**SMAD4** mutation and the combined syndrome of juvenile polyposis syndrome and hereditary haemorrhagic telangiectasia

Nithya K Iyer,1 Carol A Burke,2 Brandie H Leach,3 Joseph G Parambil1

**ABSTRACT**

Juvenile polyposis syndrome (JPS) and hereditary haemorrhagic telangiectasia (HHT) are autosomal dominant disorders with characteristic clinical phenotypes. Recently, reports of the combined syndrome of JPS and HHT have been described in individuals with mutations in the **SMAD4** gene, whose product—**SMAD4**—is a critical intracellular effector in the signalling pathway of transforming growth factor β (TGFβ). This report describes a 24-year-old man who presented to the Respiratory Institute after colectomy for JPS with a **SMAD4** mutation and who was subsequently diagnosed to have HHT with asymptomatic cerebral and pulmonary arteriovenous malformations (AVMs). Patients with JPS due to a **SMAD4** mutation should be screened for the vascular lesions associated with HHT, especially occult AVMs in visceral organs, which may potentially present catastrophically with serious medical consequences.

A 24-year-old man, who never smoked tobacco, was seen in the Respiratory Institute after identifying the presence of a deletion mutation in the **SMAD4** gene. His history began 8 months previously, when juvenile polyposis syndrome (JPS) was diagnosed after he underwent colonoscopy for an episode of haematochezia. Colonoscopy revealed multiple polyps distributed diffusely throughout the colon; biopsy of several random polyps showed hamartomatous features without evidence of dysplasia consistent with juvenile polyposis. Due to the disease burden, total colectomy with ileo-rectal anastomosis was recommended. On the day of the operation, he was premedicated with 2 mg of midazolam in the preanaesthesia holding area, following which he developed atrial fibrillation (AF). The procedure was cancelled and bedside echocardiogram was performed along with Cardiology consultation. The echo showed no evidence of structural heart disease, with normal left and right ventricular size and function, normal atrial chambers, normal valvular apparatuses and no suggestions of pulmonary hypertension. Following the intravenous injection of agitated saline there was late appearance of bubbles in the left atrium suggestive of an intrapulmonary shunt. With the use of supplemental oxygen and 25 mg of oral metoprolol, the episode of AF spontaneously terminated within 6 h and he was sent home with an event monitor. On follow-up with Cardiology a month later, he was asymptomatic and no further episodes of AF were documented on event monitoring. He was diagnosed with lone AF that was triggered by sedation, proceeded to surgery uneventfully and was discharged home in 4 days.

Due to the diagnosis of JPS, molecular genetic tests were conducted to identify mutations in the **BMPR1A** and **SMAD4** genes. Mutation analysis with PCR identified a deletion mutation, 1228-1229delCA, located within the MH2 domain of the **SMAD4** gene. His parents and five other siblings underwent screening genetic testing and the same mutation was identified in his mother, two brothers and one sister.

He was subsequently referred to the Respiratory Institute for further evaluations. On taking his history, besides the single episode of haematochezia, he reported recurrent spontaneous episodes of epistaxis since childhood, but denied haemoptysis, melena or haematemesis. He denied history of iron deficiency anaemia, or symptoms suggestive of stroke or seizures. Physical examination was remarkable for the presence of telangiectasias on the lips and nasal cavity. He had normal heart and lung sounds on auscultation, there was no evidence of cyanosis or digital clubbing, and a detailed neurological examination was normal.

Contrast-enhanced helical CT of the chest with maximum intensity projection reconstructions identified an arteriovenous malformation (AVM) in the right middle lobe with a 3.6 mm feeding vessel (figure 1) and a smaller AVM in the right lower lobe with a 1.5 mm feeding vessel. MRI of the brain showed a supratentorial dural arteriovenous fistula that was confirmed by cerebral angiography (figure 2). Doppler ultrasonography of the liver did not identify any telangiectasias or vascular masses. With this constellation of findings he met the Curaçao criteria for a diagnosis of definite haemorrhagic telangiectasia (HHT).1 Given the history of JPS and the presence of a **SMAD4** mutation, diagnosis of the combined syndrome of JPS—HHT was established. Due to the risks of serious neurological events with pulmonary AVMs supplied by a feeding artery at least 5 mm in diameter or larger, he underwent prophylactic coil embolotherapy of the right middle lobe AVM.

On follow-up in 6 months, he felt well and denied any respiratory or gastrointestinal symptoms. He continued, however, to have mild infrequent episodes of epistaxis with normal haemoglobin levels and no requirements for blood transfusions.

**DISCUSSION**

The combined syndrome of JPS—HHT is a rare disorder caused by **SMAD4** mutations that tend to cluster in the MH2 domain of the protein.2 3 Since 1980 case reports of patients with phenotypic features of both JPS and HHT began to be published and this prompted questions about a single genetic mutation.

---

1Respiratory Institute, Cleveland Clinic, Cleveland, Ohio, USA
2Digestive Diseases Institute, Cleveland Clinic, Cleveland, Ohio, USA
3Genomic Medicine Institute, Cleveland Clinic, Cleveland, Ohio, USA

Correspondence to
Joseph G Parambil, Department of Pulmonary & Critical Care Medicine, Respiratory Institute, Desk A-90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA; parambj@ccf.org

Received 23 October 2009
Accepted 6 May 2010
involvement most commonly manifests as pulmonary AVMs, although hepatic and cerebral AVMs have also been infrequently noted. The mean age of AVM detection is 26 years (range: 4 months to 60 years). Thus far, there has been no identification of patients with SMAD4-positive JPS—HHT with pulmonary arterial hypertension.

SMAD4 is a critical intracellular effector in transforming growth factor β (TGFβ) signalling which controls a plethora of cellular responses. Despite the pleiotropy of TGFβ, its downstream messenger elements remain relatively constant, including cell membrane-based type II, type I and accessory receptors, and intracellular receptor-regulated SMADs (R-SMADs) and the co-SMAD, SMAD4. TGFβ is essential for vascular integrity, as ENG (accessory receptor) and ALK1 (type II receptor) mutations lead to the failure to form cord-like vascular structures which leads to the fragility of small vessels with bleeding characteristic of HHT, or to disrupted and abnormal angiogenesis after injuries, and may explain the clinical symptoms associated with this disease. In the gastrointestinal system, TGFβ signalling is thought to exert a landscaping effect from within the microenvironment as SMAD4 and BMPR1A (type I receptor) mutations lead to mucosal hyperplasia and polyph formation.

Greater awareness of this rare syndrome and its implications is needed among respiratory physicians caring for these patients. Patients with JPS and SMAD4 mutations should be screened for the vascular lesions associated with HHT, especially occult AVMs in visceral organs that may otherwise present suddenly with serious medical consequences. Similarly, in patients with HHT with neither ENG nor ALK1 mutations, molecular testing for SMAD4 mutations should be included as their presence suggests an elevated risk of gastrointestinal polyposis, and screening for colonic and gastric polyps associated with JPS needs to be conducted.

**Competing interests** None.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**REFERENCES**


SMAD4 mutation and the combined syndrome of juvenile polyposis syndrome and hereditary haemorrhagic telangiectasia

Nithya K Iyer, Carol A Burke, Brandie H Leach and Joseph G Parambil

Thorax 2010 65: 745-746
doi: 10.1136/thx.2009.129932

Updated information and services can be found at:
http://thorax.bmj.com/content/65/8/745

These include:
References
This article cites 14 articles, 4 of which you can access for free at:
http://thorax.bmj.com/content/65/8/745#BIBL
Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/