Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section
Mini Review

STRN (striatin, calmodulin binding protein)

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Identity

Other names: MGC125642; SG2NA
HGNC (Hugo): STRN
Location: 2p22.2

DNA/RNA

Description

The gene spans 118.144 Kb on minus strand (starts at 36 928 976 bp from pter, and ends at: 37 047 119).

Transcription

Alternative splicing (see Figure 1): exon 1 of isoform I is truncated in isoform II (136 bases missing), and preceeded by another exon in 5' (81 bases); exon 8 of isoform I (111 bases) is missing in isoform II, according to Ensembl.

Protein

Description

780 amino acids (aa), 86.13 KDa (isoform I) and 731 amino acids, 80.76 KDa (isoform II). Striatin contains a high number of domains mediating protein-protein interactions. Domains:
aa 55-63 : Caveolin-binding; aa 53-120 : Coiled-coil; aa 149-166 : Calmodulin-binding; aa 461-500 : WD 1; aa 514-553 : WD 2; aa 567-606 : WD 3; aa 662-701 : WD 4; aa 704-743 : WD 5; aa 750-779 : WD 6 (30 aa only) (Isoform I, according to Swiss-Prot).
- Caveolin-binding domain: To bind caveolin, a caveolin-binding consensus is necessary: ΦXΦXXXXΦ, ΦXXXXΦXXΦ or ΦXΦXXXXΦXXΦ (Φ corresponding to aromatic amino acid) (Couet et al., 1997). Striatin contains the caveolin-binding consensus motif: LHFIQHEWARF, and binds directly caveolin-1 (Gaillard et al., 2001).

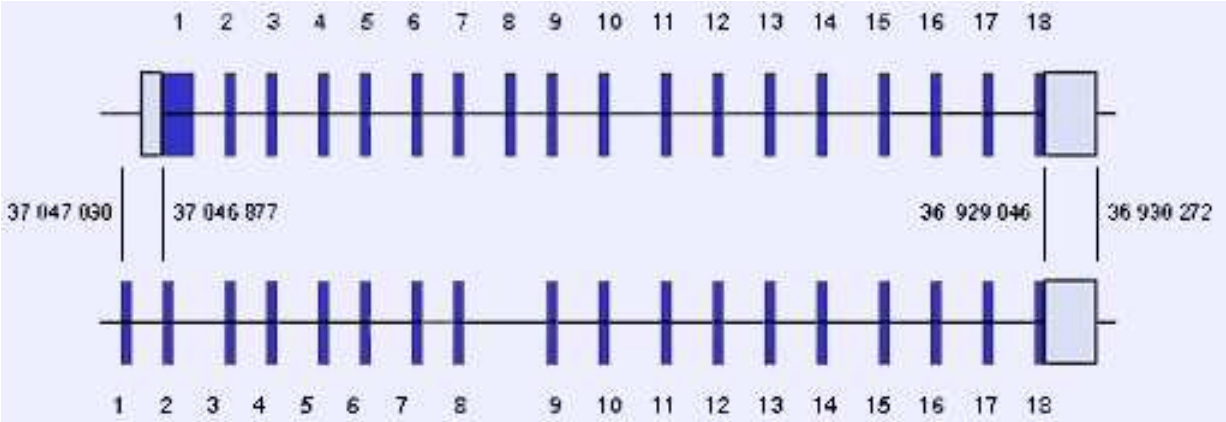

Figure 1: STRIATIN - STRN (2p12.2) DNA structure - isoforms I and II.

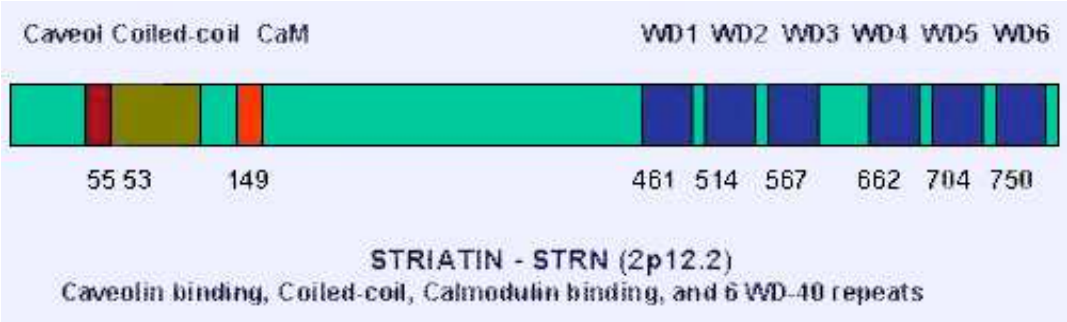

Figure 2: The domains of STRN. Isoform I is shown; amino acids are numbered according to Swiss-Prot description.

- Coiled-coil domain: Coiled-coil domains allow homo- and hetero-oligomerization. Oligomerization of striatin members is an obligatory step for the correct routing of the striatin family members to the dendritic spines (Gaillard et al., 2006).
- Ca^{2+} -calmodulin binding domain: Striatin binds calmodulin in a calcium-dependent manner. Ca^{2+} has a pleiotropic effect in cells. In dendritic spines, it plays a crucial role in the induction of most forms of synaptic potentiation and depression. Members of the striatin family could act as Ca^{2+} sensors in protein complexes, able to drive the delocalization of these complexes in different submembranous micro-domain according to the Ca^{2+} fluctuations (Benoist et al., 2006).
- WD-repeats (tryptophan-aspartate repeats): tend to form a propeller structure, stable platform that reversibly interacts with several proteins. The WD-repeat domain enables proteins to establish multiple protein-protein interactions. Striatin possesses at least 6 WD-repeats (eight were reported previously).

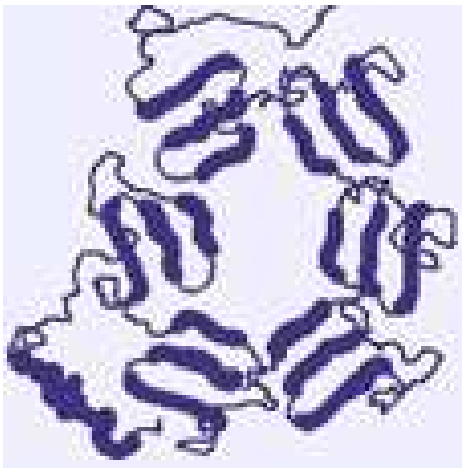

Figure 3: WD-repeats propeller structure.

Expression

Widely expressed (heart, various digestive organs, kidney, and others (Breitman et al., 2008)), but mainly in the nervous system. All members of the striatin family are expressed in the central nervous system and in the peripheral nervous system (Blondeau et al., 2003). Striatin is found in dendrites, on the post-synaptic side, in the post-synaptic densities of neuronal dendritic spines, particularly in the striatum.

Localisation

Found in the cytosol, and also found associated with membranes.

Function

Striatin, like other striatin family members, binds many proteins, and forms multi-protein complexes. Striatin family members are scaffolding proteins involved in signaling and trafficking in a Ca^{2+} dependant manner, exhibiting a dual role in endocytic process and signaling.
- Relation with caveolins: striatin directly binds caveolin-1 (Gaillard et al., 2001), a palmitoylated protein involved in caveolae and lipid rafts. Caveolins are scaffolding proteins, the main components of caveolae. Caveolae start as plasma membrane pits and form vesicles in the cytoplasm. Caveolae represent one mode of endocytosis (a clathrin independent mode of endocytosis). Caveolins also have the capacity to bind cholesterol, and are involved in signal transduction processes by directly interacting with a great number of signaling proteins such as nitric oxide synthases, G-proteins, protein tyrosine kinases, and H-Ras (Krajewska et al., 2004). Caveolin-1 is concentrated within dendritic spines of synapses in activity.
- Role in synaptic transmission: striatin down regulation in embryonic motoneurones results in the arrest of dendritic growth, but not in axon growth impairement (Bartoli et al., 1999).
Members of the striatin family have been shown to interact with phocein, a protein involved in clathrin- and dynamin-dependent membrane dynamics (Baillat et al., 2001; Haeberle et al., 2006). Phocein has been implicated in vesicular trafficking, acting in particular in the endocytic process in Purkinje cell dendritic spines (Bailly et al., 2007).
The coiled-coil domain of the striatin family members seems crucial for homo- and hetero-oligomerization of these proteins. Striatin family members are often co-expressed in the neurons. The coiled-coil domain also plays an essential role in the targeting of STRN3 within spines (Gaillard et al., 2006).

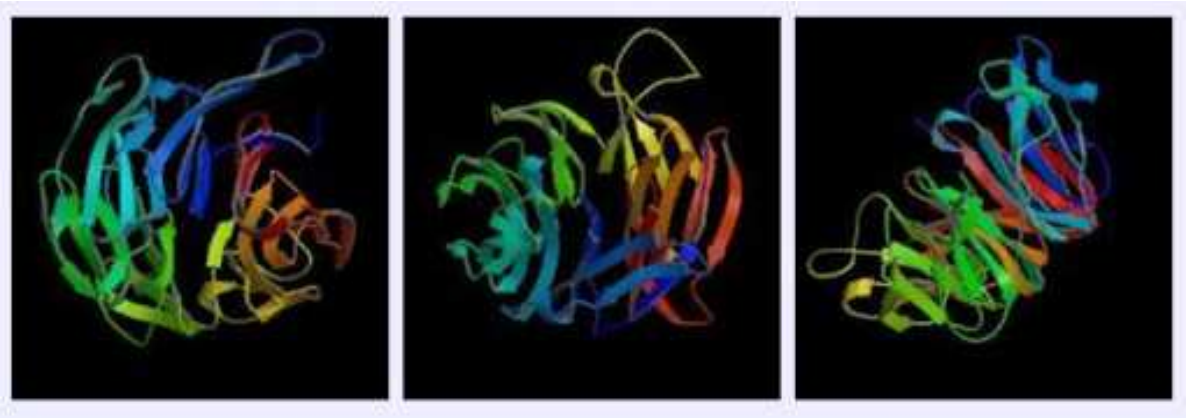

Figure 4: ModBase predicted comparative 3D structure (Front / Top / Side). Reproduced courtesy UCSC Genome Browser website.

- Role in the "non-genomic" estrogen-mediated activation of downstream signaling pathways: in vascular endothelial cells, estrogen receptor (ER) alpha is targeted by striatin (or by STRN3, there is a controversy in this) to a module in membrane caveolae that enables estrogen to activate the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3 (PI3K)-Akt kinase pathways, and endothelial NO synthase (eNOS). Striatin (or STRN3) directly binds ER alpha and anchors ER alpha to the membrane and organizes the ER alpha-eNOS membrane signaling complex (Lu et al., 2004) (Note: estrogens also act in a "genomic manner", as transcrition factors, regulating gene expression).
- Cell lines: In NIH3T3 cells, striatin and STRN3 form stable complexes with protein phosphatase 2A (PP2A), a multifunctional serine/threonine phosphatase, critical to many cellular processes (Moreno et al., 2000), including presence in the b-catenin degradation complex, leading to degradation of b-catenin and inhibition of Wnt signaling, but also F-actin binding and regulation and aPKC (a member of the Par complex) regulation.
In HEK293Tcells, striatin binds APC (Breitman et al., 2008). APC is a a multi-function protein e.g.: negative WNT signaling pathway regulation, preventing transcription of Wnt target genes; modulation of the actin cytoskeleton and influence on cell adhesion and cell motility, binding to microtubules inducing stabilization of their ends; interaction with the disks large homologs, which are scaffolding proteins. The APC armadillo repeat domain binds the WD-repeats of striatin and both proteins co-localize at epithelial cell to cell junctions and seem to play a role in junctional organization, since their depletion resulted in a F-actin network fragmentation.
- Neurones and epithelial cells: it may be possible that Striatin and APC (and perhaps PP2A) are involved in the Par complex (PAR-3, PAR-6 and aPKC), a protein complex crucial for neurite, as well as for epithelial cell, polarization (Breitman et al., 2008).

Homology

Other members of the striatin family, i.e.: STRN3 (SG2NA) (14q12) and STRN4 (zinedin) (19q13.2), are 80% and 75% homologous to STRN.

Implicated in

t(2;4)(p22;q12) in myeloproliferative disease with eosinophilia --> STRN - PDGFRA hybrid gene.

Abnormal protein

The N-term STRN - C-term PDGFRA fusion protein retains the caveolin-binding domain, the coiled-coil domain, and the calmodulin-binding domain, but not the WD-repeats of STRN, fused to a truncated WW-like domain and the kinase domain of PDGFRA; the coiled-coil domain from STRN may act as a dimerization motif that could constitutively activate PDGFRA tyrosine kinase.

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