

## FKBP14 kyphoscoliotic Ehlers Danlos syndrome in adolescent patient: the first Colombian report

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### ABSTRACT

Ehlers-Danlos syndrome (EDS) is a group of clinically and genetically heterogeneous inherited connective tissue disorders, characterized by skin hyperextensibility, poor wound healing, joint hypermobility and tissue friability. Since 1997 a new spectrum of novel rare EDS-variants has been described, among which is included the EDS kyphoscoliotic type, characterized by severe muscular hypotonia at birth, severe progressive kyphoscoliosis, osteopenia, fragile eyeballs and vascular fragility. This EDS variant is caused by mutations in the *PLOD1* gene; however, a rare recessive variant that compromises the *FKBP14* gene has been reported, with additional clinical findings that includes gross motor developmental delay, myopathy, hearing impairment and a normal ratio of lysyl pyridinoline to hydroxylysyl pyridinoline in urine. We report the first Colombian patient with a *FKBP14* c.362dupC mutation, with clinical features that include generalized hypotonia, delayed gross motor milestones, hearing loss, early-onset progressive kyphoscoliosis, joint hypermobility and foot deformities.

**Key words:** Ehlers Danlos syndrome, spinal curvature, molecular pathology.

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### INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a group of clinically and genetically heterogeneous inherited connective tissue disorders, characterized by skin hyperextensibility, poor wound healing, joint hypermobility and tissue friability.<sup>1-3</sup> Six EDS subtypes are recognized in the Villefranche nosology;<sup>1</sup> however, since 1997 a new spectrum of novel rare EDS-variants have been described.<sup>2,4</sup>

Among these subtypes of EDS is the kyphoscoliotic type (MIM #225400), previously known as EDS VIA, which is characterized by severe muscular hypotonia at birth, joint hypermobility, luxations, severe progressive kyphoscoliosis, severe skin hyperelasticity, marfanoid habitus, osteopenia, fragile eyeballs associated with ocular globe rupture and occasionally vascular fragility.<sup>1</sup> This EDS variant is caused by deficiencies of collagen-modifying enzyme procollagen-lysine 2-oxoglutarate 5-dioxygenase 1 (*PLOD1*), produced by a homozygous or compound heterozygous mutation of *PLOD1* alleles.<sup>5</sup>

In 2012, six affected individuals with a rare recessive variant of kyphoscoliotic EDS whose clinical characteristics additionally included gross motor developmental delays; myopathy (confirmed by muscle MRI, histology and electron microscopy); hearing impairment (predominantly sensorineural), and a normal ratio of lysyl pyridinoline to hydroxylysyl pyridinoline in urine were reported.<sup>6</sup> A homozygous frameshift mutation was identified as the causative factor. This mutation produces a translational frameshift and a premature stop codon in *FKBP14*.<sup>6</sup> This subtype of EDS is currently called *FKBP14*-kyphoscoliotic EDS (MIM #614557) by the 2017 International Nosology of EDS.<sup>6,7</sup>

The present work reports the first case of a Colombian patient with molecular diagnosis of *FKBP14*-kyphoscoliotic EDS, utilizing next generation sequencing techniques which revealed a previously reported homozygous mutation in *FKBP14* gene: c.362dupC (p.glu122Argfs\*7).

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## CASE REPORT

We report the case of a 17-year-old girl of mixed race ancestry, originally from the southwest of Colombia. The patient was the product of the first pregnancy of consanguineous first grade cousins. Both parents reported no significant past medical history. During pregnancy, her mother experienced severe preeclampsia, and underwent a caesarean section at 34 weeks of gestation. At birth, the patient's weight was of 1900 gr (29th percentile) and 42 cm of height (23rd percentile). During the newborn physical assessment, generalized hypotonia, congenital bilateral hip dislocation and a neonatal gastric perforation were noted; which required management in the intensive care unit for two months. Orotracheal intubation was required during the first month of life.

Further assessment during this period revealed feeding difficulties, hiatal hernia and symptoms of gastroesophageal reflux (findings associated with her underlying pathology). Later, during early childhood, the patient exhibited delayed psychomotor development, sitting at 2 years of age, crawling at 3 years and ambulating at 5 years. Due to hip and ankle instability she required the use of leg braces until 5 years of age. Progressive kyphoscoliosis was noticed at 2 years of age, requiring surgical interventions at ages 10 and 15. Other findings included pectum excavatum and ankle luxation which were treated at age 15 (see Figure 1) and moderate left-sided sensorineural hearing loss, diagnosed at age 16.

Our patient underwent initial outpatient genetic consultation at 15 years of age. During the physical assessment it was evidenced: weight of 39.2 kg (<1st percentile), height of 1.36 m (<1st percentile), generalized muscle hypotonia, myopathic gait, mid-facial hypoplasia, light blue sclera, long philtrum, micrognathia and progressive severe scoliosis (see Figure 2). Additional findings included severe shoulder, finger, wrist, ankle and toe joint hypermobility according to Beighton score (9/9);<sup>8</sup> pectus excavatum, general xerosis, wrinkled skin on her palms and soles (see Figure 3), easy bruising, multiple isolated comedones and hypertrophic scarring, particularly on her back due to previous surgical interventions (see Figure 4).

Complementary studies included transthoracic echocardiogram, visual screening, cerebral magnetic resonance angiography and cerebral and paranasal computed tomography, all of which were within normal parameters. Spirometry revealed a restrictive lung disease pattern. Next-generation sequencing panel for Ehlers-Danlos syndrome reported a homozygous pathogenic variation of the *FKBP14* gene, presenting an insertion of one cytosine residue within a 5C-nucleotide repeat in exon 3 (c.362dup). This produced a translational frameshift and a premature stop codon.

Parents received genetic counseling, while preventive follow-up for complications associated with the EDS syndrome was decided to be performed with the patient, among which are

FIGURE 1. 3D computed tomography reconstruction of thoracolumbar vertebrae

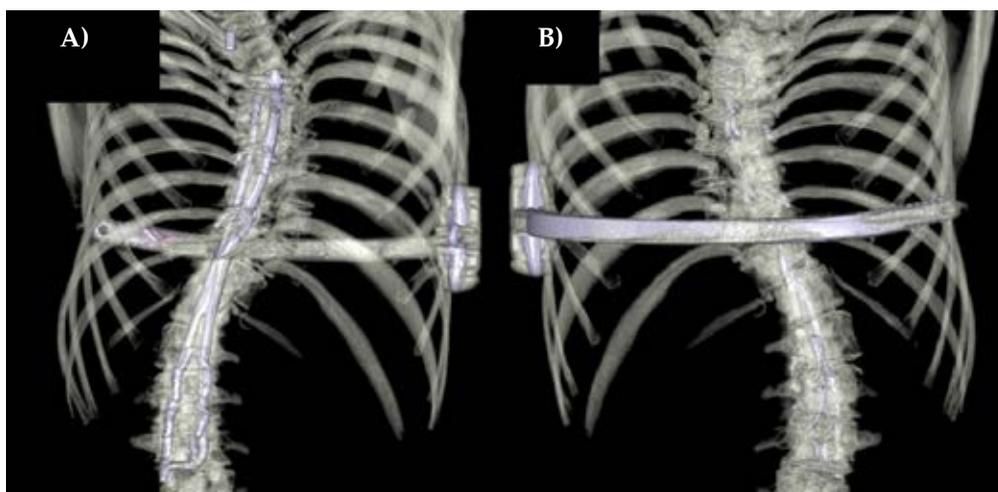


Image of right dorsal scoliosis with left lumbar compensatory curve. Osteosynthesis material is observed with fixation rods from T5 to L3, and osteosynthesis material at sternal level for correction of pectum excavatum (Nuss technique).

A) Posterior view, B) Anterior view.

FIGURE 2. Anteroposterior full-length spinal X-Ray imaging



Image taken after surgical correction of scoliosis. Notice the cervico-dorsal scoliotic curve with left convexity. Post-surgical changes with rod-type osteosynthesis material and transpedicular screws in the vertebral bodies T2, T3 and T4 in the upper segment; and L1 to L5 and sacral alierons in the lower segment.

FIGURE 3. Palms of the hands with wrinkled skin and criss-cross dermatoglyphic patterns



included routine assessment for inguinal hernia detection, ophthalmological follow-up for management and early diagnosis of glaucoma and/or retinal detachment and monitoring by neumology service due to the presence of pulmonary restrictive pattern in a patient surgically treated for kyphoscoliosis. No echocardiographic follow-up was performed during the last control, due to previous study within normal parameters; additionally, the patient continues observation by the orthopaedic surgery service.

## DISCUSSION

We report the first case of a Colombian patient with kyphoescoliotic EDS. This subtype of EDS has been generally associated with homozygous mutations in the *PLOD1* gene, who encodes the lysyl hydroxylase enzyme; however, since its first description in 2012,<sup>6</sup> some cases with homozygous or compound heterozygous mutation in *FKBP14* have been reported in the literature for this form of Ehlers Danlos.<sup>9-13</sup>

Aldeeri et al. in 2014, reported the case of a 3 year-old boy with a milder phenotype and a novel homozygous splice-site mutation in *FKBP14*. Due to the redundant umbilical skin found in this patient, they propose this sign as a potential early clinical feature for the diagnosis

FIGURE 4. Back of the patient with multiple isolated comedones and hypertrophic scarring due to previous surgical interventions



of this condition.<sup>9</sup> Murray et. al, during the same year, reported the case of a 42 year-old American man born to nonconsanguineous parents, with a phenotype that included severe kyphoscoliosis, restrictive lung disease, short stature, mild hearing loss, decreased muscle mass and vascular findings that included a dissection of the celiac artery at age 41 and the complete occlusion of the superior mesenteric artery with compensatory flow through an enlarged and tortuous inferior mesenteric artery.<sup>10</sup>

Dordoni et al., in 2016, described the case of an 8 year-old Italian male with a compound heterozygous for a recurrent and a novel *FKBP14* mutation, with a phenotype similar to that described in previous patients. This patient exhibited a pseudoaneurysm in the hypogastric artery that ruptured at 6 years of age and was safely treated with an endovascular procedure.<sup>11</sup> In 2017, Bursztejn et. al characterized the cutaneous phenotype of an adolescent female patient with features that included multiple isolated comedones and molluscoid pseudotumours. Pseudotumours have been described as a distinctive finding in patients with classic EDS, but are rarely reported in other variants.<sup>12</sup> Lately, Giunta et al., reported on 17 additional individuals from 15 unrelated families diagnosed with kyphoescoliotic EDS, representing the largest cohort of *FKBP14*-kyphoescoliotic EDS.<sup>13</sup>

Recently, the criteria for kyphoescoliotic EDS caused by pathogenic variants in either *PLOD1* or *FKBP14* have been revised. Presently, the major criteria includes (I) congenital muscle hypotonia, (II) congenital or early onset kyphoscoliosis (progressive or non-progressive) and (III) generalized joint hypermobility with dislocations/subluxations. Skin hyperextensibility and rupture/aneurysm of a medium size artery are included in the minor criteria.<sup>7</sup> D'hondt et al., reviewed the vascular complications of vascular phenotypes, in nonvascular subtypes of EDS, and found that arterial dissections are most frequently reported in *FKBP14*-kyphoescoliotic EDS.<sup>14</sup>

In the present report, our patient fulfilled all three major criteria for kyphoescoliotic EDS. At present, no vascular complications have been detected; however, due to the different reports found in the literature, we believe that screenings for vascular anomalies, in addition to dilatation of the aortic root, are justified. Despite this condition being classified as a non-vascular type of EDS, the risk of arterial dissections and aneurysms

supports a vascular surveillance approach until a better-characterized *FKBP14*-kyphoescoliotic EDS vascular phenotype indicates otherwise.

The *FKBP14* c.362dupC mutation was previously reported in the literature in patients of Italian, French, English, German and Turkish descent.<sup>6, 10</sup> This report contributes to the possibility that the recurrent c.362dupC mutation implicates small insertions or deletions in homopolymer regions, due DNA slippage, as previously discussed by Murray et al.<sup>10</sup> Further research and detailed phenotypical and molecular description of new unreported cases, will allow for a better understanding of the pathogenesis and underlying mechanisms by which mutations in this gene occur. ■

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