American Journal of Medical Case Reports, 2020, Vol. 8, No. 10, 325-327
Available online at http://pubs.sciepub.com/ajmcr/8/10/1
Published by Science and Education Publishing
DOI:10.12691/ajmcr-8-10-1

Three Novel HSPG2 Mutations Causing Schwartz-Jampel Syndrome

Andrew Wahba[1,*], Rafik ElBeblawy[2]

[1]Department of Pediatrics, McGovern Medical School at The University of Texas Health Science Center Houston,TX
[2]University of Louisville, School of Medicine, Louisville, KY
*Corresponding author: Andrew.A.Wahba@uth.tmc.edu

Received May 07, 2020; Revised June 09, 2020; Accepted June 16, 2020

Abstract Schwartz-Jampel syndrome (SJS) is a rare autosomal recessive hereditary disorder characterized by the triad of myotonia, facial dysmorphisms, and skeletal deformities. Less than 150 cases have been reported in the medical literature. SJS is caused by mutations in the gene heparan sulfate proteoglycan 2 (HSPG2) located on chromosome 1p34-36.1 which encodes perlecan, a major component of basement membranes. Here we report three novel mutations in a 6-year-old girl.

Keywords: *Schwartz-Jampel syndrome, heparan sulfate proteoglycan 2, HSPG2, myotonia*

Cite This Article: Andrew Wahba, and Rafik ElBeblawy, "Three Novel HSPG2 Mutations Causing Schwartz-Jampel Syndrome." *American Journal of Medical Case Reports*, vol. 8, no. 10 (2020): 325-327. doi: 10.12691/ajmcr-8-10-1.

1. Introduction

Schwartz-Jampel syndrome (SJS) is a rare skeletal autosomal recessive genetic disease caused by mutations in the Heparan Sulfate Proteoglycan 2 (HSPG2) gene located at Chromosome 1p34–36.1 [1]. The main features of this syndrome is the triad of myotonia, facial dysmorphism, and skeletal deformities. It was first described in the United States in 1962 by Oscar Schwartz and Robert S. Jampel [2]. They reported the initial two cases of two siblings presented with similar features, named that time "Congenital Blepharophimosis Associated with a Unique Generalized Myopathy". The HSPG2 gene encodes for perlecan, a large multifunctional protein, present in all basement membranes, and involved in cell adhesion and growth factor signaling [3]. It has an essential role to regulate the fibroblast growth factor activity, and clustering of acetylcholine receptors at the neuromuscular junctions [4]. It also has a vital role in the formation of cardiovascular, neural, and cartilaginous tissues. Mutations in this gene result in the abnormal aggregation of acetylcholinesterase and ion channel expression. A defect in perlecan causes developmental abnormalities in cartilage and bone repair functions [5,6]. Because of its essential role in many tissue and organ development, mutations in the HSPG2 gene are lethal at embryonic or neonatal phases making it harder to study. Mutations in the HSPG2 gene are documented in the literature for two skeletal disorders known as Schwartz-Jampel syndrome (SJS) and Dyssegmental dysplasia, Silverman-Handmaker type (DDSH). DDSH is a lethal condition due to null mutations fully preventing perlecan secretion into the extracellular matrix (ECM) [7]. However, reduced levels of normal perlecan secretion into the ECM is associated with the HSPG2 mutations of SJS [8].

Here we report three novel mutations in the HSPG2 gene in exons 64, 65 and 77, in a 6-year-old Hispanic female. This case report can be of a significant addition to the literature in order to understand the spectrum of genetic mutations evolving this type of neuromuscular disease, early diagnosis and assessing the correlation of certain genetic findings to severity and outcomes.

2. Case Presentation

A 6-year-old Hispanic female presented to our clinic with the past medical history of bilateral clubfoot and micrognathia reported since birth, status post bilateral tendon release at the age of 1 year for clubfoot correction. She came with her mother who had complaints of recurrent foot deformities despite surgery and casts, trouble in swallowing hard foods, and concerns about delayed cognitive development among her peers. She denies any history of seizures, headaches, or any other neurological manifestations. The patient was born at full term via cesarean section due to breech presentation. Delayed motor developmental milestones with the ability to sit down at 6 months, crawling at 15 months, and walking at 2 years. Speech development was achieved normally by putting two words together at the age of 1 year. Mother reported no similar diseases in family history, learning disabilities, early death nor birth defects. A review of systems was negative except for the difficulty in swallowing and bilateral clubfoot.

On physical examination, the patient's weight is 15.7 kg, height 105.5 cm, head circumference 48.5 cm with corresponding age curve 10th, 25th, 5th percentiles respectively. General face appearance was asymmetric and dysmorphic, with a square-shaped facial look. Eyes examination showed blepharophimosis with normal ocular movement. Ears and Nose were normal, while Mouth and Throat showed microstomia, tented upper lip, high-arched palate, darkening of teeth, and smooth philtrum. A weakness of neck flexors muscles were evident and atrophy of lower limbs with obvious clubfoot. The patient was mildly dysarthric but alert, awake, and playful. Cranial nerves were intact. Percussion myotonia was observed in thenar eminences bilaterally, and significant muscle weakness at both lower limbs. Motor reflexes were absent at ankles bilaterally however intact otherwise. Difficulty walking in tandem gait and standing on heels were evident. However, dysmetria was absent. Foot radiograph (x-ray) showed bilateral metatarsus adductus, stacked metatarsals, and hindfoot varus (Figure 1). Aldolase and creatine kinase were within normal range. SJS was confirmed by whole-exome sequencing which showed three novel mutations in the HSPG2 gene: c.8318C>T in Exon 64, c.8609G>A in Exon 65 and c.10460C>A in Exon 77.

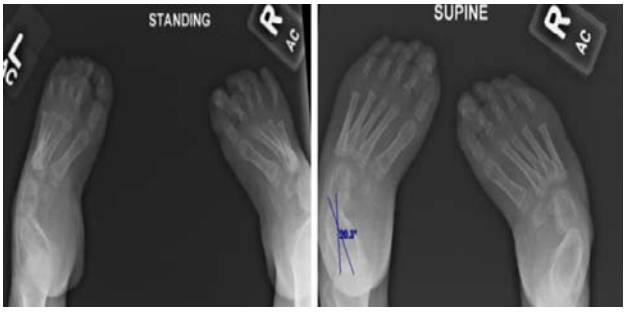

Figure 1. Foot X-ray showing bilateral metatarsus adductus, stacked metatarsals, and hindfoot varus

Table 1. Identification of single nucleotide variations in the Heparan Sulfate Proteoglycan 2 gene (HSPG2) through Whole Exome Sequencing

Gene	Location	Nucleotide change	Variant
HSPG2	Exon 64	c.8318 C>T	p.T2773I
HSPG2	Exon 65	c.8609 G>A	p.R2870Q
HSPG2	Exon 77	c.10460 C>A	p.P3487H

3. Discussion

SJS is classified into three subtypes: SJS 1 (1A, 1B) and SJS 2. Type 1A is characterized by delayed presentation at childhood with moderate myotonia and dysmorphic features. Type 1B is more profound at birth with skeletal and neuromuscular abnormalities. Early deaths are most evident in type 2 patients. Type 2 is also known as Stuve-Wiedemann syndrome. Caused by a genetic defect in the LIFR gene, which codes for the leukemia inhibitory factor receptor. It is the most severe form characterized by marked bone, pharyngeal and laryngeal deformities that prevent normal feeding [9]. The most commonly recognized type is SJS 1A, which is more apparent within the first 4 years of life. Parents usually report increased muscle stiffness of their child. Dysmorphic features and myopathy are characteristic within the first year of life. Limitation of joint movement, delayed walking, kyphosis/scoliosis, clubfoot, pectus carinatum and short stature are among the skeletal and joint deformities described [10]. The Presence of facial features are characteristic differentiation from other myotonic disorders. It presents with mask-like facies, narrow palpebral fissures, pursued lips, micrognathia, low set ears, and high arched palate [11,12]. Creatine kinase levels may be normal or slightly increased [1,8,12] and Electromyography can reveal continuous myotonic discharges at rest [5,12,13]. Prognosis is favorable specifically in type 1A compared to 1B, with no reduction in lifespan. Associated comorbidities and challenges in the management of muscle stiffness and blepharospasm are the main obstacles in treatment.

Management of SJS patients is mainly supportive through controlling the progression of myotonia and stiffness by carbamazepine, phenytoin, mexiletine, and procainamide. Physical therapy also has a vital role to improve mobility. The use of Botox (onabotulinumtoxinA injection) has shown promising results in controlling Blepharophimosis and now more commonly used than the surgical options such as levator aponeurosis resection or myectomy. Episodes of malignant hyperthermia due to lack of acetylcholinesterase expression may be fatal [14].

HSPG2 consists of 97 exons, and encodes for the protein Perlecan. Whole Exome sequencing provides the ability to analyze a patient's gene and identify mutations. Three novel missense mutations were detected in HSPG2 (Table 1), c.8318 C>T; p.T2773I in exon 64 (One cytosine ribonucleotide was altered to thymine in codon 8318, which caused a change in the reading frame from threonine to isoleucine), c.8609 G>A; p.R2870Q in exon 65 (One guanine ribonucleotide was altered to adenine in codon 8609 which caused a change in the reading frame from arginine to glutamine) and c.10460 C>A; p.P3487H in exon 77 (One cytosine ribonucleotide was altered to adenine in codon 10460 with caused a change in the riding frame from proline to histidine. The T2773I and P3487H variants are a non-conservative amino acid substitutions, which are likely to impact secondary protein structure as these residues differ in polarity, charge, size, and/or properties. The R2870Q variant is a semi-conservative amino acid substitution, which may impact secondary protein structure as these residues differ in some properties. To the best of our knowledge, these three mutations have not been reported in SJS1 previously. To date, less than 150 SJS cases are reported in the medical literature and less than 40 mutations of the HSPG2 gene are identified, however, no genotype-phenotype correlation is evident [8,11,15,16,17].

In summary, the triad of myotonia, facial dysmorphisms and skeletal deformities is specific for SJS with confirmatory DNA testing. SJS, though rare, should be identified because of the increased risk of malignant hyperthermia. This case advances the literature by providing three novel mutations in the HSPG2 gene and highlights the clinical presentation, challenges of management, and the prognosis.

References

[1] Katirji B. Chapter 17 - Peripheral nerve hyperexcitability. In: Levin KH, Chauvel P, eds. *Handbook of Clinical Neurology.* Vol 161. Elsevier; 2019: 281-290.

[2] SCHWARTZ O, JAMPEL RS. Congenital Blepharophimosis Associated with a Unique Generalized Myopathy. *Archives of Ophthalmology.* 1962; 68(1): 52-57.

[3] Preston DC, Shapiro BE. 36 - Myotonic Muscle Disorders and Periodic Paralysis Syndromes. In: Preston DC, Shapiro BE, eds. *Electromyography and Neuromuscular Disorders (Third Edition).* London: W.B. Saunders; 2013: 563-582.

[4] Sharma B, Handler M, Eichstetter I, Whitelock JM, Nugent MA, Iozzo RV. Antisense targeting of perlecan blocks tumor growth and angiogenesis in vivo. *The Journal of Clinical Investigation.* 1998; 102(8): 1599-1608.

[5] Nicole S, Davoine C-S, Topaloglu H, et al. Perlecan, the major proteoglycan of basement membranes, is altered in patients with Schwartz-Jampel syndrome (chondrodystrophic myotonia). *Nature Genetics.* 2000; 26(4): 480-483.

[6] Peng HB, Xie H, Rossi SG, Rotundo RL. Acetylcholinesterase Clustering at the Neuromuscular Junction Involves Perlecan and Dystroglycan. *Journal of Cell Biology.* 1999; 145(4): 911-921.

[7] Arikawa-Hirasawa E, Wilcox WR, Le AH, et al. Dyssegmental dysplasia, Silverman-Handmaker type, is caused by functional null mutations of the perlecan gene. *Nature Genetics.* 2001; 27(4): 431-434.

[8] Arikawa-Hirasawa E, Le AH, Nishino I, et al. Structural and Functional Mutations of the Perlecan Gene Cause Schwartz-Jampel Syndrome, with Myotonic Myopathy and Chondrodysplasia. *The American Journal of Human Genetics.* 2002; 70(5): 1368-1375.

[9] Giedion A, Boltshauser E, Briner J, et al. Heterogeneity in Schwartz-Jampel chondrodystrophic myotonia. *European journal of pediatrics.* 1997; 156: 214-223.

[10] Viljoen D, Beighton P. Schwartz-Jampel syndrome (chondrodystrophic myotonia). *Journal of Medical Genetics.* 1992; 29(1): 58-62.

[11] Stum M, Davoine C-S, Vicart S, et al. Spectrum of HSPG2 (Perlecan) mutations in patients with Schwartz-Jampel syndrome. *Human Mutation.* 2006; 27(11): 1082-1091.

[12] Mathur N, Ghosh PS. Schwartz-Jampel Syndrome. *Pediatric Neurology.* 2017; 68: 77-78.

[13] Regalo SC, Vitti M, Semprini M, et al. The effect of the Schwartz-Jampel syndrome on masticatory and facial musculatures--an electromyographic analysis. *Electromyogr Clin Neurophysiol.* 2005; 45(3): 183-189.

[14] Narayanaswami P. 17 - Treatment and Management of Disorders of Neuromuscular Hyperexcitability. In: Bertorini TE, ed. *Neuromuscular Disorders: Treatment and Management.* Saint Louis: W.B. Saunders; 2011: 285-306.

[15] Iwata S, Ito M, Nakata T, et al. A missense mutation in domain III in HSPG2 in Schwartz-Jampel syndrome compromises secretion of perlecan into the extracellular space. *Neuromuscul Disord.* 2015; 25(8): 667-671.

[16] Das Bhowmik A, Dalal A, Matta D, Kandadai RM, Kanikannan MA, Aggarwal S. Identification of a novel splice site HSPG2 mutation and prenatal diagnosis in Schwartz Jampel Syndrome type 1 using whole exome sequencing. *Neuromuscul Disord.* 2016; 26(11): 809-814.

[17] 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.