Case Report

Pulmonary Circulation

Left main coronary artery compression by a dilated main pulmonary artery and left coronary sinus of Valsalva aneurysm in a patient with heritable pulmonary arterial hypertension and FLNA mutation

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Abstract

Left main coronary artery (LMCA) disease due to external compression by a dilated main pulmonary artery (MPA) is an uncommon clinical entity. Here, we describe a 52-year-old woman with pulmonary arterial hypertension (PAH) and anteroseptal old myocardial infarction (OMI). The cause of the OMI was external compression of the LMCA by the dilated MPA and aneurysm of the left coronary sinus of Valsalva. The patient's sister (aged 56 years) had also been diagnosed with PAH and both women had a novel heterozygous splicing mutation, IVS2-2A > G (c.374-2A > G in NM_001456), in the filamin A (*FLNA*) gene. To our knowledge, this is the first report of HPAH which is likely to be due to FLNA mutation and compression of the LMCA between a dilated MPA and aneurysm of the left coronary sinus of Valsalva.

Keywords

aneurysm of the left coronary sinus of Valsalva, heritable pulmonary arterial hypertension, myocardial infarction

Date received: 11 January 2017; accepted: 27 May 2017

Pulmonary Circulation 2017; 7(3) 734–740
DOI: 10.1177/2045893217716107

Introduction

An uncommon cause of coronary artery disease is external compression of those arteries due to dilation of the main pulmonary artery (MPA). In this report, we present a patient with left main coronary artery (LMCA) disease due to external compression of the vessel; the compression resulted from dilation of the MPA and aneurysm of the left coronary sinus of Valsalva secondary to heritable pulmonary arterial hypertension (HPAH). In addition, both our patient and her sister (who had also been diagnosed with PAH) had a mutation in the gene that encodes filamin A (FLNA). Mutations in *FLNA* have been demonstrated in patients with periventricular nodular heterotopia,[1] various dysplasias,[2] otopalatodigital spectrum disorders,[3] and thoracic aortic dilatation or dissection.[4] In our patient, *FLNA*-related PAH was complicated by significant aneurysm of the left coronary sinus of Valsalva, which subsequently led to anteroseptal myocardial infarction (MI).

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Case report

A 52-year-old woman diagnosed with PAH and anteroseptal MI was referred to our institute, where she presented with progressive dyspnea on exertion and peripheral edema. She had worked as a nurse without difficulty until she was 45 years old, when she began to experience increased general everyday fatigue. She had never smoked and she denied any illicit drug use.

In 2007, the patient had undergone cardiac catheterization at another hospital (pulmonary arterial pressure [PAP]: systolic/diastolic/mean = 72/27/45 mmHg, pulmonary artery wedge pressure [PAWP] = 14 mmHg, cardiac index = 2.16 L/min/m^2, pulmonary vascular resistance [PVR] = 9.3 Wood units). Her left ventricular ejection fraction was 67%, left atrial dimension was 32 mm, and lung function was normal. She had subsequently begun combination therapy through that hospital with 125 mg bosentan twice daily and 20 mg sildenafil three times daily.

In 2009, the patient presented to her original hospital with prolonged chest pain and low blood pressure; she was considered to be in cardiogenic shock due to acute MI. Emergent coronary angiography revealed 99% stenosis of the left main coronary artery in an abnormally high position because of pressure from an aneurysm of the left coronary sinus of Valsalva (Fig. 1a); consequently a Cypher stent (Cordis Corporation, Miami Lakes, FL, USA) was implanted at the patient's original hospital during intra-aortic balloon pumping (Fig. 1b). The aneurysm was not noted at the time during the procedure but was found retrospectively on review of the imaging findings at our hospital. For this reason, no additional examinations were conducted at the time of the procedure.

In April 2014, the patient was hospitalized with progressive heart failure and was then referred to our hospital for treatment and management of her pulmonary hypertension (PH). We promptly performed cardiac catheterization (mean PAP = 47 mmHg, PAWP = 21 mmHg, right atrial pressure = 12 mmHg, cardiac index = 2.36 L/min/m^2 [Fick principle], PVR = 7.4 Wood units). Physical examination on admission revealed an increased P2 component of S2 and dilated jugular veins. No ascites was present, but the patient's lower extremities were slightly edematous. An electrocardiogram revealed right ventricular hypertrophy with ST change. The plasma brain natriuretic peptide (BNP) concentration was 450 pg/mL. Transthoracic echocardiography showed that the anteroseptal wall was thin and akinetic and the left ventricular ejection fraction was 37% (Fig. 1c); the inferior vena cava was dilated (27.7 mm) (Fig. 1d). Pulmonary perfusion scintigraphy revealed no abnormalities. We performed echocardiography and magnetic

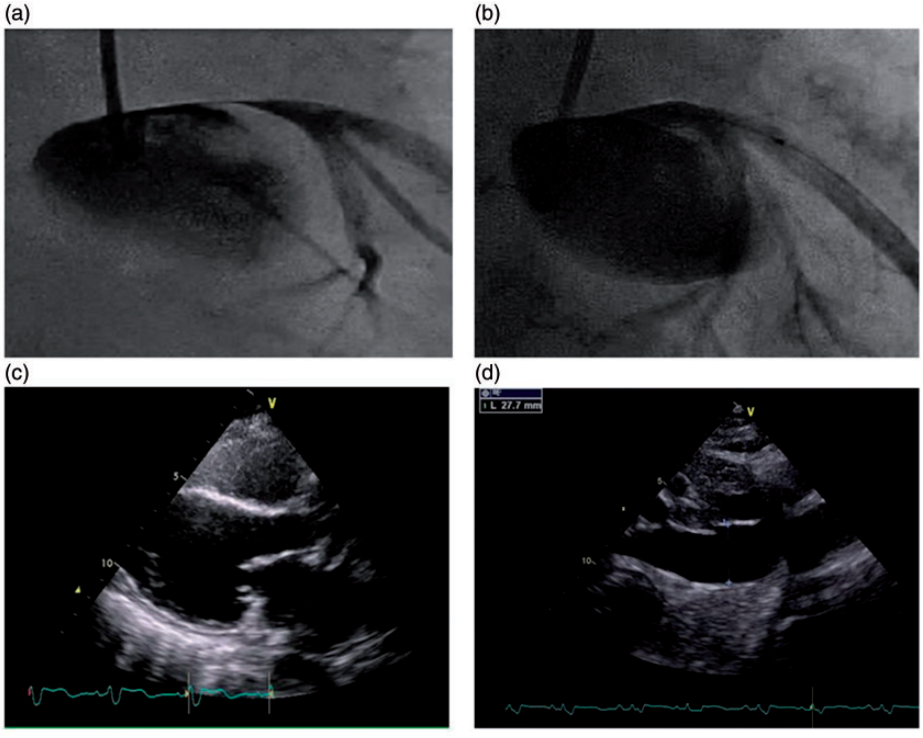

Fig. 1. Coronary angiography during the acute myocardial infarction phase and echocardiography five years after percutaneous coronary intervention, when the patient was referred to us because of progressive heart failure. (a) Coronary angiography before percutaneous coronary intervention. The ostium of the left main coronary artery (LMCA) is 99% occluded. In addition, the LMCA is in an abnormally high position because of pressure from the aneurysm of the left coronary sinus of Valsalva. (b) After stent implantation. (c) Transthoracic echocardiography five years after (a) and (b). The anteroseptal wall is thin and akinetic; the left ventricular ejection fraction is 37%. (d) Dilatation of the inferior vena cava (27.7 mm).

resonance imaging. Multiple samples of whole blood were withdrawn during cardiac catheterization to measure O_2 saturation to rule out other underlying heart diseases, such as primary left heart disease and congenital heart disease. There was no cardiac shunt, valvular disease, or lung disease. In addition, the results of both pulmonary function testing and high-resolution computed tomography (CT) were normal. Together, these findings supported the diagnosis of PH due to left heart disease (group 2 of the Dana Point 2008 classification[5]). In addition, 64-slice multidetector CT at admission showed marked dilation of the main pulmonary artery (47.7 mm) (Fig. 2a), no restenosis of the left main coronary artery, and aneurysm of the left coronary sinus of Valsalva (36.0 mm) (Fig. 2b). The stent previously placed in the left main coronary trunk was located between the main pulmonary arterial trunk and the left coronary sinus of Valsalva (Fig. 2c and 2d).

Before the patient's referral to our institution, her treatment had comprised oxygen therapy, bosentan (125 mg twice daily), sildenafil (20 mg three times daily), warfarin (4 mg daily), azosemide (60 mg daily), and spironolactone (25 mg daily); tolvaptan (7.5 mg daily) was added after referral. Thereafter, her pulmonary congestion decreased, as did her plasma BNP level (to 170 pg/mL) and mean PAP (to 38 mmHg). After one month of treatment with tolvaptan, the patient was discharged home. She has been followed through our outpatient clinic: at last review, her PH was in World Health Organization (WHO) functional class II and her plasma BNP level had remained unchanged since discharge.

The patient's elder sister had also been diagnosed with PAH (mean PAP = 35 mmHg, PAWP = 11 mmHg, PVR = 4.8 Wood units). The chest radiographs of the two women were similar in regard to the degree of pulmonary artery dilatation (Fig. 3a and 3b). However, the sister had no left main trunk stenosis and no aneurysm of the left coronary sinus of Valsalva (Fig. 4), and the left ventricle was of normal size and had normal contractility. There were no signs of left heart disease, congenital heart disease, or lung disease. Because we suspected that these sisters had HPAH, we suggested professional genetic testing. Conventional Sanger sequencing and multiplex ligation-dependent probe

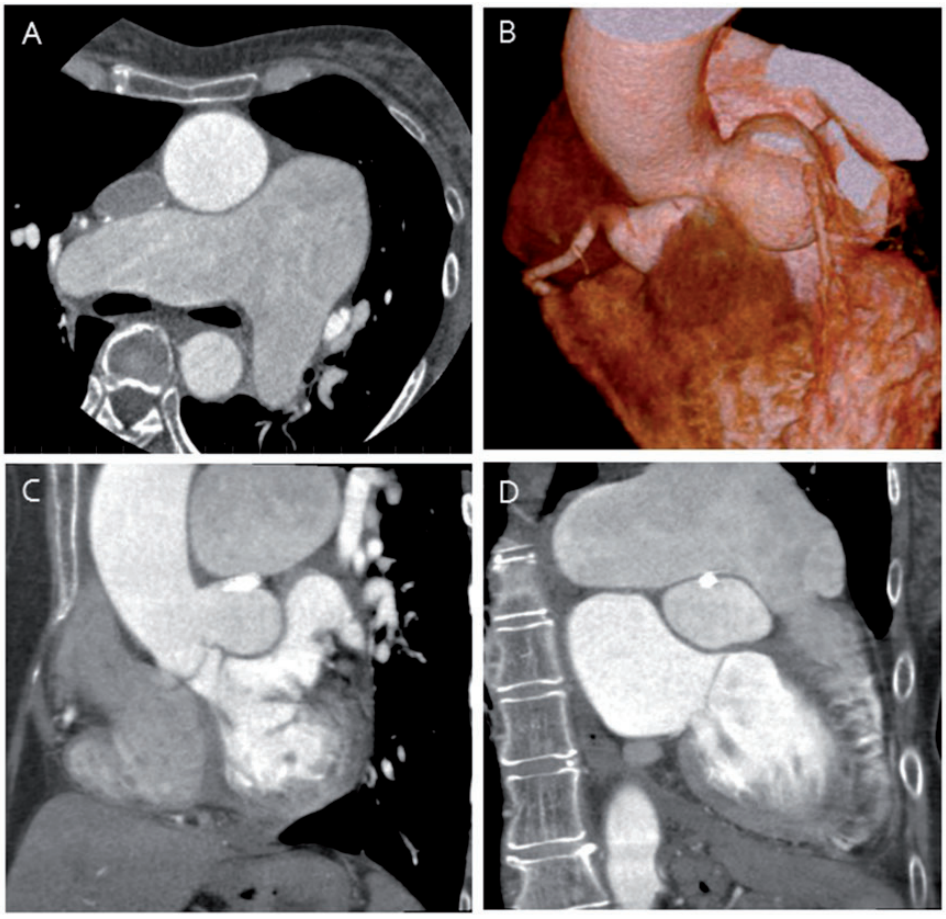

Fig. 2. CT. (a) Marked dilation of the main pulmonary artery (47.7 mm) by transverse view on conventional CT. (b) CT coronary angiography showing the stent within the unprotected left main coronary artery and aneurysm of the left coronary sinus of Valsalva. (c) The stent previously placed in the left main coronary trunk was located between the main pulmonary arterial trunk and the left coronary sinus of Valsalva by coronal view. (d) Sagittal view.

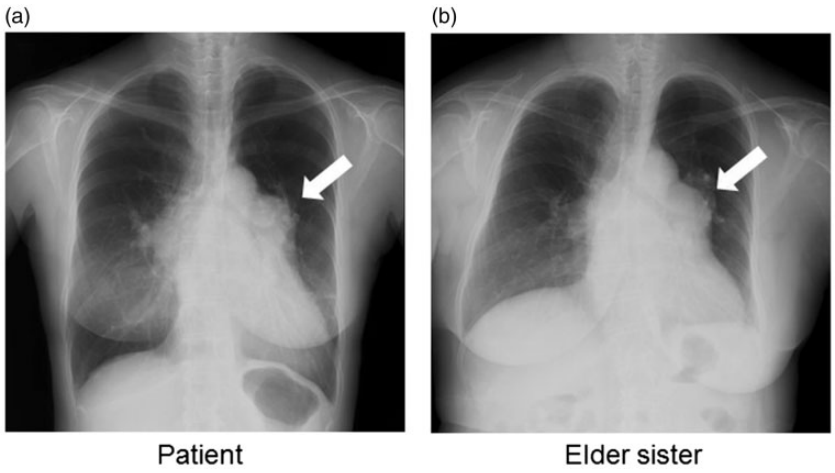

Fig. 3. Chest radiography. (a) Chest radiograph of the patient at our hospital. (b) Chest radiograph of the patient's elder sister. In both women, the pulmonary artery is extremely dilated (white arrows).

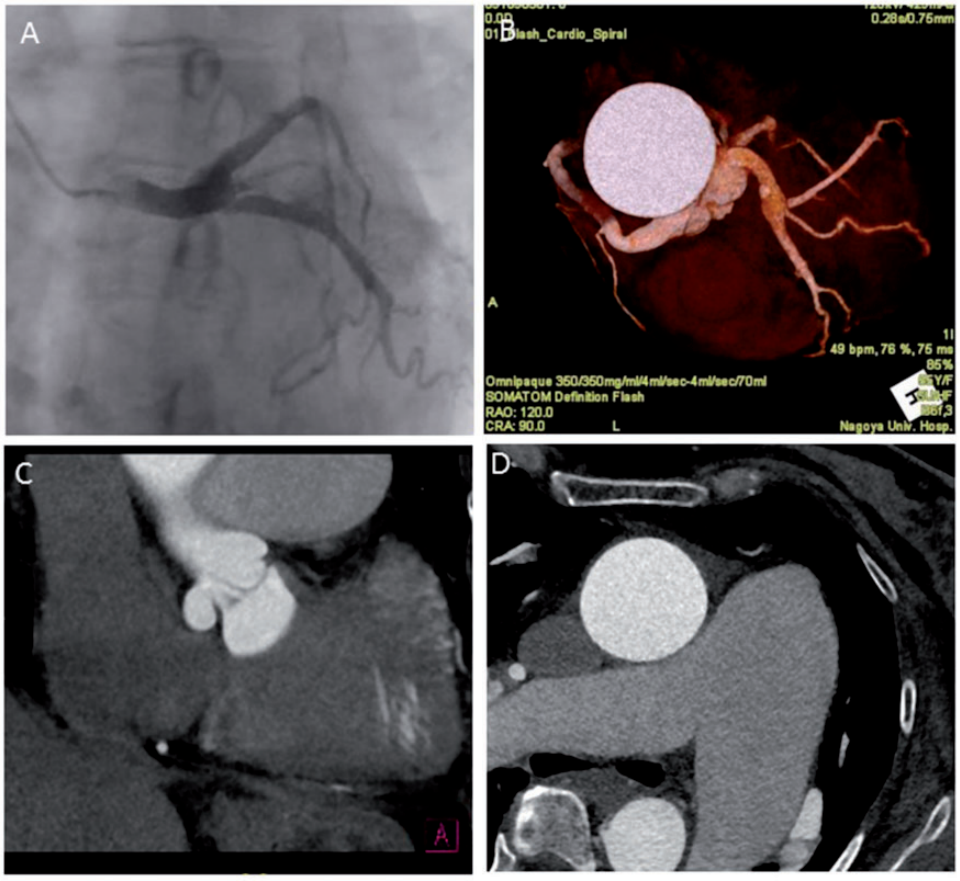

Fig. 4. Elder sister's angiography and CT scans. (a) No stenosis of left main trunk on the coronary angiography. (b) No aneurysms of aneurysm of the left coronary sinus of Valsalva on the CT coronary angiography. (c) Coronal view of the left coronary sinus of Valsalva. (d) Transverse view of dilated pulmonary artery.

amplification analysis of the genes encoding bone morphogenetic protein receptor type 2 (BMPR2) and activin A receptor type II–like kinase 1 (ACVRL1) failed to detect any pathogenic variants, but subsequent whole-exome sequencing revealed a novel heterozygous splicing mutation in the *FLNA* gene, namely IVS2-2A > G (c.374-2A > G in NM_001456) (Fig. 5) in both sisters but not in their father (aged 89 years). This mutation changed the 3' splice site

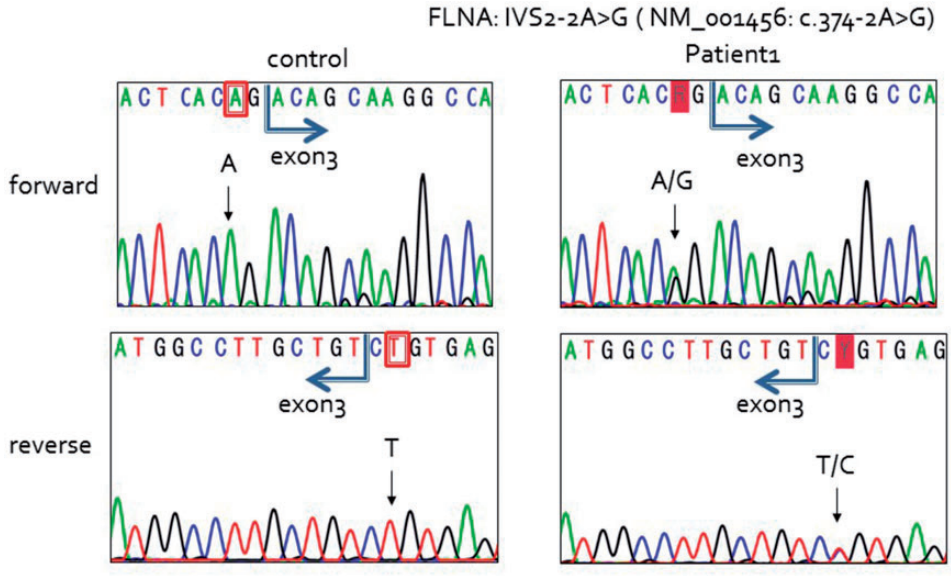

Fig. 5. Electropherograms of the *FLNA* sequence, showing a novel heterozygous splicing mutation, IVS2-2 A > G (c.374-2 A > G in NM_001456) in the proband of our patients.

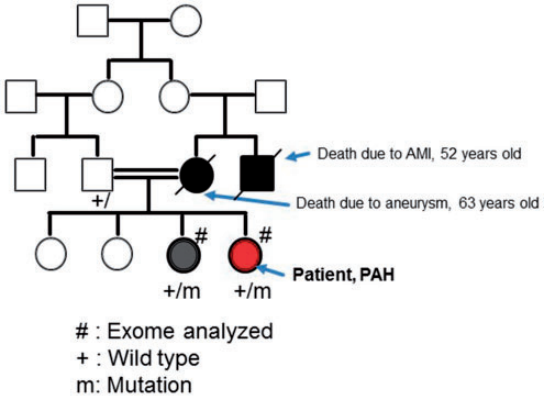

Fig. 6. Four-generation pedigree of the family. AMI, acute myocardial infarction; PAH, pulmonary arterial hypertension.

consensus sequence from AG to GG and was expected to cause aberrant splicing. A four-generation pedigree of the family was generated from their responses to a questionnaire (Fig. 6).

Discussion

We present here the rare case of a 52-year-old woman with external LMCA compression by a dilated MPA and a giant aneurysm of the left sinus of Valsalva. Both the patient and her elder sister were diagnosed with HPAH and carried the same mutation in *FLNA*.

The rarity of acute MI with cardiogenic shock due to extrinsic compression of the LMCA between a dilated pulmonary artery trunk and aneurysm of the left coronary sinus of Valsalva had caused the physicians who had performed emergent percutaneous coronary intervention at the patient's previous hospital to overlook this underlying etiology. However, after referral of the patient to our institution, this diagnosis was verified by cardiac multidetector CT, which is the modality of choice for first-line diagnosis of LMCA disease with these associated complications.

Although compression of the LMCA causing ST segment elevation MI is rare, it can lead to cardiogenic shock and thus increased mortality. Large aneurysms of the left sinus of Valsalva can cause protrusion and rupture of the pulmonary artery, left ventricle, myocardium, and epicardium.[6] Compression of the LMCA by a dilated MPA has been described in the literature,[7–10] and the prevalence of LMCA stenosis may be underestimated. Aneurysms of the sinus of Valsalva are rare cardiac anomalies as well; they may be acquired or congenital, and they typically involve the right coronary or non-coronary sinuses.[11]

Two consensus guidelines recommend that physicians offer professional genetic counseling and genetic testing to patients whose histories suggest HPAH.[12,13] Mutations of *BMPR2* have been identified as the most common genetic variants predisposing patients to HPAH, whereas *ACVRL1*, also known as *ALK1*, is the gene most often affected when PAH is associated with hereditary hemorrhagic telangiectasia.[14] Approximately 75% of HPAH patients carry mutations in genes known to be associated with the disease,[15] the genetic cause of the disease in the remaining 25% of patients remains unknown, despite careful molecular investigation of other genes besides BMPR2 and ALK1.[16]

We first performed genetic screening of known PAH genes, including *BMPR2* and *ACVRL1*, in both sisters by using direct Sanger sequencing of PCR-amplified entire coding regions and multiplex ligation-dependent probe

amplification analysis. Because no disease-causing variant was identified, we next conducted whole-exome sequencing of the sisters by using a TruSeq exome library prep kit (Illumina). Data analysis of 516 candidate genes for cardiovascular diseases and more than 4000 genes known to cause genetic syndromes are listed in TruSight One sequencing panel (Illumina), including *CAV1*, *KCNK3*, and *EIF2AK4*. After filtering to exclude benign or MAF > 0.01 variants, we identified only one shared splicing variant in *FLNA*. This variant was not found in any population-based variation databases, including dbSNP, ExAC, 1000 Genomes, and Japanese 1000 Genomes. To determine the segregation of this variant in the family, bidirectional Sanger sequencing of this exonic region was undertaken in the sisters and their father. The variant was confirmed in both sisters but not in their father, revealing that it had been inherited from their deceased mother due to thoracic aortic aneurysm and co-segregated with the phenotype in this family.

FLNA encodes filamin A, an actin-binding protein that is involved in remodeling the cytoskeleton to effect changes in cell shape and migration. Mutation in *FLNA* causes multiple malformation syndromes,[17–20] including periventricular nodular heterotopias, otopalatodigital syndromes, frontometaphyseal dysplasia, Melnick–Needles syndrome, X-linked congenital idiopathic intestinal pseudoobstruction, and Ehlers–Danlos spectrum. Recently there have been several reports of a relationship between *FLNA* mutations and cardiovascular complications, including valvular insufficiency, carotid dissection, and thoracic aortic dilatation and dissection.[4] Because *FLNA*-related disorders are inherited in an X-linked dominant manner, female patients often present with milder phenotypes. The sisters did not display skin hyperextensibility, joint hypermobility, or tissue fragility demonstrated by easy bruising and delayed wound healing with atrophic scarring. In addition, they had no thoracic aortic aneurysms.

We know of one recently reported case of external LMCA compression due to a giant aneurysm of the left sinus of Valsalva. It was successfully managed with percutaneous coronary intervention;[21] however, the underlying genetic mutation was not described. Here, the clinical characteristic shared by these sisters with PAH was an extremely dilated MPA but not particularly high PVR. Disease duration was not known accurately in either woman; however, both women had experienced successful pregnancies and deliveries when they were in their twenties. Because their elderly father did not have the *FLNA* mutation, their deceased mother was considered an obligate carrier.

The patient we presented here developed LMCA compression due to MPA dilation accompanied by aneurysm of the left coronary sinus of Valsalva in the context of HPAH and an *FLNA* mutation. To our knowledge, this report is the first to describe HPAH which is likely to be due to both *FLNA* mutation and compression of the LMCA between a dilated pulmonary artery and aneurysm of the left coronary sinus of Valsalva. The association between mutations in the *FLNA* gene and PAH remains unclear and warrants further investigation.

Acknowledgments

Akihiro Hirashiki is a former member of a department of Advanced Medicine in Cardiopulmonary Disease endowed by Actelion Pharmaceuticals Japan, Ltd. Both Takahisa Kondo and Shiro Adachi belong to a department Advanced Medicine in Cardiopulmonary Disease endowed by Actelion Pharmaceuticals Japan, Ltd.

Conflict of interest

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

Funding

This research received no specific grant from any funding body in the public, commercial, or not-for-profit sectors.

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