Identification of rare sequence variation underlying heritable pulmonary arterial hypertension.

Gräf *et al.*

Supplementary Information

Supplementary Table 1 Patient demographics and clinical characteristics by diagnostic group. Drug and anorexigen group (3 dasatinib exposures, 47 anorexigen exposures, 12 amphetamine exposures); 2 patients had multiple exposures. mPAP - mean pulmonary artery pressure, PCWP - pulmonary capillary wedge pressure, CO - cardiac output, KCO - transfer coefficient for carbon monoxide. Data presented as median [IQR] unless stated.

Group	n	Number with a family history of PAH [%]	Number with a *BMPR2* mutation [%]	WGS inferred ethnicity [% European]	Age at diagnosis (years)	Gender: number female [%]	mPAP (mmHg)	PCWP (mmHg)	CO (L/min)	Functional class 1/2/3/4 [%]	KCO (% predicted)
IPAH	908	0 [0.0%]	111 [12.2%]	806 [88.8%]	49.7 [37.0 - 64.6]	624 [68.7%]	53 [44.0 - 61.0]	10 [7 - 12]	4.0 [3.2 - 5.0]	18 [2.3%] / 165 [21.1%] / 506 [64.8%] / 92 [11.8%]	72.0 [51.6 - 87.0]
HPAH	58	58 [100.0%]	44 [75.9%]	55 [94.8%]	38.1 [30.4 - 53.5]	34 [58.6%]	54 [48.0 - 64.5]	8 [6 - 11]	3.8 [2.8 - 4.8]	0 [0.0%] / 14 [24.1%] / 37 [63.8%] / 7 [12.1%]	75.5 [69.0 - 85.0]
Drug and anorexigen exposed	60	0 [0.0%]	5 [8.3%]	53 [88.3%]	52.4 [40.6 - 60.6]	52 [86.7%]	53 [43.8 - 60.0]	9 [6.5 - 12]	4.2 [3.5 - 5.2]	0 [0.0%] / 10 [17.5%] / 40 [70.2%] / 7 [12.3%]	79.0 [64.0 - 92.6]
PVOD/PCH	22	2 [9.1%]	0 [0.0%]	20 [90.9%]	52.2 [39.7 - 68.1]	13 [59.1%]	48 [41.0 - 57.0]	10.5 [8 - 12]	3.5 [2.6 - 4.4]	1 [4.8%] / 2 [9.5%] / 14 [66.7%] / 4 [19%]	38.0 [29.6 - 47.0]

Supplementary Table 2 Copy number deletions identified in *BMPR2* (ENST00000374580) in this study. Previously in Girerd *et al.*[1] reported deletions are marked with asterisks.

Combined (quality based)						MANTA		CANVAS		
Chr	start	end	HGVS (genomic)	HGVS (cDNA)	EXON	start	end	start	end	
2	201106312	204901853	chr2:g.201106312_204901853del	c.-2135886_*1477184del	1-13/13	201106432	204901548	201106312	204901853	
2	201822159	205450144	chr2:g.201822159_205450144del	c.-1420039_*2025475del	1-13/13	201822961	205450144	201822159	205449696	
2	202772559	205218660	chr2:g.202772559_205218660del	c.-469639_*1793991del	1-13/13	202772963	205218660	202772559	205218576	
2	202999184	203486009	chr2:g.202999184_203486009del	c.-243014_*61340del	1-13/13	202999402	203485750	202999184	203486009	
2	203223399	203248850	chr2:g.203223399_203248850del	c.-18799_76+6577del	1/13	203223399	203248060	203223420	203248850	
2	203225712	203256467	chr2:g.203225712_203256467del	c.-16486_76+14194del	1/13	203226401	203255921	203225712	203256467	*
2	203228120	203905293	chr2:g.203228120_203905293del	c.-14078_*480624del	1-13/13	203228906	203905293	203228120	203905004	
2	203234119	203242446	chr2:g.203234119_203242446del	c.-8079_76+173del	1/13	203235908	203242364	203234119	203242446	
2	203325317	203332529	chr2:g.203325317_203332529del	c.77-4215_418+117del	2-3/13	203325958	203332529	203325317	203332065	
2	203327217	203331596	chr2:g.203327217_203331596del	c.77-2315_248-646del	2/13	203327217	203331596	203327390	203331395	*
2	203328407	203332511	chr2:g.203328407_203332511del	c.77-1125_418+99del	2-3/13	203329838	203332511	203328407	203332252	
2	203329730	203335416	chr2:g.203329730_203335416del	c.247+28_418+3004del	3/13	203330505	203335416	203329730	203334949	
2	203339329	203392988	chr2:g.203339329_203392988del	c.418+6917_968-2529del	4-7/13	203339329	203392988	203339531	203391830	
2	203341496	203422058	chr2:g.203341496_203422058del	c.418+9084_2866+804del	4-12/13	203342249	203422058	203341496	203421779	
2	203372762	203382260	chr2:g.203372762_203382260del	c.419-5680_622-1285del	4-5/13	203373003	203382260	203372762	203381787	
2	203379275	203389196	chr2:g.203379275_203389196del	c.530-336_967+4272del	5-7/13	203380130	203388919	203379275	203389196	
2	203383741	203388057	chr2:g.203383741_203388057del	c.818_967+3133del	6-7/13	203384088	203387879	203383741	203388057	
2	203386133	203445336	chr2:g.203386133_203445336del	c.967+1209_*20667del	8-13/13	203387039	203444732	203386133	203445336	
2	203403086	203415133	chr2:g.203403086_203415133del	c.1277-3948_1414-2306del	10/13	203403129	203415088	203403086	203415133	
2	203406092	203412701	chr2:g.203406092_203412701del	c.1277-942_1414-4738del	10/13	203406727	203412701	203406092	203412028	*
2	203406461	203414964	chr2:g.203406461_203414964del	c.1277-573_1414-2475del	10/13	203406613	203414964	203406461	203414695	*
2	203411230	203418627	chr2:g.203411230_203418627del	c.1413+4060_1586+1016del	11/13	203411808	203418627	203411230	203418411	
2	203421702	203434798	chr2:g.203421702_203434798del	c.2866+448_*10129del	13/13	203422398	203434798	203421702	203434395	

Supplementary Table 3 Summary of clinical characteristics in patients with mutations in **(a)** the previously reported PAH genes and **(b)** the novel PAH genes identified in this study. FHx - Family history; mPAP - mean pulmonary artery pressure; PCWP - pulmonary capillary wedge pressure; KCO - transfer coefficient for carbon monoxide.

Gene	Number of patients	FHx of PH [%]	WGS inferred ethnicity: European [%]	Age at diagnosis (years)	Gender: female [%]	mPAP (mmHg)	PCWP (mmHg)	Cardiac output (L/min)	Functional class 1 / 2 / 3 / 4 [%]	KCO (% predicted)
(a) Previously reported PAH disease genes.										
No mutation	802	9 [1.1%]	713 [88.9%]	52.6 [39.1 - 66.5]	562 [70.1%]	51 [42.0 - 60.0]	10 [7.0 - 12.0]	4.1 [3.3 - 5.2]	16 [2.3%] / 142 [20.5%] / 459 [66.2%] / 76 [11.0%]	69.0 [47.2 - 84.0]
BMPR2*	160	44 [27.5%]	149 [93.1%]	39.3 [32.0 - 51.2]	106 [66.2%]	57 [51.0 - 68.2]	10 [7.0 - 12.0]	3.3 [2.7 - 4.0]	2 [1.3%] / 33 [21.9%] / 90 [59.6%] / 26 [17.2%]	82.0 [73.5 - 92.5]
EIF2AK4	14	2 [14.3%]	7 [50.0%]	31.2 [23.4 - 38.6]	7 [50.0%]	50.5 [41.8 - 59.2]	10.5 [7.2 - 12.0]	4.5 [3.0 - 4.9]	0 [0.0%] / 2 [14.3%] / 9 [64.3%] / 3 [21.4%]	33.0 [29.1 - 33.0]
TBX4	14	1 [7.1%]	12 [85.7%]	56.4 [39.9 - 71.8]	9 [64.3%]	58 [48.0 - 67.0]	11 [7.5 - 13.5]	3.8 [2.9 - 4.1]	0 [0.0%] / 2 [18.2%] / 7 [63.6%] / 2 [18.2%]	89.7 [83.3 - 91.8]
ACVRL1	9	1 [11.1%]	9 [100.0%]	46.9 [44.8 - 57.7]	8 [88.9%]	54 [42.8 - 58.5]	11.5 [10.2 - 12.8]	4.6 [3.5 - 5.0]	0 [0.0%] / 4 [57.1%] / 3 [42.9%] / 0 [0.0%]	72.1 [60.5 - 77.3]
ENG	5	0 [0.0%]	4 [80.0%]	42.2 [35.7 - 47.2]	4 [80.0%]	55 [52.0 - 58.0]	6.5 [0.8 - 13.5]	3.8 [3.5 - 4.2]	0 [0.0%] / 0 [0.0%] / 3 [75%] / 1 [25%]	47.0 [46.0 - 51.0]
KCNK3	4	0 [0.0%]	4 [100.0%]	26.8 [25.1 - 38.5]	2 [50.0%]	48 [43.5 - 63.0]	7.5 [6.2 - 8.8]	3.8 [2.3 - 5.1]	0 [0.0%] / 1 [33.3%] / 2 [66.7%] / 0 [0.0%]	85.7 [85.7 - 85.7]
SMAD9	3	0 [0.0%]	2 [66.7%]	51.3 [39.8 - 56.2]	2 [66.7%]	46 [43.0 - 55.0]	11 [9.0 - 12.0]	5.0 [4.7 - 5.0]	0 [0.0%] / 0 [0.0%] / 3 [100%] / 0 [0.0%]	92.5 [81.2 - 103.8]
(b) Novel PAH disease genes.										
ATP13A3	11	0 [0.0%]	9 [81.8%]	47.5 [41.5 - 58.4]	10 [90.9%]	57 [49.5 - 62.0]	10.5 [7.5 - 16.0]	3.1 [2.6 - 4.6]	0 [0.0%] / 0 [0.0%] / 8 [88.9%] / 1 [11.1%]	88.5 [82.2 - 91.4]
SOX17	9	0 [0.0%]	9 [100.0%]	27.3 [21.4 - 40.2]	5 [55.6%]	58 [57.0 - 68.0]	10 [7.0 - 11.5]	4.1 [3.8 - 5.1]	1 [14.3%] / 1 [14.3%] / 5 [71.4%] / 0 [0.0%]	80.9 [78.3 - 83.5]
AQP1	9	2 [22.2%]	9 [100.0%]	32.2 [25.3 - 46.2]	4 [44.4%]	61.5 [48.0 - 68.2]	8 [7.5 - 8.0]	4.7 [4.3 - 5.3]	0 [0.0%] / 4 [50%] / 3 [37.5%] / 1 [12.5%]	81 [78.2 - 91.0]
GDF2	8	1 [12.5%]	7 [87.5%]	49.9 [45.0 - 53.8]	4 [50.0%]	46 [43.2 - 50.5]	8 [6.0 - 9.5]	4.8 [3.7 - 4.9]	0 [0.0%] / 2 [28.6%] / 5 [71.4%] / 0 [0.0%]	70.0 [69.0 - 71.1]

* This group includes one case with deleterious variant in *BMPR2* and *SMAD9*.

Supplementary Table 4 Case-control analysis of variants in previously reported PAH genes. Only protein-coding variants were considered after standard filtering and variants shared between cases and controls and variants of uncertain significance in cases have been removed. *P* values have been adjusted for false discovery rate.

Gene	Number of cases	Number of controls	Frequency of cases	Frequency of controls	*P*	Adj. *P*
BMPR2	148	20	0.1426	0.0031	7.77E-107	1.01E-105
EIF2AK4	14	0	0.0135	0	1.01E-12	6.59E-12
TBX4	14	15	0.0135	0.0023	9.99E-06	4.33E-05
ACVRL1	9	12	0.0087	0.0019	0.0012	0.0039
ENG	6	16	0.0058	0.0025	0.0759	0.1973
KCNK3	4	13	0.0039	0.0020	0.2057	0.4386
KLF2	3	10	0.0029	0.0016	0.2697	0.4386
SMAD9*	4	15	0.0039	0.0023	0.2699	0.4386
BMPR1B	4	17	0.0039	0.0027	0.3369	0.4867
TOPBP1	5	25	0.0048	0.0039	0.4119	0.5354
CAV1	0	5	0	8.00E-04	1	1
SMAD1	0	10	0	0.0016	1	1
SMAD4	0	8	0	0.0013	1	1

* This group includes one case with deleterious variant in *BMPR2* and *SMAD9*.

Supplementary Table 5 List of top 50 genes from rare protein truncating variant (PTV) case-control analysis, excluding patients carrying variants in previously reported genes. Genes are ranked by *P* value.

Gene	No. of individuals in cases	No. of individuals in controls	Frequency of cases	Frequency of controls	*P*	adj. *P*
ATP13A3	6	0	0.00715	0.00000	2.42E-06	0.03505
EVI5	5	1	0.00596	0.00016	0.00011	1
KDR	4	0	0.00477	0.00000	0.00018	1
CAMTA2	7	8	0.00834	0.00125	0.00077	1
RAB36	4	1	0.00477	0.00016	0.00082	1
ERI1	4	1	0.00477	0.00016	0.00082	1
KIF1C	4	1	0.00477	0.00016	0.00082	1
ALG10	4	1	0.00477	0.00016	0.00082	1
PRSS53	4	1	0.00477	0.00016	0.00082	1
ZFP69B	4	1	0.00477	0.00016	0.00082	1
LCAT	4	1	0.00477	0.00016	0.00082	1
COMT	3	0	0.00358	0.00000	0.00156	1
SRM	3	0	0.00358	0.00000	0.00156	1
ZMYM5	3	0	0.00358	0.00000	0.00156	1
FRMD1	3	0	0.00358	0.00000	0.00156	1
CYP3A4	3	0	0.00358	0.00000	0.00156	1
METTL7B	3	0	0.00358	0.00000	0.00156	1
JAG2	3	0	0.00358	0.00000	0.00156	1
FAM151A	5	4	0.00596	0.00063	0.00176	1
TARBP1	6	7	0.00715	0.00110	0.00201	1
HAP1	6	7	0.00715	0.00110	0.00201	1
CDK11A	4	2	0.00477	0.00031	0.00223	1
LILRB5	4	2	0.00477	0.00031	0.00223	1
MYH3	4	2	0.00477	0.00031	0.00223	1
IFIH1	7	12	0.00834	0.00188	0.00397	1
SHC2	4	3	0.00477	0.00047	0.00473	1
ALPPL2	4	3	0.00477	0.00047	0.00473	1
CTSF	4	3	0.00477	0.00047	0.00473	1
SUGCT	4	3	0.00477	0.00047	0.00473	1
ATP6V0A2	4	3	0.00477	0.00047	0.00473	1
EXD3	4	3	0.00477	0.00047	0.00473	1
TFAP2E	3	1	0.00358	0.00016	0.00570	1
PIGT	3	1	0.00358	0.00016	0.00570	1
TMEM62	3	1	0.00358	0.00016	0.00570	1
RHOT2	3	1	0.00358	0.00016	0.00570	1
ENAH	3	1	0.00358	0.00016	0.00570	1
KMT2D	3	1	0.00358	0.00016	0.00570	1
ANTXR1	3	1	0.00358	0.00016	0.00570	1
ZFPM1	3	1	0.00358	0.00016	0.00570	1
RXRB	3	1	0.00358	0.00016	0.00570	1
N4BP2L2	3	1	0.00358	0.00016	0.00570	1
SACS	5	8	0.00596	0.00125	0.01208	1
TTC37	5	8	0.00596	0.00125	0.01208	1

COL9A2	3	2	0.00358	0.00031	0.01303	1
UHRF1BP1	3	2	0.00358	0.00031	0.01303	1
PLEKHH3	3	2	0.00358	0.00031	0.01303	1
FMO2	3	2	0.00358	0.00031	0.01303	1
KRT32	3	2	0.00358	0.00031	0.01303	1
CRBN	3	2	0.00358	0.00031	0.01303	1
PCID2	3	2	0.00358	0.00031	0.01303	1

Supplementary Table 6 List of top 50 genes from rare missense variant case-control analysis, excluding patients carrying variants in previously reported genes. Genes are ranked by *P* value.

Gene	No. of individuals in cases	No. of individuals in controls	Frequency of cases	Frequency of controls	*P*	adj. *P*
GDF2	11	5	0.01311	0.00078	1.23E-07	0.00233
AQP1	8	4	0.00954	0.00063	1.03E-05	0.19641
OR8U1	14	28	0.01669	0.00439	0.00017	1
CACNB2	12	21	0.01430	0.00329	0.00019	1
ATP13A5	13	25	0.01549	0.00392	0.00021	1
C5orf42	20	55	0.02384	0.00861	0.00025	1
FMO4	9	12	0.01073	0.00188	0.00030	1
C5AR1	6	4	0.00715	0.00063	0.00033	1
FLNA	15	35	0.01788	0.00548	0.00037	1
PIWIL1	8	10	0.00954	0.00157	0.00048	1
MICU3	8	10	0.00954	0.00157	0.00048	1
ALPPL2	8	10	0.00954	0.00157	0.00048	1
LGR4	8	10	0.00954	0.00157	0.00048	1
DOCK8	19	54	0.02265	0.00846	0.00049	1
UNC13D	15	37	0.01788	0.00579	0.00059	1
C3orf20	9	14	0.01073	0.00219	0.00066	1
THNSL2	7	8	0.00834	0.00125	0.00077	1
CDCA7	7	8	0.00834	0.00125	0.00077	1
BTNL8	4	1	0.00477	0.00016	0.00082	1
CRYZ	4	1	0.00477	0.00016	0.00082	1
COL5A2	16	43	0.01907	0.00673	0.00083	1
MYO5A	12	26	0.01430	0.00407	0.00085	1
MYZAP	5	3	0.00596	0.00047	0.00087	1
TBC1D2	9	15	0.01073	0.00235	0.00095	1
ZNF48	10	19	0.01192	0.00298	0.00107	1
CYP4Z1	6	6	0.00715	0.00094	0.00120	1
ZXDB	6	6	0.00715	0.00094	0.00120	1
KRTAP4-11	6	6	0.00715	0.00094	0.00120	1
ZC3H6	9	16	0.01073	0.00251	0.00134	1
MFRP	10	20	0.01192	0.00313	0.00144	1
CACNA1C	11	24	0.01311	0.00376	0.00145	1
SPTBN1	14	37	0.01669	0.00579	0.00152	1
HIST1H3I	3	0	0.00358	0.00000	0.00156	1
NBPF12	3	0	0.00358	0.00000	0.00156	1
CLEC2A	3	0	0.00358	0.00000	0.00156	1
PADI4	8	13	0.00954	0.00204	0.00163	1
DEAF1	8	13	0.00954	0.00204	0.00163	1
NUP43	5	4	0.00596	0.00063	0.00176	1
MAP7D3	5	4	0.00596	0.00063	0.00176	1
CD3E	5	4	0.00596	0.00063	0.00176	1
PTPRC	9	17	0.01073	0.00266	0.00184	1
CD248	9	17	0.01073	0.00266	0.00184	1
ABCF1	9	17	0.01073	0.00266	0.00184	1

ZNF292	14	38	0.01669	0.00595	0.00186	1
KLC3	11	25	0.01311	0.00392	0.00188	1
ZNF343	7	10	0.00834	0.00157	0.00189	1
DLL4	7	10	0.00834	0.00157	0.00189	1
ADC	7	10	0.00834	0.00157	0.00189	1
DENND2D	7	10	0.00834	0.00157	0.00189	1
HOMEZ	7	10	0.00834	0.00157	0.00189	1

Supplementary Table 7 List of top 50 genes from combined rare PTV and missense variant case-control analysis, excluding patients carrying variants in previously reported genes. Genes are ranked by *P* value.

Gene	No. of individuals in cases	No. of individuals in controls	Frequency of cases	Frequency of controls	*P*	adj. *P*
GDF2	12	6	0.01430	0.00094	5.33E-08	0.00103
AQP1	9	5	0.01073	0.00078	4.30E-06	0.08294
ALPPL2	12	13	0.01430	0.00204	6.86E-06	0.13246
ATP13A3	11	14	0.01311	0.00219	4.64E-05	0.89511
OR8U1	15	30	0.01788	0.00470	9.92E-05	1
IFT74	11	17	0.01311	0.00266	0.00016	1
FLNA	16	36	0.01907	0.00564	0.00017	1
SOX17	8	9	0.00954	0.00141	0.00030	1
ATP13A5	13	27	0.01549	0.00423	0.00038	1
C3orf20	10	16	0.01192	0.00251	0.00039	1
PIWIL1	8	10	0.00954	0.00157	0.00048	1
DOCK8	20	60	0.02384	0.00940	0.00062	1
C5orf42	21	65	0.02503	0.01018	0.00064	1
RABL3	6	5	0.00715	0.00078	0.00066	1
C5AR1	6	5	0.00715	0.00078	0.00066	1
SPTBN1	15	38	0.01788	0.00595	0.00074	1
SLC9A3R1	8	11	0.00954	0.00172	0.00075	1
CD248	10	18	0.01192	0.00282	0.00078	1
BTNL8	4	1	0.00477	0.00016	0.00082	1
UNC13D	16	43	0.01907	0.00673	0.00083	1
CRTAM	5	3	0.00596	0.00047	0.00087	1
OR13C2	5	3	0.00596	0.00047	0.00087	1
ZNF292	15	39	0.01788	0.00611	0.00091	1
FMO4	9	15	0.01073	0.00235	0.00095	1
CACNB2	14	35	0.01669	0.00548	0.00099	1
MAMDC4	19	58	0.02265	0.00908	0.00100	1
COL5A2	16	44	0.01907	0.00689	0.00101	1
MICU3	8	12	0.00954	0.00188	0.00112	1
IRAK4	8	12	0.00954	0.00188	0.00112	1
LGR4	8	12	0.00954	0.00188	0.00112	1
KRTAP4-11	6	6	0.00715	0.00094	0.00120	1
ICK	7	9	0.00834	0.00141	0.00123	1
HES4	7	9	0.00834	0.00141	0.00123	1
ERMP1	13	32	0.01549	0.00501	0.00133	1
MYO5A	12	28	0.01430	0.00439	0.00141	1
CACNA1C	11	24	0.01311	0.00376	0.00145	1
CACNA1A	24	86	0.02861	0.01347	0.00153	1
OTUB1	3	0	0.00358	0.00000	0.00156	1
NBPF12	3	0	0.00358	0.00000	0.00156	1
ZNF343	8	13	0.00954	0.00204	0.00163	1
NUP43	5	4	0.00596	0.00063	0.00176	1
ZNF561	5	4	0.00596	0.00063	0.00176	1
P2RY14	5	4	0.00596	0.00063	0.00176	1

GALT	5	4	0.00596	0.00063	0.00176	1
DEPDC1	9	17	0.01073	0.00266	0.00184	1
INPP4A	9	17	0.01073	0.00266	0.00184	1
ITIH4	9	17	0.01073	0.00266	0.00184	1
SLC1A7	9	17	0.01073	0.00266	0.00184	1
ZC3H6	9	17	0.01073	0.00266	0.00184	1
TBC1D9B	14	38	0.01669	0.00595	0.00186	1

Supplementary Table 8 List of top 50 genes and *P* values identified by case-control comparison using SKAT-O, excluding carriers of deleterious variants in previously reported genes. Genes are ranked by *P* value.

Ensembl Gene	Gene	Genomic Region	*P*	adj. *P*
ENSG00000240583	*AQP1*	7:30951525-30963244	2.15E-10	4.28E-06
ENSG00000235718	*MFRP*	11:119212258-119217223	6.52E-10	1.30E-05
ENSG00000164736	*SOX17*	8:55370699-55372555	3.36E-09	6.69E-05
ENSG00000110881	*ASIC1*	12:50452550-50475432	5.81E-09	0.00012
ENSG00000187801	*ZFP69B*	1:40916634-40929261	1.17E-08	0.00023
ENSG00000163286	*ALPPL2*	2:233271605-233274582	1.53E-08	0.00031
ENSG00000172199	*OR8U1*	11:56143100-56144029	2.05E-08	0.00041
ENSG00000159377	*PSMB4*	1:151372064-151374305	2.56E-08	0.00051
ENSG00000128802	*GDF2*	10:48413578-48416693	3.99E-08	0.00079
ENSG00000168404	*MLKL*	16:74706402-74729655	4.28E-08	0.00085
ENSG00000110324	*IL10RA*	11:117857183-117870356	6.14E-08	0.00122
ENSG00000177398	*UMODL1*	21:43491426-43557730	6.56E-08	0.00131
ENSG00000197405	*C5AR1*	19:47813153-47824087	1.11E-07	0.00220
ENSG00000141837	*CACNA1A*	19:13318127-13617038	1.21E-07	0.00240
ENSG00000068366	*ACSL4*	X:108887258-108926715	1.27E-07	0.00252
ENSG00000257019	*OR13C2*	9:107366952-107367908	1.34E-07	0.00267
ENSG00000174807	*CD248*	11:66082225-66084498	1.84E-07	0.00366
ENSG00000113758	*DBN1*	5:176884434-176899211	2.41E-07	0.00479
ENSG00000004766	*CCDC132*	7:92861781-92987748	2.83E-07	0.00563
ENSG00000132746	*ALDH3B2*	11:67430686-67434406	2.97E-07	0.00590
ENSG00000128254	*C22orf24*	22:32330104-32334052	3.16E-07	0.00628
ENSG00000198755	*RPL10A*	6:35436212-35438527	3.33E-07	0.00661
ENSG00000101384	*JAG1*	20:10620146-10654178	3.51E-07	0.00699
ENSG00000138073	*PREB*	2:27354282-27357289	4.45E-07	0.00885
ENSG00000066056	*TIE1*	1:43766743-43788393	5.00E-07	0.00995
ENSG00000157240	*FZD1*	7:90894196-90896139	5.16E-07	0.01025
ENSG00000115705	*TPO*	2:1418181-1546246	5.49E-07	0.01091
ENSG00000184451	*CCR10*	17:40831571-40833841	5.71E-07	0.01136
ENSG00000125207	*PIWIL1*	12:130827137-130856143	6.11E-07	0.01214
ENSG00000183690	*EFHC2*	X:44008041-44202834	6.13E-07	0.01219
ENSG00000144354	*CDCA7*	2:174219692-174232392	7.30E-07	0.01451
ENSG00000053501	*USE1*	19:17326215-17330622	7.44E-07	0.01480
ENSG00000126773	*PCNXL4*	14:60581431-60600939	7.74E-07	0.01538
ENSG00000188177	*ZC3H6*	2:113033572-113090065	7.74E-07	0.01539
ENSG00000175785	*PRIMA1*	14:94187790-94254064	1.02E-06	0.02027
ENSG00000156414	*TDRD9*	14:104394847-104518419	1.13E-06	0.02249
ENSG00000144895	*EIF2A*	3:150264590-150301698	1.20E-06	0.02394
ENSG00000076258	*FMO4*	1:171288965-171310978	1.30E-06	0.02580
ENSG00000092929	*UNC13D*	17:73824046-73840418	1.45E-06	0.02892
ENSG00000166033	*HTRA1*	10:124221169-124273875	1.64E-06	0.03266
ENSG00000143862	*ARL8A*	1:202103595-202113700	1.69E-06	0.03365
ENSG00000005379	*BZRAP1*	17:56381731-56405281	1.80E-06	0.03576
ENSG00000108950	*FAM20A*	17:66533618-66596807	1.91E-06	0.03805
ENSG00000131126	*TEX101*	19:43910657-43922549	2.17E-06	0.04321

ENSG00000140853	*NLRC5*	16:57054625-57116440	2.31E-06	0.04599
ENSG00000268552	*AL109927.1*	1:28177085-28177255	2.43E-06	0.04825
ENSG00000163216	*SPRR2D*	1:153012604-153012822	2.53E-06	0.05039
ENSG00000130382	*MLLT1*	19:6213053-6279795	2.53E-06	0.05040
ENSG00000196782	*MAML3*	4:140640477-141074481	2.65E-06	0.05268
ENSG00000196911	*KPNA5*	6:117002498-117053486	2.70E-06	0.05373

Supplementary Table 9 PCR primers for human.

Target	Forward	Reverse
Quantitative RT-PCR		
ACTB	GCACCACACCTTCTACAATGA	GTCATCTTCTCGCGGTTGGC
AQP1	CCAGGTGGAGGAGTATGACCT	GACCCCTTCTATTTGGGCTTCA
ATP13A3	GAAAATAGGCACAGGATCAG	ATTTTACACTATGGTGGGTG
B2M	CTCGCGCTACTCTCTCTTTCT	CATTCTCTGCTGGATGACGTG
HPRT	GCTATAAATTCTTTGCTGACCTGCTG	AATTACTTTTATGTCCCCTGTTGACTGG
SOX17	GGACCGCACGGAATTTGAAC	GGACACCACCGAGGAAATGG
Familial segregation analysis		
Family II (Figure 4a)		
BMPR2ex1	GTGATACGGGCAGGATCAGT	ATTAAAGGCGATTTCCCTGG
BMPR2ex2	GTCATTCGGATAAGACAAAG	TTTAACATACTCCCATGTCC
BMPR2ex3	TAGCTTACACGTACTCTCAC	CCTGGCTTCAACCTTGAATG
BMPR2ex4	GGGTACAGCCTTTCTAAAGG	GATACTATTGAGGCTGGGTG
BMPR2ex5	GCTGCTAATCTTTCTGCAGC	GAATGAAGTCACTGTTCCAG
BMPR2ex6	CAGAGAGCTGTAGCATTCTG	AAGTGATCCACCTGCCTTAG
BMPR2ex7	TTTGCAAATTCTTTATAAGGATGC	AAAATTTCCTGTTGTGAATTTTGA
BMPR2ex8	TGTTCAATAGTCCCTTTTATTCATTG	CACCTGGCCAGTAGATGTTTT
BMPR2ex9	TGTTCTTCAGAATATGCTACGTTCTC	CTAATTTGCATCCTGCTGCT
BMPR2ex10	GCCTGAAGGGGATGAAAAA	TTGTGGCATTAGGCAACTCC
BMPR2ex11	CATGTGGTAAACTGAAAAGCTCA	TTCTTTGTTGGGTCTCAGTTTCT
BMPR2ex12a	TCAGAGGTGTTAAATTTGGAGAGA	TGAGTGGGTAAAGCAAGCTAGA
BMPR2ex12b	TGGAAACCAACAAGCTAGACC	TCTACCTGCCACACCATTCA
BMPR2ex12c	CTTGAAACAAGTCGAAACTGGA	TAAATGGCCCCAAAAGACAC
BMPR2ex13	CACCCTCCTGAGACATTGGT	GGGTGCTGACAGGAGGATAA
ACVRL1ex2	CTCTGTGATTTCCTCTGGGCA	TACATTCTCCCCAGCTTCTCAA
ACVRL1ex3	AGCTGGGACCACAGTGGCTGA	AGGGCAGGGGCCAAGAAGAT
ACVRL1ex4	AGCTGACCTAGTGGAAGCTGA	CTGATTCTGCAGTTCCTATCTG
ACVRL1ex5	AGGAGCTTGCAGTGACCCAGCA	ATGAGAGCCCTTGGTCCTCATCCA
ACVRL1ex6	AGGCAGCGCAGCATCAAGAT	AAACTTGAGCCCTGAGTGCAG
ACVRL1ex7	TGACGACTCCAGCCTCCCTTAG	CAAGCTCCGCCCACCTGTGAA
ACVRL1ex8	AGGTTTGGGAGAGGGGCAGGAGT	GGCTCCACAGGCTGATTCCCCTT
ACVRL1ex9	TCCTCTGGGTGGTATTGGGCCTC	CAGAAATCCCAGCCATGAGCCAC
ACVRL1ex10	TCTCCTCTGCACCTCTCTCCCAA	CTGCAGGCAGAAAGGAATCAGGTGCT

ENGex1	TCCCTGTGTCCACTTCTCCT	GAATACTTGGGGCCTGGTC
ENGex2	CAGGAAAGCCGTTAGCTCAT	ATCTGCCTTGGAGCTTCCTC
ENGex3	TGGGTGGCACAACCTATACA	TGACCCACAGAGATGGACAG
ENGex4	AATGGGCTGACTCCACAAAT	GGAGCTCAGATTCCTCCTGA
ENGex5	GGGGCTCTGTTAGGTGCAG	GCTTTATAAGGGACCGGAGA
ENGex6	ATCCCATAAACCCACACCTG	CTTCCCTGATCCAGAGGTTG
ENGex7	GTGGGGACACAGCAGGAC	GGTGCTTCACCAACAGTGTG
ENGex8	GGGCACACAGTGATCACACA	GGGCTAGGACCCCAAGAGT
ENGex9	GGTTGTGGTCAGTCCTTGGT	CTGCTCTCCCAAACACACCT
ENGex10	ATCTGCAAAAATGGGCGTAT	TTCCAGACACACATGGCTTG
ENGex11	GAGTCAGGCAACTCCACAGG	AGAAAGGCGGAGAGGAAGTT
ENGex12	CCGATATTTGAAGGCAGCAG	TTCCTGCAAACCACAGACCT
ENGex13	GCCAGGGAGTAAACCTGGA	CCCTTGCCATGTGCTATGT
ENGex14	CAGAGAAGTCGAGGGTCCAT	CAATCCCTCAGAGGCTTCAC
ENGex15	GTGAAGCCTCTGAGGGATTG	GGTGAGTTCACACCAGTGCT
SOX17ex1	ACAGGCCAGAACACGGG	CCTGGTTTTGGGCGTCAG
SOX17ex2a	GTTGCGCAATTCAAAGTC	TAGTACACGTGAAGGGCGC
SOX17ex2b	GACCCGGCTTTCTTCGC	TGTTCAAGTGGCAGACAAAA
Family E011942 (Figure 4b)		
AQP1_ex3a	TATGACTCTCTGCCTTCGC	CCCGTGGGTCTCCTAC
Family E012415 (Figure 4c)		
AQP1_ex2a	GAGGCCTGGGTATCCTTGG	CGCCATCCTCCACCCAAT
Family E010634 (Figure 4d)		
AQP1_ex3b	CCCCACCCTGATTGTTCTCT	CCAGAACAGGAAGGGACACT

References

1. Girerd B, Montani D, Jais X, Eyries M, Yaici A, Sztrymf B, et al. Genetic counselling in a national referral centre for pulmonary hypertension. Eur Respir J. 2016 Feb;47(2):541-52
2. den Dunnen JT, Dalgleish R, Maglott DR, Hart RK, Greenblatt MS, McGowan-Jordan J, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. Hum Mutat. 2016 Jun;37(6):564-9

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