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ARTICLE

Clinical spectrum of male patients with OFD1 mutations

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Abstract

Oral-facial-digital syndrome type 1 (OFD1) is a ciliopathy characterized by oral, facial, and digital malformations that are often accompanied by polycystic lesion of the kidney and central nervous involvement. OFD1 shows an X-linked recessive inheritance caused by mutation in the *OFD1* gene (Xp22.2). The disease is generally considered embryonic lethal for hemizygous males. However, males with *OFD1* mutations were recently reported. Here, we report four additional Japanese male patients with *OFD1* variants and describe the variable clinical manifestation and disease severity among the four patients. Patient 1 with pathogenic indels including a 19-bp deletion and 4-bp insertion (c.2600–18_2600delinsACCT) had end-stage renal disease (ESRD) with bilateral cystic kidneys and sensory hearing loss. He showed neither intellectual disability nor facial or digital dysmorphism. Patient 2 with a missense variant in exon 7 (c.539 A > T, p.Asp180Val) presented head circumference enlargement, brachydactyly, high-arched palate, micropenis, severe global developmental delay, and ESRD. Patient 3 had a single base substitution at the splice donor site of intron 16 (c.2260 + 2 T > G) causing a 513-bp deletion at the transcript level. The patient had chronic kidney disease and speech delay, but no oral, facial, or digital dysmorphism. His uncle (patient 4) carried the same *OFD1* variant and showed ESRD with extra-renal malformations including obesity and micropenis, which was previously diagnosed as Bardet-Biedl syndrome. The *OFD1* mutations were not lethal in these four male patients, likely because the three mutations were in-frame or missense. This report provided insights into the onset mechanism and phenotype-genotype association in patients with *OFD1* mutations.

Introduction

Oral-facial-digital syndrome type 1 (OFD1; MIM #311200) is a rare X-linked congenital disorder characterized by oral, facial, and digital abnormalities and is mostly seen in females. The incidence of OFD1 is approximately 1 in 50,000 live births [1]. This disorder is often accompanied with polycystic lesion of the kidney and a broad range of central nervous involvement. Cystic changes in the liver and pancreas have also been described in patients with OFD1. Central nervous involvement, which may include intellectual disability, hydrocephalus, cerebellar anomalies, porencephaly, and corpus callosum defects, is seen in 40% of patients with OFD1 [2]. Polycystic lesion of the kidney occurs in approximately 15–50% of female patients, most of

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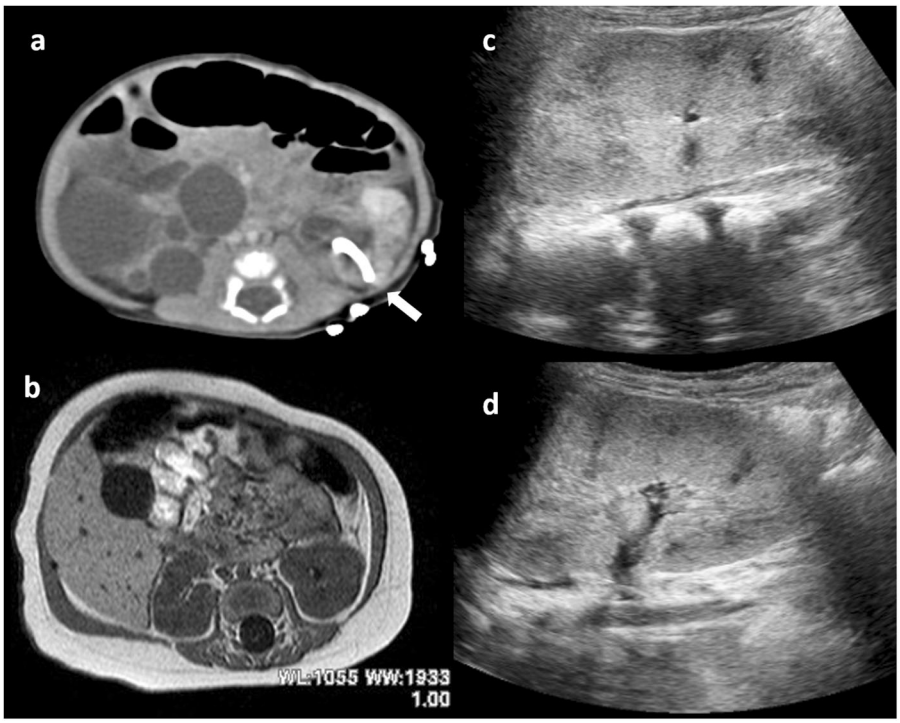

Fig. 1 Renal imaging of patient 1 (**a**), patient 2 (**b**), and patient 3 (**c** and **d**). **a** Left renal hydronephrosis and right multicystic dysplastic kidney shown by abdominal computed tomography in patient 1. White arrow indicates left nephrostomy catheter. **b** Magnetic resonance image showing bilateral enlarged kidney and small cysts in patient 2. **c**, **d** Bilateral hyperechogenic kidney (**c**, left; **d**, right) in patient 3

whom progress to end-stage renal disease (ESRD) [1, 2]. In contrast, those without polycystic lesion of the kidney have normal renal function [3]. Some patients without external features are diagnosed by visceral features such as polycystic kidney in adulthood [4].

OFD1 is located on the short arm of the X chromosome (Xp22.2), and its mutations are responsible for OFD1 [5]. To date, at least 157 *OFD1* mutation sites have been cataloged in the Human Gene Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk/). *OFD1* encodes a centrosome/basal body protein necessary for the assembly of primary cilia and left-right axis determination [6]. Mouse mutants of *Ofd1* have absent or malformed cilia in various tissues [7]. Thus, OFD1 is considered a form of ciliopathy. Phenotypic variability is often seen in affected females including those within the same family, which may be partly due to the varying degree of somatic mosaicism resulting from random X inactivation [8].

OFD1 is generally thought to cause lethality in males during the fetal period, and almost all affected patients are females. However, recently, males with *OFD1* mutation have been described. As in classical OFD1, there are four phenotypes of *OFD1* mutation in males: X-linked Joubert syndrome with polydactyly and retinal involvement (JBTS10), Simpson-Golabi-Behmel syndrome type 2 (SGBS2), retinitis pigmentosa 23 (RP23), and unclassified malformation syndromes [9]. However, male patients are so rare that very little is currently known about the phenotype-genotype correlation for OFD1 in males. We now report four Japanese male patients from three families who had novel *OFD1* mutations. They all had chronic kidney diseases including ESRD, but with varying degrees of extra-renal malformations and central nervous system involvement. Our findings may elucidate the phenotype-genotype correlation in OFD1.

Materials and methods

Patients

Patient 1

Patient 1 was an 8-year-old boy who was born to non-consanguineous parents at 36 weeks and 5 days of gestation. His birth weight was 2881 g. During the neonatal period, he was diagnosed with an acute kidney injury due to a severe upper-pole primary ureteropelvic junction obstruction of the left kidney and non-functional right kidney (Fig. 1a). Ultrasound examination showed bilateral cystic kidneys with a multicystic dysplastic right kidney. After an emergency nephrostomy, his kidney function improved temporarily but then progressively declined. At the age of 8, he progressed to ESRD and underwent a kidney transplant. He also had bilateral sensory hearing loss, but no other abnormalities including facial, oral, or digital deformities. He had no failure of growth (height 116.9 cm, body weight 20.3 kg) or intellectual disability,

and brain magnetic resonance imaging did not show abnormalities, including molar tooth sign. He is now 11 years old, and his transplanted renal function is preserved.

Patient 2

Patient 2 was a 4-year-old boy. He was also born to non-consanguineous parents at 37 weeks and 1 day of gestation. His birth weight was 3160 g. A leptomeningeal cyst and hydrocephalus were detected during the neonatal period. He presented progressively worsening kidney dysfunction at the age of 1 and has been on peritoneal dialysis due to ESRD since the age of 2. Magnetic resonance imaging showed bilateral enlarged kidneys with numerous cysts (Fig. 1b), and kidney biopsy indicated nephronophthisis. He had congenital deformations including head circumference enlargement, brachydactyly, high-arched palate, micropenis, and optic nerve hypoplasia. He also displayed a severe intellectual disability and motor developmental delay. He is now 6 years old. He undergoes peritoneal dialysis and shows growth failure (height 82.0 cm, weight 12.3 kg).

Patient 3

Patient 3 was a 3-year-old boy. He was also born to non-consanguineous parents at 38 weeks and 4 days of gestation. His birth weight was 2638 g. At the age of 1, bilateral kidney enlargement with high intensity was detected by ultrasound (Figs. 1c, d). At that time, his estimated glomerular filtration rate was 62.2 ml/min/1.73 m^2, although his urinalysis findings were normal, and he was diagnosed with chronic kidney disease. He displayed a speech delay and autistic features with hyperactivity, but no facial, oral, or digital abnormality. He exhibited short stature (85.6 cm) at the age of 3. He had a family history of renal disease, and his pedigree is shown in Fig. 2. One of his uncles (II-1 in Fig. 2) also had ESRD and died at a young age. His mother (II-4) and grandmother (I-2) had normal urinalysis findings, with no oral and dental symptoms.

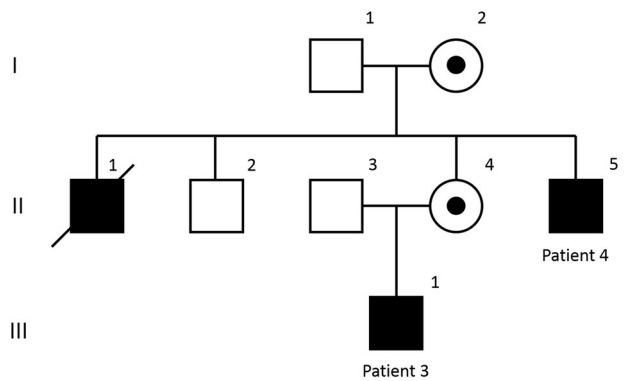

Fig. 2 Family tree of patient 3 and patient 4

Patient 4

Patient 4 was a 29-year-old male and a maternal uncle of patient 3 (II-5 in Fig. 2). He had ESRD and underwent a renal transplantation at the age of 14. At the age of 13, he also had extra-renal malformations such as obesity (height 156 cm and body weight 91.7 kg), borderline intellectual disability (his intelligence quotient was 76 at the age of 12), and micropenis. His serum levels of follicle stimulating hormone and luteinizing hormone were normal (3.56 mIU/ml and 4.06 mIU/ml), and testosterone was low (0.91 ng/dl). He had no retinal disorder or hearing loss. He was diagnosed with Bardet-Biedl syndrome based on the clinical manifestations.

Analysis of *OFD1* mutations

Genetic analysis was performed after informed consent was received. This study was approved by the institutional review board of Kobe University School of Medicine. Genomic DNA was isolated from peripheral blood leukocytes of the patients and their family using the QuickGene whole blood kit S (Kurabo, Osaka, Japan). Additionally, total RNA was extracted from blood leukocytes using the NucleoSpin RNA Blood (Macherey-Nagel, Hoerdt, France) and an RNA stabilization agent (RNAlater; Thermo Fisher Scientific, Waltham, MA, USA). Total RNA was reverse-transcribed to cDNA using SuperScript III First-Standard Synthesis SuperMix (Thermo Fisher Scientific) for cDNA analysis.

Targeted sequencing using next-generation sequencing (NGS) was conducted for 91 genes in patient 1 (Supplementary Table 1) and 128 genes in patient 2 (Supplementary Table 2) associated with congenital anomalies of the kidney and urinary tract or nephronophthisis-related ciliopathies as cataloged in the OMIM database (http://www.omim.org/) or PubMed (http://www.ncbi.nlm.nih.gov/pubmed). NGS samples were prepared using the HaloPlex target enrichment system kit (Agilent Technologies, Santa Clara, CA, USA) according to the manufacturer's instructions. The captured DNA samples were amplified by PCR and sequenced using the MiSeq platform (Illumina, San Diego, CA, USA). Analysis of the NGS data was performed using the SureCall software (Agilent Technologies). The mutations detected by NGS were confirmed by standard Sanger direct sequencing using the 3130 Genetic Analyzer (Thermo Fisher Scientific). For patient 3, the *OFD1* mutation was directly detected by standard Sanger sequencing without NGS because the patient's family tree indicated the mutation. The direct sequencing data were analyzed by

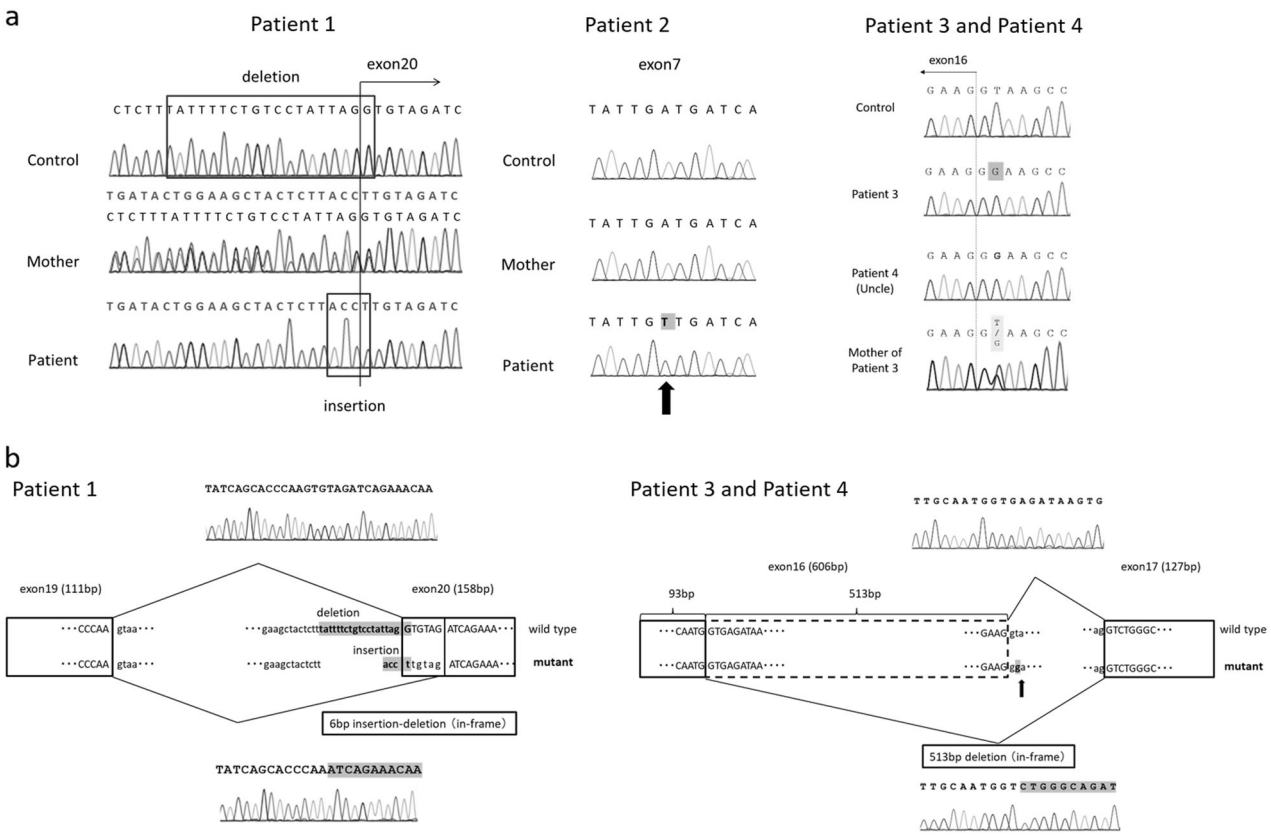

Fig. 3 Gene mutations identified in the patients. **a** Confirmation of the genetic analysis by Sanger sequencing. **b** cDNA analysis and schematic representation of the changes in *OFD1* mRNA

CLC Main Workbench version 6.7.1 (CLC bio, Aarhus, Denmark). For variant descriptions, NM_003611.2 was used as a reference sequence of *OFD1*.

For prioritized candidate novel exonic variants, wANNOVAR (http://wannovar.wglab.org/) was used as an in silico evaluation tool to predict whether the mutations were pathogenic.

Results

We identified three different mutations by NGS and direct sequencing of *OFD1* in the four male patients. In patients 3 and 4, their pedigree indicated an X-linked dominant ciliopathy; therefore, their mutations were analyzed only by direct sequencing of *OFD1*.

In patient 1, we identified a novel 19-bp deletion and 4-bp insertion (c.2600–18_2600delinsACCT) in exon 20 of *OFD1* and its splice acceptor site, resulting in an in-frame mutation (p.Ser867_Asp869delinsAsn) (Figs. 3a, b, left panels). His mother was heterozygous for this aberration.

In patient 2, we identified a novel missense variant in exon 7 of *OFD1* (c. 539 A > T, p.Asp180Val) (Fig. 3a, middle panel). His mother did not carry this mutation; thus, the mutation was likely de novo in the patient. This variant was estimated to be pathogenic by in silico analysis using wANNOVAR. The analysis showed a CADD score of 27.7 and predicted the mutation as deleterious by PROVEAN and SIFT algorithms, probably damaging by PolyPhen2, and disease-causing by Mutation Taster.

In patient 3 and 4, a single base substitution at the splice donor site of intron 16 (c.2260 + 2 T > G) was detected. The result of the cDNA analysis showed that this aberration caused a 513-bp in-frame deletion in exon 16 and 17 (Fig. 3a, b, right panels).

Discussion

We presented two familial and two sporadic male patients with novel mutations in *OFD1*. All patients had severe renal dysfunction, but they presented different extra-renal phenotypes.

Phenotype-genotype correlation in female OFD1 patients has been shown to be dependent on the location of the mutation. Previous reports indicated that the location of mutations causing typical OFD1 in female patients extends only to exon 17 out of 23 coding exons in *OFD1* [1, 10].

Table 1 Clinical manifestations in male patients with *OFD1* mutations

Patient or reference no.	Patient 1	Patient 2	Patient 3	Patient 4	9, 12, 13, 17, 18, 19	14	15	16, 20
No. of patients (families)					11 (8)	3 (1)	2 (1)	4 (2)
Clinical diagnosis	unclassified	unclassified	unclassified	BBS	JBTS	SGBS2	RP	unclassified
Facial								
Macrocephaly	−	+	−	−	5/9	1/3	N/A	3/3
Low-set ears	−	±	−	−	2/8	1/3	N/A	2/3
Microphthalmia	−	−	−	−	0/8	0/3	N/A	2/3
Hypertelorism	−	−	−	−	0/8	0/3	N/A	3/3
Short palpebral fissure	−	−	−	−	0/8	0/3	N/A	2/3
Oral								
High-arched palate	−	+	−	−	0/8	1/3	N/A	0/3
Cleft soft palate/lip	−	−	−	−	2/11	0/3	N/A	3/3
Tooth abnormality	−	+	−	−	1/8	0/3	N/A	N/A
Accessory frenulum	−	−	−	−	N/A	N/A	N/A	N/A
Digital								
Brachydactyly	−	+	−	−	4/11	1/3	N/A	0/2
Polydactyly	−	−	−	−	7/11	1/3	N/A	2/2
Neurological and Brain								
Intellectual disability	−	+	+	+	8/8	3/3	N/A	N/A
Ventricular dilatation	−	+	N/A	N/A	2/5	0/3	0/1	2/4
Molar tooth sign	−	−	N/A	N/A	11/11	0/3	0/1	0/1
Hypoplastic vermis	−	−	N/A	N/A	5/6	N/A	0/1	0/1
Hypoplastic gyri	−	−	N/A	N/A	0/4	N/A	0/1	1/2
Epilepsy	−	+	−	−	2/5	N/A	N/A	N/A
Dandy-Walker malformation	−	−	N/A	N/A	1/4	N/A	0/1	1/2
Renal								
Cystic kidney	+	+	−	−	1/11	0/3	N/A	0/4
Renal insufficiency	+	+	+	+	2/7	0/3	N/A	1/4
Others								
Obesity	−	+	−	+	2/8	1/3	N/A	1/1
Retinitis pigmentosa	−	+	−	−	1/5	1/3	2/1	N/A
Hearing loss	+	−	−	−	2/7	0/3	N/A	N/A
Micropenis	−	+	+	+	0/7	0/3	N/A	1/3
Cardiac malformation	−	−	−	−	0/7	0/3	N/A	3/3
Situs inversus	−	−	−	−	2/9	0/3	N/A	0/4
Liver fibrosis	−	−	−	−	2/2	N/A	N/A	N/A

BBS Bardet-Biedl syndrome, *JBTS* Joubert syndrome, *N/A* not available, *RP* retinitis pigmentosa, *SGBS2* Simpson-Golabi-Behmel syndrome type 2

Additionally, mutations in exon 3, 8, 9, 13, and 16 have been associated with intellectual disability [5], while those in exon 12 have been associated with renal cysts [1]. Phenotypic variability is often seen in affected females even within the same family. Thauvin-Robinet et al. suggested that skewed × inactivation is partially involved in the pathogenesis leading to the intrafamiliar clinical variability [2]. Bisschoff et al. reported that the direction of skewing is not correlated with disease severity [11]. Nevertheless, nearly all reports on the phenotype-genotype correlation in OFD1 were on female patients. Male OFD1 patients are exceedingly rare, and therefore, very little is currently known on the phenotype-genotype correlation of *OFD1* mutations in male patients.

The phenotypic spectrum associated with *OFD1* mutations has been recently extended to include JBTS10, SGBS2, RP23, and unclassified malformation syndromes as noted above. JBTS is characterized by a unique cerebellar

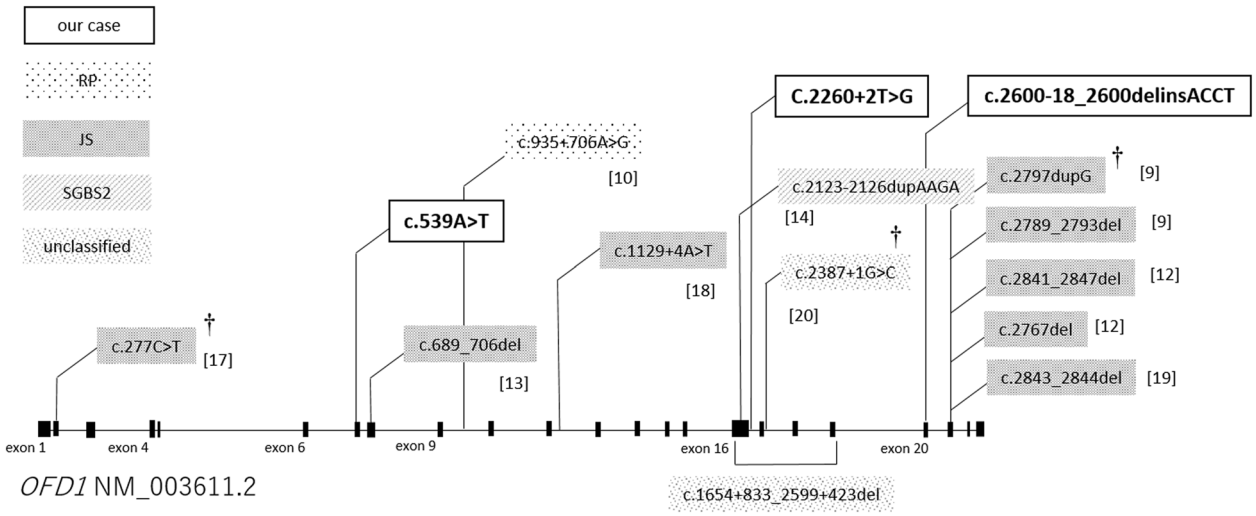

Fig. 4 Known disease-related variants of male patients with *OFD1* mutation. *JS* Joubert syndrome, *RP* retinitis pigmentosa, *SGBS2* Simpson-Golabi-Behmel syndrome type 2; †: perinatal death

and brain stem malformation, hypotonia, developmental delay, and unusual breathing pattern. Several male patients presenting symptoms of classical JBTS who have mutations in *OFD1* have been reported [12, 13]. SGBS is characterized by overgrowth, coarse face, and other congenital anomalies including heart defect. SGBS2 with an *OFD1* mutation of a male patient has also been reported [14]. The patient had a frameshift mutation in exon 16 and showed macrocephaly, severe intellectual disability, low-set ears, digital malformations, and obesity. Except for the patient, other affected males in his family died in their early postnatal period. In both JBTS10 and SGBS2, females are clinically inconspicuous. Webb et al. reported a deep intronic mutation in intron 9 of *OFD1* that produced an aberrant transcript and reduced level of correctly spliced transcript, causing X-linked RP [15]. Sharma et al. reported an atypical presentation of *OFD1* mutation in a male patient without the classical OFD1 phenotype. This patient presented ESRD without any evidence of polycystic kidney disease [16]. The spectrum of *OFD1* mutations in males reported previously is summarized in Table 1. The findings demonstrate phenotypic variability of patients with *OFD1* mutation. We were the first to report a patient with *OFD1* mutation presenting a Bardet-Biedl syndrome-like phenotype (patient 4).

Coene et al. reported a case of JBTS with *OFD1* mutation and proposed that the inverse correlation between the length of OFD1 mutant protein and phenotypic severity is due to differences in the binding of the mutant protein to functionally interacting proteins and disruption of ciliary localization [12]. They also suggested that variable degrees of RNA degradation could contribute to the differences in phenotype. Thus, the location and type of the mutation may be associated with the disease severity. To the best of our knowledge, there have been three reports to date on perinatal death of OFD1 male patients [9,17,20] with three different *OFD1* mutations: a missense mutation in exon 2 (ref. 17), a splice site mutation in intron 17 (ref. 20), and a frameshift mutation in exon 21 (ref. 9). Most *OFD1* mutations in living male patients were located at the 3′ side of exon 7 or downstream and were non-truncating mutations (Fig. 4). Male patients with *OFD1* mutation in exon 21 are alive despite the mutation producing a truncated OFD1 protein. Our patients survived past their perinatal period, which may be due to them having a non-truncating *OFD1* mutation downstream of exon 7. Three of the four patients reported here displayed intellectual disability, and all had severe renal disease. Patient 1, who had an in-frame *OFD1* mutation in exon 20, did not have intellectual disability. In contrast, patient 2 with a missense mutation in exon 7 had severe intellectual and psychomotor disabilities. Although there may be a strict genotype-phenotype correlation in psychomotor development, this may not be the case with renal disease in male patients with *OFD1* mutation.

In conclusion, the phenotypic spectrum of *OFD1* mutations is very broad; thus, evaluation of *OFD1* mutation should not be restricted to patients presenting the classical OFD1 phenotype. A comprehensive genetic analysis using NGS is also useful to determine the presence of *OFD1* mutation in patients with no family history of OFD1. Further investigations are needed to clarify the mechanisms of such phenotypic diversity of *OFD1* mutations.

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Conflict of Interest Kazumoto Iijima has received grant support from Daiichi Sankyo CO., Ltd. and Zenyaku Kogyo Co., Ltd. The remaining authors declare that they have no conflict of interest.

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