CACNA1A gene

calcium voltage-gated channel subunit alpha1 A

Normal Function

The *CACNA1A* 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. Calcium ions are involved in many different cellular functions, including cell-to-cell communication, the tensing of muscle fibers (muscle contraction), and the regulation of certain genes.

The *CACNA1A* gene provides instructions for making one part (the alpha-1 subunit) of a calcium channel called CaV2.1. This subunit forms the hole (pore) through which calcium ions can flow. CaV2.1 channels play an essential role in communication between nerve cells (neurons) in the brain. These channels are especially abundant in neurons called Purkinje cells and granule cells. These neurons are found in the part of the brain that coordinates movement (the cerebellum) .

CaV2.1 channels help control the release of neurotransmitters, which are chemicals that relay signals from one neuron to another. Researchers believe that CaV2.1 channels are also involved in the survival of neurons and the ability of these cells to change and adapt over time (plasticity).

The *CACNA1A* gene also provides instructions for making another protein called alpha1-ACT (α1ACT). This protein acts as a transcription factor, which means it attaches (binds) to specific regions of DNA and helps control the activity of particular genes. The α1ACT protein is important for the development of neurons, especially Purkinje cells.

Near the tail end of the *CACNA1A* gene, a segment of three DNA building blocks (nucleotides) is repeated multiple times. This sequence, which is written as CAG, is called a triplet or trinucleotide repeat. The number of CAG repeats in this gene typically ranges from 4 to 18.

Health Conditions Related to Genetic Changes

Episodic ataxia

Many variants (also called mutations) in the *CACNA1A* gene have been found to cause episodic ataxia type 2 (EA2), the most common form of episodic ataxia. EA2 is

associated with episodes of poor coordination and balance (ataxia) and involuntary eye movements called nystagmus.

The *CACNA1A* variants that cause EA2 are known as loss-of-function variants because they reduce the function of CaV2.1 channels. The changes can impair the production of functional CaV2.1 channels; prevent the channels from reaching the cell membrane, where they are needed to transport calcium ions; or reduce the flow of calcium through the channels. A decrease in the total flow of calcium ions into neurons disrupts the release of neurotransmitters in the brain. Studies show that changes in CaV2.1 channels can disrupt the normal signaling of Purkinje cells. Changes in the chemical signals between neurons cause the episodes of uncoordinated movement seen in people with episodic ataxia.

Familial hemiplegic migraine

Several variants in the *CACNA1A* gene have been identified in people with familial hemiplegic migraine type 1 (FHM1). This condition is characterized by migraines with a pattern of neurological symptoms known as aura. In FHM1, the aura includes temporary numbness or weakness on one side of the body (hemiparesis). Like EA2 (described above), FHM1 is commonly associated with ataxia and nystagmus. Most of the variants that cause FHM1 change single protein building blocks (amino acids) in the CaV2.1 channel. The most common variant, known as Thr666Met or T666M, replaces the amino acid threonine with the amino acid methionine at a specific location in the CaV2.1 channel. This variant has been found in more than a dozen families.

The *CACNA1A* variants that cause familial hemiplegic migraine are called gain-of-function variants, because they increase the activity of Cav2.1 channels. The variants change the structure of the CaV2.1 channels. The altered channels open more easily than usual, which increases the inward flow of calcium ions. A greater influx of calcium ions through CaV2.1 channels increases the cell's release of neurotransmitters. The resulting changes in signaling between neurons lead to the development of severe headaches in people with familial hemiplegic migraine.

In some children with FHM1 or sporadic hemiplegic migraine (described below), minor head trauma can cause life-threatening brain swelling (cerebral edema) and coma. One of the *CACNA1A* gene variants, known as S218L, replaces the amino acid serine with the amino acid leucine at a specific location within the CaV2.1 channel. Channels with this altered subunit open even more easily than channels altered by other *CACNA1A* gene variants and take longer to close. Researchers suspect that the prolonged channel activity may lead to cellular changes that cause swelling and coma.

Spinocerebellar ataxia type 6

Spinocerebellar ataxia type 6 (SCA6) is another disorder caused by *CACNA1A* gene variants. The major features of this condition include progressive ataxia, nystagmus, and impaired speech (dysarthria), most often beginning in a person's forties or fifties. SCA6 results from an increased number of copies (expansion) of the CAG trinucleotide repeat in the *CACNA1A* gene. In people with this condition, the number of CAG repeats

ranges from 20 to more than 30.

An increase in the length of the CAG segment impairs the function of the α1ACT transcription factor. As a result, genes that direct the development of Purkinje cells in the cerebellum are not turned on when they should be, and the cells cannot survive. Over time, the loss of cells in the cerebellum leads to the movement problems characteristic of SCA6.

Sporadic hemiplegic migraine

Several variants in the *CACNA1A* gene have been found in individuals with sporadic hemiplegic migraine. The signs and symptoms of this condition are identical to those of FHM1 (described above); however, sporadic hemiplegic migraine occurs in people with no family history of the condition. As in FHM1, sporadic hemiplegic migraine caused by *CACNA1A* gene variants is commonly associated with migraines with auras, ataxia, and nystagmus.

CACNA1A gene variants that cause sporadic hemiplegic migraine are acquired during a person's lifetime and are not inherited. The variants change single amino acids in the CaV2.1 channel. Many of these variants are also found in families with FHM1. The altered channels are more active than usual, which increases the release of neurotransmitters. The abnormal signaling between neurons caused by these changes leads to the headaches and auras characteristic of sporadic hemiplegic migraine.

19p13.13 deletion syndrome

The *CACNA1A* gene is located in a region of chromosome 19 that is missing in most people with 19p13.13 deletion syndrome. As a result of this deletion, many affected individuals are missing one copy of *CACNA1A* and several other genes in each cell. Features associated with 19p13.13 deletion syndrome include an unusually large head size (macrocephaly), tall stature, intellectual disability, seizures, ataxia, and other health problems. Researchers are working to determine which missing genes contribute to the specific features of the disorder. Studies suggest that the loss of one copy of the *CACNA1A* gene may cause the seizures and ataxia seen in affected individuals. The deletion reduces the number of CaV2.1 channels produced within cells, although it is unclear exactly how a shortage of these channels is related to seizures and ataxia in people with 19p13.13 deletion syndrome.

Other disorders

Variants in the *CACNA1A* gene can also cause a form of developmental and epileptic encephalopathy, which is a group of conditions characterized by repeated seizures (epilepsy) and developmental delays. People with developmental and epileptic encephalopathy caused by *CACNA1A* gene variants often experience intellectual disability, ataxia, nystagmus, and weak muscle tone (hypotonia).

Studies suggest that some variants involved in the condition increase the activity of the CaV2.1 channels, while others reduce the activity. Researchers are working to

understand how both types of changes can lead to developmental and epileptic encephalopathy.

Other Names for This Gene

- APCA
- brain calcium channel 1
- CAC1A_HUMAN
- CACNL1A4
- calcium channel, alpha 1A subunit
- calcium channel, L type, alpha-1 polypeptide, isoform 4
- calcium channel, voltage-dependent, P/Q type, alpha 1A subunit
- CAV2.1
- HPCA
- SCA6
- Voltage-gated calcium channel subunit alpha Cav2.1

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of CACNA1A (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=773[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28CACNA1A%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+1080+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- CALCIUM CHANNEL, VOLTAGE-DEPENDENT, P/Q TYPE, ALPHA-1A SUBUNIT; CACNA1A (https://omim.org/entry/601011)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/773)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=CACNA1A[gene])

References

- Auvin S, Holder-Espinasse M, Lamblin MD, Andrieux J. Array-CGH detection of ade novo 0.7-Mb deletion in 19p13.13 including CACNA1A associated with mentalretardation and epilepsy with infantile spasms. Epilepsia. 2009Nov;50(11): 2501-3. doi: 10.1111/j.1528-1167.2009.02189.x. No abstract available. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19874387)
- de Vries B, Freilinger T, Vanmolkot KR, Koenderink JB, Stam AH, Terwindt GM, Babini E, van den Boogerd EH, van den Heuvel JJ, Frants RR, Haan J, Pusch M, vanden Maagdenberg AM, Ferrari MD, Dichgans M. Systematic analysis of three FHMgenes in 39 sporadic patients with hemiplegic migraine. Neurology. 2007 Dec4; 69(23):2170-6. doi: 10.1212/01.wnl.0000295670.01629.5a. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18056581)
- Du X, Wang J, Zhu H, Rinaldo L, Lamar KM, Palmenberg AC, Hansel C, Gomez CM.Second cistron in CACNA1A gene encodes a transcription factor mediatingcerebellar development and SCA6. Cell. 2013 Jul 3;154(1):118-33. doi:10.1016/j.cell.2013.05.059. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/23827678)
- Epi4K Consortium; Epilepsy Phenome/Genome Project; Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, Eichler EE, Epstein MP, Glauser T, Goldstein DB, Han Y, Heinzen EL, Hitomi Y, Howell KB, Johnson MR, Kuzniecky R, Lowenstein DH,Lu YF, Madou MR, Marson AG, Mefford HC, Esmaeeli Nieh S, O'Brien TJ, Ottman R,Petrovski S, Poduri A, Ruzzo EK, Scheffer IE, Sherr EH, Yuskaitis CJ, Abou-KhalilB, Alldredge BK, Bautista JF, Berkovic SF, Boro A, Cascino GD, Consalvo D,Crumrine P, Devinsky O, Dlugos D, Epstein MP, Fiol M, Fountain NB, French J,Friedman D, Geller EB, Glauser T, Glynn S, Haut SR, Hayward J, Helmers SL, JoshiS, Kanner A, Kirsch HE, Knowlton RC, Kossoff EH, Kuperman R, Kuzniecky R,Lowenstein DH, McGuire SM, Motika PV, Novotny EJ, Ottman R, Paolicchi JM, ParentJM, Park K, Poduri A, Scheffer IE, Shellhaas RA, Sherr EH, Shih JJ, Singh R,Sirven J, Smith MC, Sullivan J, Lin Thio L, Venkat A, Vining EP, Von Allmen GK,Weisenberg JL, Widdess-Walsh P, Winawer MR. De novo mutations in epilepticencephalopathies. Nature. 2013 Sep 12;501(7466):217-21. doi: 10.1038/nature12439.Epub 2013 Aug 11. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23934111) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3773011/)
- Jeng CJ, Sun MC, Chen YW, Tang CY. Dominant-negative effects of episodicataxia type 2 mutations involve disruption of membrane trafficking of humanP/Q-type Ca2+ channels. J Cell Physiol. 2008 Feb;214(2):422-33. doi:10.1002/jcp.21216. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17654512)
- Jiang X, Raju PK, D'Avanzo N, Lachance M, Pepin J, Dubeau F, Mitchell WG, Bello-Espinosa LE, Pierson TM, Minassian BA, Lacaille JC, Rossignol E. Bothgain-of-function and loss-of-function de novo CACNA1A mutations cause severedevelopmental epileptic encephalopathies in the spectrum of Lennox-Gastautsyndrome. Epilepsia. 2019 Sep;60(9):1881-1894. doi: 10.1111/epi.16316. Epub 2019Aug 29. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/31468518)

- Kors EE, Haan J, Giffin NJ, Pazdera L, Schnittger C, Lennox GG, Terwindt GM, Vermeulen FL, Van den Maagdenberg AM, Frants RR, Ferrari MD. Expanding thephenotypic spectrum of the CACNA1A gene T666M mutation: a description of 5families with familial hemiplegic migraine. Arch Neurol. 2003 May;60(5):684-8.doi: 10.1001/archneur.60.5.684. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12756131)
- Kors EE, Terwindt GM, Vermeulen FL, Fitzsimons RB, Jardine PE, Heywood P, LoveS, van den Maagdenberg AM, Haan J, Frants RR, Ferrari MD. Delayed cerebral edemaand fatal coma after minor head trauma: role of the CACNA1A calcium channelsubunit gene and relationship with familial hemiplegic migraine. Ann Neurol. 2001Jun;49(6):753-60. doi: 10.1002/ana.1031. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/11409427)
- Luo X, Rosenfeld JA, Yamamoto S, Harel T, Zuo Z, Hall M, Wierenga KJ, PastoreMT, Bartholomew D, Delgado MR, Rotenberg J, Lewis RA, Emrick L, Bacino CA,Eldomery MK, Coban Akdemir Z, Xia F, Yang Y, Lalani SR, Lotze T, Lupski JR, LeeB, Bellen HJ, Wangler MF; Members of the UDN. Clinically severe CACNA1A allelesaffect synaptic function and neurodegeneration differentially. PLoS Genet. 2017Jul 24;13(7):e1006905. doi: 10.1371/journal.pgen.1006905. eCollection 2017 Jul. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/28742085) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5557584/)
- Nimmakayalu M, Horton VK, Darbro B, Patil SR, Alsayouf H, Keppler-Noreuil K, Shchelochkov OA. Apparent germline mosaicism for a novel 19p13.13 deletiondisrupting NFIX and CACNA1A. Am J Med Genet A. 2013 May;161A(5): 1105-9. doi:10.1002/ajmg.a.35790. Epub 2013 Mar 13. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23495138)
- Rajakulendran S, Schorge S, Kullmann DM, Hanna MG. Dysfunction of the Ca(V)2. 1calcium channel in cerebellar ataxias. F1000 Biol Rep. 2010 Jan 18;2:4. doi:10. 3410/B2-4. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20948794) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2948357/)
- Riant F, Ducros A, Ploton C, Barbance C, Depienne C, Tournier-Lasserve E. Denovo mutations in ATP1A2 and CACNA1A are frequent in early-onset sporadichemiplegic migraine. Neurology. 2010 Sep 14;75(11):967-72. doi:10.1212/WNL.0b013e3181f25e8f. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20837964)
- Terwindt G, Kors E, Haan J, Vermeulen F, Van den Maagdenberg A, Frants R, Ferrari M. Mutation analysis of the CACNA1A calcium channel subunit gene in 27patients with sporadic hemiplegic migraine. Arch Neurol. 2002 Jun;59(6):1016-8. doi: 10.1001/archneur.59.6.1016. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12056940)
- Tottene A, Fellin T, Pagnutti S, Luvisetto S, Striessnig J, Fletcher C,Pietrobon D. Familial hemiplegic migraine mutations increase Ca(2+) influxthrough single human CaV2.1 channels and decrease maximal CaV2.1 current densityin neurons. Proc Natl Acad Sci U S A. 2002 Oct 1;99(20):13284-9. doi:10.1073/pnas.192242399. Epub 2002 Sep 16. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12235360)

or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC130625/)

- Tottene A, Pivotto F, Fellin T, Cesetti T, van den Maagdenberg AM, PietrobonD. Specific kinetic alterations of human CaV2.1 calcium channels produced bymutation S218L causing familial hemiplegic migraine and delayed cerebral edemaand coma after minor head trauma. J Biol Chem. 2005 May 6;280(18):17678-86. doi:10.1074/jbc.M501110200. Epub 2005 Mar 2. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/15743764)
- Wan J, Khanna R, Sandusky M, Papazian DM, Jen JC, Baloh RW. CACNA1A mutationscausing episodic and progressive ataxia alter channel trafficking and kinetics.Neurology. 2005 Jun 28;64(12):2090-7. doi: 10.1212/01.WNL.0000167409.59089.C0. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15985579)
- Zhuchenko O, Bailey J, Bonnen P, Ashizawa T, Stockton DW, Amos C, Dobyns WB, Subramony SH, Zoghbi HY, Lee CC. Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage-dependentcalcium channel. Nat Genet. 1997 Jan;15(1):62-9. doi: 10.1038/ng0197-62. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/8988170)

Genomic Location

The *CACNA1A* gene is found on chromosome 19 (https://medlineplus.gov/genetics/chromosome/19/).

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