**Atlas of Genetics and Cytogenetics in Oncology and Haematology**

OPEN ACCESS JOURNAL AT INIST-CNRS

# Gene Section
## Mini Review

# HYAL2 (hyaluronoglucosaminidase 2)

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Published in Atlas Database: November 2007

Online updated version: http://AtlasGeneticsOncology.org/Genes/HYAL2ID40904ch3p21.html
DOI: 10.4267/2042/38542



## Identity

**Hugo:** HYAL2
**Other names:** LuCa-2; LUCA2
**Location:** 3p21.3
**Local order:** Telomeric to TUSC2 and centromeric to HAYL1.
**Note:** HYAL2 was identified in an EST database search of PH-20 hyaluronidase related sequences. HYAL2 appears to be an inactive hyaluronidase. Characterization of HYAL2 mostly focuses on its role as the cell entry receptor of Jaagsiekte sheep retrovirus (JSRV), and the putative function as a tumor suppressor gene, based on its specific chromosomal location.

## DNA/RNA

### Description

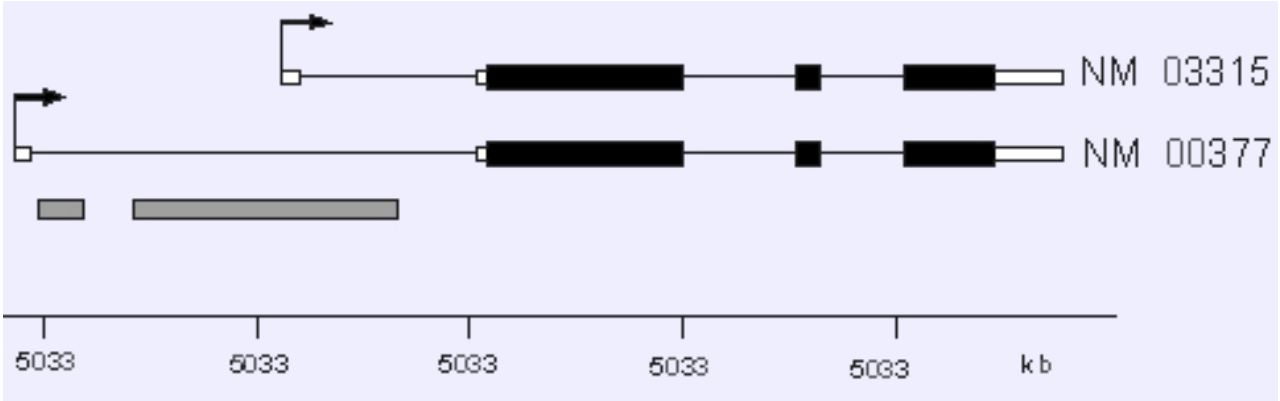
The HYAL2 gene contains 4 exons, spanning 4.99 kb.

### Transcription

The gene encodes two alternatively spliced transcripts (NM_033158 and NM_003773) which differ only in the 5' UTR. Distinct noncoding exon 1 was found in these two transcripts. Both variants encode the same protein. The ORF size is 1422 bp.

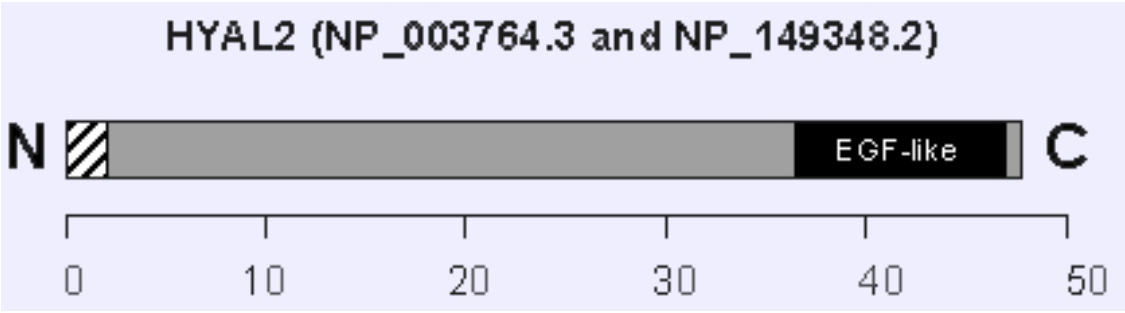
### Pseudogene

No known pseudogenes.




Two alternatively spliced variants (NM_033158.2 and NM_003773.2) of HYAL2 are shown. Both of them contain four exons. Black boxes represent the coding exons of HYAL2. White boxes represent untranslated regions.

# Protein




The HYAL2 protein contains a N-terminal signal peptide (1-20) and a epidermal growth factor (EGF)-like domain (365-469).

### *Description*

The 473 amino-acid peptide encodes the HYAL2 protein with a predicted molecular weight of 53.9 KDa. The protein is comprised of a N-terminal signal peptide (amino acids 1-20) and a epidermal growth factor (EGF)-like domain at amino acids 365-469 (by SMART prediction).

### *Expression*

High level of HYAL2 expression was detected in most tissues, including liver, kidney, lung and heart. Expression was low or absent in brain.

### *Localisation*

Originally shown to be lysosomal but subsequently proved to be a glycosylphosphatidylinositol (GPI)-anchored cell surface protein.

### *Function*

Hyaluronidases degrade hyaluronan, one of the major glycosaminoglycans of the extracellular matrix (ECM). The level of hyaluronan is regulated by a balance between hyaluronan synthase and HYAL enzyme activities. Hyaluronan is suggested to be involved in embryonic development, cell proliferation, migration and wound healing. Although originally supposed to be active at pH 4.0, HYAL2 actually displayed minimal to undetectable hyaluronidase activity in subsequent studies. The hyaluronidase activity of HYAL2 remains controversial.

### *Homology*

HYAL2 belongs to a family of hyaluronoglucosaminidases. Other members include HYAL1, HYAL3, HYAL4 and Spam1.

# Mutations

**Note:** No germline or somatic mutation is reported.

# Implicated in

### *Possible in lung cancer and breast cancer*

**Note:** HYAL2 is located within a 120-kb minimal deletion region at 3p21.3 a chromosomal segment known to harbor multiple candidate tumor suppressor genes in breast and lung cancers. Nevertheless, HYAL2 does not possess tumor suppressor function, as evident by in vitro and in vivo studies in lung cancer models.
HYAL2 serves as the cellular receptor that mediates entry of the Jaagsiekte sheep retrovirus (JSRV), and its receptor function is independent on its catalytic activity. The JSRV envelope (Env) protein is believed to be the active oncogene. The viral Env transforms epithelial cells through activation of RON receptor tyrosine kinase, also called macrophage stimulating-1 receptor (MST1R), and followed by activating PI3K/Akt signaling cascade and MAPK signaling cascade. HYAL2 physically interacts and negatively regulates RON.
JSRV infects the epithelial cells of the lower airway of sheep and goats, resulting in ovine pulmonary adenocarinoma, sharing features with human bronchioloalveolar carcinoma. Danilkovitch-Miagkova et al. (2003) demonstrated activated RON in a subset of human bronchioloalveolar carcinoma tumors, suggesting RON involvement in this type of human lung cancer.

**Disease**

Lung cancer; bronchioloalveolar carcinoma; non-Hodgkin lymphoma; breast cancer.

**Prognosis**

Increased level of HYAL2 deletions in sputum of Stage I non-small-cell lung cancer patients was associated with pack-years of smoking, but independent on patients' age, gender, histologic tumor type and tumor

size and location. HYAL2 mRNA expression was inversely correlated with lymphoma aggressiveness.

**Oncogenesis**

HYAL2 mRNA expression was lost in lung cancer cell lines. However, expression of HYAL2 was retained in esophageal squamous carcinoma and nasopharyngeal carcinoma cell lines. Highly invasive breast cancer cell lines preferentially express HYAL2.

Systemic administration of protamine-complexed vectors expressing HYAL2 inhibited lung metastatic foci in nu/nu mice. Intratumoral injection of same construct failed to suppress primary tumor growth or induce apoptosis, suggesting HYAL2 may function at the level of metastasis.

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*This article should be referenced as such:*
Chow LSN, Lo KW. HYAL2 (hyaluronoglucosaminidase 2). Atlas Genet Cytogenet Oncol Haematol.2008;12(4):279-281.