

## Gene Section

### Review

# CDH1 (cadherin 1, type 1, E-cadherin (epithelial))

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## Identity

**Hugo:** CDH1

**Other names:** Arc-1; CD324; CDHE; Cadherin-1; E-cadherin; ECAD; LCAM; UVO; Uvomorulin

**Location:** 16q22.1

## DNA/RNA

### Description

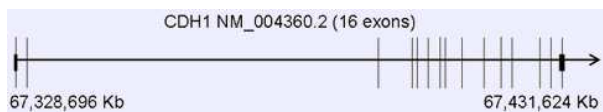
DNA contains 98250 bp composed of 16 coding exons.

### Transcription

4828 bp mRNA transcribed in centromeric to telomeric orientation; 2649 bp open reading frame.

### Pseudogene

Yes, for example, the repeat sequence named c41-cad is a pseudogene of the cadherin family. c41-cad is localized on 5q13.



DNA of CDH1 gene composed of 16 coding exons.

## Protein

### Description

The cadherins are a family of calcium-dependent transmembrane linker proteins; the first three that were discovered were named according to their tissue origin (E-cadherin from epithelium, N-cadherin from neural tissue and P-cadherin from placenta). The mature E-cadherin protein consists of three major domains: a large extracellular portion (exons 4-13), which mediates homophilic cellular interactions; and smaller transmembrane (exons 13-14) and cytoplasmic domains (exons 14-16), the latter providing a link to the

actin cytoskeleton through an association with various catenins, such as B-catenin. The protein E-cadherin is a calcium-dependent cell-cell adhesion molecule expressed in adherens junctions between epithelial cells. It is a transmembrane glycoprotein with five extracellular domains that mediate intercellular adhesion through homophilic binding. The cytoplasmic domain is bound to the actin cytoskeleton via intracellular attachment proteins, the catenins. The actin cytoskeleton forms a transcellular network mediating structural integrity, cellular polarity and epithelial morphogenesis.

### Expression

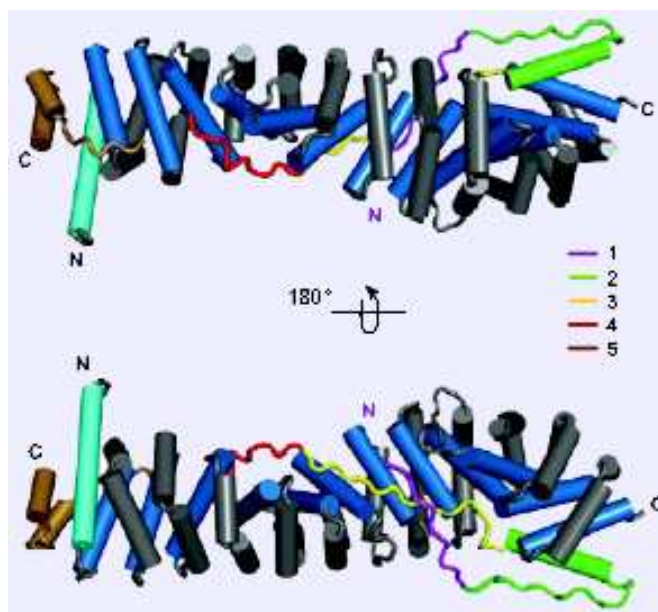
Present tissue specificity for non-neural epithelial tissues and there are high levels in solid tissues.

### Localisation

Cell junction; single-pass type I membrane protein. Anchored to actin microfilaments through association with alpha-catenin, beta-catenin and gamma-catenin. Sequential proteolysis induced by apoptosis or calcium influx, results in translocation from sites of cell-cell contact to the cytoplasm.

### Function

One of the most important and ubiquitous types of adhesive interactions required for the maintenance of solid tissues is that mediated by the classic cadherin adhesion molecules. Cadherins are transmembrane Ca<sup>2+</sup>-dependent homophilic adhesion receptors that are well known to play important roles in cell recognition and cell sorting during development. However, they continue to be expressed at high levels in virtually all solid tissues. There are many members of the classic cadherin family (which is a subset of the larger cadherin superfamily), but E-cadherin in epithelial tissues has been the most studied in the context of stable adhesions.



Three-dimensional structure of the beta-catenin arm repeat region in complex with the E-cadherin cytoplasmic domain (Huber and Weis, 2001). The arm repeats are formed by three helices, H1 and H2 (both gray) and H3 (blue). Residues 134-161, which include part of the alpha-catenin-binding site and a portion of the first arm repeat, form a single helix in this particular crystal structure (cyan). E-cadherin is divided into five regions of primary structure (1-5) that are indicated in distinct colors (Pokutta S and Weis WI, 2007).

Continued expression and functional activity of E-cadherin are required for cells to remain tightly associated in the epithelium, and in its absence the many other cell adhesion and cell junction proteins expressed in epithelial cells (see below) are not capable of supporting intercellular adhesion. In its capacity to maintain the overall state of adhesion between epithelial cells, E-cadherin is thought to act as an important suppressor of epithelial tumor cell invasiveness and metastasis.

### Homology

Pan troglodytes - CDH1; Canis lupus familiaris - CDH1; Mus musculus - Cdh1; Rattus norvegicus - Cdh1; Gallus gallus - LOC415860; Danio rerio - cdh1.

## Mutations

### Germinal

30 CDH1 germline mutations have been described in hereditary diffuse gastric cancer families. 25 have been inactivating (frameshift, nonsense, and splice-site), the remainders are missense. The mutations are distributed equally throughout the gene.

### Somatic

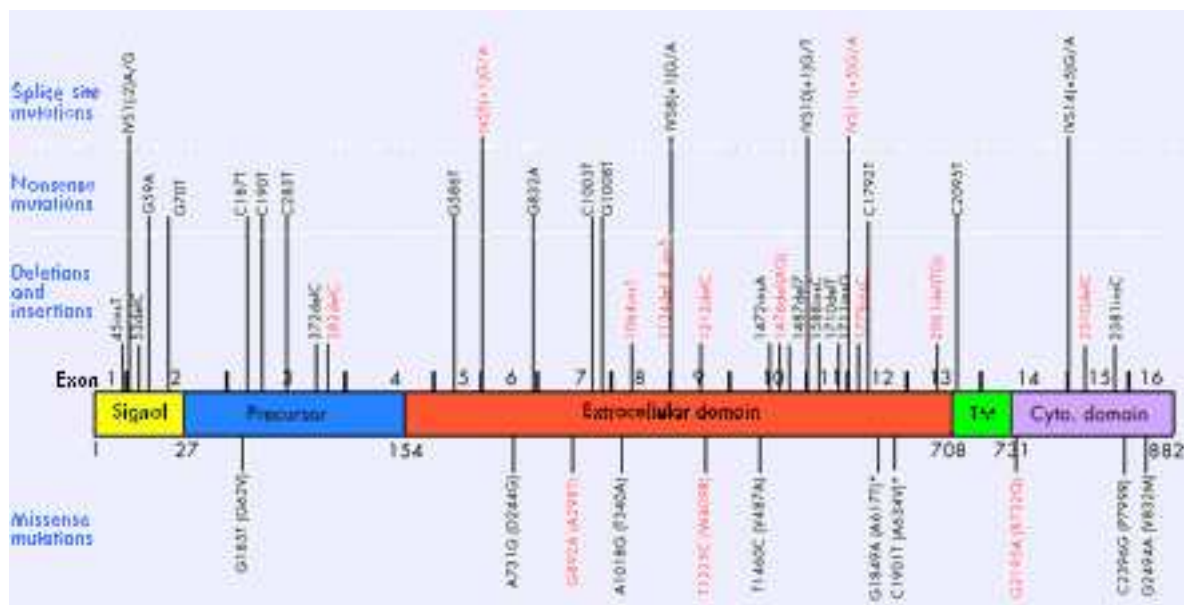
Somatically acquired mutations in CDH1 were found in about 56% of lobular breast tumors, generally (>90%) in combination with loss of the wild-type allele, while no mutations were found in ductal primary breast carcinomas. Most of these somatic mutations result in premature stop codons as a consequence of insertions, deletions and nonsense mutations. As the majority of these frameshift and nonsense mutations is predicted to

generate secreted E-cadherin fragments, the functionality of this major cell-cell adhesion protein is lost. Other cancer-confined E-cadherin mutations also result in crippled proteins. The distinctive invasive growth pattern, which is typical for lobular breast cancers, is fully compatible with this functional inactivation.

472 human tumors and 15 different cancer cell lines derived from 10 different tissues have been screened for CDH1 mutation. So far, frequent somatic mutations (50%) have been identified only in sporadic diffuse gastric cancer (DGC), Lobular Breast Cancer. For sporadic DGC, most somatic mutations are missense (exons 8, 9) or exon skipping. For sporadic Lobular Breast Cancer, most somatic mutations are truncating. 472 human tumors and 15 different cancer cell lines derived from 10 different tissues have been screened for CDH1 mutation. So far, frequent somatic mutations (50%) have been identified only in sporadic Diffuse Gastric Cancer, Lobular Breast Cancer.

Interestingly, there is a major difference between the mutation types identified in these two carcinoma types. In diffuse gastric carcinomas, the predominant mutations are exon skippings causing in-frame deletions. By contrast, most mutations identified in lobular breast cancer result in premature stop codons. In the case of the diffuse gastric carcinomas, a mutation cluster region is suggested as more than 60% of mutations cause exon skipping of exon 8 and 9.

Preliminary in vitro studies using transfected cell lines suggest that tumor-associated E-cadherin mutations reduce cell adhesion, increase cell motility, and change cell morphology possibly by dominant negative mechanisms.



57 CDH1 mutations have been found to date. 50 of these are listed in Human Gene Mutation Database. Truncating (27) and splice site (7) mutations are found above the Schema (34/45, 76%), missense mutations below it (11/45, 24%). Two marked with an asterisk have been reported as somatic mutations in sporadic diffuse gastric cancer. No Polymorphisms. No Gross deletions/duplications, complex rearrangements, repeat variations been reported. They spread out all over CDH1 gene (Brooks-Wilson et al., 2004).

On the contrary, the truncating mutations present in lobular breast cancers are obviously scattered over the entire E-cadherin gene. In line with this finding is the observation that the expression of E-cadherin protein is lost in lobular breast cancers, in contrast to the retention of expression of the mutant E-cadherin proteins in diffuse gastric carcinomas. Surprisingly, so far almost no E-cadherin mutations have been found to be located in the highly conserved cytoplasmic domain. In most cases, E-cadherin mutations are found in combination with loss of the wild-type allele.

## Implicated in

### Non-small cell lung cancer

#### Prognosis

Reduced E-cadherin correlates with lymph node metastasis. The rate of vascular invasion was statistically high in cases with the reduced expression of E-cadherin. Reduction of E-cadherin is associated with the degree of differentiation. Bohm et al. found a correlation between differentiation and E-cadherin expression in lung squamous cell carcinoma, and Bongiorno et al. found that well-differentiated lung cancers express E-cadherin, in a preserved fashion, and that poorly differentiated tumors exhibited a reduced or disorganized staining pattern. Sulzer et al. also found that E-cadherin expression significantly correlated with increasing tumor differentiation. In general, undifferentiated or poorly differentiated cancer cells tend to have a strong potential to invade tissues. These results suggest that reduction of E-cadherin correlates with tumor invasion.

#### Oncogenesis

Reduced E-cadherin expression weakens cell-to-cell attachment, and tumor cells detach from the primary tumor, invade vessels, and migrate to lymph nodes. Once tumor cells reattach to lymph nodes, E-cadherin is strongly expressed, and lymph nodes are subject to metastases.

### Melanoma

#### Oncogenesis

The major adhesion mediator between keratinocytes and normal melanocytes is E-cadherin, which disappears during melanoma progression. While normal melanocytes express E-cadherin, this molecule is not found on nevus or melanoma cells. The loss of E-cadherin likely plays a crucial role in tumor progression. Cells that have lost epithelial differentiation, as manifested by the loss of functional E-cadherin, show increased mobility and invasiveness. Keratinocytes can no longer control melanoma cells that have lost E-cadherin. When melanoma cells are forced to express E-cadherin and are cocultured with keratinocytes, they dramatically change: melanomas adhere to keratinocytes, no longer express invasion-related molecules, and lose their invasive capacities

### Oesophageal adenocarcinoma

#### Prognosis

Reduction in the expression of E-cadherin in patients with OSCC was shown to be strongly associated with postoperative blood borne recurrence, resulting in a poorer prognosis than in those patients with tumours showing normal expression before surgery.

This finding suggested that in patients with reduced E-cadherin immunoreactivity, the metastatic potential of the oesophageal cancer cells may be increased. Therefore, the evaluation of E-cadherin immunoreactivity may be useful in predicting haematogenous spread and hence recurrence, thus serving as an aid for planning adjuvant treatment after surgery in patients with OSCC. It has also been reported that E-cadherin might be an independent predictor of micrometastasis in lymph nodes that are classified as N0 by routine histopathological analysis.

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*This article should be referenced as such:*

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