

## NOTCH3 gene

notch receptor 3

### Normal Function

The *NOTCH3* gene provides instructions for making a protein with one end (the intracellular end) that remains inside the cell, a middle (transmembrane) section that spans the cell membrane, and another end (the extracellular end) that projects from the outer surface of the cell. The NOTCH3 protein is called a receptor protein because certain other proteins, called ligands, attach (bind) to the extracellular end of NOTCH3, fitting like a key into a lock. This binding causes detachment of the intracellular end of the NOTCH3 protein, called the NOTCH3 intracellular domain, or NICD. The NICD enters the cell nucleus and helps control the activity (transcription) of other genes.

The NOTCH3 protein plays a key role in the function and survival of vascular smooth muscle cells, which are muscle cells that surround blood vessels. This protein is thought to be essential for the maintenance of blood vessels, including those that supply blood to the brain.

### Health Conditions Related to Genetic Changes

#### Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

More than 270 mutations in the *NOTCH3* gene have been found to cause cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, commonly known as CADASIL. Almost all of these mutations change a single protein building block (amino acid) in the NOTCH3 protein. The amino acid involved in most mutations is cysteine. The addition or deletion of a cysteine molecule in a certain area of the NOTCH3 protein, known as the EGF-like domain, presumably affects NOTCH3 function in vascular smooth muscle cells. Disruption of NOTCH3 functioning can lead to the self-destruction (apoptosis) of these cells. Damage to vascular smooth muscle cells is thought to cause recurrent strokes and other signs and symptoms of CADASIL.

#### Lateral meningocele syndrome

At least six *NOTCH3* gene mutations have been identified in people with lateral meningocele syndrome. This disorder affects the nervous system, the bones and muscles, and other body systems. The condition is characterized by abnormalities

known as lateral meningoceles. Lateral meningoceles are protrusions of the membranes surrounding the spinal cord (known as the meninges) through gaps in the bones of the spine (vertebrae). The protrusions are most common and typically larger in the lower spine. The meningoceles associated with this disorder may damage the nerves that spread from the spine to the rest of the body.

The mutations that cause lateral meningocele syndrome occur at the end of the gene in a region known as exon 33. These gene mutations result in a NOTCH3 protein with an abnormally short (truncated) NICD. The shortened protein is missing the portion that normally causes the breakdown of the NICD after it has performed its function in the cell nucleus and is no longer needed. As a result, the presence of the NICD in the cell is prolonged, and the protein continues to affect the activity of other genes. However, the result of this prolonged NICD activity and its connection to the specific features of lateral meningocele syndrome are not well understood.

### **Other Names for This Gene**

- CADASIL
- CASIL
- Neurogenic locus notch homolog protein 3
- NOTCH3\_HUMAN
- Notch homolog 3
- Notch homolog 3 (Drosophila)

### **Additional Information & Resources**

#### Tests Listed in the Genetic Testing Registry

- Tests of NOTCH3 ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4854\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4854[geneid]))

#### Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28NOTCH3%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+720+days%22%5Bdp%5D>)

#### Catalog of Genes and Diseases from OMIM

- NOTCH RECEPTOR 3; NOTCH3 (<https://omim.org/entry/600276>)

#### Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/4854>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=NOTCH3\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=NOTCH3[gene]))

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## **Genomic Location**

The *NOTCH3* gene is found on chromosome 19 (<https://medlineplus.gov/genetics/chromosome/19/>).

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