

## Gene Section

### Mini Review

# S100A10 (S100 calcium binding protein A10)

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## Identity

**Other names:** 42C, ANX2L, ANX2LG, Annexin II ligand, CAL1L, CLP11, Ca[1], Calpactin, GP11, MGC111133, p10, p11

**HGNC (Hugo):** S100A10

**Location:** 1q21.3

**Local order:** According to NCBI Map Viewer, genes flanking S100A10 in centromere to telomere direction on 1q21 are: THEM4 (1q21) thioesterase superfamily member 4, KRT8P28 (1q21.3) keratin 8 pseudogene 28, S100A10 (1q21) S100 calcium binding protein A10, NBPF18P (1q21.3) neuroblastoma breakpoint family member 18 (pseudogene), S100A11 (1q21) S100 calcium binding protein A11.

## DNA/RNA

### Description

The S100A10 gene contains two introns, one in the 5' prime untranslated region of the gene and the other in the protein coding region. The second intron separates the codons for two corresponding amino acids which reside in the sequence connecting the two helix-loop-helix (EF-hand) motifs.

### Transcription

Transcription produces 7 different mRNAs, 6 alternatively spliced variants and 1 unspliced form.

The mRNAs differ by truncation of the 5' end, alternative splicing or retention of 2 introns.

### Pseudogene

No known pseudogenes.

## Protein

### Description

S100A10 is a member of the S100 family of Ca<sup>2+</sup> binding proteins containing 2 EF-hand calcium-binding motifs (Donato, 2001). In contrast to all other S100 proteins, S100A10 is calcium insensitive because of amino acid replacements in its calcium-binding loops that lock the protein in a permanently active state. S100A10 protein is a dimeric protein composed of two 11-kDa subunits (p11 subunits) (Waisman, 1995). S100A10 is found in most cells bound to its annexin II ligand as the heterotetrameric [(S100A10)<sub>2</sub> (annexin II)<sub>2</sub>] complex, also called annexin A2 tetramer (AII<sub>t</sub>), in which a central S100A10 dimer interacts with two annexin A2 chains (Lewit-Bentley et al., 2000).

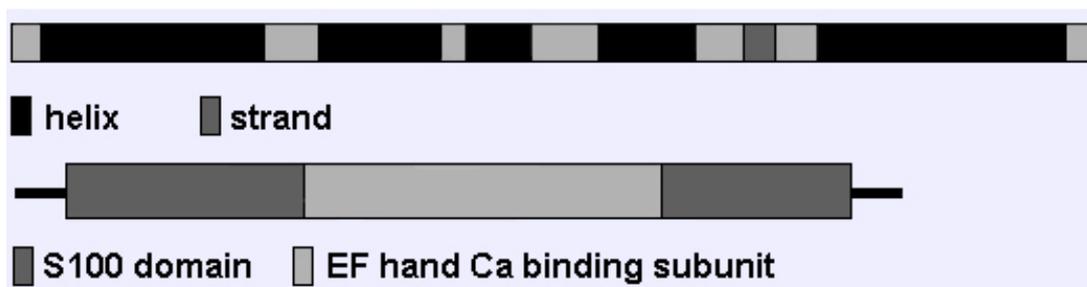
### Expression

Ubiquitous expression. S100A10 protein is highly expressed in the brain, heart and lung; moderate expression in the liver, bone marrow, spleen, skeletal muscle, pancreas, prostate and kidney.

### Localisation

Cell surface membrane, Ion channels, membrane of early endosomes and cytoplasm.





### Function

S100A10 protein plays a key role in the regulation of plasminogen/ plasmin activity. The carboxyl-terminal lysines of S100A10 bind tPA and plasminogen resulting in the stimulation of tPA-dependent plasmin production (MacLeod et al., 2003). Plasmin binds to S100A10 at a distinct site and the formation of the S100A10-plasmin complex stimulates plasmin auto-proteolysis thereby providing a highly localized transient pulse of plasmin activity at the cell surface (MacLeod et al., 2003; Kwon et al., 2005). The binding of tPA and plasmin to S100A10 also protects against inhibition by their physiological inhibitors, PAI-1 and alpha2-antiplasmin, respectively (Kassam et al., 1998). S100A10 also co-localizes plasminogen with the urokinase-type plasminogen activator/(uPA/uPAR) complex thereby localizing and stimulating uPA-dependent plasmin formation to the surface of cancer cells (Kassam et al., 1998). The loss of S100A10 from the extracellular surface of cancer cells results in a significant loss in plasmin generation. In addition, S100A10 knockdown cells demonstrate a dramatic loss in extracellular matrix degradation and invasiveness as well as reduced metastasis (Zhang et al., 2004; Choi et al., 2003). S100A10 has also been shown to be involved in the intracellular trafficking of a set of plasma membrane ion channels and receptors through direct protein interaction. S100A10 has been shown to bind to and regulate the plasma localization of the tetrodotoxin-resistant sodium channel Nav 1.8 (Okuse et al., 2002). Binding of S100A10 to the two-pore domain potassium channel TWIK-related acid sensitive K-1 (TASK 1) protein is important for TASK translocation to the plasma membrane (Renigunta et al., 2006). S100A10 is also involved in the expression of the transient receptor potential (TRP) channels, TRPV5 and TRPV6 at the cell surface (van de Graaf et al., 2003). S100A10 was also shown to bind and regulate the activity of the acid-sensing ion channel ASIC1a (Donier et al., 2005) and the plasma membrane-resident serotonin 5-HT1B receptor (Svenningsson et al., 2006). Increasing evidence suggests that the AII protein plays an important role in linking the micro-domain formation to actin rearrangements, either through direct binding to F-actin or through the recruitment of proteins that modulate the actin cytoskeleton (Hayes et al., 2004; Hayes et al., 2006). The AII complex recruits the actin-binding protein AHNAK to the

plasma membrane; this protein is involved in the development of the cell membrane cytoarchitecture in polarizing epithelial cells (Benaud et al., 2004; De Seranno et al., 2006).

### Homology

S100A10 is highly conserved between different species. Human S100A10 has 100% homology to S100A10 from *Bos Taurus*, *Macaca mulatta*, *Pan troglodytes*, *Pongo pygmaeus*, 98% homology to S100A10 from *Canis familiaris*, *equus caballus*, *Felis catus*, 91% homology to S100A10 from *Mus musculus*, 88% homology to S100A10 from *Rattus norvegicus*.

## Mutations

### Note

No mutations have been reported for S100A10 that cause congenital anomalies. A recent study tested for rare variants in p11 by resequencing promoter, exonic and flanking intronic regions in 176 Major Depressive Disorder (MDD) cases and 176 matched controls. These studies also assessed common variation by genotyping eight single nucleotide polymorphisms (SNPs), seven tag SNPs and one found through resequencing, in 641 MDD cases and 650 controls. Resequencing revealed nine novel rare variants, including a missense mutation (Asp60Glu) observed in one case and one control, and four variants that occurred only in cases and not controls. The number of rare variants in cases did not exceed that expected by chance for the length of sequence analyzed, and also was not significantly greater than that observed in controls. Resequencing also identified two known SNPs, one (rs4845720) of which was significantly more frequent in MDD cases than controls in the resequenced sample (3.1% vs. 0.9%,  $P = 0.03$ ), though not in the larger sample (3% vs. 2%,  $P = 0.15$ ). None of the tag SNPs showed any evidence of association. In conclusion these results did not support a major role for either common or rare p11 SNPs with MDD (Verma et al., 2007).

## Implicated in

### Various cancers

### Note

S100A10 has been shown to be over-expressed a number of different cancers, including thyroid

neoplasms, anaplastic large cell lymphoma, gastric cancer and renal cell carcinoma.

## Depressive disorders

### Note

S100A10 knockout mice are viable indicating that S100A10 is not required for normal development. Nevertheless these mice show a depression-like phenotype and reduced responsiveness to serotonin 1B receptor agonists. Moreover, these mice respond less to anti-depressants, suggesting a main role for S100A10 in regulating 5-HT<sub>1B</sub> receptor function and subsequent depressive disorders (Svenningsson et al., 2006).

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