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Schwartz-Jampel Syndrome (SJS1), Type 1 a Novel Variant in the *HSPG2* Gene

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Abstract

Background: Schwartz-Jampel syndrome is a rare genetic condition characterized by abnormalities of the skeletal muscles, bone dysplasia, joint contractures, and/or growth delays. Affected individuals may also have small, fixed facial features and various ocular abnormalities. The severity of the disease may vary from person to person with no definite genotype to phenotype correlation. Mutations in the *HSPG2* gene have been reported in patients presenting with this condition.

Case presentation: We report here a 14-year-old boy, born to consanguineous Sri Lankan parents, presenting with joint contractures at the age of 6 months, bilateral hip dysplasia, right-sided inguinal hernia, and bilateral clubfoot deformity at 1 year of age, with attributed progressive difficulty in walking. While he became older, he displayed other symptoms suggestive of Schwartz-Jampel Syndrome (SJS1), type 1, such as sad and fixed facies, flat face, full cheeks. Additionally, he also had hair thinning, hair loss as well as dry skin hyper pigmented skin changes including rough and dimpled skin near the chin area. His IQ sight and hearing was normal. However, bilateral blepharophimosis interfered with his otherwise normal vision. He has abnormal teeth and a beaked shaped nose. He also had a high-pitched voice. His karyotype and other metabolic indices were within normal limits. He has a healthy 18-year-old sister. There was no history of similar people in his family. Whole exome sequencing of the proband showed a novel deleterious homozygous mutation (c.10466_10467insC) in the *HSPG2* gene, resulting in a frameshift p.Leu3490AlafsTer26.

Conclusion: This is the first case of SJS type 1 reported in a Sri Lankan family and its confirmed by the recessive mutation found in the *HSPG2* gene.

Keywords: Schwartz-Jampel syndrome; SJS; Myopathy; *HSPG2;* Perlecan

Abbreviations: EMG: Electromyography; OMIM: Online Mendelian Inheritance in Man; SIFT: Scale-Invariant Feature Transform

Background

Schwartz-Jampel syndrome is a rare genetic condition characterized by abnormalities of the skeletal muscles, including muscle weakness and stiffness (myotonic myopathy), abnormal bone development (bone dysplasia), permanent bending or extension of certain joints in a fixed position (joint contractures), and/or growth delay resulting in abnormal short stature (dwarfism) [1]. Affected individuals may also have small, fixed facial features and various abnormalities of the eyes, some of which may cause impaired vision while the severity of the disease may vary from person to person [2]. Two types of SJS have been described, depending on the age of onset of the predominant clinical features. Type 2 (also referred as neonatal SJS2, OMIM 601559) is now considered as a distinct and more severe condition, also named Stuve-Wiedemann syndrome, SJS2 which is due to a mutation in the *LIFR* gene [3]. Depending on the severity and the age of onset of SJS it is further sub categorized as type 1A and 1B. Where in type 1A is considered the milder form of the two with symptoms developing later in childhood as opposed to the more severe form type B where symptoms are present at birth [4]. We describe here the first case of a 14-year-old Sri Lankan boy of Sinhalese ethnicity with SJS, which was clinically suspected to be Progeria by the referring clinician. Through this case report and literature review we wish to facilitate early detection of this rare genetic condition.

Case Presentation

A 14-year-old boy was investigated at the Human Genetics Unit, Faculty of Medicine, at the University of Colombo. He is the second child of an uneventful pregnancy to consanguineous parents. His birth weight was 2.6 kg, length 46 cm and occipitofrontal circumference 33 cm. He was admitted to the neonatal intensive care unit soon after birth and was treated for sepsis; ultrasound scan of brain was normal. He started developing contractures at the age of 6 months and experienced progressive difficulty in walking. He was diagnosed to have bilateral hip dysplasia (Grade 1), right-sided inguinal hernia, and bilateral clubfoot deformity at 1 year of age. His facial appearances changed, he looked expressionless and sad. His hair become thin and started balding. His skin was very dry, and he was described as having an aged appearance (Figure 1). His IQ was normal and there were no visual or hearing impairments. However bilateral blepharophimosis interfered with his otherwise normal vision. He has abnormal teeth and a beaked shaped nose (Figure 2). The skin near the chin area was hyper pigmented, rough and dimpled. He also had a high-pitched voice. His karyotype and other metabolic indices were normal. He has a healthy 18-year-old sister. There was no history of similar people in his family.

Whole exome sequencing of the child showed a homozygous 1 bp insertion c.10466_10467insC in exon 77 of the *HSPG2* gene, causing a frameshift p.Leu3490AlafsTer26. Mutations in this gene were reported to cause SJS (OMIM #255800).

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Figure 1: Facial features of the proband, dimpling of the skin near the chin, beak shaped nose, thinning of hair and balding.

Figure 2: Proband with multiple joint contractures and hip dysplasia.

Whole exome sequencing (WES) method and results

Whole exome sequencing was carried out using 1µg of genomic DNA per sample with Agilent Technologies Sure Select XT All Human ExonV6 Kit. Manufacturer guidelines were followed, and DNA was sheared to a fragment size of 200 bp and amplified as per SureSelect protocol. Ion OneTouch System was used to prepare the exome library and sequenced on an Ion Proton instrument (Life Technologies, Carlsbad, CA, USA) using one Ion PI chip. Human reference genome (Human GRCh37 (hg19) build) was used to align the sequence reads with the help of Torrent Mapping Alignment Program (TMAP) from the Torrent Suite (v5.0.2). Torrent Variant Caller (TVC) plugin (v5.0.2) was used to call the variants. Followed by annotation with the associated gene, location, quality-score, coverage, predicted functional consequences, protein position and amino acid changes, SIFT, PolyPhen2, Grantham and M-CAP, prediction scores, phyloP conservation scores [5-9] including 5000 genomes Minor Allele Frequencies. The following databases were used to filter common SNPs, NCBI's "common and no known medical impacts" database (ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/vcf_GRCh37/), Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org/) and the Exome Aggregation Consortium (ftp://ftp.broadinstitute.org/pub/ExAC_release/release0.2/). Next step was to remove that were present in greater than 1% of the previously 532 sequenced samples. An average read length of 184 bp was used for proband

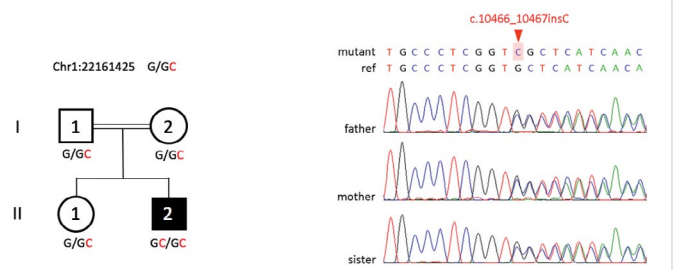

Figure 3: Pedigree with Sanger sequencing results.

analysis of 16.6 Gb. On average 95% of the bases were covered at least 20x and a coverage of 187x was achieved. Heterozygous, compound heterozygous and homozygous variants were identified across protein-coding exons, UTRs, splice sites and flanking introns which amounted to a total of 945. The affected boy was born to consanguineous parents which suggested a recessive mode of inheritance, either autosomal or X-linked. Out of the 33 exonic homozygous variants that were identified 3 were not listed in the population (gnomAD) nor in our "in-house" database containing WES results of 532 patients who were middle eastern by origin. The following variants were eliminated missense variant p.Tyr672Cys in *MCM8, miss*ense variant p.Thr344Ser in *GPC3,* Since they were associated with premature ovarian failure 10 (OMIM #612885) and Simpson-Golabi-Behmel syndrome, type 1 (OMIM #312870) respectively [10]. Only one deleterious variant remained in *HSPG2* (c.10466_10467insC). We predicted this variant to be pathogenic since it causes frameshift p.Leu3490AlafsTer26 with early stop codon. Finally, mutations in *HSPG2* were previously reported to cause Schwartz-Jampel syndrome, type 1 (SJS1, OMIM #255800), supporting our finding. Using Sanger sequencing, both parents and the unaffected sister were heterozygous, confirming that this germline mutation segregated with the disease (Figure 3).

Discussion and Conclusion

Schwartz-Jampel syndrome (SJS) is classified as a rare disease with an autosomal recessive inheritance, it is characterized by several musculoskeletal abnormalities, such as myotonia, joint contractures, and facial dysmorphisms. Schwartz and Jampel first described it in 1962 as congenital blepharophimosis associated with unique generalized myopathy [11]. SJS has a prevalence of <1:1000000, with over 100 reported cases worldwide [12]. The permanent myotonia (prolonged failure of muscle relaxation) restricts joint mobility and interferes with daily activities. Contraction of the facial muscles leads to a "mask-like" expression with blepharophimosis and pursed lips.

Studies have shown that SJS results from mutations in the *HSPG2* gene, which encodes the perlecan protein, a major component of basement membranes [13]. Functional studies using patient's cells carrying *HSPG2* mutations demonstrated loss-of-function effect. Frameshift mutation in exon 77 resulted in impaired scaffold formation and loss of extracellular matrix integrity [14]. Perlecan belongs to the heparan sulfate proteoglycan family of extracellular matrix proteins and is a fundamental component in extracellular matrices with multitudes of biological functions [15]. Hence mutations in the perlecan gene (*HSPG2*) is associated with two classes of skeletal disorders: the mild form is known as Schwartz-Jampel syndrome (SJS) and the severe more lethal form is known as Silverman-Handmaker type (DDSH) [16]. Perlecan is involved in cell signaling, cell adhesion, angiogenesis, and maintenance of basement membrane and cartilage integrity. More than 30 mutations in the *HSPG2* gene have been reported to cause Schwartz-Jampel Syndrome resulting in a considerable clinical heterogeneity in the phenotype. In these patients, mutant perlecan

molecules or reduced amounts of wild-type perlecan are secreted in the tissue matrix altering its biological functions [17].

Our patient displayed typical features of SJS as well as a few additional features that were not commonly associated with this condition such as hair thinning, hair loss as well as dry skin hyper pigmented skin changes including rough and dimpled skin near the chin area which could be a new clinical phenotype.

Commonly associated features of SJS are short stature in 90% of patients, clinical myotonia in 85%, puckered-small mouth in 80%, muscle hypertrophy in 70%, fixed facies in 55%, bone abnormalities in 45%, raised muscle enzymes in 45%, hip dysplasias in 40%, blepharophimosis and blepharospasm in 32.5%. The reduced functional perlecan at the neuromuscular junctions leads to altered muscle-signaling that causes continuous muscle contractions. As a result, myotonia is one of the cardinal features of SJS [18]. The gait and the stance of these patients are affected, and they adopt a waddling gait and a crouched stance due to joint stiffness. Short stature, pectus carinatum, kyphoscoliosis and joint contractures are the other skeletal findings [19]. Usually muscle biopsy findings are inconclusive with marginally raised creatine kinase and other muscle enzymes. EMG shows spontaneous activity that wanes at rest.

The aim of treatment of Schwartz-Jampel Syndrome (SJS) is to reduce abnormal muscle activity that causes stiffness and cramping. Treatment may include nonpharmacologic modalities such as massaging, warming, gradual warm-up prior to exercise, and gradual stretching. Medication includes anticonvulsants such as carbamazepine and phenytoin, antiarrhythmic drugs like mexiletine and procainamide to alleviate myotonia. Botulinum toxin or surgery might provide symptomatic relief in some patients.

Even though Schwartz-Jampel Syndrome (SJS) has been reported in literature this is the first confirmed case in a Sri Lankan boy of Sinhalese ethnicity. Even though uncommon we wish to report this case, as it will aid in early diagnosis of the condition especially in the South Asian region.

Declarations

Ethics approval and consent to participate

Ethics approval for the study was obtained by the Faculty of Medicine, University of Colombo Ethics Review Committee (EC-16-179). Duly filled consent forms are available with the corresponding author.

Consent to publish

Consent to publish this material was obtained via written informed consent.

Availability of data and materials

Data is not available in a public domain as the sequencing was done at A*STAR laboratories.

Competing interests

Authors declare that there are no competing interests.

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Authors contributions

DH, SB, and VHWD were the clinicians looking after the patient. ST, AYJN and BV carried out WES and variant prediction. CB performed WES analysis and identified HSPG2. DH and CB wrote the manuscript with contributions from all. BR and RS designed and guided the study. All authors reviewed, modified and approved the final version of the manuscript.

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