CACNA1F Gene

Subjects: Genetics & Heredity
Contributor: Vicky Zhou

calcium voltage-gated channel subunit alpha1 F

Keywords: genes

1. Normal Function

The *CACNA1F* gene belongs to a family of genes that provide instructions for making calcium channels. These channels, which transport positively charged calcium atoms (calcium ions) across cell membranes, play a key role in a cell's ability to generate and transmit electrical signals.

The *CACNA1F* gene provides instructions for making one part (the alpha-1 subunit) of a calcium channel called CaV1.4. This subunit forms the hole (pore) in the cell membrane through which calcium ions can flow. CaV1.4 channels are found in many types of cells, although they play a particularly important role in a specialized tissue at the back of the eye called the retina. Within the retina, the channels are located in light-detecting cells called photoreceptors. The retina contains two types of photoreceptors: rods and cones. Rods are responsible for vision in low light. Cones provide vision in bright light, including color vision.

CaV1.4 channels appear to play a critical role in normal vision. Studies suggest they help relay visual signals from rods and cones to other retinal cells called bipolar cells. This signaling is an essential step in the transmission of visual information from the eyes to the brain.

2. Health Conditions Related to Genetic Changes

2.1. X-Linked Congenital Stationary Night Blindness

More than 70 mutations in the *CACNA1F* gene have been identified in people with X-linked congenital stationary night blindness. Mutations in this gene are responsible for the incomplete form of the disorder, which is characterized by vision problems including a loss of sharpness (reduced acuity), nearsightedness (myopia), involuntary movements of the eyes (nystagmus), and eyes that do not look in the same direction (strabismus). Many affected individuals also have difficulty seeing in low light (night blindness).

CACNA1F mutations change the structure of the alpha-1 subunit, which alters or eliminates the function of CaV1.4 channels. These changes prevent the normal transport of calcium ions across the cell membrane of photoreceptor cells. A loss of calcium ion transport disrupts the ability of both rods and cones to transmit visual signals, which impairs vision.

2.2. Cone-Rod Dystrophy

Cone-rod dystrophy

2.3. Other Disorders

Mutations in the *CACNA1F* gene cause several other rare disorders that impair vision. These include Åland Island eye disease, X-linked cone-rod dystrophy, an X-linked retinal disorder in New Zealand, and retinal and optic disc atrophy. Each of these disorders has been reported in only a few individuals or families worldwide. They cause vision problems similar to those of X-linked congenital stationary night blindness.

Researchers have identified at least one *CACNA1F* mutation that can cause Åland Island eye disease (also known as Forsius-Eriksson syndrome). This condition was first described in a family from the Åland Islands, which are in the Baltic Sea off the coast of Sweden. Åland Island eye disease is characterized by reduced visual acuity, nystagmus, an irregular curvature of the front part of the eye (astigmatism), myopia, abnormal color vision, and night blindness. The mutation

associated with this disorder deletes a segment of genetic material from the *CACNA1F* gene, which significantly alters the structure of the alpha-1 subunit of CaV1.4 channels. These changes prevent the normal transport of calcium ions across the cell membrane of photoreceptor cells. A loss of calcium ion transport disrupts the ability of both rods and cones to transmit visual signals.

At least one other *CACNA1F* mutation is responsible for X-linked cone-rod dystrophy (also known as CORDX3). The signs and symptoms of this condition include reduced visual acuity, an increased sensitivity to light (photophobia), myopia, and impaired color vision. These vision problems tend to worsen over time. The mutation associated with this disorder deletes part of the alpha-1 subunit, which likely prevents the production of functional CaV1.4 channels. A loss of these channels keeps photoreceptor cells from relaying visual signals normally, which leads to impaired vision.

A *CACNA1F* mutation has also been found to cause an X-linked retinal disorder in a large Maori family from New Zealand. The major features of this disorder include reduced visual acuity, abnormal color vision, photophobia, and mild nystagmus. Some affected individuals have also had intellectual disability. The *CACNA1F* mutation associated with this condition alters a single protein building block (amino acid) in the alpha-1 subunit, which appears to overactivate CaV1.4 channels. The resulting increase in calcium ion transport probably disrupts the transmission of visual signals in the retina.

Another eye disorder, known as retinal and optic disc atrophy, has been associated with a *CACNA1F* mutation in two Japanese brothers. The affected individuals experienced a progressive decline in visual acuity and color vision. These vision problems were caused by deterioration of the retina, including an area called the optic disc (which is where the retina connects with the nerve that relays visual information to the brain). The *CACNA1F* mutation responsible for retinal and optic disc atrophy alters the structure of the alpha-1 subunit, which probably leads to the production of nonfunctional CaV1.4 channels. This mutation has also been identified in at least one Japanese family with X-linked congenital stationary night blindness. It is unclear why this single genetic change can cause different vision abnormalities in different families.

3. Other Names for This Gene

- AIED
- CAC1F_HUMAN
- calcium channel, voltage-dependent, L type, alpha 1F subunit
- Cav1.4
- Cav1.4alpha1
- COD3
- COD4
- CORDX
- CORDX3
- CSNB2
- CSNB2A
- CSNBX2
- JM8
- JMC8
- OA2

References

1. Bech-Hansen NT, Naylor MJ, Maybaum TA, Pearce WG, Koop B, Fishman GA, Mets M, Musarella MA, Boycott KM. Loss-of-function mutations in a calcium-channelalpha1-subunit gene in Xp11.23 cause incomplete X-linked congenital stationarynight blindness. Nat Genet. 1998 Jul;19(3):264-7.
2. Boycott KM, Maybaum TA, Naylor MJ, Weleber RG, Robitaille J, Miyake Y, Bergen AA, Pierpont ME, Pearce WG, Bech-Hansen NT. A summary of 20 CACNA1F mutationsidentified in 36 families with incomplete X-linked congenital stationary nightblindness, and characterization of splice variants. Hum Genet. 2001Feb;108(2):91-7.
3. Doering CJ, Peloquin JB, McRory JE. The Ca(v)1.4 calcium channel: more thanmeets the eye. Channels (Austin). 2007 Jan-Feb;1(1):3-10.Review.
4. Hemara-Wahanui A, Berjukow S, Hope CI, Dearden PK, Wu SB, Wilson-Wheeler J,Sharp DM, Lundon-Treweek P, Clover GM, Hoda JC, Striessnig J, Marksteiner R,Hering S, Maw MA. A CACNA1F mutation identified in an X-linked

retinal disordershifts the voltage dependence of Cav1.4 channel activation. Proc Natl Acad Sci U S A. 2005 May 24;102(21):7553-8.

5. Hoda JC, Zaghetto F, Koschak A, Striessnig J. Congenital stationary nightblindness type 2 mutations S229P, G369D, L1068P, and W1440X alter channel gating or functional expression of Ca(v)1.4 L-type Ca2+ channels. J Neurosci. 2005 Jan5;25(1):252-9.
6. Hoda JC, Zaghetto F, Singh A, Koschak A, Striessnig J. Effects of congenitalstationary night blindness type 2 mutations R508Q and L1364H on Cav1.4 L-typeCa2+ channel function and expression. J Neurochem. 2006 Mar;96(6):1648-58.
7. Hope CI, Sharp DM, Hemara-Wahanui A, Sissingh JI, Lundon P, Mitchell EA, MawMA, Clover GM. Clinical manifestations of a unique X-linked retinal disorder in alarge New Zealand family with a novel mutation in CACNA1F, the gene responsiblefor CSNB2. Clin Exp Ophthalmol. 2005 Apr;33(2):129-36.
8. Jalkanen R, Bech-Hansen NT, Tobias R, Sankila EM, Mäntyjärvi M, Forsius H, de la Chapelle A, Alitalo T. A novel CACNA1F gene mutation causes Aland Island eyedisease. Invest Ophthalmol Vis Sci. 2007 Jun;48(6):2498-502.
9. Jalkanen R, Mäntyjärvi M, Tobias R, Isosomppi J, Sankila EM, Alitalo T,Bech-Hansen NT. X linked cone-rod dystrophy, CORDX3, is caused by a mutation inthe CACNA1F gene. J Med Genet. 2006 Aug;43(8):699-704.
10. McRory JE, Hamid J, Doering CJ, Garcia E, Parker R, Hamming K, Chen L,Hildebrand M, Beedle AM, Feldcamp L, Zamponi GW, Snutch TP. The CACNA1F geneencodes an L-type calcium channel with unique biophysical properties and tissuedistribution. J Neurosci. 2004 Feb 18;24(7):1707-18.
11. Nakamura M, Ito S, Piao CH, Terasaki H, Miyake Y. Retinal and optic discatrophy associated with a CACNA1F mutation in a Japanese family. Arch Ophthalmol.2003 Jul;121(7):1028-33.
12. Peloquin JB, Rehak R, Doering CJ, McRory JE. Functional analysis of congenitalstationary night blindness type-2 CACNA1F mutations F742C, G1007R, and R1049W.Neuroscience. 2007 Dec 5;150(2):335-45.
13. Strom TM, Nyakatura G, Apfelstedt-Sylla E, Hellebrand H, Lorenz B, Weber BH,Wutz K, Gutwillinger N, Rüther K, Drescher B, Sauer C, Zrenner E, Meitinger T,Rosenthal A, Meindl A. An L-type calcium-channel gene mutated in incompleteX-linked congenital stationary night blindness. Nat Genet. 1998 Jul;19(3):260-3.
14. Wutz K, Sauer C, Zrenner E, Lorenz B, Alitalo T, Broghammer M, Hergersberg M, de la Chapelle A, Weber BH, Wissinger B, Meindl A, Pusch CM. Thirty distinctCACNA1F mutations in 33 families with incomplete type of XLCSNB and Cacna1fexpression profiling in mouse retina. Eur J Hum Genet. 2002 Aug;10(8):449-56.
