OXFORD

*Oxford Medical Case Reports*, 2023, **1**, 44–47
https://doi.org/10.1093/omcr/omac107
Case Report

# A case of Ehlers–Danlos syndrome presenting as short stature: a novel mutation in *SLC39A13* causing spondylodysplastic Ehlers–Danlos syndrome

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## Abstract

Ehlers–Danlos syndrome (EDS) is a heritable connective tissue disorder characterized by a varying degree of skin hyperextensibility and joint hypermobility. EDS is classified into 13 subtypes according to the most recent classification. These subtypes are clinically and genetically heterogenous. The spondylodysplastic subvariety of EDS (spEDS) is caused by homozygous mutations in B4GALT7, B3GALT6 and SLC39A13. To date, 13 individuals with molecularly diagnosed SLC39A13-related spEDS have been reported. The spEDS caused by biallelic pathogenic SLC39A13 variants are characterized by short stature, protuberant eyes with bluish sclera, finely wrinkled palms, hypermobile joints, hyperextensible skin and characteristic radiological findings. Herein, we report a case of 7-year-old-female child with spEDS associated with novel homozygous (pathogenic/likely pathogenic) missense variation of the SLC39A13 gene.

## INTRODUCTION

Ehlers–Danlos syndrome (EDS) is classified into 13 subtypes according to the 2017 international classification. The spondylodysplastic subvariety of EDS (spEDS) is caused homozygous mutations in *B4GALT7*, *B3GALT6* and *SLC39A13*. We report a case of 7-year-old-female child with spEDS associated with novel gene missense mutation in exon 6 of the *SLC39A13* gene. She presented with the classical features of spEDS.

## CASE REPORT

We report a case of 7-year-old-female child diagnosed with spEDS. She was second birth by order, born of third degree consanguineous marriage at full-term gestation by lower segment caesarean section in view of breech presentation. The antenatal course was uneventful. Her birth weight and length were normal. Megalocornea with a horizontal corneal diameter of 13 mm and vertical corneal diameter of 12.5 mm (normal horizontal corneal diameter range is 11.5–12 mm and vertical corneal diameter range is 10.5–11 mm; [1]) and blue sclerae (Fig. 2) were noticed at birth, however the neonatal period was uneventful. She was constantly under surveillance for vision affection, but had no visual impairment on follow-up. On routine developmental surveillance and screening at 9 months of age, child was found to have hypotonia, with gross motor delay (DQ—55), with normal deep tendon reflexes and no postural abnormality. Neurological examination did not reveal any abnormal findings apart from hypotonia. Other domains of development were satisfactory. Magnetic resonance imaging (MRI) brain done for evaluation of hypotonia and motor delay at 10 months revealed abnormal T2 and fluid attenuated inversion recovery (FLAIR) hyperintense signals noted involving the bilateral peritrigonal and frontal white matter and bilateral centrum semi-ovale, showing no diffusion restriction or foci of blooming, features suggestive of metachromatic leukodystrophy. Occupational therapy and physiotherapy were instituted for hypotonia. Child was followed up and on regular development surveillance, gradual improvement in motor milestones was noted. After an interval of 3 years

**Figure 1.** Short stature, height 105 cm (< −2 SD) at 7 years age.

**Received:** February 22, 2022. **Revised:** July 5, 2022. **Accepted:** August 21, 2022

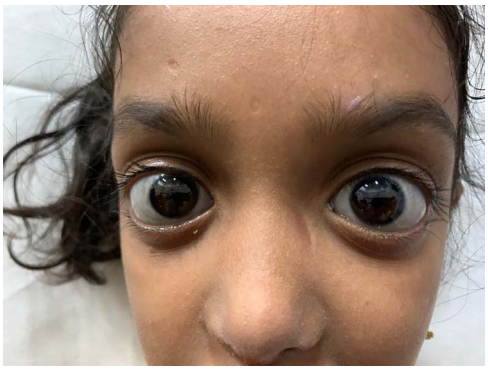

**Figure 2.** Protuberant eyes with megalocornea and bluish sclera.

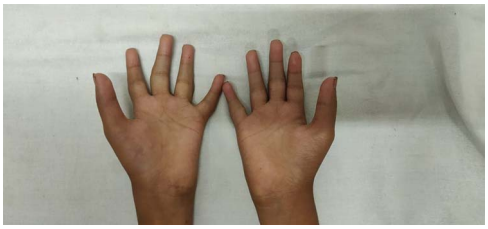

**Figure 3.** Finely wrinkled palms.

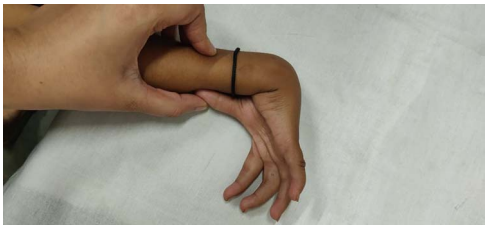

**Figure 4.** Hyperextensible joint.

of lost to follow up, she presented at 7 years with complaints of gait abnormality, hypermobile joints and short stature. The motor delay noted in infancy was not evident now and she had normal development on assessment scales. On physical examination, child had proportionate short stature with height of 105 cm (−2 standard deviation [SD] to −3 SD) (Fig. 1), with a mid-parental height of 156.5 cm (between 0 and −2SD) and weight of 15.02 kg (−2 SD to −3 SD; [2]). She was found to mild hypotonia leading to waddling gait. The rest of the neurological examination was normal. The physical examination at the time was also significant for hypermobile joints (Fig. 4) (Beighton score—8), hyperextensible skin (skin could be stretched to 2.8 cm on volar surface of forearm and to 1.5 cm on volar surface of palm), finely wrinkled palms (Fig. 3) and pes planus. There was no evidence of scars or ecchymosis. Megalocornea, which was noticed at birth had similar dimensions at this age and was of non-progressive variant and did not cause any visual impairment. No other family member demonstrated similar phenotype. When evaluated for short stature, the systemic screening and thyroid function tests were done, which was normal. Her bone age was of 6 years and height age was of 4 years age at age of 7 years. She was evaluated for short stature-systemic screening including complete blood count, basic metabolic profile, liver and renal function tests, urine analysis, stool analysis and celiac screening were done, which were normal. Karyotype was 46XX. The findings of neuroimaging done at 7 years of age were similar to MRI done at 10 months of age with no progression of white matter changes (Fig. 7).

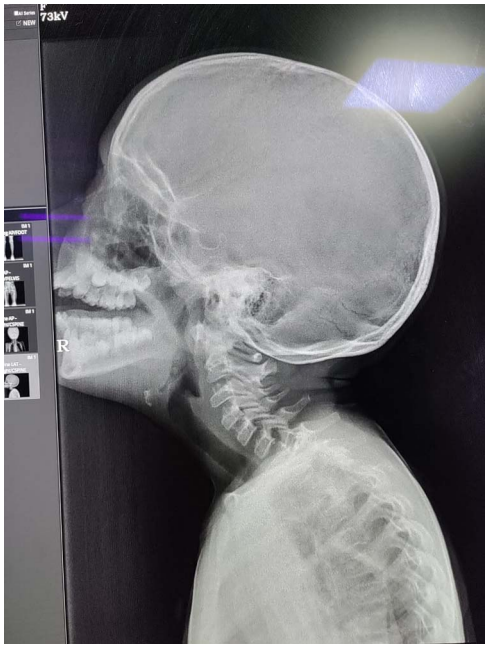


**Figure 5.** Cervical spine with platyspondyly.

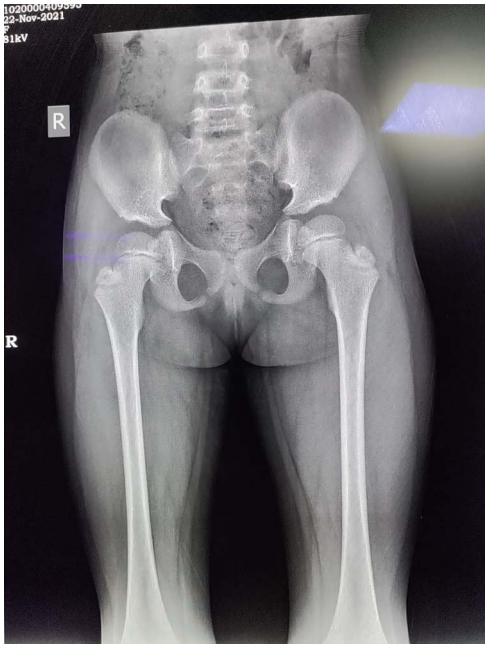


**Figure 6.** X-ray pelvis with small ilia.

In view of consortium of findings of short stature, skin and eye involvement, and neurological involvement, next generation sequencing by whole exome sequencing analysis was done. A homozygous missense variation c.682G > A in exon 6 of the *SLC39A13* gene (chr11:g.47413633G > A) that results in the amino acid substitution of Asparagine for Aspartic acid at codon 228(p.Asp228Asn) was found. The in silico predictions of this variant were predicted to be damaging by sorting intolerant from tolerant (SIFT), likelihood ratio rest (LRT) and Mutation Taster 2. Based on literature review p.Asp228Asn variant of *SLC39A13* gene has not been reported in any research publication or case study or disease databases (ClinVar/Human Gene Mutation Database/Leiden Open Variation Database). Another homozygous

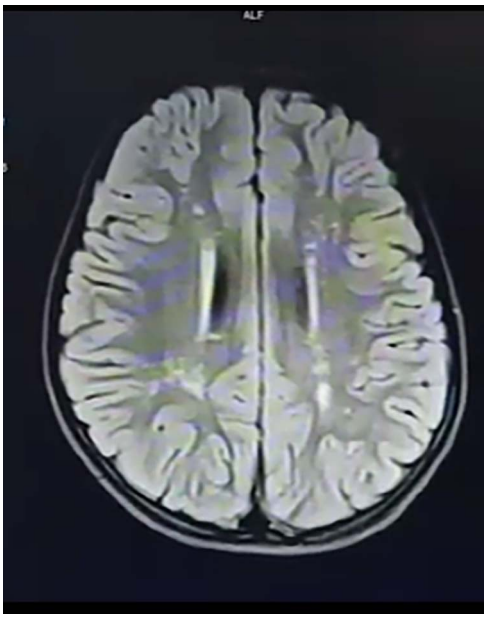


**Figure 7.** MRI imaging of the child showing metachromatic leukodystrophy.

variant of uncertain significance was found in CEP57 gene in exon 2(c.154C > T), which is known to cause mosaic variegated aneuploidy syndrome 2, not correlating with our phenotype.

EDS spondylodysplastic type 3 (OMIM#612350) is caused by homozygous mutations in the *SLC39A13* gene (OMIM∗608735). After establishing the genetic basis of our diagnosis, detailed skeletal survey was done, which was suggestive of small ilia, short and wide femoral neck and platyspondyly. 2D ECHO study was normal.

Our patient fulfils two major criteria (short stature and muscle hypotonia), three minor criteria (skin changes, pes planus and delayed motor development) for the diagnosis of spEDS and all minor criteria for SLC39A13 gene i.e. protuberant eyes with bluish sclerae, hands with finely wrinkled palms, atrophy of the thenar muscles, and tapering fingers, hypermobility of distal joints and characteristic radiologic findings (Figs. 5, 6, 7). Hereby we report a novel gene missense mutation in exon 6 of the *SLC39A13* gene leading to EDS, spondylodysplastic type 3 (EDSSPD3). She is being regularly screened and evaluated for development milestones, vision and growth.

## DISCUSSION

The EDS are a group of connective tissue disorders that are clinically and genetically heterogeneous, with all subtypes have hallmark features of joint hypermobility, skin hyper extensibility and fragile connective tissues [3]. We report a case with genetically confirmed spondylodysplastic EDS (spEDS) associated with novel homozygous missense variation of the *SLC39A13* gene.

The EDS have been classified and re-classified in the light of additions of other subtypes on discovery of mutations in genes. Lately, the International consortium devised new classification in 2017, classifying EDS into 13 subtypes accounting for the fact that mutations have been identified in collagen genes as well as genes encoding collagen modifiers via new advent in molecular diagnosis [4].

The spondylodysplastic subvariety of EDS (previously called as progeroid type), first described in 2008 [5] requires fulfilment of major criteria, radiological abnormalities and general or gene-specific minor criteria for diagnosis. The spEDS subtype is inherited in an autosomal recessive pattern, and homozygous pathogenic mutations in *B4GALT7, B3GALT6* and *SLC39A13* have been identified as etiological genes. Although the former two genes regulate production of glycosoaminoglycans, *SLC39A13* regulates the intra-cytosolic influx of Zinc. Mutation in this gene thus leads to low cytosolic zinc concentrations, causing alteration of transforming growth factor beta (TGF$\beta$) and bone morphogenetic protein signalling. Though the pathogenesis of SLC39A13 mutation is not fully understood, it has been proposed that altered levels of intracellular growth factors leads to altered functioning of skeletal muscle and cardiac muscle tissue, which is responsible for the characteristic phenotype. [6]. To date, 13 individuals with molecularly diagnosed *SLC39A13*-related spEDS have been reported [5, 7–9] and this is the first report from India to the best of our knowledge.

EDS group of disorders is not associated with short stature. However, unlike other subtypes of EDS, spEDS demonstrates a progressive growth retardation and compromised height potential, which is also a major criterion of diagnosis. Although *B3GALT6 and B4GALT7* mutations are associated with skeletal abnormalities and are classified as 'skeletal dysplasia', *SLC39A13* causes growth failure which is not associated with skeletal abnormalities and has proportionate body segment ratios. Growth faltering and compromised adult height has been consistently reported feature of *SLC39A13* deficiency, though the pathogenesis of this statural phenotype is poorly understood.

The other major clinical criterion—hypotonia, not associated with myopathy has been consistently described associated with *SLC39A13* in early years of life leading to delayed motor development. The subtle manifestations of this hypotonia are thenar/hypothenar atrophy, weakness of hands and waddling gait. However, recently a case describes associated myopathy features [8]. The hypotonia can be so profound to be diagnosed as myopathy initially. Other consistent ocular connective tissue manifestations are thin sclerae, imparting a blue hue and cornea deformities (megalocornea, myopia and keratoconus), mandating ophthalmological surveillance [10]. Dental features like dysplastic teeth and decreased number of permanent teeth are reported, however our patient is in the phase of mixed dentition currently. Vascular fragility is not a consistent feature of spEDS unlike other subtypes, and minor venous varicosities are reported. However, a report describes catastrophic intracerebral bleeding. The peculiar phenotype includes flat facial profile, hypertelorism, downward palpebral fissures, prominent eyes and small mouth. To conclude, spEDS being a connective tissue disorder, it mandates a multidisciplinary approach involving various subspecialists. Regular surveillance of vision and growth is required.

The diagnostic criteria are laid down for diagnosis of spEDS with the subcategories being major, minor and gene-specific. Short stature is a feature which differentiated sp-EDS from all other varieties of EDS. SpEDS is an autosomal recessive disorder which can be diagnosed by next generation sequencing techniques. The establishment of genetic basis helps to counsel the family regarding the further course of life and progeny, undermining its importance. Our findings of association of leukodystrophy with *SLC39A13* related spEDS expands our knowledge of the associations of this subvariety as well as spectrum of clinical presentation.

## CONCLUSION

- What is known is the characteristic clinical and etiological profile of SLC39A3 related EDS. The features in our patient comply with previously reported patients, namely hypotonia, short stature, characteristic facies with connective tissue weakness and ocular manifestations.
- What is new is discovery of association of white matter changes in form of metachromatic leukodystrophy, though non-progressive, but needs follow-up as a final outcome.

## ACKNOWLEDGEMENTS

We thank TNMC and BYL Nair Hospital for its constant support.

## FUNDING

There were no sources of funding.

## ETHICAL APPROVAL

No ethical approval required.

## CONSENT

Consent of parents taken on appropriate form provided by the institute.

## GUARANTOR

Dr Harpreet Kaur, MD, Senior resident, Department of Paediatrics, TNMC and BYL Nair Hospital.

## CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

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