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Classification of Pulmonary Arterial Hypertension by Genetic and Familial Testing

Clasificación de la hipertensión arterial pulmonar basada en el estudio genético y familiar

To the Editor,

Pulmonary hypertension is defined as a mean pulmonary artery pressure $\geq$ 25 mmHg. The pulmonary arterial hypertension (PAH) subtype of this condition is characterized by a pulmonary capillary pressure $\leq$ 15 mmHg and an increased pulmonary vascular resistance ($\geq$3 WU)[1]; untreated PAH has a poor prognosis due to right ventricular failure. Its causes include idiopathic PAH (IPAH), heritable PAH (HPAH), drug- or toxin-induced PAH, and PAH related to other causes such as congenital heart disease (PAH-CHD). It is called HPAH upon identification of a familial pattern or pathogenic mutation; *BMPR2* is the most frequently associated gene, found in up to 75% of patients with HPAH and 25% of those with IPAH.[1–3] Mutations in this gene can also favor the development of PAH in some congenital heart diseases.[4]

A genetic and family study was performed in 8 patients with PAH followed up in our center between 2013 and 2016. Our objective was to determine if the screening results would enable reclassification of the patients. The index cases were studied using massively parallel sequencing with a panel of 16 PAH-linked genes (*ACVRL1*, *BMPR1B*, *BMPR2*, *CAV1*, *EIF2AK4*, *ENG*, *FOXF1*, *GDF2*, *KCNA5*, *KCNK3*, *NOTCH3*, *RASA1*, *SMAD1*, *SMAD4*, *SMAD9*, and *TOPBP1*). Variants were considered pathogenic if they had an allelic frequency $<$ 0.01% in public databases and met the established pathogenicity criteria.[5] Pedigree charts were created and clinical and genetic screening was offered to first- and second-degree relatives.

The patients' characteristics and the genetic and family study results are detailed in Table 1. Of the 8 index cases studied, the family study allowed the identification of 2 patients with HPAH through a family history of PAH. The genetic study found pathogenic or probably pathogenic variants related to PAH in 4 patients: 1 of HPAH, 2 of IPAH, and 1 of PAH-CHD (the last 3 were later reclassified as HPAH). Only mutations in the *BMRP2* gene were detected, all previously described.

We genetically screened 14 relatives of the patients with a confirmed mutation, identifying 1 affected female carrier and 4 healthy male carriers (Table 1).

The following mutations were identified: *a)* case 1: female, 36 years old, classified as HPAH due to the identification of second-degree relatives with PAH; the *p.Cys34Phe* mutation previously described in another Spanish series[6] was found, confirming its cosegregation; *b)* case 2: male, 10 years old, with a small atrial septal defect and severe PAH-CHD disproportionate to the size of the defect; the *p.Arg491Trp* mutation was detected and the patient was considered to have dual-etiology PAH–incidental and hereditary congenital heart disease; the boy's mother had a ventricular septal defect, died during corrective surgery, and possibly had PAH; the maternal branch could not be studied because it did not reside in Spain (Figure 1); *c)* case 3: female, 41 years old, diagnosed with IPAH, with a pulmonary arteriovenous fistula $<$ 1 cm and no other typical findings of hereditary hemorrhagic telangiectasia; the cardiac output was greatly reduced, indicating that this finding had no clinical significance; because the *p.Trp13** mutation was detected in BMPR2 and no mutation was found in the genes related to hereditary hemorrhagic telangiectasia, she was reclassified as having HPAH; her father was not a carrier, and the presence of the mutation in the maternal branch could not be analyzed (Figure 1); *d)* case 6: female, 12 years old, with IPAH; because the *p.Asn442Thrfs*32* mutation was detected, she was reclassified as having HPAH (Figure 1).

Although the development of PAH has been linked to up to 21 genes,[2] our results are consistent with the literature and again show that *BMPR2* is the gene most frequently associated with PAH. Penetrance was higher in women and, due to hormonal factors, was often associated with delivery (cases 3 and 7) (Table 1).[1–3] In addition, a vasodilator response was more frequent in IPAH[6] (cases 5 and 7) (Table 1).

The European Society of Cardiology guidelines recommend the genetic screening of patients with IPAH, HPAH, hereditary hemorrhagic telangiectasia, and pulmonary veno-occlusive disease.[1,2] The genetic study of PAH-CHD patients has not been endorsed, although recent evidence shows its usefulness in this context.[4] Our series included 2 patients with PAH-CHD; 1 of these patient had a pathogenic mutation in *BMPR2*, which could indicate its diagnostic value in this subgroup, particularly when the PAH is disproportionate to the degree of the defect or when it develops after defect repair.

In conclusion, our results show that genetic and family screening of PAH enables the identification of hereditary forms and the correct classification of different subtypes, including patients with PAH-CHD with small defects. This approach not only bolsters disease management, but also genetic counseling in families, which can help to avoid transmission of the disease to offspring. For this reason, we believe that screening should be considered in routine clinical practice.

Table 1
Patients' Characteristics

Index case	Sex	Age at baseline, y	Baseline type of PAH	Final type of PAH	Other findings	Vasodilator test	mPAP, mmHg	PVR, WU	Gene	Variant detected	Previous description of the variant	Relatives			
												Carrier		With PAH	
												M	F	M	F
1	F	36	Heritable	Heritable	-	Negative	52	9.4	*BMPR2*	*p.Cys34Phe*	Probably pathogenic	2	0	0	3
2	M	10	Associated with congenital heart disease	Associated with congenital heart disease and heritable	Small ostium secundum ASD	Negative	58	12	*BMPR2*	*p.Arg491Trp*	Pathogenic	0	0	0	0
3	F	41	Idiopathic	Heritable	Pulmonary arteriovenous fistula <1 cm Postpartum	Negative	59	28.5	*BMPR2*	*p.Trp13**	Probably pathogenic	0	0	0	0
4	F	35	Associated with congenital heart disease	Associated with congenital heart disease	Large superior sinus venosus ASD	Negative	48	6.9	-	-	-	-	-	0	0
5	F	34	Idiopathic	Idiopathic	-	Positive	40	-	-	-	-	-	-	0	0
6	F	12	Idiopathic	Heritable	-	Negative	55	10.2	*BMPR2*	*p.Asn442Thrfs*32*	Pathogenic	2	0	0	1
7	F	39	Idiopathic	Idiopathic	Postpartum	Positive	37	12.2	-	-	-	-	-	0	0
8	F	65	Heritable	Heritable		Negative	49	9.3	-	-	-	-	-	0	1

ASD, atrial septal defect; F, female; PAH, pulmonary arterial hypertension; M, male; mPAP: mean pulmonary arterial pressure; PVR, pulmonary vascular resistance.

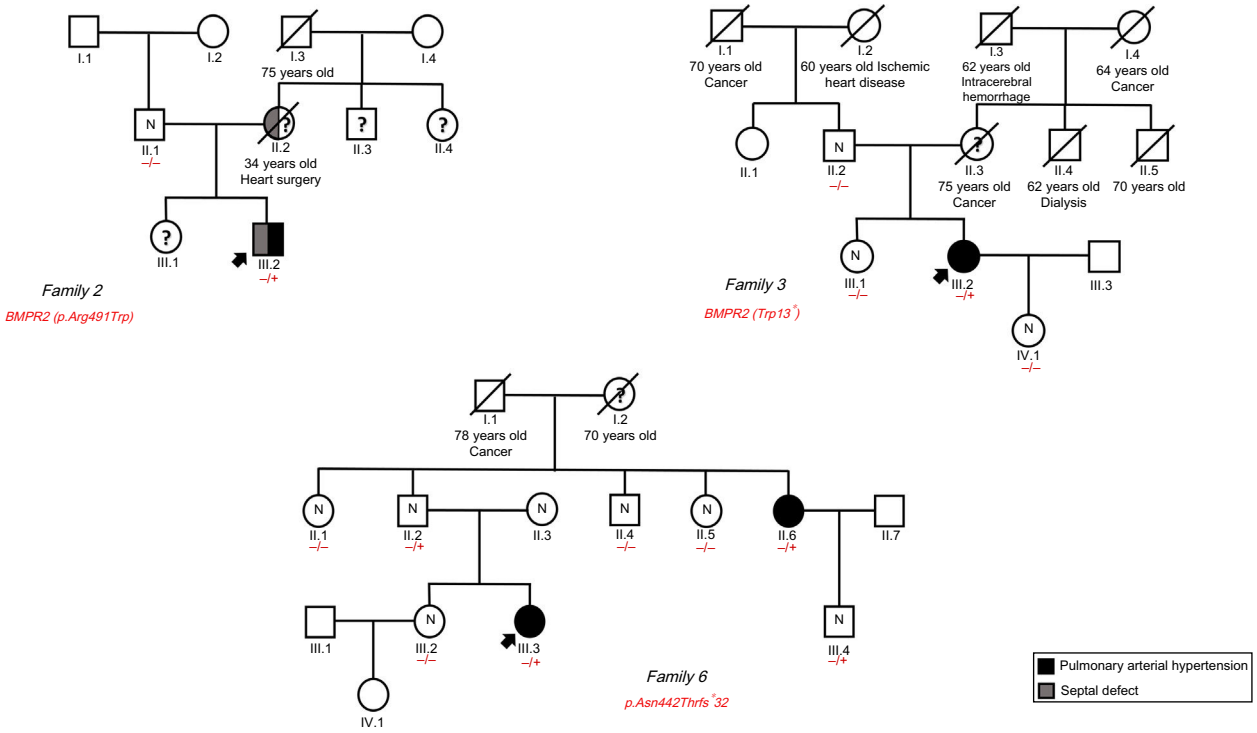

Figure 1. Pedigrees of the reclassified index cases.?, unknown phenotype; –, not carrier; +, carrier; arrow, proband; black/gray, affected; circle, female; N, not affected; oblique line, deceased; square, male.

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A Drug Utilization Study of Sacubitril/Valsartan in Catalonia

Utilización de sacubitrilo-valsartán en Cataluña

To the Editor,

Sacubitril/valsartan, indicated for the treatment of chronic heart failure with reduced ejection fraction, was released on to the market in Spain in October 2016. It is the first available drug with a combined mechanism of angiotensin II receptor and neprilysin inhibition and with demonstrated superiority to enalapril for the composite outcome of cardiovascular mortality and hospitalization for heart failure.[1] The main safety issue is hypotension.[1]

The study evaluating the safety and efficacy of sacubitril/valsartan had strict inclusion and exclusion criteria, so extrapolation of the results to clinical practice, especially the safety results, is not clear-cut. Both the clinical guidelines and the regulatory