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NLM Citation: Alexander RT, Law L, Gil-Peña H, et al. Hereditary Distal Renal Tubular Acidosis. 2019 Oct 10. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Hereditary Distal Renal Tubular Acidosis

Synonyms: Classic Renal Tubular Acidosis, Type 1 RTA

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Created: October 10, 2019.

Summary

Clinical characteristics

Individuals with hereditary distal renal tubular acidosis (dRTA) typically present in infancy with failure to thrive, although later presentations can occur, especially in individuals with autosomal dominant *SLC4A1*-dRTA. Initial clinical manifestations can also include emesis, polyuria, polydipsia, constipation, diarrhea, decreased appetite, and episodes of dehydration. Electrolyte manifestations include hyperchloremic non-anion gap metabolic acidosis and hypokalemia. Renal complications of dRTA include nephrocalcinosis, nephrolithiasis, medullary cysts, and impaired renal function. Additional manifestations include bone demineralization (rickets, osteomalacia), growth deficiency, sensorineural hearing loss (in *ATP6V0A4*-, *ATP6V1B1*-, and *FOXI1*-dRTA), and hereditary hemolytic anemia (in some individuals with *SLC4A1*-dRTA).

Diagnosis/testing

The diagnosis of hereditary dRTA is established in a proband with dRTA and biallelic pathogenic variants in *ATP6V0A4*, *ATP6V1B1*, *FOXI1*, or *WDR72*, or a heterozygous or biallelic pathogenic variants in *SLC4A1*, identified by molecular genetic testing.

Management

Treatment of manifestations: Oral alkaline therapy to correct metabolic acidosis and hypokalemia with additional potassium chloride as needed; standard treatments for sensorineural hearing loss.

Surveillance: Fasting venous blood gas or total CO_2 prior to alkali dose in rapidly growing infants and children at least every 3-4 months, and at least every 6 months in older individuals. Serum creatinine, urea, sodium, potassium, chloride, calcium, phosphate, alkaline phosphatase, and albumin in rapidly growing infants and children at least every 3-4 months, and at least every 6 months in older individuals. Urinalysis, urine creatinine,

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sodium, potassium, calcium, and citrate annually and more frequently when adjusting treatment. Annual renal ultrasound to evaluate for nephrocalcinosis, urolithiasis, and cysts in asymptomatic individuals. Audiometry annually in at-risk individuals. Bone densitometry as needed. Growth assessment with calculation of body mass index in infants at least every 3 months, and in older children at least every 6 months until achievement of final height.

Agents/circumstances to avoid: Potassium-sparing diuretics should be used with caution or avoided.

Pregnancy management: Women with hereditary dRTA may develop severe metabolic acidosis and hypokalemia during pregnancy, especially when complicated by hyperemesis gravidarum. Close monitoring of women with hereditary dRTA during pregnancy is necessary.

Genetic counseling

Hereditary dRTA caused by pathogenic variants in *ATP6V0A4*, *ATP6V1B1*, *FOXI1*, or *WDR72* is inherited in an autosomal recessive manner. Hereditary dRTA caused by pathogenic variants in *SLC4A1* is inherited in an autosomal dominant or autosomal recessive manner.

Autosomal recessive inheritance: At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

Autosomal dominant inheritance: Each child of an individual with autosomal dominant dRTA has a 50% chance of inheriting the pathogenic variant.

Molecular genetic prenatal testing is possible for pregnancies at increased risk in families in which the pathogenic variant(s) have been identified.

Diagnosis

Formal diagnostic criteria for hereditary distal renal tubular acidosis (dRTA) have not been established.

Suggestive Findings

Hereditary dRTA should be suspected in individuals with the following clinical, laboratory, and radiographic features.

Clinical features

- Failure to thrive in childhood
- Sensorineural hearing loss
- Symptoms of hypokalemia, including muscle weakness and muscle cramps
- Bone manifestations (10%-23%): osteomalacia in adults, rickets in children, fractures, bone pain
- Exclusion of secondary causes of dRTA (e.g., autoimmune, drug induced)

Laboratory features

- Hyperchloremic non-anion gap metabolic acidosis in the absence of GI losses
- Hypokalemia (blood potassium level <3.5 mEq/L)
- Hypobicarbonatemia (blood bicarbonate levels below 20 mEq/L in infants and 22 mEq/L in older children), but with normal fractional excretion of bicarbonate
- Inappropriately elevated urine pH (>5.3) in the absence of gastrointestinal bicarbonate losses
- Absence of a negative urine anion gap (UAG) in an individual with metabolic acidosis. Calculation of the UAG ($U_{AG}=[Na^+]_U+[K^+]_U-[Cl^-]_U$) can help to distinguish between primary forms of proximal and dRTA.

- Elevated urine calcium
- Decreased urine citrate
- Failure to acidify the urine (urine pH always >5.3):
  - After an ammonium chloride challenge (100 mg/kg) [Wrong & Davies 1959]; OR
  - When increased distal delivery of sodium is induced, via the co-administration of a mineralocorticoid (e.g., fludrocortisone 0.02 mg/kg) and furosemide (0.5 mg/kg) [Walsh et al 2007, Shavit et al 2016]; OR
  - In an individual who presents with spontaneous acidosis

Imaging features

- Renal ultrasound. Nephrocalcinosis is almost universal; nephrolithiasis is less common, but does occur. Medullary cysts may be detected, typically in later childhood or in adults [Igarashi et al 1991, Besouw et al 2017].
- Plain radiographs of the bones may show rachitic changes.
- Bone densitometry examination may show decreased bone density in children and adults [Besouw et al 2017].
- CT examination of the inner ear may demonstrate dilation of the vestibular aqueduct in individuals with hereditary dRTA associated with hearing loss [Palazzo et al 2017].

Establishing the Diagnosis

The diagnosis of hereditary dRTA **is established** in a proband with dRTA and biallelic pathogenic (or likely pathogenic) variants in *ATP6V0A4*, *ATP6V1B1*, *FOXI1*, or *WDR72*, or a heterozygous or biallelic pathogenic (or likely pathogenic) variant(s) in *SLC4A1*,* identified by molecular genetic testing.

* *SLC4A1*-dRTA has been associated with autosomal dominant and autosomal recessive inheritance.

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved. Because the phenotype of hereditary dRTA is relatively broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of hereditary dRTA has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of hereditary dRTA, molecular genetic testing approaches can include use of a **multigene panel**.

A multigene panel that includes the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) may identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition

discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Note: Hereditary dRTA caused by pathogenic variants in a specific gene can be associated with specific clinical features and inheritance patterns, which may or may not be recognizable at the time of clinical presentation.

- ***ATPV0A4*** and ***ATPV1B1*** are the most common causes of **autosomal recessive** dRTA.
- ***ATP6V0A4***- and ***ATP6V1B1***-dRTA commonly occur in the presence of **sensorineural hearing loss**, although onset of hearing loss varies from early childhood to adulthood. Typically, hearing loss occurs in infancy with *ATPV1B1*-dRTA and later in childhood with *ATP6V0A4*-dRTA. Pathogenic variants in ***FOXI1*** are usually associated with early-onset hearing loss.
- For **adolescent/adult presentation, autosomal dominant** inheritance, or dRTA associated with an inherited **hemolytic anemia, *SLC4A1***-dRTA is most likely.

Option 2

When the diagnosis of hereditary dRTA is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Hereditary Distal Renal Tubular Acidosis

Gene [1, 2]	Proportion of Hereditary dRTA Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
ATP6V0A4	40% [6, 7]	~98% [6, 7]	~2% [8]
ATP6V1B1	30% [6, 7]	100%	Unknown [9]
FOXI1	2 families [10]	100%	Unknown [9]
SLC4A1	15% [6]	>95% [11, 12]	See footnote 12.
WDR72	2 families [13]	100%	Unknown [9]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of Hereditary dRTA Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
Unknown	15% [6]	NA	

1. Genes are listed alphabetically.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Vargas-Poussou et al [2006], Gómez et al [2016], Besouw et al [2017], Palazzo et al [2017], Alonso-Varela et al [2018]
7. Stover et al [2002]
8. Miura et al [2013], Escobar et al [2016], Palazzo et al [2017]
9. No data on detection rate of gene-targeted deletion/duplication analysis are available.
10. Enerbäck et al [2018]
11. Bruce et al [1997], Chu et al [2010], Khositseth et al [2012]
12. Intra-exon deletions of 27-170 base pairs have been reported [Hooman et al 2015]. Depending on assay design, these deletions may be detectable by sequencing or gene-targeted deletion/duplication assays.
13. Rungroj et al [2018]

Clinical Characteristics

Clinical Description

Individuals with hereditary distal renal tubular acidosis (dRTA) typically present in infancy with failure to thrive, although later presentations can occur, especially in individuals with autosomal dominant *SLC4A1*-dRTA. Initial clinical manifestations may also include emesis, polyuria, polydipsia, constipation, diarrhea, decreased appetite, and episodes of dehydration [Besouw et al 2017, Palazzo et al 2017].

Electrolyte manifestations include hypokalemia and hyperchloremic non-anion gap metabolic acidosis with inappropriately elevated urine pH (which may lead to secondary tachypnea if severe [Besouw et al 2017, Palazzo et al 2017]). Some individuals may present with evidence of proximal tubular dysfunction (e.g., amino aciduria, decreased reabsorption of phosphate, and low molecular weight proteinuria); however, this resolves with correction of the acidosis [Besouw et al 2017].

Renal complications in dRTA include nephrocalcinosis, nephrolithiasis, medullary cysts, and impaired renal function, which may occur in childhood [Igarashi et al 1991, Besouw et al 2017].

Nephrocalcinosis, typically bilateral, results from calcium deposition in the renal parenchyma. Reports on the frequency vary in the literature, ranging from approximately 25% [Chang & Lin 2002] to 100% of children with dRTA [Pirojsakul et al 2011, Besouw et al 2017, Enerbäck et al 2018]. In a large mostly European cohort of 340 individuals with dRTA, more than 90% of individuals with molecularly confirmed hereditary dRTA had nephrocalcinosis [Lopez-Garcia et al 2019]. The occurrence appears to increase with age and with later onset of alkalinizing therapy [Caldas et al 1992].

Medullary cysts develop in many individuals during childhood or in adulthood, likely secondary to hypokalemia [Igarashi et al 1991, Besouw et al 2017].

A mild-to-moderate decrease in glomerular filtration rate can occur and increase in prevalence with age but may be present in childhood [Besouw et al 2017, Palazzo et al 2017].

Hypokalemia (blood potassium level <3.5 mEq/L) is found in the majority of individuals with dRTA [Caldas et al 1992, Domrongkitchaiporn et al 2001, Pirojsakul et al 2011]. Individuals with *ATP6V1B1*- or *ATP6V0A4*-dRTA tend to have more severe hypokalemia than individuals with autosomal dominant *SLC4A1*-dRTA [Karet 2002, Alonso-Varela et al 2018]. Symptoms of hypokalemia include muscle weakness and muscle cramps [Nilwarangkur et al 1990, Domrongkitchaiporn et al 2001, Pirojsakul et al 2011]. Paralysis and respiratory depression as a result of muscle weakness may occur with severe hypokalemia [Caldas et al 1992, Domrongkitchaiporn et al 2002a]. Renal cysts are likely related to hypokalemia.

Skeletal manifestations. The metabolic acidosis in dRTA results in the release of bicarbonate and phosphate – which are complexed with calcium – from bone. These salts act as alkalizing buffers to promote restoration of physiologic blood pH [Bushinsky & Frick 2000, Chan et al 2001, Domrongkitchaiporn et al 2001, Bushinsky et al 2003, Fry & Karet 2007].

Bone demineralization can cause rickets in children and osteomalacia in adults [Escobar et al 2013]. These conditions increase the risk of fractures and may cause bone pain. The frequency and severity of bone findings reported in the literature vary significantly. Rickets can cause bone deformities; ambulation may be impaired as a result of leg deformities [Bushinsky & Frick 2000, Domrongkitchaiporn et al 2001, Bushinsky et al 2003]. In a European cohort, rickets was present in 25% of children with dRTA [Caldas et al 1992]; however, others failed to identify any radiographic evidence of rickets in their cohort [Brenner et al 1982]. The reported prevalence of osteomalacia ranges from 10% to 23% [Nilwarangkur et al 1990, Jha et al 2011]. Low bone mass has been commonly reported in individuals of Thai descent with dRTA [Domrongkitchaiporn et al 2001]. Alkali treatment has been shown to improve bone mineral density in these individuals [Domrongkitchaiporn et al 2002b].

Growth. dRTA is often diagnosed during the evaluation of infants or young children with failure to thrive (principally manifesting as poor linear growth with normal weight for height) [Besouw et al 2017]. The majority of children with dRTA have short stature prior to adequate alkali therapy [Besouw et al 2017].The height deficit at diagnosis can be severe [Domrongkitchaiporn et al 2001, Bajpai et al 2005]. Children treated with adequate alkali therapy have improved growth velocity and catch-up growth is common, frequently allowing achievement of a normal height [Besouw et al 2017, Lopez-Garcia et al 2019].

Sensorineural hearing loss occurs in individuals with pathogenic variants in *ATP6V1B1* or *ATP6V0A4*. Both early-childhood onset and later-adult onset can occur; the hearing loss can be profound [Karet et al 1999, Vargas-Poussou et al 2006, Enerbäck et al 2018]. Increased severity and earlier-onset hearing loss is more common in individuals with *ATP6V1B1*-dRTA. Progression or appearance of hypoacusia is not prevented by medical treatment. Hearing impairment is treated with hearing aids or cochlear implants when necessary.

Hematologic manifestations. A small number of individuals with *SLC4A1*-dRTA will also have hereditary hemolytic anemia. Pathogenic variants causing both dRTA and hemolytic anemia most commonly occur in Southeast Asia and have also been reported in families in the Middle East and India. The combination of dRTA and hemolytic anemia usually presents in infants and children [Fawaz et al 2012, Khositseth et al 2012]. In one series including 78 affected individuals, hemoglobin values ranged from 4.4 to 15.7 g/dL [Khositseth et al 2012]. Biallelic *SLC4A1* pathogenic variants can result in morphologic changes in erythrocytes. These altered erythrocytes are vulnerable to hemolysis under conditions of metabolic acidosis. Alkali therapy is associated with correction of anemia and reticulocytosis [Khositseth et al 2008]. Affected individuals also respond to transfusion and iron therapy [Khositseth et al 2012].

Heterozygotes for pathogenic variants in genes typically associated with autosomal recessive complete dRTA. Heterozygous *ATP6V1B1* pathogenic variants have been identified in a few individuals with mild renal

acidification defects that do not result in altered blood pH; these individuals are said to have incomplete dRTA [Zhang et al 2014, Dhayat et al 2016]. The diagnosis can be made with an ammonium chloride or fludrocortisone/furosemide challenge, as these individuals also fail to adequately acidify their urine. These individuals also commonly have hypercalciuria and kidney stones.

Phenotype Correlations by Gene

ATP6V0A4 may be associated with a more severe metabolic acidosis and later onset of deafness [Karet et al 1999, Stover et al 2002, Vargas-Poussou et al 2006, Besouw et al 2017].

ATP6V1B1 is associated with symptom onset in infancy or childhood, and deafness typically with onset in infancy.

FOXI1 is associated with autosomal recessive dRTA and early-onset deafness [Enerbäck et al 2018].

SLC4A1 is typically associated with a milder form of dRTA; affected individuals may have a compensated hyperchloremic metabolic acidosis (low serum bicarbonate, but normal pH) [Besouw et al 2017]. Symptom onset occurs in childhood or later, with less impact on growth than in the autosomal recessive forms.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for hereditary dRTA have been identified.

Nomenclature

Hereditary dRTA includes both "complete RTA" and "incomplete RTA." Complete RTA refers to a failure to excrete acid leading to metabolic acidosis. Incomplete RTA refers to a failure to excrete acid in the absence of frank metabolic acidosis and is a mild renal acidification defect.

Hereditary dRTA may also be referred to as "secretory-defect dRTA."

Prevalence

The prevalence of hereditary dRTA is unclear; although it is certainly rare and quite low (~350 individuals have been reported in the literature).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ATP6V0A4*.

Disorders that are allelic with other dRTA-related genes are listed in Table 2.

Table 2. Allelic Disorders

Gene	Disorder	MOI
FOXI1 [1]	Pendred syndrome / nonsyndromic enlarged vestibular aqueduct	AR
SLC4A1	Cryohydrocytosis (OMIM 185020)	AD
	Southeast Asian ovalocytosis (OMIM 166900)	AD
	Spherocytosis type 4 (OMIM 612653)	AD

Table 2. continued from previous page.

Gene	Disorder	MOI
WDR72	Amelogenesis imperfecta, type IIA3 (OMIM 613211)	AR

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
1. In rare cases, Pendred syndrome and/or nonsyndromic enlarged vestibular aqueduct has been associated with double heterozygosity for one pathogenic variant in *SLC26A4* and one pathogenic variant in either *FOXI1* or *KCNJ10*.

Differential Diagnosis

Table 3. Disorder to Consider in the Differential Diagnosis of Hereditary Distal Renal Tubular Acidosis

DiffDx Disorder	Gene	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/dRTA	Distinguishing from dRTA
Osteopetrosis with renal tubular acidosis (OMIM 259730)	*CA2*	AR	dRTA	• Proximal RTA • Osteopetrosis • ID • Visual impairment from optic nerve compression

AR = autosomal recessive; DiffDx = differential diagnosis; dRTA = distal renal tubular acidosis; ID = intellectual disability; MOI = mode of inheritance; RTA = renal tubular acidosis

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hereditary distal renal tubular acidosis (dRTA), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Hereditary Distal Renal Tubular Acidosis

System/ Concern	Evaluation	Comment
Renal	Venous blood gas or total plasma CO_2	• Eval of acid-base equilibrium • Sample to be drawn in fasting conditions & immediately before scheduled dose of alkali to assess effectiveness of therapy
	Serum creatinine, urea, sodium, potassium, chloride	Evaluate glomerular filtration rate; assess hypokalemia, hydration status.
	Serum calcium, phosphate, alkaline phosphatase, magnesium	Assess for hypocalcemia, biochemical evidence of rickets, hypophosphatemia.
	Uric acid, albumin	Assess for assoc tubular dysfunction.
	Urinalysis	Detection of proteinuria, hematuria, & leukocyturia
	Isolated urine sample for creatinine, sodium, potassium, calcium, & citrate. Note: Sample should be taken simultaneously w/serum/plasma samples enabling calculation of renal tubular handling of these electrolytes.	• Excretion of sodium & potassium can be estimated by calculation of appropriate indices (mL/dL glomerular filtrate, fractional excretions of sodium & potassium) to monitor renal function & therapy. • Detection of hypercalciuria by calcium/creatinine ratio. Hypercalciuria may indicate inadequate correction of acidosis. • Detection of hypocitraturia may imply inadequate treatment.
	Ultrasound	Eval for nephrocalcinosis, urolithiasis, & medullary cysts

Table 4. continued from previous page.

System/ Concern	Evaluation	Comment
ENT	Audiometry	Eval for sensorineural hearing loss
Constitutional	Measurement of length/height & weight	Use for calculation of body mass index to assess nutritional status; baseline values to assess response to therapy (correction of height deficit expected if short stature is present) & to adjust alkali dosage.

Treatment of Manifestations

Renal tubular acidosis. The goal of treatment is to correct the metabolic acidosis and hypokalemia [Karet 2002, Rodríguez Soriano 2002, Both et al 2014]. Maintaining bicarbonate and potassium in the normal range decreases the likelihood of acute symptoms and decreases the severity of long-term complications (e.g., poor growth, nephrocalcinosis, osteomalacia, decreased GFR).

Standard of care in dRTA is oral alkaline therapy, usually in the form of a bicarbonate and/or citrate salt [Chan et al 2001, Karet 2002, Rodríguez Soriano 2002, Both et al 2014]. As these salts have a short half-life, they should be taken repeatedly throughout the day and night to maintain normal blood pH. The alkali salt is usually potassium given that hypokalemia is commonly associated, although some individuals may receive some sodium alkali preparations. Other individuals require potassium chloride as an additional source of potassium. The alkali requirement is highest in infants (>8 mEq/kg/day of alkali in some individuals) but decreases to approximately 1 mEq/kg/day in adults. Dosing is ideally every six hours, although practical considerations may lead clinicians and affected individuals to adapt dosing to accommodate sleep, work, and school schedules. Sodium salts should be avoided because of their contribution to worsening hypercalciuria.

Note: (1) Compensated metabolic acidosis (normal pH but low bicarbonate) is not sufficient to facilitate growth. (2) Alkali and citrate supplementation prevent the progression of nephrocalcinosis, but do not reverse it. (3) Treatment decreases the risk of developing urolithiasis.

Growth retardation is corrected with appropriate alkali treatment. In most cohort studies, growth with treatment is within normal range, but still below average.

Skeletal manifestations. Alkali treatment has been shown to improve bone mineral density in individuals of Thai descent [Domrongkitchaiporn et al 2002b].

Sensorineural hearing loss. Correction of metabolic acidosis does not correct hypoacusia, which should be treated according to standard procedures.

Surveillance

No surveillance guidelines have been published.

Table 5. Recommended Surveillance for Individuals with Hereditary Distal Renal Tubular Acidosis

System/ Concern	Evaluation	Comment
Renal	Venous blood gas	• In rapidly growing persons (infants & young children): at least every 3-4 mos once blood pH is normalized w/o evidence of respiratory compensation; in older children & adults: at least every 6 mos • Sample to be drawn in fasting conditions & immediately before scheduled dose of alkali
	Serum creatinine, urea, sodium, potassium, chloride, calcium, phosphate, alkaline phosphatase, albumin	• In rapidly growing persons (infants & young children), at least every 3-4 mos once adequate control is achieved • In older children & adults, at least every 6 mos
	Urinalysis, urine creatinine, sodium, potassium, calcium, citrate	Annually; more frequently when adjusting treatment
	Renal ultrasound	Annual eval for nephrocalcinosis, urolithiasis, & cysts in asymptomatic persons
ENT	Audiometry	Annual eval for hearing loss
Skeletal	Bone densitometry	No consensus exists on benefit of follow-up bone densitometry.
Constitutional	Measure length/height, & weight; calculate BMI	In infants, at least every 3 mos; in older children, at least every 6 mos until achievement of final height

BMI = body mass index; ENT = ear, nose, and throat

Agents/Circumstances to Avoid

Potassium-sparing diuretics should be used with caution or avoided altogether.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

Evaluations can include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Venous blood gas or total CO_2 and plasma electrolytes if the pathogenic variant(s) in the family are not known.

Newborns should undergo assessment of acid-base status and serum electrolytes: specifically, blood gas analysis and plasma electrolytes to identify a normal anion gap metabolic acidosis and hypokalemia while results of molecular genetic testing are completed.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Women with hereditary dRTA may develop severe metabolic acidosis and hypokalemia during pregnancy, especially when complicated by hyperemesis gravidarum. Close monitoring of women with hereditary dRTA during pregnancy is necessary [Seeger et al 2017].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

One therapy for dRTA is under investigation in Europe and North America. ADV7103 is a combination of controlled-release granules of potassium bicarbonate and potassium citrate designed to provide 24-hour control of metabolic acidosis and hypokalemia in individuals with dRTA with twice-a-day dosing. A Phase III trial has been completed in Europe, with an extension ongoing, and a second trial is ongoing in the US (ClinicalTrials.gov identifier: NCT03644706) for individuals with primary dRTA.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hereditary distal renal tubular acidosis (dRTA) caused by pathogenic variants in *ATP6V0A4*, *ATP6V1B1*, *FOXI1*, or *WDR72* is inherited in an autosomal recessive manner.

Hereditary dRTA caused by pathogenic variants in *SLC4A1* is inherited in an autosomal dominant or autosomal recessive manner.

Autosomal Recessive Inheritance

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one hereditary dRTA-related pathogenic variant).
- Heterozygotes (carriers) are usually asymptomatic and are not at risk of developing complete dRTA. However, heterozygous pathogenic variants in the B1 subunit of *ATP6V1B1* can cause mild renal acidification defects, hypercalciuria, and kidney stones (i.e., incomplete dRTA) (see Clinical Description).

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are usually asymptomatic and are not at risk of developing complete dRTA. However, heterozygous pathogenic variants in the B1 subunit of *ATP6V1B1* can cause mild renal acidification defects, hypercalciuria, and kidney stones (i.e., incomplete dRTA) (see Clinical Description).

Offspring of a proband. The offspring of an individual with autosomal recessive hereditary dRTA are obligate heterozygotes (carriers) for a hereditary dRTA-related pathogenic variant.

Other family members. Each sib of the proband's parents has a 50% risk of being a carrier of a hereditary dRTA-related pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the hereditary dRTA-related pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with autosomal dominant *SLC4A1*-dRTA have the disorder as the result of a *de novo* pathogenic variant [Gómez et al 2016, Palazzo et al 2017, Alonso-Varela et al 2018, Zhang et al 2018].
- Very few individuals diagnosed with autosomal dominant hereditary dRTA have an affected parent.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the proband most likely has a *de novo* pathogenic variant. Another possible explanation is germline mosaicism in a parent. Though theoretically possible, no instances of parental germline mosaicism have been reported.
- The family history of some individuals diagnosed with autosomal dominant hereditary dRTA may appear to be negative because of failure to recognize the disorder in family members or death of the parent before the onset of symptoms. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant is first recognized, the parent may have somatic mosaicism of the variant and may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *SLC4A1* pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known *SLC4A1* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *SLC4A1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for hereditary dRTA because of the theoretic possibilities of reduced penetrance in a parent or parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant hereditary dRTA has a 50% chance of inheriting the *SLC4A1* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the hereditary dRTA-causing pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Kidney and Urologic Diseases Information Clearinghouse (NKUKIC)**
  3 Information Way
  Bethesda MD 20892-3580
  Phone: 800-891-5390 (toll-free); 866-569-1162 (toll-free TTY)
  Fax: 703-738-4929
  Email: nkudic@info.niddk.nih.gov
  Renal Tubular Acidosis

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)
  Fax: 202-337-8314
  Email: info@agbell.org
  Listening and Spoken Language Knowledge Center

- **American Kidney Fund**
  Phone: 800-638-8299
  www.kidneyfund.org

- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org

- **European Rare Kidney Disease Reference Network (ERKNet)**
  Phone: 49 0 6221 56-34191
  Email: contact@erknet.org
  www.erknet.org

- **Kidney Foundation of Canada**
  Canada
  Phone: 514-369-4806; 800-361-7494
  Email: info@kidney.ca
  www.kidney.ca
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org
- **National Kidney Foundation**
  Phone: 855-NKF-CARES; 855-653-2273
  Email: nkfcares@kidney.org
  kidney.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hereditary Distal Renal Tubular Acidosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATP6V0A4	7q34	V-type proton ATPase 116 kDa subunit a 4	ATP6V0A4 database	ATP6V0A4	ATP6V0A4
ATP6V1B1	2p13.3	V-type proton ATPase subunit B, kidney isoform	ATP6V1B1 database	ATP6V1B1	ATP6V1B1
FOXI1	5q35.1	Forkhead box protein I1	FOXI1 database	FOXI1	FOXI1
SLC4A1	17q21.31	Band 3 anion transport protein	SLC4A1 @ LOVD Blood Group Antigen Gene Mutation Database (SLC4A1)	SLC4A1	SLC4A1
WDR72	15q21.3	WD repeat-containing protein 72		WDR72	WDR72

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Hereditary Distal Renal Tubular Acidosis (View All in OMIM)

109270	SOLUTE CARRIER FAMILY 4 (ANION EXCHANGER), MEMBER 1; SLC4A1
179800	RENAL TUBULAR ACIDOSIS, DISTAL, 1; DRTA1
192132	ATPase, H+ TRANSPORTING, LYSOSOMAL, 56/58-KD, V1 SUBUNIT B, ISOFORM 1; ATP6V1B1
267300	RENAL TUBULAR ACIDOSIS, DISTAL, 2, WITH PROGRESSIVE SENSORINEURAL HEARING LOSS; DRTA2
602722	RENAL TUBULAR ACIDOSIS, DISTAL, 3, WITH OR WITHOUT SENSORINEURAL HEARING LOSS; DRTA3
605239	ATPase, H+ TRANSPORTING, LYSOSOMAL, V0 SUBUNIT A, ISOFORM 4; ATP6V0A4
611590	RENAL TUBULAR ACIDOSIS, DISTAL, 4, WITH HEMOLYTIC ANEMIA; DRTA4

Molecular Pathogenesis

Distal renal tubular acidosis is the result of a failure of the alpha intercalated cells of the connecting tubule and collecting duct to secrete H^+. The urine is ultimately acidified in the connecting tubule / collecting duct via a V-type H^+ATPase, a multiprotein complex. The two most common causes of dRTA are impairment of complex members V1B1 (beta1) and V0A4 (alpha4), encoded by *ATPV1B1* and *ATPV0A4*, respectively. These proteins are also expressed in the ear and are involved in hearing [Karet et al 1999, Stover et al 2002], resulting in occurrence of dRTA and hearing loss [Palazzo et al 2017].

FOXI1 is a transcription factor present in acid-secreting epithelia, including the connecting tubule / collecting duct (CNT/CD) necessary for normal expression of both the V1B1 and V0A4 subunits of the H^+ATPase.

In order to secrete acid into the pro-urine, H^+ must first be generated in the alpha intercalated cell of the CNT/CD. H^+ is generated from carbon dioxide and water, a process catalyzed by carbonic anhydrase II (*CA2*; see Differential Diagnosis), which also produces bicarbonate (HCO_3^-). In order to continue to provide H^+, the bicarbonate is effluxed from the cell across the basolateral membrane, adding to the pool of circulating buffer in the blood. Transport of HCO_3^- across the basolateral membrane is mediated by the anion exchanger (AE1) encoded by *SLC4A1*, pathogenic variants in which also cause dRTA [Karet et al 1998].

The role of WDR72 in cell biology/physiology is not clear. Based on molecular homology modeling, it has been proposed that the protein product contributes to the trafficking of membrane proteins, and thus its altered function could inhibit the proper trafficking of one of the gene products described above.

Mechanism of disease causation

- Pathogenic variations in *ATP6V0A4*, *ATP6V1B1*, *SLC4A1*, *FOXI1*, and *WDR72* associated with autosomal recessive dRTA are loss-of-function variants.
- Autosomal dominant disease-causing variants in *SLC4A1* are dominant-negative variants.

Chapter Notes

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Revision History

- 10 October 2019 (sw) Review posted live
- 15 January 2019 (rta) Original submission

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