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Gene Section
Review

ACTN4 (actinin, alpha 4)

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Identity

Other names: ACTININ-4, FSGS, FSGS1

HGNC (Hugo): ACTN4

Location: 19q13.2

Local order: EIF3K, ACTN4, CAPN12.

Note

ACTN4 is positioned between EIF3K and CAPN12. Human CAPN12 and ACTN4 share 339 bases of non-coding DNA sequence at their 3' ends (NC_000019.9, green box in the diagram). In mouse genome the two genes overlap in a similar manner (Dear et al., 2000).

DNA/RNA

Description

The genomic DNA of ACTN4 (NC_000019.9) spans 82905 base pairs between coordinates 39138267 and 39221171 on chromosome 19, GRCh37.p10 Primary Assembly. ACTN4 contains 21 exons

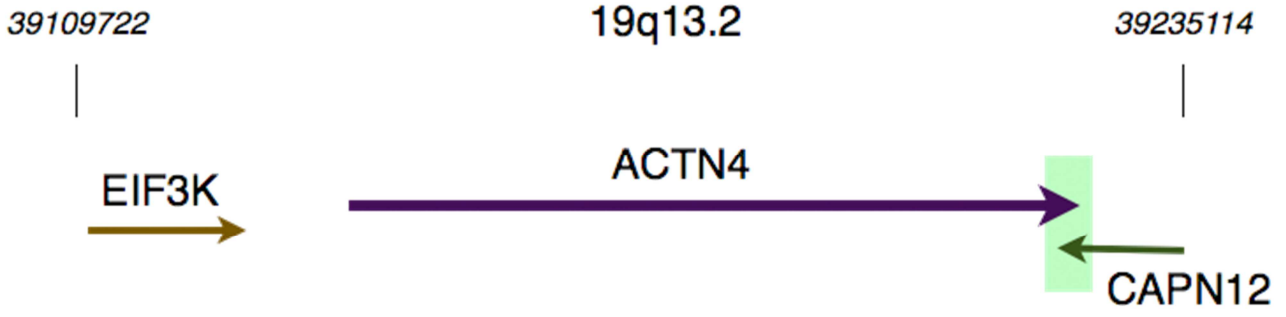
ACTN4 single nucleotide variants and insertions/deletions included in dbSNP137 (NCBI) count 1776 entities.

Transcription

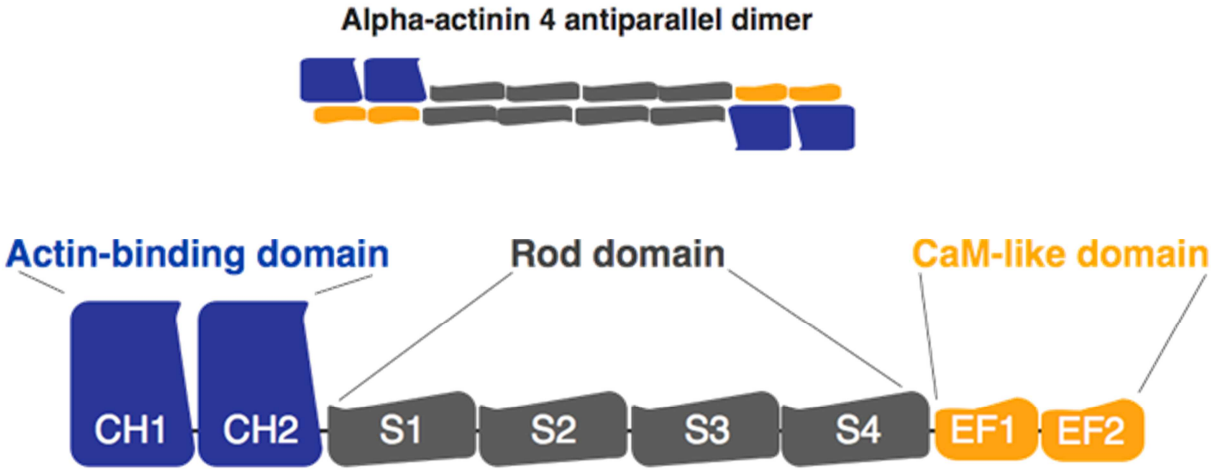
The mRNA of ACTN4 (NM_004924.4) comprises 3966 bases and bases 120-2855 form the coding sequence. Honda et al. (2004) described alternatively spliced variant originally identified in small cell lung cancer that is also detectable in normal brain and testis tissues.

In the variant, the same length alternative sequence originating from the intron 8 replaces usual exon 8. Alternatively spliced α-actinin 4 has substitutions in the following aa: N248G, A250L, S262C and higher affinity to filamentous actin in in vitro co-sedimentation assay. Alternative splicing of exon 19 alters calcium sensitivity of α-actinin 4 and has been detected in mouse brain but not in other of the investigated mouse tissue samples (Lek et al., 2010; Foley and Young, 2013).

Yeast two-hybrid screen of human cDNA library captured another splice variant lacking nt 263-1433 of the full-length mRNA thus removing part of the first and second calponin-homology domain, the first and partially second spectrin-like repeat from α-actinin 4 (Chakraborty et al., 2006).



Scheme of ACTN4 genomic locus. The fragment of chromosome 19q13.2 (19:39109722-39235114, GRCh37.p10 Primary Assembly) containing ACTN4 and surrounding DNA sequence was shown. Genes are drawn as arrows with the length approximately corresponding to the number of bases in each gene. Arrowheads point at the direction of transcription (5' to 3' end).



Organization and domain structure of α-actinin 4 molecule. Functional protein is antiparallel homodimer (upper panel). Lower panel: domains of the protein ordered from N to C-terminus. Abbreviations: CH - calponin-homology domain (CH1, aa 50-154 and CH2, aa 163-269); S - spectrin-like repeats (S1, aa 293-403, S2, aa 413-518, S3, aa 528-639, and S4, aa 649-752); EF - EF-hand motifs (EF1, aa 765-800 and EF2, aa 806-841). Amino acid positions in the α-actinin 4 are indicated according to UniprotKB/Swiss-Prot database.

Pseudogene

There are 2 known pseudogenes for ACTN4: ACTN4P1 (NG_022074.1) is located on chromosome 4q26 and ACTN4P2 (HGNC: 44032) is located on chromosome 1p34.3.

Protein

Description

α-Actinins are members of the spectrin superfamily proteins. There are four isoforms, product of different genes.

Isoform 2 and 3 ("muscle" α-actinin) are constituents of sarcomeres in the heart and skeletal muscle. Isoform 1 and 4 are "non-muscle" α-actinins found practically in every tissue.

α-Actinin 4 is a ~100 kDa protein. It has high degree of similarity to α-actinin 1 isoforms: 87% identical to isoform b (NP_001093.1) and 85% to isoform a (NP_001123476.1). α-Actinin 4 is cloned and characterized by Honda et al. (1998) in cancer cells although earlier description of two non-muscle α-actinins in chick lung exists (Imamura and Masaki, 1992).

All spectrin-related proteins share similar structure: N-terminal actin-binding site formed by a pair of calponin-homology domains, central rod domain containing variable number spectrin-like repeats and C-terminal calmodulin domain with two EF-hand motifs (Broderick and Winder, 2002).

Human α-actinin harbors 4 spectrin repeats and functions as antiparallel homodimer so that N-terminal lateral domains effectively bundle the actin filaments.

Surprisingly, very recent study has discovered α-actinin 1/α-actinin 4 heterodimers in several cancer cell lines (Foley and Young, 2013).

Expression

α-Actinin 4 is ubiquitously expressed in normal non-muscle cells and neoplastic tissue although the degree varies.

Localisation

α-Actinin 4 predominantly localizes in the cytoplasmic regions, and in some cells it can be found likewise in the nucleus.

Activation of intracellular biochemical pathways or actin depolimerization may force the protein to translocate to the nucleus. α-Actinin 4 commutes between cytosol and nucleus through the nuclear pore complexes as a result of hydrophobic interaction between the rod domain and proteins of the pores; nuclear localization is also cell cycle dependent (Kumeta et al., 2010).

Subcellular distribution of α-actinin 4 has been contrasted to that of α-actinin 1 isoform in endometrial fibroblasts (Honda et al., 1998). α-Actinin 1 has been found at the ends of actin stress fibers and adherens junctions i.e. cell membrane associated; on the other hand α-actinin 4 colocalized with the F-actin and was allocated in the cytosol and nucleus. However, there are reports showing involvement of α-actinin 4 in the structure of tight junctions (TJs) (Nakatsuji et al., 2008).

Another characteristic residence of α-actinin 4 is peripheral and dorsal cell protrusions associated with cell movement (Araki et al., 2000).

In the kidney α-actinin 4 is highly expressed and located in the foot processes of glomerular podocytes where it is essential for the kidney barrier function.

Function

ACTN4 product is a versatile protein. Structure of the molecule, particularly the central spectrin repeats

(Djinovic-Carugo et al., 2002), allows the rod domain to serve as a docking site of wide variety of cytosolic and nuclear proteins. This fact defines participation of α-actinin 4 in multiple cellular processes. Majority of the known functional interactions at present are listed below:

i/ Cytoskeletal organization and cell motility. Ability of α-actinin 4 to crosslink actin stress fibers and binding of transmembrane proteins in the cell junctions contributes to the maintenance of cell shape and anchoring to the adjacent extracellular matrix. α-Actinin 4 is involved in targeting JRAB/MICAL-L2 complex (important for recycling of occludin) to plasma membrane of TJs and participates in TJ formation (Nakatsuji et al., 2008).

Together with α-actinin 1, α-actinin 4 is essential for the formation of dorsal stress fibers in the migrating cells, composition and maturation of focal adhesions. Tyrosine phosphorylation of α-actinins is critical in those processes. In the absence of α-actinins focal adhesions have reduced affinity to extracellular matrix proteins (Feng et al., 2013).

Expression of α-actinin 4 is upregulated in the migrating cells and localized in their protrusions (Honda et al., 1998). In the stepwise process of cell movement it is believed that α-actinin 4 (most probably both non-muscle isoforms) is important for the detachment of rear cell end through organized disassembly of focal adhesions by calpain (Bhatt et al., 2002; Shao et al., 2013). Complementary mechanism promoting focal adhesions disassembly is binding of PIP3, a lipid product of phoshoinositide 3-kinase, to the α-actinins CH2 domain. That interaction reduces affinity of α-actinins to actin and integrin (Greenwood et al., 2000).

ii/ Modulation of gene transcription. It has been shown that α-actinin 4 interacts with nuclear receptors (estrogen receptor α in MCF-7 cells, vitamin D receptor in CV-1 cells, retinoic acid receptor and peroxisome proliferator-activated receptor γ in podocytes) and transcriptional co-activators (PCAF, SRC-1) through its LXXLL motif (Khurana et al., 2012a; Khurana et al., 2012b). Binding affinity to the nuclear factors was stronger in the alternatively spliced (short) isoform identified in a human cDNA library during earlier study (Chakraborty et al., 2006). All the above interactions enhance gene transcription. In addition, α-actinin 4 antagonizes histone deacetylase 7 thereby potentiating myocyte enhancer factor-2 in HeLa cells (Khurana et al., 2011).

ACTN4 product also is transcriptional co-activator of RelA/p65 subunit of NF-kB (Aksenova et al., 2013). Together with nuclear factor-Y, α-actinin 4 modulates transcription of CYP1A1, gene involved in pathogenesis of certain cases of lung and breast cancer (Poch et al., 2004).

α-Actinin 4 interacts with INO80 chromatin-remodeling complex and promote Cyclin B1 expression. In the mitotic phase, α-actinin 4 associates with upstream binding factor-dependent transcriptional complex (Kumeta et al., 2010).

iii/ Apoptosis. Endonuclease DNaseY is involved in apoptotic DNA degradation. α-Actinin 4 physically associates with DNaseY and dramatically enhances activity of the enzyme and percentage of PC12 cells developing apoptosis induced by teniposide (Liu et al., 2004).

iv/ Clathrin-mediated endocytosis. α-Actinin has been found in isolated plasma membranes containing clathrin (Burridge et al., 1980) and association of α-actinin 4 and clathrin heavy chain has been identified in prostate cancer cells. Overexpression of α-actinin 4 facilitated transferrin endocytosis (Hara et al., 2007).

v/ Function in glomerular podocytes. The presence of intact α-actinin 4 in the foot processes of podocytes is vital for the proper glomerular filtration. Elimination of the gene function in animal experiments (ACTN4 knockout mice) and mutations in human ACTN4 result in the development of focal segmental glomerulosclerosis (Kos et al., 2003; Kaplan et al., 2000).

vi/ Other. Exhaustive listing of α-actinin 4 interactions is beyond the scope of this structured review article. More details can be found at least in several excellent review publications (Sjöblom et al., 2008; Otey and Carpen, 2004; Oikonomou et al., 2011).

Homology

In variety of species there are orthologs with high identity to human ACTN4 isoform: Pongo abelii 99% (NP_001127286.1), Bos Taurus 99% (NP_001091521.1), Rattus norvegicus 98% (NP_113863.2), Mus musculus 98% (NP_068695.1), Gallus gallus 92% (NP_990457.1), Xenopus laevis 90% (NP_001087030.1), Danio rerio 86% (NP_955880.1). Molecular evolution of α-actinin has been studied (Virel and Backman, 2004).

Mutations

Note

Mice deficient in ACTN4 develop progressive proteinuria, glomerular disease, and die in several months of age. Cell motility in the absence of ACTN4 (lymphocyte chemotaxis) is increased (Kos et al., 2003).

Germinal

Autosomal dominant point mutations in ACTN4 have been found in familial focal segmental glomerulosclerosis (FSGS). Kaplan et al., 2000 identified missense substitutions K228Q, T232I, and S235P in 3 families affected by FSGS.

Somatic

Point mutation K122N has been discovered in the cell line derived from large cell carcinoma of the lung. The ACTN4-encoded protein was detected in the cDNA library and the ORF lacked the first 53 aa of the protein

(Echchakir et al., 2001). This variant was missing in the α-actinin 4 purified from B-cells in the same patient.

Implicated in

Cancer

Note

ACTN4 product protein is associated with disease progress and metastatic processes in variety of neoplasms due to its crucial involvement in cell adhesion and motility mechanisms.

Elevated α-actinin 4 in neoplastic tissue is usually negative predictor of disease prognosis although there are reports proposing suppressive effects on tumor cells growth and malignant phenotype. In some cancer types ACTN4 is candidate oncogene.

Pancreatic cancer

Note

Increased level of α-actinin 4 has been determined as independent prognostic factor associated with most unfavorable prognosis in a group of 173 patients with invasive ductal carcinoma of the pancreas (Kikuchi et al., 2008).

Amplification of chromosome 19q13.1-q13.2 has been reported in pancreatic cancer-derived cell lines and pancreatic cancer tissue.

ACTN4 is one of the putative oncogenes in that locus (Miwa et al., 1996; Höglund et al., 1998).

Breast cancer

Note

α-Actinin 4 is detected in many histological subtypes of breast cancer and subcellular localization of the molecule (nucleus vs. cytosol) is related to disease outcome.

Cytosolic localization has been found in the types of cancer with more malignant histological subtype, metastasis, and worse survival (Honda et al., 1998). Proliferation of MCF-7 breast cancer cells is promoted by α-actinin 4 although the precise mechanism was not identified (Khurana et al., 2011).

Colorectal cancer

Note

Specimens from 26 patients with colorectal cancer were immunostained to visualize the expression of α-actinin 4. In 19 preparations (73.1%) the expression was increased especially in the malignant cells in the "focal dedifferentiation" areas. In the cell line DLD1 (derived from colorectal adenocarcinoma) stable expression of ACTN4 protein dramatically changed cell morphology and increased motility. When those cells are injected into the spleens of the mice with severe combined immunodeficiency metastasis developed in the surrounding lymph nodes. On the other hand, injection of original DLD1 cells did not induce metastatic disease (Honda et al., 2005). These findings suggest involvement of ACTN4 in progression of colorectal carcinoma.

Lung cancer

Note

ACTN4 gene product has been reported to exert multiple effects on human lung cancer cell biology and disease prognosis. Moreover, the available data so far has shown that α-actinin 4 is able to promote as well as suppress the malignant development reflecting probably the diversity of mechanisms involved in oncogenesis of lung cancer. Several mutations and splice variants in ACTN4 that influence the lung cancer cell phenotype have been described.

Using highly specific monoclonal antibody, alternatively spliced variant of ACTN4 has been identified exclusively in high-grade neuroendocrine lung tumors compared to non-neuroendocrine lung cancers, 96 of 176 (55%) versus 3 of 378 (0.8%) of investigated patients, respectively. Statistical analysis revealed that variant α-actinin 4 is independent negative prognostic factor. The protein binds F-actin with higher avidity (Miyanaga et al., 2013).

Analysis of gene expression by microarray technology proved α-actinin 4 as a marker of worse disease development in non-small cell lung cancer. Higher expression of α-actinin 4 has been correlated to significantly lower survival (Yamagata et al., 2003).

Small cell lung cancer (SCLC) cell lines and tissue from the patient biopsies express ACTN4 alternatively spliced variant, normally found in the testis. Variant α-actinin 4 binds F-actin with higher affinity.

This splice variant was proposed as diagnostic marker in SCLC (Honda et al., 2004).

Immune response against the mutated ACTN4 in the patient with large cell lung cancer has been involved in the clinical evolution of the disease. Furthermore, after extraction of the primary tumor the cytotoxic T lymphocyte clone targeting mutated α-actinin 4 persisted many years in the patient's blood (Echchakir et al., 2001). In the subsequent study, it has been shown that the above point mutation removes antiproliferative effect of ACTN4 protein in the cancer cell line and supports the notion that ACTN4 may be both tumor suppressor as well as tumor promoter gene (Menez et al., 2004).

Nervous system neoplasms

Note

Similar to various carcinomas, increase of ACTN4 protein levels also appears to be involved in progression of certain brain tumors. In human astrocytoma contrasted to normal human brain tissue, Western blot densitometric quantification demonstrated ~2 times higher levels of α-actinin 4 in the tumor samples; furthermore, in higher grades astrocytomas (III-IV) α-actinin 4 has additional 1.9 fold increase compared to low grades astrocytomas (I-II).

In vitro downregulation of α-actinin 4 (RNAi) in human astrocytoma cell lines U-373, U-87, and A172 reduced cell adhesion and motility, cortical actin localization, and RhoA mRNA and protein. In U-373 cells only α-actinin 4 promoted cell growth (Quick and Skalli, 2010).

However, some experimental data support the opposite concept: a number of cytoskeleton-associated proteins show reduced expression in cancer cells and recovering their levels (e.g., in vitro transfection) transform the cells phenotype to less malignant (Glück et al., 1993). Human neuroblastoma cell lines with high malignant phenotype express lower level of α-actinin 4 compared to more differentiated and less malignant neuroblastoma cell lines. Transfection with ACTN4 has suppressed tumorigenicity and has converted neuroblasts from high to low malignant phenotype. The effect persisted until the level of α-actinin 4 in transfected cells was maintained and initial high malignancy phenotype recovered when α-actinin 4 declined (Nikolopoulos et al, 2000).

Esophageal cancer

Note

In a Chinese cohort of 12 patients suffering esophageal squamous cell carcinoma, α-actinin 4 overexpression has been detected in tumor tissue and proposed as a marker for prognostic evaluation of the disease (Fu et al., 2007).

Prostate cancer

Note

Involvement of α-actinin 4 in tumor pathophysiology is undoubtedly mediated by various mechanisms because of the large number of binding partner molecules that have been identified. In human prostate cancer cell lines (22RV1, PC-3, LNCaP) ACTN4 protein product was less abundant than in normal human prostate epithelial cells, an observation that is conflicting with the findings in the most reports investigating relationship ACTN4-cancer development. Increasing the level of α-actinin 4 in those prostate cancer cells markedly suppressed cell-growth (Hara et al., 2007). In the same report the authors propose disturbance in clathrin-mediated endocytosis as the main mechanism associated with α-actinin 4 mediated cellular effects.

Bladder cancer

Note

The promoting effect of ACTN4 gene product on cancer invasion has also been found in the bladder cancer cell lines (T24, J82) and tissue from superficial and invasive bladder cancers. ACTN4 mRNA and protein levels are higher in malignant cell lines and the tissues from the patients versus disease-free state. RNAi silencing of ACTN4 resulted in decreased cell invasion as measured by in vitro assay but did not affect the cell growth (Koizumi et al., 2010).

Ovarian cancer

Note

Increased expression of α-actinin 4 and 19q12-13 genetic locus amplification has been detected in 21% of 136 cases of advanced-stage ovarian cancer. Statistical analysis associated higher copy number of ACTN4 as negative prognostic factor in the patients with ovarian cancer (Yamamoto et al., 2007).

ACTN4 is a candidate oncogene in epithelial ovarian cancer. In subset of patients it has been found that the chromosome 19q12-q13 region is amplified correlating with higher expression of α-actinin 4 protein (Yamamoto et al., 2009).

Glomerular kidney disease - Focal segmental glomerulosclerosis (FSGS)

Note

Autosomal dominant point mutations in ACTN4 are associated with inherited form of FSGS. Aberrant α-actinin 4 disrupts glomerular podocytes especially their foot processes, which are essential in blood-urine barrier function.

Clinically the disease causes proteinuria and deteriorating renal function.

Mutant α-actinin 4 aggregates in the cytosol of podocytes and degrades faster than the normal molecule (Yao et al., 2004).

Autoimmune diseases - Systemic lupus erythematodes (SLE)

Note

Autoantibodies against double stranded DNA cross-reacting with α-actinin in the renal structures are associated with the development lupus nephritis (Mostoslavsky et al., 2001).

Lupus-prone mouse strain overexpresses α-actinin 1 and 4 in glomerular mesangial cells (Zhao et al., 2006).

In patients with lupus nephritis clinical studies have suggested the link between anti-α-actinin autoantibodies and kidney involvement (Becker-Merok et al., 2006), however in the reports there is no discrimination between the 2 "non-muscle" α-actinin isoforms.

Given the fact that α-actinin 4 is highly expressed in the affected renal structures in SLE nephritis, the involvement of isoform 4 is probable.

Autoimmune hepatitis type I

Note

Autoantibodies against α-actinin are proposed as markers for severity and activity of autoimmune hepatitis type I (Gueguen et al., 2006).

However, there is no report so far describing the exact α-actinin isoform as a target antigen.

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