CACNA1A Gene

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calcium voltage-gated channel subunit alpha1 A

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1. 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 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).

Near one 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. In most people, the number of CAG repeats in this gene ranges from 4 to 18.

2. Health Conditions Related to Genetic Changes

2.1. Episodic Ataxia

More than 80 mutations in the *CACNA1A* gene have been found to cause episodic ataxia type 2 (EA2), the most common form of episodic ataxia. In addition to problems with coordination and balance (ataxia), EA2 is associated with involuntary eye movements called nystagmus. The *CACNA1A* mutations responsible for EA2 reduce the production of functional CaV2.1 channels or prevent these channels from reaching the cell membrane, where they are needed to transport calcium ions. A decrease in the number of these channels reduces the total flow of calcium ions into neurons, which disrupts the release of neurotransmitters in the brain. Although changes in signaling between neurons underlie the episodes of uncoordinated movement seen in people with episodic ataxia, it is unclear how altered calcium ion transport causes the specific features of the condition.

2.2. Familial Hemiplegic Migraine

At least 20 mutations in the *CACNA1A* gene have been identified in people with familial hemiplegic migraine type 1 (FHM1). This condition is characterized by migraine headaches 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 mutations that cause FHM1 change single protein building blocks (amino acids) in the CaV2.1 channel. The most common mutation, which has been found in more than a dozen affected families, replaces the amino acid threonine with the amino acid methionine at protein position 666 (written as Thr666Met or T666M).

The *CACNA1A* mutations responsible for familial hemiplegic migraine change the structure of the CaV2.1 channel. 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 development of these severe headaches in people with familial hemiplegic migraine.

2.3. Spinocerebellar Ataxia Type 6

Spinocerebellar ataxia type 6 (SCA6) is another disorder caused by *CACNA1A* gene mutations. 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 CAG segment is repeated from 20 to more than 30 times.

An increase in the length of the CAG segment leads to the production of an abnormally long version of the alpha-1 subunit. The abnormal subunit is found in the cell membrane as well as in the fluid inside cells (cytoplasm), where it forms clumps (aggregates). The effect these aggregates have on cell functioning is unknown. The lack of normal calcium channels impairs the cells' ability to transport calcium ions. These changes alter the release of neurotransmitters in the brain and eventually lead to the death of neurons. Certain neurons called Purkinje cells seem to be particularly sensitive to a disruption in calcium transport. Purkinje cells are located in the part of the brain that coordinates movement (cerebellum). Over time, the loss of Purkinje cells and other cells of the cerebellum causes the movement problems characteristic of SCA6.

2.4. Sporadic Hemiplegic Migraine

At least nine mutations in the *CACNA1A* gene have been found to cause 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 mutations is commonly associated with ataxia and nystagmus in addition to migraine headaches and auras.

CACNA1A gene mutations that cause sporadic hemiplegic migraine change single amino acids in the CaV2.1 channel. Many of these mutations 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 lead to the headaches and auras characteristic of sporadic hemiplegic migraine.

2.5. 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 underlie the seizures and ataxia in affected individuals. The deletion reduces the amount 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.

3. 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

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