CLCNKB Gene

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1. Normal Function

The *CLCNKB* gene belongs to the CLC family of genes, which provide instructions for making chloride channels. These channels, which transport negatively charged chlorine atoms (chloride ions), play a key role in a cell's ability to generate and transmit electrical signals. Some CLC channels regulate the flow of chloride ions across cell membranes, while others transport chloride ions within cells.

The *CLCNKB* gene provides instructions for making a chloride channel called ClC-Kb. These channels are found predominantly in the kidneys. ClC-Kb is one of several proteins that work together to regulate the movement of ions into and out of kidney cells. The transport of chloride ions by ClC-Kb channels is part of the mechanism by which the kidneys reabsorb salt (sodium chloride or NaCl) from the urine back into the bloodstream. The retention of salt affects the body's fluid levels and helps maintain blood pressure.

ClC-Kb channels are also located in the inner ear, where they play a role in normal hearing.

2. Health Conditions Related to Genetic Changes

2.1. Bartter Syndrome

More than 30 mutations in the *CLCNKB* gene have been identified in people with Bartter syndrome type III. This form of the condition, which is also described as classical Bartter syndrome, begins in childhood and tends to be less severe than other types of Bartter syndrome.

Many of the mutations responsible for Bartter syndrome type III delete the entire *CLCNKB* gene. Other mutations change single protein building blocks (amino acids) in the ClC-Kb channel or lead to an abnormally short, nonfunctional version of ClC-Kb. A loss of functional ClC-Kb channels impairs the transport of chloride ions in the kidneys. As a result, the kidneys cannot reabsorb salt normally and excess salt is lost through the urine (salt wasting). The abnormal salt loss disrupts the normal balance of ions in the body. This imbalance underlies many of the major features of Bartter syndrome type III.

Several people with a more severe form of Bartter syndrome have had mutations in both the *CLCNKB* gene and a closely related gene called *CLCNKA*. The *CLCNKA* gene provides instructions for making a very similar chloride channel, ClC-Ka, that is also found in the kidneys and inner ear. A combination of *CLCNKA* and *CLCNKB* gene mutations causes a life-threatening form of the disorder known as Bartter syndrome type IV or antenatal Bartter syndrome with sensorineural deafness. In addition to salt wasting, this form of the disorder is characterized by hearing loss that results from a loss of ClC-Ka and ClC-Kb function in the inner ear.

2.2. Gitelman Syndrome

Mutations in the *CLCNKB* gene are a rare cause of Gitelman syndrome. Like the mutations responsible for Bartter syndrome, the genetic changes associated with Gitelman syndrome impair the kidneys' ability to reabsorb salt, leading to salt wasting. Abnormalities of salt transport also affect the reabsorption of other ions, including ions of potassium, magnesium, and calcium. The resulting imbalance of ions in the body leads to the characteristic features of Gitelman syndrome.

2.3. Other Disorders

A common variation (polymorphism) in the *CLCNKB* gene has been associated with salt-sensitive hypertension, a form of high blood pressure related to increased levels of salt in the blood. The polymorphism replaces the amino acid threonine with the amino acid serine at position 481 in the ClC-Kb channel (also written as Thr481Ser or T481S). This genetic change increases the activity of the ClC-Kb channel, which directs the kidneys to reabsorb more salt into the bloodstream. The excess salt raises blood pressure and increases the risk of developing hypertension.

3. Other Names for This Gene

- chloride channel Kb
- chloride channel protein ClC-Kb
- chloride channel, kidney, B
- chloride channel, voltage-sensitive Kb
- ClC-K2
- ClC-Kb
- CLCKB
- CLCKB_HUMAN
- hClC-Kb

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