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Gene Section
Review

CLDN6 (claudin 6)

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Identity

HGNC (Hugo): CLDN6

Location: 16p13.3

DNA/RNA

Description

5360 base-pairs DNA linear, starts at 3064713 and ends at 3070072 bp from pter with minus strand orientation. This gene contains 2 exons.

Transcription

The transcription produces 2 alternatively spliced mRNA variants:
- NM_021195.4: transcript length: 2139 bp,
- ENST00000396925: transcript length: 1739 bp.

Pseudogene

Pseudogene of claudin 6 (LOC284620) is located on chromosome 1 (859 bp).

Protein

Description

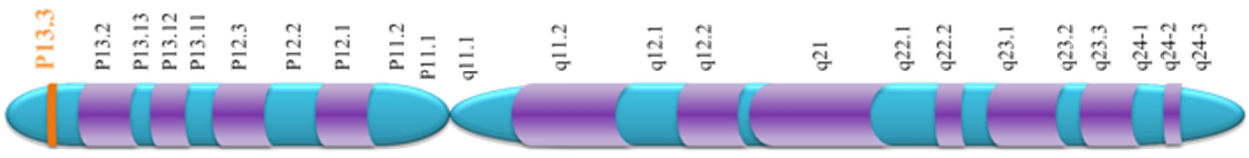
The transcription of this gene gives 1 spliced mRNA that encodes 1 protein isoform with 220 aa and 23292 Da of molecular weight.

Expression

Claudin-6 expression is mainly found in mouse embryonic stem cells (ESC), epithelial lineage cells during early development and primitive germ cell tumours such as spermatocytic seminoma, embryonal carcinoma, yolk sac tumour, choriocarcinoma, immature teratoma, mature teratoma and classic seminoma. Its expression is very weak or absent in adult mouse. In rat choroid plexus development claudin-6 is expressed postnatal between day 6 and 9. Claudin-6 expression is associated to ERα expression in human breast cancer and is inactivated by CpG island DNA hypermethylation.

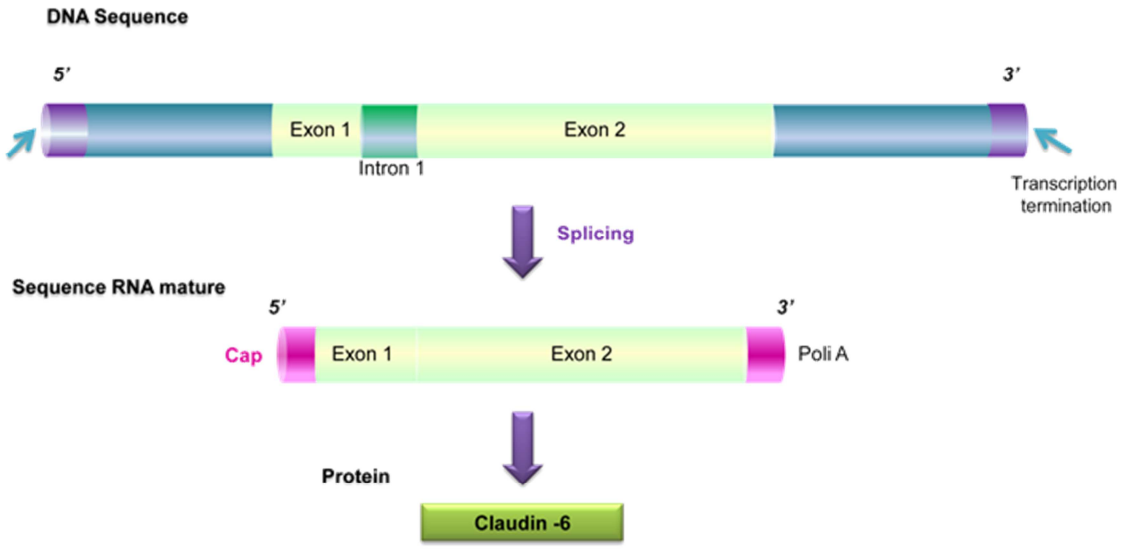
Sequence:

MASAGMQILG VVLTLLGWVN GLVSCALPMW KVTAFIGNSI VVAQVVWEGL WMSCVVQSTG
QMQCKVYDSL LALPQDLQAA RALCVIALLV ALFGLLVYLA GAKCTTCVEE KDSKARLVLT
SGIVFVISGV LTLIPVCWTA HAIIRDFYNP LVAEAQKREL GASLYLGWAA SGLLLLGGGL
LCCTCPSGGS QGPSHYMARY STSAPAISRG PSEYPTKNYV



Claudin-6 Chr 16 p13.3

Gene: Claudin-6
Location: complement 3,064,713-3,068,188 bp
Lenght: 3,476 bases



Localisation

This transmembrane protein is located in the tight junction during embryogenesis and, in certain cancer pathologies.
It can be found in the cell cytoplasm and in the nucleus.

Function

Claudin-6 regulates chloride and sodium permeability, and increases transepithelial electrical resistance in MDCK cells.
It also has a Ca^{2+} independent cell adhesion activity.
Is one of the entry cofactors for hepatitis C virus.
Claudin-6 gene methylation may be involved in esophageal tumorogenesis.

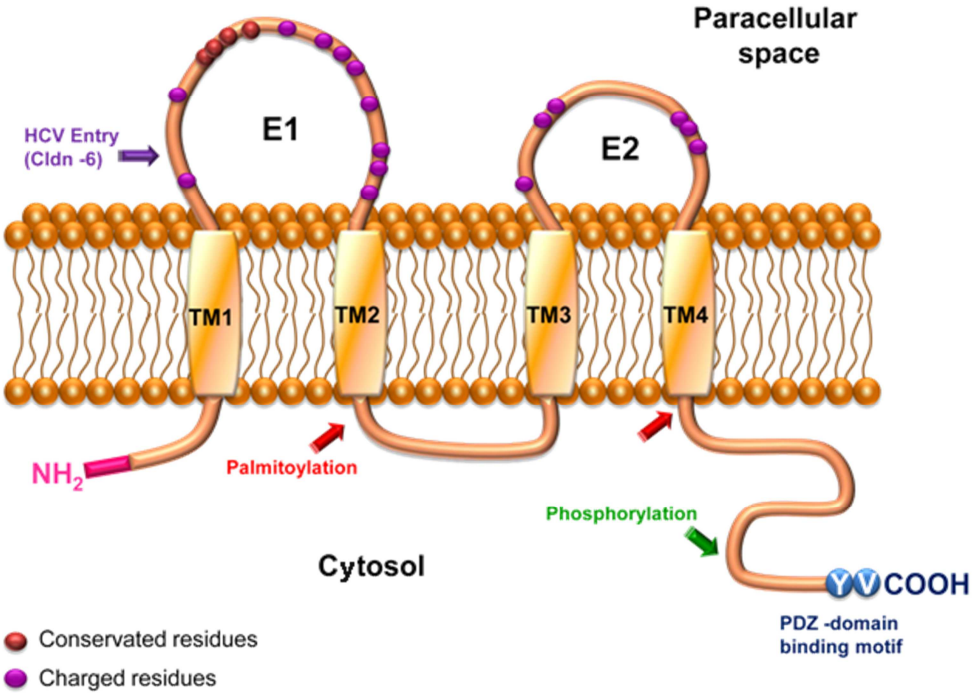
Homology

The CLDN6 gene sequence is conserved in human, chimpanzee, monkey, wolf, cow, mouse, rat, and zebrafish.

Mutations

Somatic

A heterozygous substitution (p.T33T) in position 33 in ovarian serous carcinoma, and an homozygous substitution (p.T33T) in position 135 in stomach adenocarcinoma, have been reported.



Implicated in

Breast cancer

Note

Up-regulation of claudin-6 expression in MCF-7 cells suppressed their malignant phenotype and restored tight junction integrity. Claudin-6 down-regulation contributes to the malignant progression of certain types of breast cancers.

Claudin-6 mRNA was low or undetectable in two rat mammary cancer cell lines, two human breast cancer cell lines, and one breast cancer sample compared to normal breast tissue (Quan and Lu, 2003). Decreased expression of claudin-6 promotes cellular invasiveness, transendothelial migration and an increase in matrix metalloproteinase activity (Osanai et al., 2007). The methylated phenotype of claudin-6 contributes to enhanced tumorigenic and invasive properties of breast carcinoma cells. Claudin-6 may function as tumor suppressor, particularly for breast cancer.

Gastric adenocarcinoma

Note

Abnormal claudin expression has been documented in several malignancies. Strong claudin-6 expression was associated with higher mortality rate in the diffuse- vs the intestinal-type gastric adenocarcinoma after a 2-year follow-up (Rendón-Huerta et al., 2010). Claudin-6 expression is closely related to gastric carcinogenesis, and their detection is a useful prognostic marker in gastric adenocarcinoma.

Claudin-6 overexpression in AGS cells enhanced their invasive potential (1,6-fold), cell migration and proliferation rate (13,3%); it also increased claudin-1 and zonula occludens-1 levels (Zavala-Zendejas et al., 2011). Increased expression of claudin-6 is sufficient to enhance tumorigenic properties of a gastric adenocarcinoma cell line.

Brain tumors

Note

Claudin-6 is a positive marker for atypical teratoid/rhabdoid tumors (AT/RTs) (Birks et al., 2010). AT/RTs are highly aggressive pediatric brain tumors. CLDN6 showed moderate or higher mRNA expression in eight of nine AT/RTs, with little to no expression in 114 of 115 other tumors. CLDN6 may be a useful marker to identify atypical teratoid/rhabdoid tumors AT/RTs.

Hepatitis C virus infection

Note

Claudin-6 mediates the entry of HCV into target cells. Claudin-6 is expressed in the liver, the primary site of HCV replication. Claudin-6 expressed in CD81+ (tetraspanin) cells enables the entry of HCV pseudoparticles. Claudin-1 and -6 function equally well as entry cofactors in endothelial cells but claudin-1 is more efficient in hepatoma cells (Meertens et al., 2008). This suggests that additional cellular factors modulate the ability of claudins to function as HCV entry cofactors.

Cornea

Note

Epigenetic regulators such as TSA, 5-aza, and DMSO significantly enhance the expression of claudin-9 in corneal cells, changing transcriptional signals by demethylating CpG islands (Nishikiori et al., 2008); additionally, the epigenetic regulators increase transendothelial electrical resistance and suppress fluxes of corneal cells, thus enhancing the corneal barrier function, in murine experimental corneal trauma.

Adipogenesis

Note

Claudin-6 mRNA is differentially expressed in four different adipose tissues, and up regulated in each fat depot of mice fed a high-fat diet as compared to a normal-fat diet. Levels of claudin-6 transcripts were increased during differentiation of 3T3-L1 cells in vitro but small interfering RNA-mediated reduction of claudin-6 mRNA inhibited its differentiation (Hong et al., 2005). Claudin-6 is an important regulator of adipogenesis and fat deposition.

Neonatal development

Note

Claudin-6 is a global marker of definitive endoderm and the development of the pancreas, lung and liver; CLDN6 null mice are viable and with no obvious phenotypic abnormalities (Anderson et al., 2008). Homozygous mice overexpressing claudin-6 exhibit a perturbation in the epidermal differentiation program leading to a defective epidermal permeability barrier (EPB); Inv-Cldn6 transgenic animals die within 2 days of birth, due to the lack of an intact EPB, inversely heterozygous Inv-Cldn6 mice exhibit a distinct coat phenotype and mild epidermal hyperkeratosis (Troy et al., 2005).

A defective EPB has been shown in premature birth neonates (Turksen and Troy, 2002). Claudin 6 has a major role in epithelial differentiation and EPB assembly/maintenance.

Claudin-6 expression is fundamental for the formation of the trophectoderm (TE), the first epithelium generated during mammalian early development that isolates the inner cell mass from the uterine environment and provides the turgidity of the blastocyst through elevated hydrostatic pressure (Moriwaki et al., 2007). Claudin-6 was absent from TE tight junctions, and thus the barrier function of the TE was disrupted, when embryos were cultured in the presence of Clostridium perfringens enterotoxin.

Claudin-6 expression in the neonatal proximal tubule result in an increased transepithelial resistance,

decreased chloride permeability, and decreased P(Na)/P(Cl) and P(HCO3)/P(Cl) (Sas et al., 2008).

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