

Gene Section

Review

TJP2 (tight junction protein 2 (zona occludens 2))

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Identity

Other names: MGC26306; X104; ZO2; ZO-2

HGNC (Hugo): TJP2

Location: 9q21.11

Local order: Telomeric to FXN gene (9q21.11).

DNA/RNA

Description

TJP2 gene exists as a single copy in the human genome; it contains 25 exons and is predicted to span over approximately more than 90 Kb of the genomic DNA.

Transcription

Five isoforms of TJP2 have been identified:

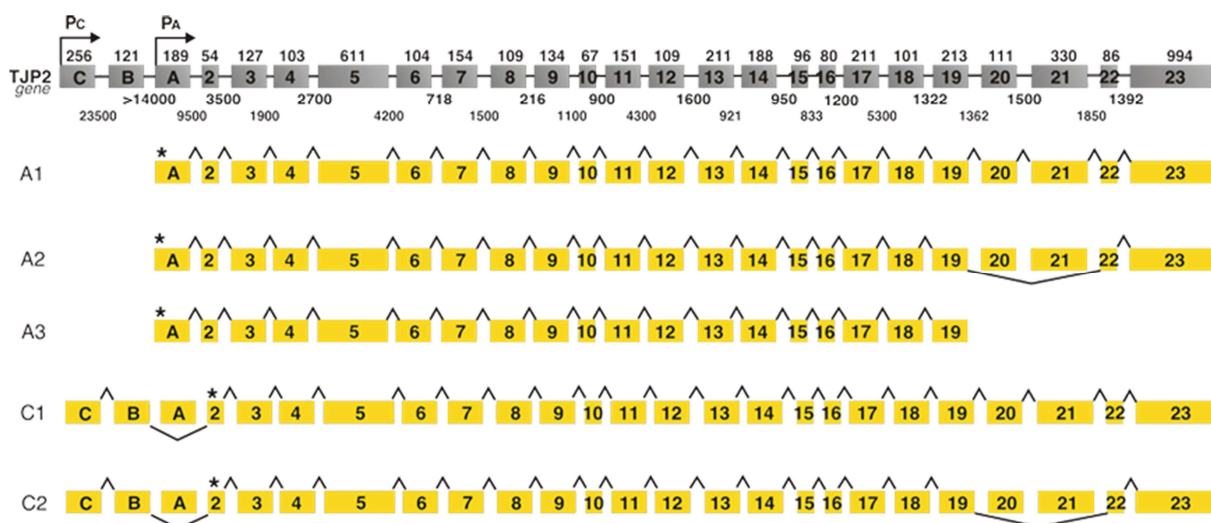
The A1 isoform (CDS: 3570 nt); lacks exons C and B

The A2 isoform (CDS: 3129 nt); lacks exons C, B, 20 and 21.

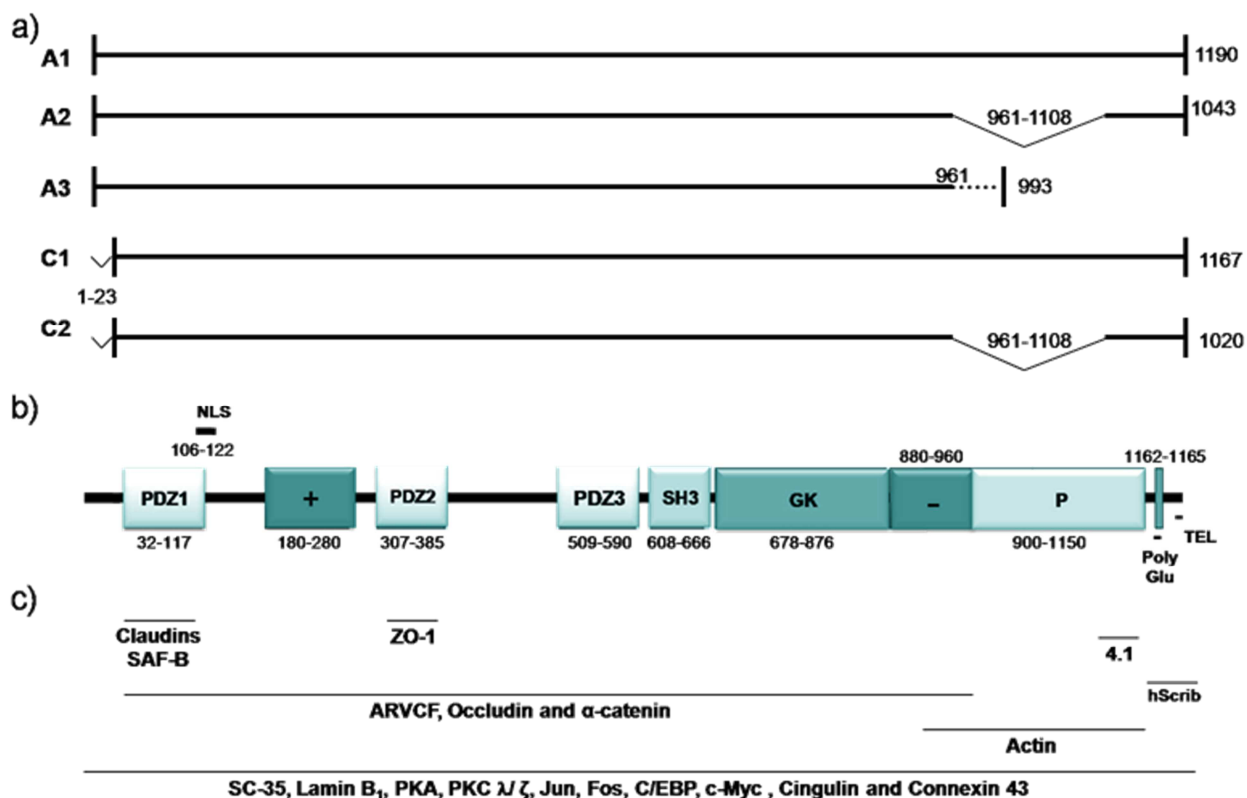
The A3 isoform (CDS: 2979 nt); lacks exons C, B, 20, 21, 22 and 23 and exhibits a longer exon 19 (979 vs 213 bp, with a stop codon at bp 313).

The C1 isoform (CDS: 3501 nt); lacks exon A.

The C2 isoform (CDS: 3057 nt); lacks exons A, 20 and 21.



Schematic diagram of the TJP2 gene comprising 25 exons (in grey) and transcript variants. The sizes in base pairs of exons (above) and introns (below) are shown. *Indicates the position of the start codons. Exons C and B are expressed from promoter C. These exons are non-coding and translations starts from the ATG located in exon 2. Exon A is transcribed from promoter A. Isoforms C lack 23 aminoacids at the amino terminus in comparison with isoforms A. Exons 20 and 21 are alternatively spliced.



Isoforms, structure and interactions of TJP2. a) Five isoforms to TJP2 have been reported. A and C isoforms are products of alternative promoter usage. A2 and C2 are consequence of alternative splicing of exons 20 and 21. Translation of A3 ends in exon 19. However in A3 exon 19 has 979 instead of 213 bp and exhibits a stop codon at bp 313. This situation makes isoforms A3 end with a sequence of 33 amino acids that are not present in any of the other TJP2 isoforms. Numbers refer to amino acids. b) TJP2 is a MAGUK protein with three PDZ domains, an SH3 module and a GK domain. Between the first two PDZ domains, a region rich in basic amino acids is found. After the GK domain in C terminus direction, an acidic region and a proline rich domain is present. The last three amino acids at the carboxyl end constitute a PDZ binding motif and the first 23 amino acid residues at the N-terminus are absent in C isoforms. Numbers refer to amino acids. c) TJP2 is a scaffold molecule that interacts with proteins that participate in cell adhesion, signaling and gene transcription. The names of these proteins and their site of interaction in TJP2 are indicated.

Northern blot analysis done with different probes for exons A and C reveals two TJP2 transcripts of the same size, approximately 4.5 Kb, that respectively correspond to TJP2A and TJP2C.

Pseudogene

Not known.

Protein

Description

The full length TJP2 protein consists of 1190 amino acids corresponding to a theoretical molecular weight of 133.958 kDa. This size is 16% smaller than the apparent molecular mass of 160 kDa determined by SDS/PAGE. The high proline content (7.1%) may be responsible for this anomalous electrophoretic migration. The protein contains three PDZ, one SH3 and one GuK domain at its NH₂ dlg-like terminal region, followed by a short COOH terminal non dlg-like region that contains an acidic and a proline rich domain. The protein belongs to the MAGUK protein family. At the carboxyl terminal end of TJP2 the type I PDZ binding motif TEL is found. TJP2 is predicted to

contain 1 nuclear localization signal (NLS; 106-122 aa) and no exportation signals (NES) following the consensus L/M/IX₁₋₄L/V/IX₂₋₃L/V/IX₁₋₂L/I.

Two isoforms named A and C arise from the activation of different promoters. In the A form the initiation codon located within a unique 5' end 189 bp sequence gives rise to a distinctive 23 aa segment, whereas in the C form the 5' end exhibits a 377 bp sequence that is not translated. In isoforms C translation starts from a codon that corresponds to the second ATG in isoforms A. Isoform A2 is generated by alternative splicing of isoform A1. It lacks amino acids 961-1108.

Isoform A3 is generated by alternative splicing of isoform A1. It lacks amino acids 994-1190 and the sequence from amino acids 961 to 993 differs from isoform A1.

Isoform C2 is generated by alternative splicing of isoform C1. It lacks amino acids 961-1108.

Expression

Normal tissue: At the mRNA level the A isoforms are abundant in the heart and brain whereas the C isoforms are expressed at a high level in kidney, pancreas, heart

and placenta. In brain and skeletal muscle only the A isoform is detectable, but there is no tissue where TJP2C is solely present. TJP2 protein is strongly expressed in epithelial and endothelial cells. During mouse embryogenesis at the 16 cell stage, TJP2 assembles at the apico-lateral contact site of blastomeres for the first time. The half-life of TJP2 protein varies according to the degree of confluence of the culture, thus in canine kidney MDCK cells half lives correspond to 8.7 and 19.1 hrs in sparse and confluent cultures respectively.

Localisation

Present at the cytoplasmic side of tight junctions in epithelial and endothelial cells. In proliferating cultures and in cells under environmental stress TJP2 is also present at the nucleus. TJP2 enters the nucleus at the late G1 phase of the cell cycle and departs during mitosis. At the nucleus TJP2 exhibits a speckled distribution and co-localizes with splicing factor SC-35 and the nuclear ribonucleo-protein scaffold attachment factor SAF-B. In fibroblasts TJP2 gives a punctate pattern at the cell borders, and in cardiac muscle cells it is detected at the intercalated discs.

Function

TJP2 is crucial during development as silencing inhibits blastocoele formation in mouse embryos and knock out mice die shortly after implantation due to an arrest in early gastrulation.

TJP2 silencing with siRNA delays in epithelial monolayers the arrival of tight junction proteins to the cell membrane, triggers the novo formation of leaky tight junctions and alters cell polarity, thus suggesting that TJP2 is critical for the correct assembly and function of tight junctions. TJP2 and TJP1 are redundant in their role as promoters of claudins polymerization into tight junction strands.

TJP2 inhibits transcription of human cyclin D1 (CD1) gene, decreases CD1 protein levels due to an increased degradation of the protein at the proteasome, blocks cell cycle progression from G1 phase to S and in consequence inhibits cell proliferation. These observations favor the image of TJP2 as a tumor suppressor protein.

Besides the above mentioned, the nuclear function of TJP2 remains elusive. It localizes in speckles with SC-35 and associates to lamin B1, to transcription factors Jun, Fos, C/EBP and Myc, to SAF-B, a chromatin component involved in the assembly of transcriptosome complexes, and enhances the nuclear localization of ARVCF, an Armadillo-repeat protein that associates with classical cadherins in adherens junctions.

Homology

TJP2 shares the following homology and identity (in parenthesis) with TJP1: 68% (54%); TJP3: 63% (45%); PSD-95: 40% (25%) and Dlg: 40% (23%).

Mutations

Germinal

Mutation 143T->C, predicted to cause a valine to alanine substitution (V48A) in TJP2 produces the loss of the alpha-helical structure of PDZ1 domain of TJP2.

Somatic

Not known.

Epigenetics

Microarray analysis indicates that in 70% of primary pancreatic cancers TJP2 is aberrantly methylated.

Implicated in

Pancreatic adenocarcinoma

Note

In ductal pancreatic cancer cell lines BxPC3, Capan2, CFPAC1, Colo357, Hs766T, MiaPaCa-2, PL3, PL4, PL7, PL8, PL10, PL11 and PL11, TJP2 gene is methylated. Instead TJP2 gene is not methylated in ductal pancreatic cancer cell lines AsPC1, Capan1, Panc1, PL1, PL5, PL6, PL9, PL13 and PL14. Treatment with the demethylating agent 5-aza-2'-deoxycytidine (5 Aza-dC) induces TJP2 expression in MiaPaCa (8.51 fold) and in Panc1 (1.41 fold) cells but not in AsPC1 and Hs766T.

Methylation analysis by digestion with restriction endonucleases reveals aberrant hypermethylation in PA promoter of isoform TJP2A from bases -383 to 87, which contains 62 CpG dinucleotides, in a variety of human primary pancreatic duct carcinomas and in the neoplastic human pancreatic duct cell lines BxPC-3, CFPAC-1, Hs700T, Hs766T, MiaPaCa-2, Su.86.86. However, demethylation of the PA does not recover normal level of TJP2A protein expression in the neoplastic cell lines except Su.86.86.

Isoform TJP2A is specifically missing in pancreatic adenocarcinoma samples and in human pancreatic duct carcinoma cell lines with the exception of line PANC-1.

Disease

Pancreatic adenocarcinoma is a disease in which malignant cells form in the regions of the pancreas that have gland like properties. Although the pancreas has exocrine and endocrine cells, about 95% of pancreatic cancers begin in exocrine cells and more than 90% of tumors of the pancreas are ductal adenocarcinomas derived from the exocrine pancreatic ducts. Depending on the extent of the cancer at the time of diagnosis, the prognosis is generally poor with less than 5% of those diagnosed still alive five years after diagnosis.

Typically pancreatic cancer first metastasizes to regional lymph nodes, then to the liver and less commonly to the lungs, although it can also directly invade surrounding visceral organs or metastasize to

any surface in the abdominal cavity via peritoneal spread.

Prostate adenocarcinoma

Note

In a prostate microarray assay the promoter sequence of TJP2 from cancerous cell lines PC3, PC3M, PC3M-Pro4, PC3M-LN4 and LNCaP showed a significantly diminished hybridization in comparison to normal prostate cell lines RWPE-1, MLCsv40 and 267B1, which indicates a greater methylation of the TJP2 promoter in prostate cancer. However in prostate adenocarcinoma cell lines loss of TJP2A protein is rare.

Disease

Prostate is a gland in the male reproductive system located below the bladder and in front of the rectum that produces seminal fluid that nourishes and transports sperm. Most cells in the prostate gland are of the glandular type; therefore the adenocarcinoma is the most common type of cancer to occur in the prostate. In the United States prostate cancer is the most common type of cancer in men, affecting about one in 8. It appears mainly in older men.

Colon cancer

Note

In colon cancer loss of TJP2A protein is rare.

Disease

Also called colorectal cancer or large bowel cancer, includes cancerous growths in the colon, rectum and appendix. It is the third most common form of cancer and the second leading cause of cancer related death in the Western world. Colon cancer is thought to arise from adenomatous polyps in the colon. Colon adenocarcinoma accounts for 95% of cases of colon cancer. Colon cancer is the fourth most common cancer of males and females in the United States.

Breast cancer

Note

In comparison to normal cells, TJP2 is found at a much lower protein level in malignant breast epithelia. In cancerous breast TJP2 immunostaining becomes more diffuse and decreases in intensity. By quantitative PCR the level of TJP2 mRNA is slightly elevated in the breast tumor tissues compared to the controls, however this result is not statistically significant.

Disease

Breast cancer is a disease in which malignant cells form in the tissues of the breast. Each breast has 15-20 sections called lobes, which have smaller sections named lobules. Lobules end in dozens of tiny bulbs that can produce milk. The lobes, lobules and bulbs are linked by thin tubes called ducts. The most common type of breast cancer is ductal carcinoma that begins in the cells of the ducts. Cancer that begins in the lobes or lobules is called lobular carcinoma and is more often found in both breasts. Because the breast is a glandular

tissue nearly all breast cancers are called adenocarcinomas. Breast cancer is the most common type of cancer in women, affecting about 1 in 8 women.

Testicular in situ carcinoma

Note

Loss of blood-testis barrier integrity and a decreased protein level expression of TJP2 is detected in testicular in situ carcinoma. In addition, ZO-2 immunoreactivity became weak and diffuse at the blood testis barrier region and spread to stain the entire lateral site of Sertoli cells as well as their cytoplasm, indicating altered localization.

Disease

Testicular cancer is a disease in which malignant cells form in the tissues of one or both testicles. The testicles are 2 egg-shaped glands located inside the scrotum that produce testosterone and sperm. Germ cells within the testicles produce immature sperm that mature as they travel through a network of tubules and tubes into the epididymis. Almost all testicular cancers start in the germ cells. The testicular in situ carcinoma also known as stage 0, is a noninvasive precursor of testicular germ cell tumors, which are the most common type of cancer in young men. In testicular in situ carcinoma, abnormal cells are found in the tiny tubules where the sperm cells begin to develop, and all tumor marker levels are normal at this stage.

Lung squamous carcinoma

Note

Squamous cell carcinomas show a 76% decrease in mRNA level for TJP2.

Disease

Lung cancer is a disease that forms in the tissues of the lung. In the United States it is the second most common malignancy after prostate cancer in men and breast cancer in women. The two main types of lung cancer are small cell lung cancers and non-small cell lung cancers, which are diagnosed based on how the cells look under the microscope. One type of non-small cell lung cancer is the squamous cell carcinoma. This cancer begins in squamous cells which are thin, flat cells that look like fish scales. It is also called epidermoid carcinoma. Squamous cell carcinoma is the second commonest type of lung cancer, accounting for 28% of all cases of lung cancer.

Lung adenocarcinoma

Note

Lung adenocarcinomas exhibit a 72% decrease in the mRNA level of TJP2.

Disease

Lung cancer is a disease that forms in the tissues of the lung. In the United States it is the second most common malignancy after prostate cancer in men and breast cancer in women. The two main types are small and

non-small cell lung cancers, which are diagnosed based on how the cells look under the microscope. One type of non-small cell lung cancer is the adenocarcinoma in which the cancer begins in the cells that line the alveoli and make substances such as mucus. Lung adenocarcinoma is the most common kind of lung cancer in smokers and non-smokers and in people under age 45, accounting for about 40% of all lung cancers.

Familial hypercholanemia (FHC)

Note

Mutation 143T-->C, predicted to cause a valine to alanine substitution (V48A) in TJP2 produces the loss of the alpha-helical structure of PDZ1 domain of TJP2. This mutation reduces PDZ1 domain stability and ligand binding in vitro. Thus binding of PDZ1 domain of TJP2 to peptides corresponding to the six C-terminal amino acids from claudin 1, claudin 2, claudin 3, claudin 5 and claudin 7 is significantly reduced when V48A mutation is present. This mutation is associated with Familial Hypercholanemia (FHC).

Disease

Mutation 143T-->C, causing a valine to alanine substitution (V48A) in TJP2 is associated to Familial hypercholanemia (FHC).

Familial hypercholanemia is characterized by elevated serum bile acid concentrations, itching and fat malabsorption. In TJP2143C/143C individuals inheritance is oligogenic, with mutations in bile acid coenzyme A amino acid N-acyltransferase (BAAT), required for clinical disease.

To be noted

Note

TJP2 is proposed to be a tumor suppressor gene because: 1) TJP2 protein and/or mRNA expression is either lost or decreased in pancreatic, prostate, breast and lung adenocarcinomas, in testicular in situ carcinoma and in lung squamous carcinoma. 2) Has 40% homology to the tumor suppressor gene Dlg. 3) TJP2 is target of the major oncogenic determinant E4-ORF1 of human adenovirus type 9 (Ad9). E4-ORF1 has a PDZ binding motif that sequesters TJP2 in the cytoplasm blocking its localization at the TJ. Additionally the over-expression of TJP2 suppresses transformation by Ad9 E4-ORF-1, activated Ras V12 and the polyomavirus middle T protein. 4) TJP2 over-expression lowers the level of cyclin D1, blocks cell cycle progression from G1 to S and inhibits cell proliferation.

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