Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Mini Review

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

Frédéric Guénard, Francine Durocher

Cancer Genomics Laboratory, Oncology and Molecular Endocrinology Research Centre, CRCHUL, CHUQ and Laval University, Québec, G1V 4G2, Canada (FG, FD)

Published in Atlas Database: September 2009

Online updated version : http://AtlasGeneticsOncology.org/Genes/BAP1ID755ch3p21.html
DOI: 10.4267/2042/44801

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Identity

Other names: DKFZp686N04275; FLJ35406; FLJ37180; HUCEP-13; KIAA0272; UCHL2; hucep-6

HGNC (Hugo): BAP1

Location : 3p21.1

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

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).

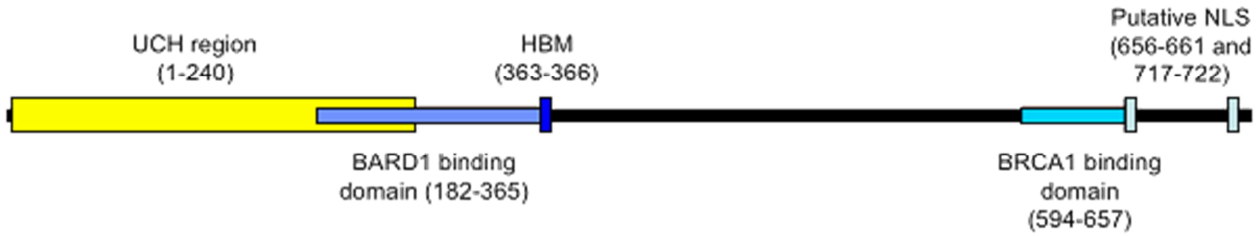
BAP1 also contains a region of extreme acidity (amino acids 396 to 408), multiple potential phosphorylation sites and N-linked glycosylation sites. The C-terminal region contains two putative nuclear localization signals.

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.



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

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.

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.

Implicated in

Breast cancer

Note

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

Note

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.

Schizophrenia

Note

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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This article should be referenced as such:

Guénard F, Durocher F. BAP1 (BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase)). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(7):670-672.