CASE REPORT

JCRPE Journal of Clinical Research in Pediatric Endocrinology

DOI: 10.4274/jcrpe.galenos.2023.2023-7-1
J Clin Res Pediatr Endocrinol

Schwartz-Jampel Syndrome Type 1: Compound Heterozygosity of Two Novel Variants

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Cite this article as: Atmaca FG, Akgün Doğan Ö, Kutlubay B, Kırmızıbekmez H. Schwartz-Jampel syndrome type 1: compound heterozygosity of two novel variants. J Clin Res Pediatr Endocrinol. [Epub Ahead of Print]

What is already known on this topic?

Schwartz-Jampel syndrome (SJS) type 1 is characterized by myotonic myopathy, chondrodystrophy, short stature, facial and eye abnormalities. SJS type 1 develops due to variations in the *HSPG2* gene, which encodes the perlecan protein, one of the main proteoglycans of the basement membrane.

What this study adds?

Our patient had "two novel" heterozygot variants in *HSPG2* together with the clinical symptoms of the syndrome, demonstrating that the "compound heterozygosity" may cause the disease. In cases of myotonia with muscle stiffness, limitation of joint movement, especially squinting in the eyes and difficulty in opening the mouth with an accompanying short stature, SJS should definitely be considered. However, it may take years for them to become recognizable, as the clinical findings of our patient were subtle until the age of 3.5.

ABSTRACT

Schwartz-Jampel syndrome (SJS) type 1 (OMIM; #255800), a rare cause of skeletal dysplasia, is characterized by myotonic myopathy, chondrodystrophy, short stature, facial and eye abnormalities. SJS type 1 develops due to variations in the *HSPG2* gene which produces the "perlecan" molecule, one of the main proteoglycans of the basement membrane. A 6-year-old girl presented with short stature, a mask face, shrunken lips, narrow palpebral opening due to blepharospasm, stiffness of facial muscles, micrognathia, overlapping teeth, a short neck, and a bell-shaped thorax due to myotonic myopathy. She was diagnosed with SJS type 1 due to compound heterozygosity of two novel variations in the *HSPG2* gene. In patients with short stature and an accompanying myotonic myopathy SJS should be considered. Compound heterozygosity may cause typical clinical findings of SJS. In case of suspicion creatinine kinase levels can be measured, and the determination of myotonia may

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Received: 04.09.2023 **Accepted:** 28.12.2023 **Epub:** 12.01.2024

require evaluation with electromyography. Once the diagnosis is made, patients should be carefully monitored in terms of growth, neuromuscular disorders, joints problems and bone health.

Keywords: *HSPG2* gene, myotonia, short stature, skeletal dysplasia

Introduction

Schwartz-Jampel syndrome (SJS) type 1 (OMIM; #255800) is characterized by myotonic myopathy, chondrodystrophy, short stature, and facial and eye abnormalities (1,2). Due to clinical heterogeneity, SJS has been classified into three types. SJS type 1A is associated with moderate bone dysplasia, which is usually recognized in childhood. Type 1B may be present at birth and the clinical picture is more severe. SJS type 1 develops due to variations in the *HSPG2* gene, which encodes the perlecan protein, one of the main proteoglycans of the basement membrane. Perlecan regulates cellular processes including bone and cartilage formation, inflammation, and angiogenesis. It binds growth factors and cell membrane receptors, regulates intracellular signals, and plays a critical role in endochondral bone formation by promoting angiogenesis for cartilage matrix remodeling and formation of endochondral bone (2). Type 2, due to variations in the *LIFR* gene, is the most severe, rarest type with a very high mortality (3,4).

Almost all patients with SJS type 1 have short stature and dysmorphic features, including mask-like face, epicanthal folds, blepharospasm, ptosis and blepharophimosis, retrognathia, upturned nose, long philtrum, short neck, low ears, and high arched palate. The mask-like face and limited ability to open the mouth widely, which is more prominent when the patient is crying, are the major clues for clinical diagnosis. Other features may include toe walking, mild kyphosis, contractures in the elbow, spine, pelvis, metaphyseal deformities, lumbar lordosis, limitation of movement in large joints, hydrocephalus, and carpal tunnel syndrome. Complications such as myelopathy, recurrent infections, stridor, and mental retardation can also be present (5,6,7).

This presented case report describes two new variations in *HSPG2*, and will serve to remind colleagues of the importance of evaluating myotonia when investigating dysmorphic findings in children with short stature.

Case Report

A 6-year-old girl was referred to the pediatric endocrinology clinic for short stature. She also had a complaint of progressive squinting in her eyelids. She was born in the 39th week of gestation with a birth weight of 3350 g to healthy, non-consanguineous parents. Her medical history showed no record of chronic disease. Her growth rate was reported to have declined over the years. Her developmental milestones were compatible with peers until 3.5 years, she walked at one year of age, she could run at two, and jump at three years of age. However, from the age of 3.5, parents recognized progressive blepharospasms, wide based gait, joint stiffness, and progressive restriction of range of motion. She frequently had a duck-like gait following prolonged immobilization, which lasted for a few minutes and resolved spontaneously. No family history regarding the same medical problems was reported. She had no history of bone fracture or severe bone pain.

On physical examination, a mask-like appearance with long philtrum, pursed lips, narrow palpebral fissures, blepharospasm, long eyelashes, thick eyebrows, short forehead, short neck, micrognathia, crowded teeth and narrow thorax were evident. Hypertrophy of deltoid, biceps and brachioradialis muscles, joint stiffness, and restriction of range of motion were also present. She had long and thin fingers with no significant deformity in hands and feet (Figure 1). The height and body mass index were 104.8 cm [-2.25 standard deviation score (SDS)] and 14.1 kg/m^2 (-0.9 SDS), respectively. The maternal height was 155 cm, the paternal height was 170 cm (mid-parental height: -1.21 SDS) (8). The sitting height/height ratio was 0.56 (0.0 SDS) (9). The bone age was 4.5 years, and growth velocity was 2.3 cm in the previous 5 months. The skeletal survey was normal except for slightly increased lumbar lordosis. The results of routine laboratory tests for growth retardation, including whole blood count, biochemical tests, thyroid hormones, tissue transglutaminase antibodies, insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3, were all in normal ranges. However elevated levels of creatinine kinase (514 U/L) were detected, supporting myotonia. Electromyography (EMG) revealed electrophysiological changes in the conduction and response of peripheral nerves in the lower and upper extremities, also consistent with myotonia. A clinical diagnosis of SJS was considered and clinical exome sequencing was performed.

Methods and Results

Automatic DNA isolation was performed by the standard protocols of the QIAamp DNA Mini (Qiagen GmbH, 40724 Hilden, Germany) kit from peripheral blood samples. The sequencing was done on an Illumina NextSeq 500 platform using SOPHIA Clinical Exome Solution (SOPHiA GENETICS SA, Rue du Centre 136, Switzerland) and Illumina V2 chemicals (5200 Illumina Way, California 92122, USA). The Sophia-DDM-V5.2 bioinformatics analysis software was used to perform variant calling and data analysis. The interpretation of the variants was performed

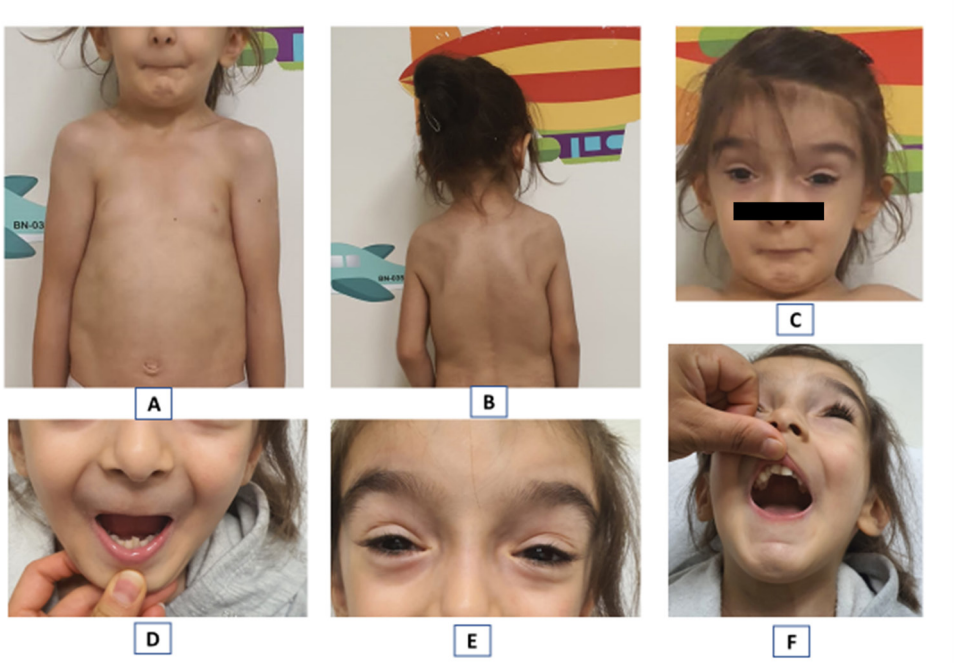

Figure 1. A) Short neck and a bell-shaped thorax, **B)** hypertrophy of muscles such as deltoid, biceps and brachioradialis leaded to a Herculean appearance, **C)** mask face with long philtrum and shrunken lips, **D)** limited mouth opening, stiffness of facial muscles, micrognathia, and overlapping teeth, **E)** narrow palpebral opening due to blepharospasm, long eyelashes, thick eyebrows, a straight and short forehead, **F)** low ears, high arched palate and overlapping teeth (consent was obtained from the parents for the use of the patient's photographs for medical and scientific purposes)

according to the 2015 American College of Medical Genetics and Genomics (ACMG) standards and guidelines. GnomAD, 1000 genome projects, dbSNP data were used as the control population. In silico prediction programs such as SIFT, Polyphen, EIGEN, FATHMM-MKL, MutationTaster, and GERP were used for variant pathogenicity predictions.

In CES (solo) analysis, *HSPG2* (NM_005529.7), c.4651C>T, p.(Arg1551Cys), heterozygous, missense variant and c.16_22dup, p.(Ala8Glyfs*31) heterozygous, frameshift variant were detected. Both variants were novel and classified as likely pathogenic according to the 2015 ACMG standards and guidelines. Segregation analysis by Sanger sequencing in parents confirmed the compound heterozygosity of the variants and thus the diagnosis of SJS.

Discussion

SJS, which is a very rare condition, was first described by Aberfeld et al. (10) in 1965, in a brother and sister with short stature, myotonic myopathy, dystrophy of epiphyseal cartilages, joint contractures, blepharophimosis, unusual pinnae, myopia, and "pigeon breast". These patients had previously been reported by Schwartz and Jampel (11) in 1962, who focused especially on the blepharophimosis. Huttenlocher et al. (12) described low muscle potassium suggesting an improper gradient of sodium and potassium due to a membrane defect. Myotonic EMG abnormalities have been described in patients. These EMG findings were also described in asymptomatic parents and siblings, while some of the patients with the syndrome had normal EMG findings (13,14,15). Minor abnormalities of toes and joints, severe microcephaly, and disproportion between skull and facial structures were described in female monozygotic twins with SJS (16). Spranger et al. (17) described four patients with SJS after further analyses who had previously been described as Kniest dysplasia, kyphomelic dysplasia, or Burton syndrome.

SJS may present with growth retardation and dysmorphic findings caused by increased muscle tone in some parts of the body. Even if these findings begin in early childhood, it may take years for them to become recognizable. Here we present a patient with novel variants in *HSPG2*, whose clinical findings were subtle until the age of 3.5 years.

Our patient had two novel heterozygote variants in *HSPG2*, together with the clinical symptoms of SJS, demonstrating that compound heterozygosity had caused the syndrome. The parents and sister of the patient had no clinical finding of skeletal dysplasia or myotonia. Similarly, Yan et al. (18) reported a 10-year-old female with SJS-1 from a Chinese family, with short stature, joint contractures, pigeon breast, and myotonia that led

to progressive stiffness of the face and limbs. They performed whole exome sequencing and Sanger sequencing for the proband and family members, finding two novel mutations (c.8788G>A; p.Glu2930Lys and c.11671+5G>A) in the *HSPG2* gene, suggesting that compound heterozygousity may be responsible for SJS-1 (18).

The *HSPG2* gene is located on chromosome 1 p34-36.1, and encodes perlecan, an important component of basement membranes. Decreased production of perlecan due to loss of function variants in *HSPG2* results in increased acetylcholine concentration at the neuromuscular junction, stimulating neuroexcitatory activity and myotonic discharges (19). Perlecan is also found in cartilage and bone marrow stromal cells and plays an important role in cartilage development and bone repair. It acts as a mechanical sensor for bone to detect external loading, and deficiency of perlecan increases the risk of osteoporosis. The skeletal abnormalities and pseudo fractures in SJS may be associated with defects in perlecan production (20,21,22,23,24).

In cases of myotonia with muscle stiffness, limitation of joint movement, but especially squinting in the eyes and difficulty in opening the mouth widely with an accompanying short stature, should suggest that SJS should be considered. Once the diagnosis is made, patients should be carefully monitored in terms of growth, neuromuscular disorders, joints problems and bone health.

Ethics

Informed Consent: Informed consent was obtained from the parents for the use of the patient's photographs for medical and scientific purposes.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Fatma Güliz Atmaca, Özlem Akgün Doğan, Büşra Kutlubay, Heves Kırmızıbekmez, Concept: Fatma Güliz Atmaca, Özlem Akgün Doğan, Heves Kırmızıbekmez, Design: Fatma Güliz Atmaca, Heves Kırmızıbekmez, Data Collection or Processing: Fatma Güliz Atmaca, Özlem Akgün Doğan, Analysis or Interpretation: Özlem Akgün Doğan, Literature Search: Fatma Güliz Atmaca, Özlem Akgün Doğan, Büşra Kutlubay, Heves Kırmızıbekmez, Writing: Fatma Güliz Atmaca, Özlem Akgün Doğan, Heves Kırmızıbekmez.

Conflict of Interest: One author of this article, Özlem Akgün Doğan, is a member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, she did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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