SLC4A1 gene

solute carrier family 4 member 1 (Diego blood group)

Normal Function

The *SLC4A1* gene provides instructions for making a protein known as anion exchanger 1 (AE1). This protein 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). Based on this function, AE1 is known as a chloride/bicarbonate exchanger (Cl^-/HCO_3^- exchanger). The main function of this exchanger is to maintain the correct acid levels (pH) in the body.

There are two versions of the AE1 protein that differ in size. The shorter version is found in specialized kidney cells, called alpha-intercalated cells, that line structures in the kidney called renal tubules. The renal tubules reabsorb substances that are needed and eliminate unneeded substances in urine. Specifically, alpha-intercalated cells release acid into the urine to be removed from the body. In alpha-intercalated cells, the exchange of bicarbonate through the AE1 protein allows acid to be released from the cell into the urine.

The longer version of AE1 is found in red blood cells. In addition to exchanging ions, the longer AE1 protein attaches to other proteins that make up the structural framework (the cytoskeleton) of red blood cells, helping to maintain their structure. In red blood cells, the AE1 protein can interact with another protein called glycophorin A, which helps ensure AE1 gets moved (trafficked) to the correct location of the cell. Glycophorin A is not found in kidney cells.

Health Conditions Related to Genetic Changes

SLC4A1-associated distal renal tubular acidosis

At least 18 *SLC4A1* gene mutations have been found to cause *SLC4A1*-associated distal renal tubular acidosis, a kidney (renal) disorder that leads to the buildup of acid in the blood (metabolic acidosis). Some people with this condition also have blood cell abnormalities, such as hereditary spherocytosis, hereditary stomatocytosis, or Southeast Asian ovalocytosis (described below). The blood cell abnormalities can lead to hemolytic anemia, in which the abnormal red blood cells are prematurely broken down. *SLC4A1* gene mutations cause both autosomal dominant and autosomal

recessive forms of *SLC4A1*-associated distal renal tubular acidosis.

The *SLC4A1* gene mutations involved in *SLC4A1*-associated distal renal tubular acidosis lead to production of altered AE1 proteins that are either stuck inside the cell or trafficked to the wrong side of the cell. 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 correct part of the cell membrane. In autosomal recessive *SLC4A1*-associated 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 trafficked correctly. 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, leading to metabolic acidosis. The inability to remove acid from the body also leads to the other features of distal renal tubular acidosis, including soft, weak bones; calcium deposits in the kidneys; and kidney stones.

Studies suggest that with the help of glycophorin A, the altered AE1 protein can often get to the cell membrane in red blood cells, 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 trafficked to red blood cell membranes. Without AE1, the red blood cells are unstable; breakdown of these abnormal red blood cells may lead to hemolytic anemia.

Hereditary spherocytosis

Mutations in the *SLC4A1* gene can cause a blood disorder called hereditary spherocytosis. This condition has an autosomal dominant inheritance pattern, which means a mutation in one copy of the *SLC4A1* gene is sufficient to cause the disorder.

The mutations involved in hereditary spherocytosis lead to a reduction of AE1 protein, which results in abnormal red blood cells that are round and spherical rather than a flattened disk shape and are more fragile than usual. The abnormal cells are prematurely broken down, causing hemolytic anemia. Other features of hereditary spherocytosis, resulting from the breakdown of red blood cells, include yellowing of the skin and whites of the eyes (jaundice), gallstones, and an enlarged spleen (splenomegaly).

Other disorders

Mutations in the *SLC4A1* gene can cause other blood disorders, including hereditary stomatocytosis and Southeast Asian ovalocytosis. As in hereditary spherocytosis (described above), these conditions have an autosomal dominant inheritance pattern, which means a mutation in one copy of the *SLC4A1* gene is sufficient to cause the disorder.

Hereditary stomatocytosis is characterized by abnormally shaped red blood cells that resemble a mouth or "stoma". This condition is caused by an abnormal AE1 protein that allows positively charged molecules of sodium (Na^+) and potassium (K^+) to leak out of

the cell. As a result, the red blood cells are unstable and are broken down more quickly than usual, leading to hemolytic anemia and related features.

Southeast Asian ovalocytosis is a blood disorder most common in regions where malaria is prevalent, primarily Southeast Asian countries including Thailand and Malaysia. The mutation that causes this disorder, often referred to as the SAO mutation, deletes nine protein building blocks (amino acids) in the AE1 protein. This change leads to a reduction of AE1 on the surface of red blood cells; as a result, the cells are unusually rigid and oval-shaped. The abnormal cells typically do not cause any health problems in affected individuals. Research indicates that Southeast Asian ovalocytosis, which is caused by a mutation in one copy of the *SLC4A1* gene, protects against severe neurological complications of malaria. However, having the SAO mutation in both copies of the gene is likely lethal before birth.

While a shortage of the AE1 protein in the cell membrane affects the structure of red blood cells in these blood disorders, researchers speculate that enough normal AE1 protein remains in kidney cells for anion exchange and acid release, so affected individuals do not develop distal renal tubular acidosis (described above).

Other Names for This Gene

- AE1
- anion exchange protein 1
- anion exchanger 1
- anion exchanger-1
- band 3 anion transport protein
- BND3
- CD233
- DI
- Diego blood group
- EMPB3
- EPB3
- erythrocyte membrane protein band 3
- erythroid anion exchange protein
- FR
- Froese blood group
- RTA1A
- solute carrier family 4 (anion exchanger), member 1 (Diego blood group)
- solute carrier family 4, anion exchanger, member 1 (erythrocyte membrane protein band 3, Diego blood group)
- solute carrier family 4, anion exchanger, number 1
- SW

- Swann blood group
- Waldner blood group
- WD
- WD1
- WR
- Wright blood group

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of SLC4A1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=6521[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28SLC4A1%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- SOLUTE CARRIER FAMILY 4 (ANION EXCHANGER), MEMBER 1; SLC4A1 (https://omim.org/entry/109270)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/6521)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=SLC4A1[gene])

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Genomic Location

The *SLC4A1* gene is found on chromosome 17 (https://medlineplus.gov/genetics/chromosome/17/).

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