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Gene Section

Review

BAP1 (BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase))

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Identity

HGNC (Hugo)

BAP1

Location

3p21.1

Other names

DKFZp686N04275, FLJ35406, FLJ37180, HUCEP-13, KIAA0272, UCHL2, hucep-6

DNA/RNA

Description

The gene spans 9.0 kb and is composed of 17 exons.

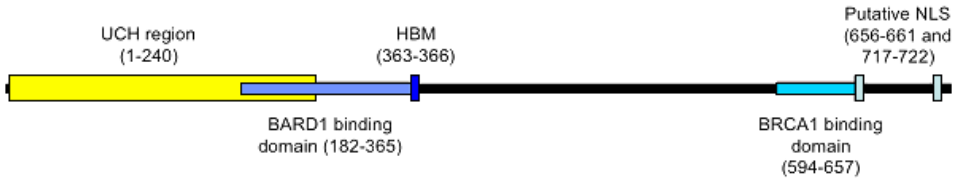
Transcription

Transcription start is 115 bp upstream of first ATG of the BAP1 ORF.

Pseudogene

No pseudogene reported.

Protein



Structure of BAP1. BAP1 is a 729 aa protein. UCH, Ubiquitin C-terminal hydrolase; HBM, HCF-binding motif (NHNY sequence); NLS, Nuclear localization signal.

Description

Human BAP1 is 729 amino acids with a molecular weight of 90 kDa. The amino-terminal 240 amino acids show homology to ubiquitin C-terminal hydrolases (UCH).

BAP1 also contains a region of extreme acidity (amino acids 396 to 408), multiple potential phosphorylation sites and N-linked glycosylation sites. The C-terminal region contains two putative nuclear localization signals.

BAP1 binds to the RING finger domain of BRCA1 through its carboxyl-terminal region (594-657 amino acids). Domain comprised by residues 182-365 of BAP1 interacts with the RING finger domain of BARD1. Interaction of BAP1 with HCF-1 (host cell factor 1; HCFC1) is dependent on the NHNY sequence resembling the HCF-binding motif (HBM).

Expression

BAP1 is expressed in a variety of human adult tissues. High expression was detected in testis, placenta and ovary, with varying levels detected in other tissues. Expression of BAP1 in normal human breast tissue was also detected.
Analysis conducted in mice revealed that Bap1 expression is up-regulated in the breast during puberty, pregnancy and as a result of parity.
BAP1 mRNA level is significantly increased in MCF10a cell line following genistein treatment, an isoflavone found in soya and proposed to prevent breast cancer.

Localisation

BAP1 is a nuclear-localized ubiquitin carboxy-terminal hydrolase.

Function

BAP1 enhances BRCA1-mediated inhibition of breast cancer cell growth and may serve as a regulator/effector of BRCA1 growth control/differentiation pathways. BAP1 interacts with HCF-1, a transcriptional cofactor found in a number of important regulatory complexes. Bap1 may help to control cell proliferation by regulating HCF-1 protein levels and by associating with genes involved in the G1-S transition.
The BRCA1/BARD1 complex possess a dual E3 ubiquitin ligase activity, promotes its own ubiquitination and targets other proteins. Although BAP1 associates with BRCA1, it does not appear to function in the deubiquitylation of the BRCA1/BARD1 complex. BAP1 inhibits the E3 ligase activity of BRCA1/BARD1 by binding the RING finger domain of BARD1 and possesses deubiquitination activity toward ubiquitin chains catalyzed by BRCA1/BARD1.
BAP1 and BRCA1/BARD1 may coordinately regulate ubiquitination during the DNA damage response and the cell cycle, BAP1 being phosphorylated by ATM and ATR in response to DNA damage and BAP1 inhibition causing S-phase retardation.
It was also proposed that specific regions and UCH activity of BAP1 play an essential role in TCR.
In the cytoplasm, BAP1 has recently been shown to localize at the endoplasmic reticulum, where it binds, deubiquitylates, and stabilizes type 3 inositol-1,4,5-trisphosphate receptor (IP3R3). This binding modulates calcium (Ca2+) release from the endoplasmic reticulum into the cytosol and mitochondria, promoting apoptosis.

Homology

The amino-terminal 240 amino acids show significant homology to a class of thiol proteases, designated UCH, which are implicated in the proteolytic processing of ubiquitin.

Mutations

Note

The mutation of a residue predicted to disrupt the helical nature of the extreme C-terminal region of BAP1 abolishes the BAP1/BRCA1 interaction. BAP1 can suppress tumorigenicity of lung cancer cells in athymic nude mice. Deubiquitinating activity and nuclear localization are both required for BAP1-mediated tumor suppression. Moreover, BAP1-mediated growth suppression is independent of wild-type BRCA1.

Squamous-cell carcinomas and large-cell undifferentiated carcinomas showed LOH for a 3p21-22 locus.
Large rearrangements, deletions, and missense mutations of the BAP1 locus have been found in lung and sporadic breast tumors and in lung cancer cell lines.
Heterozygous germline mutations of Bap1 in mice predispose to tumor formation, providing in vivo evidence that Bap1 Is a bona fide tumor suppressor. Bap1+/- mice followed for up to 20 months of age demonstrated that haploinsufficient mutant mice exhibited a markedly higher incidence and accelerated onset of asbestos-induced malignant mesothelioma when compared with similarly-exposed wild-type littermates.

Implicated in

Breast cancer

A study conducted on high-risk breast cancer families from the French population revealed that the BAP1 gene does not appear to be commonly involved in high-risk breast cancer predisposition. These results were thereafter confirmed in a larger study conducted on families with high risk of breast cancer from the French Canadian population. These studies do not rule out the possibility that BAP1 alleles might be associated with moderate or low breast cancer risk.

Selected variations of the BAP1 gene were also excluded as low penetrance risk alleles in sporadic breast cancer carried from the Spanish population.

Medulloblastoma

Medulloblastoma is a highly malignant tumor of the cerebellum. This disease with poor prognosis occurs

mostly in children. A screen of cDNA libraries with autologous sera to identify antigen-specific immune responses associated with this agressive tumor type pointed to the BAP1 gene as a possible target of immune response.

Malignant Pleural Mesothelioma (MPM)

MPM is a lethal disease resistant to most current therapies. In 2011, two independent investigations identified somatic BAP1 mutations in sporadic MPMs, and one report also identified families with MPMs resulting from germline mutations of BAP1. To date, BAP1 mutations have been found in 47-67% of sporadic MPM tumors, with 20-25% involving truncating point mutations and the remainder involving exonic deletions. The mutations occur mostly in epithelioid MPM (and many peritoneal mesotheliomas) and no significant correlation has been found between somatic mutation in BAP1 and gender, exposure to asbestos, or survival.

Abnormal protein

Identified in pleural malignant mesothelioma specimens by RNA-seq data analysis:
BAP1 (3p21.1) / CCDC66 (3p14.3) (validated by Sanger sequencing)
BAP1 (3p21.1) / WDR6 (3p21.31)
BAP1 (3p21.1) / ALDH3B1 (11q13.2)
BAP1 (3p21.1) / TNNC1 (3p21.1)
BAP1 (3p21.1) / PBRM1 3p21.1 (validated by Sanger sequencing)

Familial Mesothelioma

Metastatic Uveal Melanoma

Inactivating somatic mutations of BAP1 have been reported in nearly 85% of metastasizing uveal melanomas, the most common primary cancer of the eye and a tumor type with a strong propensity for fatal metastasis. More than one half of the mutations were predicted to cause premature protein termination, and about 20% affected BAP1's ubiquitin carboxyl-terminal hydrolase domain.

Cutaneous Melanoma

Somatic mutations have been observed in about 5% of spontaneous cutaneous melanomas and 10% of atypical Spitz tumors.

Clear Cell Renal Cell Carcinoma

BAP1 is inactivated in about 15% of clear cell renal cell carcinomas (ccRCCs). Notably, BAP1 loss is a poor prognostic indicator in ccRCC, being associated with high tumor grade.

Intrahepatic Cholangiocarcinoma

Somatic BAP1 mutations were reported in 8 of 32 (25%) intrahepatic cholangiocarcinomas in a discovery screen and in 5 of 32 (16%) independent intrahepatic cholangiocarcinomas in a subsequent prevalence screen.

Schizophrenia

The BAP1 gene was excluded as a promizing candidate gene for schizophrenia in a fine mapping association study carried out on chromosome 3p, one of the regions showing strong evidence of linkage with schizophrenia.

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