

# World Journal of *Clinical Cases*

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Editorial Board Member of *World Journal of Clinical Cases*, Ashu Seith Bhalla, MD, Professor, Department of Radiodiagnosis, All India Institute of Medical Sciences, New Delhi 110029, India

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## Multisystem smooth muscle dysfunction syndrome in a Chinese girl: A case report and review of the literature

Sai-Nan Chen, Yu-Qing Wang, Chuang-Li Hao, Yan-Hong Lu, Wu-Jun Jiang, Chun-Yan Gao, Min Wu

**ORCID number:** Sai-Nan Chen (0000-0001-9787-6639); Yu-Qing Wang (0000-0002-4153-3984); Chuang-Li Hao (0000-0002-1342-8175); Yan-Hong Lu (0000-0002-9447-6493); Wu-Jun Jiang (0000-0002-1538-9069); Chun-Yan Gao (0000-0001-6875-9652); Min Wu (0000-0001-9758-9517).

**Author contributions:** Chen SN wrote the main manuscript text; Hao CL and Wang YQ designed the study and revised the manuscript; Jiang WJ and Lu YH carried out the initial analyses; Sun HQ performed the bronchoscopy and microbiological detection; Gao CY and Wu M performed the data collection. All authors read and approved the final manuscript.

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Sai-Nan Chen, Yu-Qing Wang, Chuang-Li Hao, Yan-Hong Lu, Wu-Jun Jiang, Chun-Yan Gao, Min Wu, Department of Respiratory Medicine, Children's Hospital of Soochow University, Suzhou 215000, Jiangsu Province, China

**Corresponding author:** Yu-Qing Wang, MD, Chief Doctor, Department of Respiratory Medicine, Children's Hospital of Soochow University, No. 303, Jingde Road, Suzhou 215000, Jiangsu Province, China. [wang\\_yu\\_qing@126.com](mailto:wang_yu_qing@126.com)

**Telephone:** +86-512-67788313

**Fax:** +86-512-67786316

### Abstract

#### BACKGROUND

Multisystemic smooth muscle dysfunction syndrome (MSMDS) is a rare genetic disease worldwide. The main mutation is the actin alpha 2 (*ACTA2*) gene p.R179H. In this paper, we report a Chinese MSMDS patient and systematically review the previous literature.

#### CASE SUMMARY

Here, we report a 9.6-month-old Chinese girl who was diagnosed with MSMDS based on her history and symptoms, such as recurrent cough, wheezing, and complications with congenital fixed dilated pupils. Chest high-resolution computed tomography revealed inhomogeneous lung transparency, obvious exudative lesions, and some lung fissures that were markedly thickened. Cranial magnetic resonance imaging excluded bleeding and infarction but showed abnormal signals in the centrum ovale majus and bilateral periventricular regions. Echocardiography only showed patent foramen ovale, and no patent ductus arteriosus, pulmonary artery dilatation, or pulmonary hypertension was found. Bronchoscopy indicated moderate bronchial malacia. These examinations in conjunction with the typical eye abnormality suggested a diagnosis of MSMDS, and sequencing of exon 6 of the *ACTA2* gene demonstrated the heterozygous mutation c.536G>A, p.R179H. However, her parents' gene analyses were normal.

#### CONCLUSION

MSMDS is a rare genetic disease mainly caused by the mutation of the *ACTA2* gene p.R179H. Early genetic diagnosis should be performed for children presenting with congenital fixed dilated pupils and patent ductus arteriosus. During the process of diagnosis and treatment, clinicians should be on high alert for cerebrovascular, cardiovascular, and pulmonary complications.

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**Core tip:** Multisystem smooth muscle dysfunction syndrome (MSMDS) is a genetic disease that is clinically characterized by dysfunction of the smooth muscle throughout the whole body, leading to congenital fixed dilated pupils, patent ductus arteriosus, aortic and cerebrovascular disease, hypotonic bladder, intestinal hypoperistalsis, and pulmonary hypertension. MSMDS is rare in Chinese individuals. It is mostly caused by a p.R179H mutation in the actin alpha 2 gene worldwide. In the present study, we report a heterozygous mutation c.536G>A, p. R179H in a Chinese infant with MSMDS and describe the clinical characteristics. In addition, we further review the literature regarding MSMDS cases from the 1980s to 2018.

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## INTRODUCTION

Multisystem smooth muscle dysfunction syndrome (MSMDS) is a genetic disease caused mostly by mutation of the actin alpha 2 (*ACTA2*) gene p.R179H. Its clinical manifestation is characterized by fixed dilated pupils, patent ductus arteriosus (PDA), thoracic aortic aneurysm, pulmonary artery hypertension, cerebrovascular disease, white matter lesions, hypotonic bladder, intestinal malrotation, hypoperistalsis and so on. The *ACTA2* gene encodes an isoform of  $\alpha$ -actin. Mutations in this gene lead to disruption of smooth muscle cells (SMC)-dependent organs<sup>[1,2]</sup>. Milewicz *et al*<sup>[1]</sup> first reported six patients with a de novo missense mutation in the *ACTA2* gene and MSMDS in 2010. In China, the first case of MSMDS was not reported until 2017 by Zhou *et al*<sup>[3]</sup>. Since the *ACTA2* gene was first identified as the pathogenic gene of MSMDS in 2010, only 32 patients have been reported, according to the databases of PubMed, Wanfang, China National Knowledge Infrastructure, and VIP with the key words “multisystem smooth muscle dysfunction syndrome” and “*ACTA2*” from 1980s to 2018. Three different mutation loci have been reported to cause MSMDS, of which Arg179His is the most common mutation. Other rare mutations are Arg179Cys and Arg179Leu<sup>[2,4-7]</sup>. The Arg179His substitution is associated with the neurovascular phenotype, while the Arg179Cys mutation is especially related to brain development<sup>[6]</sup>. The most severe form is *ACTA2* Arg179His. The discovery of this mutation has been invariably associated with a high risk of infant mortality and poor prognosis<sup>[6]</sup>. Here, we report one Chinese infant with MSMDS with a heterozygous *ACTA2* Arg179His substitution who presented with patent foramen ovale, congenital nonreactive mydriasis, dyspnea, development delay, and abnormal signals in magnetic resonance imaging (MRI) of the brain. In addition, we further review the literature regarding MSMDS patients from the 1980s to 2018s. The clinical features of all identified MSMDS patients are summarized.

## CASE PRESENTATION

### Chief complaints

A girl aged 9.6 months was admitted to Children's Hospital Soochow University in May 2018 due to recurrent cough for more than half a month, which was aggravated by shortness of breath and dyspnea for three days.

### History of past illness

She had experienced pneumonia at birth and suffered from growth retardation.

### Personal and family history

The child was born by cesarean section at 35 + 2 wk. Her father and mother were healthy. Her twin sister died in April 2018 of lung infection after an operation for “atrial septal defect and ventricular septal defect”.

### **Physical examination**

She weighed 9 kg, her height was 65 cm, her body mass index was 21.3, and she presented with shortness of breath and dyspnea. Blue-purple plaques could be seen on her right face, buccal mucosa, oral tongue, and palate. Her bilateral pupils were fixed and dilated with a diameter of 5 mm. Crackles and wheezing rales were present in bilateral lungs. A grade II/6 murmur was audible on the left sternal margin. No clubbed digits were found.

### **Laboratory examinations**

Routine blood examination showed a white blood cell count of  $8.17 \times 10^9/L$ , and the C reactive protein concentration was normal. Nasopharyngeal secretion examination revealed positive respiratory syncytial virus and negative sputum culture.

### **Imaging examinations**

Chest high-resolution computed tomography revealed inhomogeneous lung transparency, obvious exudative lesions, and marked thickening of lung fissures (Figure 1). Cranial magnetic resonance imaging showed abnormal signals in the centrum ovale majus and bilateral periventricular regions (Figure 2). Abdominal ultrasonography suggested gallstones (Figure 3). Echocardiography only showed patent foramen ovale at the beginning of the disease, but the diameter of the pulmonary artery gradually widened during continuous follow-up (Figure 4). Bronchoscopy revealed redness and edema of the bronchial mucous membranes accompanied by phlegm spots and bronchomalacia (Figure 5).

### **Gene sequence analysis**

The patient underwent genetic analysis and the *ACTA2* c.536G>A (p.R179H) heterozygous mutation was found, but her parents' sample identifications were negative (Figure 6).

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## **FINAL DIAGNOSIS**

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MSMDS.

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## **TREATMENT**

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Her symptoms improved after oxygen therapy, cefazoxime administration for 3 wk, and antispasmodic and low-dose corticosteroid treatment for 3 wk.

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## **OUTCOME AND FOLLOW-UP**

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After being discharged from our hospital, the child was followed monthly in the outpatient clinic. We administered low-dose azithromycin and low-dose corticosteroid anti-inflammatory treatment. We performed regular examinations of respiratory rate, oxygen saturation, and high-resolution computed tomography of the chest to evaluate the pulmonary disease regression/progression, and echocardiography to evaluate the function of the heart. She had pulmonary infection three times, and her latest echocardiographic results suggested pulmonary artery dilatation. She weighed 10 kg, her height was 72 cm, and her body mass index was 19.3. Her overall situation has remained well to date.

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## **DISCUSSION**

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Tables 1-4 summarizes the systemic features of the reported patients with MSMDS worldwide<sup>[8-16]</sup>. SMCs are widely distributed in the gastrointestinal tract, urinary tract, respiratory tract, uterus, iris, and other body parts. Their contraction and relaxation are key to the normal operation of blood vessels as well as the digestive system, respiratory system, and urogenital system. MSMDS is mainly caused by p.R179H mutations of the *ACTA2* gene in aortic smooth muscle. This disease is a systemic disorder of smooth muscle function and manifests in a variety of ways, including

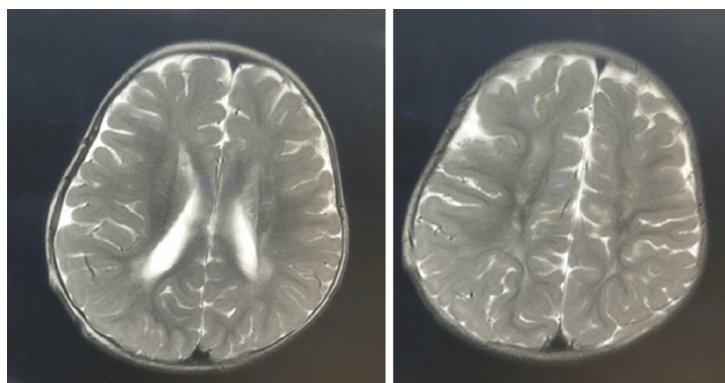


**Figure 1 Chest high-resolution computed tomography images.** A chest high-resolution computed tomography scan showed inhomogeneous lung transparency and obvious exudative lesions, and some lung fissures were markedly thickened in the lung of the patient.

fixed dilated pupils, PDA, thoracic aortic aneurysm, pulmonary artery hypertension, cerebrovascular disease, white matter lesions, hypotonic bladder, intestinal malrotation, and hypoperistalsis. Other rare symptoms, including pulmonary cystic disease, venous thrombosis, cleft palate, hypothyroidism, and deepened skin folds, need further study to confirm the relationship with this mutation.

In 2010, Milewicz *et al*<sup>[1]</sup> first reported a case of MSMDs associated with the p.R179H mutation of the *ACTA2* gene. This mutation caused systemic smooth muscle dysfunction, leading to aortic and cerebrovascular diseases, fixed dilated pupils, hypotonic bladder, intestinal malrotation, and pulmonary artery hypertension. In 2017, Zhou *et al*<sup>[3]</sup> reported the first case of MSMDs in China. Our case is the second case of MSMDs diagnosed by genetic testing in China. Similar to the reported cases, our patient had congenital mydriasis accompanied by loss of direct light reflex. Iris tissue dissociation was considered an early manifestation of these pupil symptoms<sup>[6]</sup>. Fundus examination showed no retinal vascular tortuosity in our patient. Moller *et al*<sup>[5]</sup> reported the ophthalmic characteristics of three patients with MSMDs in detail. They believed that the retinal vascular tortuosity was due to the lack of elastic lamina in the retinal artery wall, and SMC proliferation resulted in vascular obstruction. Furthermore, the incidence of retinal vascular tortuosity tended to increase with age, which may be related to changes in the vascular wall and the loss of contractility. In cardiovascular diseases, our patient had patent foramen ovale and pulmonary artery dilatation without PDA or pulmonary hypertension, which is different from the reported cases. PDA was present in all reported cases. The ductus arteriosus, similar to the muscular artery, is a duct between the aorta and the pulmonary artery. SMCs play a major role in catheter closure, and their dysfunction leads to the persistence of ductus arteriosus. It has been reported that pulmonary hypertension may be due to the combined action of large PDA and pulmonary parenchymal diseases and that the repair of PDA is essential for the recovery of pulmonary parenchymal diseases<sup>[15]</sup>. In a long-term follow-up study of three MSMDs patients by Yetman *et al*<sup>[13]</sup>, they found that the aorta dilated progressively with age, which may be related to the change in a protein structure caused by *ACTA2* mutation leading to the decrease in aortic contractility. However, the role of drug therapy in preventing these cardiovascular lesions is still unknown. With regard to cerebrovascular diseases, our patient received cranial MRI, which showed abnormal signals in the centrum ovale majus and bilateral periventricular regions. As reported, MSMDs mostly began as a pulmonary disease. Our patient had a history of "neonatal pneumonia" at birth. When she was 9 mo old, she suffered from shortness of breath, wheezing, and dyspnea and needed long-term oxygen therapy. Roulez *et al*<sup>[10]</sup> holds that decreased SMC function of pulmonary alveoles leads to tachypnea at birth, pulmonary hypertension, asthma, bronchiectasis, and emphysema. However, the relationship between the *ACTA2* gene causing MSMDs and lung pathology has not been well elucidated. Prabhu *et al*<sup>[15]</sup> believe that pulmonary vascular changes may be caused by pulmonary hypertension secondary to PDA or by elevated pulmonary pressure caused by structural disorders of abnormal alveolar growth. However, in the case of the absence of intimal hyperplasia, intimal hypertrophy of small muscle arteries may be caused by the hypercontraction of arterial smooth muscle. Our patient had skin and mucosal symptoms, which manifested as cyan-purple plaques on her right face, buccal mucosa, oral tongue, and palate. Richer *et al*<sup>[14]</sup> first reported a case of skin abnormalities in which wrinkles of ankles, knees, buttocks, and elbows were markedly deepened. This may be related to the dysfunction of myofibroblasts expressing *ACTA2* in the skin.





**Figure 2 Cranial magnetic resonance imaging of the patient.** Magnetic resonance imaging showed abnormal signals in the centrum ovale majus and bilateral periventricular regions.

Tables 1-4 summarizes the systemic features of the reported patients with MSMDs worldwide. Among the MSMDs patients, the youngest was a neonate, and the oldest was 31 years old. Twenty-three (71.9%) were female, and nine (28.1%) were male. Except for cardiovascular and cerebrovascular diseases, these patients also experienced dysfunction of other SMC-dependent organs, including depressed systolic performance of the bladder and gastrointestinal tract, resulting in hypotonic bladder, hydronephrosis, hypospadias, intestinal malrotation, hypoperistalsis, and gallstones. As shown in Tables 1-4, all patients tested positive for the *ACTA2* gene mutation. The R179H variant was the most common mutation type (81.25%), followed by R179C (12.5%) and R179L (6.25%). This mutation has always been reported to be sporadic, since few patients can survive to reproductive age, and none of the parents who had undergone genetic testing were identified as carriers. By the time of submission, five deaths had been reported in all cases. Our patient was given oxygen therapy and low-dose corticosteroid treatment after discharge. She suffered from pulmonary infection three times, and her latest echocardiographic results suggested pulmonary artery dilatation without pulmonary hypertension.

*ACTA2*, located in the long arm of chromosome 10-10q23.31, is composed of nine exons and codes for actin alpha 2, a major contractile protein in vascular smooth muscle cells. *ACTA2* is one of six actin subclasses in mammals, mainly distributed in muscle cells and is the main component of contractors. By the interaction of the contractile element  $\alpha$  actin (*ACTA2* coding) and  $\beta$  myosin heavy chain (*MYH11* coding), SMCs can achieve contraction to regulate blood pressure and blood flow. Therefore, there are many overlapping clinical manifestations of megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) caused by the mutation of *MYH11* and MSMDs caused by the mutation of *ACTA2*. Yetman *et al*<sup>[17]</sup> reported a case of MMIHS with congenital mydriasis, PDA, pulmonary hypertension, aortic dilatation, intestinal malrotation, and hypoperistalsis but no cerebrovascular abnormalities. Therefore, for children with clinical characteristics such as congenital mydriasis and PDA, genetic testing should be carried out as soon as possible. At the same time, eye fundus examination, echocardiography, and cranial MRI should also be performed to observe multisystem lesions.

## CONCLUSION

In conclusion, MSMDs is a rare genetic variant disease. According to the literature, the hotspot variant is the heterozygous mutation of the *ACTA2* gene c.536C>T (p.R179H). Early genetic testing is essential for the optimal management of suspected clinical cases. In addition to early detection of hotspot variation in these patients, clinicians need to examine and evaluate the patients' cerebrovascular, cardiovascular, and pulmonary complications to make early diagnosis and treatment.

**Table 1** Clinical characteristics of multisystem smooth muscle dysfunction syndrome patients worldwide

Characteristic	Milewicz <i>et al</i> <sup>[1]</sup> , 2010 (n = 6)						Munot <i>et al</i> <sup>[2]</sup> , 2012 (n = 6)						Moller <i>et al</i> <sup>[3]</sup> , 2012 (n = 1)
Gender	F	M	M	F	F	F	F	F	M	F	M	F	M
Age (yr)	11	14	17	11	26	27	3	6	5	2	6	0.25	6
Vision system													
Congenital mydriasis	+	+	+	+	+	+	+	+	+	+	+	+	+
Retinal vascular tortuosity	+	+											+
Cardiovascular system													
PDA	+	+	+	+	+	+	+	+	+	+	+	+	+
ASD	-	-	-	-	-	-	-	-	-	-	-	-	-
PAH	-	-	+	+	+	-							
TAA	+	+	+	+	+	-							-
AAD	-	-	-	-	-	-							+
PAD	+	+	-	+	-	-							-
Nervous system													
Development delay	+	-	+	+	-								-
Spastic seizures/epilepsy													
Cerebral infarction/hemiplegia	+	+					+	+	-	+	-	-	-
WM signal changes	+	+	+	+	+	-	+	+	+	+	+	-	+
Moyamoya-like changes	+	+	+	+	+	+	+	+	+	+	+	+	-
Digestive system													
Intestinal malrotation	-	-	+	+	-	+							
Intestinal hypoperistalsis	-	-	+	+	-	-							
Gallstones						+							
Respiratory system													
Dyspnea	+	+	+	+	-	-							+
RRTI	-	-	-	-	-	-							-
Asthma	-	-	-	-	-	+							
Urinary system													
Hypotonic bladder	+	+	+	+	+	-							+
Hydronephrosis													
Hypospadias													
ACTA2 mutation	H	H	H	H	H	H	H	H	L	H	H	H	L
Prognosis	D											D	

+: Present; -: Absent; blank: Unknown; PDA: Patent ductus arteriosus; ASD: Atrial septal defect; PAH: Pulmonary artery hypertension; TAA: Thoracic aortic aneurysm; AAD: Ascending aorta dilatation; PAD: Pulmonary artery dilatation; WM: White matter; RRTI: Recurrent upper respiratory tract infection; H: R179H; C: R179C; L: R179L; D: Death.

**Table 2 Clinical characteristics of multisystem smooth muscle dysfunction syndrome patients worldwide**

Characteristic		Meuwissen <i>et al</i> <sup>[4]</sup> , 2012	Al-Mohaissen <i>et al</i> <sup>[6]</sup> , 2012	Moosa <i>et al</i> <sup>[9]</sup> , 2013	Roulez <i>et al</i> <sup>[10]</sup> , 2014		Brodsky <i>et al</i> <sup>[11]</sup> , 2014	
<i>n</i>		1	1	1	3		1	
Gender		F	F	F	F	F	F	M
Age (yr)		3	17	7	19	14	16	9
Vision system	Congenital mydriasis	+	+	+	+	+	+	+
	Retinal vascular tortuosity	+	+		+	+	+	+
Cardiovascular system	PDA	+	+	+	+	+	+	+
	ASD	-	-	-	-	-	-	+
	PAH	+	-	-	+	-	-	-
	TAA	-	-	-	-	+	-	-
	AAD	-	+	-	-	-	+	+
	PAD	-	-	-	-	-	-	-
	Development delay	-	-	+	+	+	-	
Nervous system	Spastic seizures/epilepsy			+				
	Cerebral infarction/hemiplegia	-	-	-	-	-	-	-
	WM signal changes	+	-	+	-	+	+	-
	Moyamoya-like changes	-	-	+	+	+	-	-
Digestive system	Intestinal malrotation	+		-	-			
	Intestinal hypoperistalsis	-		+	+			
Respiratory system	Gallstones				+			
	Dyspnea	+	-	+	+	-	+	-
	RRTI	+	-	-	+	-	+	-
	Asthma	-	-	-	+	-	+	-
Urinary system	Hypotonic bladder	+	-	-	+	-	-	-
	Hydronephrosis	+						+
	Hypospadias							+
ACTA2 mutation		C	H	H	H	H	H	H
Prognosis		D						

+: Present; -: Absent; blank: Unknown; PDA: Patent ductus arteriosus; ASD: Atrial septal defect; PAH: Pulmonary artery hypertension; TAA: Thoracic aortic aneurysm; AAD: Ascending aorta dilatation; PAD: Pulmonary artery dilatation; WM: White matter; RRTI: Recurrent upper respiratory tract infection; H: R179H; C: R179C; L: R179L; D: Death.

**Table 3 Clinical characteristics of multisystem smooth muscle dysfunction syndrome patients worldwide**

Characteristic		Amans <i>et al</i> <sup>[12]</sup> , 2014	Yetman <i>et al</i> <sup>[13]</sup> , 2015	Richer <i>et al</i> <sup>[14]</sup> , 2012		De <i>et al</i> <sup>[6]</sup> , 2016		Mo re- no <i>et al</i> <sup>[7]</sup> , 2016
<i>n</i>		1	3	1		2		1
Gender		F	F F	F M		F M		F
Age(yr)		3	15 0.9	31 2		0.2		0.8
Vision system	Congenital mydriasis	+	+	+	+	+	+	+
	Retinal vascular tortuosity		+	+				
Cardiovascular system	PDA	+	+	+	+	+	+	+

	ASD	-	+	+	+	-	-	+	+
	PAH	-	+	+	+	+	+	-	-
	TAA	-	+	-	+	-	-	-	-
	AAD	-	+	+	+	+	-	+	-
	PAD	-	+	+	+	+	-	+	-
Nervous system	Development delay					+			
	Spastic seizures/epilepsy		+	-	+				
	Cerebral infarction/hemiplegia	-	-	-	-	-	-	-	-
	WM signal changes	-	+	+	+	+	-	+	-
Digestive system	Moyamoya-like changes	+	+	-	-	+	+	+	+
	Intestinal malrotation		+	+	-				+
	Intestinal hypoperistalsis		-	-	+				+
	Gallstones								
Respiratory system	Dyspnea	-	-	+	-	+		+	
	RRTI	-	-	-	-	-		-	
	Asthma	-	-	-	-	-		-	
Urinary system	Hypotonic bladder	+	+	-	+	+	-	+	+
	Hydronephrosis					-	+	+	+
	Hypospadias					+	+	+	+
ACTA2 mutation		H	H	H	H	H	C	C	C
Prognosis				D			D		

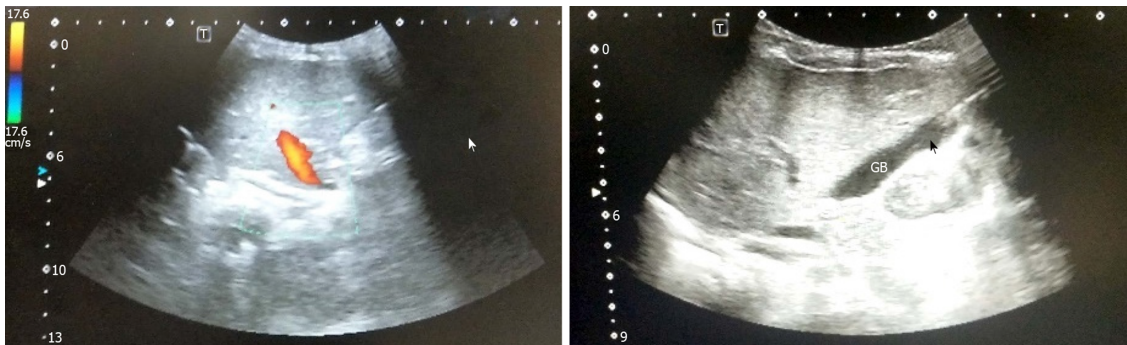
+: Present; -: Absent; blank: Unknown; PDA: Patent ductus arteriosus; ASD: Atrial septal defect; PAH: Pulmonary artery hypertension; TAA: Thoracic aortic aneurysm; AAD: Ascending aorta dilatation; PAD: Pulmonary artery dilatation; WM: White matter; RRTI: Recurrent upper respiratory tract infection; H: R179H; C: R179C; L: R179L; D: Death.

**Table 4 Clinical characteristics of multisystem smooth muscle dysfunction syndrome patients worldwide**

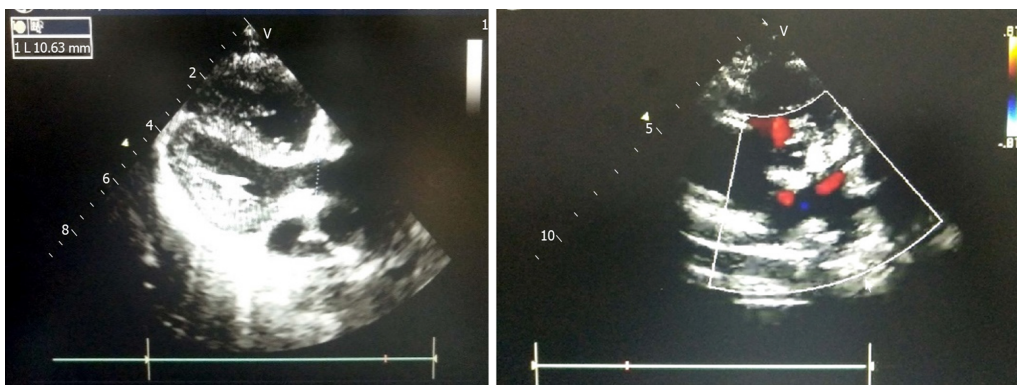
Characteristic	Prabhu <i>et al</i> <sup>[15]</sup> , 2017	Logeswaran <i>et al</i> <sup>[16]</sup> , 2017		Zhou <i>et al</i> <sup>[3]</sup> , 2017	Our patient	Observed Cases (n)	Positive cases, n (%)
n	1	2		1	1		
Gender	F	M	F	F	F	33	
Age (yr)	0.4	3 (d)	26	2	0.8		
Vision system	Congenital mydriasis	+	+	+	+	33	33 (100)
	Retinal vascular tortuosity	+	+	+	-	16	15 (93.8)
Cardio-vascular system	PDA	+	+	+	-	33	32 (97.0)
	ASD	-	-	-	-	33	6 (18.2)
	PAH	+	-	+	-	27	13 (48.1)
	TAA	-	-	+	-	27	9 (33.3)
	AAD	-	-	-	-	27	9 (33.3)
	PAD	+	-	+	+	27	11 (40.7)
Nervous system	Development delay	+		+	+	16	10 (62.5)
	Spastic seizures/epilepsy				-	5	3 (60.0)
	Cerebral infarction/hemiplegia		-	-	-	32	5 (15.6)
	WM signal changes		+	+	-	32	23 (71.9)
	Moyamoya-like changes		-	+	-	32	23 (71.9)

Digestive system	Intestinal malrotation	-	-	-	-	17	7 (41.2)
	Intestinal hypoperistalsis	-	-	-	-	17	6 (35.3)
	Gallstones		-	-	+	5	3 (60.0)
Respiratory system	Dyspnea	+			+	23	15 (65.2)
	RRTI	+			+	23	5 (21.7)
	Asthma	-			-	23	3 (13.0)
Urinary system	Hypotonic bladder		-	-		24	14 (58.3)
	Hydronephrosis		-	-	-	9	5 (55.6)
	Hypospadias		-	-	-	8	5 (62.5)
ACTA2 mutation		H	H	H	H	H	
Prognosis							

+: Present; -: Absent; blank: Unknown; PDA: Patent ductus arteriosus; ASD: Atrial septal defect; PAH: Pulmonary artery hypertension; TAA: Thoracic aortic aneurysm; AAD: Ascending aorta dilatation; PAD: Pulmonary artery dilatation; WM: White matter; RRTI: Recurrent upper respiratory tract infection; H: R179H; C: R179C; L: R179L; D: Death.

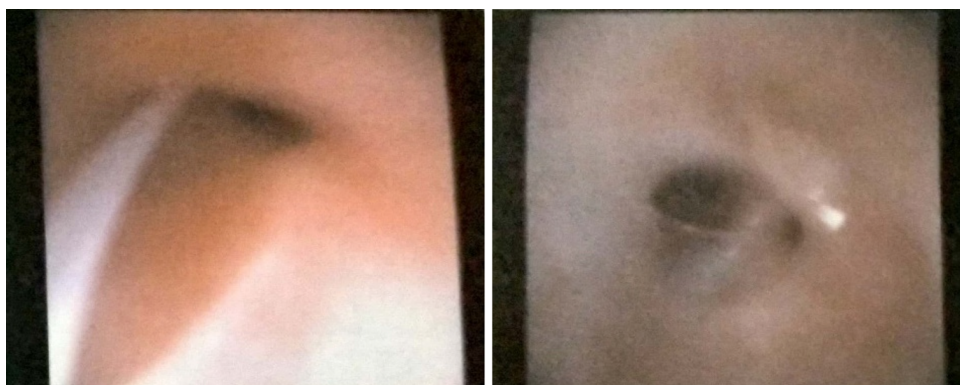


**Figure 3 Abdominal ultrasonography images.** Abdominal ultrasonography revealed a strong echo mass of approximately 4 × 6 in size in the gallbladder.

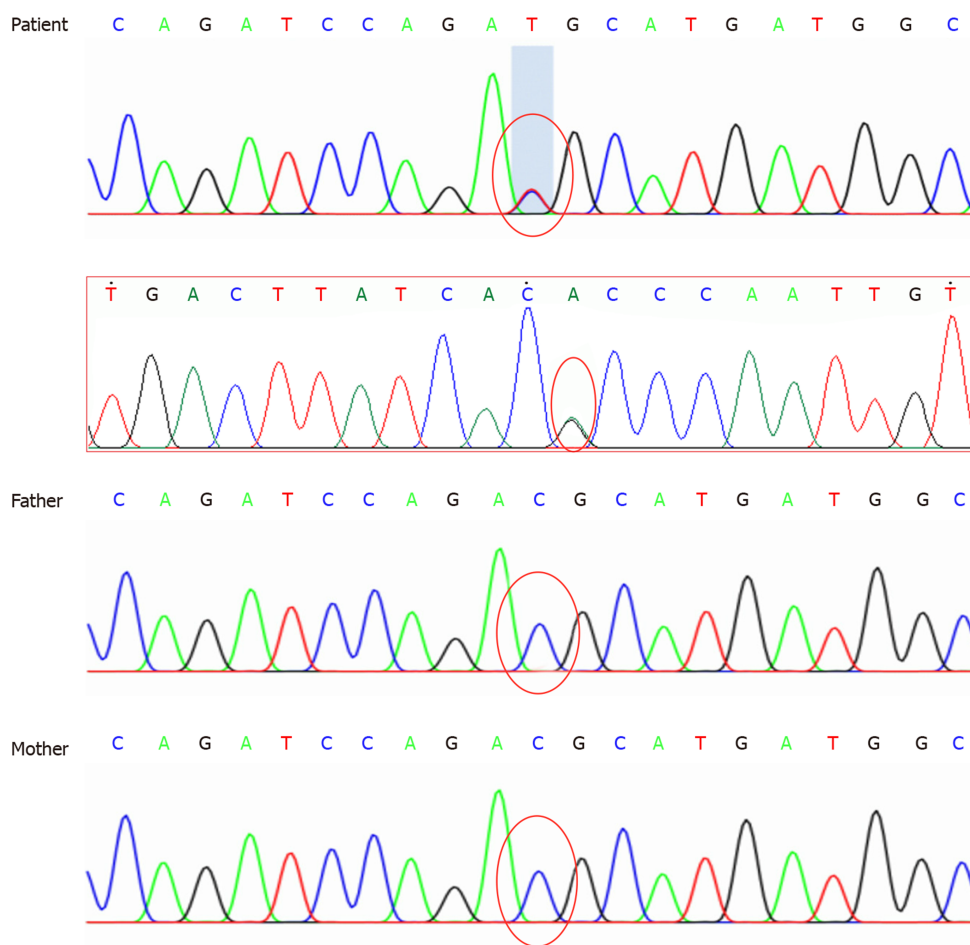


**Figure 4 Echocardiography.** Echocardiography showed a widening pulmonary artery.





**Figure 5 Bronchoscopic findings.** Bronchoscopy revealed redness and edema of the bronchial mucous membranes. Phlegm spots were observed in the left lung, and bronchomalacia was observed in bilateral lungs.



**Figure 6 Genomic sequence of the patient.** Sequencing map of the actin alpha2 (*ACTA2*) gene showed a C-T heterozygous variation at nucleotide 536 in the coding region of the *ACTA2* gene, causing 179 amino acid changes. No genetic mutations were found in her parents.

## REFERENCES

- 1 Milewicz DM, Østergaard JR, Ala-Kokko LM, Khan N, Grange DK, Mendoza-Londono R, Bradley TJ, Olney AH, Adès L, Maher JF, Guo D, Buja LM, Kim D, Hyland JC, Regalado ES. De novo *ACTA2* mutation causes a novel syndrome of multisystemic smooth muscle dysfunction. *Am J Med Genet A* 2010; **152A**: 2437-2443 [PMID: 20734336 DOI: 10.1002/ajmg.a.33657]
- 2 Munot P, Saunders DE, Milewicz DM, Regalado ES, Østergaard JR, Braun KP, Kerr T, Lichtenbelt KD, Philip S, Rittley C, Jacques TS, Cox TC, Ganesan V. A novel distinctive cerebrovascular phenotype is associated with heterozygous Arg179 *ACTA2* mutations. *Brain* 2012; **135**: 2506-2514 [PMID: 22831780 DOI: 10.1093/brain/aww172]
- 3 Zhou YL, Zhang YY, Cheng BL, Xu D, Tang LF, Chen ZM. Multisystemic smooth muscle dysfunction

- syndrome in children: a case report and literature review. *Zhonghua Erke Zazhi* 2017; 8 [DOI: [10.3760/cma.j.issn.0578-1310.2017.08.014](https://doi.org/10.3760/cma.j.issn.0578-1310.2017.08.014)]
- 4 **Meuwissen ME**, Lequin MH, Bindels-de Heus K, Bruggenwirth HT, Knapen MF, Dalinghaus M, de Coor R, van Bever Y, Winkelman BH, Mancini GM. ACTA2 mutation with childhood cardiovascular, autonomic and brain anomalies and severe outcome. *Am J Med Genet A* 2013; **161A**: 1376-1380 [PMID: [23613326](https://pubmed.ncbi.nlm.nih.gov/23613326/) DOI: [10.1002/ajmg.a.35858](https://doi.org/10.1002/ajmg.a.35858)]
  - 5 **Møller HU**, Fledelius HC, Milewicz DM, Regalado ES, Ostergaard JR. Eye features in three Danish patients with multisystemic smooth muscle dysfunction syndrome. *Br J Ophthalmol* 2012; **96**: 1227-1231 [PMID: [22790431](https://pubmed.ncbi.nlm.nih.gov/22790431/) DOI: [10.1136/bjophthalmol-2011-301462](https://doi.org/10.1136/bjophthalmol-2011-301462)]
  - 6 **de Grazia J**, Delgado I, Sanchez-Montanez A, Boronat S, Del Campo M, Vazquez E. Cerebral arteriopathy associated with heterozygous Arg179Cys mutation in the ACTA2 gene: Report in 2 newborn siblings. *Brain Dev* 2017; **39**: 62-66 [PMID: [27567161](https://pubmed.ncbi.nlm.nih.gov/27567161/) DOI: [10.1016/j.braindev.2016.08.003](https://doi.org/10.1016/j.braindev.2016.08.003)]
  - 7 **Moreno CA**, Metzke K, Lomazi EA, Bertola DR, Barbosa RH, Cosentino V, Sobreira N, Cavalcanti DP. Visceral myopathy: Clinical and molecular survey of a cohort of seven new patients and state of the art of overlapping phenotypes. *Am J Med Genet A* 2016; **170**: 2965-2974 [PMID: [27481187](https://pubmed.ncbi.nlm.nih.gov/27481187/) DOI: [10.1002/ajmg.a.37857](https://doi.org/10.1002/ajmg.a.37857)]
  - 8 **Al-Mohaissen M**, Allanson J E, O'Connor MD, Veinot JP, Brandys TM, Maharajh G, Dennie CJ, Beauchesne LM. Brachial artery occlusion in a young adult with an ACTA2 thoracic aortic aneurysm. *Vasc Med* 2012; **17**: 326-329 [DOI: [10.1177/1358863X12453973](https://doi.org/10.1177/1358863X12453973)]
  - 9 **Moosa AN**, Traboulsi EI, Reid J, Prieto L, Moran R, Friedman NR. Neonatal stroke and progressive leukoencephalopathy in a child with an ACTA2 mutation. *J Child Neurol* 2013; **28**: 531-534 [PMID: [22752479](https://pubmed.ncbi.nlm.nih.gov/22752479/) DOI: [10.1177/0883073812446631](https://doi.org/10.1177/0883073812446631)]
  - 10 **Roulez FM**, Faes F, Delbeke P, Van Bogaert P, Rodesch G, De Zaeytjij J, Depasse F, Coucke PJ, Meire FM. Congenital fixed dilated pupils due to ACTA2- multisystemic smooth muscle dysfunction syndrome. *J Neuroophthalmol* 2014; **34**: 137-143 [PMID: [24621862](https://pubmed.ncbi.nlm.nih.gov/24621862/) DOI: [10.1097/WNO.0000000000000090](https://doi.org/10.1097/WNO.0000000000000090)]
  - 11 **Brodsky MC**, Turan KE, Khanna CL, Patton A, Kirmani S. Congenital mydriasis and prune belly syndrome in a child with an ACTA2 mutation. *J AAPOS* 2014; **18**: 393-395 [PMID: [24998021](https://pubmed.ncbi.nlm.nih.gov/24998021/) DOI: [10.1016/j.jaapos.2014.02.010](https://doi.org/10.1016/j.jaapos.2014.02.010)]
  - 12 **Amans MR**, Stout C, Fox C, Narvid J, Hetts SW, Cooke DL, Higashida RT, Dowd CF, McSwain H, Halbach VV. Cerebral arteriopathy associated with Arg179His ACTA2 mutation. *J Neurointerv Surg* 2014; **6**: e46 [PMID: [24353327](https://pubmed.ncbi.nlm.nih.gov/24353327/) DOI: [10.1136/neurintsurg-2013-010997.rep](https://doi.org/10.1136/neurintsurg-2013-010997.rep)]
  - 13 **Yetman AT**, Starr LJ, Bleyl SB, Meyers L, Delaney JW. Progressive Aortic Dilation Associated with ACTA2 Mutations Presenting in Infancy. *Pediatrics* 2015; **136**: e262-e266 [PMID: [26034244](https://pubmed.ncbi.nlm.nih.gov/26034244/) DOI: [10.1542/peds.2014-3032](https://doi.org/10.1542/peds.2014-3032)]
  - 14 **Richer J**, Milewicz DM, Gow R, de Nanassy J, Maharajh G, Miller E, Oppenheimer L, Weiler G, O'Connor M. R179H mutation in ACTA2 expanding the phenotype to include prune-belly sequence and skin manifestations. *Am J Med Genet A* 2012; **158A**: 664-668 [PMID: [22302747](https://pubmed.ncbi.nlm.nih.gov/22302747/) DOI: [10.1002/ajmg.a.35206](https://doi.org/10.1002/ajmg.a.35206)]
  - 15 **Prabhu S**, Fox S, Mattke A, Armes JE, Alphonso N. Extracorporeal Life Support in Multisystem Smooth Muscle Dysfunction Syndrome. *World J Pediatr Congenit Heart Surg* 2017; **8**: 750-753 [PMID: [27549731](https://pubmed.ncbi.nlm.nih.gov/27549731/) DOI: [10.1177/2150135116658457](https://doi.org/10.1177/2150135116658457)]
  - 16 **Logeswaran T**, Friedburg C, Hofmann K, Akintuerk H, Biskup S, Graef M, Rad A, Weber A, Neubauer BA, Schranz D, Bouvagnet P, Lorenz B, Hahn A. Two patients with the heterozygous R189H mutation in ACTA2 and Complex congenital heart defects expands the cardiac phenotype of multisystemic smooth muscle dysfunction syndrome. *Am J Med Genet A* 2017; **173**: 2566 [PMID: [28816420](https://pubmed.ncbi.nlm.nih.gov/28816420/) DOI: [10.1002/ajmg.a.38329](https://doi.org/10.1002/ajmg.a.38329)]
  - 17 **Yetman AT**, Starr LJ. Newly described recessive MYH11 disorder with clinical overlap of Multisystemic smooth muscle dysfunction and Megacystis microcolon hypoperistalsis syndromes. *Am J Med Genet A* 2018; **176**: 1011-1014 [PMID: [29575632](https://pubmed.ncbi.nlm.nih.gov/29575632/) DOI: [10.1002/ajmg.a.38647](https://doi.org/10.1002/ajmg.a.38647)]



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