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Case Report

Novel Germline Variant in Tumor Suppressor *SMAD3* Gene Associates with Familial Thoracic Aortic Aneurysm and Dissection Syndrome

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Abstract

Pathogenic variant (PV) in tumor suppressor gene *SMAD3* (SMAD family member 3) causes dysregulated transforming growth factor-β (TGF-β) signaling. PV in *SMAD3* is seen in sporadic cancers as somatic variant but also in germline variant causing hereditary TGF-β vasculopathy with aneurysm condition. The clinical picture of thoracic aortic aneurysm, dilatation or dissection (TAAD) families with *SMAD3* PV has been published from the year of 2011. The phenotypic spectrum of *SMAD3* PVs has not yet been fully identified. This case report shows the family with novel *SMAD3* variant named c.860G>A with very high risk for aortic dissection approximately at the age of 50 years. The result of segregation analysis of the family strongly suggests that this variant is pathogenic. The main symptom in the family is aortic dilatation and aortic dissection.

INTRODUCTION

SMAD3 is a TGF-β pathway gene and tumor suppressor gene. Pathogenic variant (PV) in *SMAD3* causes dysregulated transforming growth factor-β (TGF-β) signaling. Somatic PV in *SMAD3* may result in tumorigenesis and germline PV in *SMAD3* may result in thoracic aortic aneurysm and aortic dissection (TAAD).

The SMAD family proteins are the main signal transducer for receptors of TGF-β [1]. TGF-β is a cytokine belonging to the TGF superfamily that regulates many cellular functions including cell proliferation, differentiation, adhesion and migration [2] by the chemical signals transmitted from the cell surface to the nucleus. The signaling SMAD family affects TGF-β creation in different ways. The family includes eight members. SMAD3 is receptor-regulated SMAD (R-SMAD), and SMAD4 is common partner SMADs (Co-SMAD) [3,4]. R-SMAD molecules are involved in direct signaling from the TGF-β receptor and are thought to be the predominant effectors of TGF-β transcriptional regulation [3,4]. SMAD3 is recruited by the TGF-β receptor and binds to SMAD4 forming a complex [3,4]. The complex enters cell nucleus acting a transcription for various genes [2].

SMAD3 is suspected to be involved in oncogenesis as its pathway is believed to be responsible for many of the inhibitory functions of TGF-β [5]. Pathogenic variant (PV) in *SMAD3* is seen in sporadic cancers as somatic PV - in less than 5% stomach cancers, 5% of colon or rectum cancers and 5% of pancreas cancers , whereas somatic PV in *SMAD4* is seen — in less than 15% of stomach cancers, 15% of colon or rectum cancers, and approximately in 25% of pancreas cancers [1]. Loss of function in *SMAD3* has been observed in the pathogeneses of sporadic enteropancreatic endocrine tumors and parathyroid adenomas [6]. Arany et al [7], reported accelerated healing in S3KO mice lacking SMAD3 and suggested that this could be used to investigate factors promoting tumor growth and metastasis.

Germline PV in *SMAD3* is associated with familial and sporadic occurrence of thoracic aortic aneurysm, dilatation or dissection (TAAD). TAAD affects one or more aortic segments in aortic root, ascending aorta, arch or descending aorta. Van der Laar et al.[8], obtained aortic tissue from persons with PV in *SMAD3* and discovered a disorganization of the tunica media with fragmentation, loss of elastic fibers, characteristic mucoid medial degeneration, and accumulation of collagen. The heterozygous PVs in *SMAD3* lead to increased aortic expression of several key players in TGF-β signaling, including SMAD3 [9]. There are also other vasculopathies in FTAAD families which are due to hereditary TGF-β with an aneurysm condition (Table 1), such as *SMAD4*-related juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome.

Aneurysm and dissection of the aorta is one of the major causes of death in humans. It has been estimated at 1-2% of deaths in Western countries [10]. After familial TAAD (FTAAD) diagnosis prognostic information on disease development and progression according to the involved gene can be informed to the patient and surveillance can be started. Diagnosis, treatment

Table 1: Genes/syndromes associated with hereditary TGF-β vasculopathies with aneurysm condition (Isselbacher 2016, Verstraeten 2016, Teekakirikul 2013, Andrabi 2011, Coucke 2006).

Gene	Syndrome
SMAD3 (SMAD family member 3)	Aneurysms-osteoarthritis syndrome/Loeys-Dietz syndrome 3
SMAD4 (SMAD family member 4)	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome
TGFBR1 (transforming growth factor-β receptor 1)	Familial TAA / Loeys-Dietz syndrome 1
TGFBR2 (transforming growth factor-β receptor 2)	Familial TAA / Loeys-Dietz syndrome 2
TGFB2 (transforming growth factor-β2)	Loeys-Dietz syndrome 4
TGFB3 (transforming growth factor-β 3)	Loeys-Dietz syndrome 5
SKI (v-SKI sarcoma oncogene homolog)	Shprintzen-Goldberg syndrome
TAA: Thoracic Aortic Aneurysms	

and surveillance are done in collaborating with clinical geneticist, cardiologist and cardiovascular surgeon. Tumor formation has not associated with heritable thoracic aortic disease.

This case report shows a family with FTAAD in four family members with a novel *SMAD3* variant c.860G>A in all affected patients.

FTAAD and SMAD3 likely pathogenic variant in the family (Figure 1)

Index patient: The index patient has been operated three times due to aortic dissection. At 54 years she had an emergency operation for ascending thoracic aortic dissection aneurysm and she underwent replacement of the aortic root with a prosthetic graft and an artificial aortic valve. Before the operation computed tomography (CT) imaging showed a dissection from the aortic root to common iliac, and the root of the aorta was dilated ad 63 mm, otherwise the diameter of the aorta was normal. After operation control CT imaging showed chronic aortic dissection without complication from the distal site of total correction, and from brachiocephalic artery and left subclavian artery to common iliac artery. The patient is in regular follow-up. At 56 years she was operated for a dissection and pseudoaneurysm in right groin. At 58 years she was operated for descending thoracic aortic dissection aneurysm. No mitral valve disease has been observed. The patient is in regular follow-up due to chronic aortic dissection.

After the first aneurysm operation the patient was referred to a clinical geneticist for further diagnosis. A diagnostic gene panel found a heterozygous variant c.860G>A, p.Arg287Gln in *SMAD3* gene. The patient has also pes planus, easy bruising, and slow wound healing. Mild myopia was also observed (D -4,25/-2,55). Additionally, two tubular adenomas with low-grade dysplasia were resected at the age of 56 years and then regular colonoscopy follow-up started.

Paternal cousin of the index patient: Died at 57 years due to aortic dissection. The family *SMAD3* variant was analyzed by bidirectional Sanger sequence analysis and the same variant was observed as in index patient.

Father of the index patient: PV in *SMAD3* named c.860G>A was observed from the index patient's and her paternal cousin's DNA sample. Therefore, the index patient's father is an obligate carrier of the family variant (Figure 1). The father had aortic dissection at the age of 53 years. He also had scoliosis and arrythmia.

Brother of the father of the index patient: PV in *SMAD3* named c.860G>A was observed from the index patient's and her paternal cousin's DNA sample. Therefore, the brother of the index patient's father is an obligate carrier of the family variant (Figure 1). He died at the age of 45 years, most likely due to aortic dissection. Before that he had some kind of heart disease, but afterwards it could not be specified in medical records.

Two sons of the index patient: They are carries of the family *SMAD3* PV and both are at regular follow-up by cardiologist. One son was diagnosed at the age of 27 years with mild aortic root dilation (38mm at sinus Valsalva).

Other symptoms in this family: The index patient's father's mother died at 43 years of age, most likely due to aortic dissection. No persons in the family have had intracranial aneurysm. Also, no persons with osteoarthritis or osteoarthritis dissecans have been reported.

The family's *SMAD3* gene variant: Next generation sequencing (NGS) panel analyzed from the index patient's DNA sample, showed in *SMAD3* (SMAD family member 3) gene a heterozygous variant c.860G>A, p.Arg287Gln (GenBank reference sequence NM_005902.3). This variant change converts a codon for arginine to a codon for glutamine which causes some chemical changes. This substitution is located in MH2-domain. Comparison of SMAD3 amino acid sequences derived from numerous species indicates that Arg287 is conserved. A missense mutation in the same residue a codon for tryptophan (Arg287Trp) has been reported in association with TAAD and classified as pathogenic variant according to Human Gene Mutation Database (HGMD) [11], supporting the functional importance of this residue and region of the protein.

The frequency of the variant in the population is extremely low as this change is not listed in gnomAD database nor in SISu (The Sequencing Initiative Suomi) database which means that this variant is not a common benign variant in population. *In silico* analysis (Polyphen, SIFT, and 11 others according to VarSome database) predicts that this variant is deleterious to the protein structure/function. There is still no functional evidence for the variant c.860G>A, p.Arg287Gln.

Table 2: Genes associated with syndromic and non-syndromic TAAD (thoracic aortic aneurysm and dissection). Non-syndromic genes in the table are associated in familial and sporadic TAAD (Vinholo 2019, Arnaud 2019, Mariscalco 2018, van der Laar 2012).

Syndrome	Gene*
Aneurysms-osteoarthritis syndrome	*SMAD3*
Loeys-Dietz syndrome	*TGFBR2, TGFBR1, SMAD3, TGFB2, TGFB3*
Marfan syndrome	*FBN1*
Multisystem smooth muscle dysfunction syndrome	*ACTA2*
Meester-Loeys syndrome	*BGN*
Vascular Ehlers-Danlos syndrome (vEDS)	*COL3A1*
Arterial tortuosity syndrome	*SLC2A10*
Cutis laxa, autosomal recessive, type IB	*EFEMP2*
Non-syndromic	*AAT1, AAT2, ACTA2, BGN, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, FAA1, FBN1, FBN2, FLNA, FOXE3, LOX, MAT2A, MFAP5, MYH11, MYLK, NOTCH1, PRKG1, SMAD3, TGFB2, TGFBR1, TGFBR2, TGFBR3*

* Note that gene may be both syndromic and non-syndromic.

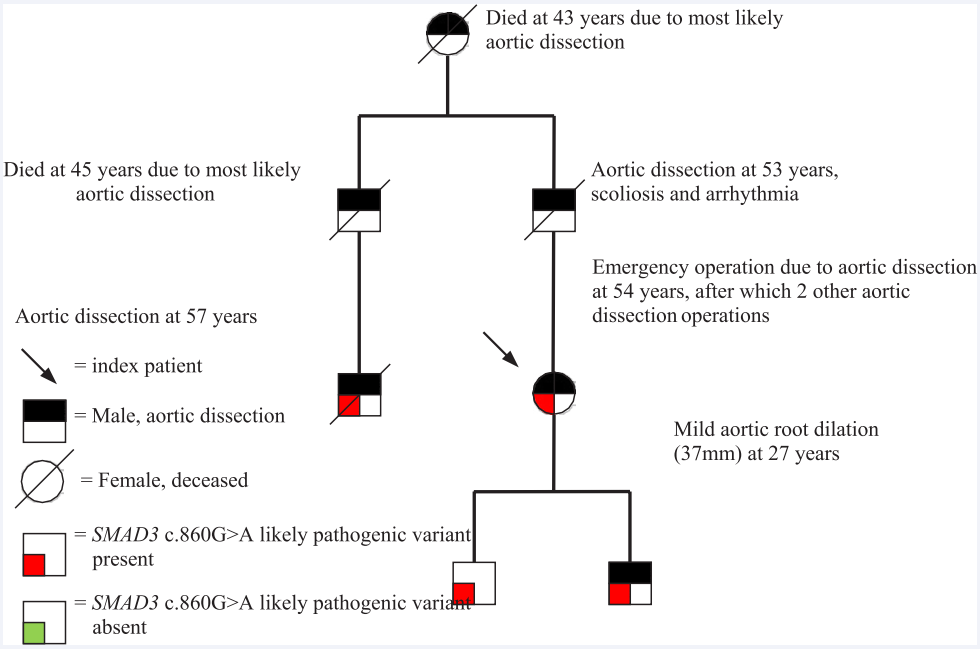

Figure 1 The index patient's lymphocyte DNA was investigated by next generation sequencing and it pointed *SMAD3* likely pathogenic variant named c.860G>A, p.Arg287Gln. The same family variant was observed in the DNA of the index patient's paternal cousin. Therefore, also two obligate carriers of family variant were identified, and they are father of the index patient and brother of the father of the index patient.

The most recent and the most common interpretation of the variant c.860G>A, p.Arg287Gln in ClinVar is likely pathogenic (updated on October 8, 2021). According to American College of Medical Genetics and Genomics (ACMG) variants are classified to 5 categories based on the knowledge on the variant: benign, likely benign, variant of uncertain significance (VUS), likely pathogenic (LPV), and pathogenic (PV) [12]. An updated ACMG classification of this variant is Class 4 – Likely pathogenicity.

Arnaud et al. [13], classified the variant as pathogenic. In this study, the segregation analysis of the family, strongly suggests that *SMAD3* variant named c.860G>A, p.Arg287Gln is pathogenic.

Study authorization and consent: Analyzed data was from patients who had been treated at Turku University hospital. As no additional samples were taken a separated ethics board permit was not required. Consent was received from the patients to present their medical information in the pedigree. Consent to present the medical information from the deceased patients has been received from next of kin. This study complies with the 1964 Helsinki Declaration and the General Data Protection Regulation 2016 (EU) of the Data Protection Directive.

DISCUSSION

Phenotype in PV of *SMAD3* named c.860G>A

PV in *SMAD3* named c.860G>A was observed from the index patient's and her paternal cousin's DNA sample. Therefore, also two obligate carriers of the family variant were identified (Figure

1) the father of the index patient and his brother. Three family members had aortic dissections and one of them possibly died from aortic dissection after heart problems. One family member has had heart arrhythmia and scoliosis. In addition to this the dilatation of aortic root has been observed in the regular follow-up of index patient´s son at young adulthood.

Germline PVs in *SMAD3* gene are associated with aneurysm-osteoarthritis syndrome (OMIM # 613795, ORPHA:284984), with Loeys-Dietz syndrome 3 (OMIM # 613795, ORPHA:91387), with non-syndromic familial TAAD (FTAAD), and with aortic root dilatation, abdominal aortic aneurysm, arterial tortuosity [9,14,15]. Also, bicuspid aortic valve and aortic root dilatation has been found in germline PV in *SMAD3* gene [16]. Currently, less than 80 different *SMAD3* PVs have been found. The variant c.860G>A observed in this study has been previously found in the study of Schepers et al. [17], and Aubart et al [18]. In this study, the segregation analysis of the family, strongly confirms that c.860G>A is pathogenic as classified by Arnaud et al [13].

SMAD3 has been just recently identified as a TAAD gene and its phenotypic spectrum has not yet been fully identified. Additionally, little is known about its genotype-phenotype correlation. In the literature a wide range of variability has been observed in *SMAD3* families, and the research suggests a strong influence of genetic modifiers in the phenotype. Renner at al. [19], deduced according to the exome sequencing study that the relatively high rate of PV/LPV/VUS negative patients may indicate to the existence of yet unknown disease loci and/or polygenic inheritance. However, in the case report family the symptoms related to *SMAD3* gene were relatively homogenic. The main symptom was aortic dissection.

The aortic aneurysms of patients with *SMAD3*-related TAAD tend to rupture at smaller aortic diameters than in Marfan syndrome [14]. Previously, it has been reported that ascending aorta diameter at dissection in the patient with PV in *SMAD3* is approximately 45 mm and the mean age of the dissection is 45 years [20]. In this family with this novel *SMAD3* variant the dissection seems to associate with a later age. In those relatives with confirmed *SMAD3* PV and whose medical records were accessible the age of aortic dissection was 54,7 years. There were two persons in the family with early death and possibly aortic dissection according to the family information. If also these relatives are considered, the age of dissection would have been 50,4 years.

Some family members in *SMAD3* TAAD families have been found to have abdominal aneurysm, intracranial aneurysm or subarachnoid hemorrhage [15,21]. If there is a susceptibility to stenosis of small arteries, this may result in early stroke or coronary artery disease. In the wide family of this case report many have had aortic dissection. However, no relatives of this family have had intracranial aneurysms or subarachnoid hemorrhage. Previously, ophthalmologic examination has revealed no abnormalities in patients with *SMAD3* PV [20,21] although in Marfan syndrome and in certain Loeys-Dietz syndrome types ophthalmological symptoms may be seen, such as in Loeys-Dietz syndrome type 4 due to PV in *TGFB2* gene [22]. In the case report's family no severe ocular abnormalities have been observed. The index patient has mild myopia.

One family member has had scoliosis which is a symptom that has previously been identified in *SMAD3* families. In *SMAD3* families congenital heart malformations can be seen with the risk of approximately 9% [14] but in this family case no congenital heart diseases were seen.

PVs in *SMAD3* may cause high incidence of early-onset osteoarthritis affecting the spine, knees, and hands and osteochondritis dissecans, in which bone underneath the cartilage of a joint is deprived of blood flow leading to necrosis [14] and intervertebral disc degeneration. Such anomalies are rarely described in Marfan syndrome. None of family members who carry *SMAD3* PV in this family have reported this kind of symptoms or have been treated with these symptoms according to the medical records.

Previously tumor formation has not been found in the patients with germline *SMAD3* PV. In this case the index patient is in follow-up due to resected sigma adenomas with low-grade dysplasia. Previously it has been reported that in ApcMin/+ mice SMAD3 deficiency promotes tumorigenesis in the distal colon [23]. It is in theory possible that the index patient's germline PV in *SMAD3* gene has been a predisposing factor for the formation of the colon adenoma.

If there are two TAAD cases in near family, familial TAAD (FTAAD) is suspected. Prevalence of FTAAD is less than 1 / 1,000,000 (Orphanet, ORPHA:91387). In 30 % of these cases a known causative germline pathogenic variant in a gene related to TAAD is found [24]. Approximately 30-50 genes are included in Marfan syndrome and TAAD NGS panels [19,24]. At least 20 genes are associated with FTAAD and others are associated with similar differential diseases [19,24-26].

Heritable thoracic aortic disease (HTAD) refers to thoracic aortic disease caused by a pathogenic variant of a gene that causes a high risk for TAAD. At least 20% of HTAD are in patients with syndromes such as Marfan, Ehlers-Danlos and Loeys-Dietz (Table 2). Majority of FTAAD families are non-syndromic. Genetic etiology of TAAD is very heterogenic. *SMAD3* accounts for approximately 2 % of all cases in both familial and sporadic TAAD [13,24,27,28]. In non-syndromic FTAAD cases the *ACTA2* causes the highest amount of cases, up to 21% of cases [26,29].

Follow-up of patients with *SMAD3* PV

Aorta aneurysm is diagnosed using the following imaging methods: ultrasound imaging, computer tomography (CT), magnetic resonance imaging (MRI), ultrasound imaging via the oesophagus, i.e. transesophageal ultrasound imaging, chest X-ray or blood vessels angiography. The same methods are used in follow-up. In persons with PV in *SMAD3* or other *FTAAD* gene regular follow-up should be offered to monitor the condition of their aortic and detect aneurysm before emergencies. For *SMAD3* PV yearly imaging of the entire aorta and its branches as well as cerebrovascular circulation are recommended [15,30].

TAAD patients have increased risk of having life-threatening aortic rupture unless the aorta has been surgically prevented from tearing. Patients in risk who have had their aortic examined and who have undergone planned aortic reconstructive surgery have a better prognosis than those who are treated after aortic

dissection [31]. Medications that reduce hemodynamic stress on the aortic wall, such as beta blockers, are generally initiated at diagnosis time by cardiologist. In patients with *SMAD3* PV angiotensin II type 2 receptor agonists offer interesting treatment alternative [32]. Pregnancy and the post- partum period convey an increase in aortic dissection risk which may be disastrous for both mother and fetus. Women with a FTAAD diagnosis should receive pre-pregnancy aortic and other vessel assessment.

Recently, the guidelines for pregnant FTAAD women have been published as it is suggested that the aortic dissection risk is approximately 1% if the aorta is less than 40 mm and 10% at larger diameters [33].

Currently, genetics of sporadic TAAD is a subject of active study. In FTAAD families with unknown PV regular ultrasound follow-up should be arranged for the first-degree relatives (parents, sibs, offspring) of an affected individual [26]. However, currently approximately 30% of non-syndromic FTAAD patients receive a specific gene diagnosis [16]. With genetic screening persons who benefit from regular monitoring can be identified and others is exempting [34-38].

CONCLUSION

This case report presented the clinical picture of a family with a novel *SMAD3* variant c.860G>A. Segregation analysis of the case family strongly suggests that the variant is pathogenic. The main symptom in this family is very high risk for aortic dissection which mainly happens over the age of 50 years. In this family early-onset osteoarthritis has not been observed. Additionally, colonoscopy follow-up has been arranged due to resected dysplastic sigma adenomas in family member. In theory, dysplastic sigma adenoma formation susceptibility may be due to the family PV in *SMAD3* as previously shown in mice studies that SMAD3 deficiency promotes tumorigenesis in the distal colon. Therefore, the clinical evaluation of colon adenoma formation in *SMAD3* families is the subject for later research.

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