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## OFD1 mutation induced renal failure and polycystic kidney disease in a pair of childhood male twins in China

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### Abstract

#### BACKGROUND

Oral-facial-digital syndrome type 1 (OFD1) is a rare ciliopathy mainly with an X-linked dominant pattern of inheritance, which is caused by mutations in the *OFD1* gene. The *OFD1* protein is located within the centrosomes and basal bodies of the primary cilia. It is reported that approximately 15%-50% cases of *OFD1* progress to end-stage renal disease (ESRD) following development of polycystic kidney diseases (PKD). Here we report a pair of childhood male twins who presented only renal failure and PKD caused by an *OFD1* mutation in China.

#### CASE SUMMARY

A pair of 14-year male twins were hospitalized with a complaint of abnormal renal function for nine days. They both complained of ankle pain for 3 mo vs 2 wk, respectively. They denied fever, abdominal pain, daytime or nighttime enuresis, urgency, dysuria, or gross hematuria. Laboratory tests at a local hospital showed renal failure (serum creatinine 485  $\mu\text{mol/L}$  vs 442  $\mu\text{mol/L}$ , blood urea nitrogen 14.7 mol/L vs 14.5 mol/L) and anemia (hemoglobin 88 g/L vs 98 g/L). The twins are monozygotic. There was no abnormal birth, past medical, or family history. Clinical data were analyzed and genetic analysis on PKD was carried out in the twins by next-generation sequencing. The results showed that the twins presented low-molecular-weight proteinuria, hyposthenuria, anemia, renal failure, and renal polycystic changes. Genetic tests showed that the twins both carried a hemizygous mutation in exon 19 c.2524G>A (p. G842R) of the *OFD1* gene. Their mother heterozygously carried the same mutation as the twins but was without any phenotypes while their father was normal.

#### CONCLUSION

We have reported a pair of childhood male twins with an *OFD1* mutation who presented ESRD and PKD but without any other phenotypes of *OFD1* in China.

**Key words:** Renal failure; Polycystic kidney disease; *OFD1* mutation; China; Case report

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**Core tip:** Oral-facial-digital syndrome type 1 (OFD1) is a rare ciliopathy mainly with an X-linked dominant pattern of inheritance, which is caused by mutations in the *OFD1* gene. It is reported that approximately 15%–50% cases of OFD1 progress to end-stage renal disease following development of polycystic kidney diseases. The phenotypic spectrum associated with *OFD1* mutations has been recently extended with an X-linked recessive pattern of inheritance. Here we report a pair of childhood male twins who presented only renal failure and polycystic kidney disease caused by an *OFD1* mutation with an X-linked recessive fashion of inheritance in China.

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## INTRODUCTION

The human *OFD1* gene is composed of 23 densely packed exons spanning about 35.59 kb of genomic DNA and maps to chromosome band Xp22.2. The OFD1 protein is located within the centrosomes and basal bodies of the primary cilia. Oral-facial-digital syndrome type 1 (OFD1) is caused by *OFD1* mutations with an X-linked dominant pattern of inheritance<sup>[1,2]</sup>. It is reported that approximately 15%–50% cases of OFD1 progress to end-stage renal disease (ESRD) following the development of polycystic kidney diseases (PKD)<sup>[3]</sup>. The phenotypic spectrum associated with *OFD1* mutations has been recently extended with an X-linked recessive pattern of inheritance, such as Joubert syndrome type 10, mental retardation with macrocephaly, Simpson-Golabi-Behmel syndrome type 2, retinitis pigmentosa and so on<sup>[4-6]</sup>.

There has been a report on *OFD1* mutation with an atypical presentation with ESRD without evidence of PKD<sup>[7]</sup>. However, there has been no report on ESRD without any other phenotypes except PKD caused by an *OFD1* mutation. Here, we report a pair of childhood male twins with an *OFD1* mutation who presented ESRD and PKD but without any other phenotypes.

## CASE PRESENTATION

### Chief complaints

A pair of 14-year male twins were hospitalized with a complaint of abnormal renal function for nine days.

### History of present illness

They both complained of ankle pain for 3 mo *vs* 2 wk, respectively. They denied fever, abdominal pain, daytime or nighttime enuresis, urgency, dysuria, or hematuria. Laboratory tests at a local hospital showed renal failure (serum creatinine 485  $\mu$ mol/L *vs* 442  $\mu$ mol/L, blood urea nitrogen 14.7 mol/L *vs* 14.5 mol/L) and anemia (hemoglobin 88 g/L *vs* 98 g/L).

### History of past illness

The twins are monozygotic. There was no abnormal birth, past medical, or family history. There was no family history of renal failure or PKD on their maternal side.

### Physical examination

At admission, their blood pressure, weight, and height were all normal. Their physical examination showed no abnormal signs, especially no abnormal dysmorphic features. No neurodevelopmental or ophthalmologic deficits were observed.

### Laboratory examinations

Laboratory tests at our hospital revealed Scr 433–486  $\mu$ mol/L *vs* 382–425  $\mu$ mol/L, BUN 20.2–24.4 mmol/L *vs* 17.1–19.9 mmol/L, serum calcium 1.39–1.80 mmol/L *vs* 1.62–1.80 mmol/L, serum phosphate 1.42–1.72 mmol/L *vs* 1.43–1.80 mmol/L,  $\text{HCO}_3^-$  23.6–26.1 mmol/L *vs* 23.0–26.3 mmol/L, intact parathyroid hormone 248.7–327.7 pg/mL *vs* 256.2–298.5 pg/mL, hemoglobin 92–101 g/L *vs* 97–110 g/L, proteinuria 27.4 mg/kg per



24 h *vs* 25.3 mg/kg per 24 h, urine specific gravity 1.008-1.010 *vs* 1.007-1.010, urine microalbumin 291 mg/L *vs* 128 mg/L, urine  $\alpha$ 1-microglobulin 194 mg/L *vs* 180 mg/L, and low-molecular-weight proteinuria 35.7% *vs* 42.1% in urine protein electrophoresis. Autoimmune profile was within the normal range, including anti-nuclear antibody, anti-double-stranded DNA antibody, complements C<sub>3</sub> and C<sub>4</sub>, and anti-neutrophil cytoplasmic antibodies (Table 1).

### Imaging examinations

Ultrasonography and magnetic resonance imaging (MRI) showed that the renal body was small (7.3-7.5 cm *vs* 7.2-7.6 cm in length and 3.7-3.8 cm *vs* 3.5-3.8 cm in width), the border of the cortex and medulla was not clear, polycystic lesions were seen in both kidneys of the twins, and cysts were irregularly distributed and located within the cortex and the medulla. No cysts were found in the liver or pancreas. Brain MRI showed no abnormal findings.

## FINAL DIAGNOSIS

Due to the presence of abnormal renal function, polycystic kidney diseases, and genetic history, an inherited renal cystic disease was suspected.

## TREATMENT

Genetic analysis was performed using next generation sequencing<sup>[8]</sup> in the genetics laboratories of MyGenostics biotechnology companies in China, using "the polycystic kidney diseases panel" which covers genes strongly correlated with this disorder<sup>[9,10]</sup>. The results showed that both the twins carried a hemizygous mutation in exon 19 c.2524G>A (p. G842R) in the *OFD1* gene (Figure 1). Their mother heterozygously carried the same mutation as the twins. But the mother showed no anemia, proteinuria, or hematuria, and her renal function was normal. Neither polycystic lesions nor abnormal dysmorphic features were seen in her kidneys. X-inactivation was not analyzed in the mother. The mutation was found in the SNP databases (rs146047094, A = 0.0011/4, 0.007/65, and 0.006/6 in 1000Genomes, ExAC, and GO-ESP, respectively), but only found in females (18 homozygous and 29 heterozygous in ExAC, 2 heterozygous in 1000Genomes). Mutation testing analysis showed that amino acid sequence was changed and protein features (might be) affected. PolyPhen-2 and SIFT analysis showed that the mutation might be healthy or tolerated. However, it was not found in 100 normal Chinese controls. No variations were found in *PKD1*, *PKD2*, *PKHD1*, *NPHPn* (*n* = 1-18, 1 L and 2 L), or other related genes.

## OUTCOME AND FOLLOW-UP

Within a follow-up period of 12 mo, renal functions of the twins continued to decline rapidly (Scr 589  $\mu$ mol/L *vs* 564  $\mu$ mol/L, BUN 28.2 mol/L *vs* 26.6 mol/L). Due to symptomatic uremia, they started on peritoneal dialysis and waited for transplant from appropriate living donors.

## DISCUSSION

*OFD1* is a rare ciliopathy with an X-linked dominant pattern of inheritance which involves multiple organs including the kidneys, tongue, nasal mucosa, oral mucosa, cranial cartilage, brain, and limbs<sup>[11]</sup>. The incidence of *OFD1* is 1/50000-1/250000 live births<sup>[12,13]</sup>. PKD is the most common renal involvement<sup>[14]</sup>. There is also a report of *OFD1* mutation in a Chinese boy with Joubert syndrome<sup>[15]</sup>. However, atypical presentation of *OFD1* and ESRD caused by *OFD1* mutations without typical polycystic changes were also reported<sup>[7]</sup>.

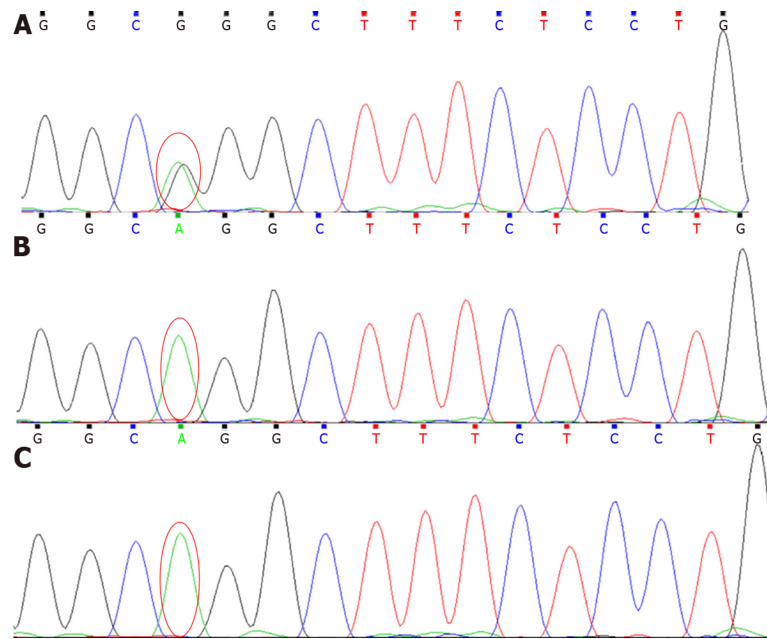
As for our twins, they both presented with low-molecular-weight proteinuria, hyposthenuria, anemia, renal failure, and renal polycystic changes, suggesting that they had an inherited renal cystic disease. Genetic tests showed that the twins both carried a hemizygous mutation in exon 19 c.2524G>A (p.G842R) of the *OFD1* gene. The mutation was found in the SNP databases (ExAC, GO-ESP, and 1000Genomes) but only homozygous or heterozygous in females but not in males. Mutation testing analysis showed changed amino acid sequence and affected protein features (might be), and SIFT and PolyPhen-2 analysis showed that the mutation might be healthy or



**Table 1** Main clinical features of the twins

Feature	Patient 1	Patient 2
Familial history	-	-
Short stature	-	-
Frontal bossing	-	-
Flat face	-	-
Hypertelorism	-	-
Epicanthus	-	-
Telecanthus	-	-
Down-slanting palpebral fissures	-	-
Hypoplasia of the nasal alae	-	-
Low set ears	-	-
Pseudocleft of the upper lip	-	-
Cleft lip/tongue/palate	-	-
Microretrognathia	-	-
Abnormal hairs	-	-
Lobulated tongue	-	-
Buccal frenulae	-	-
Lingual hamartomas	-	-
Tooth abnormalities	-	-
Cerebellar hypoplasia	-	-
Corpus callosum agenesis	-	-
Hydrocephalus	-	-
Porencephaly	-	-
Arachnoid cysts	-	-
Hands/Feet		
Brachydactyly	-	-
Clinodactyly	-	-
Syndactyly	-	-
Polydactyly	-	-
Polycystic kidney disease	+	+
Renal function abnormal	+	+
Scr (μmol/L)	433-589	382-564
BUN (mmol/L)	20.2-28.2	17.1-26.6
Proteinuria	+	+
Microalbuminuria (mg/L)	291	128
α1-microglobulinuria (mg/L)	194	180
Low molecular weight proteinuria (%)	35.7	42.1
Hematuria	-	-
Mental retardation	-	-

tolerated. Because no variations were found in *PKD1*, *PKD2*, *PKHD1*, *NPHPn*, or other related genes in our twins, and the mutation was not found in 100 normal controls in China, we suggested that it might be the genetic cause of our twins with an X-linked recessive pattern of inheritance. The mother heterozygously carried the same mutation as the twins but had no anemia, proteinuria, hematuria, abnormal dysmorphic features and her renal function was normal. Furthermore, our twins presented no malformation of the hands, feet, face, or oral cavity. And no CNS involvement was found. To our knowledge, these are the first two pediatric patients with an *OFD1* mutation that presented with renal failure and PKD with an X-linked recessive pattern of inheritance, without classic oral, facial, or digital features. However, it was a pity that we did not analyze fibroblasts from our twins to verify whether the p.G842R mutation affects cilia formation. Xiang *et al*<sup>[16]</sup> reported a fetus with Joubert Syndrome terminated at 29<sup>+</sup>4 wk of gestation, in which genetic analysis showed the c.2524G>A (p.G842R) in the *OFD1* gene, and two compound heterozygous variants in the *C5orf42* gene (c.3599C>T, p.A1200V in exon 20 and



**Figure 1 Genetic analysis of the *OFD1* gene.** A: The mother; B: Patient 1; C: Patient 2. The results showed that the twins both carried a hemizygous mutation while the mother heterozygously carried the same mutation in exon 19 c.2524G>A (p.G842R).

c.3857G>A, p.R1286H in exon 22). They speculated that the later might be responsible for the disorder of the fetus because the 36-year-old normal father also carried the c.2524G>A (p.G842R) in the *OFD1* gene. But it is a pity that there was no information on renal function and imaging examination of the father. The pathogenicity of c.2524G>A (p.G842R) in the *OFD1* gene needs further studies especially in males in the future.

PKD affects approximately 15%–50% cases of OFD1 who have a higher likelihood of developing renal failure while those without PKD have normal renal function<sup>[1,11,14]</sup>. Cystic changes can occur at any time point and are distributed and located irregularly within the cortex and the medulla. They are variable in size, multilocular, and thin-walled and contain serous fluid<sup>[17,18]</sup>. These features are similar to those of our twins. The kidney size is normal or palpably large, but they maintain their reniform shape with minimal changes of renal contour<sup>[14]</sup>. However, it is interesting that the kidneys of our twins were small in size, which is similar to the report of Sharma *et al*<sup>[7]</sup>, in which a boy aged 10 years and 6 mo with renal failure but without renal cystic changes had small kidneys (the right kidney 6.6 cm and the left kidney 7.8 cm) detected by renal ultrasound. Furthermore, it seems that the renal size can be small, normal, or large in PKD caused by *OFD1* mutations, the same as other renal cystic ciliopathies<sup>[19–21]</sup>.

There were no different features between our monozygotic twins with the same *OFD1* mutation. As for renal manifestations, our twins both presented low-molecular-weight proteinuria, besides hyposthenuria, renal failure, and polycystic changes in the kidneys but without microscopic hematuria. This was contrary to other reports that PKD caused by *OFD1* mutations mainly presented with microscopic hematuria but no proteinuria<sup>[7,11]</sup>.

## CONCLUSION

We present a pair of twins with an *OFD1* mutation inherited in an X-linked recessive fashion. These are the first two childhood patients reported with this condition, who presented only renal failure and cystic kidneys but without classic oral, facial, or digital features of OFD1. Based on this unusual presentation, maybe the phenotypic spectrum of *OFD1*-associated disorders is broader than previously anticipate. We suggest that *OFD1* screening should be considered, especially in males, if the suspicion for ciliopathy remains high in patients with renal failure and polycystic changes.

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