

Gene Section

Mini Review

XAF1 (XIAP associated factor-1)

Stéphanie Plenchette, Wai Gin Fong, Robert G Korneluk

Children's Hospital of Eastern Ontario, Apoptosis Research Centre, Research Institute, 401 Smyth Road, Ottawa, ON, K1H 8L1, Canada

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Identity

Other names: HSXIAPAF1; BIRC4BP

Location: 17p13.2

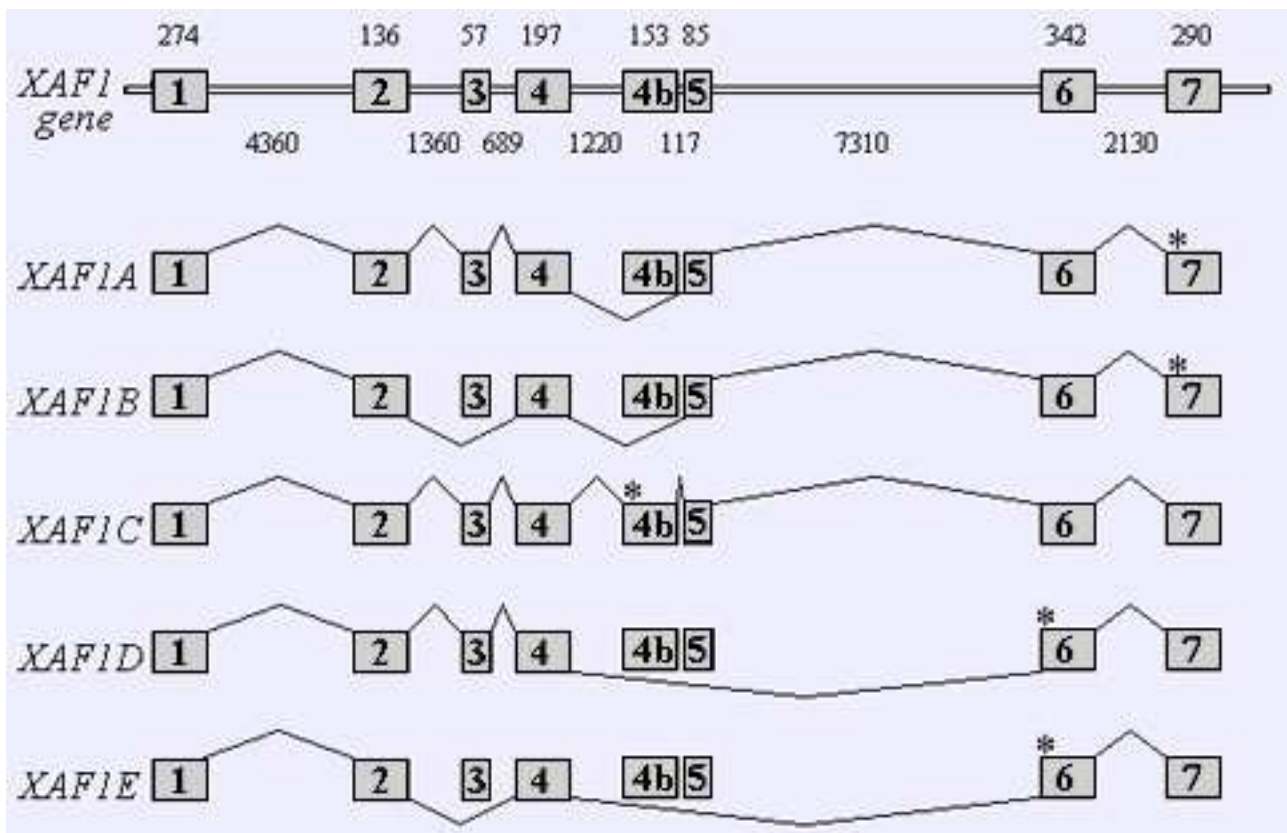
Local order: Telomeric to TP53 gene (17p13.1).

Note: XAF1 not approved by the HUGO Gene Nomenclature Committee (HGNC).

DNA/RNA

Description

The XAF1 gene exists as a single copy in the human genome; it contains 8 exons and was predicted to span over approximately 18 kb of the genomic DNA.



Schematic diagram of the XAF1 gene comprising 8 exons (in grey) and transcript variants. The sizes in base pairs (bp) of exons (above) and introns (below) are shown. (*) indicates the positions of the stop codons.

Transcription

Five isoforms of XAF1 cDNA have been identified and are expressed in a cell and tissue type specific-manner:

- The original XAF1, also called XAF1(A) (CDS: 906nt),
- The XAF1(B) isoform (CDS: 849nt); lacks exon 3,
- The XAF1(C) isoform (CDS: 495nt); contains exon 4b and a new stop codon,
- The XAF1(D) isoform (CDS: 426nt); lacks exons 4b and 5 (new stop codon in exon 6),
- The XAF1(E) isoform (CDS: 369nt); lacks exons 3, 4b and 5 (new stop codon in exon 6).

With Northern blot analysis, at least four distinct transcripts sizes have been identified in Homo sapiens (3.9 kb, 4.5 kb, 6.0 kb and 7.0 kb). How these mRNA species relate to isoform variants is not known.

Pseudogene

Not known.

Protein

Description

The full length XAF1 protein consists of 301 amino acids corresponding to a molecular weight of 33.411 kDa. The protein contains seven zinc fingers domains. The XAF1(B) isoform is predicted to lack the third N-terminal zinc finger of the previously described XAF1. The XAF1(C) is predicted to contain the first five amino-terminal zinc finger domains of the previously described XAF1 and also a unique 24 aa carboxy terminus. There is no evidence for XAF1 isoforms (C), (D) and (E) expression at the protein level.

Expression

Normal tissue: ubiquitous and differential expression in normal tissues; highest in heart and ovary and lowest in brain and testis at mRNA levels. The XAF1 protein also displays differential protein expression profile within normal cell or tissue development including placenta and motoneurons.

Cancer: as opposed to normal cells, XAF1 is found either low or undetectable in tumor cell lines at both mRNA and protein levels. Expression varies also widely among different tumor cell lines. High levels of XAF1 protein were found in glioblastoma cells (SF-539) and ovarian cells (OVCAR-5). Detectable levels were found also in various gastric and colon cancer cell lines and also myeloma cells (U266).

Localisation

Nuclear and cytoplasmic distribution.

Function

Tumor suppressor gene: loss of heterozygosity (LOH) found in 12 of 33 (36%) human primary colorectal carcinomas. The absence or reduced expression of XAF1 in cancer cell lines by genetic or epigenetic

modifications have suggested a possible role in the suppression of development and/or progression of malignancy.

IAP antagonist: XAF1 exerts a proapoptotic effect by directly interacting with BIRC4/XIAP and antagonizing its anticaspase activity. XAF1 enhances XIAP E3 ligase activity towards BIRC5/Survivin through a complex and mediates Survivin down-regulation.

Interferon (IFN)-stimulated gene (ISG): XAF1 is an important mediator of IFN-induced sensitization to TNF-related apoptosis-inducing ligand (TRAIL) in cancer.

Increasing expression of XAF1 sensitizes cells to apoptosis-induced by various stimuli including etoposide, 5-FU, TRAIL, anti-Fas Ab, TNFalpha, UV, H₂O₂, gamma-irradiation.

Homology

XAF1 shares high amino acid similarity with the zinc finger domains of FLN29 and TRAF6.

Mutations

Note: Include genetic and epigenetic modification.

Germinal

Not known.

Somatic

No somatic mutations in tumor cell lines examined. LOH described in colon tumors.

Epigenetics

Aberrant promoter hypermethylation in the 5' proximal region (from +3nt to -234 nt) in a variety of gastric, colon, bladder, kidney and prostate cancer cell lines and tumors.

Implicated in

Colorectal cancer, gastric cancer, urogenital cancer

Oncogenesis

XAF1 is proposed to be a tumor suppressor gene. Correlation of reduction in XAF1 expression with stage and grade within gastric and colorectal tumors demonstrating that the loss of XAF1 contributes to tumorigenesis.

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