# NOTCH2 Gene

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notch 2

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## 1. Introduction

The *NOTCH2* gene provides instructions for making a protein called Notch2, a member of the Notch family of receptors. Receptor proteins have specific sites into which certain other proteins, called ligands, fit like keys into locks. Attachment of a ligand to the Notch2 receptor sends signals that are important for normal development and function of many tissues throughout the body, both before and after birth. In particular, research indicates that Notch2 signaling is important for the development of cells destined to be part of the heart, liver, kidneys, teeth, bones, and other structures in a growing embryo. After birth, Notch2 signaling is involved in immune system function, tissue repair, and a process called bone remodeling, in which old bone is removed and new bone is created to replace it.

The Notch2 receptor has several major parts. A region of the receptor called the extracellular domain extends from the surface of the cell and binds to ligands. This binding triggers the part of the receptor inside the cell, known as the intracellular domain or NICD, to be cut (cleaved) from the rest of the protein. The NICD then moves into the cell's nucleus, where it interacts with other proteins to regulate the activity of specific genes. The very end of the NICD contains a region known as a proline-, glutamic acid-, serine-, and threonine-rich (PEST) domain. The PEST domain is necessary for the NICD to be broken down, which stops Notch2 signaling at the appropriate time.

## 2. Health Conditions Related to Genetic Changes

### 2.1. Alagille syndrome

*NOTCH2* gene mutations appear to be a relatively uncommon cause of Alagille syndrome, a condition that can affect the liver, heart, and other parts of the body. At least 10 mutations in the *NOTCH2* gene have been associated with the condition. These mutations can affect either the intracellular or extracellular domain of the Notch2 receptor. The genetic changes probably lead to the production of a receptor that is abnormally small or folded into the wrong 3-dimensional shape. These mutations are described as "loss-of-function" because the defective receptor is unable to bind to its ligands and trigger signaling within the cell. Disrupted Notch2 signaling is believed to affect the development of numerous organs and tissues, resulting in the signs and symptoms of Alagille syndrome.

### 2.2. Hajdu-Cheney syndrome

Several mutations in the *NOTCH2* gene have been associated with Hajdu-Cheney syndrome, a rare disorder that can affect many parts of the body, particularly the bones. Affected individuals have acro-osteolysis, which is a loss of bone tissue that affects the hands and feet most severely. Most people with this condition also have osteoporosis, which causes the bones to be brittle and prone to fracture; distinctive facial features; spinal abnormalities; and short stature. Additionally, Hajdu-Cheney syndrome can affect the joints, teeth, heart, kidneys, and other parts of the body.

The mutations associated with Hajdu-Cheney syndrome all occur near the end of the *NOTCH2* gene in a region called exon 34. These mutations lead to an abnormally shortened version of the Notch2 receptor that is missing the PEST domain. Without this domain, the receptor cannot be broken down normally, and Notch2 signaling within the cell continues after it should stop. Because the *NOTCH2* gene mutations related to Hajdu-Cheney syndrome lead to abnormally increased Notch2 signaling, they are described as "gain-of-function" mutations.

Researchers are unsure how excessive Notch2 signaling is related to the varied features of Hajdu-Cheney syndrome. They suspect that the skeletal features of the disorder, including acro-osteolysis, osteoporosis, and distinctive facial features, likely result from abnormal bone development and remodeling. Excess signaling through the overactive Notch2 receptor may increase the removal of old bone, reduce the formation of new bone, or both. It is less clear how the overactive receptor contributes to the other signs and symptoms of this condition.

### 2.3. Cancers

Mutations in the *NOTCH2* gene have also been found in certain forms of lymphoma, which is a group of cancers that arise from immune system cells. These mutations are somatic, which means that they are not inherited. Somatic mutations are acquired during a person's lifetime and are present only in certain cells. The *NOTCH2* gene mutations associated with lymphomas are described as "gain-of-function" because they increase the activity (expression) of the *NOTCH2* gene in certain immune system cells. In some affected cells, extra copies of the mutated gene have been found, further increasing gene activity. Overexpression of this gene may lead to uncontrolled cell growth and cell division in immune system cells, which can result in the development of lymphoma.

## 3. Other Names for This Gene

- hN2
- NOTC2_HUMAN
- Notch (Drosophila) homolog 2
- notch 2 preproprotein
- Notch homolog 2 (Drosophila)

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