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Genetic Diagnosis and Treatment of Inherited Renal Tubular Acidosis

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Abstract
Background: Renal tubular acidosis (RTA) is caused by various disruptions to the secretion of H^+ by distal renal tubules and/or dysfunctional reabsorption of HCO_3^- by proximal renal tubules, which causes renal acidification dysfunction, ultimately leading to a clinical syndrome characterized by hyperchloremic metabolic acidosis with a normal anion gap. With the development of molecular genetics and gene sequencing technology, inherited RTA has also attracted attention, and an increasing number of RTA-related pathogenic genes have been discovered and reported. ***Summary:*** This paper focuses on the latest progress in the research of inherited RTA and systematically reviews the pathogenic genes, protein functions, clinical manifestations, internal relationship between genotypes and clinical phenotypes, diagnostic clues, differential diagnosis, and treatment strategies associated with inherited RTA. This paper aims to deepen the understanding of inherited RTA and reduce the missed diagnosis and misdiagnosis of RTA. ***Key Messages:*** This review systematically summarizes the pathogenic genes, pathophysiological mechanisms, differential diagnosis, and treatment of different types of inherited RTA, which has good clinical value for guiding the diagnosis and treatment of inherited RTA.

Introduction

Renal tubular acidosis (RTA) is a clinical syndrome characterized by metabolic acidosis due to dysfunction of renal acidification caused by various etiologies, and the main pathophysiological changes are the dysfunction of H^+ secretion in distal renal tubules or (and) HCO_3^- reabsorption in proximal renal tubules. Clinically, RTA can be divided into four types: distal tubular acidosis (type I), proximal tubular acidosis (type II), mixed tubular acidosis (type III), and hyperkalemic tubular acidosis (type IV), among which type I and type II with hypokalemia are the most common [1, 2]. This disease can also be divided into primary and secondary RTA. Primary RTA is usually hereditary and occurs primarily in children and adolescents. The pathogenesis of RTA is associated with mutations in genes encoding proteins related to the secretion of H^+ and the reabsorption of HCO_3^- in renal tubules, and the modes of inheritance for RTA include autosomal

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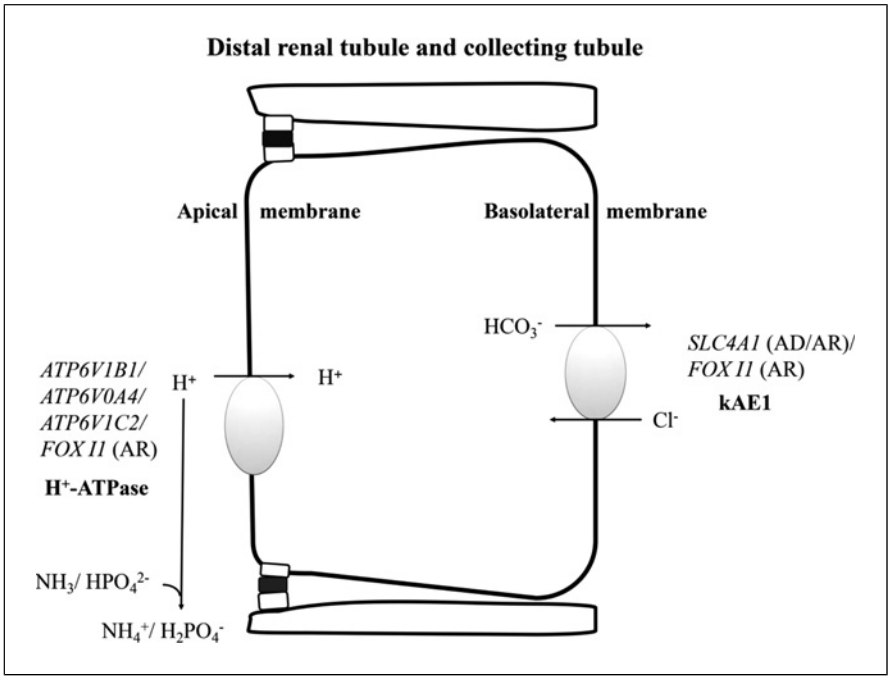

Fig. 1. Schematic diagram of the pathogenic mechanism of inherited dRTA. In distal renal tubules and collecting tubules, *ATP6V1B1*, *ATP6V0A4*, *ATP6V1C2*, and *FOX I1* genes are involved in encoding H^+-ATPase on the apical membrane, which is responsible for H^+ secretion. The *SLC4A1* and *FOX I1* genes encoding the Cl^--HCO_3^- transporter (kAE1) on the basolateral membrane side are involved in the reabsorption of HCO_3^-. Mutations occurring in genes encoding H^+-ATPase and kAE1 affect the processes of H^+ secretion and HCO_3^- reabsorption in renal tubules. This prevents HCO_3^- from exiting cells and Cl^- from transporting into cells. Moreover, the increase in intracellular pH will also affect the secretion of H^+, leading to dRTA. AD, autosomal dominant inheritance; AR, autosomal recessive inheritance.

dominant (AD) and autosomal recessive (AR) inheritance [2, 3]. The etiology of secondary RTA is complex and occurs mostly in adults, often secondary to renal disease and extrarenal disease. This paper focuses on the latest research progress of inherited RTA and systematically reviews the pathogenic genes, protein functions, clinical manifestations, internal relationship between genotypes and clinical phenotypes, diagnostic clues, differential diagnosis, and treatment strategies, aiming to improve the diagnosis and treatment level of inherited RTA.

Pathogenic Genes, Protein Functions, and the Internal Relationship between Genotypes and Clinical Phenotypes

Inherited Distal RTA

Distal RTA (dRTA), also known as type I RTA, is the most common form of RTA in the clinical setting. It is mainly caused by dysfunctional H^+ and NH_4^+ secretion by distal renal tubules. Thus, the ability of the kidney to excrete the daily acid load is reduced, which leads to progressive H^+ retention and hyperchloremic metabolic acidosis with a normal anion gap [2, 4, 5]. Inherited dRTA can be divided into AD inheritance [6–8] and AR inheritance [9–11] based on its genetic pattern.

Pathogenic Genes and Protein Functions Associated with Inherited dRTA

Autosomal Dominant Distal Renal Tubular Acidosis. Autosomal dominant distal renal tubular acidosis (AD-dRTA) is mainly caused by variants in the *SLC4A1* gene on chromosome 7q21-22, and this gene encodes the basolateral Cl^-- HCO_3^- exchanger (AE1). According to the human gene mutation database (HGMD Professional), there are approximately 31 mutation sites leading to AD-dRTA. AE1 is expressed both on the surface of human erythrocytes (eAE1) and on the basolateral membrane of type A intercalated cells in distal renal tubules (kAE1) [2, 7, 12]. As the main cells of urine acidification, type A intercalated cells secrete H^+ into the lumen. The HCO_3^- generated in the cells must be effectively transported to the peripheral blood through kAE1, and Cl^- is transported into the cells. That is, the H^+-ATPase on the apical membrane can secrete the H^+ generated by hydrated CO_2 in the cells into the lumen of the renal tubules, and the secretion of H^+ is accompanied by the exchange of Cl^-- HCO_3^- between cells and blood [4, 13], as shown in Figure 1. Mutations of the *SLC4A1* gene can affect the processes of H^+ secretion and HCO_3^- reabsorption in renal tubules, preventing the removal of HCO_3^- from the cell and the transport of Cl^- into the cell. Moreover, the increase in the intracellular pH value also affects the secretion and production of H^+, eventually leading to dRTA [14, 15].

Autosomal Recessive Distal Renal Tubular Acidosis. There are three types of pathogenic genes related to autosomal recessive distal renal tubular acidosis (AR-dRTA). 1. AR-dRTA is related to the *SLC4A1* gene. Mutations in the *SLC4A1* gene can cause AR-dRTA, but most of these mutations cause AD-dRTA [14]. In addition to the kAE1 isoform, which is expressed on the side of the basolateral membrane of type A intercalated cells in distal renal tubules, the AE1 erythroid isoform (eAE1), encoded by the *SLC4A1* gene, is also the most abundantly expressed protein on the human erythrocyte membrane, also known as band-3 protein (band-3, B3), and its transmembrane domain at the carboxyl terminus is an anchoring site for erythrocyte bone scaffolding proteins, and the amino terminus is responsible for intracellular and extracellular Cl^-- HCO_3^- ion transport, which is involved in maintaining the normal skeleton structure of erythrocytes and ion transport [12, 14]. 2. AR-dRTA is related to the *ATP6V1B1* and *ATP6V0A4* genes. The *ATP6V1B1* gene is located on chromosome 2p13, and the *ATP6V0A4* gene is located on chromosome 7q33-34. *ATP6V1B1* and *ATP6V0A4* encode the B1 and a4 subunits of the vacuolar H^+-ATPase pump, respectively, and these subunits are required for H^+ secretion and urine acidification [9, 10, 16]. The B1 and a4 subunits are expressed in type A intercalated cells of the kidney and epithelial cells of the inner ear lymphatic sac and epididymis. These subunits are involved in the assembly and synthesis of H^+-ATPase and ion transport. Both *ATP6V1B1* and *ATP6V0A4* gene mutations can cause a decrease in H^+-ATPase activity on the apical membrane side of type A intercalated cells in distal renal tubules, reduce the ability to secrete H^+, damage the body's ability to acidify urine, and ultimately lead to dRTA (shown in Fig. 1) [17, 18]. Mutations in *ATP6V1B1* are mostly related to early sensorineural hearing loss (SNHL), while mutations in *ATP6V0A4* are generally related to late SNHL or normal hearing [10, 11, 16]. The *ATP6V1B1* and *ATP6V0A4* genes have a large number of mutation sites, up to 56 and 84, respectively. Most of these mutations are missense/nonsense mutations. 3. AR-dRTA is related to other pathogenic genes. The above related pathogenic gene mutations are not found in approximately one-third of inherited dRTA patients, suggesting that there may be other new pathogenic genes that have not been identified.

In recent years, new pathogenic gene mutations have been found in AR-dRTA families, and these mutations are mainly found in the *FOXI1*, *WDR72*, and *ATP6V1C2* genes [19–21]. The forkhead transcription factor FOXI1, encoded by the *FOXI1* gene, is involved in maintaining the composition of the inner ear fluid as well as regulating electrolyte and acid-base homeostasis of the renal collecting duct system. At the transcriptional regulatory level, *FOXI1* gene mutation prevents transcription factor FOXI1 from binding to cis-acting elements of regulatory DNA regulating target gene promoters, thus interfering with cellular function, resulting in decreased expression of multiple membrane transporters (AE1 and H^+-ATPase and so on), altered ion composition/pH of the inner ear fluid, and significantly reduced ability of the kidney to secrete acid load, thus manifesting dRTA and severe early-onset sensorineural hearing loss [22]. The WDR72 protein encoded by the *WDR72* gene is likely to be involved in H^+-ATPase assembly synthesis and mediating associated ion transport, as well as in enamel formation, and mutations in the *WDR72* gene that affect H^+-ATPase activity are associated with normal enamel development and can exhibit dRTA with severe enamel hypoplasia [23, 24]. Similar to *ATP6V1B1* and *ATP6V0A4*, the *ATP6V1C2* gene is involved in the synthesis of the H^+-ATPase subunit (subunit C) and mutations in this gene similarly affect the reduced H^+-ATPase activity and the body's ability to acidify urine, which in turn leads to dRTA [21].

Clinical Manifestations of Inherited dRTA

Patients with inherited dRTA (AD/AR-dRTA) may present with multiple impaired systems 4, 5, 25: (1) In the urinary system, the hypokalemia caused by dRTA can affect the concentration and dilution functions of renal tubules, and this is associated with the early occurrence of polydipsia, polyuria, low specific gravity urine, and increased nocturia. Additionally, dRTA can inhibit the reabsorption of Ca^{2+} by renal tubules, and when the body is in long-term chronic metabolic acidosis, bone calcium mobilization occurs. The buffer base is increased. However, blood calcium decreases, and urinary calcium excretion increases. This causes secondary hyperparathyroidism, increases the use of bone calcium and bone phosphorus, and increases urinary phosphorus excretion, resulting in high urinary phosphorus, low blood phosphorus, and high urinary calcium. Thus, calcium and phosphorus cannot be deposited in bone, leading to osteoporosis or osteomalacia. When acidosis occurs, the renal tubule reabsorption of citrate increases. This leads to low urinary citrate excretion and causes alkaline urine. Calcium oxalate and calcium phosphate deposition in the urine can easily cause renal calcification and kidney stone formation and may cause kidney colic, hematuria, and urinary tract infections. Renal calcification and kidney stone formation are the results of the

combination of high urinary calcium, high urinary pH, high urinary phosphorus, and low citrate urine [26]. (2) In the digestive system, nausea, vomiting, diarrhea, constipation, and anorexia can often occur in the early stage. (3) In the skeletal, muscular, and nervous systems, growth retardation occurs in infants, rickets occurs in children, and osteomalacia occurs in adults, which can cause bone pain and fractures. Patients often show fatigue, paroxysmal limb numbness, convulsions, etc. Some patients may also have muscle weakness and/or muscle spasm or even ventilator paralysis. (4) Regarding the auditory system, patients with *ATP6V1B1* and *ATP6V0A4* gene mutations are prone to sensorineural hearing loss. This may be accompanied by enlarged vestibular aqueduct, resulting in severe deafness. (5) Regarding the hematologic system, a small number of patients with autosomal recessive inheritance caused by *SLC4A1* gene mutations may have abnormal erythrocyte morphology and anemia.

There are various common laboratory abnormalities in patients with inherited dRTA [4, 5]: (1) Due to the dysfunction of H^+ secretion in distal renal tubules, Na^+- H^+ exchange at the apical membrane side of the distal renal tubule is reduced and Na^+- K^+ exchange is increased. Additionally, the incomplete reabsorption of Na^+ leads to an increase in the excretion of Na^+ from urine. This in turn activates the renin-angiotensin-aldosterone system, causing an increase in secondary aldosterone secretion. This is followed by an increase in Na^+ and Cl^- reabsorption and finally causes hypokalemia and hyperchloremic metabolic acidosis with a normal anion gap. In addition, the dysfunction of H^+ secretion in the distal renal tubules will also cause functional changes for H^+-K^+-ATPase in the apical membrane side, inhibit lumen K^+ reabsorption, and further aggravate hypokalemia [27]. (2) Abnormally alkaline urine (urine pH ≥6) may be present. (3) Hypercalcemia is also a common laboratory abnormality in patients with inherited dRTA. The common imaging features of patients with inherited dRTA [21, 28–30] are as follows: (1) nephrocalcinosis and kidney stones, usually bilateral; (2) decreased bone mineral density; and (3) enlarged vestibular aqueduct syndrome (EVAS), for which an inner ear CT examination is helpful for diagnosis.

Internal Relationship between the Genotypes and Clinical Phenotypes of Inherited dRTA

Patients with AR-dRTA have a more severe clinical phenotype than those with AD-dRTA [5, 7]. The ages of onset and diagnosis of AR-dRTA patients are younger, and the disease can even occur in infancy or early childhood. These individuals present with severe growth retardation, metabolic acidosis, hypokalemia, and other clinical manifestations. Nephrocalcinosis and kidney stones are common in such patients. The disease progresses rapidly, and the probability of renal-related complications increases. In contrast, the onset age of AD-dRTA patients is generally older, usually after puberty. The clinical symptoms generally lack typical manifestations and patients usually present with relatively mild metabolic acidosis. Obvious clinical symptoms often do not appear until puberty, and these patients do not present with obvious nephrocalcinosis or kidney stones [31, 32].

SNHL is an important clinical manifestation of dRTA, which is mostly seen in patients with autosomal recessive-related *ATP6V1B1* and *ATP6V0A4* gene mutations. Among them, the *ATP6V1B1* mutation is mostly associated with early-onset SNHL, while patients with the *ATP6V0A4* mutation usually have normal hearing or only mild or late-onset SNHL [10, 11, 16]. The a4 subunit of H^+-ATPase is necessary for the secretion of H^+ by type A intercalated cells in renal tubules but is not absolutely necessary for the auditory system. Clinically, approximately 70% of patients with *ATP6V1B1* mutations have early-onset SNHL, and only 39% of patients with *ATP6V0A4* mutations have early-onset SNHL. These findings provide evidence for the genetic heterogeneity of AR-dRTA with SNHL [5, 16]. In addition, mutations in the *ATP6V1B1* and *ATP6V0A4* genes can also lead to EVAS [33]. EVAS is a special type of SNHL that can manifest as severe deafness. However, these patients can retain most of their hearing and gradually show a fluctuation in hearing decline with age.

Erythrocyte morphology abnormalities are another relatively specific clinical feature of dRTA. These abnormalities have been observed in a few dRTA patients with *SLC4A1* pathogenic gene mutations that were inherited mainly by autosomal recessive inheritance, and these patients are predominantly from Thailand, Malaysia, Papua New Guinea, and other Southeast Asian regions [33–36].

Inherited Proximal RTA

Compared with dRTA, proximal RTA (pRTA), namely, type II tubular acidosis, has a low incidence and different mechanism. pRTA is mainly due to the dysfunctional reabsorption of HCO_3^- and increases in the excretion fraction [2, 37, 38]. Inherited pRTA is rarely an isolated HCO_3^- transport defect and is more common in patients with isolated pRTA caused by carbonic anhydrase inhibitors [37, 38]. The common

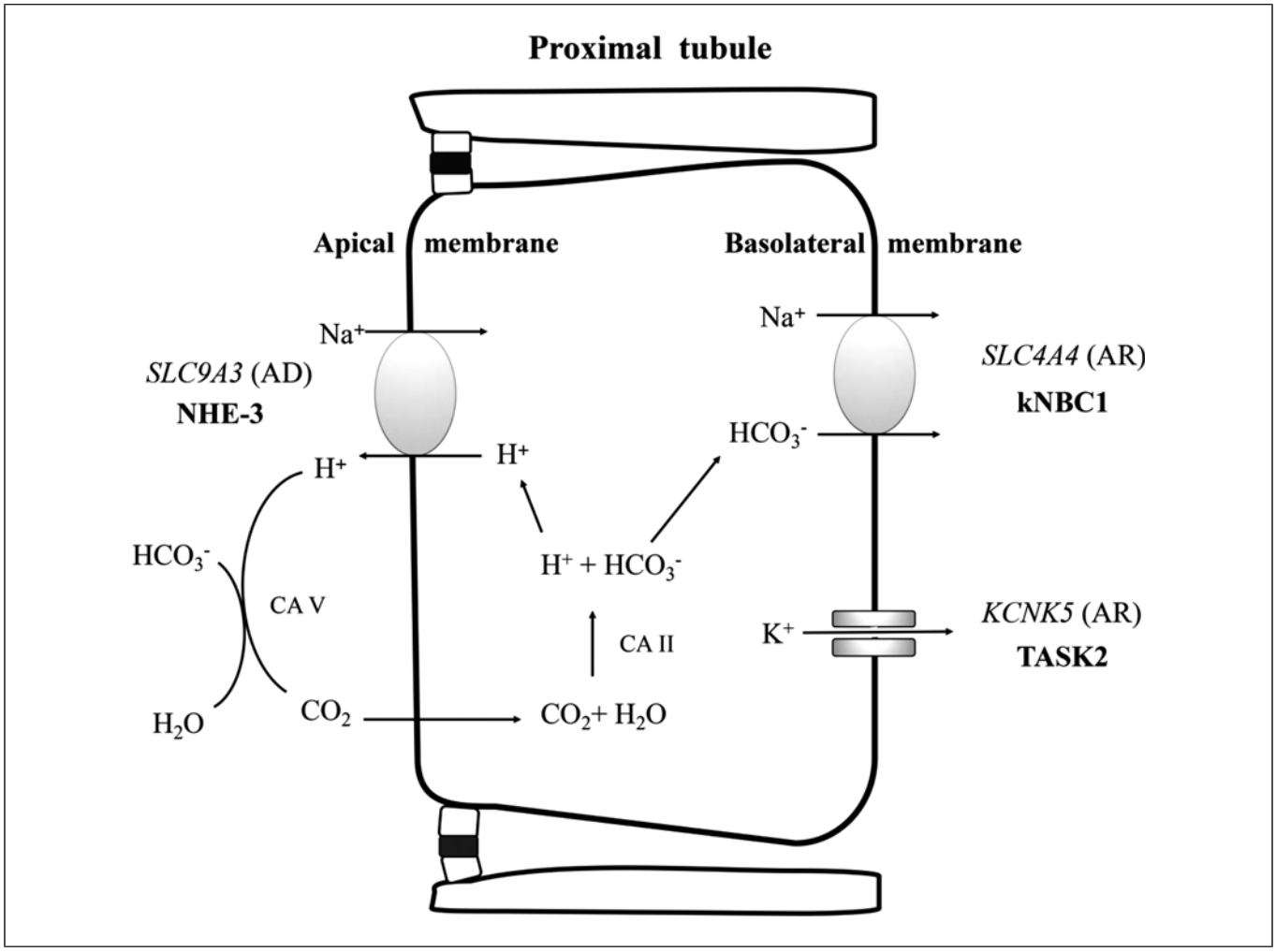

Fig. 2. Schematic diagram of the pathogenic mechanism of inherited pRTA. In the proximal renal tubules, the *SLC4A4* gene is involved in encoding the Na^+-HCO_3^- cotransporter (kNBC1) on the basolateral membrane side, which is responsible for HCO_3^- reabsorption. The *KCNK5* gene encodes the TWIK-associated acid-sensitive type 2 K^+ channel (TASK2) on the basolateral membrane side and is involved in K^+ reabsorption. The *SLC9A3* gene encodes the apical membrane side Na^+-H^+ exchanger (NHE3) and is involved in H^+ secretion. Mutations in the above genes affect the function of the corresponding encoded proteins, causing dysfunction of the reabsorption of HCO_3^- (K^+) or (and) secretion of H^+ by renal tubules, which leads to pRTA. CA II/IV, carbonic anhydrase II/IV; AD, autosomal dominant inheritance; AR, autosomal recessive inheritance.

pRTA is a component of Fanconi syndrome and is caused by a variety of congenital metabolic diseases or acquired causes. This syndrome is caused by dysfunctional reabsorption of multiple substances in the proximal renal tubules. It prevents the reabsorption of a large number of solutes (including bicarbonate, phosphate, uric acid, glucose, amino acids, and low molecular weight proteins, etc.) into the blood in the proximal renal tubules and the loss of urine, resulting in bicarbonate urine, phosphate urine, organic aciduria, renal glycosuria, amino acid urine, and renal tubule proteinuria [39].

In addition, the increased loss of HCO_3^- also leads to the loss of Na^+ in the renal tubules, resulting in a reduction in vascular volume and an increase in the flow of Na^+ into the distal renal tubules. Subsequently, the renin-angiotensin-aldosterone system is excessively activated, which leads to increased secondary aldosterone secretion and hypokalemia. Clinically, inherited pRTA can be divided into AD-pRTA and AR-pRTA with eye abnormalities. There are few reports on AD-pRTA-related genes, and several studies are inconclusive [37, 40–42]. This review mainly addresses AR-pRTA.

Pathogenic Genes and Protein Functions Associated with Inherited pRTA

Most clinical cases of inherited pRTA are inherited in an AR manner [37]. Approximately 85% of HCO_3^- filtrated by the glomerulus is reabsorbed in proximal renal tubules. This process is mainly accomplished by the synergistic action of the Na^+-H^+ exchanger at the proximal renal tubule apical membrane, the Na^+-HCO_3^- cotransporter (kidney NBC1, NBCe1) at the basolateral membrane, the apical membrane, and intracellular carbonic anhydrase. NBCe1 is encoded by the *SLC4A4* gene located on 4q21, and three isotypes exist in vivo. The NBCe1-A protein is expressed in the kidney and eye. The NBCe1-B protein is expressed in the pancreas, duodenum, and other digestive tract tissues. The NBCe1-C protein is expressed in the brain [43]. NBCe1 proteins play an important role in the reabsorption of HCO_3^- in the proximal renal tubules and in the maintenance of the acid-base balance in the body, as shown in Figure 2.

At least 22 gene mutation sites in *SLC4A4* have been identified, and most of these mutations are missense and nonsense mutations. Due to the low clinical incidence of pRTA, no mutation sites of *SLC4A4* with high pathogenicity and frequency have been found. *SLC4A4* gene mutations can disrupt the transport of the Na^+-HCO_3^- cotransporter. This leads to renal reabsorption of HCO_3^- and aqueous humor circulation disorders, ultimately resulting in pRTA and eye abnormalities [37, 42]. In addition to mutations of the *SLC4A4* gene, mutations of the *KCNK5* gene can also cause AR-pRTA. *KCNK5* is localized to autosomal 6p21 and encodes the TWIK-associated acid-sensitive type 2 K^+ channel (shown in Fig. 2), [44, 45].

Clinical Manifestations of Inherited pRTA

Similar to dRTA patients, pRTA patients may also present polydipsia, polyuria, fatigue, dehydration, and growth retardation in the early stage. Laboratory examinations may show hypokalemia, hyperchloremic metabolic acidosis with a normal anion gap, and other related manifestations, such as bone demineralization (osteomalacia, osteoporosis) [37]. Nephrocalcinosis and kidney stones are less common in pRTA patients, which may be related to various factors: (1) In pRTA, despite the obstruction of HCO_3^- reabsorption in the proximal renal tubules, the acidification function of the distal renal tubules is normal. When the blood HCO_3^- is lower than the threshold of absorption, the distal renal tubule is still able to acidify urine. This promotes the dissolution of calcium phosphate and prevents its precipitation. (2) Proximal tubule dysfunction can also lead to the increased excretion of other organic anions (including citrate anions) that can form soluble complexes with calcium. This would restrict the binding of free calcium ions to phosphates, which stabilizes these components.

In addition to clinical manifestations similar to those of dRTA, inherited pRTA patients may also present relatively specific manifestations: (1) These patients can present mental retardation [46]. (2) Regarding eye abnormalities, patients may develop cataracts, bilateral glaucoma, and corneal opacification (band keratopathy) in the early stage and even blindness in severe cases. In addition, dental lesions may occur (enamel hypoplasia) [42, 47]. (3) Some patients may present basal ganglia calcification, migraine, ataxia, transient ischemic attack, and other related manifestations (such as delirium, aphasia, myotonia, and movement disorders) [47, 48]. (4) Urine HCO_3^- excretion increases, and the HCO_3^- excretion fraction is >15% in the base load test. (5) For pRTA patients, when the absorption of HCO_3^- in proximal renal tubules is impaired, the distal renal tubules can partially increase the reabsorption of HCO_3^- and the secretion of H^+. Thus, the urine acidification capacity of the distal renal tubules is preserved. The urine pH value of these patients can be normal or decreased, and the urine pH is lower than 5.5 when severe metabolic acidosis occurs [43]. Moreover, inherited pRTA is frequently considered a clinical manifestation of Fanconi syndrome. Deficiency of the multiple substance reabsorption function of proximal renal tubules can lead to phosphate urine excretion, glucosuria, amino acid urine excretion, and hyperuricuria [37, 47, 49].

Internal Relationship between the Genotypes and Clinical Phenotypes of Inherited pRTA

AD-pRTA is clinically rare, as most patients have AR-pRTA. Consistent with dRTA, the clinical manifestations of patients with AR-pRTA are more severe than those of patients with AD-pRTA. Ocular lesions are relatively important clinical manifestations of pRTA and are more common in patients with AR-pRTA-related *SLC4A4* gene mutations. pRTA patients present specific ocular lesions, such as single/bilateral glaucoma, cataracts, and band keratopathy, and in severe cases, blindness occurs at an early stage. In addition, some patients may also exhibit signs and symptoms related to the nervous system, such as basal ganglia calcification, ataxia, migraines, and transient ischemic attack (such as delirium, aphasia, myotonia, and dyskinesia) [42, 47, 48].

Clinically, in patients with hypokalemia and hyperchloremic metabolic acidosis with a normal anion gap, the urine HCO_3^- concentration increases, or renal

glycosuria or aminoaciduria can occur. This is especially true when these conditions are accompanied by ocular lesions or nervous system involvement. Thus, after excluding other related diseases, the presence of inherited pRTA or pRTA secondary to Fanconi syndrome should be considered. Three main types of mutations have been reported in genes associated with inherited Fanconi syndrome, including mutations in *SLC34A1*, which encodes a proximal tubular apical membrane sodium phosphate cotransporter, mutations in the *EHHADH* gene encoding an enzyme involved in fatty acid peroxisomal oxidation and expressed in the proximal tubule, and in *HNF4A*, which encodes a member of the nuclear receptor superfamily of ligand-dependent transcription factors [50–52]. If necessary, genetic testing should be performed to confirm the diagnosis and avoid missed diagnosis and misdiagnosis.

Inherited Mixed RTA

Patients with mixed RTA, also known as type III RTA, may present with both dRTA and pRTA clinical manifestations, including hyperchloremic metabolic acidosis with a normal anion gap, hypokalemia, reduced urinary titratable acid and NH_4^+ excretion, and urinary HCO_3^- excretion fraction of >15%. Studies suggest that the pathogenesis of inherited type III RTA is mainly related to mutations of the *CA2* gene. *CA2* is located on chromosome 8q22 and encodes carbonic anhydrase II [53, 54]. This type of RTA has a low prevalence and can be accompanied by autosomal recessive bone sclerosis, known as Guibaud-Vainsel syndrome [55]. In addition to the clinical manifestations related to RTA, patients with this syndrome can also present fractures, osteosclerosis, short stature, mental retardation, visual defects caused by optic nerve compression, dental occlusion errors, and basal ganglia calcification. At present, there are few research reports on carbonic anhydrase II-related functional deletion mutations. Moreover, the clinical phenotype is usually serious, and fractures and severe mental retardation are relatively rare [2, 56].

Inherited Hyperkalemic RTA

Hyperkalemic RTA, also known as type IV RTA or hypoaldosteronism, is mainly due to either hypoaldosterone secretion or distal tubulopathy, which attenuates aldosterone action and causes dysfunction of distal tubular hydrogen and potassium secretion [57–59]. The pathophysiological basis of this form of RTA lies in the dysfunction of renal tubular function with aldosterone insufficiency, and the main clinical manifestations are hyperkalemia, metabolic acidosis with low renin aldosterone levels, and so on. The etiology of this type is mostly acquired, with only a few being hereditary [60], which mainly include the following three types.

1. Congenital isolated hypoaldosteronism is mainly caused by variants in the *CYP11B2* gene that encodes aldosterone synthase, resulting in a deficiency of the enzyme required for aldosterone synthesis, with a deficiency in aldosterone secretion and concomitant reduction in H^+ and K^+ secretion from the collecting duct, leading to hyperkalemic metabolic acidosis [61].
2. Pseudohypoaldosteronism type I can be divided into renal and multisystem forms. The renal form is caused by mutations in the *NR3C2* gene encoding the mineralocorticoid receptor, and structural and functional abnormalities of mineralocorticoid receptor result in impaired binding to aldosterone, which can neither drive the increase in the number or activity of the epithelial sodium channel (ENaC) nor initiate ENaC biosynthesis at the epithelial membrane, both of which work together to cause the disease. The multisystem form is caused by mutations in the *SCNN1A, SCNN1B,* and *SCNN1G* genes (encoding α, β, and γ subunits of the ENaC protein, respectively), which leads to an abnormal function of ENaC, resulting in sodium reabsorption and dysfunction of hydrogen and potassium ion secretion, and the occurrence of hyperkalemia, hyponatremia, and acidosis [62–64].
3. Pseudohypoaldosteronism type II, also known as Gordon syndrome or familial hyperkalemic hypertension, is now considered to be caused by genetic abnormalities mainly in the *WNK1, 4* and *KLHL3*, *CUL3* genes, leading to hyperactivation of the sodium chloride symporter and dysfunction of potassium channels in the renal outer medulla, thereby resulting in hyperkalemia, metabolic acidosis, hypertension, and low plasma renin activity I [65, 66].

Diagnostic Clues

Diagnostic Clues of Inherited dRTA

The possibility of inherited dRTA should be considered in clinical cases in which patients present with hyperchloremic metabolic acidosis with a normal anion gap, hypokalemia, abnormal alkaline urine, reduced urinary titratable acid, NH_4^+ excretion, urinary pH> 6.0, or growth retardation or rickets of unknown origin. After fully excluding secondary factors, the possibility of inherited dRTA should be carefully considered. The

systematic and comprehensive medical history collection of patients, combined with laboratory examinations and imaging data, the exclusion of other related diseases, and molecular genetic detection methods, if necessary, is conducive to the accurate diagnosis of inherited dRTA.

Diagnostic Clues of Inherited pRTA

The possibility of inherited pRTA should be considered in the following cases: the clinical manifestations of hereditary pRTA and dRTA are similar, including hyperchloremic metabolic acidosis with a normal anion gap, hypokalemia, hyperkalemia, and rickets with growth retardation and unknown causes. In addition, when the above manifestations are accompanied by excessive HCO_3^- excretion in urine and a HCO_3^- excretion fraction >15% in the base load test, inherited pRTA should be considered after fully excluding secondary factors.

Diagnostic Clues of Inherited Mixed RTA

The clinical incidence of inherited mixed RTA is extremely low, and this condition presents with both proximal and distal tubular acidification defects. In such cases, the urinary titratable acid and NH_4^+ are decreased, and the urine HCO_3^- excretion fraction is >15%. In addition to kidney involvement, bone sclerosis, brain calcification, low intelligence, and other renal manifestations are common. Additionally, kidney involvement is often accompanied by extrarenal manifestations, such as osteosclerosis, brain calcification, and intellectual disability.

Diagnostic Clues of Inherited Hyperkalemic RTA

Clinically, RTA can be preliminarily considered if it is accompanied by hyperchloric metabolic acidosis with a normal anion gap. If there is hyperkalemia, the activity or level of plasma aldosterone would be further detected. If the level of aldosterone is reduced, it could be diagnosed as hyperkalemic RTA after fully excluding secondary factors. Hyperkalemic RTA cannot be ruled out if aldosterone is normal or elevated, and reduced renal tubule reactivity or resistance to aldosterone should be considered.

Differential Diagnosis

Differential Diagnosis of Inherited dRTA

Identification of Inherited pRTA

Clinically, the possibility of dRTA or pRTA should be taken into account when hyperchloremic metabolic acidosis with a normal anion gap of any other cause is present. Patients with inherited dRTA have a urine pH consistently >6.0 due to the inability to excrete a daily acid load, decreased urinary titratable acids and NH_4^+. pRTA is mainly caused by decreased proximal tubule reabsorption capacity for filtered HCO_3^-, which increases with urine excretion, and an alkaline loading test reveals HCO_3^- excretion fraction >15%. Furthermore, in addition to manifesting as a simple HCO_3^- reabsorption disorder, pRTA can present with other proximal tubule dysfunctions such as phosphate, glucose, uric acid, and/or amino acid reabsorption dysfunction (known as Fanconi syndrome), and such patients can present with hypophosphatemia, renal glucosuria, hypouricemia, and/or aminoaciduria, features not shared by dRTA.

Identification of Secondary dRTA

Clinically, secondary RTA accounts for approximately 75% of RTA cases, and it is often secondary to a variety of renal diseases or extrarenal diseases. In addition to the common clinical manifestations of RTA, most patients have manifestations of the primary disease. Common renal diseases include various types of acute and chronic glomerulonephritis and interstitial nephritis, aristolochic acid nephropathy, and medullary sponge kidney. Extrarenal diseases include autoimmune diseases, such as Sjogren's syndrome, chronic diseases, such as hypertension, diabetes, cirrhosis, and inherited diseases, such as Wilson's disease. In addition, secondary RTA is partly due to drug poisoning (such as cyclosporine A, sulfonamides, amphotericin B, certain Chinese herbs, and so on) [13, 67].

Identification of Other Related Diseases

(1). Hypokalemia is the most common electrolyte disorder in RTA, and blood pressure is an important indicator in the differential diagnosis of hypokalemia. Hypokalemia with normal blood pressure is common in RTA, Gitelman syndrome, and Bartter syndrome [68]. Hypokalemia with high blood pressure is commonly seen in primary aldosteronism, Cushing syndrome, Liddle syndrome, and renin tumors. (2) Hyperchloremia is an important complication of RTA. In RTA patients, due to the obstruction of renal tubule reabsorption of HCO_3^-, the body compensates by increasing the reabsorption of Cl^- to maintain the normal anion gap, resulting in hyperchloremia. Patients with Liddle syndrome may present with elevated blood chlorine, but this is often accompanied by hypertension and metabolic alkalosis [69]. (3) Hypercalciuria and hypocalcemia are also common manifestations of RTA. Thus, patients are often

misdiagnosed with hyperparathyroidism, of which the common causes are chronic renal failure and single parathyroid adenoma. Measurement of renal size, renal function, and serum parathyroid hormone levels, as well as analysis by parathyroid ultrasound are helpful for the differential diagnosis of this condition. (4) Patients with fatigue, myasthenia, and soft paralysis are easily misdiagnosed with primary hypokalemic periodic paralysis, Gitelman syndrome, Bartter syndrome, and Liddle syndrome. However, acid-base imbalance generally does not occur in patients with primary hypokalemic periodic paralysis, and patients with Gitelman syndrome, Bartter syndrome, and Liddle syndrome often also present with metabolic alkalosis. (5) Patients with polydipsia, polyuria, and increased nocturia are easily misdiagnosed with diabetes insipidus. However, patients with diabetes insipidus often do not show acid-base imbalances. Arterial blood gas analysis and urine examination can aid in the differential diagnosis. (6) Patients with polydipsia, polyuria, emaciation, and positive urine sugar tests are easily misdiagnosed with diabetes mellitus. Fasting blood glucose, glycosylated hemoglobin A1c, and glucose tolerance tests are helpful to confirm the diagnosis. (7) Patients presenting with osteoarthritic swelling and pain are easily misdiagnosed with rheumatoid arthritis. Careful medical history inquiry and detection of rheumatoid factor, anticyclic citrullinated peptide antibodies, and other related antibodies are helpful for the differential diagnosis of this condition.

Differential Diagnosis of Inherited pRTA

The clinical manifestations of inherited pRTA and dRTA are similar, and they often involve multiple organ systems. The clinical manifestations are complex and diverse and often overlap with those of other diseases. Therefore, the disease identification process required for inherited pRTA is basically the same as that for dRTA.

Isolated pRTA is relatively rare clinically and is usually a component of the presentation of Fanconi syndrome. Therefore, patients may present with phosphaturia, glucosuria, urinary amino acids, hypercalcemia, and hyperuricemia in addition to the manifestations of RTA. Clinically, there are three main types of Fanconi syndrome: primary Fanconi syndrome (sodium-phosphate transporter mutations), inherited systemic disease-associated Fanconi syndrome (such as hereditary cystinosis), and acquired Fanconi syndrome (such as that caused by systemic Sjogren's syndrome, drug induction with cisplatin, and heavy metal or chemical poisoning) [49, 67].

Treatment Strategies

The purpose of therapy for inherited RTA is to correct metabolic acidosis and hypokalemia, prevent acute symptoms, and reduce the severity of other chronic complications (such as growth retardation, renal calcinosis, and rickets) [49, 54]. The identification of pathogenic genes in patients with clinically suspected inherited RTA is beneficial for an accurate genetic molecular diagnosis.

In clinical practice, oral alkali supplement therapy is mainly used as a treatment option; generally, citrate (such as potassium citrate and citric acid mixture) or bicarbonate is used to compensate for the HCO_3^- lost in the kidney or to balance the acid produced by protein decomposition or bone growth. For patients with dRTA, potassium citrate is often used clinically to correct metabolic acidosis and hypokalemia because the intake of sodium (such as sodium citrate and sodium bicarbonate) can increase urinary calcium excretion. After the administration of citrate, urinary calcium is excreted in the form of calcium citrate, which has high solubility. Thus, the occurrence of nephrocalcinosis and kidney stones can effectively be inhibited. Most of the biochemical abnormalities, associated bone diseases and growth and development disorders of dRTA can be effectively corrected by adequate oral alkali therapy [58]. For pRTA patients, due to the renal loss of a large amount of HCO_3^-, the patient needs to be given a larger dose of alkaline drugs. For patients with metabolic acidosis and asymptomatic bone disease, when blood HCO_3^- levels are <18 mmol/L, alkali supplement therapy can be given. However, excessive acid correction should be avoided to prevent an increase in the amount of extracellular fluid and thereby an increase in urinary calcium excretion [49]. At the beginning of the correction of metabolic acidosis, potassium citrate may be supplemented in patients with severe renal loss of potassium or hypokalemic crisis. In addition, pRTA patients secondary to Fanconi syndrome also need to pay attention to the primary disease, and supplementation of the solutes lost in the urine due to proximal renal tubule reabsorption disorders should be considered. For example, the loss of phosphate will increase the probability of rickets or osteomalacia. Therefore, the patient's phosphate and vitamin D levels should be checked and supplemented promptly. For patients with hyperkalemic RTA, they can actively correct hyperkalemia by giving furosemide or hydrochlorothiazide to excrete potassium through the kidney, or by giving sodium polystyrene sulfonate and sodium zirconium cyclosilicate powder to excrete potassium through the intestine.

Table 1. Comparison of the pathogenic genes, auxiliary examinations, and clinical features of inherited RTA

	dRTA	AR-pRTA	Mixed RTA	Hyperkalemic RTA
Pathogenic gene (functional protein)	***SLC4A1*** (***AD/AR***) (AE1) ***ATP6V1B1*** (***AR***) (H^+ -ATPase B1 subunit) ***ATP6V0A4*** (***AR***) (H^+ -ATPase a4 subunit)	***SLC4A4*** (NBC1) ***KCNK5*** (TASK2)	***CA2*** (CA II)	***NR3C2***(***AD***) (MR) ***WNK1,4*** (***AD***) (WNK1, 4 protein) ***CUL3***(***AD***) (Culli3 protein) ***SCNN1A, SCNN1B, SCNN1G*** (***AR***) (α, β, γ subunit of ENaC protein) ***CYP11B2*** (***AR***) (Aldosterone synthase) ***KLHL3*** (***AD/AR***) (Kelch-like protein 3)
Clinical manifestation	***AD*:** Late-onset (after puberty) Mild clinical manifestations Mild nephrocalcinosis/ kidney stones Less commonly associated with bone disease ***AR*:** Early onset (infants/children) More severe clinical manifestations Early nephrocalcinosis/ kidney stones, and associated bone diseases Severe cases of growth retardation SNHL/EVAS	Unusual nephrocalcinosis/ kidney stones, growth/ mental retardation, Cataracts/glaucoma/band keratopathy, basal ganglia calcification/migraine, transient ischemic attack	dRTA+pRTA, fracture/ osteosclerosis, vision deficit, basal ganglia calcification	Congenital isolated hypoaldosteronism and pseudohypoaldosteronism, hyporeninemia, hypoaldosteronemia, hyporesponsive to renin and aldosterone
Erythrocyte morphology	Abnormal erythrocyte morphology (***AR***)	/	/	/
Hematological examinations	Hypokalemia, hyperchloremic metabolic acidosis with normal anion gap			Hyperkalemia, hyperchloremic metabolic acidosis, with normal anion gap
Urine examinations	Urine pH > 6.0; Reduced urine titratable acids and/or ammonium ions	Urine pH is normal ordecreased, Urinary HCO_3^- excretion fraction >15%	dRTA+pRTA	Reduced urine ammonium ions, Urine pH <5.5
Treatment	Correcting metabolic acidosis and hypokalemia (potassium citrate available)/hyperkalemia (sodium polystyrene sulfonate and sodium zirconium cyclosilicate powder)			

AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; dRTA, distal renal tubular acidosis; pRTA, proximal renal tubular acidosis; SNHL, sensorineural hearing loss; EVAS, enlarged vestibular aqueduct syndrome; MR, mineralocorticoid receptor; ENaC, epithelial sodium channel.

Conclusion

Inherited RTA is primarily a genetic disease caused by dysfunction of H^+ secretion by distal renal tubules and/or proximal renal tubule reabsorption of HCO_3^- caused by mutations in genes encoding related ion channels or transporters; among such cases, dRTA and pRTA with hypokalemia are more common. Both dRTA and pRTA patients may have different degrees of hypokalemia, hyperchloremic metabolic acidosis with a normal anion

gap, growth retardation, associated bone diseases, and other clinical manifestations, whereas hyperkalemic RTA generally presents as hyperkalemia and low renin aldosterone activity. For patients with an unknown etiology, especially children and adolescents, timely genetic testing can provide a clear diagnosis and guidance for treatment.

Inherited dRTA is mainly related to *SLC4A1*, *ATP6V1B1*, *ATP6V0A4*, *FOXI1*, and *WDR72* gene mutations; pRTA is mainly related to *SLC4A4* gene mutations, mixed RTA is mainly related to *CA II* gene mutations and inherited hyperkalemic RTA mostly presents as hypoaldosteronism or aldosterone resistance resulting from reduced aldosterone production, including congenital isolated hypoaldosteronism and pseudohypoaldosteronism. Compared with those of AR-RTA patients, the clinical manifestations of AD-RTA patients are mild. Patients with AR-dRTA caused by mutations in the *ATP6V1B1* and *ATP6V0A4* genes often have SNHL/hearing impairment. Patients with AR-dRTA caused by *SLC4A1* mutations often have abnormal erythrocyte morphology, and patients with AR-pRTA caused by *SLC4A4* mutations often have ocular abnormalities and neurological involvement. The comparison of RTA pathogenic genes, their encoded functional proteins, and clinical characteristics is shown in Table 1.

Inherited RTA is a lifelong disease. Early diagnosis and timely and adequate correction of acidosis and disorders of potassium metabolism with citrate or bicarbonate have a satisfactory prognosis. Therefore, patients with inherited RTA need to be followed up regularly and closely monitored by blood gas analysis, biochemical examination, renal ultrasound, bone density, hearing, and vision tests. With the development of molecular genetics and gene sequencing technology, more pathogenic genes of inherited RTA are being discovered. Moreover, clinicians are required to improve their knowledge of hereditary renal tubule disease and perform timely genetic testing for clinically suspected patients to avoid missed diagnosis and misdiagnosis.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors have contributed to this review. Wenkai Guo drafted the manuscript. Pengcheng Ji provided valuable input into the article. Yuansheng Xie revised and approved the final manuscript. All authors approved the final manuscript as submitted and are accountable for all aspects of the work.

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