

CASE REPORT

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# Genetic analysis diagnosed Bardet–Biedl syndrome in a patient with a clinical diagnosis of Senior–Løken syndrome



Yuko Fujii<sup>1</sup>, Hideki Matsumura<sup>1</sup>, Akihiko Shirasu<sup>2</sup>, Hyogo Nakakura<sup>3</sup>, Satoshi Yamazaki<sup>1</sup>, Naoya Morisada<sup>4</sup>, Kazumoto Iijima<sup>4</sup> and Akira Ashida<sup>1\*</sup> 

## Abstract

**Background:** Senior–Løken syndrome (SLS) and Bardet–Biedl syndrome (BBS) are ciliopathies. SLS is characterized by retinitis pigmentosa (RP) and familial nephronophthisis, leading to end-stage kidney disease, while BBS is characterized by six major symptoms: RP, polydactyly, obesity, genital abnormalities, learning difficulties, and renal defects. Ciliopathies have been diagnosed on a phenotypic basis, but diagnosis can now be established by genetic testing, using techniques such as next-generation sequencing. Here, we report a patient clinically diagnosed with SLS but diagnosed with BBS 13 years later using next-generation sequencing.

**Case presentation:** The patient was diagnosed with RP at the age of 6 years. She had some difficulty in social interactions and pre-obesity, but no polydactyly. At the age of 8 years, she was diagnosed with chronic kidney disease, anemia, and liver dysfunction. Kidney and liver biopsy revealed renal tubule cysts, tubule membrane disruption, and liver fibrosis. Therefore, SLS was diagnosed but no *NPHP1* mutations were detected. Peritoneal dialysis was started at the age of 9 years, and she underwent kidney transplantation with a graft from her father at the age of 13 years. At the age of 21 years, she again underwent genetic testing for most of the mutations associated with ciliopathy. This revealed a homozygous frameshift mutation in intron 11 of *SDCCAG8*.

**Conclusions:** Mutations in *SDCCAG8* are known to be causative of SLS and BBS without polydactyly. The fact that the patient had RP, some difficulty in social interactions, pre-obesity, juvenile nephronophthisis, liver fibrosis, bronchial asthma, and otitis media suggested BBS. However, some of these are not specific symptoms for BBS and she had few typical symptoms of BBS. Therefore, a definitive diagnosis of BBS was difficult without genetic analysis. Because many more patients with *SDCCAG8* mutations have extrarenal manifestations like the current patient than standard nephronophthisis patients, careful monitoring of extrarenal manifestations is needed to improve patient management.

**Keywords:** Ciliopathy, Bardet–Biedl syndrome, Senior–Løken syndrome, *SDCCAG8*

\* Correspondence: [ped006@osaka-med.ac.jp](mailto:ped006@osaka-med.ac.jp)

<sup>1</sup>Department of Pediatrics, Osaka Medical College, 2-7 Daigakumachi, Takatsuki, Osaka, Japan

Full list of author information is available at the end of the article



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## Background

Senior–Løken syndrome (SLS) and Bardet–Biedl syndrome (BBS) are ciliopathies. SLS is characterized by retinitis pigmentosa (RP) and familial nephronophthisis (NPHP), which leads to end-stage kidney disease. BBS is characterized by six major symptoms: RP, polydactyly, obesity, genital abnormalities, learning difficulties, and renal defects. Although some variations in secondary symptoms have been reported, typical secondary symptoms of BBS are as follows: developmental delay, ataxia, poor coordination, speech defects, brachydactyly or syndactyly, dental defects, olfactory deficits, craniofacial dysmorphism, diabetes mellitus, congenital heart disease, hypertension, liver abnormalities, bronchial asthma, otitis, and rhinitis. A patient with more than four major symptoms, or three major symptoms with more than two secondary symptoms, can be definitively diagnosed with BBS [1, 2]. Thus far, ciliopathies have been diagnosed on a phenotypic basis; however, diagnosis can now be established by genetic testing using techniques such as next-generation sequencing. Here, we report a patient clinically diagnosed with SLS but diagnosed with BBS 13 years later using next-generation sequencing.

## Case presentation

The female patient was born at term and exhibited a normal birth weight with no apparent congenital malformation. Her parents were consanguineous cousins with no major health problems. From childhood, the patient became easily exhausted and suffered from bronchial asthma, chronic bronchitis, atopic dermatitis, and secretory otitis media, which required middle ear ventilation at the age of 5 years. Since then, she experienced poor eyesight in the evening and was diagnosed with RP at the age of 6 years. When she was 8 years old, her Rohrer index was 152 indicating pre-obesity, and she experienced right cervical lymphadenopathy and underwent a blood test because of her extremely poor general status. Her inflammatory response was very low; additional blood test results were as follows: urea nitrogen, 70.9 mg/dL; creatinine, 3.0 mg/dL; hemoglobin, 7.4 g/dL; aspartate transaminase, 137 IU/L; and alanine aminotransferase, 115 IU/L. Urinary analysis revealed a specific gravity of 1.010 and a urinary beta-2 microglobulin level of > 16,000 µg/L, together with microhematuria and microproteinuria; this indicated end-stage renal failure, anemia, and liver dysfunction. Kidney and liver biopsy procedures revealed renal tubular cysts, tubular membrane disruption, and liver fibrosis. Therefore, SLS was diagnosed, but no *NPHP1* mutations were detected.

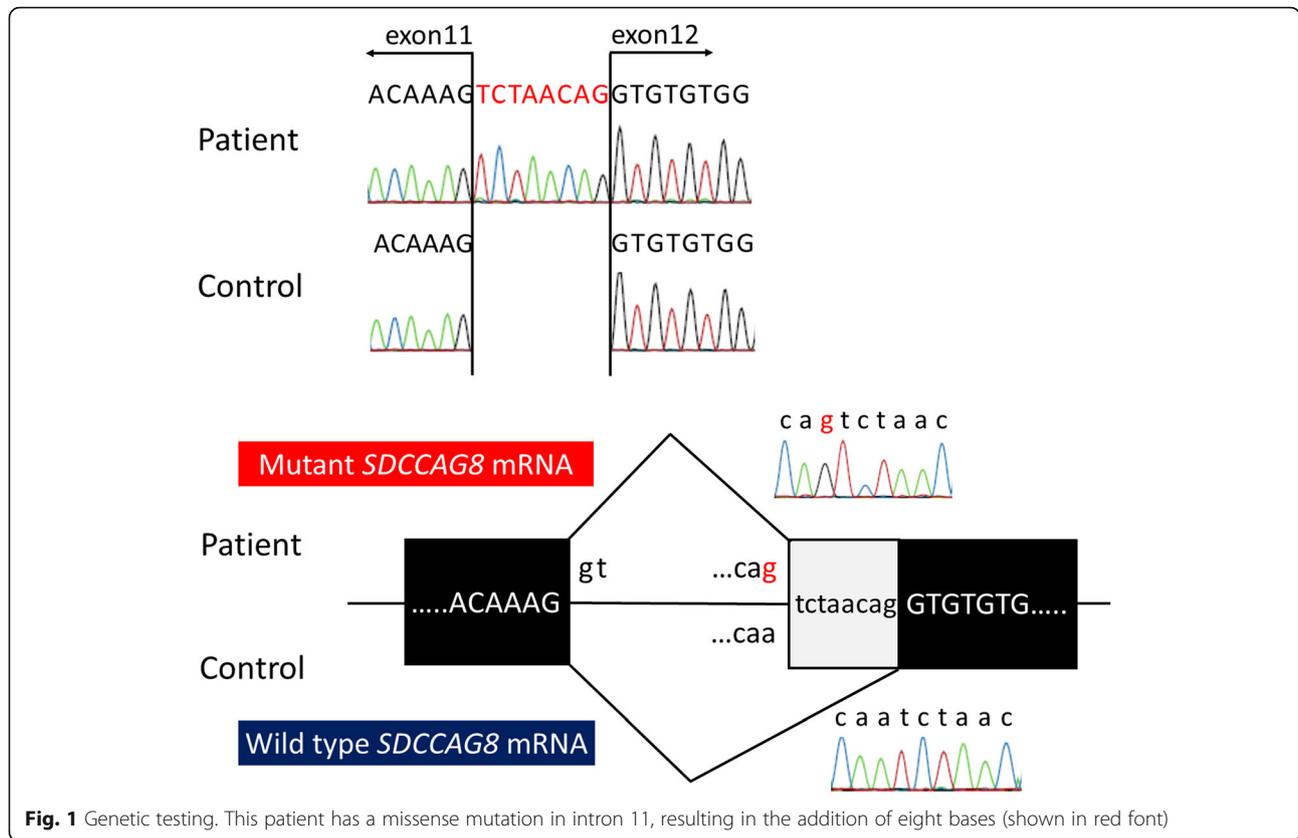
Peritoneal dialysis was begun at the age of 9 years, and she underwent kidney transplantation, with a graft from her father, at the age of 13 years. Before this, from the age of 12 years, she received growth hormone therapy

because of her extremely short height (130.4 cm, – 3.5 SD). However, at the age of 13 years, luteinizing hormone-releasing hormone agonist therapy was started to increase growth. She exhibited no morphological abnormalities in her genital organs and menarche occurred at the age of 15 years; the development of secondary sex characteristics was rather slow but almost normal. No obvious developmental delay or learning disabilities were evident. Although her behavior was rather childish and caused some difficulties in appropriate social interactions, she learned Braille and obtained a national qualification as a massage practitioner. Hypothyroidism and mild hypertension had been evident since she was an elementary school student, but she did not have diabetes mellitus, central nervous system problems, or anosmia.

At the age of 21 years, we obtained written informed consent for genetic testing from the patient and her parents, and this was approved by the ethics board of Osaka Medical College (approval number 1867-01). She underwent genetic testing for most of the mutations associated with ciliopathy; these new tests revealed a homozygous mutation in intron 11 of *SDCCAG8* (c.1357-9G>A), which caused splice site changes leading to a frameshift mutation (Fig. 1). The incidence rate of this mutation is extremely rare: 1/66,556 alleles in a genetic database of subjects in North America [3], and no alleles in a genetic database of subjects in Japan [4]. Because the *SDCCAG8* mutation can be causative of both SLS and BBS [1, 2, 5–8], we noted her possibility of having BBS. Considering her RP, pre-obesity, difficulty in appropriate social interactions, juvenile NPHP, liver fibrosis, bronchial asthma, and otitis media, we diagnosed BBS. Her mother was initially confused by this new diagnosis, but eventually appreciated that the difficulties experienced in her daughter's upbringing were partially caused by the phenotype of BBS.

## Discussion and conclusions

We experienced challenges in our attempt to diagnose a patient with BBS, largely because this is a very rare disease. Moreover, most of us are not experts in the diagnosis of BBS and we have not treated other patients with BBS before. The primary diagnostic criteria for BBS are phenotypic in nature, but blindness and end-stage kidney disease affect the interpretation of other diagnostic phenotypes. For example, blindness may affect a patient's social characteristics and learning abilities, thereby making it difficult for them to read or befriend other children; moreover, kidney disease can lead to obesity in association with malnutrition, overeating and/or drinking, and a lack of exercise. Therefore, it is difficult to know whether these symptoms are caused by blindness, kidney disease, or overall manifestations of BBS. Moreover, some forms of symptomatic treatment



may make phenotypes more difficult to clearly discern. For instance, when growth hormone therapy was administered to our patient, it may have interfered with obesity, while luteinizing hormone-releasing hormone agonist therapy could have made some genital abnormalities less prominent. Furthermore, BBS is a progressive disease, and most cases are diagnosed in older patients.

Mutations in *SDCCAG8* (*NPHP10/BBS16*) are causative of both SLS and BBS without polydactyly. However, *SDCCAG8* mutations are quite rare, with only 1–3% of BBS cases exhibiting a causative mutation in *SDCCAG8* [1, 2, 5]. In this case, we first clinically diagnosed the patient’s disease as SLS [6–8]. However, after next-generation sequencing revealed a mutation in *SDCCAG8*, we reviewed her phenotype and finally diagnosed BBS. The childish character, difficulty in social interactions, and pre-obesity (body mass index, 27) the patient had suffered from since childhood are major symptoms of BBS in addition to RP and NPHP. Additionally, she displayed some secondary symptoms including liver fibrosis, bronchial asthma, and otitis media. However, these symptoms are not limited to BBS. Moreover, patients harboring a mutation in *SDCCAG8* lack polydactyly which is a major symptom of BBS [5]. Thus, a differential diagnosis of BBS would not have been possible without genetic analysis.

Severe developmental delay or obesity is thought to be rare in cases of BBS with a *SDCCAG8* mutation. Additionally, considering the absence of polydactyly and the patient’s age at the time of sight loss and the development of end-stage renal disease, her phenotype was compatible with this diagnosis [5, 7]. We suspect that many SLS patients harboring a mutation in *SDCCAG8* may actually suffer from BBS, so are likely to remain misdiagnosed. Therefore, we urge clinicians to carefully monitor SLS patients to determine if BBS-associated complications emerge. Furthermore, as additional cases of *SDCCAG8* mutations are reported, BBS professionals can stratify characteristics associated with *SDCCAG8* mutation phenotypes; in contrast, BBS patients could be sub-classified based on mutations rather than on phenotypes.

In conclusion, we describe a Japanese female patient with ciliopathy harboring a mutation in *SDCCAG8*. At first, she was diagnosed with SLS, but subsequent genetic testing and detailed phenotypic observations strongly supported a re-diagnosis of BBS. Because only a few cases of *SDCCAG8* mutations have been reported previously of which none exhibit polydactyly, it is difficult for general pediatricians to confidently diagnose BBS. We propose that general pediatricians or physicians should perform genetic testing of NPHP patients, with

**Table 1** NPHP and NPHP-RC patients with *SDCCAG8* mutations in previous and present reports

Individual-family no.	Clinical diagnosis	ESKD age	Extrarenal manifestations	Hetero/homo	Nucleotide change	Amino acid change	Origin	Consanguineous	Journal
1-1	SLS	11	RP, generalized seizures	hom	c.421-?_740+?del	p.E141_R247del107fs	Europe	Yes	[5, 7]
2-1	SLS	7	RP						
3-2	BBS	13	RP, MR, hypogenitalism, obesity	hom	c.679A>T	p.K227X	Europe	Yes	
4-2	BBS	13	RP, MR, hypogenitalism, obesity						
5-3	BBS	22	RP, obesity, MR, hypogenitalism, peripheral neuropathy	het/het	c.696T>G/ c.740+1delG	p.Y232X/ p.R247fsX250	Northern Europe	No	
6-3	BBS	ND	RP, MR, obesity						
7-3	SLS	28	RP, obesity, clinodactyly						
8-4	BBS	23	RP, MR, obesity	hom	c.740+356C>T	Loss of exonic splicing enhancer site	Gypsy	Yes	
9-4	BBS	13	RP, MR, obesity						
10-4	SLS	10	RP, MR						
11-4	SLS	6	RP						
12-4	BBS	31	RP, obesity, hypogenitalism						
13	SLS	14	RP, intracranial arachnoid cyst, MR	hom	c.1068+1G>A	Obligatory splice site	Turkey	Yes	
14-5	SLS	7	RP, MR	hom	c.1339-1340insG	p.E447fsX463	Algeria	Yes	
15-5	SLS	4	RP						
16-6	SLS	4	RP	hom	c.1420delG	p.E474fsX493	La Réunion	Yes	
17-6	SLS	14	RP						
18	BBS	ND	RP, MR, obesity	het/het	c.1444delA/ c.1627_1630delGATA	p.T482fsX493/ p.D543fsX566	India	No	
19-7	NPHP	<10	polycystic ovary syndrome	hom	c.1796T>G	p.L599X	Pakistan	Yes	
20-7	NPHP	<9	No						
21	SLS	22	RP	hom	c.1946-1949delGTGT	p.C649fsX658	Germany	ND	
22	BBS	5	RP, MR, obesity	hom	c.1120C>T	p.R374X	Turkey	Yes	
23	SLS	17	RP	het	c.679A>T/ c.784G>T	p.K227X/p.E262X	Germany	ND	[12]
24	NPHP	5	No	hom	c.696 T>G	p.Y232X	Turkey	Yes	
25	SLS	>15	RP, polycystic ovaries, hepatomegaly	hom	c.1444delA	p.T482LfsX12	USA	ND	
26	SLS	12	RP	het	c.1420delG	p.E474SfsX20	Spain	ND	
27	NPHP	ND	No	hom	c.1444delA	p.T482LfsX12	Arab	Yes	[13]
28	SLS	3	RP, MR	hom	c.845_848delITTTG	p.C283X	Japan	Yes	[11]
29	NPHP	2	MR	hom	c.849_852delITTTG	p.C283X	Japan	No	[14]
30 (this case)	BBS	9	RP, obesity	hom	c.1357-9G>A	New acceptor AG-site	Japan	Yes	

Several patients were reported with otitis media and asthma. *ESKD* end-stage kidney disease, *SLS* Senior-Løken syndrome, *BBS* Bardet-Biedl syndrome, *NPHP* Nephronophthisis, *hom* Homozygous, *hetero* Heterozygous, *NPHP-RC* Nephronophthisis-related ciliopathies, *RP* Retinitis pigmentosa, *MR* Mental retardation, *ND* No data

informed consent of the patient and/or parents, and that those with *SDCCAG8* mutations should be carefully monitored to determine if they develop SLS or BBS-associated complications. Reporting of additional cases will help clarify phenotypic characteristics associated with *SDCCAG8* mutations and may determine whether there is a need for new groupings based on genetic mutations rather than phenotypes. These changes will contribute to improved management of patients with ciliopathies.

**Mini-review**

**NPHP and NPHP-related ciliopathies (NPHP-RC)**

NPHP is a ciliopathy characterized by the presence of small cysts in the cortico-medullary border region of the kidney and histologically progressive glomerulosclerosis and tubulointerstitial nephritis. NPHP almost always causes end-stage kidney disease and is the cause of 5–10% of all end-stage kidney diseases in pediatric patients. Although most cases of NPHP are thought to be caused by a single mutation, the causative mutation has only been detected in 40% of all NPHP patients with the remainder being unidentified. Approximately 10–20% of NPHP patients have extrarenal symptoms such as SLS and BBS, so are diagnosed with NPHP-RC [6, 8–11]. Because a single mutation associated with a disease in

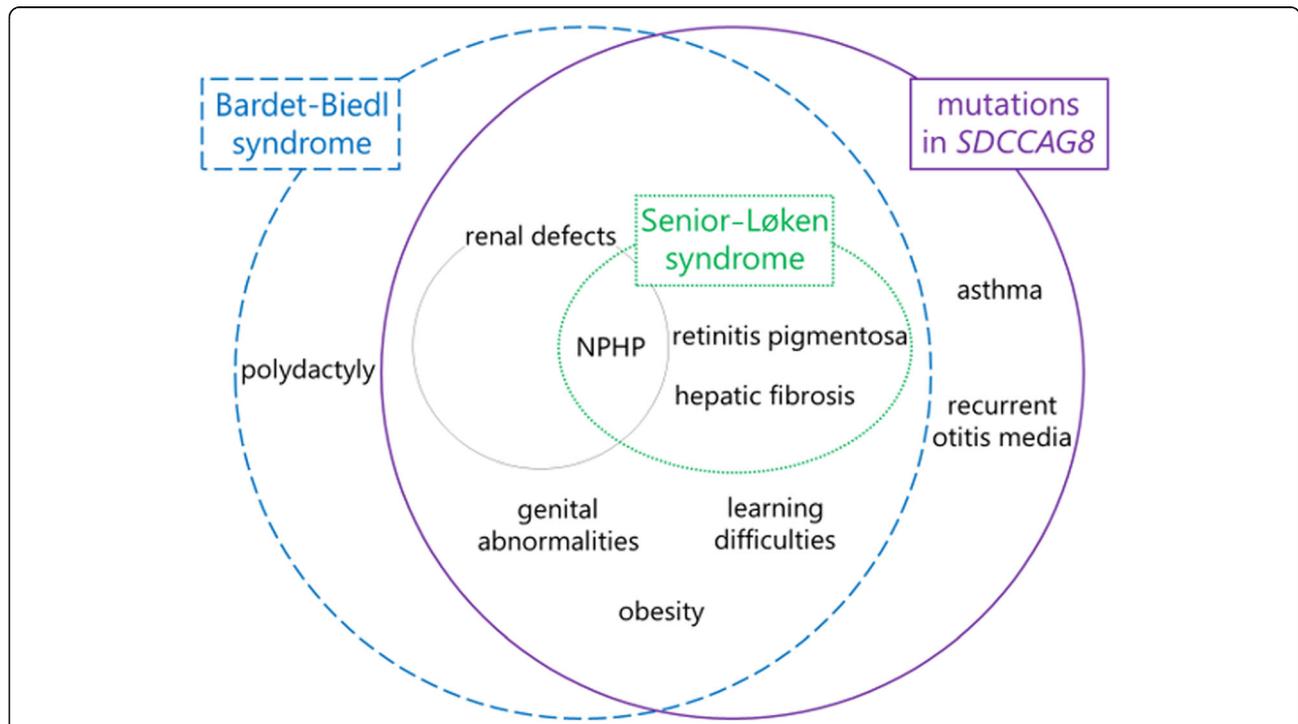
NPHP-RC often causes another disease, a definitive diagnosis is difficult for many general pediatricians. Therefore, some experts regard NPHP-RC as a comprehensive disease.

**SLS**

SLS is characterized by NPHP and RP and accounts for 10% of NPHP and NPHP-RC cases [6, 8–11]. SLS patients who are not blind from birth are described as having the late-onset form of disease. Such patients typically have night blindness then develop blindness during school age. Juvenile nephronophthisis is common, and end-stage kidney disease occurs by the age of 13 on average.

**BBS**

BBS is defined as six major symptoms: RP, polydactyly, obesity, genital abnormalities, learning difficulties, and renal defects, and several secondary symptoms also occur. A patient with more than four major symptoms, or three major symptoms with more than two secondary symptoms, can be definitively diagnosed with BBS [1, 2]. Of the major symptoms, polydactyly is a symbolic symptom of BBS but this occurs in only 63–81% of all BBS patients [1]. Obesity and learning difficulty are not specific for BBS. Genital abnormalities are symbolic for BBS boys because most are sterile, while BBS girls sometimes



**Fig. 2** Disease concepts of SLS, BBS, and NPHP-RC patients carrying *SDCCAG8* mutations. Major symptoms of SLS, BBS, and NPHP-RC patients carrying *SDCCAG8* mutations are described. No polydactyly has been reported among NPHP-RC patients with *SDCCAG8* mutations. Asthma and otitis media are common symptoms of ciliopathy and are frequently reported in NPHP-RC patients with *SDCCAG8* mutations. NPHP, nephronophthisis

have genital anomalies but menarche is not typically early or late. BBS is therefore often difficult to diagnose in girls because they lack two typical symptoms of BBS.

### **SDCCAG8**

*SDCCAG8*, encoding serologically defined colon cancer antigen 8, is also known as *NPHP10* or *BBS16*. A mutation in *SDCCAG8* is causative of both SLS and BBS [1, 2, 5–8]. However, only 1–3% of all BBS patients harbor *SDCCAG8* mutations [1, 2, 5, 7, 8].

Therefore, SLS and BBS patients carrying a *SDCCAG8* mutation lack any consistent pattern of symptoms except that none have polydactyly. Although only 10–20% of NPHP patients have extrarenal symptoms, most NPHP patients with *SDCCAG8* mutations have multiple extrarenal symptoms (Table 1). Therefore, careful monitoring of extrarenal symptoms by general physicians is needed. The concepts of SLS, BBS, and NPHP-RC patients carrying *SDCCAG8* mutations are shown in Fig. 2.

### **Abbreviations**

SLS: Senior-Løken syndrome; BBS: Bardet-Biedl syndrome; RP: Retinitis pigmentosa; NPHP: Nephronophthisis; NPHP-RC: Nephronophthisis-related ciliopathies

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### **Authors' contributions**

YF and AA wrote an initial draft of the manuscript. All of the authors collected, analyzed, and interpreted the data and revised the manuscript critically. All of the authors approved the final version of the manuscript and were responsible for all aspects of the work, ensuring that questions related to its accuracy or integrity were appropriately investigated and resolved. All of the authors read and agree with the submission of this manuscript.

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### **Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

### **Ethics approval and consent to participate**

For genetic testing, written informed consent was obtained from the patient (approval number of the ethics board of Osaka Medical College, 1867-01). For this type of case report, formal consent from a local ethics committee is not required.

### **Consent for publication**

We offered the patient and her mother the opportunity to read the manuscript and obtained their written consent for publication. The manuscript and the informed consent form were approved by the ethics board of Osaka Medical College (approval number 2017-OMC-1).

### **Competing interests**

The authors declare that they have no competing interests.

### **Author details**

<sup>1</sup>Department of Pediatrics, Osaka Medical College, 2-7 Daigakumachi, Takatsuki, Osaka, Japan. <sup>2</sup>Department of Pediatrics, Hirakata City Hospital, 2-14-1 Kinyahonmachi, Hirakata, Osaka, Japan. <sup>3</sup>Department of Hemodialysis and Apheresis, Arisawa General Hospital, 12-14 Nakamiyashigashinocho,

Hirakata, Osaka, Japan. <sup>4</sup>Department of Pediatrics, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Japan.

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