Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Mini Review

EPB41L3 (erythrocyte membrane protein band 4.1-like 3)

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Published in Atlas Database: May 2008

Online updated version : http://AtlasGeneticsOncology.org/Genes/EPB41L3ID40458ch18p11.html
DOI: 10.4267/2042/44447

Identity

Other names: 4.1B; DAL-1; DAL1; FLJ37633; KIAA0987
HGNC (Hugo): EPB41L3
Location: 18p11.32
Local order: Located between ZFP161 (Zinc Finger Protein 161 homolog; 5279018-5286039) and L(3)MBT-Like 4 (5944712-6404910).

DNA/RNA

Description

The gene consists of 23 exons, with exons 1 and 23 being non-coding. The total gene length is 4,446 bases.

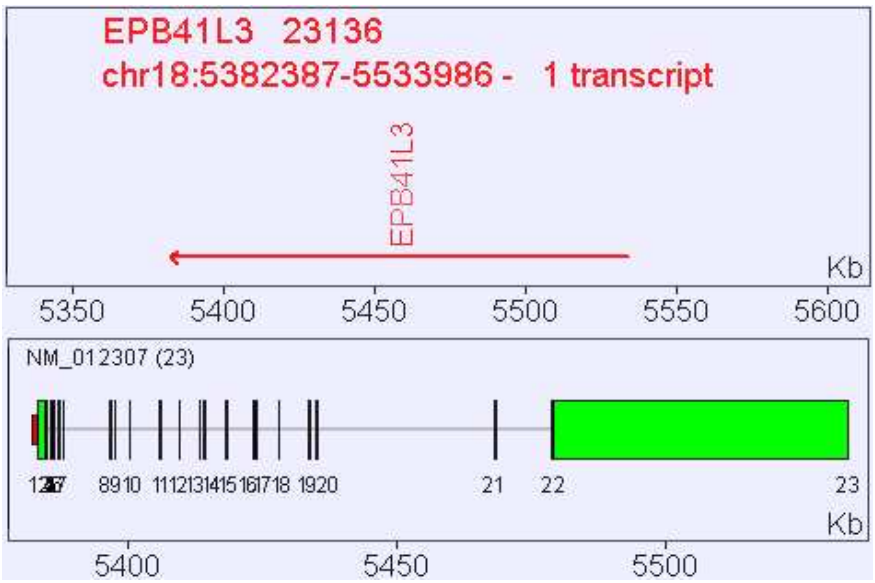
Transcription

The coding sequence (87-3350) generates an approximatively 3.3 kb mRNA transcript.

Protein

Description

Protein 4.1B is a member of the Protein 4.1 superfamily of proteins, which is characterized by the presence of a conserved N-terminal 4.1/ezrin/radixin/moesin (FERM) domain. The full-length protein consists of the following domains (N- to C-termini): U1-FERM-U2-SABD-U3-CTD ("U" = unique domains, SABD = spectrin/actin binding domain, CTD = C-terminal domain).



This protein consists of 1,088 amino acids and has been detected at sizes between 125-145 kDa by Western blot. A truncated variant of Protein 4.1B (named DAL-1) has also been found to be generated by translational initiation at Met110 and termination at Ser542, relative to full-length 4.1B. DAL-1 lacks the 4.1B N-terminal U1 domain and the entire CTD, and also has internal deletions in portions of the U2 and U3 subdomains. DAL-1 is believed to possess the full tumor suppressive capabilities exhibited by full-length Protein 4.1B.

Expression

Highly expressed in the brain and neurons, as well as in adipose tissue, adrenal gland, testis, placenta and kidney. Moderate expression in lungs and intestines. Lower expression across many other organs.

Localisation

As with other members of the Protein 4.1 superfamily, Protein 4.1B likely functions to link cellular receptors with the cytoskeleton, and thus localizes to the plasma membrane. By immunofluorescence, 4.1B has been reported to display a "honeycomb" pattern, with enrichment at points of cell-cell contact. 4.1B has also been localized to the cytoplasm and, at least in one report, to the nucleus.

Function

The tumor suppressive function of 4.1B has been reported in several studies, both in vitro and in vivo. Overexpression of 4.1B can suppress growth and, in some cases, induce apoptosis in human breast cancer, non-small cell lung cancer and meningioma cells. Although the mechanism by which 4.1B induces apoptosis remains unclear, one report has observed that overexpression of 4.1B increases caspase-8 activity in MCF-7 cells, and that inhibitors of caspase-8 can block 4.1B-mediated apoptosis. Others have reported that overexpression of 4.1B induces Rac1-dependent JNK signaling, which leads to growth suppression of meningioma cells. Truncation studies have also suggested that the U2 region of 4.1B contains the minimal growth suppressive domain when tethered to the membrane by FERM domain-mediated protein-protein interactions. Finally, downregulation of 4.1B by shRNAs has been reported to increase metastatic capability in human prostate cancer cells. However, the growth inhibitory effects of 4.1B are not general and may be cell-type-specific. For instance, overexpression of 4.1B inhibits the growth of some subclones of MCF-7 breast cancer cells, but not others, and 4.1B has been reported not to affect the growth of schwannomas.

4.1B knock-out animals are largely normal and fertile, and do not display any detectable predisposition to spontaneous tumor formation above background levels. However, in the TRAMP tumorigenesis model of prostate cancer, 4.1B null mice have been reported to display increased susceptibility for developing primary tumors and metastases. The only non-tumor phenotype observed in mutant animals is that mammary glands from 4.1B-/- female mice displayed a 60% increase in Ki67-positive epithelial cells during pregnancy, but not during the lactating or involution stages. The precise function of 4.1B remains unclear.

Homology

The FERM domain of Protein 4.1B is 73% homologous with the FERM domain of Protein 4.1R, the founding member of the Protein 4.1 superfamily of proteins. 4.1B is most similar to other members of the Protein 4.1 sub-group (e.g. 4.1R, 4.1G, 4.1N), which is one branch of the Protein 4.1 superfamily.

Mutations

Note

To date, no mutations have been linked to human developmental abnormalities or to cancer. However, the chromosomal region containing 4.1B, 18p11.3, is frequently lost during tumorigenesis for a variety of tumor types (see below).

Implicated in

Various cancers

Disease

4.1B was originally identified as a protein whose expression was reduced in human non-small cell lung carcinomas. Subsequent studies have shown that 4.1B levels are downregulated in many different types of tumors. The location of the gene encoding Protein 4.1B, 18p11.3, is a region that has been reported to be lost in 38% of human lung, brain and breast tumors. Others have reported that loss of 18p11.3 is detected in 55% of ductal carcinomas in situ, and in 67% of invasive breast cancers. In addition, 4.1B expression has been reported to be reduced in up to 70% of meningiomas, and is significantly downregulated in several studies of human clinical prostate cancer, particularly in metastatic prostate cancer.

Breakpoints

Note

None.

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This article should be referenced as such:

Wong SY. EPB41L3 (erythrocyte membrane protein band 4.1-like 3). Atlas Genet Cytogenet Oncol Haematol. 2009; 13(4):265-267.