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Gene Section
Review

ASAP1 (ArfGAP with SH3 domain, ankyrin repeat and PH domain 1)

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Identity

Other names: AMAP1, CENTB4, DDEF1, KIAA1249, PAG2, PAP, ZG14P

HGNC (Hugo): ASAP1

Location: 8q24.21

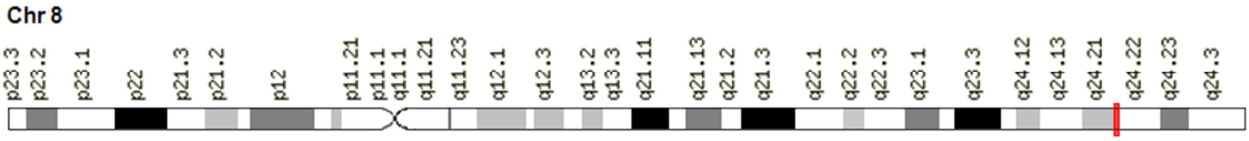
DNA/RNA

Description

The ASAP1 locus spans 391,75 kb, on the minus strand of chromosome 8 from 131456099 to 131064346.

Transcription

Transcription produces 16 different mRNAs, 12 alternatively spliced variants and 4 unspliced forms.
There are 9 probable alternative promotors, 6 non overlapping alternative last exons and 5 validated alternative polyadenylation sites.
The mRNAs appear to differ by truncation of the 5' end, truncation of the 3' end, presence or absence of 15 cassette exons, overlapping exons with different boundaries (NCBI).



The ASAP1 gene maps on chromosome 8, at 8q24.1-q24.2 according to Entrez Gene (adapted from GeneCards).

Protein

Description

P. Randazzo's group was the first to identify two variants of a 130-kDa phosphatidylinositol 4,5-bisphosphate (PIP2)-dependent Arf1 GTPase-activating protein (GAP), and named them ASAP1a and ASAP1b (ArfGAP, SH3, ankyrin repeat, PH protein) (Brown et al., 1998).

At almost the same time, T. Roberts' group isolated a homologue of ASAP1 from bovine brain as a Src SH3 domain-binding protein, and named it DEF-1 (differentiation-enhancing factor-1) because its ectopic expression in fibroblasts resulted in their differentiation into adipocytes (King et al., 1999).

J. Schlessinger's group also identified a similar protein as a Pyk2 binding protein, and named it Pap (Andreev et al., 1999). Later on, we also isolated several ArfGAPs as paxillin-binding proteins, and tentatively called them paxillin-associated ArfGAPs (PAG1, PAG2 and PAG3) (Kondo et al., 2000; Mazaki et al., 2001; Sabe et al., 2006). ASAPs were moreover identified as centaurin β3 and β4.

To avoid this confusion of naming, it was proposed internationally to unify the names according to functional domains that these proteins bear: ASAP1, DEF1, PAG2, centaurin β4 were hence proposed to be called AMAP1 (a multiple-domain ArfGAP protein 1); and Pap, DDEF2, PAG3, centaurin β3 to be called AMAP2 (a multiple-domain ArfGAP protein 2) (Kahn, 2004). Since then, we have stopped calling these proteins PAG2 and PAG3, and instead now call them AMAP1 and AMAP2.

Then after, the HUGO Gene Nomenclature Committee has nevertheless decided to call AMAP1 as ASAP1, and AMAP2 as ASAP2. We hereby call these proteins and genes according to names used in the original reports.

Expression

Epithelial cells, fibroblasts, macrophages, brain (for references see above), and endothelial cells (Hashimoto et al., 2011). Not determined with the other types of cells.

Localisation

Intracellular tubulovesicular structures and vesicles, plasma membrane protrusions and leading edges, and invadopodia/podosome structures (Hashimoto et al., 2004; Hashimoto et al., 2005; Onodera et al., 2005).

Function

ASAP1 has an ArfGAP zinc-finger domain and exhibits phosphatidylinositol 4,5-bisphosphate-dependent GAP activities for Arf1 and Arf5 but 10^2- to 10^3-fold less activity for Arf6 (Brown et al., 1998; Andreev et al., 1999). ASAP1 was shown to enhance cell motility, and this activity was proposed to be mediated by its GAP activity towards Arf1 (Furman et al., 2002). ASAP1 was also shown to associate with focal adhesion kinase (FAK) and contribute to focal adhesion assembly (Liu et al., 2002). Hashimoto et al. (2004 and 2005) have shown that AMAP1 and AMAP2 have the ability to bind stably with GTP-Arf6, but not GDP-Arf6 or other GTP-/GDP-Arf isoforms, in vitro and in vivo. Through this binding, AMAP1 and AMAP2 appear to function as downstream effectors for GTP-Arf6 (Hashimoto et al., 2004; Hashimoto et al., 2005; Onodera et al., 2005). AMAP1 binds to paxillin and cortactin, which are essential components of the invadopodia of MDA-MB-231 breast cancer cells, and acts to recruit these proteins to the sites of Arf6 activation to form invadopodia (Onodera et al., 2005). AMAP1 is hence essential for invasion and metastasis of some breast cancer cells, while AMAP2 is not a component of invadopodia (Onodera et al., 2005; Hashimoto et al., 2006; Nam et al., 2007; Morishige et al., 2008; Sabe et al., 2009). AMAP1 appears to be a useful diagnostic marker as well as therapeutic target of different types of human cancers (see below).

Implicated in

Breast cancer

Note

In primary breast cancers, AMAP1 protein, but not AMAP2 protein, is abnormally overexpressed in their significant population in a manner independent of the transcriptional upregulation of the AMAP1 gene, and levels of AMAP1 protein expression correlates well with the malignant phenotypes (Onodera et al., 2005).

Melanoma

Note

With the name DDEF1, this gene was identified to be located in an amplified region of chromosome 8q24.12, and the amplification of chromosome 8q in uveal melanomas was found to correlate most strongly with the expression of this gene in melanomas (Ehlers et al., 2005).

Colorectal cancer

Note

Protein expression of ASAP1 is upregulated in colorectal cancer cells, and this expression correlates with poor metastasis-free survival and prognosis in colorectal cancer patients (Müller et al., 2010).

It is worth noting, on the other hand, that a previous study on the copy number changes at 8q11-24 in colorectal carcinomas showed that although the MYC gene, located at 8q24.12-q24.13, is indeed amplified and correlates with the advanced stages of colorectal carcinoma, the DDEF1 gene was not amplified (Buffart et al., 2005).

Prostate cancer

Note

Additional gene copies of ASAP1 were also detected in a large population of primary prostate cancers, and ASAP1 protein staining was found to be elevated in 80% of primary prostate cancers with substantially higher amounts observed in metastatic lesions compared with benign prostate tissue (Lin et al., 2008).

Pancreatic ductal adenocarcinoma

Note

DDEF1 gene was found to be frequently amplified, most likely to be oncogenic, in pancreatic ductal adenocarcinomas, accompanied by enhanced expression of this gene (Harada et al., 2009).

VEGF- and tumor-induced angiogenesis

Note

AMAP1 protein is highly expressed in endothelial cells upon their treatment with vascular endothelial growth factor (VEGF), and an essential component of VEGF- and tumor-induced angiogenesis, and also choroidal neovascularization (Hashimoto et al., 2011).

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