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CASE REPORT

# Spondylocostal dysostosis 1 – case report and literature review

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## ABSTRACT

Spondylocostal dysostosis (SCD) type 1 (also known as Jarcho-Levin syndrome) is a rare hereditary skeletal disorder. The mutation of the *DLL3* gene leads to the Notch signalling pathway disorder, resulting in somitogenesis errors and numerous deformations within the spine and ribs. This article presents the diagnostic process of a 3-year-old girl suspected of SCD type 1. Performing Sanger method sequencing of the *DLL3* gene and computed tomography imaging with 3D reconstruction allowed us to recognize the condition and confirm its molecular basis. We also performed array-based comparative genomic hybridization and detected an incidental finding – a terminal duplication in chromosome X. The whole clinical approach and special investigations may help clinicians recognise the disease and genetic counselling.

KEY WORDS:

**short stature, Jarcho-Levin syndrome (JLS), spondylocostal dysostosis (SCD), vertebral deformity.**

## INTRODUCTION

Spondylocostal dysostosis (SCD) type 1, also called Jarcho-Levin syndrome, is a rare disorder inherited in an autosomal recessive fashion, caused by mutation of the *DLL3* gene on chromosome 19q13.2 [1]. The disease leads to disorders of axial skeleton development and is characterized, among others, by deformation of the vertebrae and ribs leading to spine and chest shortening, short stature, brachycephaly, prominent forehead and bridge of the nose, and a convex abdomen and hernia [2, 3]. To date, very few cases of such disease have been reported in the literature [4, 5].

This article presents a diagnostic process in a 3-year-old girl suspected of SCD.

## CLINICAL PRESENTATION

A 3-year-old girl was admitted to the ward to diagnose a congenital malformation syndrome of the spine and skeletal system accompanied by hearing loss.

There were no abnormalities in prenatal ultrasound examinations. The girl was born on time, through normal vaginal delivery, with a birth weight of 3150 g and a body length of 49 cm. It was the second pregnancy and the second delivery. Since birth, a disproportion of the child's body was observed: a short torso, and a prominent abdomen and occiput. The girl's development seemed normal at first because she was sitting at 6 months of age and at 12 months she started to walk. The gait was unstable. Spinal scoliosis and increased abdominal circumference were

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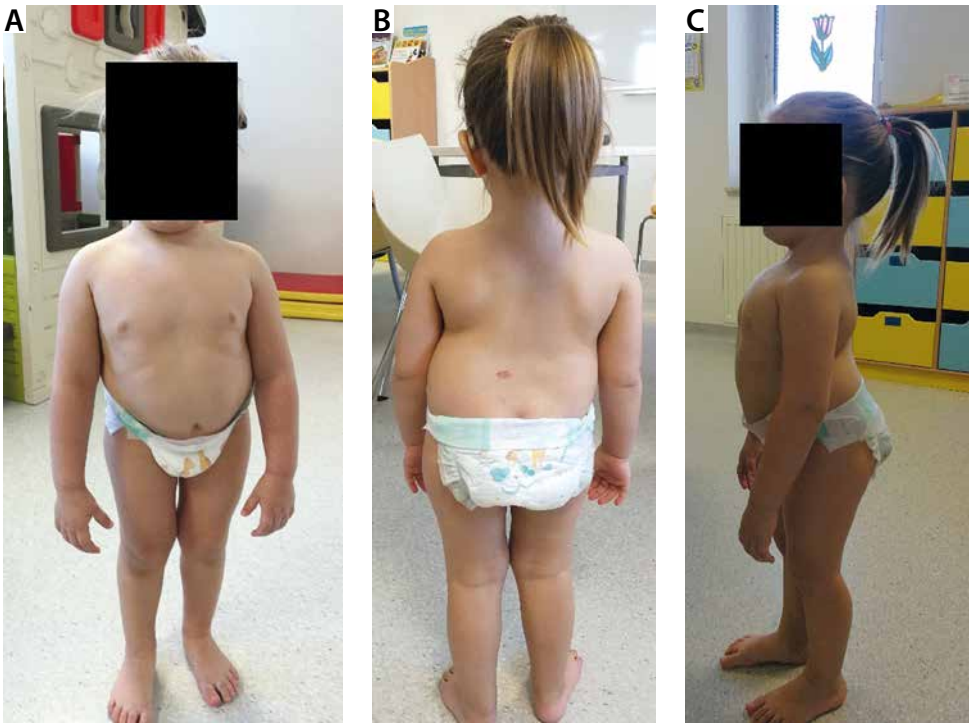


**FIGURE 1.** Photo of the patient from the front, back, and side – excessive curvature of the spine, shortened trunk and neck, deformed chest, deepened spinal lordosis, prominent abdomen, and limbs of the correct length giving the appearance of being elongated

also noticeable. Anomalies of the ribs and reduced curvature of the spine were recognized by the consulting orthopaedic surgeons. The girl was also under the care of an otolaryngologist due to hearing loss, a urologist due to a slight broadening of the calico-pyelic system of the right kidney, and a cardiologist due to haemodynamically insignificant patent foramen ovale.

During the physical examination attention was drawn to her prominent forehead, excessive curvature of the spine, shortened trunk and neck, deformed chest, deepened spinal lordosis, prominent abdomen, and limbs of the correct length giving the appearance of being elongated (Figure 1).

Radiological examination of the spine in an upright position (X-ray image in AP projection) showed a right-sided curvature of the thoracic and lumbar spine – Cobb angle (measured according to Exhibeon 2.7.12 application) of approx. 28°, which corresponds to grade II of Lippman-Cobb Scoliotic Curvature Classification; a left wing of ilium situated slightly higher than the right one, and numerous malformations of the skeletal system (8 ribs on the right side; 11 visible ribs on the left side, including rib VI and rib VII fused in their posterior segments; numerous defects in the development of the vertebrae such as semicircles, butterfly circles, and adhesions between individual vertebrae). Also, spina bifida in the lumbosacral segment was suspected. The bone age by Risser test was rated 0.

Computed tomography of the spine exposed numerous complex malformations. In the lumbosacral segment, semi-vertebrae and alternating bone blocks with a decreased number of vertebrae were dominant; 2 sacral foramina on the left side of the deformed sacrum and one on right were recognized; a bone block composed of posterior arches of L1 and L2 vertebrae on the left side; narrow non-closure of the posterior arches of most lumbar vertebrae and a broad non-closure of the sacral canal in the absence of signs of spinal canal stenosis. In the thoracic segment, semi-vertebrae and bone blocks with a decreased number of vertebrae with a subsequent reduction in the number of ribs were dominant; in most cases, asymmetrical blocks of posterior arches of the upper and middle thoracic spine and non-closure of the posterior arches of the lower thoracic spine were identified. The complete formation of 7 ribs and a partial formation of 2 (total 9) was exposed on the right side. There were 8 ribs developed completely and 2 partially (total 10) on the left side. During the test, dextroscoliosis of the thoracic spine was also revealed (Figure 2).

Spondylocostal dysostosis was suspected based on the clinical picture and the results of the radiological examination of the patient.

## GENETIC DIAGNOSTICS

Further tests were executed during the diagnostics: array comparative genomic hybridization to microarray was tested using probes with a resolution of 8 × 60 k, SurePrint G3 CGH ISCA v2 (Agilent) with a detection window of 0.10 Mb, filter of 5 probes, derivative log ratio spread < 0.3, which revealed interstitial duplication within the short arm of the X chromosome – arr[GRCh37/hg19] Xp 22.33 (492256_777847) × 3. This is an incidental finding, and it did not influence the clinical presentation. To

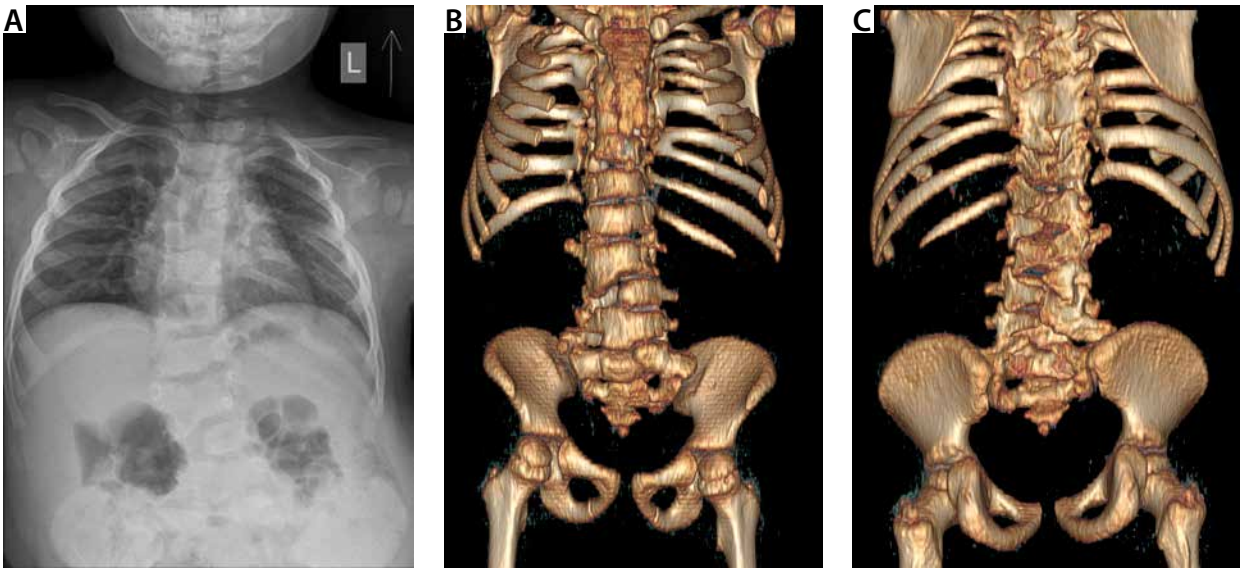


**FIGURE 2.** X-ray of the chest in the PA projection and 3D reconstruction of computed tomography – dextroscoliosis of the thoracic spine, numerous complex malformations of the spine, semi-vertebrae, and alternating bone blocks in the lumbosacral segment

confirm the molecular cause of the disease, we performed *DLL3* gene sequencing by Sanger method, which exposed mutation in exon 1 and 7 of this gene, NM_016941.3:c.2T > C and NM_016941.3:c.1125_1126insCGCTGC.

Based on the overall clinical picture and test results, SCD type I was diagnosed.

## DISCUSSION

The term dysostosis is used to refer to diseases associated with impaired bone development, in particular the ossification process, which leads to the abnormal skeletal structure. One of the best known of these is mandibulofacial dysostosis, or Treacher Collins syndrome [6]. Much rarer is SCD, characterized by disorders of vertebral segmentation and the coexistence of anomalies in the structure of the ribs, which leads to growth deficiency and shortening of the chest. In the general population, incorrect segmentation of the vertebrae, visible in the form of their fusion or unevenness, occurs relatively often – even in 1 in 1000 births [7]. However, most of these changes are not extensive, affect several vertebrae, and are only visible in the form of scoliosis of varying severity. In SCD, the changes are more severe and may even lead to respiratory disorders in the neonatal period [5].

Common features of SCD are multiple defects in vertebral segmentation with accompanying rib defects in the form of their incorrect positioning, fusion, and even reduction of their number. Before the era of genetic research, dysostosis, together with similar disorders of the ribs and vertebrae structure, were jointly referred to as Jarcho-Levin syndrome [8]. Due to the development of genetic and molecular diagnostics, 6 types of SCD have been identified, linking their aetiology to the transmission dysfunction of Notch transmembrane receptors during embryogenesis.

As a result of mesoderm segmentation, even metamers are formed on both sides of the embryonic midline. The metamers form ribs, vertebrae, intercostal discs, and paravertebral muscles. The process of somite creation takes place in cycles and occurs from front to back along the embryonic axis of the body. Somitogenesis is precisely controlled by the interaction of 2 molecular systems: the determination front and the segmentation clock. The determination front determines the spatial arrangement of mesoderm segments, while the segmentation clock works between the formation of new segments and the growth of existing ones. The basis of its action is the periodic expression of genes that oscillate in the mesoderm at intervals equal to the time needed to form a single pair of metamers. Both these systems are strictly regulated at the spatial and time level, among others by signalling molecules such as Notch, fibroblast growth factor, and Wnt, and their disruption leads to errors in embryogenesis.

The vertebrae are made of the anterior and posterior sclerotome halves; therefore, the disturbance of the segmentation pattern destabilizes the formation of normal vertebrae. The Notch signal is key in forming the boundaries of metamers and for the subsequent division of somites. To date, 6 genes that encode key Notch signalling proteins: *DLL3*, *MESP2*, *LFNG*, *HES7*, *TBX6*, and *RIPPLY2*, associated with 6 SCD subtypes, have been described. Mutations in these genes are recessive, except *TBX6*, which can spread to subsequent generations in a dominant or recessive fashion. Mutations in the *DLL3* gene are responsible for the most common of the SCD varieties – type I, in which scoliosis of fluctuating severity occurs, usually not requiring surgical stabilization of the spine [9].

The initial diagnosis of SCD is based on radiological studies, in which multiple defects of the vertebrae and ribs

are most often revealed. To confirm the diagnosis, as well as determine the type of SCD, genetic tests are performed. Sequencing of the *DLL3* gene by the Sanger method was performed, and 2 heterozygous mutations were revealed: in exon 1 c.2T > C (causing the loss of the initiation codon) and in exon 7: c.1125_1126insCGCTGC (the introduction of 2 additional amino acids in the protein – cysteine and arginine – between positions 380 and 381). The first above-mentioned variant has not been described in the literature yet, and the second one was also not frequently noted. Both of the variants have unknown significance. In addition, array comparative genomic hybridization to microarray revealed the interstitial duplication within the short arm of the X chromosome – arr[GRCh37/hg19] Xp 22.33 (492256_777847) × 3 – which includes the *SHOX* gene, mutations of which are associated with Léri-Weill dyschondrosteosis. However, chromosome variants are frequent in this area, and it is hard to assess the clinical significance of this duplication unequivocally.

In addition to the characteristic features of chest deformity, cases of co-occurrence of other malformations in children are also described in the literature. These include, among others, diaphragmatic hernia, occurring both on the left and right side of the body, containing the spleen or left lobe of the liver [10, 11]. Congenital hernias can lead to pulmonary hypoplasia and respiratory failure in the neonatal period, so when SCD is suspected, the possibility of this type of pathology should be considered.

Spondylocostal dysostosis is also associated with a meningeal hernia and some neural tube defects. Alatas *et al.* [12] analysed 28 cases of patients with SCD and central nervous system abnormalities. All patients had spina bifida, mostly with myelomeningocele. More than half of the subjects had also hydrocephalus. In addition, the authors described the occurrence of Chiari malformation, syringomyelia, spinal cord stenosis, and enlargement of the cerebellospinal reservoir (mega cisterna magna) [12]. Kansal *et al.* [13] described the case of a one-and-a-half-year-old child with SCD with diastematomyelia, which was diagnosed after the occurrence of weakness in the lower limbs that prevented the child from standing in the upright position [13]. The relatively high incidence of central nervous system defects in children with SCD indicates a possible need for imaging tests and consultation of an orthopaedic surgeon and neurosurgeon.

The main ailments reported in older patients are back pain and recurrent respiratory infections [14].

Due to the manner of inheritance, in each case of SCD, it is advisable to screen the parents for mutation, as well as for genetic counselling before possible subsequent pregnancies.

## CONCLUSIONS

In children with short stature, axial skeletal disorders, scoliosis, and hernias, it is worth remembering about rare genetic syndromes such as SCD. Radiological tests are very useful in the initial differentiation, but genetic testing is the most important for making an accurate diagnosis. Cytogenetic-molecular analysis can help to reveal a full picture of the disease, as well as direct further diagnosis and therapy. It will also make it easier for the family to make decisions about further procreation.

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## DISCLOSURE

The authors declare no conflict of interest.

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