

## SLC4A1-associated distal renal tubular acidosis

### Description

*SLC4A1*-associated distal renal tubular acidosis is a kidney (renal) disorder that sometimes includes blood cell abnormalities. The kidneys normally filter fluid and waste products from the body and remove them in urine; however, in people with distal renal tubular acidosis, the kidneys are unable to remove enough acid from the body, and the blood becomes too acidic. This chemical imbalance is called metabolic acidosis. The inability to remove acids from the body often results in slowed growth and may also lead to softening and weakening of the bones, called rickets in children and osteomalacia in adults. This bone disorder is characterized by bone pain, bowed legs, and difficulty walking. In addition, most children and adults with *SLC4A1*-associated distal renal tubular acidosis have excess calcium in the urine (hypercalciuria), calcium deposits in the kidneys (nephrocalcinosis), and kidney stones (nephrolithiasis). In rare cases, these kidney abnormalities lead to life-threatening kidney failure. Affected individuals may also have low levels of potassium in the blood (hypokalemia).

Individuals with the features described above have complete distal renal tubular acidosis, which usually becomes apparent in childhood. Some people do not develop metabolic acidosis even though their kidneys have trouble removing acids; these individuals are said to have incomplete distal renal tubular acidosis. Additionally, these individuals may have other features of distal renal tubular acidosis, such as bone problems and kidney stones. Often, people who initially have incomplete distal renal tubular acidosis develop metabolic acidosis later in life.

Some people with *SLC4A1*-associated distal renal tubular acidosis also have blood cell abnormalities. These can vary in severity from no symptoms to a condition called hemolytic anemia, in which red blood cells prematurely break down (undergo hemolysis), causing a shortage of red blood cells (anemia). Hemolytic anemia can lead to unusually pale skin (pallor), extreme tiredness (fatigue), shortness of breath (dyspnea), and an enlarged spleen (splenomegaly).

There are two forms of *SLC4A1*-associated distal renal tubular acidosis; they are distinguished by their inheritance pattern. The autosomal dominant form is more common and is usually less severe than the autosomal recessive form. The autosomal dominant form can be associated with incomplete or complete distal renal tubular acidosis and is rarely associated with blood cell abnormalities. The autosomal recessive form is always associated with complete distal renal tubular acidosis and is more commonly associated with blood cell abnormalities, although not everyone with this

form has abnormal blood cells.

## Frequency

The prevalence of *SLC4A1*-associated distal renal tubular acidosis is unknown. The condition is most common in Southeast Asia, especially Thailand.

## Causes

Both the autosomal dominant and autosomal recessive forms of *SLC4A1*-associated distal renal tubular acidosis are caused by mutations in the *SLC4A1* gene. This gene provides instructions for making the anion exchanger 1 (AE1) protein, which transports negatively charged atoms (anions) across cell membranes. Specifically, AE1 exchanges negatively charged atoms of chlorine (chloride ions) for negatively charged bicarbonate molecules (bicarbonate ions). The AE1 protein is found in the cell membrane of kidney cells and red blood cells. In kidney cells, the exchange of bicarbonate through AE1 allows acid to be released from the cell into the urine. In red blood cells, AE1 attaches to other proteins that make up the structural framework (the cytoskeleton) of the cells, helping to maintain their structure.

The *SLC4A1* gene mutations involved in either form of *SLC4A1*-associated distal renal tubular acidosis lead to production of altered AE1 proteins that cannot get to the correct location in the cell membrane. In the autosomal dominant form of the condition, gene mutations affect only one copy of the *SLC4A1* gene, and normal AE1 protein is produced from the other copy. However, the altered protein attaches to the normal protein and keeps it from getting to the correct location, leading to a severe reduction or absence of AE1 protein in the cell membrane. In autosomal recessive distal renal tubular acidosis, both copies of the *SLC4A1* gene are mutated, so all of the protein produced from this gene is altered and not able to get to the correct location. Improper location or absence of AE1 in kidney cell membranes disrupts bicarbonate exchange, and as a result, acid cannot be released into the urine. Instead, the acid builds up in the blood in most affected individuals, leading to metabolic acidosis and the other features of complete distal renal tubular acidosis. It is not clear why some people develop metabolic acidosis and others do not. Researchers suggest that in individuals with incomplete distal renal tubular acidosis, another mechanism is able to help regulate blood acidity (pH) and keep metabolic acidosis from developing.

In red blood cells, interaction with a protein called glycophorin A can often help the altered AE1 protein get to the cell membrane where it can perform its function, which explains why most people with *SLC4A1*-associated distal renal tubular acidosis do not have blood cell abnormalities. However, some altered AE1 proteins cannot be helped by glycophorin A and are not found in the cell membrane. Without AE1, the red blood cells are unstable; breakdown of these abnormal red blood cells may lead to hemolytic anemia.

Some people have nonhereditary forms of distal renal tubular acidosis; these forms can be caused by immune system problems or other conditions that damage the kidneys. These individuals often have additional signs and symptoms related to the original

condition.

Learn more about the gene associated with SLC4A1-associated distal renal tubular acidosis

- SLC4A1

## **Inheritance**

*SLC4A1*-associated distal renal tubular acidosis can have different patterns of inheritance. It is usually inherited in an autosomal dominant pattern, which means one copy of the altered *SLC4A1* gene in each cell is sufficient to cause the disorder. In most cases, an affected person inherits the mutation from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

Less commonly, *SLC4A1*-associated distal renal tubular acidosis has an autosomal recessive pattern of inheritance, which means a mutation must occur in both copies of the *SLC4A1* gene for the condition to develop. This pattern occurs with certain types of *SLC4A1* gene mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

## **Other Names for This Condition**

- Classic distal renal tubular acidosis
- Renal tubular acidosis type I
- RTA, classic type

## **Additional Information & Resources**

### Genetic Testing Information

- Genetic Testing Registry: Autosomal dominant distal renal tubular acidosis (<https://www.ncbi.nlm.nih.gov/gtr/conditions/CN280572/>)

### Genetic and Rare Diseases Information Center

- SLC4A1-associated distal renal tubular acidosis (<https://rarediseases.info.nih.gov/diseases/12355/index>)

### Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (<https://rarediseases.org/>)

### Catalog of Genes and Diseases from OMIM

- RENAL TUBULAR ACIDOSIS, DISTAL, 1; DRTA1 (<https://omim.org/entry/179800>)
- RENAL TUBULAR ACIDOSIS, DISTAL, 4, WITH HEMOLYTIC ANEMIA; DRTA4 (<https://omim.org/entry/611590>)

### Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28Acidosis,+Renal+Tubular%5BMAJR%5D%29+AND+%28distal+renal+tubular+acidosis%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D>)

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