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Molecular diagnosis of hypokalemic distal renal tubular acidosis

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Primary distal renal tubular acidosis (dRTA), often referred to as type 1 RTA, is a rare hereditary disorder and characterized by impaired ability of the α -intercalated cells in the collecting duct to secrete protons. Currently, 5 genes are recognized, mutation in which can cause dRTA: *SLC4A1*, *ATP6V0A4*, *ATP6V1B1*, *FOXI1*, and *WDR72*. *SLC4A1* encodes the anion exchanger (AE1) expressed on the basolateral aspect of the intercalated cells. *ATP6V0A4* and *ATP6V1B1* encode subunits of the proton pump (H^+ -ATPase), expressed on the apical side of the intercalated cells, as well as in the inner ear. *FOXI1* encodes a transcription factor important for acid-secreting epithelia, and *WDR72* involves intracellular trafficking, potentially affecting targeting of acid-base regulatory proteins. Clinically, dRTA is characterized by hyperchloremic (normal anionic gap) metabolic acidosis, hypokalemia, and insufficiently acidified urine. Persistent metabolic acidosis leads to release of calcium from the skeleton, which, together with impaired tubular calcium reabsorption in acidosis, results in hypercalciuria and subsequent development of nephrocalcinosis and/or nephrolithiasis. Growth retardation is another common presenting symptom in children with dRTA. dRTA can also be associated with sensorineural hearing loss, most prominently with mutations in *ATP6V1B1*, *FOXI1*, and, to a lesser degree, *ATP6V0A4*, because of their shared expression and functional relevance in kidney and inner ear.

In 2018, our group reported the prevalence and phenotypic differences of genetic mutations in 17 unrelated Korean children with dRTA. The results of our study were compared with the data of recent large international cohort study (n=340) by the European dRTA Consortium. In both studies, genetic analysis included the three-classical dRTA genes (*SLC4A1*, *ATP6V0A4*, and *ATP6V1B1*) but not the most recently discovered genes (*FOXI1* and *WDR72*).

The most striking difference between the two studies is the higher frequency of *SLC4A1* mutations in the Korean study (59% of the patients versus 15% of the patients) with two common mutations, p.R589C and p.R589H. However, the genotype-phenotype correlation analyses for the clinical features showed very similar results between the two studies. While most patients with *ATP6V0A4* or *ATP6V1B1* mutations had an earlier onset in infancy, patients with *SLC4A1* mutations had a significantly later onset in both studies. In the Korean study, patients with *ATP6V0A4* or *ATP6V1B1* mutations had more severe acidosis than patients with *SLC4A1* mutations.

Almost all patients were treated with alkali. In the European study, the prescribed dose of alkali treatment was comparable across the genetic subgroups, and prescribed doses of alkali were significantly higher in younger patients compared with older ones. Adequate metabolic control (normal serum $HCO_3^- \geq 22$ mmol/L and normocalciuria) was achieved in 65% of the patients in the Korean study and 51% of the patients in the European study. At the last follow-up, a considerable number of patients had an impaired eGFR, chronic kidney disease stage 2~4: 35% of children and 83% of adults in the European study, and 15% of children and 50% of adults in the Korean study. Current height standard deviation score for the adult population in the European study was -0.57 ± 1.16 , with no significant difference between the genetic groups. Notably, adequate metabolic control was associated with better height growth and renal function. Nephrocalcinosis was noted in most patients, and hearing loss was particularly common in patients with *ATP6V1B1* mutations and, to a lesser degree, in patients with *ATP6V0A4* mutations.

In conclusion, more than half of Korean pediatric patients with primary dRTA have dominant mutations in *SLC4A1*. The overall long-term prognosis of patients with dRTA is relatively favorable. However, adequate metabolic control, which is associated with better growth and renal function, is not achieved in a considerable number of patients.