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Gene Section
Review

CTNND1 (catenin (cadherin-associated protein), delta 1)

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Identity

Other names: CAS, CTNND, KIAA0384, P120CAS, P120CTN, p120

HGNC (Hugo): CTNND1

Location: 11q12.1

Note: Bases 57,529,234-57,586,651 on chromosome 11.

DNA/RNA

Description

DNA contains 57419 bp composed of 21 exons, 19 of which are coding exons.

Transcription

Alternative transcription produces several distinct mRNAs ranging from 5676 bp to 6329 bp, transcribed in centromeric to telomeric orientation, with open reading frames ranging from 2802 bp to 2904 bp.

Pseudogene

None.

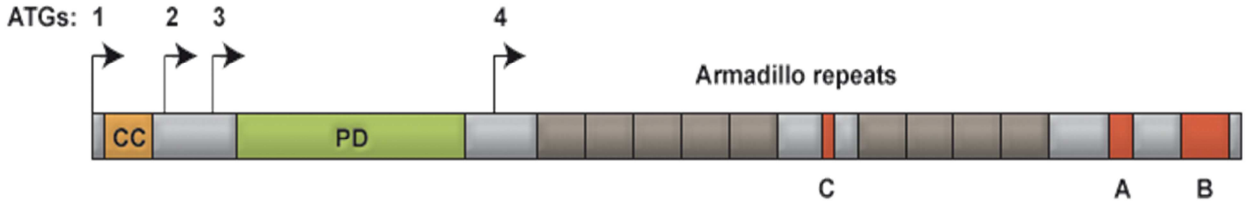
Protein

Description

This gene encodes a member of the Armadillo (Arm) family of proteins, which function in cell-cell adhesion and signal transduction, and is the prototype for a subfamily of proteins that includes p120-catenin (hereafter p120), delta-catenin, p0071, and plakophilins 1-3 (PKP1, PKP2, PKP3). CTNND1/p120 has four distinct translation start codons (isoforms 1-4) and three alternatively spliced exons (A, B, and C), potentially resulting in 32 isoforms as products of alternative splicing. A coiled-coil domain is present in the extreme amino-terminus of the long-isoform (isoform-1), and an amino terminal phosphorylation domain is present in all but the shortest isoform (isoform-4).

All p120 isoforms contain a central Arm domain consisting of nine Arm repeats. p120 has been shown to be post-translationally modified by phosphorylation on tyrosine, serine, and threonine residues, as well as by cleavage by the protease calpain.

CTNND1/p120 gene structure. DNA of CTNND1 gene (NM_001085458.1) composed of 19 coding exons (red). Untranslated regions are depicted in green.



CTNND1/p120 protein structure. p120 contains four translational start sites (1-4, arrows) and three alternatively transcribed exons A, B, and C (red boxes). Isoform-1 contains an amino-terminal coiled coil domain (CC), and a phosphorylation domain (PD) is present in all but isoform-4. All isoforms contain a central Armadillo repeat domain (gray boxes).

Phosphorylation of p120 may be regulated in part via interactions with non-receptor tyrosine kinases, (including Fer, Fyn, and Yes) and protein tyrosine phosphatases (including PTPmu, SHP-1, and DEP-1).

Expression

p120 isoforms have been detected in all tissues examined, although cells of epithelial origin tend to predominantly express isoform 3, whereas motile, fibroblastoid cells often express isoform 1.

Localisation

Cell-cell junctions (bound to cadherin molecules), cytoplasm, and nucleus.

Function

CTNND1/p120 was originally identified as a substrate for the Src oncogene and for various receptor tyrosine kinases, though its most prominent role is in stabilizing adherens junctions. Via its Arm domain, p120 binds to the juxtamembrane region of the cytoplasmic tails of type I and II cadherins. Upon removal of p120, by either gene knock-out or shRNA-mediated knock-down, adherens junction components, namely cadherin, beta-catenin, and alpha-catenin, are internalized and rapidly degraded. p120 also likely participates in the rearrangement of the actin cytoskeleton via regulation of Rho family GTPases, and p120 may also influence gene expression via its interaction in the nucleus and cytoplasm with the transcriptional repressor Kaiso.

Homology

Pan troglodytes - CTNND1; Canis lupus familiaris - CTNND1; Bos taurus - CTNND1; Mus musculus - Ctnnd1; Rattus norvegicus - Ctnnd1; Gallus gallus - RCJMB04_21j12; Danio rerio - LOC556726.

Mutations

Note

While p120 is frequently decreased in a wide variety of cancers, the only mutated p120 identified to date is found in colonic SW48 cells. In these cells, a heterozygous nonsense mutation in exon 7 at nucleotide 1908 (C to T) yields a premature stop codon that truncates the protein in the third ARM repeat. Several other cDNA abnormalities, including deletion of exon 17, retention of intron 19, or retention of both introns 19 and 20, were also identified in both p120 alleles in these cells, resulting in premature stop codons that eliminate the normal p120 COOH terminus.

Implicated in

Various cancers

Note

p120's ability to stabilize E-cadherin, a tumor suppressor, suggests that p120 may play a role in tumor and/or metastasis suppression. Indeed, p120 is often lost, downregulated, or mislocalized in human colon, breast, prostate, lung, and other carcinomas. Total p120 knockout is embryonically lethal in mice, but conditional knockout studies have shown that p120 loss in the salivary gland induces dysplasia indistinguishable from high-grade intraepithelial neoplasia, and p120 ablation in the epidermis induces hyperproliferation and inflammation. However, recent studies have also identified a requirement for p120 in anchorage-independent growth of both tumor cell lines and oncogene-transformed cell lines. Moreover, a role for p120 and its binding partner Kaiso in Wnt signaling, which is often hyperactive in colon cancer, is becoming increasingly evident.

Breast cancer

Note

cDNA microarray analysis revealed a downregulation of p120 in invasive breast cancers compared to their respective benign control breast tissues, and immunohistochemical analyses of tissue samples from 341 invasive breast cancer patients found that p120 downregulation predicted a 3.1-fold risk in breast cancer death.

Additionally, translation initiation factor eIF4GI-enhanced translation of IRES-containing p120 mRNAs has been shown to promote tumor emboli formation in inflammatory breast cancer.

Lung cancer

Note

A study of 138 patients with non-small cell lung cancer found that p120 membrane localization was reduced and ectopic cytoplasmic expression was increased in lung cancer tissues. Abnormal p120 localization correlated with TNM stage and lymph node metastasis.

Skin cancer

Note

p120 was found to be altered in squamous cell carcinomas in humans, and conditional ablation of p120 in the epidermis in mice led to progressive development of skin neoplasias.

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