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Genetic Heterogeneity in Dent Disease - Analysis of CLCN5 and OCRL1 Mutations in Patients with Dent Disease

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Background : Dent disease, an X-linked renal proximal tubulopathy caused by mutations of the chloride channel gene CLCN5, is clinically characterized by low molecular weight proteinuria, hypercalciuria and nephrocalcinosis. In some patients, nephrolithiasis, hypophospatemic rickets, glomerulosclerosis, and chronic renal failure may develop. Lowe syndrome, an X-linked multisystem disease characterized by renal tubulopathy (proximal renal tubular acidosis), congenital cataracts, and mental retardation, is associated with mutations in the OCRL1 gene, which encodes a phosphatidylinositol 4, 5-bisphosphonate 5-phosphatase. Genetic heterogeneity has been suggested in Dent disease. Recently, there is a report that some mutations in OCRL1 can phenocopy typical Dent disease without cataract, renal tubular acidosis, and neurological abnormalities. In this study, we screened CLCN5 and OCRL1 mutations in patients with Dent disease and analyzed genotype-phenotype correlations.

Methods : A review of medical records and mutational analyses of CLCN5 and OCRL1 were performed in 13 unrelated boys, who met the clinical diagnostic criteria for Dent disease. In addition, phenotype and genotype analyses for 5 boys with full-blown Lowe syndrome were also performed.

Results : Eight different CLCN5 mutations were detected in 10 patients (77%); 3 nonsense mutations, 2 missense mutations, 1 short deletion, and 2 short insertions. Three mutations in OCRL1 (F226S, Q260E and c.455delA) were identified in 3 remaining patients (23%). The renal phenotypes of these 3 patients were same as the patients with CLCN5 mutations. The patient with F226S mutation had no extrarenal symptoms. The patient with Q260E mutation had cataract, but it may be the caused by superimposing congenital CMV infection. The patient with c.455delA mutation had mild degree of developmental delay and elevation of muscle enzymes. The OCRL1 gene analysis was done in 2 patients with full-blown Lowe syndrome, and 2 nonsense mutations (R646X, R805X) were detected.

Conclusion : We confirmed genetic heterogeneity in Dent disease and phenotypic heterogeneity in Lowe syndrome. Thus, there is a continuing spectrum of phenotype in patients with CLCN5 or OCRL1 mutations. One end is classical Dent disease with CLCN5 mutations, and the other end is full-blown Lowe syndrome. In the middle, there are isolated renal form, which phenocopy Dent disease, and atypically mild form of Lowe syndrome with OCRL1 mutations.