Inherited Renal Acidoses

Inherited acidosis may result from a primary renal defect in acid-base handling, emphasizing the central role of the kidney in control of body pH; as a secondary phenomenon resulting from abnormal renal electrolyte handling; or from excess production of acid elsewhere in the body. Here, we review our current understanding of the inherited renal acidoses at a genetic and molecular level.

Strict homeostatic control of acid-base balance is essential for survival, with optimal functioning of most physiological processes being dependent on maintenance of human body fluid pH within a narrow range of around pH 7.4. Acid is produced in the body through the metabolism of food, and although the bulk of this is excreted by the lungs (in the form of CO₂), the kidneys act as a key regulator of this process through secretion of protons into the urine and reclamation of filtered bicarbonate.

The causes of acidosis can be subdivided into four groups:
1) Inherited acidoses of renal origin: primary failure of the kidney to secrete acid or reclaim bicarbonate, or secondary due to defects in handling of other electrolytes.
2) Acquired acidoses of renal origin, most commonly seen as a result of impaired renal function.
3) Inherited acidoses of non-renal origin, with the excess production of acid elsewhere in the body due to an inherited metabolic defect.
4) Acquired acidoses of non-renal origin, e.g., lactic acidosis as a result of poor tissue oxygenation.

This review will focus on the inherited acidoses of renal origin. We shall first examine the control of acid-base homeostasis by the kidney in more detail.

Physiology of Renal Acid-Base Homeostasis

The role of the renal tubule in acid-base regulation may be summarized thus: 1) proximal reclamation of filtered bicarbonate and 2) distal secretion of H⁺, with phosphate buffers and ammonium. Acidosis originating from the kidney (renal tubular acidosis or RTA) thus arises from either a failure of proximal mechanisms of bicarbonate conservation or of distal acid secretion.

Proximal tubule bicarbonate reabsorption

Bicarbonate is freely filtered at the glomerulus, with 80–90% of this being reabsorbed in the proximal tubule (reviewed in Ref. 51) (FIGURE 1A). Filtered HCO₃⁻ combines with H⁺ in the tubular lumen in a reaction catalyzed by carbonic anhydrase IV, which is bound to the luminal membrane of proximal tubular cells. The CO₂ thus produced rapidly diffuses into the tubular cells and is combined with water to produce intracellular H⁺ and HCO₃⁻, catalyzed by soluble cytoplasmic carbonic anhydrase II (CA II). HCO₃⁻ is then cotransported with Na⁺ into blood [with a probable stoichiometry of 3 HCO₃⁻ to 1 Na⁺ (52)] via the Na⁺/HCO₃⁻ cotransporter NBC1, situated on the basolateral cell membrane. The H⁺ is secreted into the tubular lumen predominantly via the Na⁺/H⁺ exchanger NHE3 in the luminal membrane, using the sodium concentration gradient generated by the action of a basolateral membrane Na⁺-K⁺-ATPase. It should be noted that there is minimal net acid excretion in the proximal tubule; most of the H⁺ is used to reabsorb bicarbonate (53); any remaining will be buffered by phosphate as titratable acid. The rate of HCO₃⁻ reabsorption is determined by luminal HCO₃⁻ concentration and pH, luminal flow rate, peritubular PCO₂, and angiotensin II.

Proximal tubular cells are capable of generating “extra” bicarbonate through the deamination of glutamine to glutamate, then forming α-ketoglutarate and eventually glucose (FIGURE 1A). This produces HCO₃⁻ and NH₄⁺: the former reclaimed via the basolateral membrane and the latter secreted into the tubular lumen. This process can be upregulated in states of chronic acidosis (37).

Distal tubule acid secretion

The α-intercalated cell (α-IC) of the distal nephron is responsible for net acid excretion (FIGURE 1B). As in the proximal tubule, intracellular CA II catalyses the formation of H⁺ and HCO₃⁻. H⁺ are pumped into the tubular lumen by an H⁺-ATPase, functionally coupled to basolateral HCO₃⁻ exit via the Cl⁻/HCO₃⁻ exchanger AE1. H⁺ in the tubular lumen combine with phosphate (forming further titratable acid) and with NH₄⁺. Initially secreted as NH₄⁺ in the proximal tubule and then reabsorbed by the cells of the thick ascending limb of the Loop of Henle, NH₄⁺ passes into the medullary interstitium and dissociates to NH₃ (74). This may simply diffuse into the collecting duct lumen, but there is also evidence for active basolateral uptake of NH₄⁺ by cells of the cortical collecting duct (possibly mediated by a Na⁺-K⁺-ATPase and the
Specific knockout of distal nephron CLC-K2 function will be necessary for further interrogation of Cl⁻ recycling (31).

**Classification and Clinical Features of RTA**

RTA is characterized by the presence of a normal anion gap (hyperchloraemic) metabolic acidosis in the setting of otherwise preserved kidney function (i.e., normal or near-normal glomerular filtration rate). Clinical and functional studies allow classification into four types, historically numbered in the order of discovery: proximal (type 2), classic distal (type 1), hyperkalemic distal (type 4) and combined proximal and distal (type 3). As is evident from an understanding of acid-base handling by the kidney, proximal RTA results from a failure of bicarbonate reclamation, and distal RTA from a failure of acid secretion, either of which may be inherited or acquired. Although acquired forms of the disease may be more common in clinical practice, it is from study of the inherited renal tubular transport disorders that investigators have been able both to clarify the genetic basis of the related diseases and to enhance our understanding of normal renal physiology (see Table 1).

**RTA: Individual Conditions**

**Inherited classic distal RTA**

Distal RTA (dRTA) represents a failure of the α-intercalated cell to acidify the urine and, in its inherited form,
has three variants: autosomal dominant and autosomal recessive with or without deafness. In the clinic, acquired forms predominate, most often as a result of autoimmune disease (e.g., Sjögren’s syndrome), other systemic disorders, or drugs. Primary dRTA results in a metabolic acidosis of variable severity, usually with hypokalemia, hypercalciuria, and hypocitraturia. Rickets and osteomalacia can develop in both dominant and recessive forms, although dominant disease typically presents more mildly in adolescence or adulthood, and recessive in infancy/early childhood, where growth retardation is common (33). The low urine citrate results from upregulated citrate reabsorption in the proximal tubule to create new bicarbonate. The hypercalciuria is multifactorial, probably because of a combination of increased calcium release from bone (as an attempt to buffer the systemic acidosis (50)), acidosis-induced downregulation of renal Ca\(^{2+}\) transport proteins (45), and increased distal sodium delivery. These factors, together with the high urine pH, favor abnormal renal calcium deposition as nephrocalcinosis and/or renal stones, both of which may result in renal failure in the long term. Sensorineural hearing loss is seen in the majority of patients with autosomal recessive dRTA. Erythrocytosis may result in those with nephrocalcinosis, although this is not pathognomonic. It is thought to arise as a consequence of increased erythropoietin production secondary to tissue hypoxia, combined with urinary concentration defects causing reduced plasma volume (17).

Diagnosis of classic dRTA is based on the finding of a high urine pH in the setting of a systemic metabolic acidosis. The systemic pH may be fully compensated

Table 1. The inherited renal tubular acidoses

<table>
<thead>
<tr>
<th>Type of RTA</th>
<th>Subtype and Inheritance</th>
<th>Age at Presentation</th>
<th>Clinical Features</th>
<th>Protein</th>
<th>Gene(s)</th>
<th>OMIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal (type 1)</td>
<td>Dominant</td>
<td>Older/adult</td>
<td>Mild/compensated metabolic acidosis, Hypokalemia (variable), Hypercalciuria, Hypocitraturia, Nephrolithiasis, Nephrocalcinosis, Sometimes rickets/osteomalacia, Secondary erythrocytosis</td>
<td>AE1</td>
<td>SCL4A1</td>
<td>179800</td>
</tr>
<tr>
<td>Recessive</td>
<td>Childhoood</td>
<td>Metabolic acidosis with hemolytic anemia, Only reported in Southeast Asian populations</td>
<td>AE1</td>
<td>SCL4A1</td>
<td>602722</td>
<td></td>
</tr>
<tr>
<td>Recessive with early onset hearing loss</td>
<td>Infancy/childhood</td>
<td>Metabolic acidosis, Early nephrocalcinosis, Vomiting/dehydration, Growth retardation, Rickets, Bilateral sensorineural hearing loss, from childhood</td>
<td>B1 subunit of H(^{+})-ATPase</td>
<td>ATP6V1B1</td>
<td>267300</td>
<td></td>
</tr>
<tr>
<td>Recessive with later onset hearing loss</td>
<td>Infancy/childhood</td>
<td>As above, but later onset hearing loss in some (a few with normal hearing)</td>
<td>a4 subunit of H(^{+})-ATPase</td>
<td>ATP6V0A4</td>
<td>602722</td>
<td></td>
</tr>
<tr>
<td>Proximal (type 2)</td>
<td>Recessive with ocular abnormalities</td>
<td>Infancy</td>
<td>Metabolic acidosis, Hypokalemia, Ocular abnormalities (band keratopathy, cataracts, glaucoma), Growth retardation, Defective dental enamel, Intellectual impairment, Enamel, Brain ganglia calcification</td>
<td>NBC1</td>
<td>SLC4A4</td>
<td>604278</td>
</tr>
<tr>
<td>Combined proximal and distal (type 3)</td>
<td>Recessive with osteopetrosis</td>
<td>Infancy/childhood</td>
<td>Metabolic acidosis, Hypokalemia, Osteopetrosis, Blindness, Deafness, Early nephrocalcinosis</td>
<td>CA II</td>
<td>CA2</td>
<td>259730</td>
</tr>
</tbody>
</table>
(so-called “incomplete” dRTA), in which case a failure of urinary acidification should be demonstrated pharmacologically. Traditionally, this is achieved through an oral ammonium loading test, but the more palatable combination of furosemide/ldrocortisone has been proposed as an alternative (74). Treatment with moderate doses of oral alkali (1–3 mEq • kg⁻¹ • day⁻¹ of bicarbonate) is sufficient to reverse the metabolic acidosis and normalize bone growth but does not affect the severity or progression of deafness (85).

**Autosomal dominant distal RTA-AE1**

AE1, the basolateral Cl⁻/HCO₃⁻ exchanger of α-ICs, is encoded by SLC4A1 on chromosome 17, a member of the SLC4 family of 10 genes encoding bicarbonate transporters (see Ref. 1). In mammals, the only other major site of expression of AE1 is in the erythrocyte (eAE1; often referred to as “band 3” because of its major site of expression of AE1 transporters (see Ref. 1). In mammals, the only other kidney isoform (kAE1). This extra NH₂-terminal sequence confers additional roles on eAE1, including facilitation of red cell metabolism and maintenance of erythrocyte structural stability via interaction with a glycolytic enzyme complex and cytoskeletal elements, respectively (reviewed by Ref. 1). Hence, the largest group of mutations in human AE1 are associated with autosomal-dominant red cell dysmorphologies: hereditary spherocytic anemia (HS; also caused by mutations in ankyrin, spectrin, and protein 4.2) and south-east Asian ovalocytosis (SAO), where renal acid-base handling is normal (reviewed in Ref. 20). Although the majority of metabolic/structural protein-eAE1 interactions occur within the NH₂-terminal 65 amino acids (81), this is not always simple. For example, ankyrin binds at residues 175–185, although the conformation of this binding site is dependent on the presence of residues 57–65, explaining the lack of affinity between ankyrin and kAE1 (9).

Metabolic interactions are not exclusively restricted to the eAE1 NH₂ terminus, however, with the COOH-terminal cytoplasmic tail containing a binding site for CA II via a highly conserved acidic sequence LDADD beginning at residue 886 (78, 79). This leads to the intriguing suggestion that the two proteins interact to form a “metabolon” to facilitate bicarbonate export by the α-IC and erythrocyte. Similar interactions may exist with other basolateral resident proteins such as the Na⁺-K⁺-ATPase (19, 29), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which co-localizes with kAE1 to the basolateral membrane of α-ICs (16), and glucose transporter(s) (29), suggesting the presence of a transport protein complex centered on AE1. The intramolecular bases of these predicted interactions are unknown.

To date, eight different AE1 mutations have been reported to cause autosomal dominant dRTA, the majority involving R589 (R589H, R589S, R589C) in the intracellular loop between the sixth and seventh transmembrane spans (7, 30, 36). The other reported mutations are G609R and S613F, both in transmembrane segment 7, A838D in the final transmembrane segment, and two COOH-terminal deletions: R901X and A889X (7, 8, 11, 36, 54). Many of these mutants have been cloned and expressed in Xenopus oocytes and exhibit essentially normal anion exchange function (7, 8, 30, 54, 71), indicating that abnormal anion transport per se is not the disease mechanism. Similarly, AE1 is known to form oligomers, but co-expression of mutant and wild-type AE1 appears not to affect wild-type function (7).

The hypothesis thus arose that mutant AE1 may be exerting its effect through mis-targeting away from the basolateral membrane within the polarised α-IC (7). A number of groups have now demonstrated intracellular retention of AE1 in nonpolarized cells (48, 71), and in polarized cells either mis-targeting of mutant AE1 to the apical membrane [R901X and G609R mutations (14, 54, 70)] or intracellular retention [R589H and S613F (12, 70)]. The presence of potential targeting motifs within the COOH-terminal tail has provided information regarding the underlying trafficking mechanisms. Within the deleted tail of the R901Stop mutant is the sequence YXX₀, which was thought to correspond to the YXX₀ tyrosine-based targeting motif (where X is any amino acid and φ is a hydrophobic residue). YXX₀ motifs interact with adaptor protein complex μ subunits, including μ1B, which mediates basolateral sorting in polarized epithelial cells (18). However, transfection of LLC-PK₁ cells, a renal tubular cell line lacking μ1B, with wild-type kAE1 or the R901Stop mutant led to basolateral and apical targeting, respectively, indicating that μ1B is not implicated in the intracellular sorting of AE1. Replacement of the valine residue (φ in the motif failed to alter basolateral residency (13), providing further evidence that this is not a canonical YXX₀ motif. The tyrosine residue is crucial, however, as substitution of Tyr904 resulted in either an apical pattern of surface expression similar to that observed with the R901X truncation mutant [Y904A (14)] or intracellular retention [Y904F (70)]. Phosphorylation of Tyr904 (and a NH₂-terminal tyrosine at residue 359) may be important both in the intracellular targeting of AE1 and regulation of its expression at the basolateral membrane (73).

Binding to scaffolding proteins of the PDZ (postsynaptic density protein, Drosophila disc large tumor suppressor, Zo-1 protein) family may help retain AE1...
Autosomal recessive distal RTA-AE1

Although mutations in AE1 are responsible for all cases of autosomal dominant dRTA, AE1 mutations causing autosomal recessive dRTA in association with hemolytic anemia have also been demonstrated in south-east Asian kindreds, the first reported being G701D in a Thai family (69, 84). Erythroid anion exchange function of the G701D mutant is normal. Expression of G701D in Xenopus oocytes resulted in impaired trafficking of the mutant protein, but this could be rescued by the addition of the chaperonin glycophorin A. This protein is found in erythrocytes but not in the kidney, suggesting a mechanism for functional failure of the α-IC, although the mechanism of hemolytic anemia remains unclear (69).

Vasuvattakul et al. found that patients with both dRTA and SAO were compound heterozygotes for the G701D mutation and the SAO allele and that patients with the SAO allele alone had normal urinary acidification (77). Bruce et al. described a further series of mutations causing both recessive and dominant dRTA with SAO in kindreds from Papua New Guinea and Malaysia and suggested that different mechanisms may account for the disease in each mutation, e.g., defective ion transport with ΔV850 and mis-targeting with A858D (8). Additional compound heterozygous mutations have since been described in patients with autosomal recessive dRTA (63), and both Cordat et al. (12) and Sawasdee et al. (56) demonstrated the presence and nature of trafficking defects in a number of mutations (both recessive and dominant dRTA). The mutations causing recessive dRTA do so when homozygous or as compound heterozygotes with the SAO allele, confirming co-dominant, or “apparent” recessive, inheritance. To date, no AE1 mutations causing recessive dRTA have been found in Caucasian patients.

Homozygosity for the band 3 Coimbra mutation (V488M, which causes typical HS in the heterozygous state) has been described in a single human case. This resulted in complete absence of AE1 in a child born with hydrops fetalis and severe hemolytic anemia, who developed renal tubular acidosis with nephrocalcinosis by the age of 3 months (49). Complete absence of AE1 has been reported in Japanese Black cattle where it is associated with the development of severe hemolytic anemia, but only a mild metabolic acidosis, possibly because of the minimal acid load in a ruminant diet (28).

Recessive distal RTA: the proton pump

The renal tubular apical proton pump is a member of the ubiquitous family of vacuolar H+-ATPases. Although these are present intracellularly in the membranes of organelles in all tissues, they are also found, in specialized form, in the plasma membrane of cells in various tissues, particularly kidney, ear, male genital tract, and bone (reviewed in Ref. 80). They consist of two domains, membrane-bound V_o and cytoplasmic V_i, each formed of multiple subunits (α–ε and A–H, respectively). Although subunit numbers are constant, some subunits are encoded by alternative genes with tissue-specific expression. For example, with regard to the G subunit, G1 expression is ubiquitous, G2 is only found in brain, and G3 is only found in the renal tract (61).

Genome-wide linkage analyses in a cohort of mainly consanguineous kindreds, largely of Middle Eastern and Turkish descent, have allowed the identification of two genes for recessive dRTA (34, 35, 62). Analysis of kindreds affected by both dRTA and sensorineural hearing loss first identified genetic linkage to a region of chromosome 2p. This contained a likely candidate gene encoding the B1-subunit of H+-ATPase (ATP6V1B1), screening of which identified mutations co-segregating with dRTA (35). ATP6V1B1 expression in the human cochlea was also discovered, where the H+-ATPase appears to be required to maintain normal endolymph pH.

Linkage analysis in a cohort with recessive dRTA who presented with normal hearing implicated a second genetic locus at 7q33-34. Positional cloning identified the novel ATP6V0A4 gene (34), shown to encode a new kidney-specific form (a4) of the proton pump’s α-subunit (62). Further work on new kindreds by Stover et al. demonstrated additional ATP6V1B1 and ATP6V0A4 mutations. Several patients developed later-onset hearing loss (as opposed to the early childhood deafness generally seen in patients with ATP6V1B1 mutations), and ATP6V0A4 was also shown to be expressed within the inner ear (65). Early onset deafness has now been reported in some patients with ATP6V0A4 by Vargas-Pousso et al., who also reported a series of new mutations in both genes (76). Thus there is considerable variability of phenotypic severity within recessive dRTA, and the basis of this remains unclear.

It is notable that, although the B1 subunit has not been observed in the proximal tubule, the a4 subunit is present there (64). Despite this difference in expression, the phenotypes associated with both genes are of preserved proximal tubular function (when potassium levels are normalized). There is therefore assumed to be a degree of functional redundancy among different a-subunit homologs. In fact, the a4 subunit appears to
be localized slightly differently, as it is reported to be below the brush border in the area of recycling vesicles (reviewed in Ref. 80), but the redundancy argument can still be invoked, since there is no evidence of proximal tubular dysfunction amongst α4 mutation-bearing individuals.

The gene defect remains unidentified in some affected families that are unlinked to either of the two known loci. Several other of the proton pump's subunits that are alternate forms prevalent in the kidney are good candidates in this respect; these include the kidney-specific G3 subunit gene and also C2, d2, and the recently identified e2 subunit genes (2, 61). However, interrogation of suitable kindreds (by virtue of absence of mutations in, and/or linkage to, \( \text{ATP6V1B1} \) and \( \text{ATP6V0A4} \)) has not revealed any potentially pathogenic sequence variations in these genes.

Another attractive candidate gene for recessive dRTA is that encoding KCC4, the basolateral \( K^+\)-\( Cl^- \) cotransporter. This is because KCC4 knockout mice do indeed develop metabolic acidosis together with sensorineural deafness (3). However, the role of KCC4 in the human kidney remains to be elucidated.

Wider consideration of possible candidate genes for recessive dRTA is possible from studies to identify the proton pump's interacting proteins. For example, rodent studies reveal that the B1 subunit's COOH terminus, which contains the PDZ-binding motif DTAL, is capable of interaction with the PDZ protein NHERF-1 (6). However, in the distal nephron, expression of this protein is not found in \( \beta^+\)ICs but is confined to \( \beta^-\)ICs, which essentially reverse \( \alpha^-\)IC function to secrete bicarbonate. In man, \( \beta^-\)ICs play a much less prominent role in acid-base homeostasis thanks to the net acid load of the average human diet.

Glycolytic enzymes are also important interactors of the pump. The E subunit binds aldolase, whereas the a-subunit has been shown to interact with PFK-1 (44, 67). However, these enzymes are ubiquitously expressed, and it is hard to envisage a kidney-limited disease phenotype resulting from mutations in the genes encoding them. The muscle isoform of PFK-1 is in fact associated with type VII glycogen storage disease.

### Inherited Proximal RTA

Proximal RTA (pRTA) may arise as a primary and isolated lesion, either inherited and persistent from birth or as a transient phenomenon during infancy (secondary to tubular immaturity, which resolves with development) (27, 51). Primary, isolated, pRTA is a rare disorder and may be inherited as an autosomal recessive or dominant trait. The underlying cause is a failure of proximal bicarbonate reabsorption. This produces an abnormally low threshold for renal bicarbonate reabsorption since the distal nephron is unable to compensate and reabsorb the large bicarbonate load presented to it. However, distal acidification mechanisms are intact, and acid urine can be produced. The clinical phenotype is of a metabolic acidosis with hypokalemia, and although metabolic bone disease is common, nephrocalcinosis and nephrolithiasis are

### Table 2. Some causes of renal Fanconi syndrome

<table>
<thead>
<tr>
<th>Inherited renal disease (Idiopathic Fanconi's)</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited syndromes (inborn errors of metabolism)</td>
<td>Intrinsic renal disease</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>Autoimmune conditions, e.g.,</td>
</tr>
<tr>
<td>Tyrosinaemia type 1</td>
<td>Sjögren's syndrome</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>Hypokalemic nephropathy</td>
</tr>
<tr>
<td>Oculocerebral dystrophy (Lowe's syndrome)</td>
<td>Renal transplant rejection</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>Hematological disease</td>
</tr>
<tr>
<td>Hereditary fructose intolerance</td>
<td>Myeloma</td>
</tr>
<tr>
<td>Sporadic (most common)</td>
<td>Drugs</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>X-linked (Dent disease)</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td></td>
<td>Sodium valproate</td>
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<tr>
<td></td>
<td>Heavy metals</td>
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<tr>
<td></td>
<td>Lead</td>
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<tr>
<td></td>
<td>Cadmium</td>
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<tr>
<td></td>
<td>Mercury</td>
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<tr>
<td></td>
<td>Organic compounds</td>
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<tr>
<td></td>
<td>Toluene (glue-sniffing)</td>
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<tr>
<td></td>
<td>Nutritional</td>
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<td></td>
<td>Kwashiorkor (protein-energy malnutrition)</td>
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<tr>
<td></td>
<td>Hormonal</td>
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<td>Primary hyperparathyroidism</td>
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</table>
rare. The acidosis is generally milder than in distal disease. Because of a lowering of the tubular threshold for bicarbonate reabsorption, once the plasma bicarbonate is reduced, the threshold can be reached and a steady state maintained at a plasma [HCO₃⁻] of around 15 mM. In contrast, plasma [HCO₃⁻] can fall to <10 mM in dRTA.

Administration of large amounts of alkali (10–20 mEq kg⁻¹ day⁻¹) may be required to normalize plasma [HCO₃⁻] in pRTA, resulting in a highly alkaline urine (containing >10–15% of the filtered load) due to the low threshold for bicarbonate reabsorption.

More commonly clinically is secondary pRTA, which is accompanied by other proximal tubular defects (renal Fanconi syndrome) with impaired reabsorption of amino acids, phosphate, and glucose as well as HCO₃⁻. Causes of the renal Fanconi syndrome are given in Table 2.

**Autosomal recessive pRTA**

Isolated autosomal recessive pRTA usually occurs with ocular abnormalities (band keratopathy, cataracts, and glaucoma, often leading to blindness), short stature, enamel defects of the teeth, and intellectual impairment. Calcification of the basal ganglia may be present (26).

This disorder is caused by mutations in the gene encoding the sodium bicarbonate cotransporter NBC1 (SLC4A4, from the same SLC family as AE1) (26). Located in the basolateral membrane in proximal tubular cells (FIGURE 1A), NBC1 consists of intracytoplasmic NH- and COOH termini connected by 10 transmembrane spans. Igarashi et al. were the first to demonstrate two different SLC4A4 mutations (R298S and R510H) in patients with pRTA and ocular abnormalities, both of which demonstrated reduced functional activity when assayed in a mammalian cell expression system (24). A number of other mutations have subsequently been described (15, 22, 25). In addition to reduced functional activity, defects of intracellular trafficking have since been described in some of these mutations: intracytoplasmic retention of R510H and aberrant apical expression of S427L (43). The R881C mutation has been shown to possess normal ion channel activity but is retained at the endoplasmic reticulum in a polarized renal epithelial cell model, with reduced surface expression (72). In addition to failure of proximal tubular bicarbonate reabsorption causing pRTA, ocular tissues have also been shown to express NBC1 and various mechanisms proposed as to how this may relate to the eye abnormalities (26, 75). NBC1 is also expressed in the pancreas, and pancreatitis may be associated with NBC1 mutations (55).

**Autosomal dominant pRTA**

It has been hypothesized that a single pedigree consisting of nine members of a Costa Rican family with hyperchloremic metabolic acidosis, normal ability to acidify urine, normal renal function, and growth retardation follows an autosomal dominant pattern of inheritance (5). NHE3 (encoded by SLC9A3) was considered a likely candidate gene. However, the NHE3 knockout mouse has reduced proximal tubular HCO₃⁻ reabsorption but only mild metabolic acidosis (26, 57). To date, no human mutations have been described.

**Mixed proximal and distal RTA (type 3)**

This shares the features of both proximal and distal lesions, with a reduced tubular threshold for bicarbonate reabsorption coupled with an inability to maximally acidify the urine despite the presence of systemic acidosis. The condition is due to an inherited deficiency of carbonic anhydrase II, giving rise to an autosomal recessive pattern of inheritance with the clinical phenotype mirroring the expression of this enzyme in bone, kidney, and brain (51, 60). Affected patients develop osteopetrosis due to osteoclast dysfunction as well as RTA, with the key role of CAII in both proximal and distal renal tubules explaining the mixed acidosis. This association of osteopetrosis and RTA is known as Guibaud-Vainsel syndrome or marble brain disease. Osteopetrosis is a condition of increased bone density but also increased bone fragility, leading to increased fracture risk, plus intracerebral calcification, intellectual impairment, growth failure, and facial dysmorphism. Excess bone growth leads to conductive deafness and can also cause blindness through compression of the optic nerve. The co-existence in CA II-deficient individuals of the “bone-thinning” metabolic acidosis has been suggested to ameliorate some of the bone thickening that results from osteopetrosis (82). Treatment involves alkali supplementation for the acidosis, with the potential for bone marrow transplantation to reverse the osteopetrosis (47).

Various different mutations in CA2 (the gene encoding CA II) have been described; for example, the common “Arabic” mutation, consisting of a novel splice junction at the 5’ end of intron 2 (23). There is a considerable degree of heterogeneity, both in the predominance of proximal or distal acidosis and in the osteopetrotic phenotype (58). A single additional patient has been described with the phenotype of osteopetrosis and dRTA, who had a homozygous mutation in TCIRG1, the osteoclast-specific form of the H⁺-ATPase a-subunit accounting for the bone disease, and a homozygous mutation in ATP6V1B1 encoding the kidney specific B1 H⁺-ATPase subunit (see earlier) explaining the dRTA (4).

**Inherited Renal Disease Resulting in a Secondary Acidosis**

A primary defect in electrolyte handling by the kidney may also produce a secondary metabolic acidosis, thus demonstrating the linked handling of electrolytes and acid/base by the kidney. The interplay between
renal Na⁺ and H⁺ handling is demonstrated most effectively by the various types of pseudohypoaldosteronism (PHA).

**PHA type I**

Characterized by renal salt wasting, hyperkalemia, and metabolic acidosis, the clinical picture is that of renal resistance to mineralocorticoids with elevated serum aldosterone levels. PHA I can be subdivided into the milder autosomal dominant (OMIM 177735) or sporadic form, and the more severe autosomal recessive (OMIM 264350) form. Both present in early infancy, but, whereas the former remits, the later persists into adulthood and requires life-long treatment (46). Dominant PHA I is caused by heterozygous loss-of-function mutations in the mineralocorticoid receptor (21), and recessive PHA I by homozygous mutations in the subunits of the epithelial sodium channel (ENaC) (10, 66). Both types of mutation result in a natriuresis, and loss of sodium uptake into the cells of the distal nephron reduces the transepithelial potential for potassium and proton secretion, explaining the hyperkalemia and metabolic acidosis.

**PHA type II**

PHA type II, or Gordon’s syndrome (OMIM 145260), is an autosomal-dominant disorder with the phenotype of hypertension, hyperkalemia, hyperchloremic metabolic acidosis, and chloride-dependent sodium retention. Serum aldosterone levels are either low or normal, but the failure to secrete potassium suggests renal aldosterone resistance. PHA II is caused by mutations in either the WNK4 or WNK1 genes encoding a particular subtype of serine kinases lacking a lysine residue at the active site (WNK = with no K [lysine]). WNK1 is widely expressed throughout the body and has an inhibitory effect on WNK4, which has more limited expression and in the kidney is found only in the distal nephron (83). WNK4 itself inhibits sodium and chloride reuptake by the co-transporter NCCT in the distal convoluted tubular cells and inhibits potassium efflux from collecting duct principal cells via the ROMK2 channel. Kahle et al. have demonstrated that WNK4 mutations in PHA II act both to reduce its inhibitory effect on NCCT, causing constitutive overactivity, and to increase its inhibitory effect on ROMK2, resulting in increased uptake of sodium and chloride with reduced potassium efflux (32). Transgenic mice containing a mis-sense WNK4 mutation from individuals with PHA II develop hypertension and the biochemical phenotype of hyperkalemia, hyperchloremic metabolic acidosis, and hypercalciuria, together with hyperplasia of the distal convoluted tubule (42). These effects were reversed both by treatment with a thiazide diuretic (which blocks NCCT), or by breeding mice combining the WNK4 mutation together with mice homozygous deficient for NCCT, demonstrating that interaction with functional NCCT is essential for the disease phenotype.

PHA II is successfully treated with thiazide diuretics, used in the treatment of hypertension. Increased understanding of the molecular basis of PHA II may lead to new targets for future antihypertensive agents.

**Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC)**

This is another cation-handling disorder associated with acidosis. Predominant biochemical features of this condition are, as the name suggests, hypomagnesemia, hypermagnesuria, hypercalciuria with a metabolic acidosis, and affected patients develop nephrocalcinosis and progressive renal failure (OMIM 248250). A subset of patients also suffer from ocular abnormalities with visual impairment (OMIM 248190). FHHNC without ocular involvement is caused by mutations in Claudin-16 (CLDN16, chromosome 3q), present at the intercellular tight junctions between epithelial cells in the thick ascending limb of the Loop of Henle (59). It forms a paracellular ion channel for Mg²⁺ and Ca²⁺, and disease-causing mutations lead to intracellular retention or defective paracellular Mg²⁺ transport (38). In FHHNC with ocular involvement, mutations in the CLDN19 gene (chromosome 1p), encoding the related tight-junction protein Claudin-19, result in defective intracellular trafficking or protein assembly (40). CLDN19 is expressed in renal tubules and the retina, hence the oculo-renal phenotype.

**Conclusions**

The inherited renal metabolic acidoses are predominantly disorders of acid-base handling by the kidney, but they may also arise due to aberrant tubular handling of other electrolytes. Understanding the genetic basis of these conditions has permitted identification of the molecular defects responsible, predominantly in transporter proteins or enzymes, and should in turn both aid disease classification and prognostication for affected individuals and prompt development of novel therapeutic strategies. These may also have broader application to renal and bone disease.

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**References**


