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Gene Section

Review

CDH17 (cadherin 17, LI cadherin (liver-intestine))

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Identity

Other names: CDH16, HPT-1, HPT1

HGNC (Hugo): CDH17

Location: 8q22.1

DNA/RNA

Description

Human CDH17 DNA contains 90138 bp composed of 18 exons (Gessner and Tauber, 2000; Wendeler et al., 2006).

Transcription

Two transcripts (NM_001144663.1 and NM_004063.3) encode the same protein according to Entrez gene. 2499 bp open reading frame.

Protein

Description

Cadherins are calcium-dependent cell-cell adhesion molecules which play important roles in organ development, the maintenance of tissue integrity and cancer development (Pokutta and Weis, 2007; Berx and van Roy, 2009). Cadherin 17 (CDH17) is a transmembrane glycoprotein with seven extracellular cadherin repeats. The cytoplasmic domain of human CDH17 only has 23 amino acids, whereas other classical cadherins contain 150 to 160 conserved amino acids forming complexes with catenins (Gessner and Tauber, 2000; Lee et al., 2010). CDH17 belongs to seven-domain (7D) cadherin subfamily which shares low sequence homology with the classical cadherins, such as E-cadherin. The structure difference of CDH17 makes this molecule unique among the known classical cadherin family members (Nollet et al., 2000; Angst et al., 2001). Recent work suggests its role in tumor progression and cancer prognosis (Liu et al., 2009).

Expression

In rats, CDH17 is expressed in the liver and small intestine (Berndorff et al., 1994). In mouse and human, CDH17 is highly expressed in the small intestine and colon (Angres et al., 2001; Takamura et al., 2004), but absent or very low level in other organs, such as liver, heart and kidney etc. It is also linked predominantly to a high incidence of tumorigenesis in the human liver, stomach, intestine and pancreas by displaying an aberrant expression in their cancerous state (Lee et al., 2010).

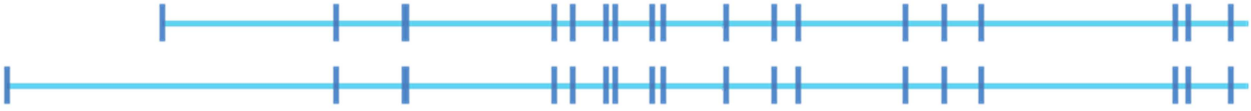

Figure 1. Cadherin 17 (CDH17) DNA with introns and exons.

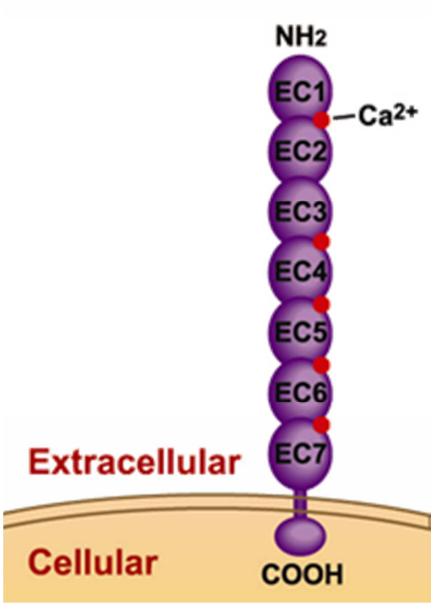

Figure 2. A schematic diagram illustrates the structural feature of cadherin-17 (CDH17) in having seven cadherin repeats (EC1-EC7) at the extracellular amino-terminus (NH_2), followed by a transmembrane region and a short cytoplasmic domain at the carboxyl-terminus (COOH). Calcium ions (denoted by red dots) are located between cadherin repeats in mammalian CDH17.

Localisation

CDH17 is mainly localized on basolateral cell membrane.

Overexpressed CDH17 can also be detected throughout the cytoplasm of liver cancer, gastric cancer and colon cells (Wong et al., 2003; Grötzinger et al., 2001; Takamura et al., 2004).

Function

CDH17 was originally cloned from rat liver and identified as a novel cell adhesion molecule (Berndorff et al., 1994).

Homotypic trans-interaction of CDH17 is dependent on extracellular calcium concentration. It might serve as a calcium-regulated adhesion switch (Wendeler et al., 2007).

CDH17 is also reported as an intestinal peptide transporter.

It facilitates the oral absorption of beta-lactam antibiotics and angiotensin-converting enzyme inhibitors from the intestine into enterocytes lining the luminal wall (Dantzig et al., 1994). Knockout CDH17 by a mutant CDH17 deficient mouse showed that CDH17 may also participate in B lymphocyte development (Ohnishi et al., 2005). Recent studies suggested CDH17 important roles in tumorigenesis. Overexpression CDH17 can promote tumor growth, while suppression of CDH17 inhibits cancer cell growth, migration and adhesion (Liu et al., 2009).

Homology

Human CDH17 shares ~20-30% sequence identity with other cadherin family members, such as cadherin-16 (30%), cadherin-13 (30%), and cadherin-1 (26%). It also shares ~79% identify with cyno-, mouse-, rat-cadherin-17.

Mutations

Note

No mutation has been reported for CDH17 so far.

Somatic

Alternative mRNA splicing isoform of CDH17 was reported in hepatocellular carcinoma patient samples. The isoform skips exon 7 which leads to open reading frame shift. The mRNA isoform is associated with shorter overall survival time. The functions or mechanisms of the isoform in cancer are unclear (Wang et al., 2005).

Implicated in

Hepatocellular carcinoma (HCC)

Prognosis

CDH17 overexpression is detected in approximately ~80% of HCC patients (Liu et al., 2009). The elevated level of CDH17 in HCC is correlated to high serum AFP level, microvascular invasion, and advanced stage tumor, associating with shorter overall survival as well as higher incidence of tumor recurrence, of HCC patients. Over half of HCC patients have genomic amplification of CDH17 gene in their tumors. Alternative mRNA splicing of CDH17 was also reported in half of the HCC patient tumor specimens and associated with shorter overall survival time (Ding et al., 2009; Wong et al., 2003; Wang et al., 2006; Kaposi-Novak et al., 2006). The CDH17 overexpression can also be detected in other tumorigenic conditions including gastric cancer (GC). Therefore, CDH17 expression can be a potential biomarker for HCC and GC.

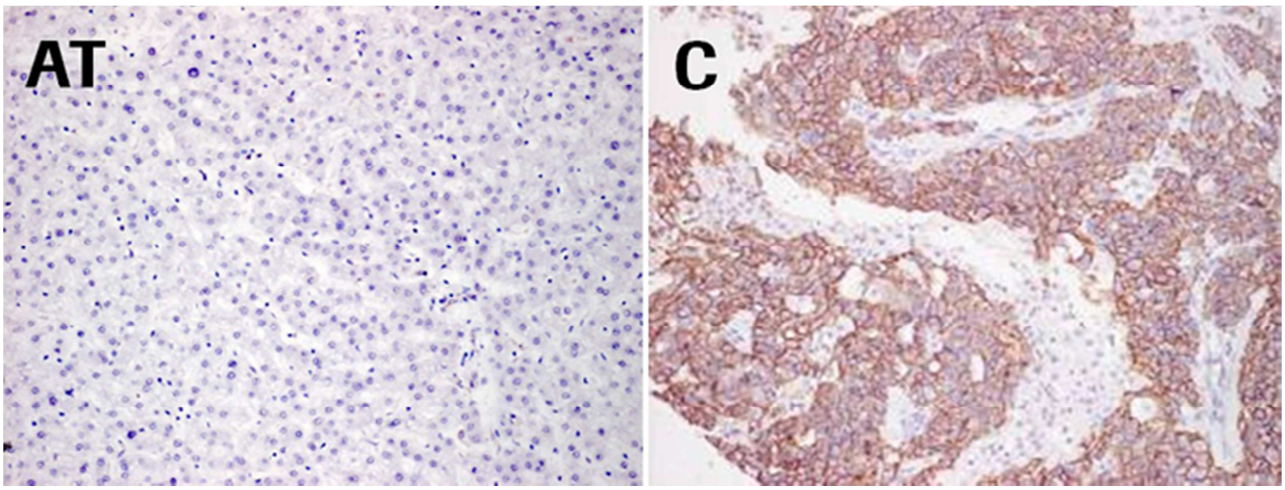

Figure 3. CDH17 expression in hepatocellular carcinoma (C) but not in adjacent non-tumor tissues (AT).

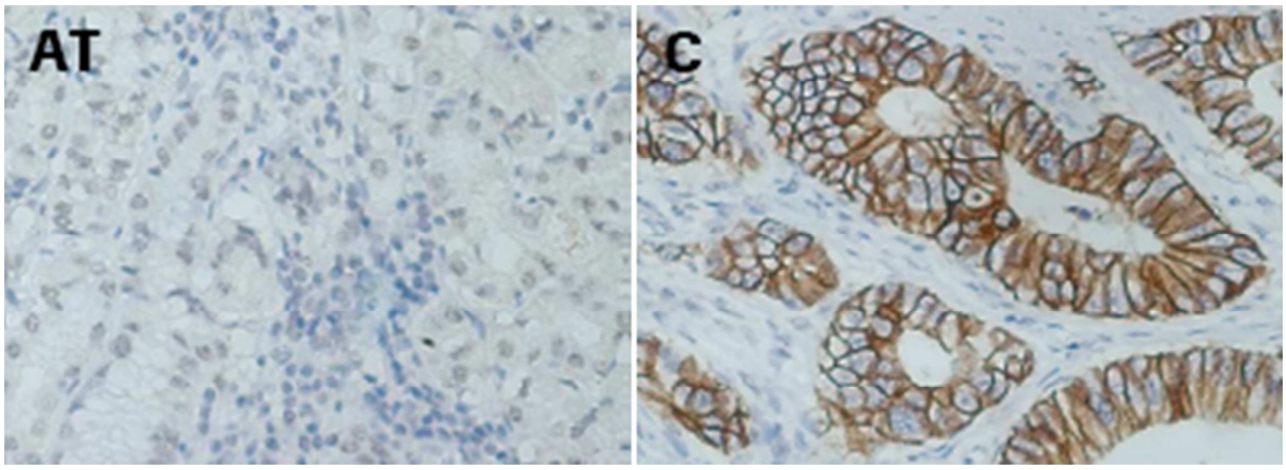

Figure 4. CDH17 expression in gastric cancer (C) but not in adjacent non-tumor tissues (AT).

Oncogenesis

Overexpression of CDH17 can transform premalignant liver progenitor cells to liver carcinomas in mice. RNAi-mediated knockdown of CDH17 inhibited proliferation of both primary and metastatic HCC cell lines in vitro and in vivo. The HCC cell migration, invasion, colony formation and adhesion were also inhibited by CDH17 knockdown. CDH17 shRNA resulted in relocalization of β-catenin to the cytoplasm with the reduction of cyclin D1, and increased caspase 3, Bax and Bcl-xL levels. Therefore, CDH17 is a potential oncogene in HCC by regulating cell cycle and apoptosis via Wnt pathway (Liu et al., 2009).

Gastric cancer

Prognosis

CDH17 expression level in normal human stomach epithelium cells is very low, whereas it is overexpressed in ~60-80% of gastric cancer cells (Grötzinger et al., 2001; Ko et al., 2004). CDH17 level is correlated with advanced stages of gastric cancer, and associated with a poor prognosis and lymph node metastasis. By serial analysis of gene expression (SAGE), CDH17 was found associating with an intestinal type of gastric cancer (Yasui et al., 2009).

It was reported as a negative prognostic factor of pN0 gastric cancer and a new biomarker for early detection of gastric intestinal metaplasia (Wang et al., 2012; Grötzinger et al., 2001).

Oncogenesis

CDH17 knockdown by siRNA, shRNA or miRNA in gastric cancer cell lines can inhibit the cell proliferation, migration, invasion and adhesion in vitro, as well as tumor growth in xenograft models (Zhang et al., 2011; Liu et al., 2010). Overexpression of CDH17 in gastric cancer cell line MGC-803 cells promotes tumor growth in xenograft mouse model (unpublished data).

Pancreatic cancer

Prognosis

Unlike the normal liver and gastric tissues, CDH17 is found focally expressed in normal pancreatic ducts. In carcinoma, well-differentiated carcinoma cases expressed high level LI-cadherin, whereas less differentiated areas and poorly differentiated carcinoma

cases expressed less or were negative. The high CDH17 expression correlated with good survival in pancreatic ductal adenocarcinoma (Takamura et al., 2003).

Colorectal cancer

Prognosis

In normal colorectal epithelial cells, CDH17 immunoreactivity was present at the basolateral plasma membrane. In colorectal carcinoma, the expression of CDH17 is diminished in tumor tissues. It can be observed in well-differentiated adenocarcinoma cells with tight cell-cell adhesion, but expression was reduced in dedifferentiated adenocarcinoma cells. Reduced expression of CDH17 in colorectal cancer tissues correlated with dedifferentiation of tumors and poor survival of patients (Takamura et al., 2004; Kwak et al., 2007; Su et al., 2008). The expression patterns of CDH17 in different cancer types suggest its cell-context dependent roles in organs.

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