CYP24A1 gene

cytochrome P450 family 24 subfamily A member 1

Normal Function

The *CYP24A1* gene provides instructions for making an enzyme called 24-hydroxylase. This enzyme helps control the amount of active vitamin D available in the body. When active, vitamin D is involved in maintaining the proper balance of several minerals in the body, including calcium and phosphate, which are essential for the normal formation of bones and teeth. One of vitamin D's major roles is to control the absorption of calcium and phosphate from the intestines into the bloodstream. Vitamin D is also involved in several processes in addition to bone and tooth formation.

The 24-hydroxylase enzyme breaks down the active form of vitamin D, called 1,25-dihydroxyvitamin D_3 or calcitriol, to an inactive form when the vitamin is no longer needed. The enzyme also breaks down 25-hydroxyvitamin D (also known as calcidiol), which is the form of vitamin D that is stored in the body.

Health Conditions Related to Genetic Changes

Idiopathic infantile hypercalcemia

More than 20 mutations in the *CYP24A1* gene have been found to cause a type of idiopathic infantile hypercalcemia called infantile hypercalcemia 1, which is characterized by high levels of calcium in the blood (hypercalcemia) and urine (hypercalciuria) and deposits of calcium in the kidneys (nephrocalcinosis). The hypercalcemia typically causes vomiting, poor feeding, and an inability to grow and gain weight at the expected rate (failure to thrive) in infancy, although some affected individuals do not develop signs and symptoms of the condition until adulthood. Features in affected adults, whether they had symptoms in infancy or not, typically include hypercalciuria, nephrocalcinosis, and kidney stones (nephrolithiasis), although they may not cause any obvious health problems.

The *CYP24A1* gene mutations that cause infantile hypercalcemia 1 reduce or eliminate the activity of the 24-hydroxylase enzyme. A shortage of this enzyme's function impairs the breakdown of calcitriol. The resulting excess of calcitriol increases calcium absorption into the bloodstream, causing hypercalcemia. Dysregulation of calcium absorption in the kidneys leads to hypercalciuria, nephrocalcinosis, and nephrolithiasis.

Idiopathic infantile hypercalcemia is a condition characterized by high levels of calcium in the blood (hypercalcemia). Two types of idiopathic infantile hypercalcemia have been identified and are distinguished by their genetic causes: infantile hypercalcemia 1 and infantile hypercalcemia 2. In infants with either type, hypercalcemia can cause vomiting, increased urine production (polyuria), dehydration, constipation, poor feeding, weight loss, and an inability to grow and gain weight as expected (failure to thrive). As they age, affected babies usually have delayed development of mental and movement abilities (psychomotor delay). Individuals with infantile hypercalcemia 1 or 2 may also have high levels of calcium in their urine (hypercalciuria) and deposits of calcium in their kidneys (nephrocalcinosis). With treatment, the outward symptoms of hypercalcemia, such as vomiting, dehydration, failure to thrive, and psychomotor delay, usually improve in childhood. However, affected children still tend to have higher-than-normal amounts of calcium in their blood and urine and calcium deposits in their kidneys. By adulthood, long-term hypercalcemia and hypercalciuria can lead to the formation of kidney stones (nephrolithiasis) and may damage the kidneys and impair their function. Affected adults may also develop calcium deposits in the joints or in the clear outer covering of the eye (the cornea), and some have low bone mineral density (osteoporosis).

In rare cases, affected individuals do not have symptoms of hypercalcemia in infancy, and the condition begins in later childhood or adulthood. These individuals usually develop hypercalciuria, nephrocalcinosis, and nephrolithiasis, although the features may not cause any obvious health problems.

Although most signs and symptoms are similar between the two known types of idiopathic infantile hypercalcemia, individuals with infantile hypercalcemia 2 have low levels of a mineral called phosphate in the blood (hypophosphatemia), while phosphate levels are typically normal in people with infantile hypercalcemia 1.

Infantile hypercalcemia 1 and 2 are thought to be rare conditions, although their prevalence is unknown.

The two known types of idiopathic infantile hypercalcemia are caused by mutations in different genes. Infantile hypercalcemia 1 is caused by *CYP24A1* gene mutations, and infantile hypercalcemia 2 is caused by *SLC34A1* gene mutations. Both genes help maintain the proper balance of calcium or phosphate in the body, a process that can involve vitamin D. When turned on (active), this vitamin stimulates the absorption of both phosphate and calcium from the intestines into the bloodstream. Vitamin D can be acquired from foods in the diet or made in the body with help from sunlight exposure.

The enzyme produced from the *CYP24A1* gene helps control the amount of active vitamin D in the body. This enzyme, called 24-hydroxylase, helps break down active vitamin D when it is no longer needed, for example when the proper balance of calcium or phosphate in the body is reached. Mutations in the *CYP24A1* gene reduce or eliminate the activity of the 24-hydroxylase enzyme, which impairs the breakdown of active vitamin D.

The amount of phosphate in the body can also be maintained through reabsorption of the mineral in the kidneys so that it is not removed in urine. Reabsorption occurs by transport of the mineral through special channels formed from a protein called sodium-dependent phosphate transporter 2A (NaPi-IIa), which is produced from the *SLC34A1* gene. Mutations in the *SLC34A1* gene prevent the NaPi-IIa channels from transporting phosphate, reducing the amount of phosphate in the body. To increase phosphate levels, vitamin D is activated.

Mutations in either the *CYP24A1* or *SLC34A1* gene result in too much active vitamin D in the body. This excess increases calcium absorption into the bloodstream, causing hypercalcemia. The abnormal balance of calcium leads to high levels of the mineral in urine and can result in deposition of calcium in the kidneys and the formation of kidney stones.

It is thought that other factors, such as the amount of calcium in the diet, vitamin D supplementation, or prolonged sunlight exposure can influence the development and severity of signs and symptoms in affected individuals.

Some people with idiopathic infantile hypercalcemia do not have mutations in the *CYP24A1* or *SLC34A1* gene. The cause of the condition in these cases is unknown. Other genes that have not been identified may be involved in development of the condition.

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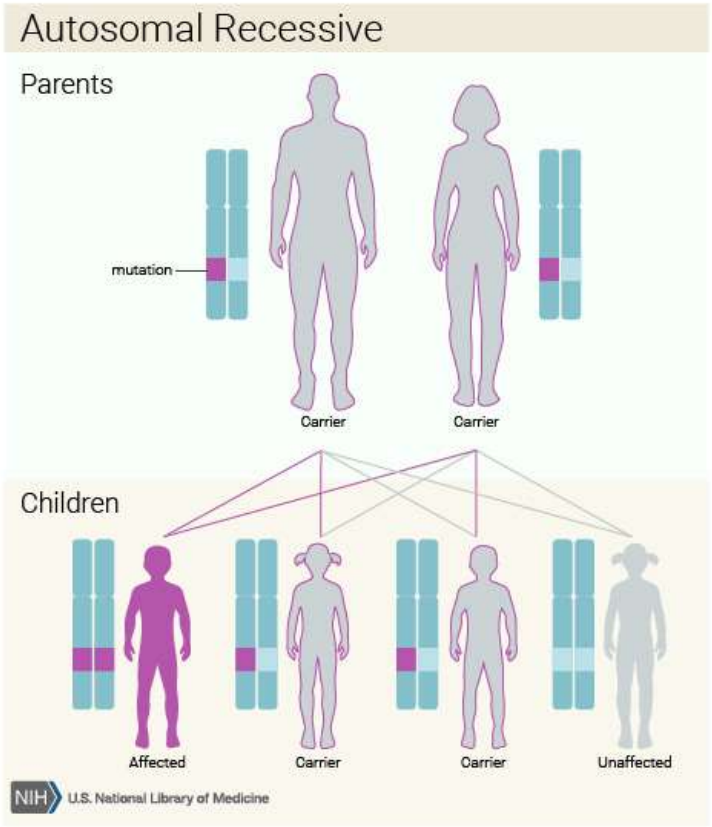
Infantile hypercalcemia types 1 and 2 are thought to be inherited in an autosomal recessive pattern, which means both copies of the respective gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. In some instances, individuals with one copy of the mutated gene have higher-than-normal levels of calcium in their blood or urine and may be more likely to develop kidney stones, but they do not typically have early, severe symptoms of infantile hypercalcemia 1 or 2. Nongenetic factors, such as the amount of calcium in the diet, vitamin D supplementation, or prolonged sunlight exposure, may influence whether signs and symptoms develop in individuals with one altered copy of the gene.



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