

# A novel BMPR2 mutation in a patient with heritable pulmonary arterial hypertension and suspected hereditary hemorrhagic telangiectasia

## A case report

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### Abstract

**Rationale:** *BMPR2* mutation is the most common cause of heritable pulmonary arterial hypertension (HPAH), but rare in hereditary hemorrhagic telangiectasia (HHT). *ACVRL1*, *ENG* and *SMAD4* are the most common gene mutations reported in HPAH with HHT.

**Patient concerns:** We report a 11-year-old boy with a definite diagnosis of pulmonary hypertension and suspected HHT with recurrent epistaxis. The results of gene detection showed that there was a nonsense mutation in *BMPR2*. The results of gene detection of *ACVRL1*, *ENG* and *SMAD4* were normal.

**Diagnoses:** Heritable pulmonary arterial hypertension with suspected hereditary hemorrhagic telangiectasia.

**Interventions:** Patient was treated with ambrisentan 2.5 mg qd. About a month later, the patient developed massive gastrointestinal bleeding and sudden convulsions. The patient's vital signs were stable after symptomatic treatment.

**Outcomes:** After discharging from hospital, the patients continued to take ambrisentan. No epistaxis or gastrointestinal bleeding was found in one month of follow-up, but the symptoms of chest tightness were not significantly alleviated.

**Lessons:** *BMPR2* with a nonsense mutation is more likely to cause HPAH with HHT and are more likely to be life-threatening.

**Abbreviations:** ActRIIA = type-IIA activin receptor, *ACVRL1* = activin receptor-like kinase 1, AVT = acute pulmonary vasodilator testing, *BMPR2* = bone morphogenetic protein receptor 2, CTPA = computed tomographic pulmonary angiography, *ENG* = endoglin, HHT = hereditary hemorrhagic telangiectasia, HPAH = heritable pulmonary arterial hypertension, *SMAD4* = mothers against decapentaplegic homolog 4 - $\beta$ .

**Keywords:** bone morphogenetic protein receptor 2 mutation, hereditary hemorrhagic telangiectasia, heritable pulmonary arterial hypertension, nonsense mutation

## 1. Introduction

Heritable pulmonary arterial hypertension (HPAH) is a group of diseases characterized by persistent increase of pulmonary

vascular resistance and progressive right heart failure caused by genetic factors, which includes clinically sporadic idiopathic PAH with germline mutations and clinical familial cases with or

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The datasets generated and analysed during the current study are not publicly available [because the data relate to a human research participant, it may not be appropriate to make them publicly available] but are available from the corresponding author on reasonable request.

Written informed consent was obtained from the parents of the patient for the genetic study and publication of this case report. The study was approved by the Ethics Committee of Wenzhou People's Hospital.

Written consent for publication of this case report was obtained from the parents of the patient.

The authors report no conflicts of interest.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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**Figure 1.** Electrocardiograph revealed a sinus rhythm, and right axis deviation reached +132°.

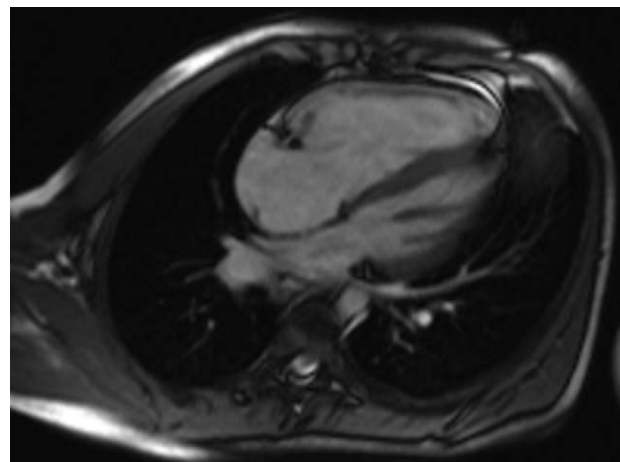
without identified germline mutations.<sup>[1]</sup> The bone morphogenetic protein receptor 2 (*BMPR2*) gene mutation is an important pathogenic factor of HPAH.<sup>[2,3]</sup> It exists in around 70% to 80% of families with PAH and 10% to 20% of IPAH cases.<sup>[4]</sup>

Hereditary hemorrhagic telangiectasia (HHT) is usually associated with mutations in endoglin (*ENG*), activin receptor-like kinase 1 (*ACVRL1*), mothers against decapentaplegic homolog 4 (*SMAD4*), etc. Only 1 case reported that *BMPR2* gene analysis is indicated in patients affected with both HHT and HPAH.<sup>[5]</sup> Here we report an 11-year-old boy diagnosed with HPAH and suspected HHT, which may be associated with a novel nonsense mutation of *BMPR2*.

## 2. Case report

A 11-year-old boy was admitted to our outpatient department on October 15, 2018, with chest tightness after exercise for 5 years, aggravated in half a month, and repeated hemorrhagia for 2 years. The patient had a history of syncope 1 year ago. His grandmother had a history of pulmonary hypertension. On admission examination, his heart rate was 78 beats/min, his blood pressure was 102/65 mm Hg, and his SpO<sub>2</sub> was 96%. The heart sounds were regular, and no murmur was detected. No obvious abnormalities were observed in the rest of the physical examinations. Blood tests noted normal hemoglobin (146 g/L, normal 130–175), increased N-terminal pro-brain natriuretic peptide (NT-ProBNP, 643 pg/ml, normal <125), increased total bilirubin (30 μmol/L, normal 3.4–21.1), increased direct bilirubin (10.1 μmol/L, normal <6.8), increased indirect bilirubin (20.6 μmol/L, normal <3.1–17.0), and increased alkaline phosphatase (324 U/L, normal 45–125). Electrocardiograph (ECG) revealed a sinus rhythm, and right axis deviation reached +132° (Fig. 1). Transthoracic echocardiography revealed a right atrial dimension of 40 mm, a right ventricular dimension of 30 mm, a left atrial dimension of 28 mm, a left ventricular end-diastolic

dimension of 43 mm, a left ventricular end-systolic dimension of 30 mm, a left ventricular ejection fraction of 73%, a tricuspid annular plane systolic excursion of 15 mm, a maximum tricuspid regurgitation velocity, and a pulmonary artery systolic pressure of 91 mm. Cardiac magnetic resonance revealed an enlargement of right atrium and right ventricle (Fig. 2). Cardiopulmonary exercise test showed that the overall functional status of cardiopulmonary motor function, the effectiveness of oxygen uptake ventilation and nitrogen dioxide ventilation were significantly limited. Computed tomographic pulmonary angiography (CTPA) showed enlargement of right ventricle, dilatation of main pulmonary artery, changes of pulmonary hypertension, and diffuse small patches of light ground glass opacity in both lungs.



**Figure 2.** Cardiac magnetic resonance revealed an enlargement of right atrium and right ventricle.

**Table 1****Rare mutation of *BMPR2* in this patient.**

Chromosome	Reference	Mutation	Mutation region	gene	Mutation type	Amino acid changes
2	G	A	exonic	<i>BMPR2</i>	nonsense	<i>BMPR2</i> ,NM_001204,exon11,c.1452G>A,p.W48 4X

The patient underwent right cardiac catheterization, acute pulmonary vasodilator testing (AVT) and pulmonary angiography on October 29, 2018. Details are as follows: (1) Baseline blood pressure was 115/54/74 mm Hg, pulmonary arterial pressure (PAP) was 95/40/59 mm Hg, pulmonary artery wedge pressure was 8/7/6 mm Hg, cardiac output was 4.23L/min, cardiac index was 2.9L/min/m<sup>2</sup>, and pulmonary vascular resistance was 12.53 Wood U, (2) PAP was 109/32/60 mm Hg after inhalation of vantamivir (AVT negative), (3) Pulmonary angiography showed dilatation of left and right pulmonary arteries, no obvious stenosis, filling defect or occlusive lesions, no decrease or absence of distal segmental perfusion, and the perfusion velocity was acceptable.

Later, we used high-throughput gene sequencing technology to detect all exon genes for the patient. Genetic tests revealed that the patient carried a non-sense mutation of *BMPR2*, c. 1452G > A, which resulted in the termination of *BMPR2* protein at 484 position and significantly affected the function of the protein (Table 1). Mutation analysis of *ACVRL1*, *ENG*, and *SMAD4* was normal.

According to the symptoms, signs and examination results, we diagnosed familial pulmonary arterial hypertension and suspected hereditary hemorrhagic telangiectasia. The patient was discharged from hospital on October 28, 2018, and was treated with ambrisentan 2.5 mg qd.

On November 26, 2018, the patient had a large amount of black stool. The stool was hard and normal in shape, and there was little blood on the surface. The patient had abdominal discomfort and no bleeding and ecchymosis on the skin. At 4 AM on November 28, 2018, the patient woke up in sleep, followed by convulsion, characterized by sudden loss of consciousness, eyeball upturn, sudden generalized and ankylosing facial and extremity muscle convulsions, cyanosis of lips, incontinence of urine and feces, and self-remission after 30 seconds. The patient was immediately admitted to the emergency department. Blood tests noted decreased hemoglobin (62 g/L, normal 130–175), increased NT-ProBNP (1010pg/ml, normal < 125), increased creatine kinase (721U/L, normal 55–170), increased lactate dehydrogenase (247U/L, normal 135–225). Faecal occult blood test was positive. There were no significant changes in echocardiographic data. Short-range video electroencephalogram was normal. No obvious abnormalities were found in cranial magnetic resonance imaging and magnetic resonance angiography. We planned to have further gastrointestinal endoscopy, but the patient's family refused. Acute gastrointestinal bleeding and convulsions caused by acute ischemic-hypoxic encephalopathy were considered in the diagnosis. Therapeutically, omeprazole was given to inhibit gastric acid secretion, tranexamic acid and etamsylate were used to stop bleeding, and suspended red blood cells were infused. On December 2, 2018, hemoglobin was 104 g/L, and fecal occult blood test was negative. During the follow-up for the next month, the patient had no black stool, no hemorrhinina, and no significant changes in chest tightness.

### 3. Discussion

In view of the hereditary pulmonary arterial hypertension in this patient, the mutation of *BMPR2* gene was considered. The 1452 base G of exon 11 of *BMPR2* gene in this patient was replaced by base A, which resulted in the change of tryptophan at position 484 to termination code, that is nonsense mutation.

*BMPR2* gene belongs to the transforming growth factor- $\beta$  (TGF- $\beta$ ) receptor family. TGF- $\beta$  superfamily signal transduction pathway can inhibit the proliferation and induce apoptosis of vascular smooth muscle and endothelial cells. BMP binds to *BMPR2* and is phosphorylated, then activates *BMPR1* to form a complex. The serine/threonine disability in Gly-Ser region of *BMPR1* is phosphorylated by *BMPR2*, followed by the phosphorylation of Smad1, 5, 8 proteins, which dissociates with *BMPR1*. Two Smad1 and Smad4 bind to the nucleus and bind to specific transcriptional promoters or repressors, which act on transcriptional regulators to inhibit cell proliferation and promote cell apoptosis.<sup>[6]</sup> Therefore, it is presumed that abnormal *BMPR2*, as a cell surface receptor, may disrupt the signal pathway mediated by *BMPR2*, leading to uncontrolled proliferation of pulmonary artery wall cells, thus causing pulmonary arterial hypertension.<sup>[7]</sup>

HHT is an autosomal dominant vascular disorder. The disease is caused by pathogenic mutations of either *ACVRL1* or *ENG*,<sup>[8–11]</sup> and, rarely, Smad 4, which is also associated with juvenile polyposis.<sup>[3]</sup> The patient had recurrent epistaxis and massive gastrointestinal hemorrhage. CTPA showed diffuse small patches of light ground glass opacity in both lungs. According to the diagnostic criteria of HHT,<sup>[12]</sup> the presence of suspicious hereditary hemorrhagic telangiectasia was considered.

BMP9 signaling in endothelial cells is a key mechanism in the pathogenesis of HHT.<sup>[5]</sup> It is a special ligand for ALK1, *ENG*, *BMPRII*, and the type-IIA activin receptor (*ActRIIA*) which can maintain BMP9 signaling, so that *BMPR2* mutations do not usually lead to overt HHT.<sup>[13]</sup> However, a *BMPR2* mutation [c.1297C>T (p.Q433X)] in which *ActRIIA* cannot complement *BMPRII* function has been reported, and leads to the manifestation of HHT in HPAH patients.<sup>[5]</sup> Our patient also had nonsense mutations in *BMPR2*, so we suspect that premature termination of translation of the *BMPR2* gene may result in greater *BMPRII* dysfunction. This may seriously affect the BMP9 signal, even if *ActRIIA* works.

### 4. Conclusion

The novel *BMPR2* mutation we report is extremely dangerous because it not only causes pulmonary hypertension, but also manifests as HHT. In this patient, hemorrhagic anemia aggravates the decrease of cardiac output caused by pulmonary hypertension, leading to severe hypoxemia and acute ischemic-hypoxic encephalopathy. Through active treatment, although the vital signs of the patient has been stabilized, the therapeutic effect of ambrisentan on PHA is not ideal at present. The patient needs a

longer follow-up to assess the efficacy of antibiotics and the long-term prognosis of this *BMPR2* mutation.

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### Author contributions

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