


CASE REPORT

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# Arterial tortuosity syndrome (variants in *SLC2A10* gene) in two pediatric patients in the same city of Spain: a case report

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## Abstract

**Background:** Arterial tortuosity syndrome (ATS) (OMIM #208050) is a very rare autosomal recessive connective tissue disease characterized by elongation, tortuosity, and predisposition of aneurysms formation in medium and large-caliber arteries, vascular dissection, and ischemic events. To date, approximately 100 patients have been reported carrying some of the fewer than 35 causal mutations in the *SLC2A10* gene.

**Case presentation:** Here we present the clinical and molecular characterization of two new Spanish pediatric ATS patients from two unrelated families in the same city in a short period of time. Due to the knowledge of the pathology through the first case this pathology was suspected from birth in the second case, requesting the directed genetic study.

**Conclusion:** In addition to arterial tortuosity and connective tissue features, sequencing analysis revealed the homozygous and heterozygous *Frameshift Deletion*. Confirm diagnosis in the first few years of life is the most critical for possible life-threatening events and to offer adequate genetic counseling.

**Keyword:** Arterial tortuosity syndrome, Connective tissue diseases, Exome, Transthoracic echocardiography, Magnetic resonance angiography, Case report

## Background

Arterial tortuosity syndrome (ATS) (OMIM #208050) is a rare autosomal recessive (AR) connective tissue disease characterized by elongation, tortuosity, and predisposition of aneurysms in medium and large-caliber arteries, vascular dissection, and ischemic events. Approximately 100 ATS patients have been described, and more than 35 causal mutations (80 families) have been identified in the *SLC2A10* gene. Associated with pulmonary artery stenosis and / or aorta with or without dysmorphic features, skeletal, ophthalmic abnormalities, and hypotonia

in addition to hyperextensible skin, joint laxity, and other connective tissue features. This syndrome is caused by loss-of-function mutations in the *SLC2A10* (*Solute Carrier Family 2 Member 10*) gene, locus 20q.13.12 cytoband (Coucke et al. 2006; Ritelli et al. 2014; Faiyaz-Ul-Haque et al. 2009; Morris 2015; Beyens et al. 2018; Kocova et al. 2018), encoding the facilitative glucose transporter GLUT10. The diagnosis of ATS is established in a proband with generalized arterial tortuosity and biallelic (homozygous or compound heterozygous) pathogenic variants in *SLC2A10* identified on molecular genetic testing.

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## Case presentation

### Patient 1 (family A)

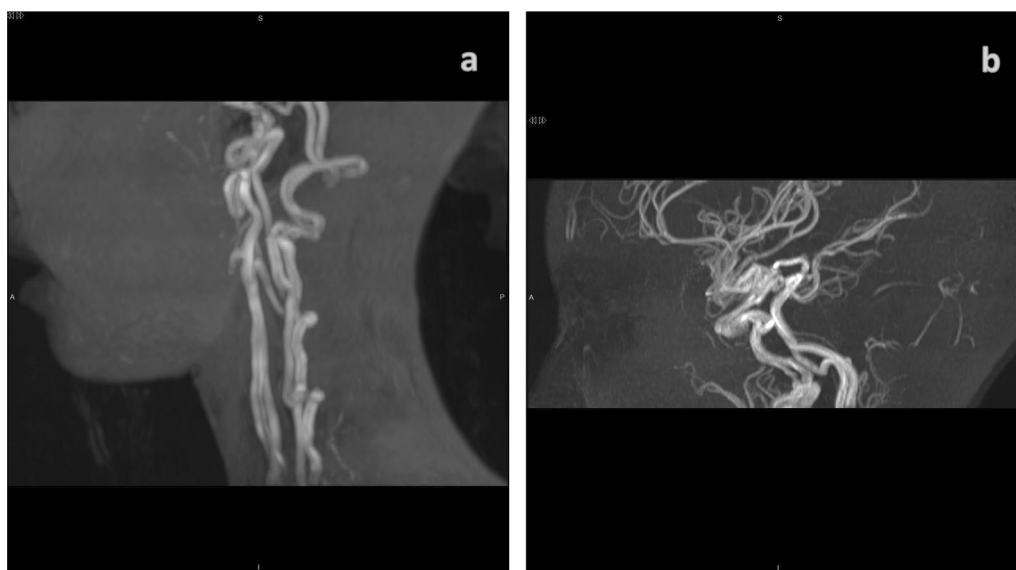
His perinatal period and psychomotor development were normal. The following features were observed on examination at 2 months hyperlaxity, elongated face, high palate, beaked nose, high-arched palate, micro-retrognathia, elongated philtrum, and hyperextensible skin and moderate generalized hypotonia and was referred to neuropsychiatry. An electromyogram and electroneurogram was performed at 7 months and revealed signs of denervation on deltoid and biceps muscles. On examination at 2 years of age was referred for cardiological evaluation for possible collagen disease due to elongation of the aortic arch, detected on a plain chest radiograph. Echocardiography excluded heart disease and revealed tortuosity and elongation of aortic arch, supra-aortic trunks and compressing the inferior vena cava. A heart magnetic resonance angiography (MRA) revealed a severe elongation and tortuous aorta and brachiocephalic vessels with supra-aortic trunks with crooked hypoplasia distal. The aorta heads back framing heart, crossing right side zigzag at the level of the diaphragm compressing the inferior vena cava. Striking elongation of celiac trunk, superior mesenteric and renal as vertebral, subclavian, axillary and brachial arteries and cerebral vascular loops. Both parents (non-consanguinity) and the brother of the index case, asymptomatic, also presented the pathogenic variant in heterozygosity. On magnetic resonance angiography (MRA) control at 6 years findings were similar

than previous MRA study with elongations and tortuous arteries both of supra-aortic trunks (Fig. 1a) and of the Willis polygon, without appreciate signs of arteriovascular malformations (AVM) or aneurysms (Fig. 1b).

He was monitored clinically without intervention and grew well at 6 years of age.

The skeletal signs included mild scoliosis (T7-L2-D7), patella hyperlaxity, genu recurvatum. Aspirin was added for stroke prevention.

Molecular genetic study: Targeted exome [*TNXB*, *ADAMTS2*, *CHST14*, *B4GALT7*, *PLOD1*, *ZNF469*, *COL6A1*, *BMP1*, *COL5A1*, *SERPING1*, *PPIB*, *COL1A2*, *COL3A1*, *COL5A2*, *COL5A3*, *ALDH18A1*, *ATP7A*, *COL1A1*, *COL6A3*, *CRTAP*, *FBN1*, *FKBP10*, *FKBP14*, *FLNA*, *KIF22*, *P3H1*, *PLOD2*, *PLOD3*, *SERPINH1*, *SLC2A10*, *SLC39A13*, *SP7*; 32 genes associated with joint hypermobility], next generation sequencing (NGS), (ExoNIM<sup>®</sup>, NIMGenetics, Madrid) was studied. It was detected a pathogenic variant in homozygosity in *SLC2A10* gene related to STA. This variant is a deletion of a nucleotide c.1334delG (NM\_030777.3) in exon 3 of *SLC2A10* gene (GAGATA<sup>^</sup>CGAGgAAGAGCCTTC), generates a stop codon and is therefore considered a loss of function mutation. This change of place to the substitution of a glycine by a glutamic acid at position 455 of the protein, causing a change in the reading pattern (frameshift) that generates a premature stop codon (p.Gly445Glufs\*40). This variant has been previously identified in homozygosity in four individuals with ATS from a consanguineous family of Italian origin (Coucke



**Fig. 1** Patient 1. MR *angiography* at 6 years of age. **a** 3D TOF acquisition of supra-aortic trunks, without contrast injection. Severely elongated and tortuous vessels. **b** 3D TOF acquisition of polygon of Willis vessels, without contrast injection. Multiple vascular elongations and loops in Willis polygon, without observing signs of AVM or aneurysms

et al. 2006). This variant has not been identified in a homozygous state in population control.

Both parents were asymptomatic carriers of this variant in heterozygous. The brother of index case was carrier of this pathogenic variant in heterozygous.

**Patient 2 (Family B)** was a pre-term male neonate presented with a heart murmur along with, joint hypermobility, and abnormal facies at birth. Characteristic facial features: elongated face, high palate, beaked nose, high-arched palate, microretrognathia, elongated philtrum, large and sparsely folded ears, and other connective tissue features (hyperextensible skin, joint laxity, moderate generalized hypotonia, redundant skin on extremities, especially wrists and ankles, long arms and fingers. The weight at birth was 2.77 kg, which was in the 75th–90th centile (35 + 4 GA). After birth an echocardiography performed due to fetal echocardiography revealed pulmonary stenosis and tricuspidal regurgitation and revealed mild right ventricle dilatation and mild tricuspidal regurgitation and showed a very tortuous aortic arch with abnormal takeoff of the neck vessels. Collagen disease was suspected and molecular studies was performed.

Alterations in suction-deglutition at 3 months was observed. Assessed by rehabilitation treatment and early intervention service. Videoelectroencephalogram and brainstem auditory evoked responses were normal.

In patient 2 (Family B) genetic study, clinical exome was made in order to identify variants related to signs or symptoms present in the patient in genes that may have an association with their genotype, identified a series of variants with a probable genotype–phenotype association in this case (see Table 1).

Patient 2 presented two variants in *SLC2A10* gene: c.685C>T and c.1334del confirmed clinical diagnosis of STA. Both parents non-consanguinity, asymptomatic, also were carrier of one of these variants in heterozygosity. The rest of detected variants did not justified clinical symptoms.

At 3 month of age, a heart magnetic resonance angiography (MRA) demonstrated severe arterial tortuosity of the aorta and its branches and pulmonary artery and its branches. Elongated and dilated ascending aorta. No aneurysms or stenosis was found.

## Discussion

The clinical and molecular data for 40 newly identified ATS families including 50 affected individuals and a clinical review of 52 patients described in the literature was published by Beyens et al. (2018) in 2019. After this study, individual cases of pediatric and adult patients have been published.

Despite these manifestations, ATS is often misdiagnosed as other heritable connective tissue diseases (HCTDs), including Loeys Dietz syndrome (LDS), Marfan syndrome (MFS), and Ehlers–Danlos syndrome (EDS).

The diagnostic suspicion of physicians in one of the different clinical fields of interest for this HCTDs. In a specialized center, the careful clinical evaluation and the assessment of the reported findings is sufficient to confirm the diagnosis in the majority of the cases. Only in pediatric patients and in patients without a complete or with a borderline phenotype the diagnosis is doubtful and requires a second evaluation in older age or targeted molecular testing for the exclusion of overlapping disorders.

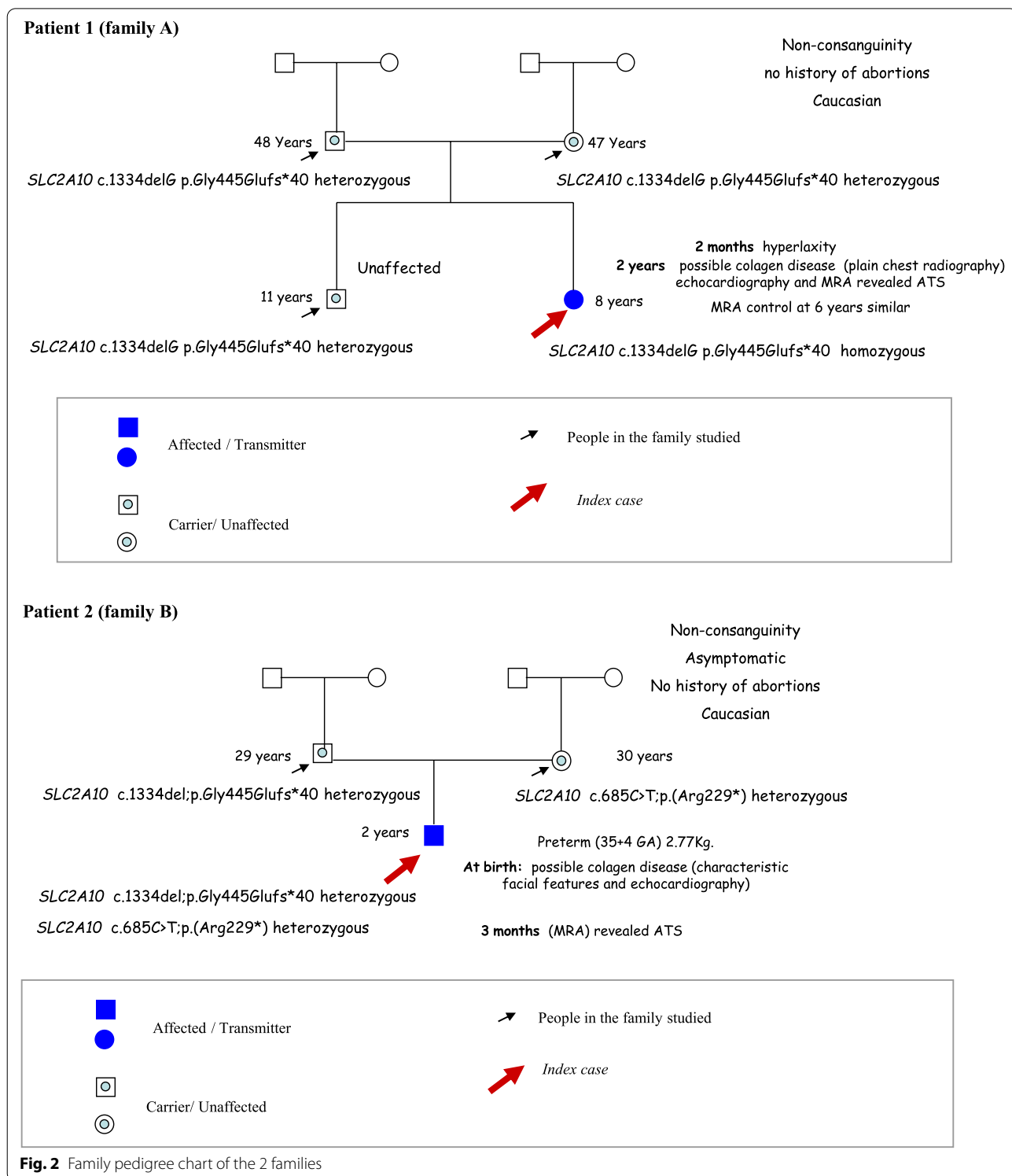
When specific signs of the different HCTDs are found, the initial diagnosis is addressed accordingly. When the presence of other (MFS, LDS, ATS) is suspected, additional investigations for the assessment of vascular, skeletal, ophthalmologic, and bone health should be performed.

When ATS is suspected: facial dysmorphisms (elongated face, hypertelorism, cleft palate and/or bifid uvula, and micro/retrognathia), keratoconus, abdominal hernias, joint hypermobility and instability, and other skeletal anomalies, pulmonary artery stenosis, acute

**Table 1** Genomic variants identified in clinical exome in peripheral blood (ExoNIM<sup>®</sup> NIMGenetics) in patient 2

Gene	Variant nomenclature	Exon	Intron	Cygoty	Effect	Variant categorization	Inheritance	Phenotype
<i>SLC2A10</i>	c.685C>T;p.(Arg229*)	2	–	Het	<i>Nonsense</i>	PV	AR	Arterial tortuosity syndrome
<i>SLC2A10</i>	c.1334del;p.(Gly445Glufs*40)	3	–	Het	<i>Frameshift</i>	PV	AR	Arterial tortuosity syndrome
<i>TPM2</i>	c.766C>G;p.(Leu256Val)	8	–	Het	<i>Missense</i>	VUS	AD	Distal arthrogriposis tipo 2B4 y tipo 1A; capped myopathy
<i>CIC</i>	c.4192-6A>G;p.(?)	–	10	Het	<i>Splicing</i>	VUS	AD	Type 54 intellectual disability
<i>RASA1</i>	c.1393C>T;p.(Arg465Cys)	10	–	Het	<i>Missense</i>	VUS	AD	Capillary malformation-Arteriovenous malformation
<i>ASXL2</i>	c.3425A>G	13	–	Het	<i>Missense</i>	VUS	AD	Shashi-Pena syndrome

Het heterozygosis, VUS variant of unknown significance, PV pathogenic variant, AR autosomal recessive, AD autosomal dominant



**Fig. 2** Family pedigree chart of the 2 families

respiratory insufficiency and/or cardiac failure in early childhood), and the suspicion of a vascular disorder persists, extensive vascular imaging (i.e., whole body or brain angio-MRI plus thoracic and abdominal angio-CT, or heart, abdominal aorta, and limb vessels) is mandatory.

For patients without cardiovascular complications, is difficult to suspect for the cutaneous, articular and skeletal signs; in these cases, cardiovascular evaluation and *SLC2A10* molecular analysis allow the distinction between these disorders.

When MFS is suspected (Marfanoid habitus, ectopia lentis, aortic root, dilatation/aneurysm, Ghent criteria) heart ultrasound for mitral valve prolapse and aortic root ectasia, ocular evaluation for ectopia lentis and/or myopia, and spine MRI for dural ectasia must be performed (Colombi et al. 2015).

ATS usually begins in early childhood, with variable clinical manifestations, depending on the arterial territory involved. Early diagnosis and exhaustive follow-up through imaging tests and screening for associated abnormalities will try to avoid complications by offering a better long-term prognosis. Due to the knowledge of the pathology through the first case (Palanca Arias et al. 2020), this pathology was suspected from birth, requesting the directed genetic study. Confirm diagnosis in the first few years of life is the most critical for possible life-threatening events.

Although invasive therapy is often required for severe pulmonary artery stenosis, aortic arch abnormalities do not need intervention in most cases of ATS. Antiplatelet therapy for stroke prevention to reduce clot formation and possible embolic phenomenon was described (Naunheim et al. 2011).

Further works in the comprehension of disease presentation and complications onset, particularly in pediatric age, and on molecular diagnosis is mandatory to distinguish ATS from other CTDs with strictly overlapping clinical signs and with a high rate complications.

In patient 1, the presence of this variant in heterozygosity in the parents (non-consanguinity) and the absence of homozygosity in the healthy sibling with the clinical signs of the index case supports the causal relationship of the variant with the phenotype. The same occurs in patient 2. In this case, parents were carrier of one of the variants in heterozygosity.

The genetic study allowed an early diagnosis helping parents to plan their future offspring, offering them different reproductive options (prenatal and/or preimplantation diagnosis). Their offspring will have a 50% probability of being asymptomatic carrier, like their parents, 25% of developing ATS and 25% of not inheriting any of the variants from their parents.

In case that brothers/sisters of index cases and brothers/sisters of each of the parents were carriers of a variant in heterozygosity it should be made genetic study, sequencing *SLC2A10* gene to their reproductive partners (family pedigree chart; Fig. 2).

## Conclusions

Hereby we report the clinical and molecular characterization of two novel ATS pediatric patients from two unrelated families in the same city in a short period of

time. Due to the knowledge of the pathology through the first case this pathology was suspected from birth in the second case, requesting the directed genetic study.

Overall, three ATS unrelated families are known in Spain so far (Rodríguez-Capitán et al. 2020).

In these two families the advances in genetic diagnostic techniques, NGS, helps to establish a genotype–phenotype relationship, offering adequate genetic counseling to parents and first-degree relatives.

The majority of the reported ATS patients are infants or children in whom collagen disease was suspected and molecular studies was performed.

Early diagnosis in the first few years of life through echocardiography and imaging tests is the most critical for possible life-threatening events and early recognition of complications.

## Abbreviations

ATS: Arterial tortuosity syndrome; MRA: Magnetic resonance angiography; AVM: Arteriovascular malformations; HCTDs: Heritable connective tissue diseases; LDS: Loeys Dietz syndrome; MFS: Marfan syndrome; EDS: Ehlers–Danlos syndrome.

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## Author contributions

DP and SI conceived of the presented idea. DP wrote the manuscript with support from AA. LJ, ML contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. MC and VE authors contributed to the final version of the manuscript. VE designed the figure. SI contributed to the study and genetic analysis. CG contributed to the study and image analysis. All authors read and approved the final manuscript.

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## Availability of data and materials

The data used to support the findings of this study are included within the article.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

We have a copy of our institutional consent to send at any stage. All data generated or analyzed during this study are included in this published article [and its Additional files].

### Competing interests

The authors declare that they have no competing interests.

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