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► To cite this version:

Pascal Delsart, Clémence Vanlerberghe, Francis Juthier, Jonathan Sobocinski, Olivia Domanski, et al.. The natural history of a family with aortic dissection associated with a novel ACTA2 variant. *Annals of Vascular Surgery*, 2021, 77, pp.348.e7-348.e11. <10.1016/j.avsg.2021.05.034>. <hal-04464675>

HAL Id: hal-04464675

<https://hal.science/hal-04464675v1>

Submitted on 22 Jul 2024

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1 **The natural history of a family with aortic dissection associated with a novel *ACTA2***
2 **variant**

3

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23 Declarations of interest: none.

24 ABSTRACT

25 Disease-causing heterozygous variants in the *ACTA2* gene cause an autosomal dominant
26 heritable thoracic aortic disease (HTAD) with thoracic aortic aneurysm and dissection as main
27 phenotype, and occasional extravascular abnormalities such as livedo reticularis. *ACTA2*-
28 HTAD accounts for an important part of non-syndromic HTAD, with detection rates varying
29 between 1.5-21% according to different studies. A consensus statement for the screening and
30 management of patients with pathogenic *ACTA2* variants has been recently published by the
31 European reference network for rare vascular diseases (VASCERN). However, management
32 of *ACTA2* patients is often challenged by extremely variable inter- and intra-familial clinical
33 courses of the disease.

34 Here we report a family harboring a disease-causing *ACTA2* variant. The proband and
35 two siblings presented with acute type A aortic dissection and rupture involving nondilated
36 aortic segments before the age of 30. Their mother died at 49 years-old from type 1 aortic
37 dissection and rupture. Genetic testing revealed the heterozygous novel p.(Pro335Arg) variant
38 in the *ACTA2* gene in the proband and in the affected siblings. The clinical history of this
39 family highlights the difficulty of adopting effective prevention strategies in *ACTA2* patients.

40

41 KEY WORDS

42 *ACTA2*; thoracic aortic aneurysm and dissection; aortic rupture; heritable thoracic aortic
43 disease

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49 **CASE REPORT**

50 The proband (III-3, Fig. 1) presented with acute DeBakey type 1 aortic dissection at the age of
51 29 (Fig. 2-Panel A). She underwent Tirone-David procedure and partial arch replacement.

52 Aorta was not dilated at the time of the dissection (38 mm at the sinus level and 34 mm at the
53 ascending aorta and her aortic valve was tricuspid. There was no evidence of elastic fibers

54 anomalies nor atherosclerotic plaques at pathology. Her cardiovascular risk factors included

55 controlled hypertension with two drugs, obesity (body mass index 34 kg/m²), smoking, and a

56 family history of death caused by nondilated type B aortic dissection and rupture at the age of

57 49 year in her mother (II-2, Fig. 1). She didn't display livedo reticularis. She had three

58 apparently healthy daughters. No obstetrical or vascular complication during her pregnancies

59 were reported. Genetic testing was performed by targeted next generation sequencing analysis

60 of a panel of genes associated with thoracic aortic aneurysms and/or dissections as previously

61 described [1] and revealed the c.1004C>G p.(Pro335Arg) *ACTA2* variant at the heterozygous

62 state. This variant was novel, absent from gnomAD (accessed on October 26, 2020), it affects

63 a highly conserved amino acid and prediction tools (PolyPhen-2, SIFT, CADD) were in favor

64 of the pathogenicity of this variant. It was classified as likely pathogenic according to the

65 American College of Medical Genetics criteria (PM2, PP1, PP2, PP3, PP4)[2]. Familial

66 screening was performed on this specific variant using Sanger sequencing (Figure 1) [1],

67 echocardiography and CT-Angiogram of the aorta were then offered to all first-degree

68 relatives.

69 A few months after the identification of this variant in our proband, her young brother

70 (III-5, Fig. 1) underwent emergency aortic valve sparing root replacement surgery with

71 Yacoub's procedure because of a type A dissection limited to the ascending aorta (DeBakey

72 type 2) at the age of 21 years (Fig. 2-Panel B). Dissection involved nondilated aortic

73 segments, documented on a CT-angiogram a few months before dissection occurred.

74 Pathology of the aorta revealed no atherosclerotic plaque and the absence of elastic fibers
75 anomalies. He displayed no livedo reticularis. His cardiovascular risk factors included
76 smoking and family history of HTAD. Genetic testing revealed that he carried the *ACTA2*
77 variant previously identified in the proband.

78 Soon after, a sister of the proband (III-4, Fig. 1) died at the age of 29 because of
79 nondilated aortic rupture in acute type B dissection extending from the origin of the left
80 subclavian artery to the renal arteries (Fig. 2-Panel C). She had been admitted to the intensive
81 care unit because of type B dissection. Since there was no associated aortic dilatation nor
82 evidence of visceral malperfusion, she was managed medically with aggressive blood
83 pressure control. Unfortunately, on the first day after admission she presented with a sudden
84 cardiogenic shock associated with pericardial effusion and she died before entering the
85 surgical room. Her aortic valve had a tri-leaflet structure and she displayed no aortic valve
86 disease. She had no hypertension (resting blood pressure 137/75 mmHg), no cardiovascular
87 risk factor and normal body mass index. The cardiovascular assessment performed four
88 months prior to her death revealed normal thoracic and abdominal aortic diameters. Aortic
89 diameters determined by transthoracic echocardiography (TTE) were 27 mm (Z score = -1.3),
90 24.5 mm and 26 mm at the sinus level, sinotubular junction and ascending aorta, respectively.
91 Computed tomography (CT) scan showed aortic diameters of 27 mm, 22 mm, and 13 mm at
92 the aortic arch, aortic isthmus, and abdominal aorta, respectively on a CT-angiogram (Figure
93 3). Moreover, the aorta was not dilated at the time of the dissection. No livedo reticularis had
94 been noted at clinical examination. Her presymptomatic genetic testing was on going at time
95 of death and revealed that she carried the *ACTA2* variant.

96 Cardiac and vascular assessment in the older sister of the proband (III-2, Fig. 1), who
97 didn't carry the *ACTA2* variant, revealed normal aortic diameters and the presence of an
98 aneurysm of the right renal artery at 34 years of age.

99 The proband's daughters (IV-3 14 Y-O, IV-4 12 Y-O, and IV-5 10 Y-O, Fig. 1) had
100 normal thoracic aortic diameters measured by TTE and they underwent presymptomatic
101 genetic testing. Two of them (IV-3 and IV-4, Fig. 1) carry the *ACTA2* variant and undergo
102 annually cardiac monitoring. A preventive treatment with beta-blockers has been initiated,
103 and their physical activity level has been adjusted by the referring cardiologist. Computed
104 tomography has already been performed twice in the oldest daughter, because of acute
105 thoracic pain. She needed psychological support because of her tragical familial history and
106 her positive presymptomatic genetic testing.

107 The father of the proband (II-3, Fig. 1) was diagnosed at 55 years-old with
108 atherosclerotic abdominal aorta aneurysm associated with cardiovascular risk factors
109 including hypertension and smoking (10 cigarettes/day). He was not available for genetic
110 testing.

111

112 **DISCUSSION**

113 We describe a novel *ACTA2* disease-causing variant associated with variable acute aortic
114 disease manifestation, without prior dilated aorta. This clinical family history highlights the
115 difficulty of an efficient preventive strategy for the *ACTA2*-mutated patients. *ACTA2* disease-
116 causing variants are the most frequent cause of non-syndromic HTAD. HTAD caused by
117 variants in the *ACTA2* gene confers a high risk thoracic aortic aneurysm and dissection
118 associated with life-threatening complications, including aortic dissection and rupture [3].

119 According to the literature [4], type A dissections occurred in 53.8% of *ACTA2* patients at a
120 median age of 36 years. Type B dissections occurred less frequently (21.2%), but at younger
121 ages compared with type A dissections (median age, 27 years). Most *FBNI*-patients (Marfan
122 syndrome) (80%) or *TGFBR2*-patients (Loeys-Dietz syndrome) (91%) are identified with
123 aortic root dilation before developing an aortic event, compared with only 17% of *ACTA2*-

124 patients [4]. A third of the individuals with *ACTA2* disease-causing variant had dissection at
125 aortic diameters smaller than 5 cm [5].
126
127 Identification of patients at risk of developing *ACTA2*-HTAD allows regular aortic
128 surveillance that is warranted for early identification and treatment of aortic aneurysm. A
129 consensus statement for the screening and management of patients with pathogenic *ACTA2*
130 variants has been recently published by the European reference network for rare vascular
131 diseases (VASCERN) [6]. According to this statement, transthoracic echocardiography is to
132 be performed yearly from the age of diagnosis in both children and adults, although intervals
133 can be changed depending on clinical judgment. A complete vascular imaging of the thorax
134 and abdomen using CT angiography or MRI, depending on local expertise and availability, is
135 recommended as a screening test at the age of 18 years (or at time of diagnosis in adults) and
136 repeated every 2 to 5 years. Elective aortic root replacement should be considered in
137 asymptomatic patients with a maximal aortic diameter between 45-50 mm. Elective
138 replacement of the descending thoracic aorta should be performed according to the ESC,
139 AHA and European Society for Thoraco Vascular Surgery (ESTVS) guidelines and generally
140 avoiding endoprostheses [6–9]. Two different variants; ie p.Arg179 and p.Arg258 disruption
141 have a higher risk of aortic dissection at a younger age compared to all others variants [4]. As
142 this *ACTA2* variant has not been previously reported, we cannot hypothesize on its association
143 with a poor prognosis. When identifying a pre symptomatic genetic disorder, an educational
144 support must be established, including clinical sign requiring an emergency call. Beta-
145 blockers therapy should be considered from the age of 4 years in all *ACTA2* patients,
146 disregarding the presence of dilated or nondilated aortas. Finally, patients should be screened
147 and monitored for arterial hypertension and treated in order to fully control blood pressure.
148 Despite the published recommendation, operative decisions are often made difficult by the

149 extremely inter-familial and intra-familial clinical courses of the disease [4,6]. Besides,
150 psychological impact of the positive presymptomatic genetic testing in the children has to be
151 studied to precise the benefit-to-risk ratio of each preventive strategy.

152 Here we reported a family presenting with aortic dissection at a young age and
153 involving non dilated aortic segments in association with a novel variant in the *ACTA2* gene.
154 Our observations highlight the challenges in managing *ACTA2* patients. Some patients may
155 benefit of a preventive surgery before the threshold of 45 mm as it is suggested in patients
156 carrying *TGFBR2* and *TGFBR1* disease-causing variants [10,11]. Further reports of clinical
157 data from a greater number of families and studies aimed at identifying the risk factors that
158 predict aortic dissections and ruptures in individuals with minimal or no aortic dilatation are
159 needed in order to implement current management recommendations and guidelines.

160

161 **Declaration of interest**

162 Declaration of interest: None.

163

164 **Funding**

165 This research did not receive any specific grant from funding agencies in the public,
166 commercial, or not-for-profit sectors.

167

168 **Authors' Contributions**

169 C.V. and P.D. collected patient data and wrote the first draft of the report. L.M. conceived the
170 case report and made the final edits of the report. N.H and P.A. conducted the genetic testing
171 of the patient and edited the sections of the paper regarding the patient's genetic testing. FJ
172 and JS ensured the surgical management. BL ensures the radiologic evaluation. OD is
173 involved in the children's evaluation and follow-up.

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230 Figures legends

231 Figure 1: Pedigree of the family. Women are represented by circles. Men are represented by
232 squares. Affected individuals are shown as filled symbols. The arrow points to the proband. A
233 diagonal slash indicates a deceased individual. The symbols + and - indicate the presence or
234 absence of the heterozygous *ACTA2* variant, respectively.

235

236 Figure 2: **(A)** CT-scan of patient III.3 (proband) showing an acute type aortic dissection (top
237 row: axial view; bottom row: coronal view). **(B)** CT-scan of patient III.4 showing an acute
238 type B aortic dissection (top row: axial view; bottom row: oblique sagittal view). **(C)** CT-scan
239 of patient III.5 showing acute type II aortic dissection (top row: axial view; bottom row:
240 oblique sagittal view).

241

242 Figure 3. CT-angiogram prior acute aortic dissection reveals no aortic aneurysm (A: cinematic
243 volume rendering; B: axial view; C: oblique sagittal view).





