

Gene Section

Mini Review

NCOA3 (Nuclear Receptor Coactivator 3)

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Identity

Other names: AIB1 (amplified in breast cancer-1); ACTR; RAC3 (RAR-associated coactivator 3); SRC3 (steroid receptor coactivator protein 3); TRAM-1 (thyroid hormone receptor activator molecule 1); pCIP (p300/CBP-integrator associated protein; mouse)

HGNC (Hugo): NCOA3

Location: 20q13.1

RNA Expression: Highly expressed in placenta, heart, pancreas, muscle, brain, liver, uterus, pituitary, mammary gland, and testis. Lower levels of expression are found in lung and kidney.

Transcription

Transcription is from centromere to telomere. There are two reported transcripts: Isoform a (7935 bp) and isoform b (7923 bp). Isoform b uses an alternate in-frame splice site and lacks exon 3.

DNA/RNA

Description

The human AIB1 gene spans approximately 155 kb and has 23 exons.



AIB1 (20q12)



Genomic structure of NCOA3 with NCBI Build 35.1 genomic positions indicated. Black boxes indicate exons. The translational start (*) and stop codons (^) are also shown. UTR, untranslated region.

Pseudogene

Chromosome 8 (AF010227).

Protein

Description

A member of the p160/steroid receptor coactivator family. 1424 amino acids. 155 kDa (130 kDa encoded by isoform b).

Expression

Protein expression found in testis, lung, liver, brain, mammary gland, and heart.

Localisation

Mainly cytoplasmic and weakly nuclear. The protein translocates to the nucleus upon TNF activation and phosphorylation.

Function

A transcriptional coactivator that interacts with nuclear hormone receptors to enhance their transcriptional activation. AIB1 interacts with other transcription factors including TP52, NfκB, and ER81. It has intrinsic histone acetyltransferase activity and recruits CREB Binding Protein (CBP)/p300 cointegrators to a multisubunit coactivator complete.

Mutations

Somatic

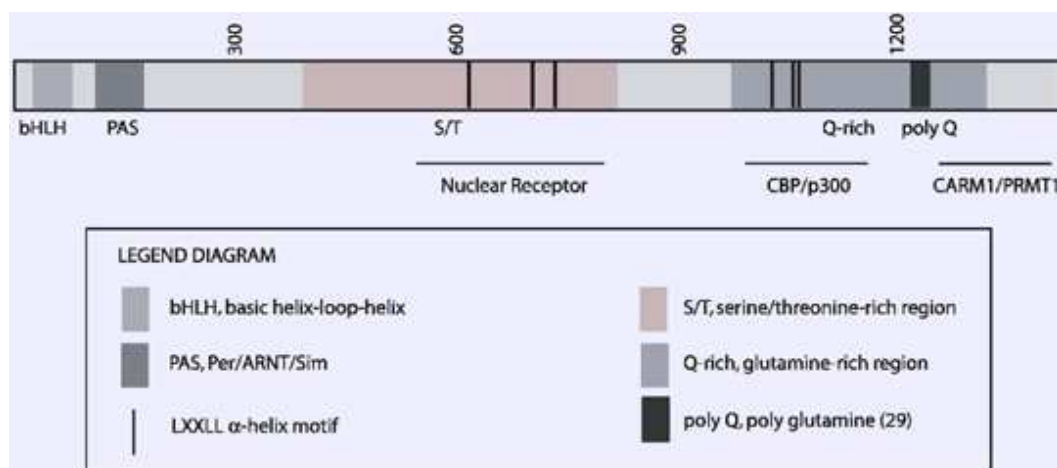
The gene copy number and expression levels are altered in several cancer types. Overexpression has been found in breast, ovarian, endometrial, gastric, and pancreatic cancers. Amplification of AIB1 in hepatocellular carcinoma is associated with poor prognosis. Increased numbers of polyglutamine repeats correlate with higher breast cancer risk in BRCA1 and BRCA2 mutation carriers. However, the polymorphic repeat genotype does not influence postmenopausal breast cancer risk among Caucasian women in the general population.

To be noted

Note

Overexpression of AIB1 in tamoxifen-treated patients is associated with tamoxifen resistance and worse survival. Tamoxifen behaves as estrogen in breast cancer cells that express high levels of AIB1 and HER2, resulting in de novo resistance.

An N-terminally deleted isoform (AIB1-Delta3) which lacks exon 3 was identified and found to be overexpressed in breast cancer cell lines and in tumors from breast cancer patients. Of interest, this splice variant has more potent transcriptional coactivation properties on estrogen and progesterone receptors than the full-length AIB1 protein.



Structural features of AIB1. AIB1 contains a basic helix-loop-helix preceding a PAS (Per/Arnt/Sim) region, serine- and threonine-rich regions, and a charged cluster. There is also a glutamine-rich region that contains a polyglutamine tract. The central portion of the protein contains three LXXLL motifs (L=leucine, X=any amino acid) that are critical for interaction with ligand-bound nuclear receptors. An activation domain located C-terminal to the nuclear receptor interaction domain contains three LXXLL motifs that are important for interaction with general transcription cointegrators, CREB binding protein (CBP)/p300. A second transcriptional activation domain is responsible for interaction with histone methyltransferases, coactivator-associated arginine methyltransferase 1 (CARM1) and PRMT1.

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