

Gene	Mutation Category	Nucleotide change	Amino Acid change	Clinically defined disease	References
BMPR2	Nonsense	c.39G>A	p.Trp13*	sporadic PAH	[1]
BMPR2	Nonsense	c.244C>T	p.Gln82*	sporadic PAH	[2]
BMPR2	Splice-site	c.248-2A>G	p. ?	sporadic PAH	[3]
BMPR2	Frameshift	c.350dupG	p.Cys117Trpfs*3	sporadic PAH	This study
BMPR2	Missense	c.367T>A	p.Cys123Ser	sporadic PAH	[3]
BMPR2	Splice-site	c.418+1del	p. ?	sporadic PAH	This study
BMPR2	Nonsense	c.439C>T	p.Arg147*	fPAH, sporadic PAH	[3]
BMPR2	Nonsense	c.491del	p.Leu164*	sporadic PAH	This study
BMPR2	Nonsense	c.631C>T	p.Arg211*	sporadic PAH	[3]
BMPR2	Nonsense	c.961C>T	p.Arg321*	sporadic PAH	[3]
BMPR2	Splice-site	c.968-12T>G	p.Asp323Valfs*15	sporadic PAH	This study
BMPR2	Nonsense	c.994C>T	p.Arg332*	fPAH	[3]
BMPR2	Missense	c.1118C>T	p.Ala373Val	sporadic PAH	This study
BMPR2	Missense	c.1471C>T	p.Arg491Trp	4 sporadic PAH , fPAH,	[3]
BMPR2	Nonsense	c.1483C>T	p.Gln495*	sporadic PAH	[3]
BMPR2	Nonsense	c.2359G>T	p.Gly787*	sporadic PAH	This study
BMPR2	Nonsense	c.2617C>T	p.Arg873*	fPAH	[3]
BMPR2	Nonsense	c.2695C>T	p.Arg899*	fPAH, sporadic PAH	[3]
BMPR2	Deletion	c.(?- 1148)_(76+1 _77-1)del	p.?	2 sporadic PAH	[3]
BMPR2	Deletion	c.(?- 1148)_(1276 +1_1277- 1)del	p.?	sporadic PAH	This study
BMPR2	Deletion	c.(1276+1_12 77- 1)_(1413+1_ 1414-1)del	p. ?	sporadic PAH	[3]
BMPR2	Deletion	c.(76+1_77- 1)_(247+1_2 48-1)del	p.?	sporadic PAH	[3]
BMPR2	Deletion	c.(76+1_77- 1)_(418+1_4 19-1)del	p.?	fPAH	[3]
BMPR2	Deletion	c.(1276+1_12 77- 1)_(1413+1_ 1414-1)	p. ?	sporadic PAH	[3]
ACVRL1	Missense	c.1120C>T	p.Arg374Trp	sporadic PAH	[4]
ACVRL1	Missense	c.1450C>T	p.Arg484Trp	sporadic PAH	[5]
TBX4	Nonsense	c.121G>T	p.Gly41*	sporadic PAH	This study
TBX4	Frameshift	c.143dup	p.Pro50Thrfs*24	sporadic PAH	This study
TBX4	Frameshift	c.153_181del	p.Val54Hisfs*10	sporadic PAH	This study
TBX4	Frameshift	c.1458dup	p.Pro487Alafs*16	sporadic PAH	This study
TBX4	Deletion	c.(549+1_550 - 1)_(702+1_7 03-1)	p. ?	sporadic PAH	This study
BMP9	Nonsense	c.451C>T	p.Arg151*	sporadic PAH	This study

BMP9	Frameshift	c.990delinsG T	p.Ser331Phefs*22	sporadic PAH	This study
SMAD9	Deletion	c.(?- 186)_(*3846 ?)del	p.?	sporadic PAH	This study
BMP10	Nonsense	c.370C>T	p.Arg124*	sporadic PAH	This study
EIF2AK4	Missense	c.361G>A compound HTZ	p.Val121Met	PVOD	[6]
EIF2AK4	Nonsense	c.951G>A	p.Trp317*	PVOD	This study
EIF2AK4	Nonsense	c.1387C>T	p.Arg463*	PVOD	[7]
EIF2AK4	Missense	c.1754G>A HMZ	p.Arg585Gln	PVOD	[7]
EIF2AK4	Frameshift	c.2475_2476 del HMZ	p.Trp826Glufs*15	PVOD	This study
EIF2AK4	Missense	c.2968C>T HMZ	p.Pro990Ser	PVOD	This study
EIF2AK4	Nonsense	c.3097C>T compound HTZ	p.Gln1033*	PVOD	[8]
EIF2AK4	Nonsense	c.3406C>T HMZ	p.Arg1136*	PVOD	[7]
EIF2AK4	Frameshift	c.4205dup HMZ	p.Ser1403Lysfs*45	PVOD	[7]
EIF2AK4	Frameshift	c.4593del compound HTZ	p.Ile1533Leufs*2	PVOD	This study
EIF2AK4	Nonsense	c.4769del compound HTZ	p.Leu1590*	PVOD	[8]

Supplementary Table 1. Mutations identified in the cohort.

When the same mutation was identified in more than one patient of the study, the number of patients is mentioned in the column “clinically defined disease”.

References of the table.

1. Hamid R, Hedges LK, Austin E, Phillips JA, Loyd JE, Cogan JD. Transcripts from a novel BMPR2 termination mutation escape nonsense mediated decay by downstream translation re-initiation: implications for treating pulmonary hypertension. *Clin. Genet.* 2010; 77: 280–286.
2. Machado RD, Aldred MA, James V, Harrison RE, Patel B, Schwalbe EC, Gruenig E, Janssen B, Koehler R, Seeger W, Eickelberg O, Olschewski H, Elliott CG, Glissmeyer E, Carlquist J, Kim M, Torbicki A, Fijalkowska A, Szewczyk G, Parma J, Abramowicz MJ, Galie N, Morisaki H, Kyotani S, Nakanishi N, Morisaki T, Humbert M, Simonneau G, Sitbon O, Soubrier F, et al. Mutations of the TGF-beta type II receptor BMPR2 in pulmonary arterial hypertension. *Hum Mutat* 2006; 27: 121–132.
3. Machado RD, Southgate L, Eichstaedt CA, Aldred MA, Austin ED, Best DH, Chung WK, Benjamin N, Elliott CG, Eyries M, Fischer C, Gräf S, Hinderhofer K, Humbert M, Keiles SB, Loyd JE, Morrell NW, Newman JH, Soubrier F, Trembath RC, Viales RR, Grünig E. Pulmonary Arterial Hypertension: A Current Perspective on Established and Emerging Molecular Genetic Defects. *Hum. Mutat.* 2015; 36: 1113–1127.

4. Berg JN, Gallione CJ, Stenzel TT, Johnson DW, Allen WP, Schwartz CE, Jackson CE, Porteous ME, Marchuk DA. The activin receptor-like kinase 1 gene: genomic structure and mutations in hereditary hemorrhagic telangiectasia type 2. *Am J Hum Genet* 1997; 61: 60–67.
5. Trembath RC, Thomson JR, Machado RD, Morgan NV, Atkinson C, Winship I, Simonneau G, Galie N, Loyd JE, Humbert M, Nichols WC, Morrell NW, Berg J, Manes A, McGaughan J, Pauciulo M, Wheeler L. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. *N Engl J Med* 2001; 345: 325–34.
6. Montani D, Girerd B, Jaïs X, Levy M, Amar D, Savale L, Dorfmüller P, Seferian A, Lau EM, Eyries M, Le Pavec J, Parent F, Bonnet D, Soubrier F, Fadel E, Sitbon O, Simonneau G, Humbert M. Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study. *Lancet Respir. Med.* 2017; 5: 125–134.
7. Eyries M, Montani D, Girerd B, Perret C, Leroy A, Lonjou C, Chelghoum N, Coulet F, Bonnet D, Dorfmüller P, Fadel E, Sitbon O, Simonneau G, Tregouet DA, Humbert M, Soubrier F. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. *Nat Genet* 2014; 46: 65–69.
8. Hadinnapola C, Bleda M, Haimel M, Screatton N, Swift A, Dorfmüller P, Preston SD, Southwood M, Hernandez-Sanchez J, Martin J, Treacy C, Yates K, Bogaard H, Church C, Coghlan G, Condliffe R, Corris PA, Gibbs S, Girerd B, Holden S, Humbert M, Kiely DG, Lawrie A, Machado R, MacKenzie Ross R, Moledina S, Montani D, Newnham M, Peacock A, Pepke-Zaba J, et al. Phenotypic Characterization of EIF2AK4 Mutation Carriers in a Large Cohort of Patients Diagnosed Clinically With Pulmonary Arterial Hypertension. *Circulation* 2017; 136: 2022–2033.

BMP10 Homo sapiens	300	LQMRSNIIYDSTARIRRNAKGNYCKRTPLYIDFKEIGWDSWIIAPPGYEAYEC	R GVGNYP	359
BMP10 Pan troglodytes	300	LQMRSNIIYDSTARIRRNAKGNYCKRTPLYIDFKEIGWDSWIIAPPGYEAYEC	RGVGNYP	359
BMP10 Felis catus	300	LQMRSNIIYDSTARIRRNAKGNYCKRTPLYIDFKEIGWDSWIIAPPGYEAYEC	RGVGNYP	359
BMP10 Ictidomys tridecemlineatus	298	LQMRSNIIYDSTARIRRNAKGNYCKRTPLYIDFKEIGWDSWIIAPPGYEAYEC	RGVGNYP	357
BMP10 Equus caballus	300	LQMRSNIIYDSTARIRRNAKGNYCKRTPLYIDFKEIGWDSWIIAPPGYEAYEC	RGVGNYP	359
BMP10 Camelus ferus	300	LQMRSNIIYDSTARIRRNAKGNYCKRTPLYIDFKEIGWDSWIIAPPGYEAYEC	RGVGNYP	359
BMP10 Canis lupus familiaris	300	LQMRSNIIYDSTARIRRNAKGNYCKRTPLYIDFKEIGWDSWIIAPPGYEAYEC	RGVGNYP	359
BMP10 Cavia porcellus	300	LQMRSNIIYDSTARIRRNAKGNYCKRTPLYIDFKEIGWDSWIIAPTGYEAYEC	RGVGNYP	359
BMP10 Rattus norvegicus	297	LQMRSNMIDDSTARIRRNAKGNYCKKTPLYIDFKEIGWDSWIIAPPGYEAYEC	RGVGNYP	356
BMP10 Mus musculus	297	LQMRSNMIDDSSARIRRNAKGNYCKKTPLYIDFKEIGWDSWIIAPPGYEAYEC	RGVGNYP	356
BMP10 Xenopus laevis	297	LQMRSNIIYDASSRIRRNAKGNYCKKTPLYIDFSEIGWNSWIIAPQGYEAYEC	RGVCSYP	356
*****:* *:.:*****:*****.****:***** *******.*				

Supplementary table 2. Alignment of BMP10 sequences in mammalian species and xenopus laevis. The human Arginine residue 353 mutated into Cysteine in one patient is conserved in all species tested and is boxed.