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Original Article

ELN gene triplication responsible for familial supravalvular aortic aneurysm

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Abstract Supravalvular aortic aneurysms are less frequent than abdominal ones. Among Supravalvular aortic aneurysm aetiologies, we focused on dystrophic lesions as they can be secondary to genetic causes such as elastin anomaly. We report on a familial 7q11.23 triplication – including the *ELN* gene – segregating with a supravalvular aortic aneurysm. During her first pregnancy, our index patient was diagnosed with tuberous sclerosis and with a Supravalvular aortic aneurysm. The foetus was affected equally. For the second pregnancy, parents applied for preimplantation diagnosis, and a subsequent prenatal diagnosis was offered to the couple, comprising *TSC1* molecular analysis, karyotype, and multiplex ligation probe amplification. *TSC1* mutation was not found on foetal deoxyribo nucleic acid. Foetal karyotype was normal, but multiplex ligation probe amplification detected a 7q11.23 duplication. Quantitative-polymerase chain reaction and array-comparative genomic hybridisation carried out to further assess this chromosome imbalance subsequently identified a 7q11.23 triplication involving *ELN* and *LIMK1*. Foetal heart ultrasound identified a Supravalvular aortic aneurysm. A familial screening was offered for the 7q11.23 triplication and, when found, heart ultrasound was performed. The triplication was diagnosed in our index case as well as in her first child. Of the 17 individuals from this family, 11 have the triplication. Of the 11 individuals with the triplication, 10 were identified to have a supravalvular aortic aneurysm. Of them, two individuals received a medical treatment and one individual needed surgery. We provide evidence of supravalvular aortic aneurysm segregating with 7q11.23 triplication in this family. We would therefore recommend cardiac surveillance for individuals with 7q11.23 triplication. It would also be interesting to offer a quantitative-polymerase chain reaction or an array-comparative genomic hybridisation to a larger cohort of patients presenting with isolated supravalvular aortic aneurysm, as it may provide further information.

Keywords: 7q11.23 triplication; *ELN*; supravalvular aortic aneurysm

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AORTIC ANEURYSM IS DEFINED BY A LOCALISED dilatation of the aorta with loss of parallelism of the three walls: endothelium, adventitia, and media. It can be symptomatic – pain, compression, systemic embolism – or not. The purpose of early diagnosis is to prevent vital complications such as aortic rupture. Supravalvular aortic aneurysms are rare compared with abdominal aortic aneurysms (7–10% in European cohorts).[1,2] Supravalvular aortic aneurysms' known causes are anatomic, dystrophic, degenerative, atherosclerotic, inflammatory, infectious,

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Table 1. Ascending aortic aneurysm causes.[2]

Anatomic congenital abnormalities	Valsalva sinuses aneuryms Bicuspid aorta and ascending aortic aneurysms Kommerell diverticulum and aneurysm Turner syndrome
Connective tissue disorders	Marfan disease Ehlers–Danlos disease Cutis laxa disease Affected smooth muscle cells (ACTA2 mutations)
Degenerative	Secondary supravalvular aortic Secondary hypertension
Atherosclerosis	Multiple localisations
Inflammatory	Takayasu disease Horton disease Behçet disease
Infectious	Syphilis Endocarditis, septicaemia
Traumatic	

or traumatic (Table 1).[2] Dystrophic media lesions including alterations of the elastin, its main component, can cause supravalvular aortic aneurysms.[3–5] Supravalvular aortic aneurysms can indeed occur in Marfan disease (*FBN1* mutations), Ehlers–Danlos syndrome (collagen mutations), or autosomal dominant cutis laxa with *ELN* mutations.[3–5] The *ELN* gene had been mapped to 7q11.23 and was identified in 1989.[6] It comprises 33 exons and encodes elastin.[4,7] *ELN* deletions and mutations have been reported as responsible for vascular abnormalities such as supravalvular aortic stenosis.[7–10] 7q11.23 deletions account for Williams Beuren syndrome. Williams Beuren syndrome includes facial dysmorphic features such as broad forehead, narrow palpebral fissures, wide mouth, thick, and everted lower lip; visuo-spatial difficulties; hypersociability; cardiac abnormalities such as supravalvular aortic stenosis, pulmonary artery stenosis, and aortic coarctation; and kidney abnormalities such as nephrocalcinosis secondary to hypercalcaemia.[11] Williams Beuren syndrome is a contiguous gene syndrome involving at least 30 genes.[12] It can either be diagnosed by fluorescent in situ hybridisation[9] or by array comparative genomic hybridisation.[13] Williams Beuren syndrome is not the only chromosomal abnormality associated with ascending aorta abnormalities. Indeed, recently rare copy number variants such as 16p13.1 duplication, comprising *MYH11*, have been reported with a similar vascular phenotype.[14,15]

We present a familial case of supravalvular aortic aneurysms with a 7q11.23 triplication including *ELN*.

Patients and methods

The index patient (II3, Fig 1) is a 27-year-old woman. She was initially referred to a dermatologist for toe nail lesions. She was in good health with no significant medical history. Her father (I4, Fig 1) had a posterior cerebral artery aneurysmal rupture at 51, which was treated surgically. II3 was in her first pregnancy when peri-ungual fibromas were diagnosed and tuberous sclerosis was suspected. Her husband (II4, Fig 1) had no personal or familial medical history. They were not related.

Tuberous sclerosis was confirmed and a *de novo TSC1* gene mutation was identified (R45X, exon 8). A cardiac ultrasound revealed a 53 mm supravalvular aortic aneurysm, involving the aortic root and tubular ascending aorta (Fig 2). The kidneys were normal on computed tomography scan performed after delivery. A brain Magnetic Resonance Imaging highlighted several hamartomas. The electroencephalogram was normal. Ophthalmological examination and a spinal magnetic resonance imaging were normal. Supravalvular aortic aneurysm was treated initially with beta-blockers and by surgery after the delivery, considering the risk of aortic dissection.

Owing to the autosomal dominant mode of inheritance of tuberous sclerosis and its variable expression, we offered prenatal diagnosis on amniotic fluid and the foetus was affected. Foetal chromosomes on amniotic fluid were normal. Prenatal ultrasound identified cardiac rhabdomyomas. Foetal brain magnetic resonance imaging revealed bilateral ventriculomegaly, subependymal heterotopias, and abnormal gyration of the frontal lobes. The couple decided to carry on with the pregnancy.

The baby (III5, Fig 1) was born at term with normal growth parameters and normal Apgar scores. Severe encephalopathy was diagnosed soon after birth, and he presented later on with severe developmental delay. The kidneys and ophthalmological examination were normal. Neonatal echocardiography identified several rhabdomyomas. A 24.2 mm diameter (Z-score 3.9) SVAA was diagnosed at 4 years on a follow-up heart ultrasound.

Given the recurrence risk of tuberous sclerosis and prognosis uncertainty, a preimplantation diagnosis was offered for a further pregnancy. According to the preimplantation diagnosis centre's guidelines, *TSC1* molecular analysis was performed on amniotic fluid (III6, Fig 1) at 17 weeks' gestation. A routine karyotype and multiplex ligation probe amplification were also offered given the cytogenetic laboratory's recommendations, using the Multiplex Ligation Probe Amplification Kit No. P290 (MRC Holland, Amsterdam, Netherlands) with 49 probes, of which two were in *ELN* and *LIMK1*.

Subsequently, a chromosomal imbalance was found on multiplex ligation probe amplification at

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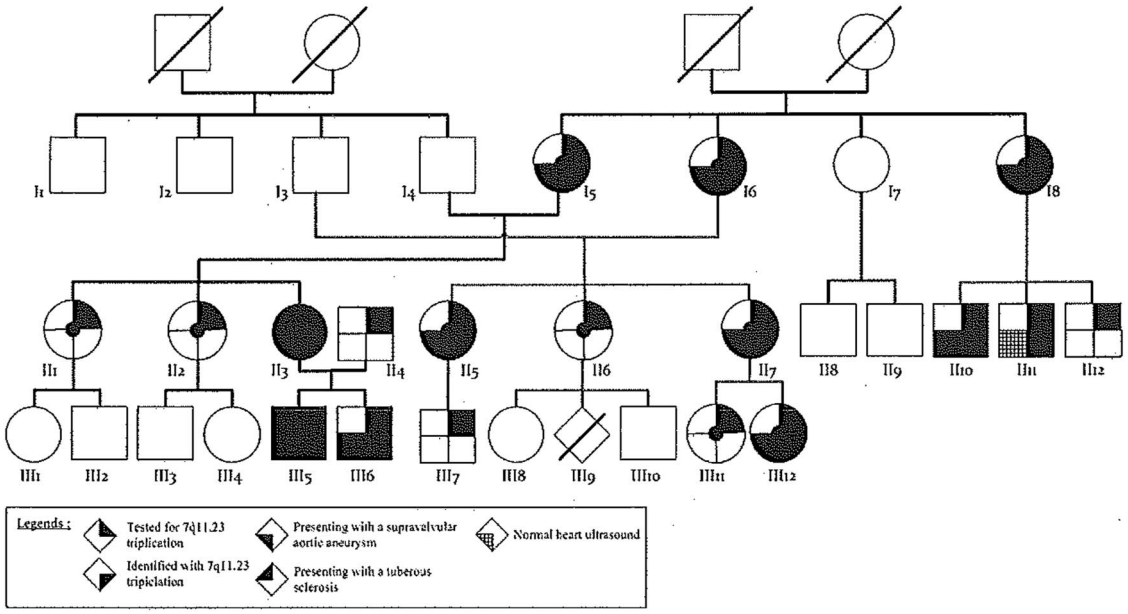

Figure 1.
Family pedigree.

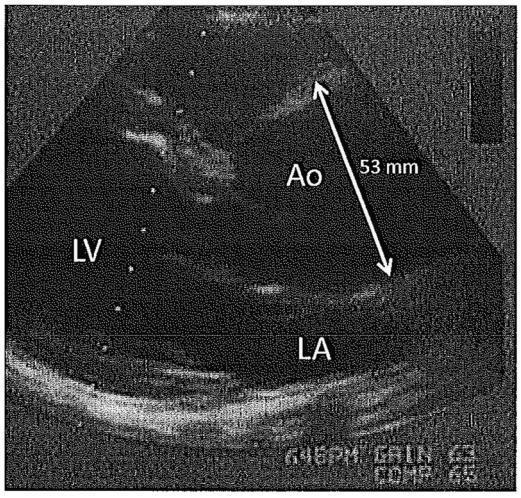

Figure 2.
2D echocardiography in parasternal long-axis view of the index patient showing the dilated ascending aorta (Ao) with an anteroposterior diameter of 53 mm. LA = left atria; LV = left ventricle.

7q11, and further analyses were performed on the foetal deoxyribo nucleic acid, such as fluoresecent in situ hybridisation, quantitative-polymerase chain reaction and array-comparative genomic hybridization. Fluorescent in situ hybridisation was done on metaphase cells following standard techniques using 150 kb locus specific identifier *ELN* to screen for large deletions or duplications. Quantitative-polymerase chain reaction with ELN probe as well as array-comparative genomic hybridisation with oligonucleotides – from nucleotides 28147 – Agilent 44 K protocol with foetal deoxyribo nucleic acid (cyanine 5) against normal control deoxyribo nucleic acid (cyanine 3) Promega were performed. Array-comparative genomic hybridisation was interpreted according to the algorithm used and ADM2 version hg18 genome build 36. A routine prenatal ultrasound follow-up was also offered. We hypothesised that the supravalvular aortic aneurysm was linked to the 7q11.23 imbalance because of *ELN* disruption. Family screening was offered by quantitative-polymerase chain reaction on extracted deoxyribo nucleic acid after patients were seen in the Genetics Clinic. Blood was taken after informed consents were obtained. Heart ultrasound was offered considering the cardiac risk when the triplication was identified. Supravalvular aortic aneurysm was defined when the supravalvular aorta diameter was >21 mm/m^2. For foetuses and children, supravalvular aortic aneurysm was defined according to echo Z-score calculators (http://parameterz.blogspot.fr/2009/10/fetal-echo-z-scores-boston-childrens.html).

Results

TSC1 mutation was not identified on III6's AF (Fig 1). Foetal karyotype was normal. Multiplex ligation probe amplification suspected a 7q11.23 duplication with a ratio between 1.5 and 2 (Fig 3). Fluorescent in situ hybridisation did not reveal deletion or duplication. Quantitative-polymerase chain reaction diagnosed a 7q11.23 triplication (Fig 4). Array-comparative genomic hybridisation showed that the triplication included *ELN* and *LIMK1*, which are located between 73.1 and 73.15 Mb

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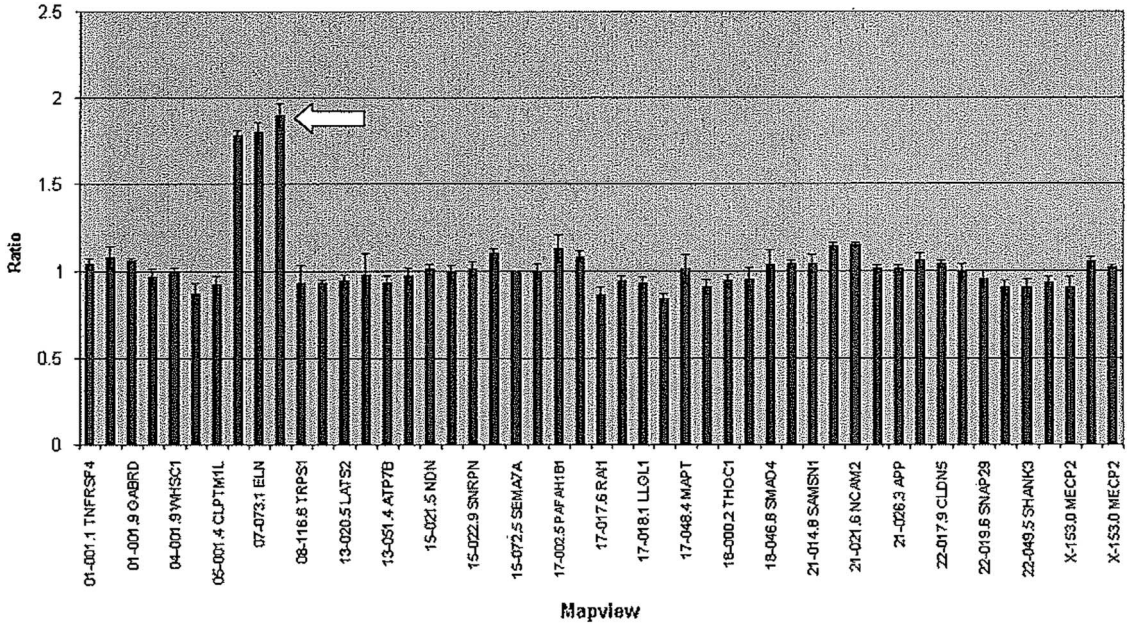

Figure 3.
Multiplex ligation probe amplification on foetal deoxyribo nucleic acid (case III6): copy number variant at 7q11.23 (Williams Beuren syndrome locus). Ratio 2: in favour of triplication.

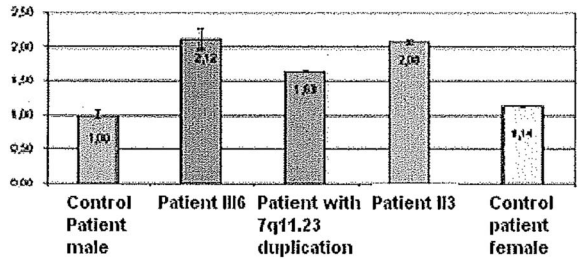

Figure 4.
Quantitative-polymerase chain reaction on foetal deoxyribo nucleic acid (case III6): 7q11.23 triplication.

(73,083,675-73,163,216 hg18). Foetal cardiac ultrasound performed at 30 weeks' gestation revealed an 8.2 mm supravalvular aortic aneurysm (+3 Z-score). The child (III6, Fig 1) was born at term with normal growth parameters and normal Apgar scores. Progression of supravalvular aortic aneurysm was noted (18.5 mm (+3.6 Z-score)) at the age of 4 months. No specific treatment apart from regular monitoring by heart ultrasound was instituted.

The 7q11.23 triplication was found on quantitative-polymerase chain reaction in II3 and III5, who also have Tuberous Sclerosis (Fig 1). A total of 18 family members were observed in the Genetics Clinic, and blood was taken from 17 patients (Fig 1, Table 2). A total of 11 patients were identified to present with the 7q11.23 triplication with a mean age of 30 years (6 months–65 years). Of them, 10 were also identified to have supravalvular aortic aneurysms (Table 2).

Discussion

We report on the association of isolated non-syndromic supravalvular aortic aneurysms and a 7q11.23 triplication, including the *ELN* gene that was diagnosed by quantitative-polymerase chain reaction and confirmed on array-comparative genomic hybridisation. The triplication was not confirmed on fluorescent in situ hybridisation, with it probably being too small (79–284 kb) to be spotted by the examiner's eyes. Of the patients, 11 were identified with the triplication, and 10 of them were diagnosed with supravalvular aortic aneurysm. Therefore, we assumed that supravalvular aortic aneurysms was linked to the 7q11.23 triplication in this family. All patients were asymptomatic and there was no medical history of sudden death in this family. At first, we did not offer heart ultrasounds to family members who did not have the triplication. We now think that these individuals could benefit from a heart ultrasound if they wanted to, and normal results would then support our hypothesis. No other supravalvular aortic aneurysm aetiology was found in our patients. We then collected 25 deoxyribo nucleic acid samples from individuals referred with isolated supravalvular aortic aneurysms to the Marfan syndrome reference centre in Paris, France, after obtaining informed consents for 7q11.23 triplication testing. No further 7q11.23 triplication was identified.

Abdominal aortic aneurysms and one case of supravalvular aortic aneurysms have already been incidentally reported in Tuberous Sclerosis;[16–20] however, in this family, only II3 presented with

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Table 2. Clinical and Genetic results.

Case	Sex	Age	Medical history	Clinical examination	7q11.23 triplication	Echocardiography	Treatment
I4	M	66	Intracerebral aneurysm rupture	N	–	Not done	No
I5	F	65	No	N	+	Aortic aneurysm (40.9 mm)	Medical
I6	F	62	No	N	+	Aortic aneurysm (35.3 mm)	Medical
I7	F	66	No	N	–	Not done	No
I8	F	52	No	N	+	Aortic aneurysm (38 mm)	No
II1	F	38	No	N	–	Not done	No
II2	F	35	No	N	–	Not done	No
II3	F	30	TS	Toe nail fibromas	+	Aortic aneurysm (53 mm)	Medical and surgical
II4	M		No	N	–	Not done	No
II5	F	36	No	N	+	Aortic aneurysm (39 mm)	No
II6	F	37	No	TOP for trisomy 18	–	Not done	No
II7	F	35	No	N	+	Aortic aneurysm (38.5 mm)	No
II10	M	23	No	N	+	Aortic aneurysm (37.5 mm)	No
II11	M	21	No	N	+	No aneurysm	No
II12	M	19	No	N	–	Not done	No
III5	M	$4^{1/2}$	TS	Severe encephalopathy	+	Aortic aneurysm (24.6 mm), Z-score: 3.9	No
III6	M	9 m	No	N	+	Aortic aneurysm (19.2 mm) Z-score: 3.8	No
III7	M	1 m	No	N	–	Not done	No
III11	F	11	No	N	–	Not done	No
III12	F	6 m	No	N	+	Aortic aneurysm (17 mm) Z-score: 4	No

M = male; F = female; TS = tuberous sclerosis; N = normal; TOP = termination of pregnancy, Z-score according to http://parameterz.blogspot.fr/.

Tuberous Sclerosis, and therefore supravalvular aortic aneurysms is likely not related to this condition. *ELN* and *LIMK1* genes are part of the Williams Beuren syndrome 7q11.23 deletion.[9,11,12] Only one case of 7q11.23 triplication has been reported so far and the patient's heart examination has been, since the publication, performed and is normal.[11] Cardiovascular abnormalities are frequent in Williams Beuren syndrome (50–80%),[9] the most common being supravalvular aortic stenosis, pulmonary artery stenosis, and aortic arch hypoplasia.[18,19] Coronary stenosis with infarction, renal artery stenosis, tetralogy of Fallot, ventricular septal defect, and atrioventricular defect have also been reported.[9] Cardiovascular abnormalities in 7q11.23 duplications seem to be less severe,[9] although one case of association between 7q11.23 duplication and supravalvular aortic aneurysms has already been reported.[14]

To the best of our knowledge, supravalvular aortic aneurysms have not been previously reported in Williams Beuren syndrome patients.[9,11,21,22] As *ELN*'s haploinsufficiency is associated with a more severe phenotype than when the 7q11.23 region is duplicated, we assumed that excess of elastin could be responsible for elastic fibres' loss of resistance to haemodynamic stress. Indeed, blood pressure is more important in the supravalvular aorta and could explain why aortic aneurysms are occurring at this level.[2] It seems to be the same mechanism when copy number variants and supravalvular aortic aneurysms are significantly associated. In these cases, duplications contain genes encoding proteins involved in smooth muscle cell adhesion and contractility regulation, and the imbalances seem to promote supravalvular aortic aneurysms onset.[14,15] For example, in 16p13.1 duplications comprising the *MYH11* gene, dysfunction of the myosin contractile unit occurs and leads to supravalvular aortic aneurysms.[15]

We therefore assumed that the mechanism responsible for supravalvular aortic aneurysms is the same as autosomal dominant cutis laxa. Cutis laxa is a heterogeneous group of acquired and inherited connective tissue disorders characterised by loose and redundant skin folds. The syndromic forms of cutis laxa can be X-linked, autosomal dominant, or autosomal recessive.[4,5] Some forms of autosomal dominant cutis laxa result in mutations or partial deletions of the elastin gene. Histological analyses show that tropoelastin – the elastin precursor – is organised as globular deposits composed of elastin only when mutations occur, and the elastic fibres become shorter and rarer. The media is then less resistant to haemodynamic stress and supravalvular aortic aneurysms can appear, leading to potential aneurysm rupture.[3,4] However, our patients present the aortic root and ascending aorta tubular dilatation, rather than isolated aortic root dilatation that occurs in connective

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tissue disorders such as Marfan syndrome, Ehlers–Danlos syndrome, or cutis laxa, reinforcing the quantitative hypothesis.[3–5]

The 7q11.23 triplication also involves *LIMK1*. LIMK1 substrats are cofilin1, also known as non-muscle cofilin; cofilin2, also known as muscle cofilin; and destrin, also known as actin depolymerising factor or ADF. LIMK1's substrats have the ability to depolymerise filamentous actin. *LIMK1* also has an action on *VEGF* and *LATS1*. LIM kinase plays an important role in the development of the central nervous system development, tumour cell invasion, and metastasis.[9,23,24] However, this role in tumour development has only been reported in point mutations,[23,24] and patients with 7q11.23 duplications have never been described as presenting with an increased tumour risk.[9] Consequently, monitoring should be the same as that for the general population. LIMK1 also decreases the number of cochlear outer hair cells and the distance between the cochlear cilia and tectorial membranes. This could explain oversensitivity to sounds, hyperacusis, and phonophobia observed in Williams Beuren syndrome patients.[25] No hearing abnormality was detected in our series.

We report on the association between a 7q11.23 triplication and supravalvular aortic aneurysms within a family, comprising at least 11 affected individuals. It would be interesting to extend this study to a larger cohort of patients presenting with non-syndromic supravalvular aortic aneurysms and to non-affected controls, to better understand whether this association is significant or not. Moreover, pathological analysis of the aortic tissues could provide additional information on the consequences of the 7q11.23 triplication.

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Conflicts of Interest

None.

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