CASR Gene

Subjects: Genetics & Heredity
Contributor: Vicky Zhou

calcium sensing receptor

genes

1. Normal Function

The *CASR* gene provides instructions for making a protein called the calcium-sensing receptor (CaSR). Calcium molecules attach (bind) to CaSR, which allows this protein to monitor and regulate the amount of calcium in the blood. The receptor is turned on (activated) when a certain concentration of calcium is reached, and the activated receptor sends signals to block processes that increase the amount of calcium in the blood.

The CaSR protein is found in abundance in cells of the parathyroid glands. The parathyroid glands produce and release a hormone called parathyroid hormone that works to increase the levels of calcium in the blood. When large amounts of calcium bind to CaSR in the parathyroid glands, the production of parathyroid hormone is blocked, which prevents the release of more calcium into the blood. CaSR signaling also blocks the growth and division (proliferation) of cells that make up the parathyroid glands.

The CaSR protein is also found in kidney cells. Kidneys filter fluid and waste products in the body and can reabsorb needed nutrients and release them back into the blood. Increased calcium binding to CaSR in kidney cells blocks the reabsorption of calcium from the filtered fluids.

2. Health Conditions Related to Genetic Changes

2.1. Autosomal Dominant Hypocalcemia

Mutations in the *CASR* gene can cause a condition called autosomal dominant hypocalcemia type 1, which is characterized by low levels of calcium in the blood (hypocalcemia). Some affected individuals also have a shortage of parathyroid hormone (hypoparathyroidism).

Most *CASR* gene mutations involved in this condition change single protein building blocks (amino acids) in the CaSR protein. The changes (called activating mutations) lead to an overactive CaSR that is more sensitive to calcium, meaning even low levels of calcium can trigger signaling. The overactive CaSR blocks the release of parathyroid hormone, which prevents the release of calcium into the blood. In addition, the overactive CaSR

prevents reabsorption of calcium from the fluids filtered through the kidneys. Hypocalcemia can cause muscle cramping and seizures, although about half of people with this condition have no associated health problems.

2.2. Familial Isolated Hyperparathyroidism

Mutations in the *CASR* gene have been found in some people with familial isolated hyperparathyroidism, a condition characterized by overactivity of the parathyroid glands (primary hyperparathyroidism). Primary hyperparathyroidism disrupts the normal balance of calcium in the blood, which can lead to kidney stones, thinning of the bones (osteoporosis), nausea, vomiting, high blood pressure (hypertension), weakness, and fatigue in people with familial isolated hyperparathyroidism. This condition is caused by changes to one copy of the gene in each cell. The *CASR* gene mutations associated with this condition change single amino acids in the CaSR protein. These genetic changes are called inactivating mutations because the altered CaSR protein is less sensitive to calcium and therefore requires an abnormally high concentration of calcium to trigger signaling. As a result, parathyroid hormone is produced even when the concentration of calcium in the blood is elevated, allowing the calcium levels to continue to rise. In addition, parathyroid cells may proliferate without control, which occasionally causes enlargement of the parathyroid glands in people with familial isolated hyperparathyroidism. Overproduction of parathyroid hormone from these abnormal glands may further stimulate the release of calcium into the blood. The high levels of calcium cause the signs and symptoms of familial isolated hyperparathyroidism.

Some researchers believe that familial isolated hyperparathyroidism caused by *CASR* gene mutations is a more severe form of a similar condition called familial hypocalciuric hypercalcemia (described below).

2.3. Kidney Stones

Kidney stones

2.4. Other Disorders

Mutations in the *CASR* gene are involved in several other conditions associated with abnormal calcium levels. Inactivating mutations that lead to a reduction in CaSR function can cause familial hypocalciuric hypercalcemia. This condition is characterized by high levels of calcium in the blood (hypercalcemia) and low levels of calcium in the urine (hypocalciuria), but affected individuals typically have no symptoms related to the condition. Rarely, affected individuals have enlarged parathyroid glands and slightly elevated levels of parathyroid hormone. Like familial isolated hyperparathyroidism, this condition is caused by mutation of a single copy of the *CASR* gene.

A more serious condition called neonatal severe hyperparathyroidism is caused by genetic mutations that lead to very little or no CaSR function. In people with this condition, both copies of the *CASR* gene are altered. Neonatal severe hyperparathyroidism is a potentially fatal condition that becomes apparent in infants under the age of 6 months. Affected babies often have overgrowth of one or more of their parathyroid glands (parathyroid hyperplasia), causing high levels of parathyroid hormone in their blood. The excess hormone abnormally stimulates the release of calcium into the blood, causing hypercalcemia. The calcium is often removed from bone, resulting in

skeletal abnormalities. The extreme hypercalcemia in these individuals can lead to neurological problems because the excess calcium interferes with nerve signaling.

3. Other Names for This Gene

- calcium-sensing receptor
- CAR
- extracellular calcium-sensing receptor
- GPRC2A
- parathyroid Ca(2+)-sensing receptor 1
- parathyroid cell calcium-sensing receptor
- PCAR1

References

1. Carling T, Szabo E, Bai M, Ridefelt P, Westin G, Gustavsson P, Trivedi S,Hellman P, Brown EM, Dahl N, Rastad J. Familial hypercalcemia and hypercalciuria caused by a novel mutation in the cytoplasmic tail of the calcium receptor. JClin Endocrinol Metab. 2000 May;85(5):2042-7.
2. Hannan FM, Nesbit MA, Christie PT, Lissens W, Van der Schueren B, Bex M,Bouillon R, Thakker RV. A homozygous inactivating calcium-sensing receptormutation, Pro339Thr, is associated with isolated primary hyperparathyroidism:correlation between location of mutations and severity of hypercalcaemia. ClinEndocrinol (Oxf). 2010 Dec;73(6):715-22. doi: 10.1111/j.1365-2265.2010.03870.x.
3. Hendy GN, Guarnieri V, Canaff L. Calcium-sensing receptor and associateddiseases. Prog Mol Biol Transl Sci. 2009;89:31-95. doi:10.1016/S1877-1173(09)89003-0.
4. Kinoshita Y, Hori M, Taguchi M, Watanabe S, Fukumoto S. Functional activities of mutant calcium-sensing receptors determine clinical presentations in patients with autosomal dominant hypocalcemia. J Clin Endocrinol Metab. 2014Feb;99(2):E363-8. doi: 10.1210/jc.2013-3430.
5. Ranieri M, Tamma G, Di Mise A, Vezzoli G, Soldati L, Svelto M, Valenti G.Excessive signal transduction of gain-of-function variants of the calcium-sensingreceptor (CaSR) are associated with increased ER to cytosol calcium gradient.PLoS One. 2013 Nov 14;8(11):e79113. doi: 10.1371/journal.pone.0079113.
6. Raue F, Pichl J, Dörr HG, Schnabel D, Heidemann P, Hammersen G, Jaursch-HanckeC, Santen R, Schöfl C, Wabitsch M, Haag C, Schulze E, Frank-Raue K. Activatingmutations in the calcium-sensing receptor: genetic and clinical spectrum in 25patients with autosomal dominant hypocalcaemia - a German survey. Clin Endocrinol(Oxf). 2011 Dec;75(6):760-5. doi: 10.1111/j.1365-2265.2011.04142.x.

7. Thim SB, Birkebaek NH, Nissen PH, Høst C. Activating calcium-sensing receptor gene variants in children: a case study of infant hypocalcaemia and literaturereview. Acta Paediatr. 2014 Nov;103(11):1117-25. doi: 10.1111/apa.12743.
8. Warner J, Epstein M, Sweet A, Singh D, Burgess J, Stranks S, Hill P,Perry-Keene D, Learoyd D, Robinson B, Birdsey P, Mackenzie E, Teh BT, Prins JB,Cardinal J. Genetic testing in familial isolated hyperparathyroidism: unexpected results and their implications. J Med Genet. 2004 Mar;41(3):155-60.