Molecular Genetics and Metabolism Reports 40 (2024) 101125

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Expanding genetic and clinical aspects of Schwartz-Jampel syndrome: A report of two cases with literature review

Iman Elahi Vahed [a], Sahand Tehrani Fateh [b], Melika Kamali [c], Farzad Hashemi-Gorji [d], Zahra Esmaeilzadeh [e], Hossein Sadeghi [e], Mohammad Miryounesi [d,e,*], Mohammad-Reza Ghasemi [e,**]

[a] School of Medicine, Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran
[b] School of Medicine, Tehran University of Medical Sciences (TUMS), Tehran, Iran
[c] School of Pharmacy, Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran
[d] Genomic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[e] Department of Medical Genetics, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Schwartz-Jampel syndrome
HSPG2
Whole exome sequencing

ABSTRACT

Schwartz-Jampel syndrome (SJS) is a rare autosomal recessive disorder characterized by muscle stiffness (myotonia) and chondrodysplasia. This disease is caused by biallelic loss of function mutations in the *HSPG2* gene, which encodes the core protein of perlecan. This study aims to investigate causative variants in two sisters born to consanguineous Iranian parents. Both patients were presented with myotonia and a mask-like face; moreover, they showed a less common symptom, gastrointestinal bleeding, which is not typical of SJS and has only been reported in one patient. Regarding the crucial role of perlecan in vascular structure and mucosal stability, bleeding disorders could be expected in perlecan dysfunctions. In addition to the case study, a comprehensive literature review was conducted to gather information on similar genetic variants, associated clinical features, and possible disease mechanisms. Results of this study contribute to our understanding of the genetic and clinical aspects of Schwartz-Jampel syndrome, and more importantly, the manifestation of gastrointestinal bleeding in patients with Schwartz-Jampel syndrome.

1. Introduction

Schwartz-Jampel syndrome (SJS; OMIM #255800) is an autosomal recessive disorder that affects less than one in one million people' characterized by muscle stiffness (myotonia) and chondrodysplasia. Schwartz-Jample syndrome is caused by the loss-of-function mutation in the heparan sulfate proteoglycan 2 (*HSPG2*) gene, which contains 97 exons [1]. The *HSPG2* gene encodes the core protein of perlecan and is located on chromosome 1p36.1-p35, spanning over 120 kb [2–5]. Perlecan is a large proteoglycan composed of five domains (I-V) [6]' that is deposited in all basement membranes as well as in matrices produced in muscle, cartilage, and bone marrow. It also has other functions, including growth factor signaling, cell adhesion, angiogenesis, and acetylcholinesterase anchoring at neuromuscular junction [1,7].

Two genetic disorders are associated with *HSPG2* gene mutations, SJS type 1 (SJS) and Dyssegmental Dysplasia, Silverman-Handmaker Type (DDSH). As referred to, SJS is characterized by myotonia, chondrodysplasia (dwarfism, pectus carinatum, kyphoscoliosis, and bowing of the legs), mask-like face (narrow palpebral fissures, blepharophimosis, and pursed lips) [1,8]. The onset of symptoms ranges from birth to early childhood (up to 4 years of age) [8]. The severity of SJS depends on the location of the mutation and the extent of the preserved protein, which causes a different amount of perlecan production and secretion into the extracellular matrices [9,10]. DDSH is the more severe and less prevalent form of chondrodysplasia, and in most cases, patients die in the prenatal period or early infancy.

This study aims to report two cases of Schwartz-Jampel syndrome with a novel variant in an Iranian family. Alongside this investigation, a comprehensive literature review was performed to gather relevant information on similar genetic variants, associated clinical features, and possible disease mechanisms. By combining the findings from the novel case study and the comprehensive literature review, the study aimed to

* Corresponding author at: Genomic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
** Corresponding author at: Department of Medical Genetics, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail addresses: miryounesi@gmail.com (M. Miryounesi), ghasemimr891@gmail.com (M.-R. Ghasemi).

https://doi.org/10.1016/j.ymgmr.2024.101125
Received 16 December 2023; Received in revised form 20 July 2024; Accepted 21 July 2024

enhance our understanding of the genetic and clinical aspects of this rare disorder. Ultimately, the study aimed to contribute to the existing knowledge base on *HSPG2*-related disorders, potentially improving diagnostic approaches and patient management strategies.

2. Material and methods

2.1. Clinical case presentation

2.1.1. Case VI-1

The first proband was recruited for genetic testing in October 2018, 12 years after death (Fig. 1A). The girl was born full-term by cesarean section. In the first four months of life, she has been suitable in growth and feeding, but the physical examination showed neuro-developmental delay (NDD). After five months of age, she started showing symptoms like myotonia, muscle weakness, poor feeding, and inability to sit or walk. Other symptoms in the next follow-ups at 9 months and 1 year of age included narrow palpebral fissure, blepharophimosis, ptosis, long eyelashes in irregular rows, small mouth, pursed lips, chest deformity, small mandible and elbow, wrist, and finger contractures. She had a history of vesicoureteral reflux (VUR) and recurrent urinary tract infection (UTI) that caused her to be admitted to the hospital up to 4 times in one year. She also had peptic ulcer disease (PUD) that once caused her to present with hematochezia.

2.1.2. Case VI-2

The second proband was also recruited for genetic testing in January 2019, a year after death (Fig. 1A). She was born full-term by cesarean section and has been good with feeding and neurodevelopment in the first 18 months, but she weighed 7–8 kg at the end of 18 months. Her neurological exam was good, and she could walk three steps at the end of 18 months and talk after nine months. After this time, she became extremely weak, stopped gaining weight, and could not walk. She also had other symptoms of SJS during the next follow-ups after two years, including generalized hirsutism, narrow palpebral fissure, blepharophimosis, myopia, long eyelashes in irregular rows, ptosis, small mouth, pursed lips, chest deformity, small mandible, myotonia, elbow, wrist, and fingers contractures, and small, high-pitched voice. She had a history of PUD, gastrointestinal bleeding (GIB), four hospital admissions due to melena and anemia, and one episode of hematochezia.

2.2. Genetic analysis

The Shahid Beheshti University of Medical Sciences Ethical Committee has approved this study. The study was carried out in accordance with the Declaration of Helsinki's tenets. Informed consent was obtained from parents prior to participation in the study. Genomic DNA was extracted using the conventional salting-out method from blood samples of the patients as well as their parents. Whole-exome sequencing (WES) was then carried out for the patients using the SureSelectXT V6 + UTRs Kit (Agilent Technologies, Lake Forest, CA, USA) to enrich genomic DNA. Next, using the NovaSeq6000 platform, paired-end sequencing was carried out in accordance with the manufacturer's instructions (Illumina, San Diego, CA, USA). Using Burrows-Wheeler Aligner (BWA v0.5.9), reads were aligned against the human reference genome (UCSC hg19, NCBI build 37.1). Duplicate reads were removed using the Picard tool (v1.118). The test platform generally examined >95% of the targeted regions with a sensitivity above 99%, and the average target coverage was 100×. The Genome Analysis Toolkit (GATK v3.7) was used to implement variant calling, which allows for the detection of indels and single-nucleotide polymorphisms (SNPs). Moreover, the variant annotation was performed with ANNOVAR software. We utilized the 1000 Genomes Project, dbSNP 138, NHBL Exome Variant Server (EVS), ESP6500, and Iranome (www.iranome.com) to select variations based on a minor allele frequency of <0.01. Additional filtering was performed based on mutation effects, frequency of variants in other populations, and previous reports of mutations in literature and Clinvar database. Eventually, variant prioritization was done based on phenotypic plausibility. The identified variant was confirmed by Sanger sequencing in both patients. Targeted sequencing of the parents was performed to examine the possibility of being the carrier for the particular variant.

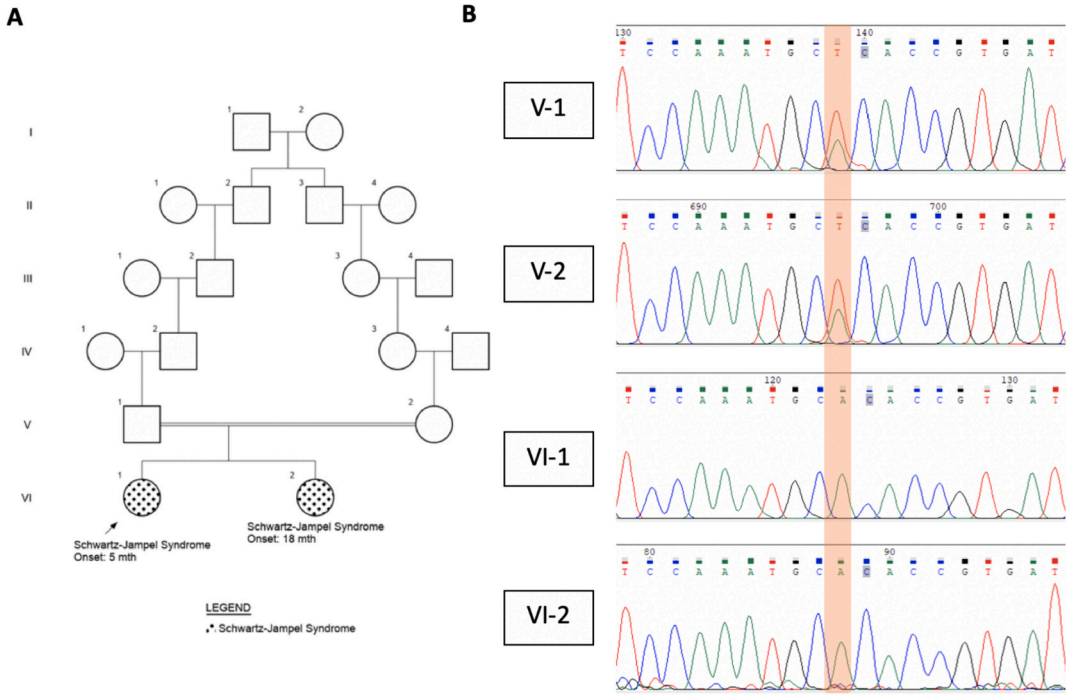

Fig. 1. A) The pedigree of the family. B) Sanger sequencing of probands shows one novel homozygous variant c.4314 + 4 A > T in *HSPG2* gene, while their parents are heterozygous for this variant.

2.3. Data gathering of SJS patients reported molecularly and clinically

An extensive literature search was conducted to compile a comprehensive collection of reported cases of SJS, encompassing both molecular and clinical data. Relevant keywords and MeSH terms were utilized to systematically search electronic databases such as PubMed, Scopus, and Web of Science. The investigation was limited to English-language studies published from the start of the databases until August 31, 2023. Inclusion criteria involved studies that reported on patients diagnosed with SJS based on clinical presentation and molecular genetic testing targeting the *HSPG2* gene. Studies that did not specifically address SJS or were not directly related to SJS, such as studies examining other conditions or unrelated topics, were excluded. Additionally, studies that did not provide adequate molecular or clinical information relevant to SJS were also excluded. Two independent reviewers evaluated the identified articles' titles, abstracts, and full texts to select relevant studies. Any discrepancies were resolved through consensus or consultation with a third reviewer. Data, including demographic information, clinical features, *HSPG2* gene mutations, and outcomes, were extracted and synthesized from the selected studies. Subsequently, the data were analyzed to provide an overview of the reported cases of SJS, encompassing molecular findings and clinical characteristics (Table 1).

3. Results

The WES analysis results revealed one novel homozygous variant, NM_005529.7:c.4314 + 4 A > T, located in intron 34 of the *HSPG2* gene in both probands. This variant was not reported in the gnomAD or RGC Million Exome Variant Browser databases, and there is no report of pathogenicity of this variant in Clinvar except for the one that was submitted by this center (Genomic Research Center, Shahid Beheshti University of Medical Sciences). The identified variant was following the patients' clinical presentation and was confirmed by Sanger sequencing in patients. Segregation analysis of the parents showed that they are heterozygous for variant c.4314 + 4 A > T in the *HSPG2* gene. This variant was classified as a likely pathogenic variant regarding the ACMG classification.

A comprehensive review of cases with SJS that reported genetic mutations has also been conducted. A total of 50 patients from 12 previous studies and the present study have been included (Table 1), with 44 reported variants in the *HSPG2* gene (NM_005529.7).

Among these variants, the most prevalent variant is the missense mutation c.4432C > T in 3 families with Turkish, Belgian, and Mauritian origins. There are also two other missense mutations, c.10982G > A and c.10355G > A, and one splicing mutation, c.11208-7G > A, each reported in two families of different nationalities.

Gender distribution in our study population was seven males, seven females, and 36 patients of unknown gender. Data also shows a diverse distribution of SJS patients and *HSPG2* variants in different countries, with the highest incidence in the Tunisian (9 patients) and Turkish (7) populations. Other nationalities include Saudi Arabian (4), Indian, Chinese, French (3), South African, Brazilian, Irish, Iraqi, Taiwanese (2), Dutch, Belgian, Mauritian, Japanese, and Caucasian (1). There were also four patients with unknown nationalities. We reported the first variant in two Persian probands in the present study. Two cases studied by Lin et al. have 30 and 27 years of age at onset of symptoms. Other patients in this study represented the symptoms in the range of neonatal period to 5 years of age with a mean of 18 months (SD = 14.53). Thirty-one out of fifty patients have a family history of consanguineous marriage.

In analyzing the zygosity of study patients, 28 cases are mutant homozygous, and 20 subjects are compound heterozygous for the *HSPG2* gene. Furthermore, the variants were classified into different mutation types, and the most prevalent type was missense mutations (12), followed by splicing mutations (9), frameshift mutations (8), nonsense and non-coding mutations (each one 3), and deletion (2) and ten mutations were also unknown mutation types. Forty-five patients showed all SJS diagnostic features, including myotonia, chondrodysplasia, and mask-like face. While all 50 cases showed at least two of the three mentioned features, only two cases did not show myotonia, two did not show chondrodysplasia, and one patient had an undetermined mask-like face. Only three patients in previous studies and our two cases show neurodevelopmental delay. Other signs and symptoms, including infantile-onset seizure, chronic respiratory failure, atrial septum defect, kidney dysfunction, and DM type 2, were only observed in three patients who had shown other gene mutations in WES.

4. Discussion

This investigation presents the clinical manifestations and molecular features of two patients from an Iranian family with consanguineous marriage, displaying myotonia, chondrodysplasia, and mask-like faces suggestive of SJS. After conducting whole-exome sequencing (WES), we discovered a novel homozygous variant within the *HSPG2* gene (NM_005529.7:c.4314 + 4 A > T) which was segregated within the family. According to the ACMG guidelines, this variant was classified as likely pathogenic. This novel variant could probably alter the splicing of the HSPG2 gene and hence disrupt the structure and function of the Perlecan's core protein, leading to clinical manifestations of SJS.

SJS is a genetic condition characterized by permanent muscle stiffness (myotonia) and bone abnormalities (chondrodysplasia) caused by a mutation in the *HSPG2* gene on chromosome 1p36.1-p35. Myotonia interferes with eating, sitting, and walking, leading to a mask-like face due to sustained contraction of facial muscles. Although this disorder's symptoms usually become prominent in early childhood, most patients experience an expected lifespan. Two patients in this study displayed common signs and symptoms of SJS in early childhood, along with a history of peptic ulcer disease (PUD) and gastrointestinal bleeding (GIB), which are not typical of SJS.

Furthermore, we have provided an updated literature review of the previous *HSPG2* variants causing SJS. A total of 44 reported variants in the *HSPG2* gene (NM_005529.7) have been identified. Our data demonstrate a diverse distribution worldwide and an equal gender distribution among study patients. Notably, our patients represent the first SJS cases of Persian origin. These variants were further categorized into different mutation types, with missense, splicing, and frameshift mutations being the most prevalent. Most of the reviewed cases in this study showed a family history of consanguinity, and all of these patients had a homozygous mutation. Whereas 14 subjects who did not have consanguineous marriage in their family history, all showed compound heterozygous mutations. This information is in line with the autosomal recessive inheritance of SJS. The perlecan protein coded by the *HSPG2* gene has five domains. Stum et al. conducted research and found that variants that cause SJS are located in domains 2–5, while no variants were found in domain 1. In three different studies carried out later, three other variants, namely c.337G > A, c.318 + A > G, and c.212G > A were discovered, which are related to SJS and are located in domain 1 of the perlecan protein.

Forty-five of the reviewed patients showed all SJS diagnostic features, including myotonia, chondrodysplasia, and mask-like face. While all 50 cases showed at least two of the three mentioned features, only two cases did not show myotonia, two did not show chondrodysplasia, and one patient had an undetermined mask-like face. Only three patients in previous studies, as well as our two cases, exhibited neurodevelopmental delay, which is uncommon among SJS patients. It should be mentioned that all three previously reported cases had other variants in the *WWOX* and *PRMT7* genes along with the *HSPG2* gene, and these variants could be responsible for their neurological disorder.

Regarding gastrointestinal bleeding, this phenomenon has only been reported in one study. In 2016, Polat and colleagues published a case report that presented a 17-month-old patient with SJS experiencing severe iron deficiency anemia and chronic gastroduodenal bleeding. This was the first instance of such symptoms being observed in a patient

Table 1
A review of cases with SJS that reported genetic mutations and clinical data.

No	patient number in study	Gender	Nationality	Zygosity	Mutation at the cDNA level (NM_005529.7)	Mutation at the protein level	Consanguinity	Age at onset	myotonia	Chondrodysplasia	Mask-like face	Neuro-developmental delay	Rare manifestations	Study
–	1	F	Iranian	Hom	c.4314 + 4 A > T	Splicing	Y	4 m	Y	Y	Y	Y	GI bleeding	Present study
–	2	F	Iranian	Hom	c.4314 + 4 A > T	Splicing	Y	18 m	Y	Y	Y	Y	GI bleeding	
1	1	NR	Tunisian	Hom	c.8464 + 4 A > G	Splicing	Y	2y, 6 m	Y	Y	Y	NR	NR	Nicole et al. [1]
2	2	NR	Tunisian	Hom	c.8464 + 4 A > G	Splicing	Y	2y, 6 m	Y	Y	Y	NR	NR	
3	3	NR	Tunisian	Hom	c.8464 + 4 A > G	Splicing	Y	2y, 6 m	Y	Y	Y	NR	NR	
4	4	NR	Tunisian	Hom	c.4740G > A	p.S1580S	Y	2y	Y	Y	Y	NR	NR	
5	5	NR	Tunisian	Hom	c.4740G > A	p.S1580S	Y	3y	Y	Y	Y	NR	NR	
6	6	NR	Turkish	Hom	c.4595G > A	p.C1532Y	Y	1y	Y	Y	Y	NR	NR	
7	1	M	NR	Compound Het	c.7374 + 4 A > G complete loss of intron 60	Splicing Large deletion	NR	3y	Y	Y	Y	NR	N	Arikawa-Hirasawa et al.
8	2	M	NR	Compound Het	c.8544G > A c.8759-3del9	p.K2848K Splicing	NR	4 m	Y	Y	Y	NR	N	al. [16]
9	1	NR	NR	Hom	7108-bp homozygous deletion beginning at the 5′ portion of exon 96 and extending well beyond the 3′ flanking sequence of *HSPG2*	Large deletion	NR	3 m	Y	Y	Y	NR	N	
10	1	NR	Tunisian	Hom	c.4741-10 T > G	Splicing	Y	2y, 6 m	Y	Y	Y	NR	NR	Stum et al. (2006)
11	2	NR	Tunisian	Hom	c.4741-10 T > G	Splicing	Y	2y, 6 m	Y	Y	Y	NR	NR	
12	3	NR	Tunisian	Hom	c.4741-10 T > G	Splicing	Y	2y, 6 m	Y	Y	Y	NR	NR	al. [8]
13	4	NR	Tunisian	Hom	c.11208-7G > A	Splicing	Y	1y	Y	Y	Y	NR	NR	
14	5	NR	Saudi Arabian	Hom	c.11208-7G > A	Splicing	Y	1 m	Y	Y	Y	NR	NR	
15	6	NR	Saudi Arabian	Hom	c.11208-7G > A	Splicing	Y	6 m	Y	Y	Y	NR	NR	
16	7	NR	Saudi Arabian	Hom	c.11208-7G > A	Splicing	Y	9 m	Y	Y	Y	NR	NR	
17	8	NR	Saudi Arabian	Hom	c.11208-7G > A	Splicing	Y	2y	Y	Y	Y	NR	NR	
18	9	NR	Turkish	Hom	c.574 + 481C > T	Intronic	Y	6 m	Y	Y	Y	NR	NR	
19	10	NR	Turkish	Hom	c.12899 + 1G > A	Splicing	Y	3 m	Y	Y	Y	NR	NR	
20	11	NR	Turkish	Hom	3424 bp deletion (c.720_1654del) extending from nucleotide 17 of exon 8 to nucleotide 293 of intron 13	Large deletion	Y	6 m	Y	Y	Y	NR	NR	
21	12	NR	Turkish	Compound Het	c.4432C > T c.12191delC	p.R1478C p.P4065RfsX5	N	3y	Y	N	Y	NR	NR	
22	13	NR	Turkish	Hom	c.4648C > T	p.R1550C	Y	2y	Y	Y	Y	NR	NR	
23	14	NR	South African	Hom	c.7006 + 1G > A	Splicing	Y	birth	Y	Y	Y	NR	NR	
24	15	NR	South African	Hom	c.7006 + 1G > A	Splicing	Y	birth	Y	Y	Y	NR	NR	
25	16	NR	Dutch	Compound Het	c.10982G > A c.11192delG	p.R3661Q p.G3731EfsX30	N	2y, 6 m	Y	Y	Y	NR	NR	
26	17	NR	Belgian	Compound Het	c.4432C > T c.10354C > T	p.R1478C p.R3452X	N	2y	Y	Y	Y	NR	NR	
27	18	NR	Mauritian	Homo	c.4432C > T	p.R1478C	Y	NR	Y	Y	Y	NR	NR	

(*continued on next page*)

Table 1 (*continued*)

No	patient number in study	Gender	Nationality	Zygosity	Mutation at the cDNA level (NM_005529.7)	Mutation at the protein level	Consanguinity	Age at onset	myotonia	Chondrodysplasia	Mask-like face	Neuro-developmental delay	Rare manifestations	Study
28	19	NR	French	Compound Het	c.4473-4475del c.10355G > A	p.L1491del p.R3452Q	N	1y	Y	Y	Y	NR	NR	
29	20	NR	French	Compound Het	c.7874-2 A > G c.9642delC	Splicing p.Q3215KfsX7	N	4y	Y	Y	Y	NR	NR	
30	21	NR	French	Compound Het	c.6179delC The second mutant allele was not reported	p.P2060LfsX3	N	2y	Y	Y	Y	NR	NR	
31	22	NR	Indian	Compound Het	c.11792-11793insC The second mutant allele was not reported	p. L3932AfsX32	N	8 m	Y	Y	Y	NR	NR	
32	23	NR	Indian	Compound Het	c.11792-11793insC The second mutant allele was not reported	p. L3932AfsX33	N	8 m	Y	Y	Y	NR	NR	
33	24	NR	Indian	Compound Het	c.665-675del The second mutant allele was not reported	p.R222QfsX5	N	2y	Y	Y	Y	NR	NR	
34	25	NR	Brazilian	Hom	c.9326delA	p. H3109PsfX16	Y	9 m	Y	Y	Y	NR	NR	
35	26	NR	Brazilian	Hom	c.9326delA	p. H3109PsfX16	Y	9 m	Y	Y	Y	NR	NR	
36	27	NR	Irish	Compound Het	c.3055C > T c.10355G > A	p.P1019L p.R3452Q	N	2y	Y	Y	Y	NR	NR	
37	28	NR	Irish	Compound Het	c.8680C > T c.10982G > A	p.Q2894X p.R3661Q	N	birth	Y	Y	Y	NR	NR	
38	1	F	Chinese	Compound Het	c.10776delT c.5702-5G > A	p.A3592SfsX6 Splicing	NR	8 m	Y	Y	Y	N	N	Dai et al. [17]
39	1	NR	NR	Homo	c.4740 + 5G > A	Splicing	Y	1y	Y	Y	Y	N	N	Das Bhowmik et al. (2015)
40	1	M	Japanese	Compound Het	c.3263 T > C c.9181C > T	p.L1088P p.Q3061X	N	2y, 3 m	Y	Y	Y	N	N	Iwata et al. [18]
41	1	F	Chinese	Compound Het	c.8788G > A c.11671 + 5G > A	p.E2930L Splicing	NA	2y	Y	Y	Y	N	N	Yan et al. [19]
42	1	F	Caucasian	Compound Het	c.337G > A c.3059C > T	p.E113K p.P1020L	N	neonatal	Y	Y	NR	Y	infantile onset seizure, chronic respiratory failure, atrial septum defect	Davids et al. [20]
43	1	F	Turkish	Hom	IVS24A > G	NR	Y	4y	Y	Y	Y	NR	N	Gürbüz et al. [21]
44	1	M	Chinese	Compound Het	c.10736 T > G c.1208G > A	p.I3578S p.C403Y	N	5y	Y	N	Y	N	N	Ding et al. [22]
45	1	M	Taiwanese	Hom	c.1125C > G	p.C375W	Y	30y	Y	Y	Y	N	N	Lin et al.
46	2	F	Taiwanese	Hom	c.1125C > G	p.C375W	Y	27y	Y	Y	Y	N	N	[23]
47	1	M	Iraqi	Compound Het	c.10721–2dupA c.212G > A	Splicing p.S71N	Y	6 m	N	Y	Y	Y	seizure, kidney dysfunction, DM type 2	Poquérusse et al. [24]
48	2	M	Iraqi	Compound Het	c.10721–2dupA c.212G > A	Splicing p.S71N	Y	birth	N	Y	Y	Y	seizure, kidney dysfunction, DM type 2	

Hom: Homozygous, Het: Heterozygous, Y: Yes, N: No, M: Male, F: Female, NR: Not Reported.

with SJS [11]. Other studies have investigated the role of perlecan, a heparan sulfate proteoglycan found in the extracellular matrix of various tissues, in the development of bleeding disorders. In a study by Costel et al. on Perlecan-null mice, exhibited bleeding in multiple tissues, including the heart, brain, lungs, and skin, which were associated with the formation of microaneurysms [12]. Another study on perlecan-null mice also showed severe bleeding within several tissues, such as the lung, skin, and brain, caused by the weakening of the blood vessel wall [13]. Further research by Nonaka et al. in 2015 revealed that a deficiency in perlecan leads to endothelial dysfunction, as evidenced by a reduction in endothelial nitric oxide synthase (eNOS) gene expression. This endothelial dysfunction was manifested by endothelium-dependent relaxation [14]. Siegel's study demonstrated that perlecan plays a crucial role in regulating membrane polarization in endothelial cells and smooth muscle cells (SMCs). Perlecan also, along with type IV collagen, interacts with other basal membrane components and provides basal membrane stability; hence, mutations in perlecan and type IV collagen have been associated with brain and pericardial hemorrhage. Moreover, perlecan is attached to the endothelial cells in the lumen of blood vessels and regulates vasoconstriction and relaxation of blood vessels [15].

Considering all these studies together, perlecan seems to be pivotal in the vascular structure and interacts with various extracellular component matrices and could play a crucial role in mucosal stability; hence, any disruption in perlecan function and structure could lead to bleeding in different organs [12]. Overall, these studies provide valuable insights into the role of perlecan in the development of bleeding disorders and endothelial dysfunction. This evidence could lay a basis regarding the various clinical manifestations of bleeding in patients with SJS, and the reported patients in this study with PUD and GIB also support this evidence.

In conclusion, in the present study, we reported two patients with SJS caused by a novel homozygous variant of *HSPG2*. Both patients showed a less common symptom, GIB, and unfortunately, both have passed away. This study could provide evidence regarding bleeding disorders in SJS patients and underscores the importance of considering chronic gastrointestinal blood loss in the approach to SJS patients. Furthermore, we provided a comprehensive literature review on reported variants related to SJS and analyzed the different molecular and clinical aspects of this syndrome.

Ethical approval and consent to participate

This study was approved by the Research Ethics Committee of Faculty of Medicine, Shahid Beheshti University of Medical Sciences (Approval Number: IR.SBMU.MSP.REC.1398.575), and was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from adult participants to participate in the study. Written informed consent was obtained from parents of kin next of kin for all participants aged under 18.

Consent for publication

Informed consent for publication of identifiable information/ images in open access journal was obtained from all study participants.

ClinVar accession

SCV000784480.

Funding

No external funding was used for this study.

CRediT authorship contribution statement

Iman Elahi Vahed: Writing – original draft. **Sahand Tehrani Fateh:** Writing – review & editing. **Melika Kamali:** Formal analysis, Data curation. **Farzad Hashemi-Gorji:** Writing – review & editing, Formal analysis, Data curation. **Zahra Esmaeilzadeh:** Writing – review & editing. **Hossein Sadeghi:** Writing – review & editing, Formal analysis. **Mohammad Miryounesi:** Writing – review & editing, Supervision, Conceptualization. **Mohammad-Reza Ghasemi:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing Interest

The authors declare no conflict of interest.

Data availability

The data and materials that support the findings of this study are available from the corresponding authors, upon request.

Acknowledgments

Sincere gratitude to the families for their participation in this study.

References

[1] S. Nicole, C.S. Davoine, H. Topaloglu, et al., Perlecan, the major proteoglycan of basement membranes, is altered in patients with Schwartz-Jampel syndrome (chondrodystrophic myotonia), Nat. Genet. 26 (4) (2000) 480–483, https://doi.org/10.1038/82638.

[2] M.C. Farach-Carson, D.D. Carson, Perlecan–a multifunctional extracellular proteoglycan scaffold, Glycobiology 17 (9) (2007) 897–905, https://doi.org/10.1093/glycob/cwm043.

[3] R.F. Wintle, R. Kisilevsky, D. Noonan, A.M. Duncan, In situ hybridization to human chromosome 1 of a cDNA probe for the gene encoding the basement membrane heparan sulfate proteoglycan (HSPG), Cytogenet. Cell Genet. 54 (1–2) (1990) 60–61, https://doi.org/10.1159/000132956.

[4] G.R. Dodge, I. Kovalszky, M.L. Chu, et al., Heparan sulfate proteoglycan of human colon: partial molecular cloning, cellular expression, and mapping of the gene (HSPG2) to the short arm of human chromosome 1, Genomics 10 (3) (1991) 673–680, https://doi.org/10.1016/0888-7543(91)90451-j.

[5] P. Kallunki, R.L. Eddy, M.G. Byers, M. Kestila, T.B. Shows, K. Tryggvason, Cloning of human heparan sulfate proteoglycan core protein, assignment of the gene (HSPG2) to 1p36.1——p35 and identification of a BamHI restriction fragment length polymorphism, Genomics 11 (2) (1991) 389–396, https://doi.org/10.1016/0888-7543(91)90147-7.

[6] M. Paulsson, P.D. Yurchenco, G.C. Ruben, J. Engel, R. Timpl, Structure of low density heparan sulfate proteoglycan isolated from a mouse tumor basement membrane, J. Mol. Biol. 197 (2) (1987) 297–313, https://doi.org/10.1016/0022-2836(87)90125-2.

[7] R.V. Iozzo, Basement membrane proteoglycans: from cellar to ceiling, Nat. Rev. Mol. Cell Biol. 6 (8) (2005) 646–656, https://doi.org/10.1038/nrm1702.

[8] M. Stum, C.S. Davoine, S. Vicart, et al., Spectrum of HSPG2 (Perlecan) mutations in patients with Schwartz-Jampel syndrome, Hum. Mutat. 27 (11) (2006) 1082–1091, https://doi.org/10.1002/humu.20388.

[9] K.D. Rodgers, T. Sasaki, A. Aszodi, O. Jacenko, Reduced perlecan in mice results in chondrodysplasia resembling Schwartz-Jampel syndrome, Hum. Mol. Genet. 16 (5) (2007) 515–528, https://doi.org/10.1093/hmg/ddl484.

[10] J.R. Martinez, A. Dhawan, M.C. Farach-Carson, Modular proteoglycan Perlecan/HSPG2: mutations, phenotypes, and functions, Genes (Basel) 9 (11) (2018), https://doi.org/10.3390/genes9110556.

[11] I. Polat, P. Karaoglu, U. Yis, S.H. Kurul, Schwartz-Jampel syndrome with gastroduodenal bleeding, J. Pediatr. Neurosci. 11 (3) (2016) 255–257, https://doi.org/10.4103/1817-1745.193351.

[12] M. Costell, E. Gustafsson, A. Aszodi, et al., Perlecan maintains the integrity of cartilage and some basement membranes, J. Cell Biol. 147 (5) (1999) 1109–1122, https://doi.org/10.1083/jcb.147.5.1109.

[13] E. Arikawa-Hirasawa, H. Watanabe, H. Takami, J.R. Hassell, Y. Yamada, Perlecan is essential for cartilage and cephalic development, Nat. Genet. 23 (3) (1999) 354–358, https://doi.org/10.1038/15537.

[14] R. Nonaka, T. Iesaki, S. de Vega, et al., Perlecan deficiency causes endothelial dysfunction by reducing the expression of endothelial nitric oxide synthase, Physiol. Rep. 3 (1) (2015), https://doi.org/10.14814/phy2.12272.

[15] G. Siegel, M. Malmsten, E. Ermilov, Anionic biopolyelectrolytes of the syndecan/perlecan superfamily: physicochemical properties and medical significance, Adv. Colloid Interf. Sci. 205 (2014) 275–318, https://doi.org/10.1016/j.cis.2014.01.009.

[16] E. Arikawa-Hirasawa, A.H. Le, I. Nishino, et al., Structural and functional mutations of the perlecan gene cause Schwartz-Jampel syndrome, with myotonic myopathy and chondrodysplasia, Am. J. Hum. Genet. 70 (5) (2002) 1368–1375, https://doi.org/10.1086/340390.

[17] L. Dai, F. Fang, Y. Huang, H. Cheng, C. Ren, Clinical and genetic features of Schwartz-Jampel syndrome in a Chinese child: case report and literature review, Zhonghua Er Ke Za Zhi 53 (11) (2015) 855–859.
[18] S. Iwata, M. Ito, T. Nakata, et al., A missense mutation in domain III in HSPG2 in Schwartz-Jampel syndrome compromises secretion of perlecan into the extracellular space, Neuromuscul. Disord. 25 (8) (2015) 667–671, https://doi.org/10.1016/j.nmd.2015.05.002.
[19] W. Yan, J. Dai, D. Shi, et al., Novel HSPG2 mutations causing Schwartz-Jampel syndrome type 1 in a Chinese family: a case report, Mol. Med. Rep. 18 (2) (2018) 1761–1765, https://doi.org/10.3892/mmr.2018.9143.
[20] M. Davids, T. Markello, L.A. Wolfe, et al., Early infantile-onset epileptic encephalopathy 28 due to a homozygous microdeletion involving the WWOX gene in a region of uniparental disomy, Hum. Mutat. 40 (1) (2019) 42–47, https://doi.org/10.1002/humu.23675.
[21] G. Gurbuz, H.M. Albayrak, Schwartz Jampel syndrome responding positively to carbamazepine therapy: a case report and a novel mutation, Turk. J. Pediatr. 61 (6) (2019) 967–970, https://doi.org/10.24953/turkjped.2019.06.023.
[22] M. Zhang, X. Ding, Q. Zhang, et al., Exome sequencing of 112 trios identifies recessive genetic variants in brain arteriovenous malformations, J. Neurointerv. Surg. 13 (6) (2021) 568–573, https://doi.org/10.1136/neurintsurg-2020-016469.
[23] P.Y. Lin, J.H. Hung, C.K. Hsu, Y.T. Chang, Y.T. Sun, A novel pathogenic HSPG2 mutation in Schwartz-Jampel syndrome, Front. Neurol. 12 (2021) 632336, https://doi.org/10.3389/fneur.2021.632336.
[24] J. Poquerusse, W. Whitford, J. Taylor, et al., Novel PRMT7 mutation in a rare case of dysmorphism and intellectual disability, J. Hum. Genet. 67 (1) (2022) 19–26, https://doi.org/10.1038/s10038-021-00955-5.