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Supravalvular aortic stenosis - Novel pathogenic *ELN* variant in siblings with a wide spectrum of clinical cardiovascular features and a long follow-up from infancy to adulthood

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ABSTRACT

Background: Supravalvular aortic stenosis (SVAS) is an autosomal dominantly inherited congenital cardiovascular disease caused by disruption of elastin gene (*ELN*), encoding elastin, an essential component of elastic arteries. It usually affects the middle layer of the wall of the aorta but also the pulmonary and coronary arteries may be affected.
Methods: We report a family with six affected siblings who were closely followed up from infancy to early adulthood at a pediatric cardiology outpatient clinic. Whole-exome sequencing was performed using DNA of the index patient. Targeted variant testing was performed for other family members.
Results: The affected siblings presented with a wide spectrum of clinical features of SVAS, ranging from mild pulmonary artery stenosis with or without pulmonary artery branch stenoses to severe supravalvular aortic obstruction and coronary artery stenosis with fatal outcome. Genetic analysis identified a novel pathogenic 1-bp deletion c.1983delG, p. (Pro662Leufs*13) in the *ELN* gene. Males tended to have a more severe cardiac disease than females. However, if interventions were successful during infancy or early childhood, the outcome was fairly favorable. Moreover, supravalvular pulmonary stenosis, even when combined with a stenotic pulmonary valve and severe pulmonary artery branch stenoses, tended to resolve during follow-up.
Conclusions: We describe a family with six siblings showing elastin arteriopathy with variable disease severity and outcome. A novel pathogenic *ELN* gene variant was detected in five of them, indicating that there are obviously yet unknown genetic and environmental modifying factors that affect the severity and outcome in individual patients.

1. Introduction

Supravalvular aortic stenosis (SVAS; OMIM 185500) is a rare autosomal dominant cardiovascular disorder affecting 1 in 20,000 individuals [1]. It is an elastin arteriopathy that can be further classified as non-syndromic SVAS or a manifestation of Williams-Beuren syndrome (WBS) [2,3]. Less often SVAS has been reported in patients with RASopathies, Alagille syndrome, cutis laxa and familial hypercholesterolemia [4]. In addition to SVAS and pulmonary artery stenosis, WBS is characterized by e.g. short stature, distinctive craniofacial appearance, intellectual disability, and hypersociability [5]. WBS is caused by a microdeletion encompassing the *ELN* gene (OMIM 130160) on the 7q11.23 chromosome region [5], whereas non-syndromic SVAS is mainly caused by point mutations, translocations, or gross deletions that disrupt *ELN* and lead to functional elastin haploinsufficiency in the medial layer of elastic arteries [1,6–11]. In a normal arterial wall, elastin is organized in concentric lamellae and the number of lamellae confers to the tensional force in the artery wall [12]. The properly organized elastin makes the aortic wall strong and flexible to withstand the energy created in the cardiac cycle during systole and release the energy during diastole [12]. Functional *ELN* haploinsufficiency leads to insufficient elastin production that in turn leads to focal or more diffuse stenosis in large arteries, most frequently affecting the aorta above the aortic valve and other arteries such as pulmonary and coronary arteries [12,13]. Previous reports have demonstrated variable intrafamilial expressivity of

Abbreviations: AR, aortic valve regurgitation; *ELN*, elastin gene; LCA, left coronary artery; PA, pulmonary artery; PG, pressure gradient; PS, pulmonary valve stenosis; RCA, right coronary artery; SVAS, supravalvular aortic stenosis; SVPS, supravalvular pulmonary stenosis; WBS, Williams-Beuren syndrome.

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the disease [1,14–17], varying from asymptomatic pathogenic variant carriers to fatal cardiac disease in infancy [1].

In the present study, we report a non-syndromic arteriopathy of variable severity in six out of seven siblings of a family. Genetic analysis identified a novel pathogenic variant c.1983delG, p. (Pro662Leufs*13) in *ELN* gene in five siblings and their asymptomatic mother. We retrospectively gathered clinical follow-up data from all the affected siblings from infancy to early adulthood, showing a high penetrance and highly variable phenotype and outcome but, on the other hand, fairly favorable outcome for those having had successful corrective surgery or balloon angioplasty in infancy. Moreover, mild to moderate stenoses in aorta and pulmonary arteries tended to resolve spontaneously during follow-up.

2. Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Detailed methods are available in the Supplementary file.

3. Results

3.1. Clinical reports

The family pedigree, with the main cardiac findings reported in all affected siblings, is shown in Fig. 1. None of the family members had other anomalies, syndromic features or neurologic, metabolic, or developmental problems.

The first child of the family (II-1) was born after an uneventful full-term pregnancy. Routine postnatal clinical examination revealed a coarse systolic murmur on cardiac auscultation. Echocardiography showed mild pulmonary valve stenosis (PS) that developed into a severe one during the first few months of life, with a peak systolic pressure gradient (PG) of 73 mmHg on echocardiography at age 4 months. Cardiac catheterization and pulmonary valvuloplasty was performed. The pulmonary valve appeared thick and dysplastic and pulmonary artery (PA) branches hypoplastic. During the follow-up, also SVAS developed (peak systolic PG of 84–92 mmHg on echocardiography) that required surgical correction at 5 years of age. Later on, she was asymptomatic, and the residual findings resolved gradually. The last echocardiography at age 17 years only showed mild aortic valve regurgitation (AR) but no residual SVAS or supravalvular pulmonary stenosis (SVPS). The coronary arteries were normal.

The second child (II-2), also born full-term and in good condition, underwent echocardiography at age 2 weeks and a moderate PS was identified. At 3 months of age, severe PS and SVPS and a moderate SVAS were seen. Moreover, main right and left pulmonary arteries were hypoplastic. Cardiac catheterization at age 4 months showed a severe SVPS with peak systolic PG of 75 mmHg and mild SVAS. However, disease progressed so that peak systolic PG was over 100 mmHg in the ascending aorta and 78–94 mmHg in PA at age 10 months. He showed no symptoms, hemodynamic disturbances nor ECG changes preoperatively. Open-heart surgery, with reconstruction of the ascending aorta and main PA with Gore-Tex and homograft patches, respectively, took place at age 14 months. During the operation, massive ST depressions indicating myocardial ischemia were seen on ECG, followed by ventricular fibrillation and asystole. Perioperative coronary artery angiography showed severe left coronary artery (LCA) ostium stenosis and wall thickening in both coronary arteries. Extensive resuscitative measures were not successful, and the patient expired. Autopsy was not performed, but histologic examination of the myocardial specimens taken perioperatively demonstrated fibromuscular dysplasia in both coronary arteries. DNA was not available for genetic studies.

In the index case (II-5), echocardiography showed mild SVAS and PS at age 2 days. One week later, moderate PA branch stenoses were seen. ECG and echocardiography showed biventricular hypertrophy. Cardiac catheterization at age 3 months showed severe SVPS with peak systolic PG of 80 mmHg and moderate SVAS. The PGs increased steadily and were 70–75 mmHg in the supravalvular parts of aorta and PA. At age 9 months, he underwent open-heart surgery, with reconstruction of both great arteries with homograft patches. Moreover, reconstruction of the right coronary artery (RCA) was performed. Left ventricular assist device (Biomedicus) was required for poor left ventricular function for three days, after which postoperative recovery was uneventful. Later on, the patient was asymptomatic and the residual SVAS and SVPS gradually resolved. PA branches also normalized in size spontaneously. Cardiac MRI showed normal left and right ventricular volumes and ejection fractions, mild AR, and normal ventricular walls with no late gadolinium enhancement. Normal findings were seen in serial cardiac exercise tests and 24-hour ECG recordings.

The youngest of the siblings (II-7) was born at 35 weeks of gestation with no complications of prematurity. She was diagnosed with mild SVAS during the first day of life. A severe SVPS developed by age 6 weeks and severe PA branch stenosis by age 3 months. Cardiac catheterization and balloon valvuloplasty were performed at age 3.5 months. Only marginal resolution of SVPS was seen, with the right ventricular pressure being 70 % of the systemic vascular pressure after the intervention. Following months showed mild SVAS and PA branch stenosis on echocardiography, but she was asymptomatic, and her growth and development were normal. Cardiac catheterization, performed at age 15 months, showed only mild SVPS and PA branch stenosis and no indication for balloon dilatation. Later on, SVPS, SVAS, and PA branch stenosis gradually resolved and the findings on ECG and echocardiography were normal by age 12 years. No progression was seen by age 16 years.

Two other daughters (II-4, II-6) were diagnosed in early infancy with mild to moderate SVAS, SVPS, or PA branch stenoses, which all resolved spontaneously by ages 6–7 years. Both were regularly followed up until adulthood with normal findings on ECG and echocardiography.

One of the daughters (II-3) had a regular follow-up by a pediatric cardiologist until age 14 months. She was healthy and asymptomatic, with no pathologic findings at clinical examination, on ECG, or echocardiography.

The mother (I-1) is clinically healthy and asymptomatic. She declined cardiac examinations. The father is clinically unaffected and was not

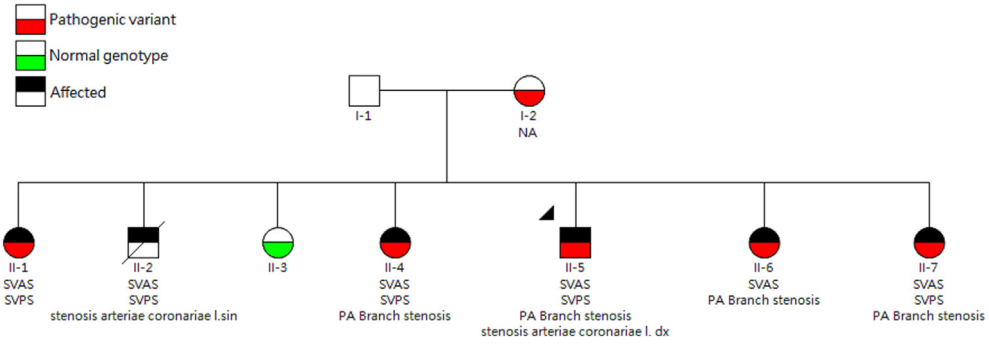

Fig. 1. The family pedigree.
PA, pulmonary artery; SVAS, supravalvular aortic stenosis; SVPS, supravalvular pulmonary stenosis; NA, not available.

genetically tested, because the likely pathogenic *ELN* variant was already found in the mother's sample.

The data on findings on echocardiography and cardiac catheterization, surgical and non-surgical interventions, and outcome for all the affected siblings are shown in Table 1.

Whole-exome sequence analysis of the index case (II-V) identified a heterozygous 1-bp deletion c.1983delG, p.(Pro662Leufs*13) in *ELN* gene exon 28. This causes a premature termination codon 13 amino acids afterwards, leading to loss of normal protein function either through protein truncation or nonsense-mediated decay. The same heterozygous *ELN* gene variant was detected in targeted variant testing in the asymptomatic mother and all clinically affected siblings from whom DNA was available but not in the healthy sister. To our knowledge, this variant is novel and has not been previously reported in the variant databases (Clinvar, HGMD) or published in the literature. Moreover, the variant is rare and has not been reported in the large reference population cohorts of Genome Aggregation Database (gnomAD). Based on these facts and the result from the segregation analysis, the variant is considered pathogenic.

4. Discussion

ELN gene, located in chromosome 7q11.23, encodes elastin, an essential component of the medial layer of medium-sized and large elastic arterial walls, where elastin accounts for up to 50 % of the vessel's dry weight [5]. Crosslinking domains of elastin are important in force distribution, while hydrophobic domains are associated with stretching. The mechanisms by which elastin insufficiency causes large vessel arteriopathy are not fully understood but e.g. increased proliferation and migration of smooth muscle cells, medial fibrosis, cytokine and inflammatory signaling pathways, and reactive oxygen species may play a role [5,18].

In both WBS and non-syndromic SVAS, elastin arteriopathy is characterized by focal (hourglass shaped) or long-segment (tubular) stenosis of the large elastic arteries and globally narrow and thick-walled arteries (Figs. 2A, B and 3). Most common features are SVAS and SVPS, showing considerable variability in severity. While stenoses in pulmonary arteries often improve with age and are usually not a limiting factor in the patient's prognosis [19], SVAS is usually a progressive disease, especially in infancy [19,20].

To date, over 100 pathogenic variants in *ELN* have been reported in patients with non-syndromic SVAS [10]. The majority of them are heterozygous loss-of-function variants including mainly frameshift, splice site and 3′-UTR variants, and a minor proportion are missense variants [21]. The variant identified in the present study most likely caused loss of normal protein function and elastin haploinsufficiency, i.e. reduced amounts of elastin, followed by increased amounts of hypertrophic smooth muscle, and increased collagen content in arterial walls. These changes have been shown to result in narrowed arterial lumen and increased arterial structural stiffness in both clinical and experimental studies [11,12,18,22–24].

In the present study, a novel heterozygous deletion in *ELN* gene (c.1983delG, p.(Pro662Leufs*13)), resulting in a premature termination codon, was identified in five of the clinically affected siblings and their asymptomatic mother but not in their healthy sister. There was no DNA available from the deceased brother, but according to his typical clinical findings of SVAS he obviously carried the same pathogenic *ELN* variant as the other affected family members.

Penetrance of the disease in the studied family was high, with all the siblings carrying the novel *ELN* variant expressing a typical non-syndromic SVAS phenotype. Whether this high penetrance was because of the unique genetic background in this family or genetic and environmental modifying factors, or both, is currently not known. Interestingly, previous studies have reported a more severe outcome in patients with variants in distal exons (20 or higher) of *ELN* than those with variants in proximal exons 1 to 17 [21]. However, the significance of this new variant in exon 28 remains to be seen in the future.

Cardiac manifestations in all the clinically affected siblings consisted of SVAS, PS, SVPS and PA branch stenosis of various severity and combinations. A fairly mild phenotype during the neonatal period often progressed towards a more severe one during the first postnatal weeks or months, requiring catheter interventions or surgical procedures (Table 1). This finding is similar to those in previous studies, which have reported the most rapid progress rate of SVAS occurring during the first years of life, simultaneously with the most rapid period of somatic growth [19].

The most severe phenotypes of SVAS were seen in the two brothers. The older one underwent corrective surgery at age 14 months in 1997 and the younger at 9 months in 2003. At that time, we did not perform routine coronary artery imaging preoperatively, since both brothers had been asymptomatic and had not shown any signs of myocardial ischemia on ECG or cardiac dysfunction on echocardiography before surgical intervention. Moreover, both had undergone an uneventful cardiac catheterization in anesthesia a few months before cardiac surgery. However, both brothers suffered from severe myocardial ischemia and showed severe coronary artery stenosis perioperatively, which resulted in fatal outcome in the older one. Whether male sex is an independent risk factor for unfavorable outcome cannot be concluded from the results of our study. However, previous studies have reported a male preponderance in the prevalence of SVAS [20,25–28] and an increased tendency to complications in male patients [5,29].

As compared to the two brothers, a much more benign outcome was seen in the four sisters in our study. Only one of them developed a hemodynamically significant SVAS that required surgical intervention. She and another clinically affected sister required balloon dilatation for SVPS, while the two sisters with mild to moderate SVAS, SVPS, and PA branch stenosis in infancy did not undergo any interventions and all the PA stenoses resolved spontaneously. This finding is consistent with the findings in earlier studies including patients with both non-syndromic SVAS and WBS, supporting the idea that treatment of PS and PA branch stenoses is often unnecessary [10,17,19,24,30], although more aggressive interventional strategies have also been reported [17,27,28].

It is possible that the incidence of impaired coronary blood flow in the patients with SVAS was underestimated in the past [26,31]. This was

Table 1
Cardiac findings, performed interventions, and outcome in the six siblings with elastin arteriopathy.

Family member	Sex	Cardiac findings	Interventions	Outcome
II-1	F	SVAS, PS, PA branch stenosis	Balloon valvuloplasty of PS at 4 mo. Surgical correction of SVAS at 5 yr	Spontaneous resolution of residual findings. Mild AR
II-2	M	SVAS, SVPS, PA branch stenosis, coronary artery stenosis	Reconstr. Ao asc with Gore-Tex patch, Reconstr. PA with homograft patch at 14 mo	Myocardial ischaemia/infarction and VF perioperatively. Exitus
II-4	F	Mild SVAS, PA branch stenosis	–	Spontaneous resolution of all findings
II-V	M	SVAS, SVPS, PA branch stenosis,	Reconstr. Ao asc and PA with homograft patches. Reconstr. A. coronariae at 9 mo	Spontaneous resolution of all residual findings. Mild AR
II-VI	F	Mild SVAS, PA branch stenosis	–	Spontaneous resolution of all findings
II-VII	F	SVAS, PS, SVPS, PA branch	Balloon valvuloplasty of PS at 3 mo	Spontaneous resolution of residual SVAS, PVPS, and PA branch stenosis

Ao asc, ascending aorta; AR, aortic valve regurgitation; F, female; M, male; PA, pulmonary artery; PS, pulmonary valve stenosis; SVAS, supravalvular aortic stenosis; SVPS, supravalvular pulmonary stenosis; VF, ventricular fibrillation.

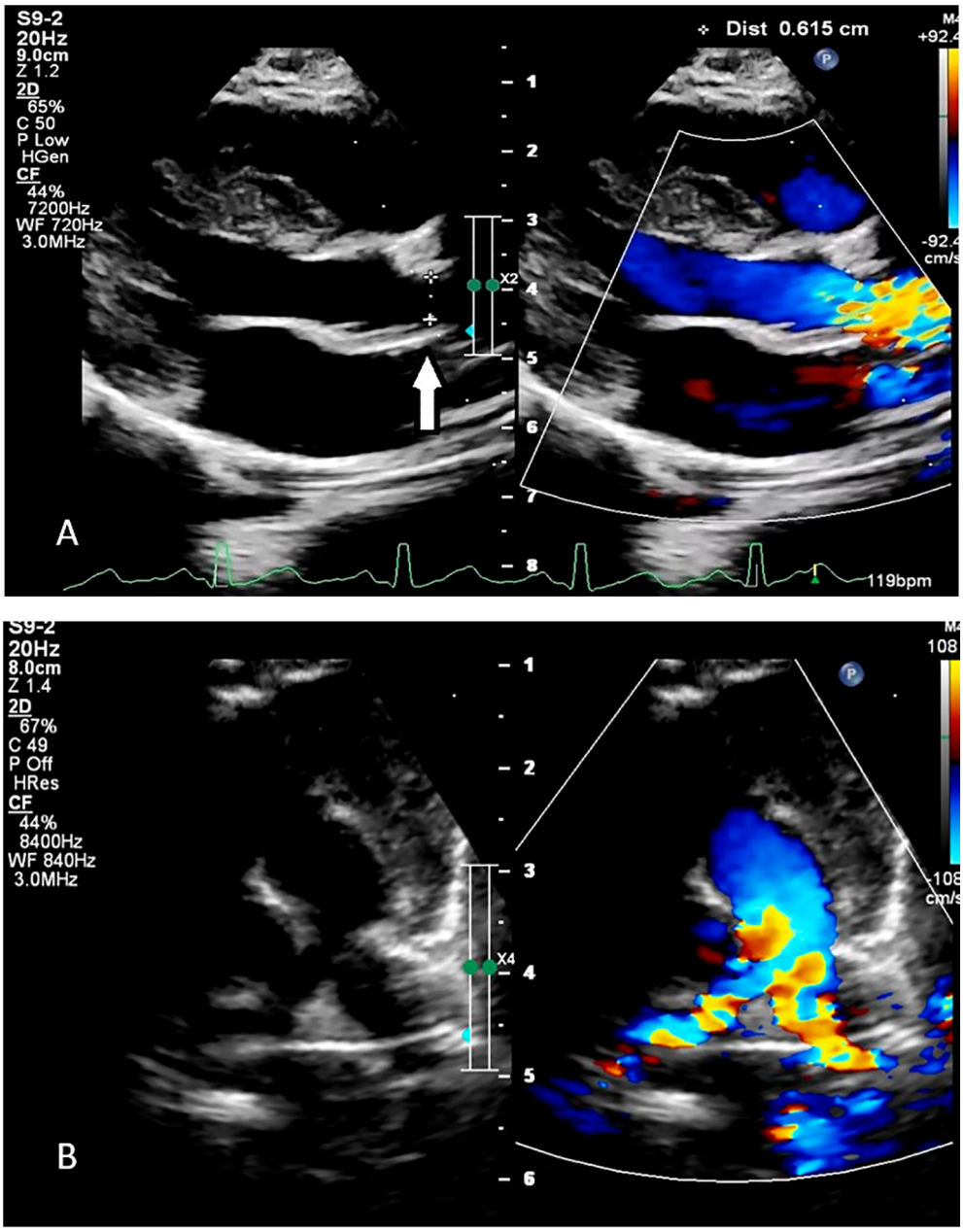

Fig. 2. A two-dimensional color Doppler echocardiogram of the left ventricular parasternal long-axis view (A) of the left ventricular outflow tract showing typical findings of SVAS. Aorta is narrow in the STJ (arrow) and the blood flow becomes turbulent from this point onward (arrow). Distal PA and both PA branch arteries are hypoplastic (B). PA, pulmonary artery; STJ, sino-tubular junction; SVAS, supravalvular aortic stenosis.

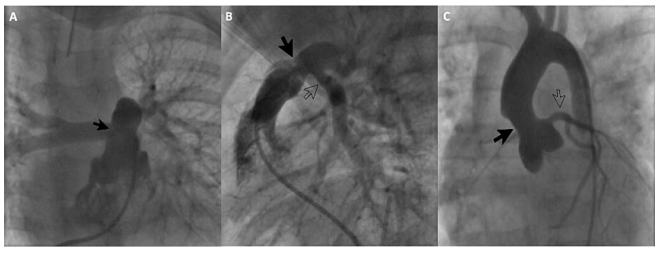

Fig. 3. Right ventricular angiography of a patient with SVAS. Antero-posterior (A) and lateral (B) views show narrowing of the main PA (black arrow). A mild narrowing of the right PA branch artery is also seen (empty arrow in B). Lateral view of aortic angiography (C) shows mild SVAS (black arrow). Left main coronary artery and its branching is normal (empty arrow).
PA, pulmonary artery; SVAS, supravalvular aortic stenosis.

obviously true also in our study. Sudden death, occurring in conjunction with surgical or other interventions and even during anesthesia or sedation has been described in several recent studies in patients with elastin arteriopathies [24,26,29,31]. There may be both ostial and diffuse coronary artery stenoses, with LCA more frequently affected [31,32]. Thickened aortic wall can also directly narrow coronary ostia [31]. Patients with SVAS are especially sensitive to falls in blood pressure during sedation and anesthesia, potentially resulting in sudden and rapid hemodynamic deterioration associated with hypotension and bradycardia and no response to resuscitation [26,29,31,32]. The risk is highest in small children under age 3 years and those with biventricular outflow tract obstruction [29]. Therefore, we and other authors of several previous studies recommend every patient with SVAS to undergo preoperative coronary artery screening with CT angiography that may be performed without or with minimal sedation [26,29,32]. Moreover, any surgical or other interventions of these hemodynamically fragile patients are recommended to be performed

in tertiary care centers with highly trained professionals and expertise in taking care of these patients [26,32].

It is estimated that about one third of patients with SVAS will ultimately require surgical correction with associated perioperative mortality of 3–7 % [24,33]. Min et al. [21] reported that over 70 % of the patients with SVAS required at least one surgical and catheter re-intervention for cardiovascular lesions, with the median intervention-free survival being 1.1 (0.3–5.9) years. They suggested that elastin insufficiency could predispose to a proinflammatory process which in turn could contribute to the high incidence of vascular restenosis after initial surgical or catheter interventions [21]. However, long-term outcome in the patients in our study seemed to be more favorable as only one of the sisters (II-1) having undergone percutaneous valvuloplasty in infancy required surgical intervention at age 5 years.

Whereas a non-syndromic SVAS is usually a progressive disease in children, progression during adulthood has been shown to be rare after successful surgical patch aortoplasty in childhood [20]. Adverse cardiovascular events, the most common being arrhythmias and new onset heart failure, have been reported in about 10 % of adult patients and about 10 % needed cardiac surgery in the median follow-up of 6 years [20]. Recently, 30-year survival rates of 90 % in surgically corrected SVAS patients were reported [33,34]. In contrast to pediatric patient populations, acute coronary syndromes seem to be rare in adults, probably explained by the fact that coronary lesions are associated with abnormal growth of the aortic root during the early life when somatic growth is fastest [21].

The long follow-up period (mean 17.4 years) in the six clinically affected siblings in the present study showed that those with a severe and even progressive elastin arteriopathy during early childhood had a favorable outcome if the early interventions were successful. However, coronary artery obstruction or reduced coronary blood flow have been shown to be the strongest predictors of poor outcome in children with SVAS [24], as was demonstrated also in the present study. In general, SVPS, PS, and PA branch stenoses tend to have a more favorable outcome and only infrequently require interventions [10,19,24,30].

All patients diagnosed with SVAS should be offered genetic testing. In non-syndromic patients, the focus should be in targeted gene panels including *ELN* gene sequencing and deletion/duplication analysis. As non-syndromic SVAS related to *ELN* pathogenic variants is inherited in an autosomal dominant manner, family evaluation and cascade genetic screening is an essential part of preventive care to detect those individuals in need for surveillance and early interventions. Prenatal diagnosis is controversial since fetal cardiac ultrasound screening or genetic studies cannot be considered reliable methods in determining penetrance and severity of phenotype after birth. A close collaboration with a clinical geneticist is recommended.

There are several strengths in this study. To our knowledge, this is the first study with a long follow-up at the same pediatric cardiology center at a tertiary-care university hospital from early infancy to adulthood. Detailed information of clinical findings, ECG, and echocardiography of all the siblings from every outpatient visit were available. The siblings showed a wide clinical spectrum of SVAS with variable outcomes from gradual spontaneous resolution of cardiac abnormalities to severe, progressive disease. The long-term outcome seemed favorable as none of the siblings required re-operations after early childhood, were clinically asymptomatic and had no significant residual stenotic lesions or valvular abnormalities on echocardiography and/or cardiac MRI as teenagers or young adults.

Because of the retrospective nature of the study, information was not complete for all the clinically affected siblings as far as details from cardiac catheterizations and open-heart surgery were concerned. Data on fetal echocardiography were only available from the two youngest children, showing normal cardiac structure and function. Although the family had an appointment with a clinical geneticist soon after the birth of the second child, more precise molecular genetic studies were not performed until the siblings were teenagers and were ready to decide for themselves. DNA was not available from the deceased brother, although he obviously carried the same pathogenic variant of *ELN* than the other affected siblings. Finally, no clinical nor echocardiographic data was available from the mother or her first-degree relatives.

In conclusion, we report a novel pathogenic *ELN* variant in five of the six siblings with a variable combination and severity of autosomal dominant non-syndromic elastin arteriopathy. As we could follow all the siblings from early infancy to adulthood, we could show that the most severe clinical findings were seen in infancy, with the male patients tending to have a more severe disease. However, if the surgical or non-surgical interventions early in life were successful, cardiovascular condition remained stable during childhood and adolescence. Coronary artery anomalies with resulting ischemia were the strongest predictors of unfavorable prognosis. SVPS, PS and PA branch stenosis, even when severe during infancy, tended to resolve spontaneously towards adulthood. Future investigations are warranted to find environmental factors and genetic modifiers that contribute to disease severity and outcome in individual patients. Understanding the cellular and molecular mechanisms behind this challenging disease will help in developing novel therapies.

CRediT authorship contribution statement

Sini Keskinen: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Conceptualization. **Jussi Niemelä:** Writing – review & editing, Visualization, Validation, Resources, Methodology, Investigation. **Hannele Koillinen:** Visualization, Validation, Resources, Investigation. **Talvikki Boldt:** Visualization, Resources, Investigation. **Anita Arola:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Conceptualization.

Consent

Informed consent was obtained from all tested family members for publication of their genetic and clinical data. No need for approving the ethics committee related to this article. The study conforms to Declaration of Helsinki.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that there was no use of generative AI and AI-assisted technologies in scientific writing.

Sources of funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2025.04.027.

Data availability

The data generated in this article is available upon reasonable request.

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