Renal tubular acidosis (RTA) is an uncommon disorder; however, the subgroup of isolated familial proximal RTA (pRTA) is exceedingly rare. The term ‘isolated’ pRTA distinguishes these disorders from Fanconi syndrome, in which proximal RTA (pRTA) is exceedingly rare. The term ‘isolated’ pRTA distinguishes these disorders from Fanconi syndrome, in which...
hyperamylasaemia. In addition to its expression in the renal proximal tubule, NBC-1 is also present in the epithelia of eye, brain and pancreas, which is likely to explain the diverse findings.

’Sporadic isolated pRTA’ is a non-familial, transient pRTA observed in early childhood. Affected individuals present with pRTA, short stature and vomiting. Alkali therapy is helpful and the disorder disappears after a few years [3]. It is held that continued immaturity of KNBC-1 beyond the neonatal period is involved but disappears later in life. ‘Autosomal dominant pRTA’ is a disorder of pRTA and short stature but no other abnormalities. It has thus far been described only once in nine members of a single family [4] over 20 years ago. Because of the kidney specific distribution of NHE-3 and based on a knock-out model of NHE-3 in mice [5], it was predicted that mutations of NHE-3 would be found, explaining autosomal dominant pRTA. However, the report by Katzir et al., in this issue of NDT, casts doubt on that proposal.

Katzir et al. [1] describe only the second family in the literature with autosomal dominant pRTA. The affected individuals had a pH in blood of 7.13, bicarbonate of 13.9 mmol/L, hyperchloremia and a low urinary pH of 5.4. An oral bicarbonate loading test partially corrected the metabolic acidosis, the urinary pH increased to 6.8 and the fractional excretion of bicarbonate rose to 22%. The findings were therefore the characteristic of pRTA. However, sequencing of genomic DNA from the patient and four affected family members failed to uncover mutations of NHE-3 and its regulatory proteins NHRF1 and NHRF2, nor were there any mutations of other candidate genes (Figure 1) found.

What are the implications of these unexpected results? Is the technique or the concept at fault? The authors amplified and sequenced the coding areas and splice sites of the genes of interest. They also performed a haplotype analysis of introns and regulatory sequences of the candidate genes, using three to four microsatellite markers in each gene. If the reconstructed haplotypes were dissimilar between affected individuals, they were excluded as potential causes of the phenotypic defect. A lot of analysis must have been involved in this work; however, there may still be a possibility that three to four microsatellite markers are not sufficient to fully study the introns and the promoter area of a gene, or to exclude small changes such as a point mutation. It is notoriously difficult to completely exclude technical difficulty; we shall not know this with any certainty until more clusters of patients are studied.

What if our concept of obligatory proteins in pRTA (Figure 1) was deficient? Could there be transporters in pRTA that have been overlooked? The authors consider that a new enzyme or a regulatory factor related to the trafficking of NHE-3 might be involved. Indeed in the present work, the authors were unable to fully exclude the regulatory protein of NHE-3 NHRF1 from being involved. Given the limited phenotype of autosomal dominant pRTA and the kidney-specific distribution of NHE-3, they might conceivably be correct. Alternatively is it possible that a luminal H+−ATPase has a role in the human proximal tubule? In the rat it was shown that an apical vacuolar H+−ATPase contributed about one-third to bicarbonate reclamation in that segment [6]. Still other experiments in the salamander suggested the presence of tertiary active hydrogen ion secretion in the proximal tubule [7]. This mechanism utilizes an apical Na+−lactate and a basolateral membrane H+−lactate cotransporter. Finally bicarbonate has a paracellular backleak pathway into the tubular fluid in the late proximal tubule of the rat [8]. Could it become leakier than physiological and thus contribute to pRTA in humans?

Taken together, the inability of Katzir et al. to explain clear-cut pRTA in their patients on the basis of known transport mechanisms brings up the question as to whether other mechanisms could be involved and what they are. It will be exciting to see how this enigma unravels in the future.

Conflict of interest statement. None declared.


References


