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Clinical and genetic analysis of Dent disease with nephrotic range albuminuria in Shaanxi, China

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Dear Editor,

Dent disease is a rare X-linked recessive disease that was first reported by Charles Enrique Dent and M. Friedman in 1964 (Dent and Friedman, 1964). Dent disease is caused by mutations in the *CLCN5* (Dent disease 1) or *OCRL1* (Dent disease 2). The condition is characterized by proximal renal tubular dysfunction that manifests as low molecular weight proteinuria (LMWP), hypercalciuria, nephrocalcinosis or nephrolithiasis, and progressive renal failure. Typically, the total protein excretion in tubular proteinuria is lower than that in glomerular diseases; therefore, nephrotic range proteinuria (NP) is not prevalent in patients with documented *CLCN5* or *OCRL1* mutations. Here, we report the cases of six Chinese children with Dent disease who manifested NP and were finally diagnosed using genetic analysis. Our aim was to elucidate the characteristics of Dent disease in Shaanxi area to facilitate possible improvements in its detection and treatment.

We conducted retrospective clinical and genetic analyses of six unrelated Chinese children with Dent disease. Five patients (cases 1–5) presented with isolated proteinuria, whereas one (case 6) presented with nephrotic syndrome. None of the patients showed edema. The characteristics of the cases were massive proteinuria (median: 91.65 mg/kg/24 h; range: 57.82–284.82 mg/kg/24 h), LMWP (>50%), and hypercalciuria (median: 0.27 mmol/kg/24 h; range: 0.14–0.59 mmol/kg/24 h; n=6). All six patients exhibited the histopathological findings of mesangial proliferative glomerulonephritis (MsPGN) (Figure 1A). One patient was diagnosed with acute renal tubular injury following repeat renal biopsy.

All six patients underwent genetic testing to assess the mutational status of the *CLCN5* and *OCRL1*. *CLCN5* mutations were detected in three patients (cases 4, 5, and 6) and their parents. *OCRL1* mutations were detected in three patients (cases 1, 2, and 3) and their parents (Figure 1B). Genetic analysis of *CLCN5* and *OCRL1* revealed six different mutations; these included three frameshift deletion (cases 2, 3, and 5) and three missense mutations (cases 1, 4, and 6). The mutations were scattered throughout the *CLCN5* and *OCRL1* gene coding sequence. In three patients, the molecular defect resulted in premature codon termination (cases 2, 3, and 5), whereas in three patients (cases 1, 4, and 6), it resulted in an amino acid substitution. To date, five of these genetic variations (p.D523N, p.183fs, p.104fs, p.L571F, and p.T153Tfs*15) have not been reported. All six variations were caused by hemizygous alleles. The mutations were

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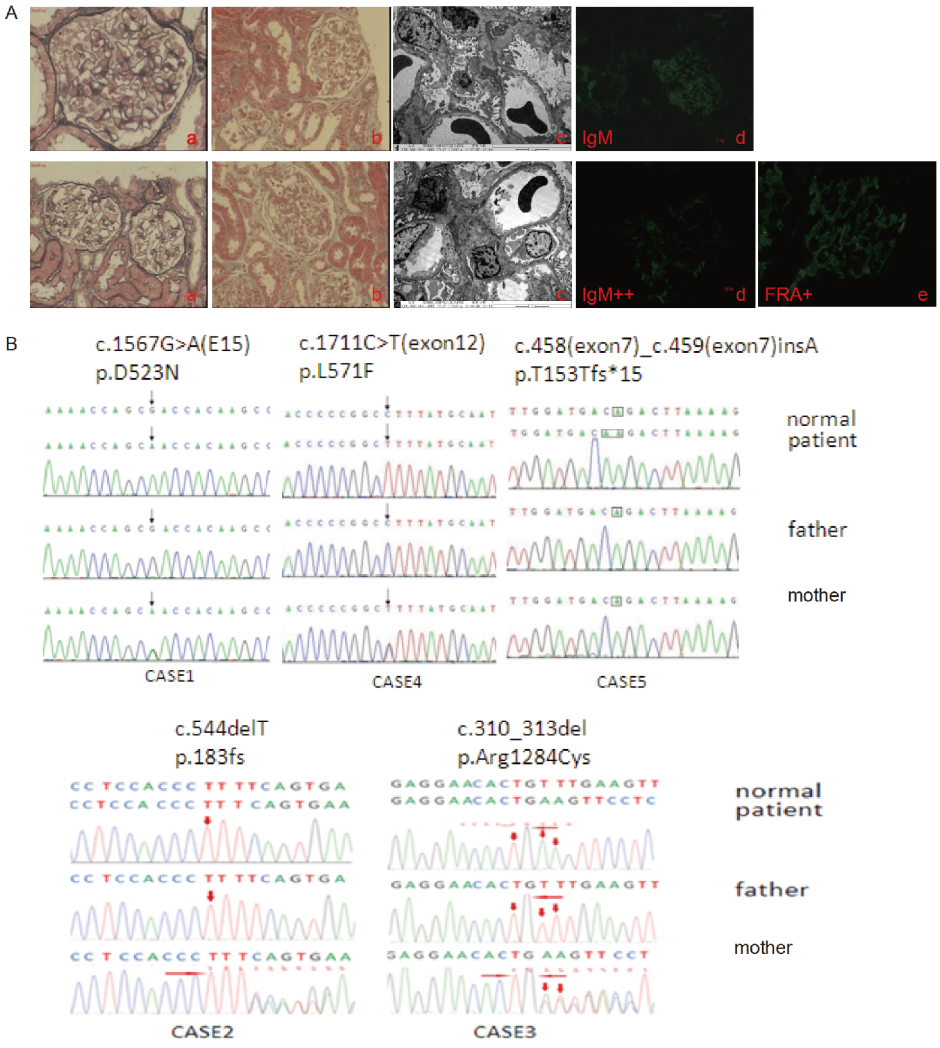

Figure 1 Renal pathological changes and genetic analysis results. A, Renal pathological changes: mesangial proliferative glomerulonephritis (MsPGN). a, PASM stain (original magnification 10×40); b, Masson stain (original magnification 10×20); c, Electron microscopy (original magnification 5000×); d and e, Immunofluorescence. B, Genetic test results demonstrating the mutations in patients and their parents. The figure illustrates the cDNA sequencing results of the aberrant transcripts, i.e., three *OCRL1*mutations (cases 1–3) and two *CLCN5* mutations (cases 4 and 5).

analyzed using a series of bioinformatics software (Polyphen, SIFT, and Mutation Taster) and no data assessing five genetic mutations of the six cases were available. Several prediction programs classified these mutations as probably damaging or disease-causing.

The mothers of cases 1–4 were heterozygous; however, no abnormalities were identified in the fathers, indicating that the pathogenic features in these cases were inherited via X-linked recessive inheritance. Along with clinical manifestation, the genetic mutations were attributed to pathogenic significance. Nevertheless, there was no genetic mutation in the parents of patients 5 and 6. However, a mutation was detected in case 6 that has been reported as a pathogenic mutation for Dent disease (Tosetto et al., 2006); in addition, a mutation was detected in case 5, the pathogenicity of which was established (PVS1+PM2+PS2) based on the guidelines of American College of Medical Genetics and Genomics (ACMG) and clinical manifestations.

The pathognomonic causes of Dent disease are attributed to *CLCN5* mutations (Dent disease 1) or *OCRL1* mutations (Dent disease 2), both located on the X-chromosome. Moreover, 30%–80% of these patients progress to end-stage renal disease by the age of approximately 30–50 years. Although Dent disease is marked by the involvement of proximal renal tubule, a few patients exhibit glycosuria, aminoaciduria, and other symptoms of Fanconi syndrome. Typical Dent disease is observed solely in boys and rickets is a common complication of the disease.

Although >300 families have been reported worldwide as of 2017, the incidence and prevalence of Dent disease remain uncertain. The Dent disease is typically recognized as a monogenic disease, which is consistent with the present re-

sults. Previous research has shown that approximately 60% cases are caused by *CLCN5* mutation, whereas 15%–20% cases are caused by *OCRL1* mutation; no specific gene defect has been identified in the remaining cases (Zaniew et al., 2017). It is possible that there are other unrecognized disease-associated genetic abnormalities. Genetic heterogeneity attributable to as yet unidentified genetic mutations is presumed to be responsible. To date, only one case has been reported with both *CLCN5* and *OCRL1* mutations (Addis et al., 2013). In our series, three cases were caused by *CLCN5* mutation, whereas the remaining three were caused by *OCRL1* mutation. The proportion of cases caused by *OCRL1* mutations was 50%, which is higher than that reported in a previous study (Sekine et al., 2014). In recent years, genome analysis strategies have been widely used for the diagnosis of pediatric diseases in China. We reviewed previously reported mutations and their associated phenotypes in 75 male pediatric patients with Dent disease in China by 2018; 18% patients experienced nephrocalcinosis, 2% experienced kidney failure, and 85% of the cases were caused by *CLCN5* mutation.

It should be noted that LMWP is the main clinical manifestation of Dent disease; the presence of NP possibly leads to misdiagnosis. All six patients in our series exhibited NP; however, all patients exhibited LMWP and hypercalciuria, with no edema, hypoalbuminemia, or hypercholesterolemia. There were no ophthalmic or mental abnormalities. There are several similarities in the clinical manifestations of type 1 and type 2 Dent disease; however, extra renal manifestations (such as mild mental retardation or mild cataract) are often observed in Dent disease 2. Several recent papers have reported that Dent disease 1 presents with high range proteinuria and that LMWP was considered a unique clinical feature (van Berkel et al., 2016). Because the proteinuria in Dent disease is mainly tubular proteinuria, these patients typically do not develop edema or hypoalbuminemia, despite the presence of severe proteinuria. LMWP is the hallmark of Dent disease and should be tested in patients with NP who have no edema or hypoalbuminemia to avoid potentially harmful immunosuppressive therapy.

As a rare hereditary renal tubular disease, the association between phenotype and genotype of Dent disease has not yet completely been characterized (Wong et al., 2017). First, the genotype may have some effects on the phenotype. However, although all six patients in this series exhibited the same phenotypes, they demonstrated different mutations; this difference suggests that some other factors may also influence the phenotype of Dent disease. This aspect requires further research for clarification. Second, the renal pathological changes may exert some influence on the phenotype. The mechanism via which *OCRL* and *CLCN5* mutations lead to a series of clinical manifestations and the possible reasons for the variable genotype-phenotype correlation remain unclear.

Dent disease is an incurable congenital genetic disease. The main principle of treatment is to control high calcium levels in urine, and delay the occurrence of renal tubular fibrosis and chronic renal failure. Children with proteinuria should undergo urine protein electrophoresis as soon as possible. Identification of small molecular protein should prompt the consideration of renal tubular diseases, particularly Dent disease. To avoid mistreatment, genetic analysis should be immediately conducted to establish a definitive diagnosis.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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SUPPORTING INFORMATION

Table S1 Primer sequences used for genetic analysis in the six cases

Table S2 Mutations in patients with Dent disease

Table S3 Urinary and blood tests of patients with Dent disease

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