Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Mini Review

TFAP2A (transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha))

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Published in Atlas Database: September 2009

Online updated version : http://AtlasGeneticsOncology.org/Genes/TFAP2AID42526ch6p24.html
DOI: 10.4267/2042/44818

Identity

Other names: AP-2; AP-2alpha; AP2-alpha; AP2TF; BOFS; FLJ51761; TFAP2

HGNC (Hugo): TFAP2A

Location: 6p24.3

DNA/RNA

Description

The gene encompasses 22.882 kb of DNA; 7 exons.

Transcription

mRNA, NM_001042425; NM_003220; NM_001032280.

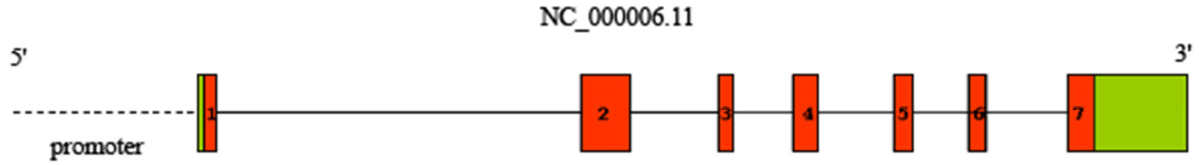

Figure 1 : TFAP2A human gene including promoter, 7 exons and 6 introns.
Modified from Entrez Gene (Genomic DNA).

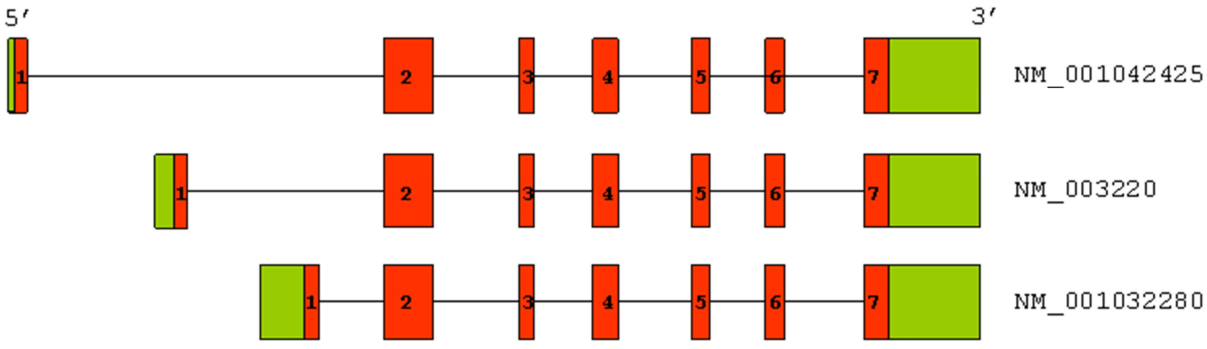

Figure 2 : Three main transcripts are shown. Exons: red and green. Red: protein-coding sequences; Green: 5' and 3' Untranslated (UTR) regions. Black lines: introns. Modified from Entrez Gene (Transcripts).

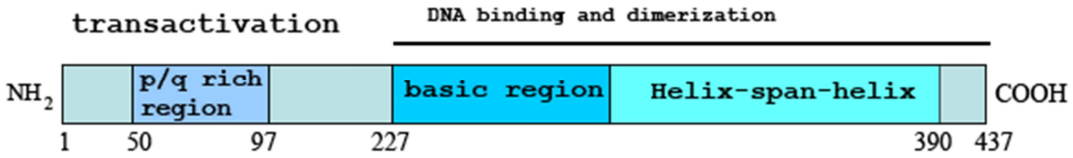

Figure 3. Modified from Williams and Tjian, 1991.

Protein

Description

The main TFAP2A isoform consists of 437 amino acids and has a molecular weight of 52 kDa. TFAP2A proteins contain a unique, highly conserved helix-span-helix dimerization motif at the C-terminal half of the protein, a central basic region and a less conserved proline- and glutamine-rich domain at the amino terminus. The helix-span-helix motif and the basic region mediate DNA binding and dimerization while the proline- and glutamine-rich region is responsible for transcriptional transactivation (see figure 3).

Expression

Ubiquitous. Abnormal expression is found in a variety of human tumours.

Localisation

Located predominantly in the nucleus.

Function

The TFAP2A proteins are able to form hetero- as well as homo-dimers and bind to GC-rich DNA sequences within regulatory regions of their target genes, mediating both activation and repression of gene transcription. Functional TFAP2 binding sites, such as 5'-GCCN3GGC-3' or 5'-GCCN4GGC-3' or 5'-GCCN3/4GGG-3' or 5'-CCCCAGGC-3' have been identified and regulate genes involved in physiological or pathological processes such as development, cell growth, differentiation, apoptosis and tumorigenesis. Examples of activated genes are CDKN1A, TGFA, estrogen receptor, keratinocyte-specific genes, KIT, ERBB2 and IGFBP5 while MCAM/MUC18, C/EBPA, MYC and DCBLD2/ESDN/CLCP1 are repressed by TFAP2A. TFAP2A protein expression is highly cell-type specific, showing different spatial and temporal expression during development and in various tissues. The TFAP2A proteins are essential during embryogenesis as demonstrated by mouse genetic studies. Loss of TFAP2A impairs cranial closure and leads to severe dismorphogenesis of different organs and death at birth. Loss of TFAP2A activity in general alters proliferation and induces premature differentiation and/or apoptosis in various cell types as demonstrated by in vivo and in vitro studies. Because of their involvement in these fundamental cellular processes TFAP2A proteins are essential for maintaining cellular homeostasis. Deregulation of TFAP2A protein levels alter the cell functions in such a drastic way that it can eventually lead to cancer formation and/or progression. In fact, several studies have associated aberrant TFAP2A activity with tumorigenesis (see below).

Homology

With the other members of the TFAP2 family: TFAP2B, TFAP2C, TFAP2D, TFAP2E.

Mutations

Note

Found in branchio-oculo-facial syndrome (BOFS).

A de novo 10529A-G transition in exon 4 of the TFAP2A human gene was found in an 18-year-old man with branchio-oculo-facial syndrome (BOFS), a rare autosomal-dominant cleft palate-craniofacial disorder with variable expressivity. The mutation leads to arg255-to-gly (R255G) substitution in a highly conserved residue in the basic region of the DNA-binding domain, a change that replaces a charged polar side chain with a nonpolar side chain with a predicted conformational space change. Four additional BOFS patients were found to have de novo missense mutations in the highly conserved exons 4 and 5. No mutations were found in more than 300 controls (Milunsky et al., 2008).

A de novo deletion of 18 and insertion of 6 nucleotides, resulting in LPGARR deletion and RI insertion between amino acids 276 and 281, was found within the basic DNA binding and dimerization domains of TFAP2A in a 4-year-old girl with congenital sensorineural deafness associated with inner ear malformation. The girl also had pseudocleft lips, skin defects, auricle abnormalities, and unilateral multicystic dysplastic kidney, leading to the diagnosis of branchio-oculo-facial (BOF) syndrome (Tekin et al., 2009).

Implicated in

Various cancers

Note

TFAP2A has been implicated in various cancers, first of all in melanoma and breast tumors. However several evidences link deregulation of TFAP2A to prostate and ovarian carcinomas as well as gliomas.

Melanoma

Note

Malignant melanoma follows the transformation

and proliferation of melanocytes, normally present in the basal cell layer of the epidermis. Tumor growth consists of a horizontal or radial initial growth phase (RGP) followed by a subsequent vertical growth phase (VGP) corresponding to the infiltration of the dermis and hypodermis (biphasic growth). Alternatively the growth pattern can be only vertical (monophasic growth). When the lesion enters the vertical growth phase, the expression of adhesion molecules changes as the tumor enters the dermis and acquires the capacity to metastasize. Deregulated expression or activity of a number of transcription factors and their downstream target genes (including those involved in invasion and motility) has been found and TFAP2A is one of them. In fact, in cutaneous malignant melanoma, reduced nuclear TFAP2A expression has been associated with aggressive clinicopathological outcomes. Moreover low TFAP2A levels predict shorter recurrence-free survival. In melanoma cell lines, loss of TFAP2A associates with enhanced invasion, metastasis formation as well as angiogenesis as tested in mouse models, due to events such as overexpression of the cell adhesion molecule MCAM/MUC18, protease protease-activated receptor 1 (F2R/PAR1), MMP2 as well as downregulation of the tyrosine kinase receptor KIT. On the other hand TFAP2A re-expression in melanoma cells suppresses tumorigenicity and metastatic potential.

Breast cancer

Note

TFAP2A nuclear or total expression is significantly reduced in invasive carcinomas compared to benign breast epithelium (BBE) or ductal carcinoma in situ (DCIS) and associates with adverse clinicopathological parameters suggesting a tumor suppressor function for this transcription factor. However, there are reports showing increased TFAP2A expression in breast tumors. Discrepancies could be related to the low specificity of the tools (mostly antibodies) used to analyze TFAP2A expression. In fact, other TFAP2-family members with biological or pathological functions, could have been identified in those experiments. One possible mechanism by which TFAP2A could function as a tumor suppressor is by inducing growth arrest and apoptosis via induction of $p21^{WAF1}$ expression, inhibition of MYC-related transactivation and BCL2 expression. TFAP2A expression in breast cancer has also been related to high sensitiveness to chemotherapeutic drugs due to massive induction of apoptosis in TFAP2A highly expressing cells.

Prostate cancer

Note

TFAP2A expression is associated with luminal differentiation of normal prostate tissues but its expression is lost early when prostate adenocarcinomas develop. Increase cell proliferation has been observed in prostate tumors with low cytoplasmic TFAP2A expression. In TFAP2A-negative prostate cancer cells, TFAP2A expression inhibits tumorigenicity and leads to deregulation of relevant genes such as VEGF.

Ovarian cancer

Note

Reduced cytoplasmic TFAP2A expression predicts poor overall survival of epithelial ovarian tumors and in ovarian cancer cells this transcription factor suppresses cell proliferation and invasion parallel to decreased phosphorylation of HER2, AKT and ERK pathways, reduced pro-MMP2 levels and increased CDH1/ECAD expression.

Gliomas

Note

High nuclear levels of TFAP2A associate with better differentiation of human gliomas, absence of MMP2 and VEGF expression and offer some survival advantage to the patients.

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This article should be referenced as such:

Orso F, Taverna D. TFAP2A (transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(8):735-738.