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CLINICAL REPORT

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Novel *SMAD3* p.Arg386Thr genetic variant co-segregating with thoracic aortic aneurysm and dissection

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Abstract

Background: Pathogenic variants in the *SMAD3* gene affecting the TGF-β/SMAD3 signaling pathway with aortic vessel involvement cause Loeys-Dietz syndrome 3, also known as aneurysms–osteoarthritis syndrome.

Methods: Description of clinical history of a family in Sweden using clinical data, DNA sequencing, bioinformatics, and pedigree analysis.

Results: We report a novel *SMAD3* variant, initially classified as a genetic variant of uncertain clinical significance (VUS), and later found to be co-segregating with aortic dissection in the family. The index patient presented with a dissecting aneurysm of the aorta including the ascending, descending, and abdominal parts. Genotype analysis revealed a heterozygous missense *SMAD3* variant: NM_005902.3(*SMAD3*): c.11576G > C (p.Arg386Thr). The same variant was also identified in a 30 years old formalin-fixed paraffin-embedded block of tissue from a second cousin, who died at 26 years of age from a dissecting aneurysm of the aorta.

Conclusion: A "variant of uncertain significance" according to the ACMG guidelines has always a scope for reappraisal. Genetic counselling to relatives, and the offering of surveillance service is important to families with aortic aneurysm disease. The report also highlight the potential use of FFPE analysis from deceased relatives to help in the interpretation of variants.

KEYWORDS

aortic aneurysm and dissection, Loeys-Dietz syndrome 3, *SMAD3*, TAAD

1 | INTRODUCTION

Thoracic aortic aneurysm and dissection (TAAD) is a potentially lethal condition showing familial clustering. Approximately 20% of non-syndromic thoracic aortic aneurysm patients have a familial history of TAAD (Biddinger, Rocklin, Coselli, & Milewicz, 1997; Coady et al., 1999). Mutations in various genes have been associated with this condition. One of these genes is the Mothers against decapentaplegic homolog 3 gene (*SMAD3*) (OMIM 603,109). Mutations in *SMAD3* are known to affect the transforming growth factor-β (TGF-β) signaling pathway, causing a clinical picture initially described as a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis

(van de Laar et al., 2011). This is nowadays preferentially referred to as Loeys-Dietz Syndrome (LDS) type 3, which implicates widespread arterial involvement, vascular tortuosity, a high risk of aneurysms and dissections throughout the arterial tree, and an aggressive vascular outcome (Regaldo et al., 2011; van de Laar et al., 2011). A recent mutation update included 67 possibly disease causing variants of the *SMAD3* gene (Schepers et al., 2018). In this study we report a novel *SMAD3* p.Arg386Thr variant, classified as a variant of uncertain significance (VUS), which co-segregates with TAAD in the family.

2 | CLINICAL REPORT

The index patient, a 59-year-old male, presented in 2014 with blurred speech, sensory loss in both legs and pain in the neck. Computer tomography (CT) showed an acute type A dissection from the aortic root to the aortoiliac bifurcation. The patient underwent emergency aortic valve, root, and ascending aorta replacement with a Bentall procedure (Bentall & De Bono, 1968) (Figure 1a). A coronary artery bypass grafting of the right coronary artery was also performed because of profuse bleeding from the dissected and fragile right coronary main stem. There was no history of connective tissue disease, hypertension, diabetes mellitus, or smoking and even though the patient himself mentioned lumbago and vertebral disc degeneration on x-ray at the age of 19, he had no clinical diagnosis of osteoarthritis.

The family history seemed significant (Figure 2a). Noteworthy is the suspected cardiac death of a 59 years old brother (III:5) who had suffered from recurrent episodes of cardiac syncope. The patient's mother (II:3) died suddenly at the age of 77 years, with a history of recurrent episodes of atrial fibrillation. Furthermore, a second cousin on the maternal side (III:2) died of ruptured aortic aneurysm at the age of 26 years. His father (II:2) was said to have died 35 years old of aortic aneurysm. An aunt (II:1) died 49 years old in a heart attack. She was not autopsied.

2.1 | Echocardiography (UCG) controls prior to the dissection

Because of the family history, the patient had been included in a control program with annual screening for heart and aortic abnormalities. Two check-ups preceding the dissection are documented. In 2013, 18 months before the dissection, the aortic root measured 47 mm, with dilated sinuses of Valsalva. The arcus was reported as of normal size and the left ventricle as of normal systolic function. A moderate aortic insufficiency was seen. There were no signs of arterial pulmonary hypertension. One year later, that is, 6 months before the dissection, the UCG showed a possible progress of the aortic root dilatation to 48 mm and dilatation of the ascending aorta with a maximum diameter of 53 mm, narrowing to 34 mm at arcus. There was moderate aortic insufficiency, but no stenosis. He had mitral valve prolapse and there was a slight mitral insufficiency. The left ventricle was slightly dilated with normal systolic function.

2.2 | Further procedures following the aortic dissection

Within 3 months following the aortic dissection, the proximal descending thoracic aorta dilated from 40 mm to 59 mm (Figure 1b). A second procedure was conducted, at which the aortic arch and the descending aorta was treated with a branched hybrid graft, Thoraflex™ Hybrid Plexus prosthesis (Vascutek, Inchinnan) (Ma, Zheng, Sun, & Elefteriades, 2015) (Figure 1c). The non-stented portion of the graft replaced the aortic arch and the proximal parts of its branches. The stented part of the graft was placed in the descending aorta providing a landing zone for further treatment with endovascular stent grafting. At this stage, the almost 6 cm dilatation of the proximal descending aorta was still exposed for pressure. Consequently, endovascular stenting was later performed from the previously installed hybrid graft in the descending aorta to the iliac arteries bilaterally. The main abdominal branches from aorta, that is, the coeliac trunk, the superior mesenteric artery, as well as both renal arteries were stented (Figure 1d). The patient was eventually discharged in good health and went back to work with a recommendation of annual echocardiograms. At follow-up CT-scan examinations, a normalization of the thoracic aorta size, but also a slow progress of the infrarenal aneurysm size from 44 mm to 47 mm, due to a distal endoleak from the right common iliac artery (type 1a), has been observed. This will be treated in the case of further progress.

2.3 | Editorial policies and ethical compliance

Written informed consent was obtained from the patients for genetic studies. Ethical approval for this study was obtained from Ethic Committee of Linköping (Dnr 2016/389-31).

2.4 | Genetic investigation

Next generation sequencing with a gene panel for sudden cardiac death (SCD) including 80 genes revealed that the index patient (III:10) was heterozygous for a *SMAD3* variant NM_005902.3(*SMAD3*): c.1157G > C (p.Arg386Thr),

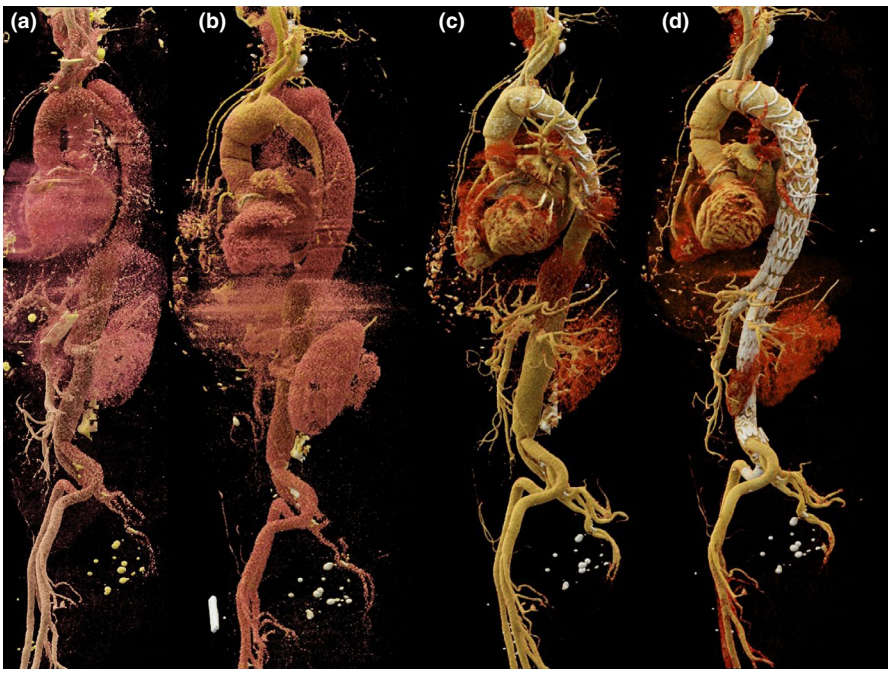

FIGURE 1 (a-d) Reconstruction from CT scan (a) after emergency aortic valve, root, and ascending aorta replacement, (b) proximal descending aorta dilated, (c) reconstruction of arcus, proximal parts of its branches and stented part of the graft placed in descending aorta, (d) endovascular stenting from previously installed graft to the iliac arteries bilaterally

suggesting a possible Loeys-Dietz syndrome 3. No other presumptively disease causing variant was found in the bioinformatic analysis performed with prediction tools, ALAMUT and HGMD. The American College of Medical Genetics and Genomics criteria (Richards et al., 2015) were used for predicting pathogenicity. Accordingly, the variant *SMAD3* c.1157G > C (p.Arg386Thr) was predicted to be of "uncertain significance" (VUS). CADD score 29.7. The variant has been submitted to ClinVar.

The testing of genetic material from formalin fixed paraffin embedded (FFPE) cardiac tissue was performed as follows. DNA was extracted from 10 μm sections using QiaAmp DNA FFPE Tissue Kit (Qiagen). A sequencing panel of 84 cardiac genes, custom designed using SureDesign (Agilent Technologies) with high Sensitivity, and FFPE settings, and molecular barcodes was employed. Library preparation was performed using the HaloPlex Target Enrichment System (Agilent Technologies) according to recommendations from the manufacturer. Paired-end sequencing was performed using a MiSeq instrument (Illumina). FASTQ files (including files for molecular barcoding) were analyzed using SureCall (Agilent Technologies). Detected variants were also checked visually using IGV, to ensure that the variant position was covered by multiple amplicons, and reads originating from several different DNA molecules.

2.5 | Clinical and genetic follow-up of relatives

DNA analysis performed on formalin fixed paraffin embedded (FFPE) material from the deceased second cousin (III:2) revealed that he was heterozygous for the *SMAD3* variant c.1157G > C (p.Arg386Thr). His son (IV:1) also tested positive for the same mutation. He is 34 years old and has regular UCG controls. In 2017, the aortic root was at the upper limit of 37 mm, unchanged from previous check-up. Normal values were found for aorta ascendens (30 mm) and the aortic arcus (23 mm). He has a tricuspid aortic valve, normal sized left ventricle, and normal systolic and diastolic function. So far, 12 family members have been offered genetic testing (Figure 2a and 2b). As seen in Figure 2, and family history in the case report, the mutation co-segregates with TAAD and arrhythmias.

3 | DISCUSSION

The novel missense *SMAD3* c.1157G > C (p.Arg386Thr) gene variant described here seems to be the probable cause of vascular disease in a family where TAAD is inherited in an apparently autosomal dominant pattern with reduced penetrance. These findings are consistent with the aneurysms-osteoarthritis syndrome (AOS), with complex features including aneurysms, dissections, and arterial tortuosity (van der Laar et al., 2011). The phenotype of AOS, including widespread cardiovascular aneurysms, dissections and arterial tortuosity in the thorax and abdomen was in 2012 further delineated (van der Linde et al., 2012). It was reported structural congenital heart defects, left ventricular hypertrophy in the absence of hypertension or aortic stenosis (19% of patients), history of atrial fibrillation (21% of patients), and a higher aortic pulse wave velocity (aPWV) in 33% of patients with a mutation in the *SMAD3* gene (van der Linde et al.,

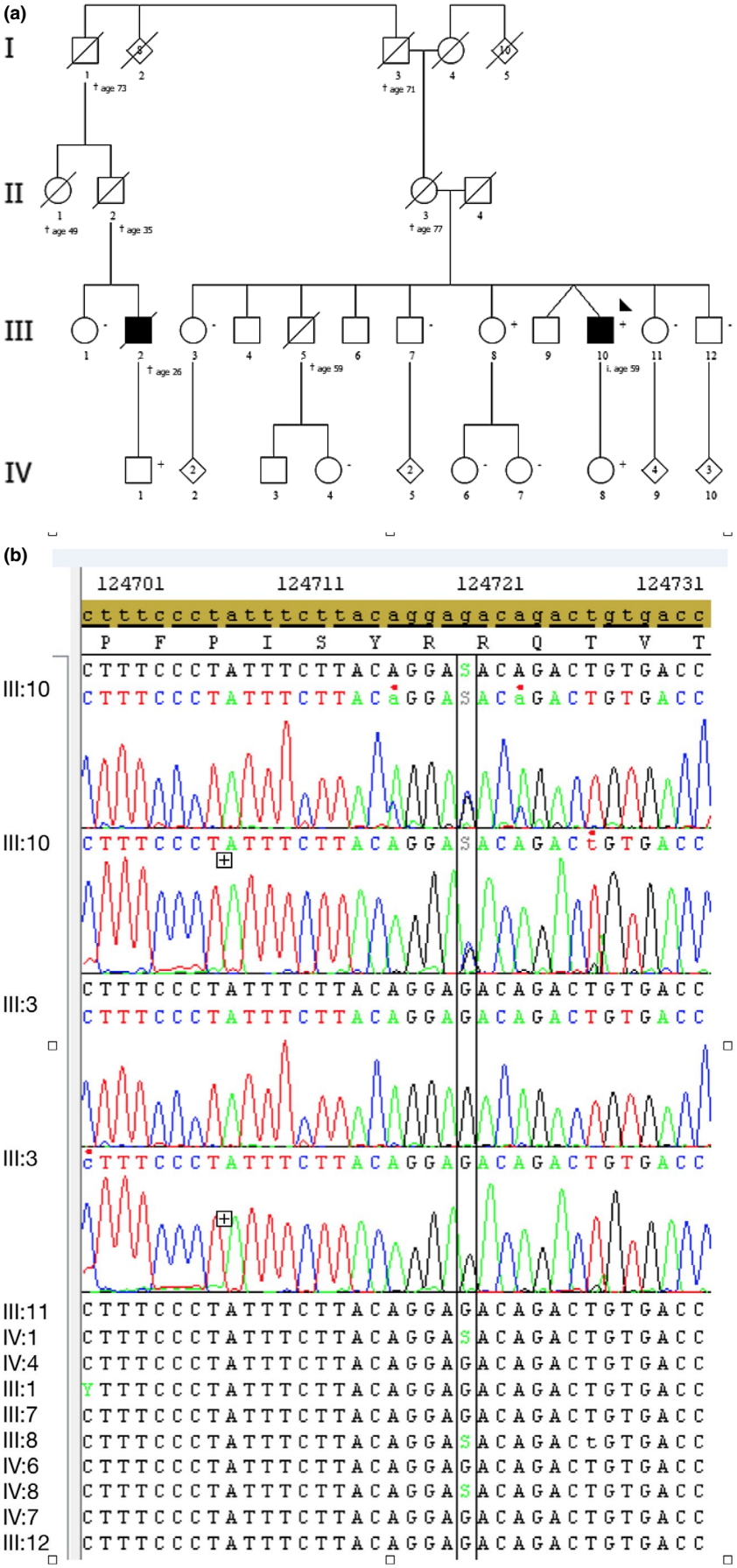

FIGURE 2 (a) Pedigree analysis of the family in the study. Circles in the pedigree denote females, squares males, filled symbols verified TAAD. A crossed-over symbol indicates that the individual has died. A dagger is followed by the age at death. The arrowhead points to the index patient. Carriers of the genetic variant *SMAD3* c.1157G > C are marked by "+" sign, tested non-carriers by "-". Reported symptoms of interest are presented in the article. (b) Sangersequencing results showing heterozygous (III:10, III:3 etc in Figure 2a for NM_005902.3(SMAD3):c.1157G > C p.Arg386Thr). The variant nucleotide position is indicated by parallel vertical lines

2012). This is in agreement with the findings in our study where several family members, whose aortic status we do not know, suffered from recurrence of atrial fibrillation and/or sudden cardiac death. Van der Linde et al also investigated the cardiovascular phenotype of AOS with the aim to provide clinical recommendations for treatment. In their study, aortic root aneurysm was found in 27 of 38 patients (71%), with missing data for 6 patients who died before examination. In 8 out of 24 patients (33%), aneurysms were found in other arteries, that is, the descending thoracic and abdominal aorta, pulmonary trunk, superior mesenteric arteries, and other vessels. It was also found that the aortic root most often was dilated at the level of sinus Valsalva (van der Linde et al., 2012).

Although the first published data for AOS indicated that 100% of the patients had early onset osteoarthritis (van de Laar et al., 2011), with a mean debut age for osteoarthritis of 42 years (van der Linde et al., 2012), associated with the finding of cardiovascular disease, there are later studies showing a lower incidence of joint pain and osteoarthritis (Regaldo et al., 2011; Schepers et al., 2018; Wischmeijer et al., 2013), suggesting that *SMAD3* mutations should be suspected in patients with Loeys-Dietz syndrome(LDS)-like phenotype, no matter if early onset osteoarthritis is present or not. There was a report of lumbago and vertebral disc degeneration on x-ray at the age of 19 in our index patient's records. This is possibly an indication that he, even though he has not been given the diagnosis osteoarthritis, might have had a similar intervertebral disc abnormality as described by van der Laar et al. (2011).

MacCarrick et al. (2014) proposed that a mutation in any of the genes known to affect TGF-β signaling (paradoxical up-regulation of both canonical and noncanonical TGF-β signaling), in combination with arterial aneurysm or dissection or family history of Loeys-Dietz syndrome should be enough for the diagnosis of LDS. The name Loeys-Dietz type 3 was proposed for the syndrome, previously reported as AOS, caused by mutations in the *SMAD3* gene (Loeys et al., 2006).

LDS type 1 and LDS type 2 are well described, and an update was published presenting mutations that have been identified so far in the LDS-associated genes *TGFB*2/3 and *SMAD*2/3 (Schepers et al., 2018). A broad clinical variability makes the genetic testing an important tool for recognizing patients with high cardiovascular risk. Since the time when AOS/LDS type 3 was first proposed, more genes affecting the TGF-β signaling pathway (paradoxical up-regulation of both canonical and non-canonical TGF-β signaling) have been reported, for example, the *TGFB3* gene variants causing syndromic presentations of aortic aneurysms, where some symptoms overlap with LDS, Shprintzen-Goldberg and Marfan syndromes (Bertoli-Avella et al., 2015). However, mutations in *SMAD3* and *TGFBR*1/2 are generally more aggressive (Bradley, Bowdin, Morel, & Pyeritz, 2016; Verstraeten, Alaerts, Van Laer, & Loeys, 2016). The reported mutations suggest loss of function of the cognate protein (Isselbacher, Lino Cardenas, & Lindsay, 2016). Mutations in *TGFBR1* and *TGFBR2* causing vascular disease have exclusively been missense mutations. Interestingly, deletions of *TGFBR1* do not cause vascular disease (Isselbacher et al., 2016). On the other hand, disease-causing variants of the *SMAD3* gene include missense, frameshift, nonsense, splice-site mutations, and whole and partial gene deletions (Schepers et al., 2018; van de Laar et al., 2011). Mutations in *SMAD3* lead to disorganization of the arterial tunica media with fragmentation of elastic fibers, loss of elastic fibers, and disruption of the collagen architecture (van de Laar et al., 2011). Majority of the mutations, including the *SMAD3* c.1157G > C (p.Arg386Thr) variant, are located in the MH2 domain of the protein, which is evolutionary highly conserved among species and SMAD proteins.

In contrast to Marfan syndrome, cerebrovascular abnormalities frequently occur in LDS type 3. Out of 16 patients with a *SMAD3* mutation and subject to cerebrovascular imaging, 9 (56%) had cerebrovascular abnormalities (van der Linde et al., 2012). There was, however, no intracranial hemorrhage reported as cause of death in their study. Thus, from the literature, it seems that the risk of rupture of intracranial aneurysms associated with *SMAD3* (i.e., patients with LDS type3) is unknown and possibly low. On the contrary, 3 out of 25 patients testing positive for LDS variants in *TGFBR1* and *TGFBR2,* were shown to have dissections of the carotid and vertebrobasilar arteries (Rodrigues, Elsayed, Loeys, Dietz, & Yousem, 2009), bearing in mind that cervical dissections can also result from extension of a Stanford type A dissection (Goshgarian, Lugo, & Salazar, 2013).

Also in contrast to findings in other familial thoracic aortic aneurysms syndromes, we are not aware of any case of maternal mortality or aortic dissections reported in pregnant women with *SMAD3* mutations. If this is indicative of milder symptoms for women with *SMAD3* mutations than for men has not been further studied. Increased risk during pregnancy is not mentioned as a possibility in the latest update by Schepers et al. (2018), and no clear risk of obstetric complications was reported by van Hagen et al. (2017). In the family presented here there was no report of complications during pregnancy. However, Blinc et al. (2015) published a case where a woman presented with dissection of the left anterior descending coronary artery as well as dissection of the left internal carotid artery during the postpartum period. Exome sequencing detected a novel mutation in *SMAD3*.

To the best of our knowledge, the *SMAD3* c.1157G > C (p.Arg386Thr) variant described in this paper has not been reported before. Bioinformatic analysis using predictive tools was not consistent. SIFT, PolyPhen-2 and Mutation Taster predicted the variant to be deleterious and disease causing, whereas Align GVD predicted it to be benign and not

causative. The CADD score for the variant is 29.7. Using American College of Medical Genetics and Genomics (ACMG) criteria (Richards et al., 2015) for predicting pathogenicity of genetic variants, the *SMAD3* c.1157G > C (p.Arg386Thr) mutation was ranked as a Class 3 "variant of uncertain significance" (VUS). In spite of the fact that the same variant was also identified in a second cousin who died at the age of 26 years from a dissecting aneurysm of the aorta the interpretation of "likely pathogenic" is not supported by the ACMG guidelines. There is, until today, no functional study performed for the variant.

Several lines of evidence support the conjecture that this variant is indeed responsible for the clinical picture of TAAD in the family: (1) The sequence variant co-segregates with a disease phenotype in distantly related family members, indicating an autosomal dominant inheritance pattern with reduced penetrance; (2) The variant is not noted in the Exome Sequencing Project, 1,000 Genome, dbSNP139 or GnomAD; (3) The missense variant affects an evolutionary highly conserved amino acid residue within the MH2 domain, a domain that resides 61% of known pathogenic mutations in *SMAD3* (Schepers et al., 2018). The well conserved MH2 region is important for oligomerization of SMADs (Schepers et al., 2018); (4) We have recently found the same variant in a possibly unrelated TAAD patient.

Unfortunately, the original ACMG guidelines for classification of genomic variants did not include guidelines for quantitative classification of cosegregation data. According to those Guidelines, the evidence for pathogenicity in our case is PM2 and PP3, where PM2 (absent in population databases) is moderate, and PP3 (multiple lines of computational evidence supporting a deleterious effect on the gene or gene product [CADD = 29,7]) is supporting evidence. Thus there was insufficient evidence for a classification of the *SMAD3* mutation as a pathogenic variant and it could only be classified as a "variant of uncertain significance". However, the Jarvik and Browning (2016) recommendations for quantification of segregation data would support our data (BF≈56) as strong evidence for a causative mutation. The variant in *SMAD3* has not been reported before and is obviously extremely rare. We assume that the relatives, connecting those who carry the variant, would be obligate carriers. The pedigree indicates that if not neutral the *SMAD3* variant has a reduced penetrance. In this context, it seemed reasonable to use likelihood ratio methods to assess the genetic evidence for clinical significance. Accordingly, a Bayes factor of 56, supporting a causal relation, was calculated with the aid of LINKAGE (Lathrop, Lalouel, Julier, & Ott, 1984) assuming 50% penetrance and a phenocopy rate of 0.3%.

We hope this study will increase the awareness that a "variant of uncertain significance" according to the ACMG guidelines has always a scope for reappraisal, and also that genetic counselling to relatives, and the offering of surveillance service is important to families with aortic aneurysm disease. Finally, we would like to emphasize the potential use of FFPE analysis of material from deceased relatives to help in the interpretation of variants.

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CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

KE, CG, and FV conceived and designed the analysis. KE, CT, and FV collected the data. KE, MR, AG, and JJ performed the analysis. KE, CG, FV, and JJ wrote the paper.

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