Further Delineation of *FKBP14*-Related Ehlers–Danlos Syndrome: A Patient with Early Vascular Complications and Non-Progressive Kyphoscoliosis, and Literature Review

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FKBP14-related Ehlers–Danlos syndrome (EDS) is an extremely rare recessive connective tissue disorder described for the first time in 2012 by Baumann and coworkers. The causal gene, *FKBP14*, encodes a member of the F506-binding family of peptidyl-prolyl cis-trans isomerases. The paucity of patients described so far makes this disorder poorly defined at clinical level. Here, we report an additional pediatric patient, who is compound heterozygous for a recurrent and a novel *FKBP14* mutation, and compare his phenotype with those available in literature. This evaluation confirms that kyphoscoliosis (either progressive or non-progressive), myopathy, joint hypermobility, and congenital hearing loss (sensorineural, conductive, or mixed) are the typical features of the syndrome. Since the patient showed a severe cardiovascular event in childhood and atlantoaxial instability, this report expands the phenotype of the disorder and the allelic repertoire of *FKBP14*.
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Key words: Ehlers–Danlos syndrome; *FKBP14*; vascular complications; joint hypermobility; kyphoscoliosis; atlantoaxial instability

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INTRODUCTION

Ehlers–Danlos syndromes (EDS) are clinically and genetically heterogeneous connective tissue disorders (CTDs) characterized by involvement of skin, joints, ligaments, vasculature, and internal organs [Steinmann et al., 2002]. Six EDS types are included in the Villefranche nosology [Beighton et al., 1998] and several rare variants were more recently delineated [Colombi et al., 2015]. Among these, Baumann et al. [2012] reported a rare recessive variant of EDS characterized by joint hypermobility, progressive kyphoscoliosis, myopathy, and sensorineural hearing loss due to recessive mutations in *FKBP14*. This gene encodes a member of the F506-binding family of peptidyl-prolyl cis-trans isomerases found in the lumen of the endoplasmic reticulum, where it is thought to catalyze cis-trans-isomerization of peptidyl-prolyl peptide bonds and to accelerate protein folding, particularly of procollagens [Galat, 2003]. To date, eight patients with *FKBP14*-related EDS from seven independent families have been described: five pediatric (≤12 years), one young woman (16 years), and two adults (48 and 42-year-old) [Baumann et al., 2012; Aldeeri et al., 2014; Murray et al., 2014].

Here we report an 8-year-old patient affected by *FKBP14*-related EDS due to compound heterozygosity for a recurrent and a novel *FKBP14* mutation and compare the proband's clinical presentation with the features of the patients available in literature. Our patient presented with vascular rupture at 6 years and showed atlantoaxial instability, never described before in *FKBP14*-related EDS, thus expanding the clinical phenotype of this rare disorder.

CLINICAL REPORT

The patient, an 8-year-old Italian male, was born from healthy non-consanguineous parents at 36 weeks by cesarean for cephalic presentation. At birth, measurements were within normal range (weight 3rd–15th centile, length 50th centile). Perinatal presentation was abnormal, with severe muscle hypotonia and poor suck. Newborn hearing screening with Auditory Brainstem Response Audiometry suggested congenital bilateral profound hearing loss. He underwent transtympanic drains due to impaired middle ear ventilation; audiometric testing, performed subsequently, revealed a partial improvement of hearing loss. At age 8 years, he had mixed hearing loss of mild degree. Gross motor milestones were delayed; he walked without help at the age of 2.6 years. Non-progressive and non-surgical kyphoscoliosis was first observed at 6 months and successfully treated with lumbar orthosis. At the age 2 years, EDS VIA was excluded by lysyl pyridinolines to hydroxylysyl pyridinoline (LP/HP) urinary ratio analysis, which resulted within the normal range. A flexion extension radiograph of the cervical spine performed at the age 6 years revealed an asymptomatic atlantoaxial instability with enlarged atlanto-epistropheal distance in flexion (Fig. 1A, a,b).

Given generalized muscle hypotonia, at age 3 years primary myopathy was suspected and histopathological examination of muscle biopsy specimens revealed changes in muscle fiber diameters, which were first linked to a nemaline myopathy. *ACTA1*, *TPM2*, and *TPM3* molecular analysis involved in nemaline myopathy types 3, 4, and 1, respectively were negative. Muscle hypotonia slowly improved with psychomotor rehabilitation programs. At age 6 years, the patient was admitted to emergency unit for acute abdomen caused by left hypogastric artery pseudoaneurysm rupture, safely treated with endovascular procedure (Fig. 1A, c). Thoracic and abdominal magnetic resonance angiography (MRA) performed after the vascular event did not show other arterial malformations, such as ectasia, aneurysm, pseudoaneurysm, or tortuosity. Echocardiogram was normal. At age
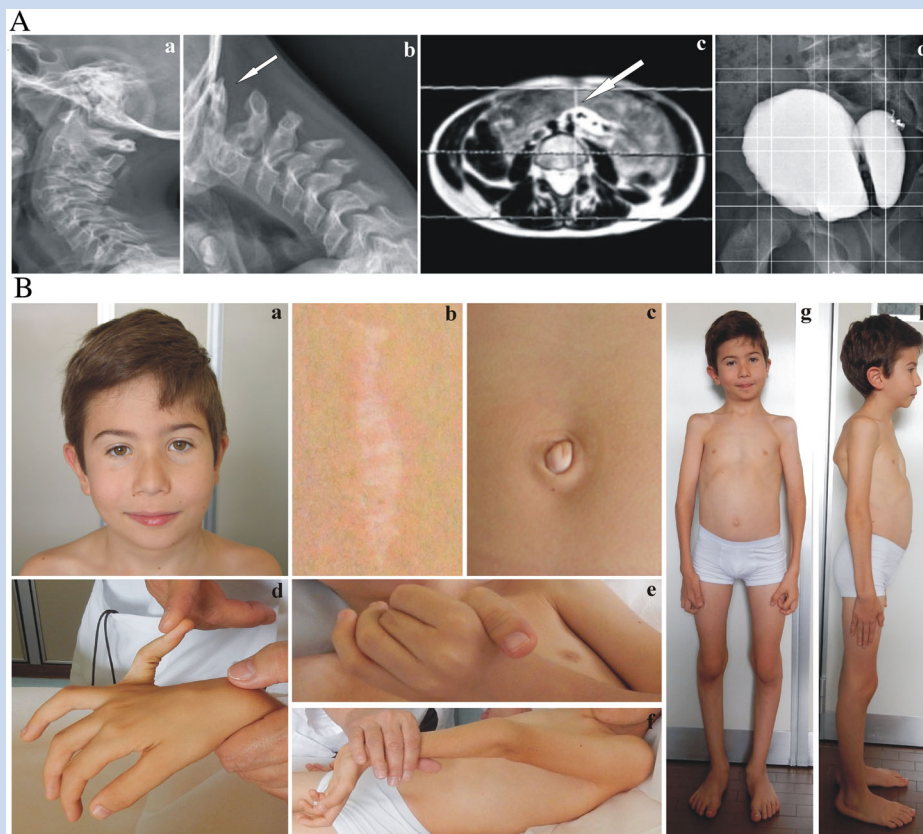
FIG. 1. Radiological and physical findings of the patient. A: Atlanto-axial instability (a,b) with enlarged atlanto-epistropheal distance in flexion (arrow). Thoraco-abdominal MRA performed after endovascular procedure for left hypogastric artery pseudoaneurysm rupture (arrow) at 7 years (c); Cystography with contrast at 7 years showing a large left postero-lateral bladder diverticulum (d); B: Epicanthal folds, palpebral skin redundancy, elongated philtrum, micrognathia (a); enlarged post-bioptic scar (b); umbilical skin redundancy (c); hypermobility of the joints of hands and elbow (d–f); generalized muscle hypotonia and atrophy, mild kyphoscoliosis, hyperlordosis, winged scapulae, genua valga, mild pectus excavatum, leg length discrepancy, valgus knee, and pes planus (g, h). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga].

8 years, an asymptomatic arachnoid cyst of the dorsal spine was successfully surgically removed. Diagnostic evaluation for voiding dysfunction, in particular urinary retention, lead to the diagnosis of a large bladder diverticulum by ultrasound; uroflussometry performed at the age of 8 revealed detrusor dyssynergia of I–II grades (Fig. 1A, d). The patient used braces for ankle instability from 3 to 5 years. At age 6, vitamin D supplementation was initiated due to radiological findings of osteopenia.

The patient came to our attention at age 8 years; clinical examination revealed normal stature (1.27 m, 25th–50th centile) and weight (22 kg, 10th–25th centile), generalized muscle hypotonia with myopathic gait, palpebral and umbilical skin redundancy, epicanthal folds, periorbital creases, light blue sclerae, long philtrum, micrognathia, bifid uvula, an atrophic scar on the knee, an enlarged scar after muscle biopsy, joint hypermobility according to Beighton score (6/9), high palate, winged scapulae, kyphoscoliosis of mild degree, mild pectus excavatum, bilateral valgus elbow, valgus knee, and pes planus (Fig. 1B).

MOLECULAR CHARACTERIZATION

After informed consent was obtained from the parents, molecular characterization was performed on genomic DNA purified from peripheral blood leukocytes using standard procedures. All exons and intron-flanking regions of *FKBP14* were PCR amplified by using optimized genomic primer sets, as previously described [Baumann et al., 2012]. PCR products were purified with ExoSAP-IT (USB Corporation, Cleveland, OH) followed by bidirectional sequencing with the BigDye Terminator v1.1 Cycle Sequencing kit on an ABI 3130XL Genetic Analyzer (Applied Biosystems, Carlsbad, CA). *FKBP14* sequence analyses revealed compound heterozygosity for the paternal and recurrent c.362dup (p.Glu122Argfs*7) and the maternal novel c.573_576del (p.Glu191del) mutations (Fig. 2), thus confirming the diagnosis of *FKBP14*-related EDS.

DISCUSSION

The clinical presentation of the patient reported here was strongly suggestive for *FKBP14*-related EDS, as he showed all the typical signs of this extremely rare CTD, that is, kyphoscoliosis, muscle hypotonia, and hearing loss. In addition to these cardinal features, at age 6 years, he had a left hypogastric artery dissection, and atlantoaxial instability. Clinical features and biochemical findings of the nine patients affected by *FKBP14*-related EDS, proven by molecular analysis, are summarized in Tables I and II, respectively. Differential diagnosis should take into account other EDS types with early onset/congenital kyphoscoliosis and myopathic signs, that is, EDS kyphoscoliotic type, *CHST14*-related EDS, in addition to CTDs with vascular involvement including EDS vascular type, Marfan and Loeys–Dietz syndromes, and myopathies, particularly those with joint laxity, such as Ullrich congenital dystrophy and Bethlem myopathy. The hearing loss distinguishes *FKBP14*-related EDS from these disorders. Moreover, *FKBP14*-related EDS differs from EDS kyphoscoliotic type by the normal ratio of urinary LP/HP crosslinks [Rohrbach et al., 2011], from *CHST14*-related EDS by the absence of congenital contracture of thumbs and
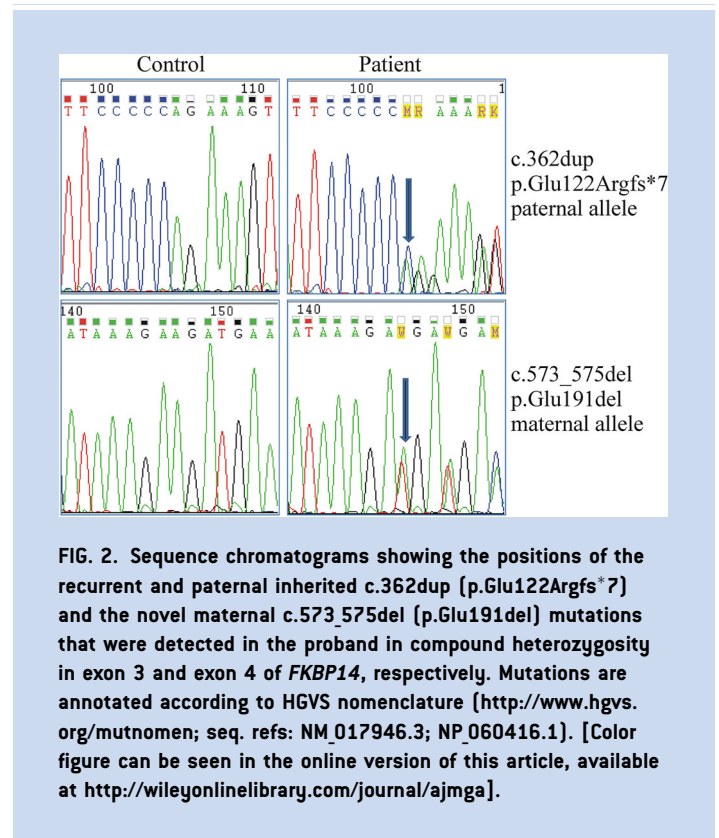
FIG. 2. Sequence chromatograms showing the positions of the recurrent and paternal inherited c.362dup (p.Glu122Argfs*7) and the novel maternal c.573_575del (p.Glu191del) mutations that were detected in the proband in compound heterozygosity in exon 3 and exon 4 of *FKBP14*, respectively. Mutations are annotated according to HGVS nomenclature (http://www.hgvs.org/mutnomen; seq. refs: NM_017946.3; NP_060416.1). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga].

fingers, and from the above mentioned CTDs with vascular involvement by the absence of a typical facial appearance and visceral rupture, marfanoid habitus, craniosynostosis, and widespread aortic/arterial aneurysms [Colombi et al., 2015]. Absence of respiratory muscle failure, improvement of muscle hypotonia with age and presence of an unspecific myopathic pattern on electrophysiological and muscle biopsy studies are useful aids to differentiate *FKBP14*-related EDS form primary myopathies [Baumann et al., 2012].

All the reported *FKBP14*-related EDS patients showed the cardinal features of the disease, that is, hearing loss, early-onset kyphoscoliosis, and myopathic signs, though with high variability (Table I). Hearing impairment can vary from sensorineural (6/8), to conductive (1/8), or mixed (present case) (Table I). In our patient, because of the mixed origin of this sign, hearing improved after transtympanic drains. Kyphoscoliosis is noted at a mean of 12 months (range 2–18 months) and it can be non-progressive (three patients including ours) or progressive (6). Orthotic treatment seemed successful in case of non-progressive kyphoscoliosis, as in our patient; progressive kyphoscoliosis required a surgical approach. Myopathic signs include muscle hypotonia and atrophy (9/9), poor head control in infancy (7/7), and delayed motor development (9/9) (Table I). Muscular weakness seems to regress with age and all of the subjects-but one-became able to walk at the mean age of 33 months. The outcome is very variable and the final ability to walk ranges from myopathic gait, impossibility of walking without aids, to a motor self-sufficiency from 200 m to 1 km (Table I). Muscle biopsy always shows pathological results with a broad spectrum of findings; creatine kinase generally results

TABLE I. Clinical Findings of the nine *FKBP14*-EDS Related Patients

	P1 Family A Present case	P2 Family B Baumann et al. [2012]	P3 Family B Baumann et al. [2012]	P4 Family C Baumann et al. [2012]	P5 Family D Baumann et al. [2012]	P6 Family D Baumann et al. [2012]	P7 Family F Baumann et al. [2012]	P8 Family G Murray et al. [2014]	P9 Family H Aldeeri et al. [2014]
Sex/Age	M/8	M/16	F/48	F/11	F/16	M/11	F/3	M/42	M/3
Family history		+	+						
Perinatal presentation	Severe hypotonia Poor sucking	Severe hypotonia Poor sucking	Severe hypotonia	Severe hypotonia Poor sucking	Hypotonia	Hypotonia Severe poor sucking	Hypotonia Poor sucking	Hypotonia Poor sucking	Hypotonia Poor sucking
	Muscle atrophy						Low oxygen saturation		
Age at diagnosis	?	16	48	11	16	11	3	42	3
FACIAL DYSMORPHISMS									
Epicanthal folds	+	na	na	na	na	na	na	+	+
Hypotelorism		na	na	na	na	na	na	na	+
Square nasal root		na	na	na	na	na	na	na	+
Uvula abnormalities	+ bifid							+	na
Micrognathia	+			na	na	+	na	+	na
Long-narrow face		na	na	na	na	na	na	+	na
OCULAR									
Myopia	+	+	+		+		+	+	na
Hypermetropia	+	+						na	
MUCOCUTANEOUS									
Hyperextensible skin	+	+	+	+		+	+	na	+
Soft texture	+	+	+	+	+	+	+	+	na
Umbilical skin redundancy		na	na	na	na	na	na	na	+
Follicular hyperkeratosis		+		+	+		+	na	na
Hernia		+ inguinal	+ umbilical	+ umbilical		+ umbilical		na	na
Defective scars	+	+		+				na	na
Bluish sclerae	+	+		+				na	na
SKELETAL									
Height (centile)	Normal for age (25–50th)	Normal for age (10–25th)	Normal for age (50th)	Normal for age (10th)	Short stature (<3rd)	Normal for age (10–25th)	Normal for age (10–25th)	Short stature (<3rd)	na
Palate deformities	+ high	+		+	+	+ cleft	+ cleft	+ high	+
Kyphoscoliosis	+	+	+	+	+	+	+	+	+
Age of onset	6 mth	2 mth	6 mth	4 mth	18 mth	12 mth	18 mth	12 mth	8/9
Evolution	non progressive	progressive	progressive	progressive	progressive lumbar orthosis and surgery,12 y	non progressive	non progressive	progressive surgery, 3 and 10 y	+
Treatment	lumbar orthosis	lumbar orthosis	surgery, 11y	surgery, 4 y					
Pectus deformity	+ mild *excavatum*	+ secondary to scoliosis						+ *carenatum*	
Flat feet	+	+	+	+	+	+	+		na
Club foot		+			+ left		+ left	+ bilateral	na
Joint hypermobility (Beighton score)	+ 6/9	+ 6/9	+ 6/9	+ 8/9	+ 6/9	+ 9/9	+ 9/9	+	+ 8/9
Osteopenia	Na	+	+	+	+	+	+	+	+
Fractures						+			
NEUROMUSCULAR									
Muscle hypotonia	+	+	+	+	+	+	+	+	+
Muscle atrophy	+	+	+	+	+	+	+	+	+
Poor head control in infancy	+	+		+		+	+	na	na

TABLE I. (Continued)

	P1 Family A Present case + 30 mth	P2 Family B Baumann et al. [2012] + 30 mth	P3 Family B Baumann et al. [2012] + 30 mth	P4 Family C Baumann et al. [2012] + 48 mth	P5 Family D Baumann et al. [2012] + 24 mth	P6 Family D Baumann et al. [2012] + 48 mth	P7 Family F Baumann et al. [2012]	P8 Family G Murray et al. [2014] + na	P9 Family H Aldeeri et al. [2014] + 48 mth
Walking independently/ Actual walking	myopathic gait, low autonomy	independently walking up to 1 km	independently low autonomy	myopathic gait wheelchair after walking 200 m	na	myopathic gait	wheelchair	myopathic gait	myopathic gait
Weakness improvement	+	+	+	+	+	+	+	+	na
NEUROLOGICAL									
Arachnoid cyst	+							na	na
Subdural hygroma		+						na	na
CARDIOVASCULAR									
Valvular abnormalities			na		+	+			
Patent ductus arteriosus			na						+
Aortic aneurysm/ Pseudoaneurysm (age, site)	+ 6 y, left hypogastric artery pseudoaneurysm		na					+ 41 y, left hypogastric artery	
Vascular dissection (age, site)	6 y, left hypogastric artery							+ celiac artery	
VISCERAL									
Bladder diverticulum	+	+	na	na	na	+	na	na	na
Neurogenic bladder	+		na	na	na	na	na	na	na
Rectal prolapse	+	na	na	na	na	na	na	na	na
OTOLOGIC									
Congenital, non-progressive hearing loss	+ mixed	+ sensorineural	+ sensorineural	+ sensorineural	+ conductive	+ sensorineural	+ sensorineural	+ sensorineural	na
Recurrent otitis	+	na	na	na	na	na	na	+	na

na, not available.

TABLE II. Biochemical and Instrumental Findings of the *FKBP14*-Related EDS Patients

	P1 Family A Present case	P2 Family B Baumann et al. [2012]	P3 Family B Baumann et al. [2012]	P4 Family C Baumann et al. [2012]	P5 Family D Baumann et al. [2012]	P6 Family E Baumann et al. [2012]	P7 Family F Baumann et al. [2012]	P8 Family G Murray et al. [2014]	P9 Family H Aldeeri et al. [2014]
Sex/Age	M/8	M/16	F/48	F/11	F/16	M/11	F/3	M/42	M/3
LABORATORY									
Creatin kinase	Normal	Normal	Slightly elevated	Normal	Normal	Slightly elevated	Normal	na	na
Urinary crosslinks	Normal	Normal	Normal	Normal	Normal	Normal	Normal	na	na
NEUROMUSCOLAR EVALUATION									
Nerve conduction	Normal	Normal	Normal	Normal	Normal	Normal	Normal	na	na
Electromyography age and results	1 mth, Normal	3 mth, Normal 15 y, Myopathic	6 y, Normal 30 y, Myopathic	4 mth, Normal 2 y, Normal	1 y, Myopathic	na	na	na	3 y, Myopathic
Muscle CT/MRI age and results	7 mth Normal	15 y Normal	na	na	12 y signal abnormalities in rectus femoris, vastus lateralis, and soleus	12 y signal abnormalities in rectus femoris, vastus lateralis, medial head of gastrocnemius, soleus, paraspinal	na	na	na
Muscle biopsy age, site and results	2 y, quadriceps, chronic muscle suffering compatible with congenital myopathy; EM: variability of myofibrillar diameter, fiber hypotrophy, roundish fiber microgranulation with nemaline rods, increased endomysial connective tissue intermyofibrillar alteration	2 y, quadriceps, Irregular oxidative enzymes; EM: focal myofibrillar rearrangement	2 y, quadriceps, Marked fiber atrophy; 4 y, na, marked atrophy, fatty tissue proliferation; 7 y, anterior tibial, myopathic fatty tissue proliferation; 30 y paraspinal, mildly myopathic atrophic fibers	4 mth, quadriceps, mildly myopathic; 4 y paraspinal, areas with fiber atrohy, slightly increased intrafusal fat; 6 y paraspinal, areas with central activity defects of oxidative enzymes; EM: focal myofibrillar rearrangement	1 y, quadriceps, mildly myopathic; 6 y, na, myopathic; 12 y dorsal myopathic with increased variation of fiber diameter; EM: sarcomeres bifurcation, small zone of Z-band streaming and disorganized myofibrils	1 y, quadriceps, myopathic	1 y, quadriceps, mildly myopathic	na	na
Brain MRI age and results	1 y Normal	na	na	na	na	9 y Mild white matter atrophy	na	36y, Normal 41 y, mild/moderate volume loss minimal periventricular and subcortical white matter hypersynthesis	na
CARDIOVASCULAR EVALUATION									
Echocardiogram	7 y Normal	13 y Normal	na	na Normal	13 y Tricuspid valve insufficiency	na	na	41y Normal	na

TABLE II. [*Continued*]

	P1 Family A Present case	P2 Family B Baumann et al. [2012]	P3 Family B Baumann et al. [2012]	P4 Family C Baumann et al. [2012]	P5 Family D Baumann et al. [2012]	P6 Family E Baumann et al. [2012]	P7 Family F Baumann et al. [2012]	P8 Family G Murray et al. [2014]	P9 Family H Aldeeri et al. [2014]
Carotid US doppler	na	na	na	na	na	na	na	36 y Normal	3 y Patent ductus arteriosus
Thoraco-abdominal MRA age and results	7 y Normal, regular embolization of left hypogastric artery	na	na	na	na	na	na	na	na
Spirometry	na	na	na	na	na	na	na	41 y Obstructive/restrictive lung disease	na
Flexion extension X-rays of cervical spine	6 y Atlantoaxial instability with enlarged atlanto-epistropheal distance in flexion	na	na	na	na	na	na	na	na

OTHERS

na, not available.

within the normal range (5/7) and electromyographic pattern can vary with age (Table II).

In addition to these hallmarks, *FKBP-14*-related EDS patients show a variable constellation of signs due to connective tissue impairment affecting ocular, mucocutaneous, skeletal, nervous central, and cardiovascular systems (Table I). The cardiovascular risk in *FKBP14*-related EDS is not well defined (Table I). Vascular complications are described in P8 (Table I), who presented a celiac artery pseudoaneurysm rupture at the age of 41, and in the older sister of P3 (Table I), likely affected but without molecular confirmation, who died due to unspecified aortic rupture at age 12 years. Celiac artery pseudoaneurysm rupture was observed in our patient at age 6 (Fig. 1). Atlantoaxial instability is reported here for the first time, the other patients presented uncomplicated joint hypermobility without recurrent dislocations/sprains or chronic pain (mean value of Beighton score 7/9) (Table I). Facial dysmorphisms are not always described and a facial "gestalt" is not recognizable, some patients had epicanthal folds (3/3), micrognathia (3/4), hypotelorism (1), square nasal root (1), or long-narrow face (1) (Table I). Height is generally within the normal range, but at lower level (10th–25th centile in 4 of 8), two patients had short stature (lower than third centile) (Table I). Tissue fragility in *FKBP14*-related EDS may lead to large bladder diverticulum (Fig. 1) or rectal prolapse (present case).

In conclusion, our report supports many of the clinical data available in literature for *FKBP14*-related EDS, confirming the variability observed for the cardinal features. In addition, this report describes a potentially life-threatening vascular complication in early pediatric age and atlantoaxial instability, suggesting the need for *FKBP14*-related EDS patients of tailored follow-up that includes cardiovascular monitoring, that is, cerebral, thoracic and abdominal MRA, and cervical dynamic radiograph. Further studies are needed to better delineate the phenotype of *FKBP14*-related EDS.

ACKNOWLEDGMENTS

REFERENCES

Aldeeri AA, Alazami AM, Hijazi H, Alzahrani F, Alkuraya FS. 2014. Excessive redundant umbilical skin as a potential early clinical feature of Morquio Syndrome and *FKBP14*-related Ehlers–Danlos syndrome. Clin Genet 86:469–472.

Baumann M, Giunta C, Krabichler B, Rüschendorf F, Zoppi N, Colombi M, Bittner RE, Quijano-Roy S, Muntoni F, Cirak S, Schreiber G, Zou Y, Hu Y, Romero NB, Carlier RY, Amberger A, Deutschmann A, Straub V, Rohrbach M, Steinmann B, Rostásy K, Karall D, Bönnemann CG, Zschocke J, Fauth C. 2012. Mutations in *FKBP14* cause a variant of Ehlers–Danlos syndrome with progressive kyphoscoliosis, myopathy, and hearing loss. Am J Hum Genet 90:201–216.

Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. 1998. Ehlers–Danlos syndromes: Revised nosology, villefranche. Am J Med Genet 77:31–37.

Colombi M, Dordoni C, Chiarelli N, Ritelli M. 2015. Differential diagnosis and diagnostic flow chart of joint hypermobility

syndrome/Ehlers–Danlos syndrome hypermobility type compared to other heritable connective tissue disorders. Am J Med Genet C Semin Med Genet 169C:6–22.

Galat A. 2003. Peptidylprolyl cis/trans isomerases (immunophilins): Biological diversity-targets-functions. Curr Top Med Chem 3:1315–1347.

Murray ML, Yang M, Fauth C, Byers PH. 2014. *FKBP14*-related Ehlers–Danlos syndrome: Expansion of the phenotype to include vascular complication. Am J Hum Genet 164:1750–1755.

Rohrbach M, Vandersteen A, Yiş U, Serdaroglu G, Ataman E, Chopra M, Garcia S, Jones K, Kariminejad A, Kraenzlin M, Marcelis C, Baumgartner M, Giunta C. 2011. Phenotypic variability of the kyphoscoliotic type of Ehlers–Danlos syndrome (EDS VIA): Clinical, molecular, and biochemical delineation. Orphanet J Rare Dis 23:6–46.

Steinmann B, Royce PM, Superti-Furga A. 2002. The Ehlers–Danlos syndrome. In: Royce PM, Steinmann B, editors. Connection tissue and its heritable disorders, 2nd edition. New York: Wyley-Liss. pp 431–523.