CACNA1D gene

calcium voltage-gated channel subunit alpha1 D

Normal Function

The *CACNA1D* gene belongs to a family of genes that provide instructions for making calcium channels. These channels transport positively charged calcium atoms (calcium ions) across cell membranes. The *CACNA1D* gene provides instructions for making one part (the alpha-1 subunit) of a calcium channel called CaV1.3. This subunit forms the hole (pore) through which calcium ions can flow. CaV1.3 channels are found in many types of cells, although they play a particularly important role in the adrenal glands, which are small hormone-producing glands located on top of each kidney. In the adrenal glands, the flow of calcium through CaV1.3 channels appears to help regulate the production of the hormone aldosterone, which helps control blood pressure by maintaining proper salt and fluid levels in the body. CaV1.3 channels are also found in the brain, heart, and inner ear, although their roles in these tissues are not well understood.

Health Conditions Related to Genetic Changes

Aldosterone-producing adenoma

Mutations in the *CACNA1D* gene have been found to cause aldosterone-producing adenomas, which are noncancerous (benign) tumors that form in the adrenal glands. The genetic changes involved in these tumors, called somatic mutations, are acquired during a person's lifetime and are present only in adrenal gland cells that give rise to the tumors. Such mutations in the *CACNA1D* gene account for approximately nine percent of cases of aldosterone-producing adenoma.

CACNA1D gene mutations associated with this condition lead to production of CaV1.3 channels that transport calcium ions more readily than normal or do not stop when they should. It is thought that the abnormal influx of calcium ions in adrenal gland cells overactivates a process called the calcium/calmodulin pathway that increases production of a hormone called aldosterone. Aldosterone helps control blood pressure by maintaining proper salt and fluid levels in the body, and abnormally high amounts of this hormone lead to high blood pressure (hypertension) and an increased risk of heart attack and stroke. Overactivation of the calcium/calmodulin pathway in the adrenal glands also increases cell growth and division (proliferation), which promotes adenoma formation.

Other disorders

Inherited *CACNA1D* gene mutations have been found to cause other genetic conditions. Unlike the mutations that cause aldosterone-producing adenomas (described above), the mutations that cause these conditions are present in essentially every cell in the body. Inherited mutations that increase the flow of calcium into cells have been identified in individuals with a condition called primary aldosteronism, seizures, and neurological abnormalities (PASNA). As in aldosterone-producing adenomas, the increased flow of calcium in adrenal gland cells increases aldosterone production, causing primary aldosteronism. It is thought that the increased flow of calcium in nerve cells (neurons) in the brain affects their function, leading to seizures and other neurological problems. Some individuals with similar *CACNA1D* gene mutations also have signs and symptoms of autism spectrum disorder, which affects communication and social skills. It is unclear if these individuals have PASNA or a separate condition.

Inherited *CACNA1D* gene mutations that reduce the flow of calcium through CaV1.3 channels have been found in individuals with sinoatrial node dysfunction and deafness (SANDD), which is characterized by an abnormally slow and irregular heartbeat (bradycardia and arrhythmia) and hearing problems. These mutations likely impair the CaV1.3 channel's function in inner ear cells, impairing hearing, and in the cluster of cells in the heart that acts as the heart's natural pacemaker (the sinoatrial node), leading to abnormal heart rhythms.

Other Names for This Gene

- CACH3
- CACN4
- CACNL1A2
- calcium channel, neuroendocrine/brain-type, alpha 1 subunit
- calcium channel, voltage-dependent, L type, alpha 1D subunit
- Cav1.3
- CCHL1A2
- voltage-gated calcium channel alpha 1 subunit
- voltage-gated calcium channel alpha subunit Cav1.3

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of CACNA1D (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=776[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28CACNA1D%5BTIAB%5

D%29+OR+%28calcium+voltage-gated+channel+subunit+alpha1+D%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1D SUBUNIT; CACNA1D (https://omim.org/entry/114206)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/776)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=CACNA1D[gene])

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Genomic Location

The *CACNA1D* gene is found on chromosome 3 (https://medlineplus.gov/genetics/chromosome/3/).

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