Published in final edited form as:
Am J Med Genet A. 2013 January ; 161(1): 185–191. doi:10.1002/ajmg.a.35659.

Thoracic Aortic Disease in Two Patients with Juvenile Polyposis Syndrome and *SMAD4* mutations

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Abstract

Dilation or aneurysm of the ascending aorta can progress to acute aortic dissection (Thoracic Aortic Aneurysms and Aortic Dissections, TAAD). Mutations in genes encoding TGF-β related proteins (*TGFBR1, TGFBR2, FBN1,* and *SMAD3)* cause syndromic and inherited TAAD. *SMAD4* mutations are associated with juvenile polyposis (JPS) and a combined JPS-hereditary hemorrhagic telangiectasia (HHT) known as JPS-HHT. A family with JPS-HHT was reported to have aortic root dilation and mitral valve abnormalities. We report on two patients with JPS-HHT with *SMAD4* mutations associated with thoracic aortic disease. The first patient, an 11-year-old boy without Marfan syndrome features, had JPS and an apparently *de novo SMAD4* mutation (c. 1340_1367dup28). Echocardiography showed mild dilation of the aortic annulus and aortic root, and mild dilation of the sinotubular junction and ascending aorta. Computed tomography confirmed aortic dilation and showed small pulmonary arteriovenous malformations (PAVM). The second patient, a 34-year-old woman with colonic polyposis, HHT, and Marfan syndrome, had a *SMAD4* mutation (c.1245_1248delCAGA). Echocardiography showed mild aortic root dilation. She also had PAVM and hepatic focal nodular hyperplasia. Her family history was significant for polyposis, HHT, thoracic aortic aneurysm, and dissection and skeletal features of Marfan syndrome in her father. These two cases confirm the association of thoracic aortic disease with JPS-HHT resulting from *SMAD4* mutations. We propose that the thoracic aorta should be screened in patients with *SMAD4* mutations to prevent untimely death from dissection. This report also confirms that *SMAD4* mutations predispose to TAAD.

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The authors declare no conflict of interest.

Keywords

aortic dilation; hereditary hemorrhagic telangiectasia; juvenile polyposis Syndrome; *SMAD4*; TGF-beta signaling; thoracic aortic aneurysm and dissection

INTRODUCTION

Thoracic aortic aneurysm leading to acute aortic dissections (TAAD) is a vascular complex that is a common cause of premature death. Thoracic aortic aneurysms are typically asymptomatic and under-diagnosed and often lead to an acute aortic dissection with life-threatening complications including sudden catastrophic death [Hiratzka et al., 2010; Hoyert et al., 2001; Milewicz and Regalado 2003; van de Laar et al., 2011]. A predisposition for TAAD can be inherited in an autosomal dominant manner as part of a syndrome or in the absence of syndromic features, termed familial TAAD. Mutations in the TGFβ receptors type I and type II (*TGFBR1*; OMIM: 190181 and *TGFBR2*; OMIM: 190182, respectively) have been reported to be associated with the Loeys-Dietz syndrome (OMIM: 609192, Marfan syndrome type 2 (OMIM: 610380, and familial TAAD (OMIM: 608967) [Loeys et al., 2005; Matyas et al., 2006; reviewed in Milewicz and Regalado 2003; Mizuguchi et al., 2004; Pannu et al., 2005]. Mutations in *SMAD3* (OMIM: 603109) encoding a downstream signaling protein in the TGFβ signaling pathway, have been reported to cause TAAD alone and TAAD with other arterial aneurysms [Regalado et al., 2011] and the Aneurysms-Osteoarthritis syndrome (AOS) (OMIM: 613795) [van de Laar et al., 2011]. More recently, mutations in the gene encoding one of the TGFβ ligands, TGFβ2 (*TGFB2*: OOMIM 190220) have been identified as a cause of inherited TAAD with mild systemic manifestations of Marfan syndrome [Boileau et al., 2012]

Hereditary hemorrhagic telangiectasia (HHT; OMIM: 187300) is an autosomal dominantly inherited vascular dysplasia characterized by multiple arteriovenous malformations (AVM) in large visceral organs (e.g., lung, brain and liver) and telangiectases on the skin and/or mucous membranes. The HHT phenotype is caused by mutations in genes that are also part of the TGFβ signaling pathway, including endoglin (*ENG;* OMIM: 131195) and *ACVRL1 (ALK1;* OMIM: 601284) [Gallione et al., 2004; reviewed in Shovlin 2010]. Juvenile polyposis syndrome (JPS; OMIM: 174900) is characterized by hamartomatous polyps in the gastrointestinal tract with increased risk for early-onset malignancy [Gallione et al., 2004; Gallione et al., 2006] and is associated with mutations in either *BMPR1A* (OMIM: 601299) or *SMAD4* (OMIM: 600993) [Howe et al., 2001; Howe et al., 1998]. *SMAD4* mutations can also cause a combined JPS and HHT syndrome (JPS-HHT; OMIM: 175050) [Gallione et al., 2004; Gallione et al., 2006; Iyer et al., 2010]. A family with JPS and a *SMAD4* mutation was recently described as having aortic root dilation, along with mitral valve dysfunction, suggesting that *SMAD4* mutations may also cause aortic disease [Andrabi et al., 2011].

We report on two patients with JPS-HHT and thoracic aortic enlargement associated with *SMAD4* mutations (one novel, one previously reported) and discuss implications for management and treatment. Although TAAD and JPS-HHT might occur together by chance, the patients described here and the previously reported family suggests that the clinical spectrum associated with *SMAD4* mutations may include TAAD.

CLINICAL REPORTS

Patient 1

An 11-year-old Caucasian boy with JPS and a pathogenic *SMAD4* mutation was referred for genetic counseling and clinical management (Table I). At 6 years of age, he had dizziness

and pallor, and was diagnosed with anemia followed one month later by massive hematochezia. Colonoscopy showed multiple juvenile polyps and biopsy of some demonstrated low-grade dysplasia. *SMAD4* sequencing detected a c.1340_1367dup28 (NM_005359.5) variant in the coding region of exon 10, which had not been previously reported. This mutation was not detected in his parents' DNA, indicating the mutation was apparently *de novo* in the proband. Analysis of *BMPR1A* was negative. At 10 years of age, the proband underwent a total abdominal colectomy, rectal mucosectomy and ileocecal pull-through procedure with a J-pouch reservoir. At that time, there was no history of epistaxis, seizures, palpitations, chest pain, shortness of breath, or respiratory symptoms.

On physical examination, his weight was 30.6 kg (~15th centile), height was 146.8 cm (~90th centile), and calculated body surface area was 1.145 m^2. The facial shape, pinnae, sclerae, palate, and uvula were normal. A single 2 mm blanching dark red oval lesion on the left forearm was noted. There were several well-healed surgical scars and no striae. His oxygen saturation was normal in both upright and supine positions, neurological examination was intact, and there was no pectus deformity, scoliosis, or excessive joint laxity. He did not require eyeglasses.

Echocardiography showed normal aortic valve morphology, mild to moderate dilation of the aortic valve annulus and aortic root, and mild dilation of the sino-tubular junction and ascending aorta. The following aortic diameter measurements were recorded: aortic annulus 2.40 cm (z-score = 4.19); aortic root (sinuses of Valsalva) 3.29 cm (z-score = 4.04), mean for BSA = 2.38 cm (normal range: 1.87–2.80 cm); sinotubular junction 2.44 cm (z-score = 2.13); ascending aorta 2.72 cm (z-score = 2.63), and descending thoracic aorta 1.8 cm (normal less than 2.6 cm). There was a small patent ductus arteriosus with continuous left to right flow. The mitral valve leaflets were mildly redundant without mitral valve prolapse, and there was trace mitral regurgitation. Subsequent cardiac computed tomography (CT) confirmed the dilation of his aortic root, but did not show tortuosity of the aorta, or abnormalities of the head and neck arteries. There were small pulmonary AVMs in the right upper lobe (2 mm) and left perifissural region (3 mm). Cranial Magnetic Resonance Imaging (MRI) did not show any cerebral AVMs or other abnormalities.

Shortly afterwards, the patient had a spontaneous and self-limited epistaxis. Examination showed a nasal septum deviation to the left, a tiny traumatic lesion on the left side of the nasal septum from digitation, but no telangiectasia on either side of the nasal septum or in the oral pharynx. Liver imaging showed a prominent common bile duct, but otherwise normal abdominal ultrasound with Doppler, and no evidence of AVM. At 12 years of age, he was clinically well and the most recent echocardiography showed no progression in aortic dilation. An exercise test was performed at 12 years of age showed no arterial oxygen desaturation. He was not on any medications.

Patient 2 is a 34-year-old Caucasian woman who presented to the adult genetics clinic for evaluation of features of Marfan syndrome and a family history of TAAD (Table I). On review of her medical history, she had colonic polyps at 6 years of age and underwent partial colectomy and subsequent multiple polypectomies. At 28 years of age, she was diagnosed with HHT after presenting with pulmonary AVM and epistaxis, and subsequently developed hepatic focal nodular hyperplasia. She also had a history of a patent foramen ovale, myoclonic epilepsy, transient ischemic attacks, migraines, sleep apnea, and spondylolisthesis. Review of symptoms was negative for chest pain, shortness of breath, or other respiratory symptoms. She had myopia, bruised easily, and had poor wound healing.

On physical examination, her weight was 82 kg, height 175.3 cm, and BSA 2.0 m^2. She had a reduced upper to lower segment ratio (0.79) and slightly increased arm span to height ratio

(1.06). She had a high and narrow palate, normal uvula, and bluish sclera. Examination of the heart, lungs and chest were normal, without cyanosis or digital clubbing. Her skin was soft in texture with visible veins and multiple striae. The incisional scar was well healed with no hypo-or hypertrophic features. She had scoliosis (32° curvature treated with a spinal brace), pes planus, long and slender fingers (positive wrist and thumb signs), and marked joint hypermobility with a Beighton score of 9/9. The neurological examination was intact. Her ophthalmology exam was negative for ectopia lentis.

The echocardiogram showed that the aortic root at the sinuses of Valsalva was mildly dilated measuring 3.8 cm (based on nomograms for BSA 2.0, upper limit of normal = 3.7 cm) [Roman et al., 1989]. The annulus, sinotubular junction and ascending aorta measured 2.0 cm, 3.2 cm, and 3.5 cm, respectively. The valves were normal in structure and function. The estimated right ventricular systolic pressure was normal at 28 mmHg. Reviews of previous echocardiograms showed that the aortic root had been slowly dilating from 2.9 to 3.8 cm during the past ten years. She had a patent foramen ovale, which had been successfully closed by percutaneous procedure at age 27 years. Her cranial MRI showed minor foci of chronic lacunar infarction and increased signal intensity of the T1 weighted sequences and medial portion of the basal ganglia. A cranial magnetic resonance arteriogram showed normal intracranial circulation.

Her father died suddenly at 60 years of age from an acute aortic dissection and rupture of the ascending aorta. Prior to his death, he was diagnosed with an aneurysm of the aortic root or ascending aorta that measured 5.4 cm (images were not available and it is unclear whether the measurement was taken at the sinuses of Valsalva or higher); the aortic arch measured 4.2 cm and the descending aorta measured 3.2 cm. He was reported to have tall stature (6′4″), long arms and legs, bilateral inguinal hernias, multiple hyperplastic colon polyps, and a clinical diagnosis of HHT manifested by epistaxis. Cranial MRI reportedly showed right occipital lobe hemorrhage and hematoma, and multiple small vessel periventricular abnormalities. The patient's 62-year-old mother was reportedly healthy. Her paternal grandparents died in their 70s of unrelated causes, and there was no reported history of TAAD, sudden death, JPS, HHT or other inherited disorders in any other family members.

Sequencing of *SMAD4* identified a c.1245_1248delCAGA (NM_005359.5) variant in the coding region of exon 9(, a mutation previously reported [Aretz et al., 2007; Friedl et al., 1999; Gallione et al., 2010; Howe et al., 1998; Howe et al., 2004; Pyatt et al., 2006; Sayed et al., 2002]. Since her clinical findings were suggestive of Loeys-Dietz syndrome, DNA sequencing of *TGFBR1* and *TGFBR2* was also performed but no causative mutation was identified in either gene. *FBN1* (OMIM: 134797) sequencing was not pursued at the patient's request.

DISCUSSION

We report on two unrelated patients with JPS-HHT resulting from one novel and one previously reported S*MAD4* mutations, and both patients have an enlarged aortic root. Similar aortic root dilation was identified in a family with JPS and a *SMAD4* mutation, c. 1333C>T/p.Arg445Ter [Andrabi et al., 2011] (Table I). The father of Patient 2 had features of JPS-HHT, an enlarged aorta, and died of an acute aortic dissection, suggesting that the aortic root enlargement associated with *SMAD4* mutations can progress to acute aortic dissection and premature death. It is also notable that affected individuals from both Patient 2 and the previously published patient have features of Marfan syndrome, including long and slender fingers, scoliosis, hyperextensible joints, and cutaneous striae (Table II). In fact, Patient 2 met the current clinical diagnostic criteria for Marfan syndrome [Loeys et al., 2010]. Although this is a small number of patients, the data support the notion that *SMAD4*

mutations can cause aortic dilation that progresses to aortic dissection, along with skeletal and cutaneous features of Marfan syndrome.

The genetic predisposition to TAAD can be inherited in families as part of syndromic features of connective tissue disorders, such as Marfan syndrome, Loeys-Dietz syndrome, and Aneurysms-osteoarthritis syndrome, or in the absence of syndromic features (Table II) [Biddinger et al., 1997; Coady et al., 1999; Milewicz and Regalado 2003; van de Laar et al., 2011]. Both Loeys-Dietz syndrome and Aneurysms-osteoarthritis syndrome result from mutations in genes that are critical for TGFβ cellular signaling (*TGFBR1, TGFBR2* and *SMAD3*), suggesting a crucial role of TGFβ and downstream signal propagators in the pathogenesis of TAAD [Milewicz et al., 2008; van de Laar et al., 2011]. Although many of the mutations in these genes are predicted to cause loss of function, there is evidence of increased TGFβ signaling in the cells in the diseased aortic tissues of the patients with syndromic TAAD, including those with mutations in either *FBN1*, *TGFBR1*, *TGFBR2*, or *SMAD3* [Habashi et al., 2006; Loeys et al., 2005; van de Laar et al., 2011]. Recently, loss of function *TGFB2* mutations have been reported, which lead to reduced levels of TGF-β2 in smooth muscle cells and fibroblasts explanted from mutation carriers [Boileau et al., 2012]. Surprisingly, aortic tissue from these same patients paradoxically showed increased *TGFB2* expression and TGFβ2 protein levels.

Both JPS and HHT are dominantly inherited rare disorders with clinically distinct manifestations due to defects in genes encoding members of the TGFβ signaling superfamily [Gallione et al., 2004]. The JPS is characterized by the presence of multiple hamartomatous polyps in the gastrointestinal tract, especially in the stomach and colon, predisposing to gastrointestinal malignancy [Gallione et al., 2004; Gallione et al., 2006]. The two genes that have been associated with JPS include *SMAD4* and *BMPR1A* [Howe et al., 2001; Howe et al., 1998]. By contrast, HHT vascular dysplasia with a prevalence of 1/5,000 [Faughnan et al., 2011] is characterized by multiple AVMs as evidenced by telangiectases on the skin and/or mucosa and AVMs in large visceral organs, such as lungs, liver and brain. The HHT phenotype is caused by mutations in *ENG* and *ACVRL1 (ALK1)* (reviewed in [McDonald and Pyeritz, 2009]). Recent reports of both JPS and HHT diagnosed in the same patients suggest that the phenotypic overlap is due to the same causative gene [Gallione et al., 2004]. This led to the establishment of a combined syndrome of JPS and HHT (JPS-HHT), and *SMAD4* is the only gene currently associated with JPS-HHT [Gallione et al., 2010; Gallione et al., 2004].

Molecular genetic analyses in the two patients described here showed 4-bp deletion and 28-bp duplication in exons 9 and 10 of *SMAD4*, respectively. These are predicted to lead to premature termination of translation; nonsense mediated decay of the message will occur with the exon 9 mutation and may also occur with the exon 10 mutation. Thus, the exon 9 mutation is predicted to lead to haploinsufficiency of SMAD4. *SMAD4*, which encodes only co-SMAD molecule in humans, is one of the mediators in TGFβ signaling pathway. It is notable that the mutations causing either syndromic TAAD or HHT are in genes involved in the TGFβ superfamily signaling and are located upstream in the signaling pathway to *SMAD4*.

Among the patients with JPS-HHT reported to date, no clear genotype-phenotype correlations have emerged [Gallione et al., 2010; Loeys et al., 2010]. Although the *SMAD4* missense mutations in patients with JPS-HHT are localized in the MH2 domain of the protein, other nonsense and frameshift mutations are predicted to lead to haploinsufficiency, similar to the prediction for the *SMAD4* mutations associated with thoracic aortic disease. Additionally, the identical mutation in *SMAD4* could occur in both patients with JPS-HHT and patients with JPS, suggesting variable expressivity [Gallione et al., 2010]. Because there

are few patients with JPS-HHT and thoracic aortic dilation, the ability to make a conclusion of genotype-phenotype correlations is limited.

Recently, *SMAD4* mutations have been reported to cause Myhre syndrome (OMIM: 139210) a rare developmental and connective tissue genetic disorder characterized by short stature, short hands and feet, dysmorphic facial features, muscular overgrowth, congenital heart defects (no aortic dilation), and deafness [Le Goff et al., 2012; Caputo et al., 2012; van Steensel et al., 2005]. In contrast to mutations identified in the patients reported here, all three unique *SMAD4* mutations identified among 11 patients with Myhre syndrome were apparently *de novo* missense mutations disrupting the same amino acid (Ile500), and leading to a defect in SMAD4 monoubiquitination and depressed expression of downstream TGFβ target genes, Thus, the *SMAD4* mutations causing Myhre syndrome may have a distinct functional consequence from the *SMAD4* mutations causing JPS-HHT [Le Goff et al., 2012; Caputo et al., 2012].

Thoracic aortic dilation can be progressive and result in an acute thoracic aortic dissection. To prevent morbidity and untimely death, careful monitoring of the thoracic aortic diameter has been recommended, ensuring the proper surgical intervention in a timely fashion [Hiratzka et al., 2010]. In light of the thoracic aortic disease in the patients with JPS-HTT and *SMAD4* mutations reported here and previously, we propose that the thoracic aorta should be screened for aneurysms and regularly monitored using transthoracic echocardiography in all patients with JPS-HHT with *SMAD4* mutations. Such monitoring should detect aortic root dilation and allow for intervention to prevent premature deaths due to acute aortic dissection. In cases of severe aortic enlargement, surgical repair or replacement of the aortic aneurysm can be life saving. However, the small number of patients currently identified does not allow for meaningful risk stratification. Identification of further patients with JPS-HHT and thoracic aortic disease will help to determine if other arterial aneurysms, and skeletal and cutaneous features of Marfan syndrome are also part of this association.

Acknowledgments

We are grateful to the patients and their families for their cooperation and grant support from RO1 HL62594 (D.M.M.). We thank Lorraine Potocki, M.D. and Thomas W. Prior, Ph.D. for providing supplemental information related to the mutation described in their article [Andrabi et al., 2011].

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TABLE I

Characteristics of Two Patients with *SMAD4* Mutations and TAAD

Clinical findings	Patient 1	Patient 2	Index patient with JPS, aortopathy and mitral valve dysfunction[1]
SMAD4 (mutation, exon)	c.1340–1367dup28, exon 10	c.1245_1248delCAGA, exon 9	c.1333C>T/p.Arg445Ter, exon 10
Age (years) (BSA)	11 (BSA 1.29 m^2)	34 (BSA 2.0 m^2)	11
Age of diagnosis of gastrointestinal polyps (years)	7	6	11
Diagnosis of JPS [Jass et al., 1988]	Definite	Definite	Definite
1. > 5 polyps of colorectum	Yes	Yes	No
2. JP throughout GI tract	Yes	Yes	Yes
3. Any # of JPS with a family history of JPS	No	Yes	Yes
Age of HHT Diagnosis (years)	11	28	n/a
Diagnosis of HHT [Shovlin et al., 2000]	Possible	Definite	Uncertain
1. Spontaneous recurrent epistaxis	Yes	Yes	Yes
2. Multiple telangiectases	No	No	n/a
3. Visceral lesions	Yes	Yes	n/a
4. Family history	No	Yes	n/a
Genetic testing	*SMAD4, BMPR1A*	*SMAD4, TGFBR1, TGFBR2*	*SMAD4*
Aortic root measurement (Z-score)	3.29 cm (Z +4.04)	3.8 cm	Normal[2]
Other cardiovascular findings	Small PAVMs, small PDA, PFO	PAVM, PFO	Mildly redundant mitral valve leaflets and mild mitral regurgitation
Other clinical findings	Reading disabilities	TIA, migraines, sleep apnea, myoclonic epilepsy, focal nodular hyperplasia, spondylolisthesis	Reactive airway disease and bronchitis, recurrent epistaxis, constipation
Features of syndromic TAAD	None	High palate, reduced upper/lower segment ratio, long and slender fingers, scoliosis, joint hypermobility, multiple striae, thin skin	Mild pectus excavatum, long and slender fingers, mild hyperextensibilty of the fingers, lumbar lordosis, thoracolumbar scoliosis

[1] A family with JPS, aortopathy and mitral valve dysfunction segregating *SMAD4* mutation [Andrabi et al., 2011];

[2] Measurement not provided; BSA, Body surface area; HHT, Hereditary hemorrhagic telangiectasia; JPS, Juvenile polyposis syndrome; PAVM, Pulmonary arteriovenous malformation; PDA, Patent ductus arteriosus; PFO, Patent foramen ovale; TAAD, Thoracic aortic aneurysms and aortic dissections; TIA, Transient ischemic attack

TABLE II

Comparison of the Clinical findings in Patients with Aortopathy Due to Mutations in the TGFβ Signaling Pathway[2]

	Clinical syndrome (*N*, %)					
	Patient 1 (*N*=1)	**Patient 2 and Aortopathy and Mitral valve dysfunction with JPS (*N*=5)[1]**	**Aneurysm-Osteoarthritis syndrome (*N*=27)[2]**	**Marfan syndrome (*N*=1,013)[3]**	**Loeys-Dietz syndrome, I (*N*=40)[4]**	**Loeys-Dietz syndrome, II (*N*=12)[4]**
Associated Gene	*SMAD4 (frameshifting indel)*	*SMAD4 (deletion)*	*SMAD3*	*FBN1*	*TGFBR1, TGFBR2*	*TGFBR1, TGFBR2*
Clinical findings						
Cardiovascular:						
Aortic root dilation/dissection	1/1 (100)	4/6 (67)[5]	15/26 (58)	775/1,013 (77)/ 145/1,013 (14)	39/40 (98)	12/12 (100)
Aneurysm other vessels	0/1 (0)	0/1 (0)	7/17 (41)	unknown	21/40 (52)	8/11 (73)
Arterial tortuosity	0/1 (0)	0/1 (0)	9/17 (53)	unknown	21/25 (84)	6/9 (67)
Mitral valve abnormalities (MVP/MR)	1/1 (100)	5/6 (83)	13/22 (59)	533/983(54)/ 313/959(33)	unknown	unknown
Congenital heart defects	1/1 (100)	1/6 (17)	1/22 (5)	unknown	9/40 (22)	unknown
Patent ductus arteriosus	1/1 (100)	0/6 (0)	1/22 (5)	unknown	14/40 (35)	unknown
Other heart diseases	0/1 (0)	0/6 (0)	7/22 (32)[6]	unknown	unknown	unknown
Musculoskeletal:						
Pectus deformity	0/1 (0)	1/4 (25)	3/19 (16)	570/962 (59)	27/40 (68)	unknown
Scoliosis	0/1 (0)	3/4 (75)	9/21 (43)	508/965 (53)	20/40 (50)	unknown
Joint laxity (Beighton score >5)	0/1 (0)	3/4 (75)	3/16 (19)	600/956 (63)	27/40 (68)	12/12 (100)
Osteoarthritis (≥1 joint)	0/1 (0)	0/1 (0)	21/21 (100)	unknown	unknown	unknown
Disc degeneration	0/1 (0)	0/1 (0)	18/20 (900	unknown	unknown	unknown
Craniofacial appearance:						
Hypertelorism	0/1 (0)	0/1 (0)	7/19 (37)	unknown	36/40 (90)	0/12 (0)
Abnormal palate/uvula	0/1 (0)	0/1 (0)	11/19 (58)	unknown	36/40 (90)	3/12 (25)
Craniosynostosis	0/1 (0)	0/1 (0)	0/27 (0)	unknown	19/40 (48)	0/12 (0)
Skin/Integument:						
Velvety skin	0/1 (0)	0/1 (0)	12/18 (67)	unknown	11/40 (28)	9/11 (82)
Striae	0/1 (0)	2/4 (50)	11/18 (61)	444/945 (47)	unknown	unknown
Umbilical/Inguinal hernia	0/1 (0)	0/1 (0)	9/18 (50)	96/988 (10)	unknown	4/11 (36)

	Clinical syndrome (*N*, %)					
	Patient 1 (*N*=1)	**Patient 2 and Aortopathy and Mitral valve dysfunction with JPS (*N*=5)[1]**	**Aneurysm-Osteoarthritis syndrome (*N*=27)[2]**	**Marfan syndrome (*N*=1,013)[3]**	**Loeys-Dietz syndrome, I (*N*=40)[4]**	**Loeys-Dietz syndrome, II (*N*=12)[4]**
Ocular:						
Ectopia lentis	0/1 (0)	0/4 (0)	0/27 (0)	542/1,013 (54)	0/40 (0)	unknown
Myopia	0/1 (0)	1/4 (25)	unknown	453/865 (52)	unknown	unknown
CNS:						
CNS involvement	0/1 (0)	1/1 (100)	unknown	154/1,013 (15)	unknown	unknown
Pulmonary:						
Arteriovenous malformation	1/1 (100)	1/1 (100)	unknown	unknown	unknown	unknown

[1] A family with JPS, aortopathy and mitral valve dysfunction seqregating *SMAD4* mutation [Andrabi et al., 2011];

[2] Adapted from Table 2 [van de Laar et al., 2011];

[3] Table 2 [Faivre et al., 2007];

[4] Table 1 and 2 [Loeys et al., 2006];

[5] Proband's relatives have *SMAD4* mutation with colonic polyps, mitral regurgitation, MVP and aortic dilation along with Marfan features.;

[6] Left ventricular hypertrophy and atrial fibrillation; JPS, Juvenile polyposis syndrome, MVP, Mitral valve prolapse; MR, Mitral regurgitation