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

Short title: Schwartz-Jampel Syndrome Type-1

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What is already known?
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 does this case report add?
Our patient had “two novel” heterozygous variants in HSPG2 together with the clinical symptoms of the syndrome, demonstrating that the “compound heterozygosity” may cause the disease.

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 myotonia 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 definitely 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 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:
Short stature is defined as the height below -2 standard deviations (SD). Short stature may be either a variant of normal growth or caused by a disease. The goal of the evaluation of a child with short stature is to identify the pathologic causes, such as malnutrition, systemic diseases, hormone deficiencies, syndromes, and skeletal dysplasia. Pathologic variations in linear growth are related to the balance between proliferation and senescence of chondrocytes at the growth plate. This process is regulated by endocrine mechanisms (growth hormone, insulin-like growth factor 1 (IGF-1), androgens, estrogens, and thyroid hormone), proinflammatory cytokines, paracrine mechanisms (fibroblast growth factors, bone morphogenetic proteins, parathyroid hormone-related protein), cartilage extracellular matrix (collagens, proteoglycans, and other proteins), and chondrocyte transcription factors. Cartilage formation occurs early during embryonic development and is required for the formation of skeletal structures. Skeletal dysplasias associated with short stature are caused by inherited defects in cartilage/bone development (1).

Perlecan is a large heparan sulfate proteoglycan that is typically found in basal lamina of embryonic tissues. Recent studies have demonstrated that perlecan accumulates impressively during cartilage development and is maintained as the major heparan sulfate proteoglycan of adult cartilage. Deficiencies in perlecan result in skeletal defects. Studies indicate that perlecan can stimulate early stages of cartilage differentiation and cooperate with chondrogenic growth factors (2).

Schwartz-Jampel Syndrome (SJS) type-1 (OMIM; #255800), a very rare disease, develops due to variations in the HSPG2 gene, which encodes the perlecan protein. It is characterized by myotonic myopathy, chondrodystrophy, short stature, facial and eye abnormalities (3). 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 (4-6). 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 endochondral bone formation (7). Height was reported usually below the 10th centile in all age groups (8).

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, high arched palate. The mask like face and limitation of wide mouth opening which is more prominent when the patient is crying are the major clues for clinical diagnosis. Toe walking, mild kyphosis, contractures in the elbow, spine, pelvis, metaphysal deformities, lumbosacral lordosis, limitation of movement in large joints, hydrocephalus, carpal...
tunnel syndrome are some of the other features. Complications such as myelopathy, recurrent infections, stridor, and mental retardation can also be present (9-10).

This case is presented to report two new variations in HSPG2, as well as to remind the importance of evaluating myotonia when evaluating dysmorphic findings in children with short stature.

Case Report:
A 6-year-old girl was referred to pediatric endocrinology clinics 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 grams, to healthy non-consanguineous parents. Her medical history was uneventful for chronic disease. The growth rate was reported to decline 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 neither had a history of bone fracture nor severe bone pain.

On physical examination, mask-like appearance with long philtrum, pursed lips, narrow palpebral fissures, blepharospasm, long eyelashes, thick eyebrows, short forehead, shorth neck, micrognathia, crowded teeth and narrow thorax were detected. 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 significant deformity in hands and feet. The height and body mass index were 104.8 cm (-2.25 SDS) and 14.1 kg/m² (+0.9 SDS), respectively. The paternal height/height ratio was 1.21 (SDS) (11). The bone age was 4.5 years. Growth velocity in the follow-up was 3.8 cm/year between 6 and 7 years of age. 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 and IGF-binding protein-3, were all in normal ranges. However elevated levels of creatinine kinase (514 U/L) were detected supporting myotonia. Electrophysiology (EMG) revealed electrophysiological changes in the conduction and response of peripheral nerves in the lower and upper extremities, consistent with myotonia. A clinical diagnosis of SJS was considered and clinical exome sequencing was performed.

Method and Results:
Automatic DNA isolation was performed by the standard protocols of the QIAAmp DNA Mini Kit from peripheral blood samples. Within the test scope, the sequencing was done on Illumina NextSeq 500 platform using SOPHIA Clinical Exome Solution using Illumina V2 chemicals. The Sophia-DDM-V5.2 bioinformatics analysis software performed variant calling and data analysis. The interpretation of the variants was performed according to the 2015 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 revealed the compound heterozygosity of the variants confirming the diagnosis of SJS.

Discussion:
Schwartz-Jampel syndrome may present 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 Schwartz-Jampel syndrome presented with short stature and findings of myopathy due to two novel variants in HSPG2. Her clinical findings were subtle until 3.5 years of age and gradually progressed over the years.

Schwartz-Jampel syndrome was first described by Aberfeld et al. 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 (13). These patients had previously been reported by Schwartz and Jampel in 1966, who focused specially on the blepharophimosis (14). Huttonlocher et al. described low muscle potassium suggesting an improper gradient of sodium and potassium due to a membrane defect (15). Myotonic EMG abnormalities have been described in patients. These EMG findings were often described in asymptomatic parents and siblings, while some of the patients with syndrome had normal EMG findings (16-18). Minor abnormalities of toes and joints, severe microcephaly, disproportion between skull and facial structures were described in female monozygotic twins with SJS (19). Spranger et al. (2000) described 4 patients with SJS after further analyses who had previously been described as Kniest dysplasia, kyphomelic dysplasia, or Burton syndrome (20).

Our patient had two novel heterozygous variants in HSPG2 together with the clinical symptoms of the syndrome, demonstrating the compound heterozygosity causing the disease. The parents and sister of the patient had no clinical finding of skeletal dysplasia or myotonia. Like ours, Yan et al reported a 10-year-old female child from a Chinese family, with short stature, joint contractures, pigeon breast, and myotonia that led to progressive stiffness of the face and limbs. They had performed whole exome sequencing and Sanger sequencing for the proband and family members showing two novel mutations (c.8788G>A; p.Glu2930Lys and c.11671+5G>A) in HSPG2 gene, suggesting the compound heterozygosity to be responsible for SJS (21).

Decreased production of pericelin results in increased acetycholine concentration at the neuromuscular junction stimulating neuroexcitatory activity and myotonic discharges (22). In a study, among HSPG2 knockout mice approximately 40% died at embryonic period with defective cephalic development, the remaining died just after birth with skeletal dysplasia characterized by micromelia, broad and bowed long bones, narrow thorax, and craniofacial abnormalities. HSPG2 -/- cartilage showed severe disorganization of the columnar structures of chondrocytes and defective endochondral ossification. The abnormal phenotypes of the HSPG2 -/- skeleton were like those of thanatophoric dysplasia type I, which is caused by activating mutations in FGFRL3 (23).

While short stature can be attributed to the dysplastic development of growth plate cartilage, other causes were also investigated. In the literature, growth hormone responses have been investigated in patients with this syndrome, and there is case reports showing that some had adequate, and some had inadequate responses to stimulation tests. However, even though responses are inadequate in some patients, changes in the skeletal structure have made it difficult to say that short stature is due to growth hormone deficiency. In these cases, it has been reported that there is no improvement in growth rate or metabolic variables with growth hormone treatment (24,25).

Pericelin is 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 pericelin increases the risk of osteoporosis. The skeletal abnormalities and pericelin-related gross SJS can be associated with defects in pericelin production (26-30).

Pericelin also plays critical roles in the maintenance of the morphology and functions of adipose tissue and skeletal muscle. Adipose tissue acts as a fat storage depot in terms of energy sources, and it protects against abnormal lipid deposition in other organs. Smaller sized adipocytes contribute to the prevention of metabolic syndrome by secreting adiponectin, which elicits anti-inflammatory effects and enhances insulin
sensitivity. Hypertrophic adipocytes degrade the metabolic status by the secretion of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and resistin. Perlecan deficiency reduces the size of white adipocytes, may promote a reduction in the fat storage of white adipose tissue. Fats are the preferred energy source in perlecan deficiency and increased fat oxidation may contribute to the resistance to obesity. Alterations in skeletal muscle also increase β-oxidation and insulin sensitivity (31).

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

References


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)

Figure-2: A: Lateral vertebra radiograph showing increased lumbar lordosis, B: Anteroposterior radiograph showing bell-shaped thorax