Gene name: **NOTCH1** **Previous HGNC Symbols for NOTCH1 Gene:** TAN1
External Ids for NOTCH1 Gene: HGNC: 7881 NCBI Gene: 4851 Ensembl: ENSG00000148400
OMIM®: 190198 UniProtKB/Swiss-Prot: P46531

NCBI Gene Summary: This gene encodes a member of the NOTCH family of proteins. Members of this Type I transmembrane protein family share structural characteristics including an extracellular domain consisting of multiple epidermal growth factor-like (EGF) repeats, and an intracellular domain consisting of multiple different domain types. **Notch signaling is an evolutionarily conserved intercellular signaling pathway that regulates interactions between physically adjacent cells through binding of Notch family receptors to their cognate ligands**. The encoded preproprotein is proteolytically processed in the trans-Golgi network to generate two polypeptide chains that heterodimerize to form the mature cell-surface receptor. This receptor plays a role in the development of numerous cell and tissue types. Mutations in this gene are associated with aortic valve disease, Adams-Oliver syndrome, T-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, and head and neck squamous cell carcinoma.
CIViC Summary: NOTCH1 is one of four known genes encoding the NOTCH family of proteins, a group of receptors involved in the Notch signaling pathway. NOTCH proteins are characterized by N-terminal EGF-like repeats followed by LNR domains which form a complex with ligands to prevent signaling. The Notch signaling pathway is involved in processes related to cell fate specification, differentiation, proliferation, and survival. Activation of Notch has been shown to be correlative with mammary tumorigenesis in mice and increased expression of Notch receptors has been observed in a variety of cancer types including cervical, colon, head and neck, lung, renal, pancreatic, leukemia, and breast cancer. A number of treatment modalities have been explored related to Notch inhibition especially in breast cancer with mixed results.
GeneCards Summary: NOTCH1 (Notch Receptor 1) is a Protein Coding gene. Diseases associated with NOTCH1 include Aortic Valve Disease 1 and Adams-Oliver Syndrome 5. Among its related pathways are Constitutive Signaling by NOTCH1 HD+PEST Domain Mutants and Pre-NOTCH Expression and Processing. Gene Ontology (GO) annotations related to this gene include *DNA-binding transcription factor activity* and *sequence-specific DNA binding*. An important paralog of this gene is NOTCH2.
UniProtKB/Swiss-Prot Summary: Functions as a receptor for membrane-bound ligands Jagged-1 (JAG1), Jagged-2 (JAG2) and Delta-1 (DLL1) to regulate cell-fate determination. Upon ligand activation through the released notch intracellular domain (NICD) it forms a transcriptional activator complex with RBPJ/RBPSUH and activates genes of the enhancer of split locus. Affects the implementation of differentiation, proliferation and apoptotic programs. Involved in angiogenesis; negatively regulates endothelial cell proliferation and migration and angiogenic sprouting. Involved in the maturation of both CD4(+) and CD8(+) cells in the thymus. Important for follicular differentiation and possibly cell fate selection within the follicle. During cerebellar development, functions as a receptor for neuronal DNER and is involved in the differentiation of Bergmann glia. Represses neuronal and myogenic differentiation. May play an essential role in postimplantation development, probably in some aspect of cell specification and/or differentiation. May be involved in mesoderm development, somite formation and neurogenesis. May enhance HIF1A function by sequestering HIF1AN away from HIF1A. Required for the THBS4 function in regulating protective astrogenesis from the subventricular zone (SVZ) niche after injury. Involved in determination of left/right symmetry by modulating the balance between motile and immotile (sensory) cilia at the left-right organiser (LRO). (NOTC1_HUMAN,P46531)
Cellular localization: mainly in cytosol, nucleus, extracellular and plasma membrane.
Full Name: *Notch Receptor 1*
Protein Type: Transmembrane receptor (single-pass), part of the Notch signaling pathway

🔬 Biological Function of NOTCH1

NOTCH1 is a central component of the evolutionarily conserved Notch signaling pathway, which regulates cell fate decisions, differentiation, proliferation, and apoptosis.

🛠️ Main Functions:

1. Cell-cell communication:
    - NOTCH1 is a receptor activated by direct interaction with ligands (Delta-like and Jagged family) on neighboring cells.
2. Regulates immune cell development:
    - Controls T cell lineage commitment in the thymus.
    - Modulates dendritic cell maturation, monocyte activation, and macrophage polarization.
3. Balances pro- vs. anti-inflammatory signaling:
    - Influences cytokine expression (such as, IL-6, IL-10).
    - Plays a context-dependent role in either amplifying or suppressing inflammation.
4. Regulates endothelial and vascular function:
    - Controls angiogenesis and endothelial barrier integrity.

🦠 Role of NOTCH1 in Sepsis

NOTCH1 has dual roles in immune regulation and vascular responses, both highly relevant in sepsis:

Early Sepsis:

- Activation of NOTCH1 signaling in monocytes/macrophages may promote:
    - Pro-inflammatory cytokine release (such as, TNF-α, IL-6)
    - Innate immune cell activation
- In endothelial cells:
    - Supports vascular barrier integrity
    - Regulates angiogenesis and tissue perfusion

Prolonged/Severe Sepsis:

- Dysregulation of NOTCH1 contributes to:
    - Endothelial dysfunction and capillary leakage
    - Exaggerated inflammation or immune paralysis, depending on context
    - Impaired lymphocyte development and antigen presentation
- Some studies suggest loss of NOTCH1 activity promotes immune exhaustion and impaired host defense

📈 Clinical Relevance of NOTCH1 in Sepsis

Diagnostic Potential:

- NOTCH1 expression changes dynamically in sepsis:
    - Upregulated in some immune cells early
    - Downregulated in T cells or endothelial cells later

Prognostic Relevance:

- Altered NOTCH1 expression is associated with:
    - Organ dysfunction, especially vascular and immune-related
    - Potential link to sepsis-induced immunosuppression
- NOTCH1 is part of transcriptomic signatures associated with sepsis subtypes (e.g., immunoparalysis vs. hyperinflammation)

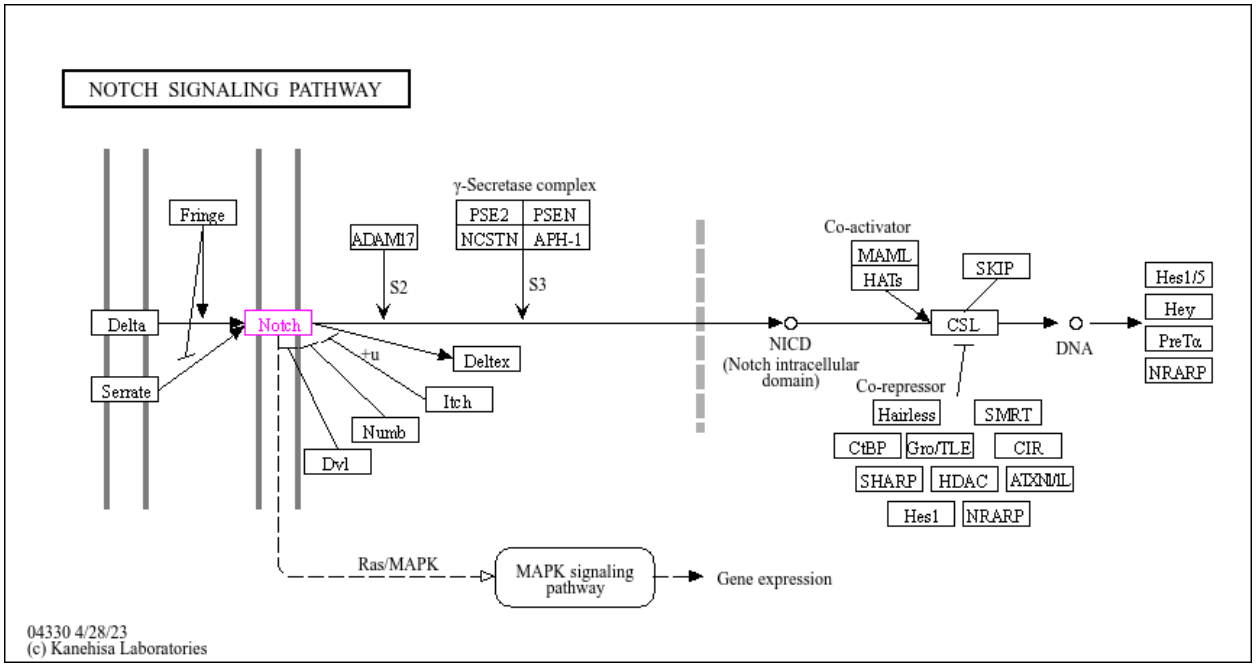
Therapeutic Potential:

- Targeting NOTCH1 signaling is under investigation in:
    - Sepsis
    - Autoimmune diseases
    - Cancer immunotherapy
- Approaches include:
    - γ-secretase inhibitors (GSIs) to block NOTCH activation
    - Agonists or ligands to enhance NOTCH1 activity in certain immune contexts

📚 Key Supporting Studies

Doi: 10.3390/ijms24043458
Doi: 10.1155/2015/539841
Doi: 10.1016/j.intimp.2019.105907
Doi: 10.3389/fimmu.2023.1134556
Doi: 10.1016/j.bcp.2025.116892

KEGG



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