

Improving outcomes for patients with distal renal tubular acidosis: recent advances and challenges ahead

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Abstract: Primary distal renal tubular acidosis (dRTA) is a rare genetic disorder caused by impaired distal acidification due to a failure of type A intercalated cells (A-ICs) in the collecting tubule. dRTA is characterized by persistent hyperchloremia, a normal plasma anion gap, and the inability to maximally lower urinary pH in the presence of systemic metabolic acidosis. Common clinical features of dRTA include vomiting, failure to thrive, polyuria, hypercalciuria, hypocitraturia, nephrocalcinosis, nephrolithiasis, growth delay, and rickets. Mutations in genes encoding three distinct transport proteins in A-ICs have been identified as causes of dRTA, including the B1/*ATP6V1B1* and a4/*ATP6V0A4* subunits of the vacuolar-type H⁺-ATPase (H⁺-ATPase) and the chloride–bicarbonate exchanger AE1/*SLC4A1*. Homozygous or compound heterozygous mutations in *ATP6V1B1* and *ATP6V0A4* lead to autosomal recessive (AR) dRTA. dRTA caused by *SLC4A1* mutations can occur with either autosomal dominant or AR transmission. Red blood cell abnormalities have been associated with AR dRTA due to *SLC4A1* mutations, including hereditary spherocytosis, Southeast Asia ovalocytosis, and others. Some patients with dRTA exhibit atypical clinical features, including transient and reversible proximal tubular dysfunction and hyperammonemia. Incomplete dRTA presents with inadequate urinary acidification, but without spontaneous metabolic acidosis and recurrent urinary stones. Heterozygous mutations in the AE1 or H⁺-ATPase genes have recently been reported in patients with incomplete dRTA. Early and sufficient doses of alkali treatment are needed for patients with dRTA. Normalized serum bicarbonate, urinary calcium excretion, urinary low-molecular-weight protein levels, and growth rate are good markers of adherence to and/or efficacy of treatment. The prognosis of dRTA is generally good in patients with appropriate treatment. However, recent studies showed an increased frequency of chronic kidney disease (CKD) in patients with dRTA during long-term follow-up. The precise pathogenic mechanisms of CKD in patients with dRTA are unknown.

Keywords: urinary acidification, clinical features, treatment, prognosis, gene, pathogenesis

Introduction

Primary distal (type 1) renal tubular acidosis (dRTA) is a rare genetic disorder caused by impaired distal acidification due to a failure of type A intercalated cells (A-ICs) of the collecting tubule.¹ dRTA is characterized by persistent hyperchloremia, a normal plasma anion gap, and the inability to maximally lower urinary pH in the presence of systemic metabolic acidosis.² Common clinical features of dRTA include vomiting, failure to thrive, polyuria, hypercalciuria, hypocitraturia, nephrocalcinosis, nephrolithiasis, growth delay, and rickets.^{1,2} The clinical variant of dRTA that presents with inadequate urinary acidification without spontaneous metabolic acidosis is termed incomplete dRTA (idRTA).^{2,3}

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Mutations in genes encoding three distinct transport proteins have been identified as causes of dRTA: the B1/*ATP6V1B1* and a4/*ATP6V0A4* subunits of the vacuolar-type H^+ -ATPase (H^+ -ATPase) and the chloride–bicarbonate exchanger AE1/*SLC4A1*.³ However, because a genetic cause is determined in only 70%–80% of patients with dRTA,^{4,5} mutations in additional genes are likely to cause dRTA.^{3,6}

The clinical manifestations of patients with dRTA depend on the underlying gene mutations.³ For example, the majority of patients with dRTA caused by mutations in genes encoding for H^+ -ATPase develop sensorineural hearing loss (SNHL).⁶ Autosomal dominant (AD) dRTA with heterozygous AE1 gene mutations causes less severe clinical manifestations.⁷ However, a recent study showed that clinical features are not specific indicators of the underlying causal gene.⁵

Herein, we review the recent advances in the pathogenesis, underlying gene mutations, atypical clinical features, incomplete type, kidney stone formation, treatment, and long-term outcome of dRTA.

Mechanisms of renal acid excretion

The western diet plus endogenous metabolism generates 1 mmol/kg body weight per day of nonvolatile acids in adults.⁸

An additional 1–2 mmol/kg body weight per day of nonvolatile acids is produced from the formation of hydroxyapatite from growth bone in children.⁷ The kidneys maintain acid–base homeostasis by reabsorbing filtered HCO_3^- , excreting acid in the form of NH_4^+ and titratable acids, and producing new HCO_3^- to replenish that lost to metabolism.³ The distal nephron is responsible for the secretion of H^+ that is then buffered by NH_3 and titratable acids, leading to urinary acidification.^{6,7}

The distal convoluted tubules and cortical collecting ducts consist of principal cells, which reabsorb sodium via the epithelial sodium channels, acid-secreting A-ICs, and base-secreting type B intercalated cells (B-ICs). A-ICs mainly contribute to urinary acidification by generating new HCO_3^- and excreting NH_3 into the urine (Figure 1).^{3,9,10} CO_2 is hydrated by cytosolic carbonic anhydrase type II (CAII) that is present in all intercalated cells (ICs) of the collecting tubule and forms H^+ and HCO_3^- . A-ICs secrete H^+ by apical H^+ -ATPase with an additional contribution from H^+ - K^+ -ATPase. A-ICs release HCO_3^- into the blood in exchange for Cl^- via the basolateral anion exchanger AE1. Cl^- exits the cell by the potassium chloride co-transporter (KCC4) or the chloride channel (ClC-Kb).⁷ B-ICs express an apical

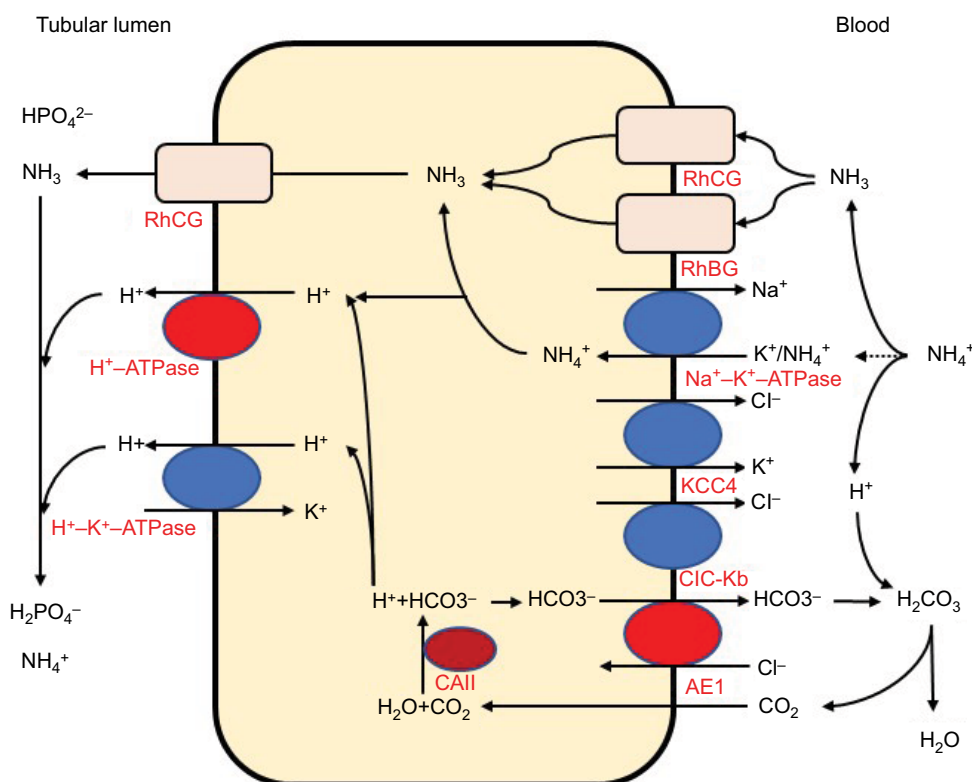


Figure 1 Acid and ammonia secretion in type A intercalated cells in the distal nephron.

Abbreviations: AE1, anion exchanger 1; CAII, carbonic anhydrase type II; ClC-Kb, chloride channel Kb; H^+ -ATPase, vacuolar H^+ -ATPase; KCC4, potassium chloride co-transporter 4; RhBG, rhesus blood group type B glycoprotein; RhCG, rhesus blood group type C glycoprotein.

Cl^- - HCO_3^- exchanger, pendrin, and a basolateral H^+ -ATPase, responsible for net base secretion. Chronic acidosis converts B-ICs to A-ICs, which is mediated by an extracellular matrix protein hensen/DMBT1, and increases net acid secretion.^{11,12} Although the mechanism by which ICs sense a change in blood pH is unclear, Schwartz et al recently showed that principal cells respond to acid by producing SFD1 which regulates ICs subtype distribution.¹³

Because the capacity of the distal nephron to excrete acid as free H^+ is limited, the distal nephron excretes the majority of acid coupled to urine buffers, ammonia (NH_3), and titratable acids (mainly HPO_4^{2-}). Therefore, the net acid secretion in urine is the sum of the ammonium (NH_4^+) charge plus the titratable acid (H_2PO_4^-) charge minus the HCO_3^- charge.⁸ Under normal conditions, the kidneys excrete approximately one-third to one-half of the net acids as titratable acids and one-half to two-thirds as NH_4^+ . Under conditions of chronic acidosis or acid load, NH_4^+ excretion can increase several-fold to tenfold, while titratable acid excretion shows only a small increase.⁸ Therefore, the excretion of NH_4^+ is the main mechanism for urine acidification under conditions of chronic acidosis.

In contrast to most urinary solutes, the majority of urinary NH_3 is generated in the kidney.¹⁴ NH_4^+ is generated from glutamine in the proximal tubular cells and is secreted into the urine in the proximal tubule lumen, which is coupled with HCO_3^- recovery resulting from glutamine metabolism. NH_4^+ is primarily reabsorbed by the Na-K-2Cl co-transporter NKCC2 in the thick ascending limb of the loop of Henle and is accumulated in the interstitium. Interstitial $\text{NH}_3/\text{NH}_4^+$ is then secreted into the cortical and medullary collecting duct lumen by several mechanisms: diffusion of medullary NH_3 across the basolateral and apical membranes into the lumen; basolateral Na^+ - K^+ -ATPase that transports NH_4^+ into the cell by substituting NH_4^+ for K^+ in the inner medullary collecting duct; NH_3 uptake across the basolateral membrane via the rhesus blood group glycoproteins, RhBG and RhCG; and NH_3 secretion across ICs via RhCG. Collecting duct NH_3 secretion occurs by parallel NH_3 and H^+ transport, and apical H^+ secretion involves both H^+ -ATPase and H^+ - K^+ -ATPase (Figure 1).^{8,14,15}

Pathogenic mechanisms of dRTA

dRTA is caused by the failure of the kidney A-ICs to acidify the urine normally, which results from a dysfunction in any of the transporters involved in this process. Mutations in three transporter genes expressed in A-ICs have been identified as causes of dRTA, including the B1 (*ATP6V1B1*) and a4

(*ATP6V0A4*) subunits of H^+ -ATPase and the AE1/*SLC4A1*.¹⁶ However, because mutations in these genes are identified in only 70%–80% of patients with dRTA,^{4,5} dRTA is also likely to be caused by mutations in other genes.^{3,17} In addition to its genetic component, dRTA can also be acquired.⁷

Vacuolar H^+ -ATPase gene (*ATP6V1B1* and *ATP6V0A4*) mutations

H^+ -ATPases are multisubunit enzymatic proton pumps, which consist of two domains, the V_1 cytoplasmic domain (subunits A–H) and the V_0 membrane domain composed of subunits a, d c'', c, and e.¹⁸ The V_0 domain mediates proton transfer and requires ATP hydrolysis by the V_1 domain.^{18,19} The B1 subunit is expressed in the kidney, inner ear, epididymis, and ciliary body of the eye. The a4 subunit is only expressed in the kidney, inner ear, and epididymis. In the kidney, the B1 subunit is expressed only in ICs of the late distal tubule, connecting segment, and collecting duct, while the a4 subunit is expressed in the proximal tubule, loop of Henle, and ICs of the late distal tubule, connecting segment, and collecting duct.²⁰ Homozygous or compound heterozygous mutations in B1 and a4 lead to autosomal recessive (AR) dRTA.

Karet et al were the first to identify homozygous mutations in *ATP6V1B1* in AR dRTA patients with early SNHL.²¹ Subsequently, Smith et al detected homozygous mutations in *ATP6V0A4* in AR dRTA patients without SNHL.²² However, it became later obvious that a number of patients with AR dRTA with homozygous or compound heterozygous mutations in *ATP6V0A4* developed SNHL in early childhood²³ or in young adulthood.²⁴ Compound heterozygous mutations in *ATP6V1B1* were also found in some patients with dRTA.^{23,25,26}

Premature termination codons, frameshift mutations, or splice-site mutations, which are predicted to disrupt the encoded protein, are found in most patients with *ATP6V1B1* or *ATP6V0A4* mutations, while missense mutations have been described in only a few patients.^{21–24} Experimental studies using rat inner medullary collecting duct cell culture or yeast models showed that dysfunction or impaired assembly of the B1 subunit with other protein complex subunits is the most common outcome of missense mutations in *ATP6V1B1*.^{27,28} Su et al recreated previously reported missense mutations of the a4 subunit G820R²² and R807Q²⁴ in yeast to examine the effects on protein expression. They found that the G820R mutation caused a loss of required phosphofructokinase-1 (PFK) binding to the a4 subunit, while the R807Q mutation resulted in a loss of pump protein.²⁹

In mouse models, mice deficient in the B1 subunit show more alkaline urine without systemic acidosis when fed a standard diet. These mice also develop more severe metabolic acidosis after an acid load compared to normal mice, indicating a failure of normal urinary acidification.³⁰ The B1-deficient mice do not develop hearing impairment or nephrocalcinosis. In contrast, mice lacking the $\alpha 4$ subunit demonstrate dRTA with severe metabolic acidosis, hypokalemia, early nephrocalcinosis, and severe hearing impairment with enlarged cochlear and endolymphatic ducts in the inner ear.^{31,32} In addition, these mice develop proximal renal tubular dysfunction with defective endocytic trafficking, proteinuria, and phosphaturia, which has not been reported in humans.³³ This may be due to compensatory changes in the $\alpha 1$, $\alpha 2$, and $\alpha 3$ subunits in the proximal tubules of dRTA patients with the *ATP6V0A4* mutation.^{17,34}

Chloride–bicarbonate exchanger AE1 gene (*SLC4A1*) mutations

The Cl^- – HCO_3^- exchanger AE1, encoded by *SLC4A1*, is expressed in the red blood cells (RBCs; eAE1, Band 3) and in the A-ICs of kidney (kAE1). *SLC4A1* mutations can cause dRTA or RBC abnormalities including hereditary spherocytosis (HS), Southeast Asia ovalocytosis (SAO), hereditary stomatocytosis, and hereditary xerocytosis.³⁵ Most mutations cause either dRTA or RBC abnormalities, whereas only a few mutations lead to abnormalities in both.³ dRTA caused by AE1 gene mutations can occur with either an AD or AR transmission (Table 1).^{1,6} AE1 mutations are rare and usually have an AD transmission in Caucasians, while AR dRTA is common in Asians.¹⁷ The clinical symptoms are more severe and the age of onset is earlier in patients with

AR dRTA compared to patients with AD dRTA.⁷ Patients with AD dRTA can present with complete dRTA or idRTA, whereas patients with AR dRTA always present with complete dRTA.¹⁶ Although RBC abnormalities have been associated with AR dRTA, hemolytic anemia is extremely rare in AD dRTA, and only one family with AD idRTA and HS due to a heterozygous splicing mutation (c.1432–1G>A, Band 3^{PRIBRAM}) has been reported.³⁶

AD AE1 gene (*SLC4A1*) mutations

Wrong et al reported a family with AD dRTA caused by a heterozygous mutation of R589H in AE1.³⁷ Subsequent studies described AD dRTA with AE1 gene mutations including R589H,^{38–40} R589C,³⁸ R589S,³⁹ S613F,³⁸ R901X,³⁹ A858D,⁴¹ A888L+889X,⁴² G609R,⁴³ D905Gfs15,⁴⁴ D905dup,⁴⁵ and M909T.⁴⁶

Experimental studies using transfected cell models showed that AE1 gene mutations caused normal or modestly reduced anion transport activity and impaired trafficking with retention in the endoplasmic reticulum (ER). Heterodimers with the wild-type AE1 polypeptide caused a dominant negative trafficking phenotype (R589H and S613F)^{35,47–49} or mistargeting to the apical membranes or to both the apical and basolateral membranes (G609R, R901X, and M909T).^{43,46,49–51}

In *in vivo* studies, mice lacking Ae1 exhibited complete dRTA with hemolytic anemia, while mice heterozygous for Ae1 showed no apparent defect.^{52,53} Mumtaz et al recently generated an Ae1 R607H knockin (KI) mouse, corresponding to the most common AD dRTA mutation in human AE1, R589H.⁵⁴ They found that both homozygous and heterozygous R607H KI mice exhibited idRTA without RBC abnormalities.⁵⁴ Mutant mice exhibited decreased levels of Ae1 in A-ICs, but preserved basolateral targeting of the mutant protein, and reduced expression of H^+ -ATPase due to impaired targeting to the apical membranes.^{9,54}

AR AE1 gene (*SLC4A1*) mutations

Tanphaichitr et al first reported AR dRTA with a homozygous AE1 gene loss-of-function mutation, G701D, in two siblings in Thailand who had xerocytic hemolytic anemia with normal RBC AE1 activity.⁵⁵ AE1 G701D interacts with an RBC AE1 chaperon, glycophorin A (GPA), which rescues the mutant protein in RBCs. GPA is not expressed in renal ICs, which explains the normal erythroid AE1 expression in these patients.^{35,55} Subsequently, Yenchtisomanus et al reported a homozygous AE1 G701D mutation in five out of eight Thai families with AR dRTA with mild RBC morphological

Table 1 *SLC4A1* mutations in dRTA

Mutations in AD dRTA	Mutations in AR dRTA
Band 3 ^{PRIBRAM} (c.1432–1G>A) ^a	SAO (Δ Ala400–Ala408)
R589H	V488M (Coimbra)
R589C	R602H (Songkla I)
R589S	G701D (Bangkok I)
G609R	S773P (Siriraj I)
F613F	Δ V850
A858D ^a	A858D
A888L+890X	F667F (Courcouronnes)
R901X (Walton)	C479W (Edmonton I)
D905Gfs15	C447X (null ^{VIENNA})
D905dup	G494S
M909T	

Note: ^aHeterozygous Band 3^{PRIBRAM} and A858D mutations cause incomplete dRTA. **Abbreviations:** AD, autosomal dominant; AR, autosomal recessive; dRTA, distal renal tubular acidosis; SAO, Southeast Asia ovalocytosis.

abnormalities without hemolytic anemia and suggested that AE1 G701D was a common molecular defect in Thailand.⁵⁶

SAO is a common hereditary condition in South East and Melanesia. SAO is caused by the AE1 (Δ Ala400-Ala408) mutation, which causes ovalocytic erythrocytes to be resistant to invasion by the malarial parasite.⁵⁷ Vasuvattakul et al reported two patients from Northeast Thailand with AR dRTA and SAO resulting from compound heterozygous AE1 G701D/SAO mutations.⁵⁸ Bruce et al described AE1 gene mutations associated with AR dRTA and SAO in families from Malaysia and Papua New Guinea. The mutations included compound heterozygous AE1 G701D/SAO and Δ V850/SAO and homozygous AE1 Δ V850/ Δ V850.⁴¹ Patients with compound heterozygous AE1 A858D/SAO mutations in this study exhibited dRTA and SAO with AD transmission. Subsequently, other mutations were identified, including R602H/SAO from South Thailand,⁵⁹ Q759H/SAO from Malaysia,⁶⁰ and G701/SAO from the Philippines.⁶¹ Although homozygous SAO was long thought to be lethal,⁶² Picard et al recently reported a child with homozygous SAO mutations who had AR dRTA with severe dyserythropoietic and hemolytic anemia with SAO red cells.⁶³

Approximately 20% of HS cases are caused by heterozygous AE1 gene mutations.⁶⁴ Hence, HS can be associated with AR dRTA. Ribeiro et al reported a child with severe HS and AR dRTA caused by homozygous AE1 V488M (Band 3 Coimbra).⁶⁵ Toye et al reported that homozygous S667F (Band 3 Courcouronnes) causes HS and idRTA.⁶⁶ Subsequently, it was found that compound heterozygous E522K/G701D⁶⁷ and C479W (Band 3 Edmonton I)/G701D⁶⁸ and homozygous A858D⁶⁹ cause AR dRTA with HS.

Several other AE1 mutations have been reported to cause AR dRTA with RBC abnormalities other than SAO or HS. These include compound heterozygous Δ V850/A858D (red cells of bizarre shapes and anemia)⁴¹ and G701D/A858D (ovalocytes and acanthocytes),⁷⁰ homozygous A858D (hemolytic anemia with elliptocytosis, stomatocytosis, and acanthocytosis⁷¹ or acanthocytosis and echinocytosis),⁷² and nonsense mutation of S447X, Band 3 null^{VIENNA} (severe hemolytic anemia).⁷³ In addition, AE1 mutations causing AR dRTA without RBC abnormalities have been reported, including homozygous Δ V850⁴¹ and compound heterozygous G494S/G701D⁴⁴ and S773P/G701D.⁵⁹

Experimental studies using transfected cell models have revealed that these mutations cause Golgi retention due to impaired trafficking with loss of function, which is rescued by GPA (G701D),^{48,55,74} misfolding and targeting for degradation (S773P),^{48,74} decreased AE1 function (Δ V850),⁴¹

ER retention due to impaired trafficking with normal anion transport function, which is rescued by GPA (S667F),⁶⁶ mild trafficking impairment (E522K),⁶⁷ and ER retention due to impaired trafficking and misfolding (C479W).⁶⁸

Other candidate genes for dRTA

Because ~20% of patients with dRTA do not have mutations in genes for H⁺-ATPase or AE1, additional candidate genes have been identified in mouse models of dRTA.^{3,6} These include *HKα2* (colonic H⁺-K⁺-ATPase),⁷⁵ *Kcc4* (K⁺-Cl⁻ co-transporter, *Kcc4*),⁷⁶ genes for the H⁺-ATPase C, G, and d subunits,⁷⁷ *Foxi1* (the Forkhead transcription factor, *Foxi1*),⁷⁸ *Rhcg* (the ammonia transporter, *Rhcg*),^{79,80} *Slc26a7* (Cl⁻-HCO₃⁻ exchanger, *Slc26a7*, co-localized with AE1),⁸¹ *DMBT1* (component of the pathway of acidosis-induced conversion of B-ICs into A-ICs, *hensin*),¹¹ *GPR4* (proton sensing G protein-coupled receptor, *GPR4*),⁸² *NHE4* (Na⁺-H⁺ exchanger 4, *NHE4*),⁸³ *SLC4A5* (Na⁺-HCO₃⁻ co-transporter, *NBCe2*),⁸⁴ *Atp6ap2* (ATPase H⁺ transporting lysosomal accessory protein 2, *atp6ap2*),⁸⁵ and *Ncoa7* (nuclear receptor coactivator 7, *Ncoa7*: an H⁺-ATPase interacting protein), as shown in Table 2.⁸⁶ Although most of these genes have not been previously identified in human disease, Enerbäck et al identified homozygous *FOXII* mutations in two families with AR dRTA and early-onset SNHL.⁸⁷ Furthermore, a recent study found homozygous or compound heterozygous *WDR72* (tryptophan-aspartate repeat domain 72, *WDR72*: a protein possibly associated with intracellular

Table 2 Candidate genes for distal renal tubular acidosis

Gene	Protein
<i>HKα2</i>	Colonic H ⁺ -K ⁺ -ATPase
<i>Kcc4</i>	K ⁺ -Cl ⁻ co-transporter
<i>ATP6V1C2</i>	H ⁺ -ATPase C2
<i>ATP6V1G2</i>	H ⁺ -ATPase G3
<i>ATP6V0D2</i>	H ⁺ -ATPase d2
<i>Foxi1</i> ^a	Forkhead transcription factor, <i>Foxi1</i>
<i>Rhcg</i>	Ammonia transporter, <i>Rhcg</i>
<i>Slc26a7</i>	Cl ⁻ -HCO ₃ ⁻ exchanger, <i>Slc26a7</i>
<i>DMBT1</i>	<i>Hensin</i>
<i>GPR4</i>	Proton sensing G protein-coupled receptor, <i>GPR4</i>
<i>NHE4</i>	Na ⁺ -H ⁺ exchanger 4, <i>NHE4</i>
<i>SLC4A5</i>	Na ⁺ -HCO ₃ ⁻ co-transporter, <i>NBCe2</i>
<i>Atp6ap2</i>	ATPase H ⁺ transporting lysosomal accessory protein 2, <i>Atp6ap2</i>
<i>Ncoa7</i>	Nuclear receptor coactivator 7, <i>Ncoa7</i>
<i>WDR72</i> ^a	Tryptophan-aspartate repeat domain 72, <i>WDR72</i>

Note: ^aMutations in these genes were recently reported in humans.

endocytic vesicle trafficking) mutations in two families with AR dRTA (Table 2).⁸⁸

Causes of acquired dRTA

The main causes of acquired dRTA include medications and, most commonly, autoimmune diseases, with Sjögren syndrome being the most frequent cause. Although the precise pathogenic mechanisms of dRTA development in Sjögren syndrome are unclear, several studies suggest that autoantibodies against carbonic anhydrase or A-ICs transporters are involved in the pathogenesis.⁸⁹ Systemic lupus erythematosus, thyroiditis, and renal transplantation have been reported as other autoimmune causes of dRTA.²

Medications including amphotericin B, foscarnet, analgesic abuse, lithium, melphalan, and amiloride also cause dRTA.^{2,7} In the case of amphotericin B and foscarnet, the mechanisms mediating these effects involved increased membrane permeability in the collecting duct and increased mitochondrial dysfunction in renal tubular cells, respectively.⁹⁰ The mechanisms associated with other drugs are not clear.

Atypical clinical features of dRTA

Some patients with dRTA exhibit atypical clinical features, which include transient and reversible proximal tubular dysfunction and hyperammonemia.

Reversible proximal tubular dysfunction in patients with dRTA

Reversible proximal tubular dysfunction has been reported in patients with dRTA. This appears to involve defects in bicarbonate reabsorption,^{91,92} low-molecular-weight proteinuria,⁹³ hypouricemia with uricosuria, phosphaturia, and generalized aminoaciduria.^{94,95} Besouw et al recently reported that 16 of 24 patients with dRTA showed transient and partial Fanconi syndrome that resembled Dent disease or Low syndrome. Proximal tubular dysfunction was only seen in children with mutations in subunits of the H⁺-ATPase and in those with unknown mutations.⁹⁶

Although the exact mechanism underlying reversible proximal tubular dysfunction is unclear, it has been suggested to involve hypokalemic nephropathy^{32,94} and/or dysfunction of the receptor-mediated endosomal pathway in renal proximal tubule cells.^{3,97} The chloride transporter CIC-5 (2Cl⁻-H⁺ exchanger) is expressed in the apical endosomes of renal proximal tubules containing H⁺-ATPase. CIC-5 normally acts in the endosomal pathway by coupling with H⁺-ATPase. Mutations of the CIC-5 gene cause Dent disease.⁹⁸ Picollo et al demonstrated that low extracellular pH or acidosis inhibits

CIC-5 function by reducing the driving force for 2Cl⁻-H⁺ exchange.⁹⁹ Therefore, inhibition of CIC-5 function due to systemic acidosis may lead to partial renal Fanconi syndrome in patients with dRTA.⁹⁷

Hyperammonemia in patients with dRTA

Hyperammonemia, first described by Miller and Schwartz in dRTA, was not initially recognized as an important clinical feature of dRTA.¹⁰⁰ Subsequently, Miura et al reported a high frequency of hyperammonemia in patients with dRTA (four of six patients with available data), suggesting that hyperammonemia is a common feature of dRTA.²⁵ Hyperammonemia was reported in 15 patients with dRTA in a recent systematic review¹⁰¹ and in a case report.¹⁰² In these patients, a negative correlation was observed between blood ammonia and bicarbonate levels, and alkali therapy resulted in a rapid normalization of ammonia levels.¹⁰¹ Increased renal ammonia synthesis in response to acidosis, without appropriate ammonia excretion, may result in hyperammonemia in dRTA.^{100,101}

Incomplete distal renal tubular acidosis

idRTA, first described in 1959, presents with inadequate urinary acidification without spontaneous metabolic acidosis.¹⁰³ Failure to acidify urinary pH <5.3 in the NH₄Cl load was considered diagnostic for idRTA.⁸⁹ However, because urinary acidification capacity is a continuous trait, idRTA is not a distinct entity, and may be a variant of normal urinary acidification.^{89,104}

Patients with idRTA commonly exhibit hypocitraturia, hypercalciuria, nephrocalcinosis, and nephrolithiasis.^{105,106} A wide range of idRTA prevalence has been reported in patients with recurrent urinary stones.¹⁰⁴ Bone abnormalities also have been frequently reported in patients with idRTA, including rickets¹⁰⁷ or growth failure¹⁰⁸ in children and osteoporosis and osteopenia in adults.^{109–111} However, other studies found no association between idRTA and lower bone mass.^{1,65,112}

Although the molecular basis for idRTA is unknown in most patients, heterozygous mutations in *SLC4A1* (Band 3^{PPRIBRAM} and A858D),^{36,41} *ATP6V1B1* (F468fsX487),¹¹³ and *ATP6V0A4* (S544L)¹¹⁴ have been reported. Furthermore, Dhayat et al reported that recurrent kidney stone formers with H⁺-ATPase B1 subunit p.E161K single-nucleotide polymorphism have idRTA with an increased prevalence of calcium phosphate kidney stones.¹¹⁵ A recent experimental study revealed that Ncoa7 (H⁺-ATPase interacting protein)-

knockout mice have idRTA.⁸⁶ Another study showed that haploinsufficiency of *Atp6v1b* in mice causes idRTA.¹¹⁶

Kidney stone formation in dRTA

The combination of hypercalciuria, hypocitraturia, and high urine pH contributes to the development of kidney stone formation and/or nephrocalcinosis in dRTA.⁶

Because bicarbonate is depleted from the extracellular fluid in dRTA, buffering of the retained nonvolatile acids promotes the release of calcium phosphate from bone, which increases urinary excretion of calcium and phosphate in dRTA.^{6,7} Moreover, metabolic acidosis decreases the function and expression of the TRPV5 calcium channel in the distal tubule, independent of parathyroid hormone and vitamin D, which also contributes to hypercalciuria in dRTA.¹¹⁷

Urinary citrate inhibits stone formation by complexing with calcium, inhibiting spontaneous nucleation, and preventing the growth of crystals.¹¹⁸ Metabolic acidosis increases citrate reabsorption in the proximal tubule via increased activity of sodium-dependent dicarboxylate transporter 1.^{17,117,118}

A high urine pH increases the supersaturation of calcium phosphate in the tubular lumen, thereby increasing the risk of kidney stone formation.¹¹⁷

Treatment

The primary objectives of dRTA treatment are correction of metabolic acidosis and avoidance of disease-related complications, which include failure to thrive, growth retardation, rickets, osteoporosis, nephrolithiasis, and nephrocalcinosis.^{3,16,89} It is especially important to prevent nephrocalcinosis because progressive nephrocalcinosis may lead to chronic kidney disease (CKD) and end-stage renal disease in patients with dRTA.⁸⁹

Alkali in the form of sodium and/or potassium bicarbonate or citrate salts should be administered to maintain a normal serum bicarbonate concentration of >20 mEq/L in infants and >22 mEq/L in children and adults.^{6,89} However, excessive sodium bicarbonate will increase the extracellular volume and decrease the reabsorption of proximal tubular HCO_3^- , which increases the need for alkali.⁶ In addition, because the increase in sodium intake after sodium citrate or sodium bicarbonate administration can result in increased urinary calcium excretion, potassium salts may be more effective than sodium salts for treatment of dRTA with kidney stones.^{119,120} As citrate salts can also correct hypocitraturia and prevent nephrolithiasis, potassium citrate is usually recommended.^{16,89}

Young children with dRTA need higher doses of alkali because of the greater rate of acid production caused by the

formation of hydroxyapatite associated with bone growth.⁷ The amount of alkali needed usually decreases with age from as much as 5–8 mEq/kg/day in infants to 3–4 mEq/kg/day in children after the age of 6 years to 1–2 mEq/kg/day in adults.^{6,89,92} A recent study showed that children with mutations in *ATP6V1B1* or *ATP6V0A4* generally needed higher doses of alkali compared to those with *SLC4A1* mutations.⁹⁶ In patients with severe hypokalemia despite administration of potassium citrate, potassium supplementation may be required.⁹⁶

Dietary modifications to increase urinary citrate excretion may benefit dRTA patients with kidney stones and hypocitraturia. Dietary modifications include increased intake of fluid and citrus fruits, normal intake of calcium, and restricted intake of sodium, oxalate, animal proteins, and fructose.¹¹⁸

Normalization of serum bicarbonate level, urinary calcium excretion, urinary low-molecular-weight protein levels (β_2 microglobulin or α_2 microglobulin), and growth rate are good markers for adherence to and/or adequacy of treatment.^{6,93,96} In addition, abdominal ultrasonography should be regularly checked to detect nephrocalcinosis and nephrolithiasis.

Long-term outcome

The prognosis of dRTA is generally good in patients treated with early and sufficient doses of alkali, but alkali administration does not improve hearing impairment in patients with dRTA and SNHL.^{16,96} Moreover, recent studies showed an increased frequency of CKD in patients with dRTA during long-term follow-up. Besouw et al reported 9 of 24 (37.5%) children with dRTA developed CKD stage 2.⁹⁶ Palazzo et al also showed 16 of 51 (31.3%) patients with dRTA developed CKD during long-term follow-up and after puberty.⁵ Although the precise pathogenic mechanisms of CKD in patients with dRTA are unknown, the combination of nephrocalcinosis and hypokalemia, which results in tubulointerstitial damage, or kidney damage after repeated episodes of dehydration and acute kidney injury have been suggested as potential causal factors.^{5,17}

Disclosure

The author reports no conflicts of interest in this work.

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