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Gene Section
Review

CDH3 (Cadherin 3, Type 1, P-Cadherin (Placental))

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Abstract

Review on CDH3, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: CDHP, HJMD, PCAD

HGNC (Hugo): CDH3

Location: 16q22.1

DNA/RNA

Description

DNA contains 54807 bp containing 16 coding exons.

Transcription

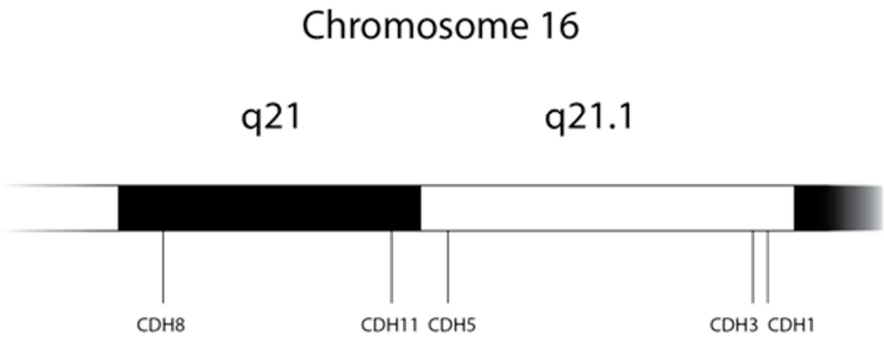
4276 bp mRNA transcribed in centromeric to telomeric orientation; 2490 bp open reading frame (CCDS10868.1).

Concerning CDH3/P-cadherin gene regulation, the main transcriptional activators described for the CDH3/P-cadherin gene promoter are β-catenin (Faraldo et al., 2007), p63 (Shimomura et al., 2008) and C/EBPβ (Albergaria et al., 2010; Albergaria et al., 2013).

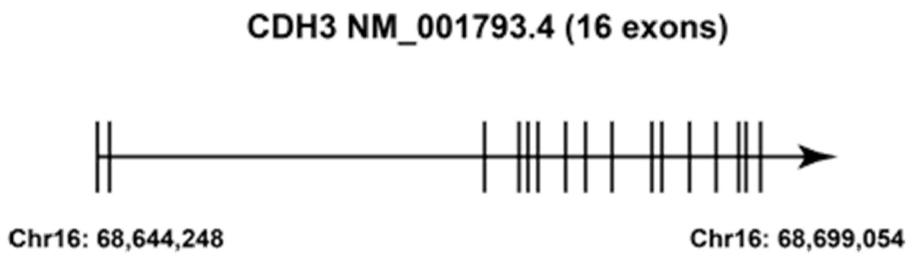
In contrast, BRCA1/c-Myc/Sp1 complex acts as a transcriptional repressor of the CDH3 promoter (Gorski et al., 2009).

It was also demonstrated that ER can indirectly repress P-cadherin expression by promoting epigenetic changes in the CDH3 gene promoter (Paredes et al., 2004; Albergaria et al., 2010).

This gene has 12 transcripts (splice variants), of which 5 are protein coding transcripts, 4 are transcripts suffering nonsense mediated decay, and 3 transcripts do not code for any protein product (ensemble ENSG00000062038 and vega genome OTTHUMG00000137560).



Localization of CDH3 gene (P-cadherin). 5 cadherin genes (CDH1; CDH3; CDH5; CDH8; and CDH11) are clustered in the 16q21-q22.1 region. The CDH3 gene is localized in the larger arm of chromosome 16, just 32Kb upstream of the gene encoding CDH1 (E-cadherin) (Bussemakers et al., 1994; Kremmidiotis et al., 1998).



The genomic structure of the CDH3/P-cadherin gene is constituted by 16 coding exons (NCBI Reference Sequence: NM_001793.4): the extracellular part of P-cadherin is encoded by 10 exons (exons 4-13), whereas the transmembrane and the intracellular domains are codified by the last 3 exons (exons 14-16) (Albergaria et al., 2011) (NCBI Reference Sequence: NM_001793.4).

Protein

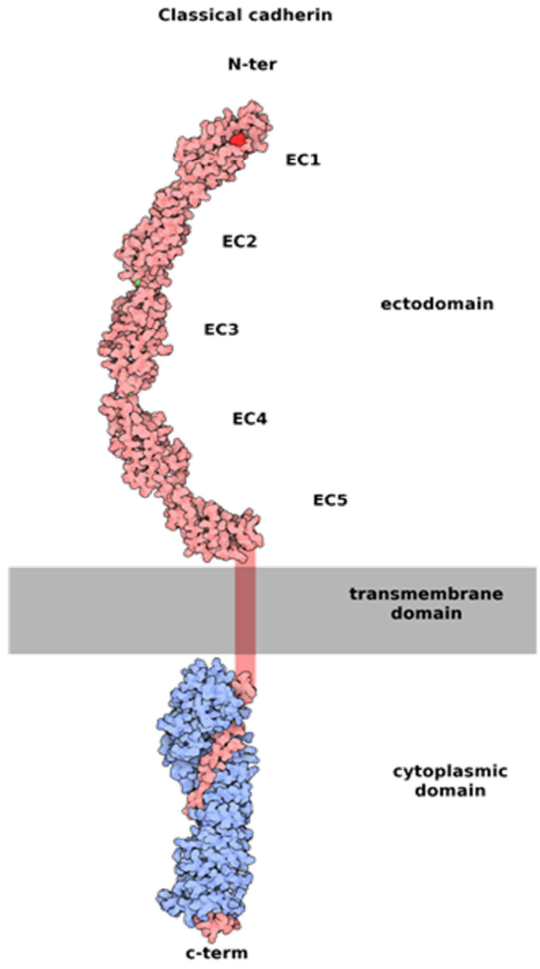


Image of a classical type I cadherin, adapted with permission from the RCSB PDB March 2008 Molecule of the Month feature by David Goodsell (doi: 10.2210/rcsb_pdb/mom_2008_3). P-cadherin is a transmembrane protein included in the classical cadherin family, with an ectodomain containing 5 cadherin repeats (which interacts with another cadherin's ectodomain in a cis or trans manner) and a highly conserved cytoplasmic domain that binds to catenins. Sharing about 67% of homology with the CDH1/E-cadherin gene, P-cadherin differs mainly in the extracellular portion and it is far less characterized.

Description

Described for the first time in 1986, as "a novel class of cadherin that appeared in developing mouse embryos", this adhesion molecule was found in the tissues that gave rise to its name, the placenta (Nose and Takeichi, 1986). P-cadherin is a transmembrane glycoprotein that belongs to a large family of molecules that mediate calcium-dependent homophilic cell-cell adhesion. It plays a role in many cellular processes such as embryonic development, differentiation, cell polarity, growth and migration (Larue et al., 1996).

P-cadherin is composed by three domains: 1) an extracellular portion responsible for calcium-dependent homotypic cadherin-cadherin interaction (which has 5 repeated cadherin domains); 2) a single pass transmembrane domain; and 3) a highly conserved cytoplasmic domain that binds to the intracellular catenins p120-catenin and β-catenin. Catenins have a dual role, acting as signalling mediators or as adaptor molecules that stabilize the cadherin complex at the membrane and link the cadherin molecule to the actin filaments of the cytoskeleton (Wheelock et al., 2001).

Expression

It is expressed in the placenta of mice (hence, its name). It is also expressed in human placental tissues, albeit at lower levels (Shimoyama et al., 1989; Sahin et al., 2014).

Despite being expressed in several human fetal structures, in the adult it is only expressed in certain tissues, usually co-expressed with E-cadherin, such as the basal layer of the epidermis, the breast and the prostate, as well as the mesothelium, the ovary, the hair follicle, and the corneal endothelium (Nose and Takeichi, 1986; Imai et al., 2008).

According to human protein reference database (HPRD:00227), the major sites of expression include endometrium, the glomerulus, hair follicle, keratinocytes, mammary myoepithelium, melanocytes, oocytes, spermatozoa, placenta, prostate, retina, serum, skin. An 80 KDa fragment of P-cadherin (known as soluble P-cadherin) is also found in human breast milk (Soler et al., 2002),

nipple aspirates (Mannello et al., 2008), semen (De Paul et al., 2005) and urine (Adachi et al., 2006).

Localisation

Cell junctions: a single-pass type I membrane protein anchored to actin microfilaments through association with α-catenin, β-catenin and γ-catenin. Sequential proteolysis induced by apoptosis or calcium influx, results in translocation from sites of cell-cell contact to the cytoplasm.

Function

Cell-cell adhesion: cadherin mediated cell-cell adhesion is accomplished by homophilic interactions between two cadherin molecules at the surface of the respective cells in a cis and/or trans manner (Cavallaro and Dejana, 2011) and the cadherin-catenin complex constitutes the main building block of the adherens-type junctions. These complexes also represent a major regulatory mechanism that guides cell fate decisions, influencing cell growth, differentiation, cell motility and survival (Cavallaro and Dejana, 2011).
Cell signalling: P-cadherin shares common interplayers with the wnt signalling pathway (eg. : β-catenin) (Kamposioras et al., 2013; Samuelov et al., 2013) and Integrin signalling (Vieira et al., 2014). In cancer, it may have a tumour suppressive or a cancer promoting function, depending on the cellular and tissue context (see below).

Homology

Sharing about 67% of homology with the CDH1/E-cadherin gene, P-cadherin differs mainly in the extracellular portion and it is far less characterized.
64 organisms have orthologs with the human CDH3 gene. For example, the CDH3 gene is conserved in chimpanzee, dog, cow, mouse, rat and chicken (HomoloGene:20425).

Mutations

Note

According to the Human Gene Mutation Database, 21 mutations have been described for the P-cadherin/CDH3 gene, namely 9 missense/nonsense mutations, 4 splicing mutations, 1 regulatory mutation, 1 gross deletion, 5 small deletions and 1 small insertion (The Human Gene Mutation Database). There are no reported descriptions of small indels, gross insertions/duplications, complex rearrangements or repeat variations. 16 mutations are associated with Hypotricosis with Juvenile Macular Dystrophy (HJMD) and 2 mutations are implicated with Ectodermal dysplasia, Ectrodactyly and Macular dystrophy (EEM) syndrome (The Human Gene Mutation Database).
Regarding polymorphisms, several SNPs have been reported for the CDH3 gene that have no clinical significance because they code for synonymous codons or related residues (ClinVar).

Missense/nonsense mutations

HGMD accession	HGMD codon change	HGMD amino acid change	HGVS (nucleotide)	HGVS (protein)	Phenotype	Reference	Source
CM032866	TTG-TAG	Leu168Term	503T>A	L168*	Hypotrichosis with juvenile macular dystrophy	Indelman (2003) *J Invest Dermatol* 121:1217	PubMed 14708629
CM070663	cCGA-TGA	Arg221Term	661C>T	R221*	Hypotrichosis with juvenile macular dystrophy	Indelman (2007) *Clin Exp Dermatol* 32:191	PubMed 17342797
CM121458	TACa-TAA	Tyr249Term	747C>A	Y249*	Hypotrichosis with juvenile macular dystrophy	Avitan-Hersh (2012) *Int J Dermatol* 51:325	PubMed 22348569
CM109686	GGC-GTC	Gly277Val	830G>T	G277V	EEM syndrome	Basel-Vanagaite (2010) *Mol Syndromol* 1:223	PubMed 22140374
CM051019	AAT-ATT	Asn322Ile	965A>T	N322I	EEM syndrome	Kjaer (2005) *J Med Genet* 42:292	PubMed 15805154
CM023041	CGT-CAT	Arg503His	1508G>A	R503H	Hypotrichosis with juvenile macular dystrophy	Indelman (2002) *J Invest Dermatol* 119:1210	PubMed 12445216
CM070664	tGAG-AAG	Glu504Lys	1510G>A	E504K	Hypotrichosis with juvenile macular dystrophy	Indelman (2007) *Clin Exp Dermatol* 32:191	PubMed 17342797
CM070662	CAC-CGC	His575Arg	1724A>G	H575R	Hypotrichosis with juvenile macular dystrophy	Indelman (2007) *Clin Exp Dermatol* 32:191	PubMed 17342797
CM053172	TATg-TAA	Tyr615Term	1845T>A	Y615*	Hypotrichosis with juvenile macular dystrophy	Indelman (2005) *Br J Dermatol* 153:635	PubMed 16120155

Splicing mutations					
HGMD accession	**HGMD splicing mutation**	**HGVS** (nucleotide)	**Phenotype**	**Reference**	**Source**
CS071159	IVS2 ds G-A +1	c.160+1G>A	Hypotrichosis with juvenile macular dystrophy	Indelman (2007) *Clin Exp Dermatol* 32:191	PubMed 17342797
CS106952	IVS10 as G-A -1	c.1425-1G>A	Hypotrichosis with juvenile macular dystrophy	Kamran-ul-Hassan Naqvi (2010) *Arch Dermatol Res* 302:701	PubMed 20140736
CS086158	IVS10 as G-T -1	c.1425-1G>T	Hypotrichosis with juvenile macular dystrophy	Jelani (2008) *Clin Exp Dermatol* 34:68	PubMed 19076794
CS103100	IVS12 as A-G -2	c.1796-2A>G	Hypotrichosis with juvenile macular dystrophy	Shimomura (2010) *Dermatology* 220:208	PubMed 20203473

Regulatory mutation				
HGMD accession	**Sequence**	**Phenotype**	**Reference**	**Source**
CR1111034	CCAATGACGTCAGGCATTTTAAACCTTTAG(AG)GGAAATTCAGCTTTCTCGGATGTCTGCTTT +3233 relative to transcription initiation site	Increased promoter activity	Benson (2011) *Physiol Genomics* 43:1038	PubMed 21771879

Small deletions					
HGMD accession	**Deletion** (^ exon number)	**HGVS** (nucleotide)	**Phenotype**	**Reference**	**Source**
CD033181	ACAGC^163CCCCCtGAGGGTGTCT	c.462delT	Hypotrichosis with juvenile macular dystrophy	Indelman (2003) *J Invest Dermatol* 121:1217	PubMed 14708629
CD033182	CGGAGC^278ACAGgCACCATCAGC	c.829delG	EEM syndrome	Kjaer (2005) *J Med Genet* 42:292	PubMed 15805154
CD013142	ATGCT^328CCCATgTTTGACCCCC	c.981delG	Hypotrichosis with juvenile macular dystrophy	Sprecher (2001) *Nat Genet* 29:134	PubMed 11544476
CD110819	GTGCAC^618CTTTctctGTCTGACCAT	c.1859_1862delCTCT	Hypotrichosis, autosomal recessive	Basit (2011) *Clin Genet* 79:273	PubMed 20528890
CD033183	GCGAA^704GAGGGgGGTGGCGAAG	c.2117delG	Hypotrichosis with juvenile macular dystrophy	Indelman (2003) *J Invest Dermatol* 121:1217	PubMed 14708629

Small insertions					
HGMD accession	**Insertion**	**HGVS** (nucleotide)	**Phenotype**	**Reference**	**Source**
CI110820	GAGAAT^341GCAGgTGGGCCATGA	c.1024dupG	Hypotrichosis, autosomal recessive	Basit (2011) *Clin Genet* 79:273	PubMed 20528890

Gross deletions					
HGMD accession	**DNA level**	**Description**	**Phenotype**	**Reference**	**Source**
CG1210199	gDNA	8815bp incl ex. 12-13	Hypotrichosis with juvenile macular dystrophy	Halford (2012) *Arch Ophthalmol* 130:1490	PubMed 23143461

Summary of the human CDH3 gene mutations. 21 mutations have been described for the P-cadherin/CDH3 gene, namely 9 missense/nonsense mutations, 4 splicing mutations, 1 regulatory mutation, 5 small deletions, 1 small insertion and 1 gross deletion (The Human Gene Mutation Database).

Germinal

Human germline mutations for the CDH3 gene have been reported to carry the phenotype of HJMD and EEM syndromes (Sprecher et al., 2001;Kjaer et al., 2005; Avitan-Hersh et al., 2012; Halford et al., 2012).
The germline deletion of CDH3 in the mouse causes breast secretory immaturity and premature mammary gland differentiation.
The P-cadherin mutant mice develop hyperplasia and dysplasia of the mammary epithelium with age and, in contrast to humans, no reports regarding development defects have been described (Radice et al., 1997).

Implicated in

Various cancers

Note

P-cadherin is altered in various human tumours, but its effective role in the carcinogenesis process remains object of debate, since it can behave differently depending on the studied tumour cell model and context.
For example, in melanoma, P-cadherin seems to have a tumour suppressive function, exactly as E-cadherin (Van Marck et al., 2005).
In breast cancer P-cadherin is often overexpressed and it is reported to exhibit tumour promoting effects (Paredes et al., 2012).
Importantly, P-cadherin upregulation is also found in other malignancies such as gastric, endometrial, colorectal and pancreatic carcinomas (Hardy et al., 2002; Stefansson et al., 2004; Taniuchi et al., 2005; Imai et al., 2008).

Breast cancer

Note

P-cadherin aberrant expression is found in 20% to 40% of invasive breast carcinomas, as well as in 25% of pre-invasive (in situ) ductal carcinomas. Aberrant P-cadherin expression was shown to be associated with tumours of high histological grade, as well as with well established markers of poor prognosis, like Ki-67, EGFR, CK5, vimentin, p53 and HER-2 expression, and negatively associated with age at prognosis and hormonal receptors (ER and PgR) expression.
None of these reports showed a significant association with tumour size and lymph node metastasis (Turashvili et al., 2011; Peralta Soler et al., 1999; Gamallo et al., 2001; Paredes et al., 2002; Paredes et al., 2005).
P-cadherin aggressive behaviour in breast cancer is dependent on an E-cadherin positive background (Ribeiro et al., 2013) and it is substantially attributed to an increased migratory and invasive capacity of cancer cells (Ribeiro et al., 2010), increased stem cell activity (Vieira et al., 2012) and cross-talk with integrin oncogenic signalling pathways (Vieira et al., 2014).
P-cadherin up-regulation is predominantly found in the basal-like subgroup of breast cancers (Matos et al., 2005; Paredes et al., 2007a; Paredes et al., 2007b) and it is strongly associated with the presence of BRCA1 mutation (Arnes et al., 2005) and poor clinical outcome (Paredes et al., 2005; Turashvili et al., 2011). It has been proposed that P-cadherin in conjugation with vimentin and CK14 constitutes a better criterion for the identification of basal-like breast carcinomas by immunohistochemistry (Sousa et al., 2010).

Prognosis

P-cadherin overexpression in breast cancer is an independent factor of poor prognosis (poor disease free and overall survival) (Paredes et al., 2005; Turashvili et al., 2011).

Hypotrichosis with juvenile macular dystrophy (HJMD)

Note

In humans, the loss of P-cadherin induces characteristic genetic syndromes.
CDH3 gene mutations have been shown to cause P-cadherin functional inactivation, leading to developmental defects associated with hypotrichosis with juvenile macular dystrophy (HJMD) (Sprecher et al., 2001; Avitan-Hersh et al., 2012; Halford et al., 2012).

Disease

Hypotrichosis with juvenile macular dystrophy (HJMD; OMIM: 601553) is a rare recessive disorder, characterized by hair loss heralding progressive macular degeneration and early blindness. Affected HJMD individuals are born with seemingly normal hair but develop alopecia of the scalp at around 3 months. After the age of 3 years, affected individuals develop progressive macular degeneration with slight peripheral retinal dystrophy. The severe degenerative changes of the retinal macula culminate in blindness during the second to third decade of life. Since Sprech er et al. (2001) first established a link between this disease and a mutation in gene encoding CDH3/P-cadherin (Sprecher et al., 2001), several other mutations were found, which essentially disturb the Ca2+ binding and the cadherin functional domains or result in the synthesis of a truncated form of P-cadherin or in the absence of P-cadherin expression.

Cytogenetics

The following allelic variants are responsible for HJMD:
- CDH3, c981delG - (Sprecher et al., 2001)
- CDH3, Arg503His - (Indelman et al., 2002)
- CDH3, Leu168Term - (Indelman et al., 2003)

- CDH3, Arg221Term - (Indelman et al., 2007)
- CDH3, Tyr249Term - (Avitan-Hersh et al., 2012)
- CDH3, Glu504Lys - (Indelman et al., 2007)
- CDH3, His575Arg - (Indelman et al., 2007)
- CDH3, Tyr615Term - (Indelman et al., 2005)
- CDH3, IVS2 ds G-A +1 - (Indelman et al., 2007)
- CDH3, IVS10 as G-A -1 - (Jelani et al., 2009; Kamran-ul-Hassan Naqvi et al., 2010)
- CDH3, IVS12 as A-G -2 - (Shimomura et al., 2010)
- CDH3, c.462delT - (Indelman et al., 2003)
- CDH3, c.2117delG - (Indelman et al., 2003)
- CDH3, gDNA 8815bp deleted incl exons 12-13 - (Halford et al., 2012)

Ectodermal dysplasia, ectrodactyly and macular dystrophy (EEM)

Note

CDH3 gene mutations have been shown to cause P-cadherin functional inactivation, leading to ectodermal dysplasia, ectrodactyly, and macular dystrophy (EEM syndrome), a developmental defect associated syndrome. This inherited disease is characterized by sparse hair and macular dystrophy of the retina, and split hand/foot malformation (Kjaer et al., 2005).

Disease

This ectodermal defect is characterised by hypotrichosis with sparse and short hair on the scalp, sparse and short eyebrows and eyelashes, and partial anodontia. Different degrees of absence deformities as well as syndactyly have been described, the hands often being more severely affected than the feet. The retinal lesion appears as a central geographic atrophy of the retinal pigment epithelium and choriocapillary layer of the macular area with coarse hyperpigmentations and sparing of the larger choroidal vessels.

Kjaer et al. (2005) first established a link between families with ectodermal dysplasia, ectrodactyly, and macular dystrophy (EEM; OMIM: 225280) and homozygous mutations in CDH3/P-cadherin in affected individuals: a missense mutation (114021.0003) and a deletion (114021.0004), respectively (Kjaer et al., 2005).

Cytogenetics

The following allelic variants are responsible for EEM:

- CDH3, Asn322Ile - (Kjaer et al., 2005)
- CDH3, c.829delG - (Kjaer et al., 2005)
- CDH3, Gly277Val - (Basel-Vanagaite et al., 2010)

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