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Case Report

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” 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 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

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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 mount 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, metaphyseal deformities, lumbar 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 no 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 maternal height was 155 cm, the paternal height was 170 cm (mid-parental height: -1.21 SDS) (11). The sitting height/height ratio was 0.56 (0.0 SDS) (12). 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. Electromyography (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 (Qiagen) 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 1962, who focused specially on the blepharophimosis (14). Huttenlocher 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 also 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 heterozygot 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 SJS1 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 the HSPG2 gene, suggesting the compound heterozygosity to be responsible the SJS1 (21).
Decreased production of perlecan results in increased acetylcholine 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 FGFR3 (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 are 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).
Perlecan 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 perlecan increases the risk of osteoporosis. The skeletal abnormalities and pseudo fractures in SJS can be associated with defects in perlecan production (26-30).
Perlecan 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

1. Erick J Richmond, Alan D Rogol. Causes of short stature. UpToDate (ed. Peter J Snyder, Mitchell E Geffner); last updated June 05, 2023.
2. Gomes RR Jr, Farach-Carson MC, Carson DD. Perlecan functions in chondrogenesis: insights from in vitro and in vivo models. Cells Tissues Organs. 2004;176(1-3):79-86. doi:10.1159/00007502
3. Online Mendelian Inheritance in Man, OMIM®. Cassandra L. Kniffin (12/15/2006) . World Wide Web URL: https://omim.org/
4. Dave M, Lavanya SR, Khamesra R, Bapat P, Prasath A. Schwartz Jampel Syndrome (SJS)-One in a Million Syndrome. J Assoc Physicians India. 2020;68(8):89-90.
5. Giedion A, Boltshauser E, Briner J, et al. Heterogeneity in Schwartz Jampel chondrodystrophic myotonia. Europ J Pediat 1997; 27:214-23.
6. Nicole S, Davoine CS, Topaloglu H, et al. Perlecan, the major proteoglycan of basement membranes, is altered in patients with Schwartz-Jampel syndrome (chondrodystrophic myotonia). Nat Genet. 2000;26(4):480-483.
7. Ishijima M, Suzuki N, Hozumi K, et al. Perlecan modulates VEGF signaling and is essential for vascularization in endochondral bone formation. Matrix Biol. 2012;31(4):234-245. doi:10.1016/j.matbio.2012.02.006
8. Viljoen D, Beighton P. Schwartz-Jampel syndrome (chondrodystrophic myotonia). J Med Genet. 1992;29(1):58-62. doi:10.1136/jmg.29.1.58
9. Kulkarni ML, Pillai R. Schwartz-Jampel syndrome. Indian Pediatr. 2004;41(3):285.
10. Basiri K, Fatehi F, Katirji B. The Schwartz-Jampel syndrome: Case report and review of literature. Adviomed Res. 2015; 4:163.
11. Demir, K., Özen, S., Konakçı, E., Aydın, M., & Darendeliler, F. A comprehensive online calculator for pediatric endocrinologists: ÇEDD Çözüm/TPEDS metrics. Journal of Clinical Research in Pediatric Endocrinology 2017; 9: 182-184. https://doi.org/10.4274/jcrpe.4526
12. Bundak R, Bas F, Furman A, et al. Sitting height and sitting height/height ratio references for Turkish children. Eur J Pediatr. 2014;173(7):861-869.
13. Aberfeld, D. C., Hinterbuchner, L. P., Schneider, M. Myotonia, dwarfism, diffuse bone disease and unusual ocular and facial abnormalities (a new syndrome). Brain 1965; 88: 313-322.
14. Schwartz, O., Jampel, R. S. Congenital blepharophimosis associated with a unique generalized myopathy. Arch. Ophthal.1962; 68: 52-57.
15. Huttenlocher, P. R., Landwirth, J., Hanson, V., Gallagher, B. B., Bensch, K. Osteo-chondro-muscular dystrophy. A disorder manifested by multiple skeletal deformities, myotonia, and dystrophic changes in muscle. Pediatrics 1969; 44:945-958.
16. van Huffelen, A. C., Gabreels, F. J. M., van Luypen-van den Horst, J. S., Slooff, J. L., Stadhouders, A. M., Korten, J. J. Chondrodystrophic myotonia: a report of two unrelated Dutch patients. Neuropadiatrie 1974; 5: 71-90.
17. Pavone, L., Mollica, F., Grasso, A., Cao, A., Gullotta, F. Schwartz-Jampel syndrome in two daughters of first cousins. J. Neurol. Neurosurg. Psychiat. 1978; 41: 161-169.
18. Moodley, M., Moosa, A. Chondrodystrophic myotonia (Schwartz-Jampel syndrome) in South African children. Neuropediatrics 1990; 21: 206-210.
19. Pinto-Escalante, D., Ceballos-Quintal, J. M., Canto-Herrera, J. Identical twins with the classical form of Schwartz-Jampel syndrome. Clin. Dysmorph. 1997; 6: 45-49.
20. Spranger, J., Hall, B. D., Hane, B., Srivastava, A., Stevenson, R. E. Spectrum of Schwartz-Jampel syndrome includes micromelic chondrodysplasia, kyphomelic dysplasia, and Burton disease. Am. J. Med. Genet. 2000; 94: 287-295.
21. Yan W, Dai J, Shi D, et al. Novel HSPG2 mutations causing Schwartz-Jampel syndrome type 1 in a Chinese family: A case report. Mol Med Rep. 2018;18(2):1761-1765. doi:10.3892/mmr.2018.9143
22. Ho NC, Sandusky S, Madike V, Francomano CA, Dalakas MC. Clinico-pathogenetic findings and management of chondrodystrophic myotonia (Schwartz-Jampel syndrome): a case report. BMC Neurol 2003;3:3.
23. Arikawa-Hirasawa E, Watanabe H, Takami H, Hassell JR, Yamada Y. Perlecan is essential for cartilage and cephalic development. Nat Genet. 1999;23(3):354-358. doi:10.1038/15537
24. Pavone L, Mollica F, Grasso A, Cao A, Gullotta F. Schwartz-Jampel syndrome in two daughters of first cousins. J Neurol Neurosurg Psychiatry. 1978;41(2):161-169. doi:10.1136/jnnp.41.2.161
25. Edwards WC, Root AW. Chondrodystrophic myotonia (Schwartz-Jampel syndrome): report of a new case and follow-up of patients initially reported in 1969. Am J Med Genet. 1982;13(1):51-56. doi:10.1002/ajmg.1320130109
26. French MM, Smith SE, Akanbi K, Sanford T, Hecht J, Farach-Carson MC, et al. Expression of the heparan sulfate proteoglycan, perlecan, during mouse embryogenesis and perlecan chondrogenic activity in vitro. J Cell Biol. 1999;145:1103–15.
27. Schofield KP, Gallagher JT, David G. Expression of proteoglycan core proteins in human bone marrow stroma. Biochem J. 1999;343:663–8.
28. Brown AJ, Alicknavitch M, D'souza SS, Daikoku T, Kirn-Safran CB, Marchetti D, et al. Heparanase expression and activity influences chondrogenic and osteogenic processes during endochondral bone formation. Bone. 2008;43:689–99.
29. A Gubbiotti MA, Neill T, Iozzo RV. A current view of perlecan in physiology and pathology: A mosaic of functions. Matrix Biol. 2017;57-58:285-298. doi:10.1016/j.matbio.2016.09.003
30. Arikawa-Hirasawa E. Impact of the heparan sulfate proteoglycan perlecan on human disease and health. Am J Physiol Cell Physiol. 2022;322(6):C1117-C1122. doi:10.1152/ajpcell.00113.2022
31. Yamashita Y, Nakada S, Yoshihara T, et al. Perlecan, a heparan sulfate proteoglycan, regulates systemic metabolism with dynamic changes in adipose tissue and skeletal muscle. Sci Rep. 2018;8(1):7766. Published 2018 May 17. doi:10.1038/s41598-018-25635-x

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)

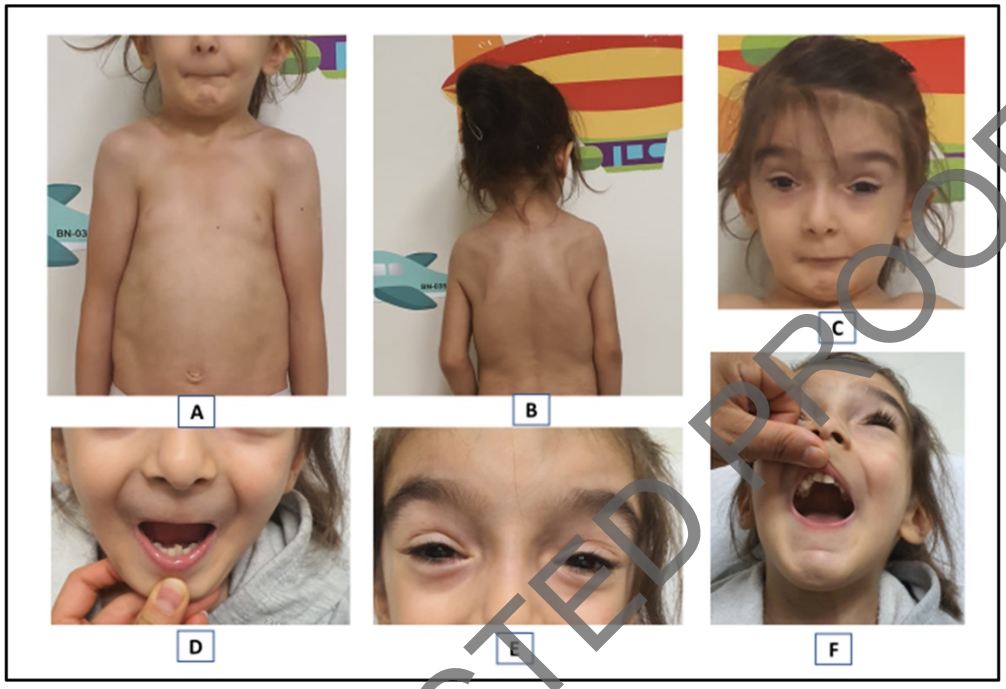

Figure-2: A: Lateral vertebra radiograph showing increased lumbar lordosis**. B:** Anteroposterior radiograph showing bell-shaped thorax