive 2020 |
| *NOTCH1* | D-Mis | Adams-Oliver syndrome  Aortic valve disease | JM1357 | F | 1 | EUR | APAH | CHD | TOF | Failure to thrive |  | 52 | 8 | NA | NA | Deceased (11 y) |
| *NUCB1* | LGD |  | JM171 | F | 5 | EUR | IPAH |  |  | NA | NA | NA | NA | NA | NA | NA |
| *OLFML2B, RAF1* | D-Mis | *RAF1*: Cardiomyopathy  LEOPARD syndrome  Noonan syndrome | JM1088\* | F | 13 | EUR | IPAH |  |  | Failure to thrive | Myxomatous AV valve (neoplasm) | NA | NA | NA | NA | NA |
| *PSMD12* | LGD | Stankiewicz-Isidor syndrome | 06-095 | F | 1 | EUR | APAH | CHD | PDA |  |  | 65 | 5 | 2 | 30.00 | NA |
| *PTPN11* | D-Mis | LEOPARD syndrome  Leukemia  Metachondromatosis  Noonan syndrome | JM155 | F | 6 | EUR | APAH | CHD | ASD | Noonan syndrome |  | 46 | 8 | 3.7 | 10.27 | NA |
| *PTPRK* | D-Mis |  | JM200 | F | 2 | EUR | APAH | CHD | ASD, PDA, TOGV, VSD |  |  | 82 | 5 | 1.7 | 45.29 | Deceased (9 y) |
| *RASA2* | D-Mis |  | JM138 | F | 0.42 | AMR | APAH | CHD | PDA | Congenital diplegia, small stature for age |  | 51 | 8 | NA | NA | NA |
| *SLC25A24* | D-Mis | Fontaine progeroid syndrome | JM216 | F | 2 | EUR | IPAH |  |  |  | Cystic fibrosis | 39 | 11 | 3.1 | 9.03 | Alive 2020 |
| *SRPRA* | D-Mis |  | FPPH133-01 | F | 15 | EUR | FPPH | HHT |  | Autism | Obsessive compulsive disorder | 69 | 10 | 3.2 | 18.44 | Deceased |
| *TBX4* | D-Mis | Ischiocoxopodopatellar syndrome with or without PAH  Posterior amelia with pelvic and pulmonary hypoplasia syndrome | JM0002 | F | 2 | Unknown | APAH | CHD | NA |  |  |  |  |  |  |  |
| *TBX4* | D-MIS | Ischiocoxopodopatellar syndrome with or without PAH  Posterior amelia with pelvic and pulmonary hypoplasia syndrome | 01-008 | F | 7 | EUR | IPAH |  |  |  |  | 40 | 8 | 4.8 | 6.67 |  |
| *TBX4* | LGD | Ischiocoxopodopatellar syndrome with or without PAH  Posterior amelia with pelvic and pulmonary hypoplasia syndrome | FPPH9002 | M | 2 | EUR | FPAH | Portal |  | NA | NA | NA | NA | NA | NA | NA |
| *TBX4* | LGD | Ischiocoxopodopatellar syndrome with or without PAH  Posterior amelia with pelvic and pulmonary hypoplasia syndrome | JM847 | M | 1-day | EUR | APAH | CHD | Alveolar hypoplasia |  |  | 66 | 10 | NA | NA | NA |
| *ZMYM2* | LGD |  | JM630 | M | 3 | EUR | IPAH |  |  | Actelectasis, bilateral lung; traction bronchiectasis; rib irregularities, bilateral; idiopathic scoliosis |  | 61 | 13 | 2.8 | 17.14 | Alive 2020 |

Abbreviations: AML, acute myeloid leukemia; RUSAT2,Radioulnar synostosis and amegakaryocytic thrombopenia; TRH, thyroid hormone deficiency.

\*Multiple *de novo* variants identified in patient 15-002 (*ALDH9A1*, *TUBB6*), patient LP2001061 (*BMPR2* and *MECOM*), patient FPPH4004 (*GAMT*, *MFN2*), patient JM0004 (*AMOT*, *ZNF620*), patient JM0010 (*MANEA*, *RALGAPA1*), patient JM0028 (*CSNK2A2*, *TRH*), patient JM140 (*BRWB3*, *GDPD4*), patient JM1088 (*OLFML2B*, *RAF1*).