Goldberg-Shprintzen Syndrome Associated with a Novel Variant in the *KIFBP* Gene

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Established Facts

- Goldberg-Shprintzen syndrome (GOSHS) is associated with *KIFBP* gene mutations.
- To date, 16 different biallelic *KIFBP* mutations have been identified in 34 patients with GOSHS.

Novel Insights

- This novel homozygous frameshift deletion mutation in the last exon of the *KIFBP* gene provides enrichment of mutational databases.
- This is the closest mutation to the 3'-UTR of the gene in the last exon and contributes to the understanding of the phenotypic features of the syndrome

Keywords

KIFBP · Novel mutation · Megacolon

Abstract

Goldberg-Shprintzen syndrome (GOSHS) is characterized by microcephaly, developmental delay, dysmorphic features, Hirschsprung disease (HSCR), and brain anomalies. The kinesin family binding protein (*KIFBP*; MIM 60937) gene has been identified as the responsible gene of the syndrome. To date, 16 different biallelic *KIFBP* mutations have been identified in 34 patients with GOSHS. Even though most of these mutations are nonsense and frameshift, 3 missense mutations have also been described. Here, we report an 18-month-old patient with microcephaly, developmental delay, dysmorphic features and HSCR. Exome analysis was performed to

clarify the etiology of the clinical features. A previously unreported homozygous c.1723delC (p.H575Ifs*19) variant was detected in the last exon 7 of *KIFBP* which led to GOSHS. According to our findings, we suggest that this mutation expands mutational databases and contributes to the understanding of the phenotypic features of the syndrome.

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Introduction

Goldberg-Shprintzen syndrome (GOSHS; 609460) is an autosomal recessive disease characterized by intellectual disability, gyral abnormalities, Hirschsprung disease (HSCR), and dysmorphic facial features. It was first described by Goldberg and Shprintzen [1981]. The *KIFBP*

Table 1. Clinical and molecular features of the GOSHS patients

Exon	KIFBP variant protein	Case	Reference	Aganglionic megacolon	Brain malformation	Developmental delay	Microcephaly	Dysmorphic features
1	Glu84*	4	Hurst, 1988	3	4	4	4	4
1	Arg90*	5	Brooks et al., 1999, 2005; Drevillon et al., 2013	4	5	5	4	5
2–3	Asn143fsX1	2	Valence et al., 2013	–	2	2	2	1
3	Pro189Ser	1	MacKenzie et al., 2020	1	1	1	1	1
3	Ser200*	2	Drevillon et al., 2013	2	2	2	2	2
3	Arg202Ilefs*2	2	Drevillon et al., 2013	1	2	2	2	2
4	Glu240*	2	Brooks et al., 2005	1	2	Not available	1	2
5–6	EX5–6DEL	3	Dafsari et al., 2015; MacKenzie et al., 2020	2	–	3	3	
6	EX6 DEL	2	MacKenzie et al., 2020	1	1	2	2	
6	Gln326*	1	Salehpour et al., 2017	1	1	1	1	1
7	Ala373Asnfs*17	2	Murphy et al., 2006	–	2	2	2	1
7	Ser427Gly	1	MacKenzie et al., 2020	–	1	1	1	–
7	Tyr466X	1	Bruno et al., 2011	1	–	1	1	1
7	Ile506Asnfs*3	2	MacKenzie et al., 2020	1	1	2	2	2
7	Gln518Asnfs*11	2	Goldberg and Shprintzen, 1981	2	2	2	2	2
7	Glu565 AsnfsX15	1	MacKenzie et al., 2020	1	1	1	1	1
7	H575Ifs*19	1	Present case	1	1	1	1	1
34				22/34 (64%)	28/34 (82%)	32/34 (94%)	32/34 (94%)	26/34 (76%)

gene was identified by Brooks et al. [2005] revealing homozygous mutations which caused GOSHS. The *KIFBP* gene encodes a KIF-binding protein (KBP) which is expressed in the central and enteric nervous systems [Drévillon et al., 2013]. KBP dysfunction affects neuronal migration, axonal extension, and neuronal apoptosis; therefore, it is thought to cause brain anomalies in patients with GOSHS [Chang et al., 2019]. Most patients also have HSCR, which is caused by a delay or arrest of enteric neural crest cell migration [Webster, 1973]. To date, 16 different *KIFBP* mutations have been described in patients with GOSHS, the clinical findings of these 34 patients are summarized in Table 1 [Hurst et al., 1988; Brooks et al., 1999, 2005; Murphy et al., 2006; Bruno et al., 2011; Drévillon et al., 2013; Dafsari et al., 2015; Salehpour et al., 2017; MacKenzie et al., 2020].

In this current case report, we present an 18-month-old patient with GOSHS associated with a novel homozygous variant in the last exon of *KIFBP*.

Clinical Report

A 3-month-old female patient presented to our clinic with dysmorphic facial findings and developmental delay. She was born by normal vaginal delivery at term as the first child of her parents who were first-degree cousins. Birth weight (3,300 g, 50th percentile), birth height (50 cm, 50th percentile), and head circumference (33 cm, 10th–25th percentile) were normal. At birth, she had hypoto-

nia and dysmorphic facial features including hypertelorism, downslanting palpebral fissures, and a preauricular skin tag. She had feeding difficulties when she was 2-days-old, and bilious vomiting and no stool production were observed on day 7.

Abdominal ultrasound imaging showed dilated bowel loops; the clinical findings and radiologic studies were considered as intestinal malrotation. During surgery, the cecum was at the upper right quadrant of the abdomen and Meckel's diverticulum was detected. The small intestines were observed to be highly dilated due to the obstructive occlusion. A meconium plug was removed, and an ileostomy was performed at the level of the terminal ileum. Ganglion cells were not seen in the pathologic specimen examination.

Two months later, she underwent surgery for a second time due to small bowel perforation. The posterior fossa was found as small in transfontanelle ultrasound imaging.

When she was aged 3 months, her physical examination was as follows: weight 3,550 g, height 53 cm, head circumference 33.5 cm. Dysmorphic features were sparse hair, microcephaly, acrobrachycephaly, metopic ridge, ptosis, hypertelorism, downslanting palpebral fissures, and a thick philtrum (Fig. 1). Furthermore, she had severe hypotonia, and her developmental milestones were delayed. In an examination at age 10 months, failure to thrive and microcephaly were additional findings, and her weight was 5,850 g (<3rd percentile), height 65 cm, (<3rd percentile), and head circumference 36.5 cm (<3rd percentile). She was unable to hold her head up. Brain MRI revealed cerebral atrophy in the parietal and occipital lobes and pachygyria. No epileptic discharge was observed in her EEG. An eye examination revealed bilateral lower oblique hyperfunction and poor object tracking. Large copy number variations were excluded with chromosomal microarray (CytoScanOptima Suite, Affymetrix). Exome sequencing was performed using the IDT xGEN Exome Research Panel on an Illumina Nova-

Fig. 1 Facial dysmorphic features of the patient. **a** Sparse hair, metopic ridge, hypertelorism. **b** Downslanting palpebral fissures, thick philtrum, and tented upper lip.

Fig. 2 Sanger sequencing analysis of *KIFBP* gene variants. **a** Proband with homozygous deletion. **b** Mother of the proband with heterozygous deletion. **c** Father of the proband with heterozygous deletion.

Seq platform. The variants were evaluated according to ACMG2015 [Richards et al., 2015]. Analysis revealed a likely pathogenic novel homozygous deletion variant c.1723delC (p.H575Ifs*19) in the last exon of the *KIFBP* (NM_015634.3) gene. This frameshift deletion was closer to the 3'-UTR region than in previously reported 16 *KIFBP* mutations. Segregation analysis revealed both parents were in the heterozygous state, which validates the transmission from the parents to the proband (Fig. 2).

Discussion

GOSHS is a rare disease caused by homozygous mutations in the *KIFBP* gene. To date, 16 different *KIFBP* gene mutations have been reported in 34 patients, most of which were nonsense and frame-shift mutations leading to loss of

KBP function (Table 1). In our case, we describe a female patient with microcephaly, dysmorphic facial findings, developmental delay, HSCR, and cerebral atrophy carrying a novel homozygous frameshift deletion variant in the last exon of the *KIFBP* gene. Microcephaly, central nervous system findings, HSCR, distinctive facial features, and developmental delay are the main features of the syndrome and are present in most patients with GOSHS.

Microcephaly, reported in 32 of the previous 34 patients with GOSHS, is the most common finding of the disease and accompanies other brain anomalies in most patients, especially polymicrogyria and cerebral atrophy. These anomalies usually cannot be diagnosed in early cranial imaging; nevertheless, cranial MRI was performed in our patient with microcephaly at the age of 10 months, and cerebral atrophy was detected; however, because gyrus anomalies could not be detected, they could not be ruled out.

HSCR is generally recognized with meconium plug syndrome and intestinal obstruction in the neonatal period and may accompany Meckel's diverticulum, as in our patient. HSCR was reported in 22 of 34 patients with mutations in the *KIFBP* gene, suggesting that there is a lack of penetrance for HSCR. However, HSCR may not be present in every patient, thus gastrointestinal findings differ among individuals with *KIFBP* mutations.

Genetic syndromes in which HSCR is the main symptom include GOSHS and Mowat-Wilson syndrome. Although these 2 syndromes have common findings such as microcephaly, intellectual disability, and HSCR, they differ from each other by facial features and molecular diagnoses. In our case, exome analysis allowed a simultaneous search of variants in many genes that led to similar phenotypic findings and allowed us to reach a diagnosis more quickly.

Hypertelorism and prominent ears are the most common distinctive dysmorphic features reported in patients with GOSHS, accompanying developmental delay occurs in 94% of all the patients. Our patient's facial features were similar to those previously reported in patients with GOSHS. Hypotonia, microbrachycephaly, hypertelorism, and short philtrum were the most prominent dysmorphic features of the current case. Although not previously reported in patients with GOSHS, she had bilateral pre-auricular skin tags, which were considered an incidental finding because they were also present in her grandfather.

In conclusion, we present a patient with microcephaly, cerebral atrophy, developmental delay, dysmorphic facial features, and HSCR, and define a new homozygous frameshift deletion mutation in the last exon of the *KIFBP* gene. This is the first Turkish patient with GOSHS in the literature.

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Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki Principles. Written informed consent was obtained from the patient's parents for the publication of this case report and accompanying images.

Conflict of Interest Statement

The author has no conflict of interest to declare.

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Author Contributions

The current case report was designed and written by Pelin Ozyavuz Cubuk. The data was collected by Pelin Ozyavuz Cubuk.