



# A case of Dent disease type 2 with large deletion of *OCRL* diagnosed after close examination of a school urinary test

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## Abstract

A 7-year-old boy visited our hospital for a detailed examination of proteinuria identified in a school urinary test. He had short stature, misaligned teeth, and mild intellectual disability. A urinary examination identified mild proteinuria and extremely high levels of beta-2 microglobulin. On blood examination, his protein, albumin, and creatinine levels were found to be normal; however, his lactate dehydrogenase and creatinine phosphokinase levels were slightly elevated. Upon histological examination, no abnormalities in glomeruli or tubules were found. Considering these results, we diagnosed our patient with Dent disease type 2 (DD2). Although the whole exome sequencing revealed large deletion of *OCRL*, which was seen only in Lowe syndrome and not in DD2 previously, our final diagnosis for the patient is DD2. A phenotypic continuum exists between Dent disease and Lowe syndrome, and several factors modify the phenotypes caused by defects in *OCRL*. Although patients have thus far been diagnosed with DD2 or Lowe syndrome on the basis of their symptoms, accumulation and analysis of cases with *OCRL* defects may hereafter enable more accurate diagnoses.

**Keywords** Dent disease type 2 · Lowe syndrome · *OCRL* · Low molecular weight proteinuria · Congenital cataract

## Introduction

Dent disease is a tubular disease caused by X-linked genetic defects. The major symptoms are low molecular weight proteinuria, renal calcification, and end-stage renal failure, which typically occur in patients in their 50 s. Lowe syndrome, which also presents with low molecular weight proteinuria, shows symptoms that are more severe; these include seizures, intellectual disabilities, progressive movement disorders, Fanconi syndrome, and congenital cataracts. Dent disease and Lowe syndrome are currently distinguished depending on the patient's symptoms. If the only major symptom is low molecular weight proteinuria, the patient is typically diagnosed with Dent disease; if the symptoms are more severe, the patient is diagnosed with Lowe syndrome. However, to distinguish cases with mutations in the *OCRL*

from Dent disease type 1 with *CLCN5* mutations, the term Dent disease type 2 (DD2) was introduced [1]. Kidney disorders are usually milder in DD2 than in Lowe syndrome, but end-stage renal diseases can occur during the progress of Fanconi syndrome [2]. Additionally, in DD2, mild extra-renal Lowe syndrome-like symptoms, including peripheral cortical lens opacities, short stature, mild intellectual disability, and elevation of serum lactate dehydrogenase (LDH)/creatinine phosphokinase (CPK) levels, can occur. Of all Dent disease patients, 60% patients show defects in *CLCN5*, whereas 10% patients show defects in *OCRL*; patients with defects in *OCRL* are diagnosed with DD2 [3]. Similarly, the gene responsible for Lowe syndrome is *OCRL*.

Here, we report a case of DD2 that was diagnosed upon close examination after a school urinary test. Our patient showed low molecular weight proteinuria, mild intellectual disability, short stature, and mildly elevated levels of LDH and CPK. Although a genetic test revealed a large deletion in *OCRL* that was previously only found in Lowe syndrome, the patient's final diagnosis was DD2 because he exhibited no ocular symptom and his other symptoms were mild. In this report, we discuss the relationship between clinical symptoms and genetic defects in our patient.

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## Case report

A 7-year-old boy visited our hospital requesting a closer examination after a school urinary test revealed proteinuria. Although he had been diagnosed with proteinuria after a health checkup when he was 3 years old, he did not undergo further examination because he had no subjective symptoms. He did not have any relevant medical history except for common cold. He had no family history of renal disease, but his elder brother had passed away by sudden death during infancy for unknown reasons. He had mildly short stature ( $-1.9$  SD), but his body weight was within the normal range ( $+0.5$  SD). His blood pressure was 84/52 mmHg. There were no signs of cataract, but his teeth were misaligned. His breathing sounds were normal and he did not have a heart murmur. Congenital cardiac anomalies were not found on echo-cardio-sonography. His abdomen was soft and no organomegaly was detected. On abdominal sonography, the sizes and shapes of both kidneys were normal; no calcification or cysts were observed. No edema of the eyelids and lower extremities was observed. However, during examination, the patient repeated the same question several times habitually and could not remain still. On the Wechsler Intelligence Scale for Children Fourth Edition, he scored 74, which is slightly lower than the standard level. Blood examination revealed normal complete blood count and renal function values, but his LDH and CPK levels were 416 IU/L and 330 IU/L, respectively, which were slightly above normal (Table 1). Immunoglobulin and complement values were in the normal ranges. In a urine dipstick test, the protein level was 2+, while the occult blood test result was negative (Table 2). The urinary protein/creatinine ratio had risen to 2.34 g/gCre and the urinary beta-2 microglobulin level was

**Table 2** Urinalysis

Gravity	1.025	Urinary chemistry	
pH	7.0	BUN	920.4 mg/dL
Prot	2+	Cre	73.81 mg/dL
Glu	–	UA	64.3 mg/dL
OB	–	Na	193 mEq/L
Ket	–	K	57.4 mEq/L
Sediment		Cl	169 mEq/L
RBC	0–1/hpf	Ca	16.2 mg/dL
WBC	0–1/hpf	IP	77.4 mg/dL
Hyaline cast	1–/WF	TP	172.5 mg/dL
Granulocyte cast	1–/WF	ALB	288.33 $\mu$ g/mL
AcrySTALLINE phosphate	Trivial	Glu	14 mg/dL
		NAG	12.0U/L
		$\beta$ 2MG	158,600 $\mu$ g/L

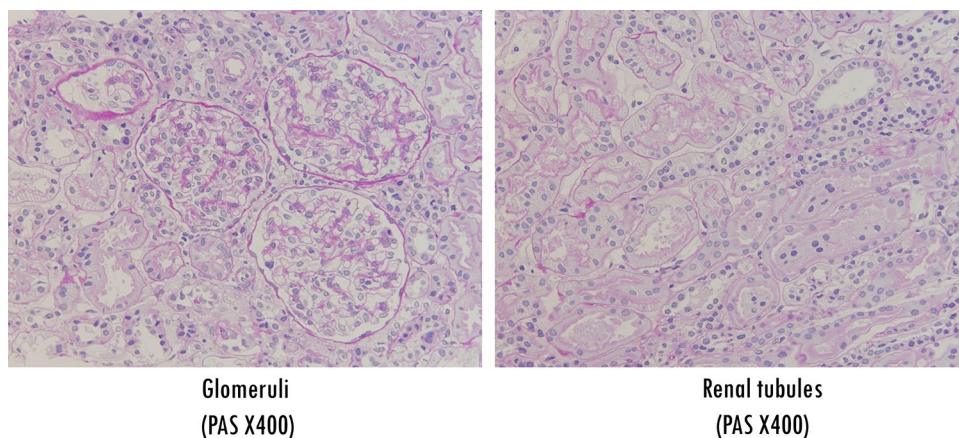
158,600  $\mu$ g/L; which was extremely high compared with normal range. Urinary albumin excretion was 346 mg/day; this also exceeded the normal range. The urinary calcium/creatinine ratio was 0.22 g/gCre, which was within the normal range.

Considering the persistent urinary protein levels, we performed renal biopsy for further examination. Renal histological analysis showed no evidence of glomerular sclerosis, renal tubular atrophy, or interstitial fibrosis upon light microscopy (Fig. 1). Moreover, no immunological deposition was found on immunofluorescence analysis; there was no evidence of glomerular basement membrane thickening, podocyte fusion, or renal tubular atrophy upon electronic microscopy (Fig. 2). These results did not indicate renal disease that could have caused proteinuria in our patient.

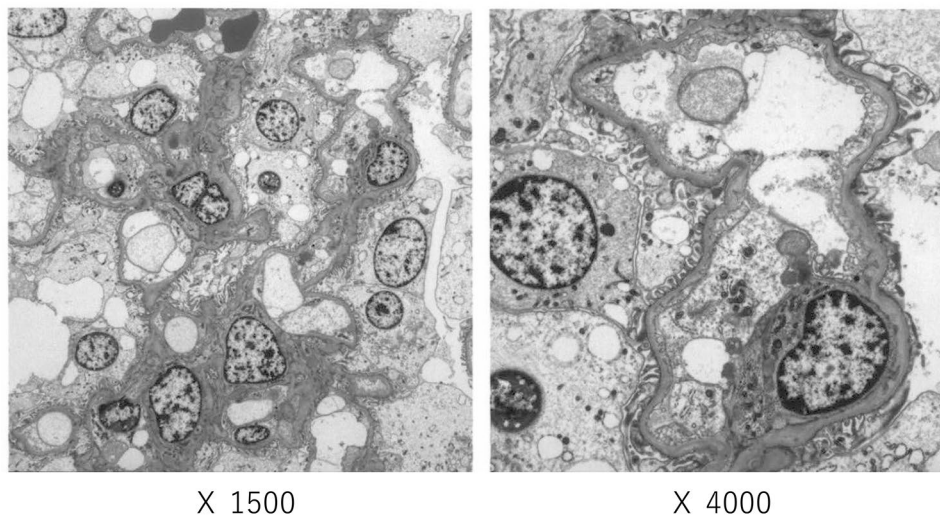
**Table 1** Blood examination

Complete blood count		Chemistry		Immunology	
WBC	7200/ $\mu$ L	TP	7.0 g/dL	IgG	996 mg/dL
RBC	444 $\times$ 10 <sup>4</sup> / $\mu$ L	Alb	4.5 g/dL	IgA	122 mg/dL
Hb	12.4 g/dL	BUN	15.3 mg/dL	IgM	64 mg/dL
Plt	17.7 $\times$ 10 <sup>4</sup> / $\mu$ L	Cre	0.32 mg/dL	C3	124 mg/dL
Blood gas analysis (vein)		UA	3.7 mg/dL	C4	22 mg/dL
pH	7.372	Na	138 mEq/L	ANA	< 40
pCO <sub>2</sub>	38.7 mmHg	K	3.9 mEq/L	Anti-DNA-Ab	< 2
HCO <sub>3</sub> <sup>-</sup>	22.5 mmol/L	Cl	107 mEq/L	MPO-ANCA	< 0.5
BE	- 1.9 mmol/L	Ca	9.2 mg/dL		
		IP	4.6 mg/dL		
		AST	42 IU/L		
		ALT	20 IU/L		
		LDH	416 IU/L		
		CK	330 IU/L		
		CRP	0.041 mg/dL		

**Fig. 1** Renal histology: light microscopy analysis. Light microscopy revealed no evidence of glomerular sclerosis, renal tubular atrophy, or interstitial fibrosis



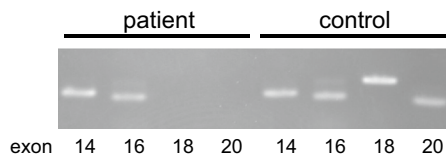
**Fig. 2** Renal histology: electronic microscopy. Electronic microscopy revealed no evidence of glomerular basement membrane thickening, podocyte fusion, or renal tubular atrophy



Given the low molecular weight proteinuria, short stature, mild intellectual impairment, slight elevation in LDH and CPK levels, and renal histological findings in our patient, we diagnosed him with Dent disease. For further analysis, we performed genetic analysis using whole exome sequencing (WES). Genomic DNA was extracted from the patient's peripheral white blood cells of the patient using QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany). Informed consent for genetic analyses was obtained from the patient's guardian. The exome sequences were enriched using SureSelect Human All Exon v6 Kit (Agilent Technologies, Santa Clara, CA, USA), in accordance with the manufacturer's instructions. The DNA samples were subjected to sequencing using Illumina NovaSeq6000 sequencing system (Illumina, Santiago, CA, USA). Short reads were aligned to the reference genome (hg19) using Burrows–Wheeler alignment with default parameter settings. Single-nucleotide variants and indels were annotated against the reference sequence database. WES data were then evaluated for causative mutations in *OCRL* and *CLCN5*. The mean depth coverage in this study was 82.8. The coding

sequence and exon–intron boundaries of *OCRL* were amplified from genomic DNA via polymerase chain reaction (PCR). The study was approved by the Ethics Committee of Tokyo Women's Medical University (approval no. 380D). WES revealed the deletion of *OCRL* exon 17 and all subsequent exons of *OCRL* in the patient. Genomic DNA PCR confirmed that exons 18 and 20 were not amplified (Fig. 3). Although these WES results were previously only reported in patients with Lowe syndrome, we diagnosed our patient with DD2 because he exhibited no ocular symptom and his other symptoms were mild.

He is presently under close observation in our outpatient department and his kidney function and general condition has not deteriorated thus far.



**Fig. 3** Genetic analysis. PCR analysis of genomic DNA from the patient and control samples. Primers used in this analysis were *OCRL* exon14: Fwd 5'-ATAGGAACAGTGGCTTATCAAC-3' and Rev 5'-CAATATGGAGGGTCAGAAAT-3'; *OCRL* exon16: Fwd 5'-GTTAGATAATCTCCAAGGGAG-3' and Rev 5'-TTCTGTGCTAAC CACAGTGAG-3'; *OCRL* exon18: Fwd 5'-CTGGAGGTTTTTCCTA TTACC-3' and Rev 5'-AGAAGACAGAAGCACAAAG-3'; *OCRL* exon20: Fwd 5'-GGTAATCATCATAACCTCAG-3' and Rev 5'-TATAGGTGCGAAGAAGAGT-3'. Exons 18 and 20 of *OCRL* were not amplified in the patient sample

## Discussion

We encountered a patient with DD2 who exhibited large deletion of *OCRL*. A diagnosis of DD2 was based on the absence of clinically evident extra-renal symptoms, such as congenital cataract and severe mental retardation [2]. *OCRL* is located on Xq25-26 and comprises 24 exons occupying 52 kb [4]. *OCRL* mRNA produces two splice isoforms: A and B. Isoform B lacks exon 19 (also referred to as 18a) that encodes eight amino acids and is present in isoform A (901 amino acids). Isoform A is ubiquitously expressed, whereas isoform B is expressed in all tissues except the brain. Isoform A binds to clathrin, a protein that plays a major role in the formation of coated vesicles, with higher affinity than to isoform B. Additionally, isoform A is involved in the endocytosis of low molecular weight proteins and intracellular membrane trafficking in the proximal tubule [5]. Both *OCRL1* protein and *CIC-5* protein, which participates in the uptake of albumin and low molecular weight proteins, are speculatively linked through their C-terminal domains to actin dynamics, perturbation of the fine mechanisms of cell polarity, and/or cytokinesis as common pathogenic mechanisms [6]. It has been suggested that mutations in the C-terminal portion of *OCRL* produce disease by preventing the correct localization of the protein and that disruption of its interaction with *APPL1*, which regulates vesicle trafficking and endosomal signaling, plays a key role in pathogenesis. Through *APPL1*, *OCRL1* protein can be linked to the small scaffold protein *GIPC* and subsequently to megalin, the scavenger receptor that mediates the uptake of low molecular weight proteins in the kidneys [7].

According to the Human Gene Mutation Database, approximately 250 *OCRL* disease-causing mutations have been described including missense and nonsense mutations (49%), splicing mutations (12%), small deletions (20%), small insertions (9%), and gross deletions and insertions. Missense and nonsense mutations occur throughout *OCRL*;

they are mainly found in exons 9–24, which contain the 5-phosphatase, abnormal spindle-like microcephaly-associated protein (*ASPM*)-*SPD2*-Hydin (*ASH*), and Rho-GTPase activating protein (*RhoGAP*) domains. In DD2, nonsense mutations are clustered in exons 4–8 [5]. However, no clear differences in this distribution were observed when Lowe syndrome was previously compared with DD2 [8]. Moreover, deletions were found only in exons 3, 4, 5 and 7 in DD2; they were found throughout the gene in Lowe syndrome.

Several speculations related to *OCRL* defects and phenotypes have been previously reported. First, Hichri et al. reported that no significant differences in the *OCRL* mRNA expression levels were found in patients with a missense mutation, compared with control expression levels [8]. However, patients harboring stop, frameshift, or splicing mutations showed very low mRNA levels, which indicates either decreased transcription or, more likely, mRNA instability resulting from a nonsense-mediated decay mechanism. Although very low mRNA levels can be observed in various types of genetic defects, mRNA levels do not directly explain the symptom severity. Additionally, *OCRL* mRNA expression levels did not differ between patients with Lowe syndrome and patients with DD2.

Second, in a study of *OCRL*-mutated fibroblasts from patients with DD2 and patients with Lowe syndrome, *OCRL* loss-of-function mutations led to decreases in actin stress fibers [9]. The authors described that DD2 fibroblast showed intermediate phenotypes between Lowe syndrome and control fibroblasts. However, there was no difference in the expression level of *OCRL1* protein between fibroblasts from patients with Lowe syndrome and fibroblasts from patients with DD2. Shrimpton et al. previously proposed a model to explain the phenotype variability on the basis of *OCRL* mutations with persistent altered *OCRL* protein in some patients and presence of an otherwise unaltered shorter *OCRL* isoform in patients with DD2 [10].

Third, comparable reduction in the activity of phosphatidylinositol 4, 5-bisphosphate [ $PI(4,5)P_2$ ] 5-phosphatase, encoded by *OCRL*, is usually observed in patients with DD2 and patients with Lowe syndrome [8].  $PI(4,5)P_2$  is located at the cell membrane and influences the function of many important signaling proteins. The clinical variability in  $PI(4,5)P_2$  activity may be explained by the presence of modifying factors (e.g., compensatory phosphatases or interacting proteins) for which expression depends on the patient's genetic background.

A phenotypic continuum is thought to exist between DD2 and Lowe syndrome. This continuum has been observed both in patients harboring different *OCRL* mutations and in patients harboring the same mutations [8]. The same two missense variants (p.Ile274Thr, p.Arg318Cys) have been detected in siblings with both the mild DD2 phenotype and the classic Lowe syndrome

phenotype. The types of genetic variants in DD2 and Lowe syndrome are not correlated with clinical severity. The precise mechanism by which our patient showed mild phenotypes is unknown. Most large genomic deletions have been described in the 5' half of the *OCRL* gene, involving exons 1–7. All of these deletions may remove some or all of the critical exons of the gene, such as 9–15, encoding the phosphatase domain, which is required for the expression of the gene [10]. Conversely, genomic deletion of exon 17 and all subsequent exons identified in our patient may result in reservation of the function of OCRL1 protein, which may explain that our patient presented with mild symptoms.

Renal disease in Lowe syndrome is primarily attributable to specific tubular dysfunctions of variable extents; only low molecular weight proteinuria and albuminuria are present in all patients. An obvious negative relationship exists between age and glomerular filtration rate. Renal failure was observed in 32% of the mildly affected patients (i.e., patients with DD2) and in 74% of patients with classic Lowe syndrome [11].

Serum levels of LDH, CPK, or both were elevated in most patients with DD2 and in all patients with classic Lowe syndrome for which these measures were available [11]. The origins of the LDH and CPK increases are not yet known; they may reflect muscle involvement or nonspecific damage in renal cell membranes because both LDH and CPK are reportedly involved in the metabolism of proximal tubular cells.

We could not clarify the relationship between the genotype and phenotype in our patient. We could not elucidate why our patient exhibited large deletion of *OCRL* and his phenotype was consistent with DD2. A better understanding of disease etiology will provide the basis for developing therapies and preventive strategies, that can assist with renal function. Further studies will help to determine whether phenotypic variability is caused by the different effects of mutations/variants in other genes and/or is attributable to environmental effects [11].

In conclusion, we have reported a case of DD2 with large deletion of *OCRL*, which was previously only observed in Lowe syndrome and not in DD2; however, our patient's clinical symptoms were consistent with a diagnosis of DD2. A phenotypic continuum exists between Dent disease and Lowe syndrome, and several factors modify the phenotypes of *OCRL* defects. Although patients have thus far been diagnosed with DD2 or Lowe syndrome on the basis of their symptoms, the accumulation and analysis of DD2 cases

involving *OCRL* defects may enable more accurate future diagnoses.

## Declarations

**Conflict of interest** The authors have declared that no conflict of interest exists.

**Ethics approval** This article does not contain any studies with human participants performed by any of the authors.

**Informed consent** Written informed consent was obtained from the patient and his guardian for the publication of this case report and any accompanying images.

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