Case Report

Pulmonary Circulation

Different forms of pulmonary hypertension in a family with clinical and genetic evidence for hereditary hemorrhagic teleangectasia type 2

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Abstract

Hereditary hemorrhagic telangiectasia (HTT) is an autosomal dominant disease, most frequently caused by a mutation in either *ENG* or *ACVRL1*, which can be associated with pulmonary arterial hypertension (PAH). In this report, we describe a new unpublished *ACVRL1* mutation segregating in three members of the same family, showing three different types of pulmonary hypertension (PH) in the absence of *BMPR2* mutations. The first patient has a form of heritable PAH (HPAH) in the absence of hepatic arteriovenous malformations (AVMs); the second one has a severe form of portopulmonary hypertension (PoPAH) associated with multiple hepatic AVMs; the third one has hepatopulmonary syndrome (HPS) with numerous hepatic arteriovenous fistulas and a form of post-capillary PH due to high cardiac output. In summary, a single mutation in the *ACVRL1* gene can be associated, in the same family, with an extreme phenotypic variability regarding not only the clinical presentation of HHT but also the type of PH in the absence of *BMPR2* mutations. More studies are needed to evaluate if this variability can be explained by the presence of additional variants in other genes relevant for the pathogenesis of HHT.

Keywords

Hereditary hemorrhagic telangiectasia, *ACVRL1*, pulmonary arterial hypertension, hepatic arteriovenous malformations, hepatopulmonary syndrome

Date received: 18 March 2018; accepted: 20 May 2018

Pulmonary Circulation 2018; 8(4) 1–4
DOI: 10.1177/2045894018782664

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease characterized by vascular malformations as telangiectases and arteriovenous malformations (AVMs) in internal organs, including the liver and lungs. Two genes are commonly mutated in HHT: *ENG* (OMIM*131195; Endoglin; HHT1) and *ACVRL1* (OMIM*601284; activin A receptor, type II-like I or ALK1; HHT2). The clinical diagnosis of HHT is based on the Curaçao criteria.[1]

HHT may be associated with typical pulmonary arterial hypertension (PAH), called portopulmonary hypertension (PoPAH), which carries a poor prognosis.[2–8] Another

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clinical entity that may lead to pulmonary hypertension (PH) in HHT patients is hepatopulmonary syndrome (HPS), a disease characterized by abnormal arterial oxygenation caused by intrapulmonary vascular dilatations in the setting of advanced liver disease, portal hypertension, or congenital portosystemic shunts.[9] HPS is a consequence of alterations in the pulmonary microvasculature that impair gas exchange.[10–13] Large hepatic or pulmonary AVMs are common in HHT patients and may variably contribute through the high cardiac output to the development of PH and right ventricular failure.[2]

Case description

We report a family with three patients carrying the c.595 G>C (p.A199P) mutation in *ACVRL1* (Fig. 1); co-segregation of the mutation with HHT and PAH phenotype and results of *in silico* analyses (MutationTaster-2, Polyphen-2 and VEP) demonstrate that the variant observed is pathogenic. This mutation has already been reported in association with PH by Song et al.[14] and leads to a substitution of a conserved residue in the GS domain of ALK1. The three patients showed the clinical manifestations of HHT but different forms of PH. Sequencing of *BMPR2* coding regions failed to show any pathogenic mutation.

Patient 1 was born in 1955. In 2004 she complained of dyspnea. Left heart disease and lung diseases were excluded. The computed tomography (CT) angiography scan showed no sign of chronic thromboembolic pulmonary disease, but it revealed the presence of a dilated pulmonary trunk (maximum diameter = 48 mm) and several little aneurysms of the splenic artery. No pulmonary or hepatic AVMs were observed. Right heart catheterization (RHC) showed high pulmonary artery pressures (sPAP/dPAP/mPAP = 51/27/37 mmHg), normal pulmonary artery wedge pressure (PAWP; 7 mmHg), normal right atrial pressure (RAP;

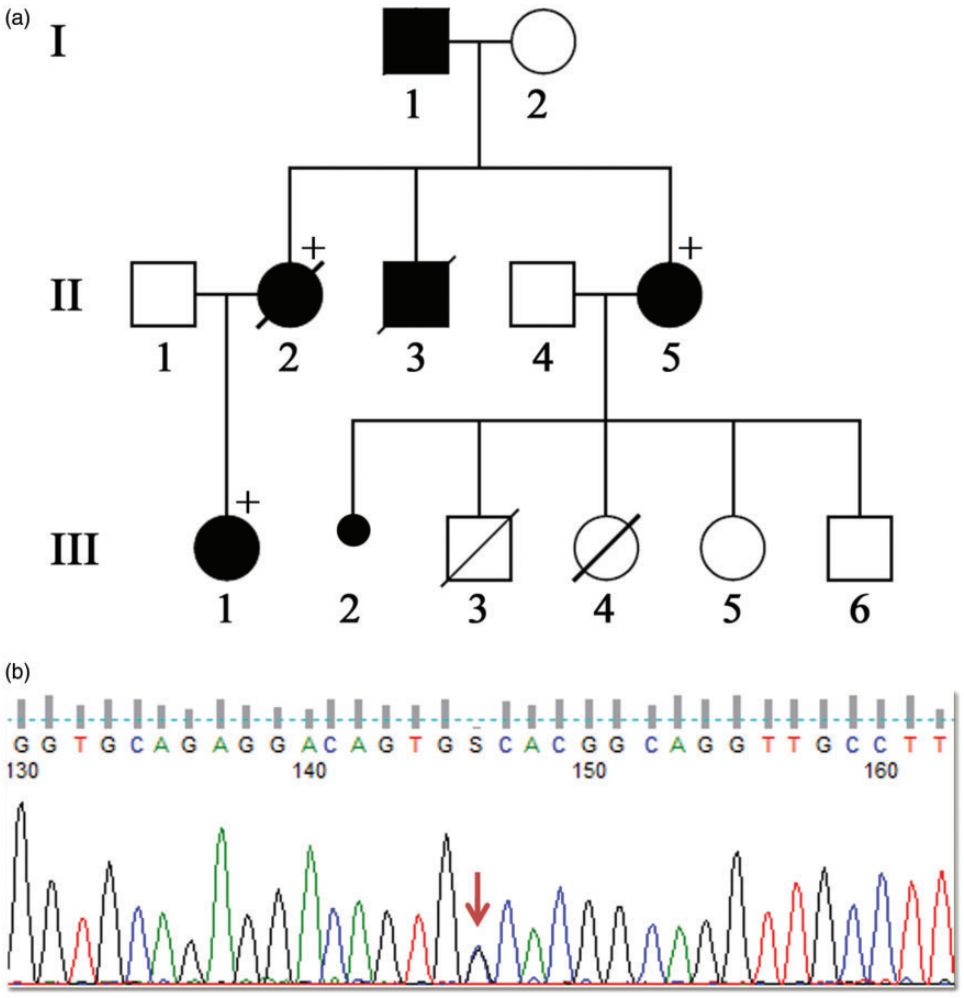

Fig. 1. (a) Genealogical three of the family. In black, patients presenting with HHT symptoms. The "+" symbol indicates individuals with proven pulmonary complications and (b) Portion of the electropherogram of *ACVRL1* exon 5. Red arrow shows the G>C change observed in the three patients.

1 mmHg), high pulmonary vascular resistance (PVR; 6.2 WU), and normal cardiac index (CI; 3.1 L/min/mq) (Table 1).

The patient also fit the diagnostic criteria for HHT as she presented mild epistaxis, telangiectases on the tongue and lips, and a positive family history for HHT. The final diagnosis was heritable PAH (HPAH). The patient was in World Health Organization (WHO) functional class (FC) II and started PAH-specific therapy with bosentan. In 2014, abdominal ultrasound showed the presence of a millimetric liver AVM in the VIII hepatic segment and the thoracic CT scan showed a dilated pulmonary trunk (49–50 mm), aneurysmatic features of bronchial arteries, but no evidence of pulmonary AVMs. In 2018, she is alive in WHO FC II on oral therapy.

Patient 2 was born in 1945. She was diagnosed with HHT in her early 30 s as she fitted the diagnostic criteria for HHT: mild epistaxis since childhood; telangiectases on the tongue, palate, lips, and fingertips; hepatic AVMs; and positive family history. An occasional ECG performed in 2010 demonstrated signs of right ventricular overload. The subsequent echocardiographic examination showed a dilated right ventricle with mild tricuspid regurgitation and the estimated sPAP was 100 mmHg. RHC revealed pre-capillary PH (sPAP/dPAP/mPAP = 105/47/72 mmHg; PAWP = 5 mmHg) with normal RAP (5 mmHg), normal CI (3.15 L/min/mq), and very high PVR (13.9 WU) (Table 1). The CT angiography scan described the presence of diffuse intrahepatic AVMs, while there was no evidence of pulmonary AVMs. The diagnosis of PoPAH was made and the patient started PAH-specific therapy with bosentan. She died in 2012 during abdominal surgery.

Patient 3 was born in 1968. In 2010, she complained of mild effort dyspnea and underwent transthoracic echocardiography that showed initial dilatation of the right ventricle with an estimated sPAP of 40 mmHg. The patient refused to perform further examinations until December 2016 when echocardiography showed a dilated right ventricle with mild diastolic compression of left ventricle and an estimated PAP of 55 mmHg. The patient was in WHO FC II. In February 2017, RHC demonstrated a form of moderate post-capillary PH due to high cardiac output: PAP and PAWP were elevated (sPAP/dPAP/mPAP = 48/18/32 mmHg; PAWP = 18 mmHg), CI was high (4.35 L/min/mq) and PVR was low (PVR = 2 WU) (Table 1). The lung CT scan showed the presence of AVMs between the left hepatic artery and portal branches. An abdominal ultrasound detected the presence of ectasia of the hepatic artery (diameter = 7–8 mm) and a mild enlargement of the portal vein (diameter = 14 mm); there was a shunt between the hepatic artery and the portal vein. The final diagnosis was HPS. In March 2017, an abdominal CT scan confirmed the presence of several vascular shunts in the left hepatic lobe. The left hepatic artery showed a tortuous course and the presence of an AVM with the corresponding portal branch. Additional AVMs were detected in segments IV, VI, and VII. An AVM of about 5 mm was found in the uncinate process of the pancreas. In June 2017, the patient underwent an angiography of the portal circulation that confirmed the presence of multiple hepatic AVMs. In October 2017, the patient underwent a closure of multiple hepatic AVMs with embolization with a microcatheter. At three-month follow-up, hepatic function was normal.

Table 1. Hemodynamic data in three patients.

	Patient 1 (HPAH)	Patient 2 (PoPAH)	Patient 3 (HPS)
sPAP (mmHg)	51	105	48
dPAP (mmHg)	27	47	18
mPAP (mmHg)	37	72	32
PAWP (mmHg)	7	5	18
RAP (mmHg)	1	5	8
PVR (WU)	6.2	13.9	2
CI (L/min/mq)	3.1	3.15	4.35

HPAH, heritable pulmonary arterial hypertension; PoPAH, portopulmonary hypertension; HPS, hepatopulmonary syndrome; sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressures; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; PVR, pulmonary vascular resistance; CI, cardiac index.

Discussion

We report a unique family in which an *ACVRL1* novel mutation causes a typical HHT phenotype including the known intrafamilial clinical variability. In addition, these members of the family also showed PH. Recently, Revuz et al. described the different PH subtypes observed in a large cohort of HHT patients,[8] but to the best of our knowledge, this is the first time that different forms of PH are described within the same family. The first patient has a form of HPAH of moderate severity in the absence of hepatic AVMs. The second one presented a severe form of PoPAH. The third patient was diagnosed with HPS and has a form of Group 2 PH due to the high cardiac output state, which was treated by embolization of the hepatic AVMs.

BMPR2 is the major gene involved in HPAH, but in 2001 Trembath et al.[6] demonstrated that *ACVRL1* mutations also cause a form of PH clinically and histologically indistinguishable from primary PH. In the family presented here, the concomitant presence of PH and clinical signs of HHT suggested the involvement of HHT-related genes and we were able to identify a novel *ACVRL1* disease causing mutation but we excluded the presence of mutations in the coding regions of *BMPR2*.

The family presented here is relevant to stress the need for extensive genetic investigation and for extended clinical work-up; the clinical variability in the presence of the same mutation is a challenge in the perspective of precision medicine. Collecting similar cases or families is relevant to

discuss why we may observe even large differences in clinical pictures related to the same genotype. The extension of genetic analyses to the whole genome and epigenetic studies might identify variants and factors, respectively, impacting the clinical presentation. Thus, it will be possible to explain, at least in part, the inter- and intra-familial phenotypic heterogeneity.[15]

Acknowledgments

The authors thank all the patients who took part in this study.

Declaration of conflicting interests

The author(s) declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. This work is part of the results of research activity by SP, who holds a research fellowship (2/R.C./2016, no. 20160028774) from the IRCCS Fondazione Policlinico San Matteo, Pavia, Italy.

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