NOTCH3

NOTCH3 is a gene that encodes the **Notch 3 receptor**, which is a transmembrane protein involved in cell signaling. This receptor plays a crucial role in the regulation of cell differentiation, cell proliferation, and apoptosis, particularly in vascular smooth muscle cells and pericytes, which are essential for maintaining vascular integrity and function.

Key Points about NOTCH3:

1. **Gene and Protein Function**:

   1. **NOTCH3** belongs to the Notch family of genes, which are known for their role in signaling pathways that control cell fate decisions during development and tissue homeostasis.
   2. The Notch 3 receptor, encoded by the **NOTCH3** gene, is primarily expressed in vascular smooth muscle cells and plays a key role in maintaining the structure and function of blood vessels, particularly small arteries and arterioles.

2. **Role in Disease**:

   1. Mutations in the **NOTCH3** gene are most notably associated with **Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)**, a hereditary form of cerebral small vessel disease. CADASIL is characterized by recurrent strokes, migraine with aura, cognitive decline, and subcortical dementia.
   2. The pathogenic mutations typically involve **missense mutations** that result in the replacement of cysteine residues, leading to an abnormal accumulation of the Notch 3 receptor and toxic effects in the vasculature of the brain.

3. **Molecular Mechanism**:

   1. **NOTCH3** mutations often cause dysfunction in the signaling pathway that results in the loss of proper regulation of vascular smooth muscle cells. This can lead to structural abnormalities in the blood vessel walls, thickening, and stenosis, contributing to reduced blood flow and ischemic damage to brain tissue.

4. **Importance in Research**:

   1. The **NOTCH3** gene is a significant focus in research for understanding the mechanisms underlying cerebral small vessel diseases, as well as for developing potential therapeutic interventions to mitigate the effects of these mutations.

Overall, **NOTCH3** is a critical gene in vascular biology, and its dysfunction due to genetic mutations has profound implications for cerebrovascular health and disease.

Notch is present in all metazoans, and mammals possess four different notch receptors, referred to as NOTCH1, NOTCH2, NOTCH3, and NOTCH4.

Neurogenic locus notch homolog protein 3 is a protein that in humans is encoded by the NOTCH3 gene.

Function

This gene encodes the third discovered human homologue of the Drosophilia melanogaster type I membrane protein notch. In Drosophilia, notch interaction with its cell-bound ligands (delta, serrate) establishes an intercellular signaling pathway that plays a key role in neural development. Homologs of the notch-ligands have also been identified in human, but precise interactions between these ligands and the human notch homologs remain to be determined.

Pathology

Mutations in NOTCH3 have been identified as the underlying cause of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Mutations in NOTCH3 have also been identified in a Turkish family with Alzheimer's disease.

Adult Notch3 knock-out mice show incomplete neuronal maturation in the spinal cord dorsal horn, resulting in permanently increased nociceptive sensitivity.

Mutations in NOTCH3 are associated to lateral meningocele syndrome.

The screened Intracranial aneurysm (IA)-related gene NOTCH3 was determined by bioinformatic data mining. Li et al. verified the Intracranial aneurysm-related indicators of NOTCH3. Association was found between IA and the NOTCH3 SNPs rs779314594, rs200504060 and rs2285981. Levels of NOTCH3 mRNA were lower in IA tissue than in control tissue, but higher in peripheral blood neutrophils from IA patients than in neutrophils from controls. Levels of NOTCH3 protein were lower in IA tissue than in cerebral artery tissue. NOTCH3 also decreased the expression of angiogenesis factors in human umbilical vein endothelial cells. Variation in NOTCH3 and alteration of its expression in cerebral artery or neutrophils may contribute to IA. The findings also describe a bioinformatic-experimental approach that may prove useful for probing the pathophysiology of other complex diseases [1)].

Pharmaceutical target

Notch3 is being investigated as a target for anti-cancer drugs, as it is overexpressed in several types of cancers.

Early clinical trials of Pfizer's PF-06650808, an anti-Notch3 antibody linked to a cytotoxic drug, showed efficacy against solid tumors.

Retrospective cohort studies

NOTCH3 variants are the leading cause of hereditary cerebral small vessel disease (SVD). While monoallelic cysteine-involving missense variants in NOTCH3 are well-studied in cerebral autosomal

dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), patients with biallelic variants in NOTCH3 are sporadic and not well characterized.

Iruzubieta et al. present clinical and genetic data from 25 patients with biallelic NOTCH3 variants and conduct a literature review of another 25 cases (50 patients in total). Brain magnetic resonance imaging (MRI) was analyzed by expert neuroradiologists to better understand the phenotype associated with biallelic NOTCH3 variants.

The systematic analyses verified distinct genotype-phenotype correlations for the two types of biallelic variants in NOTCH3. Biallelic loss-of-function variants (26 patients) lead to a neurodevelopmental disorder characterized by spasticity, childhood-onset stroke, and periatrial white matter volume loss resembling periventricular leukomalacia. Conversely, patients with biallelic cysteine-involving missense variants (24 patients) fall within the CADASIL spectrum phenotype with early adulthood onset stroke, dementia, and deep white matter lesions without significant volume loss. White matter lesion volume is comparable between patients with biallelic cysteine-involving missense variants and individuals with CADASIL. Notably, monoallelic carriers of loss-of-function variants are predominantly asymptomatic, with only a few cases reporting nonspecific headaches.

They propose a NOTCH3-SVD classification depending on dosage and variant type. This study not only expands our knowledge of biallelic NOTCH3 variants but also provides valuable insight into the underlying mechanisms of the disease, contributing to a more comprehensive understanding of NOTCH3-related SVD [2].

[1]
Li M, Dong X, Chen S, Wang W, Yang C, Li B, Liang D, Yang W, Liu X, Yang X. Genetic polymorphisms and transcription profiles associated with intracranial aneurysm: a key role for NOTCH3. Aging (Albany NY). 2019 Jul 23;11. doi: 10.18632/aging.102111. [Epub ahead of print] PubMed PMID: 31339861.

[2]
Iruzubieta P, Alves CAPF, Al Shamsi AM, ElGhazali G, Zaki MS, Pinelli L, Lopergolo D, Cho BPH, Jolly AA, Al Futaisi A, Al-Amrani F, Galli J, Fazzi E, Vulin K, Barajas-Olmos F, Hengel H, Aljamal BM, Nasr V, Assarzadegan F, Ragno M, Trojano L, Ojeda NM, Çakar A, Bianchi S, Pescini F, Poggesi A, Al Tenalji A, Aziz M, Mohammad R, Chedrawi A, De Stefano N, Zifarelli G, Schöls L, Haack TB, Rebelo A, Zuchner S, Koc F, Griffiths LR, Orozco L, Helmes KG, Babaei M, Bauer P, Chan Jeong W, Karimiani EG, Schmidts M, Gleeson JG, Chung WK, Alkuraya FS, Shalbafan B, Markus HS, Houlden H, Maroofian R. Clinical and neuroradiological spectrum of biallelic variants in NOTCH3. EBioMedicine. 2024 Aug 26;107:105297. doi: 10.1016/j.ebiom.2024.105297. Epub ahead of print. PMID: 39191170.