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Gene Section
Review

TACC2 (transforming, acidic coiled-coil containing protein 2)

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Abstract

Review on TACC2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: AZU-1, ECTACC

HGNC (Hugo): TACC2

Location: 10q26.13

Note

Based on published GenBank sequences, this gene has seven potential transcription start sites located at 123748689 bp, 123754142 bp, 123872554 bp, 123886229 bp, 123922941 bp, 123951963 bp, 123969557 bp from pter.

DNA/RNA

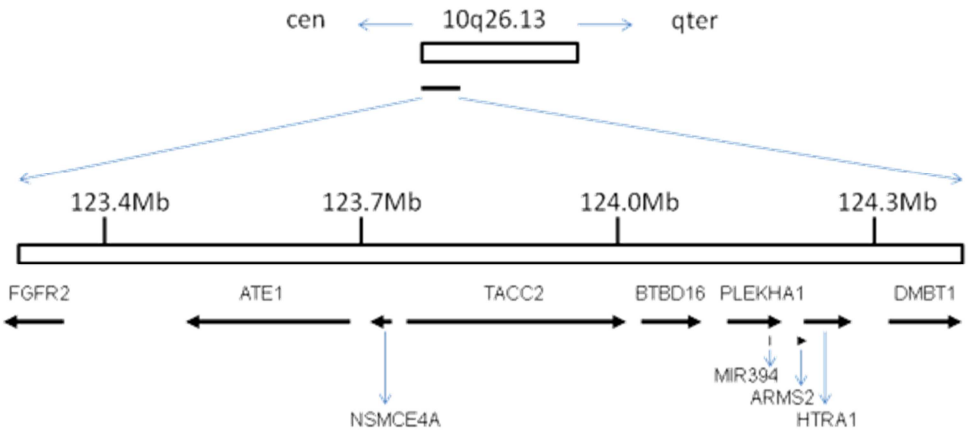
Description

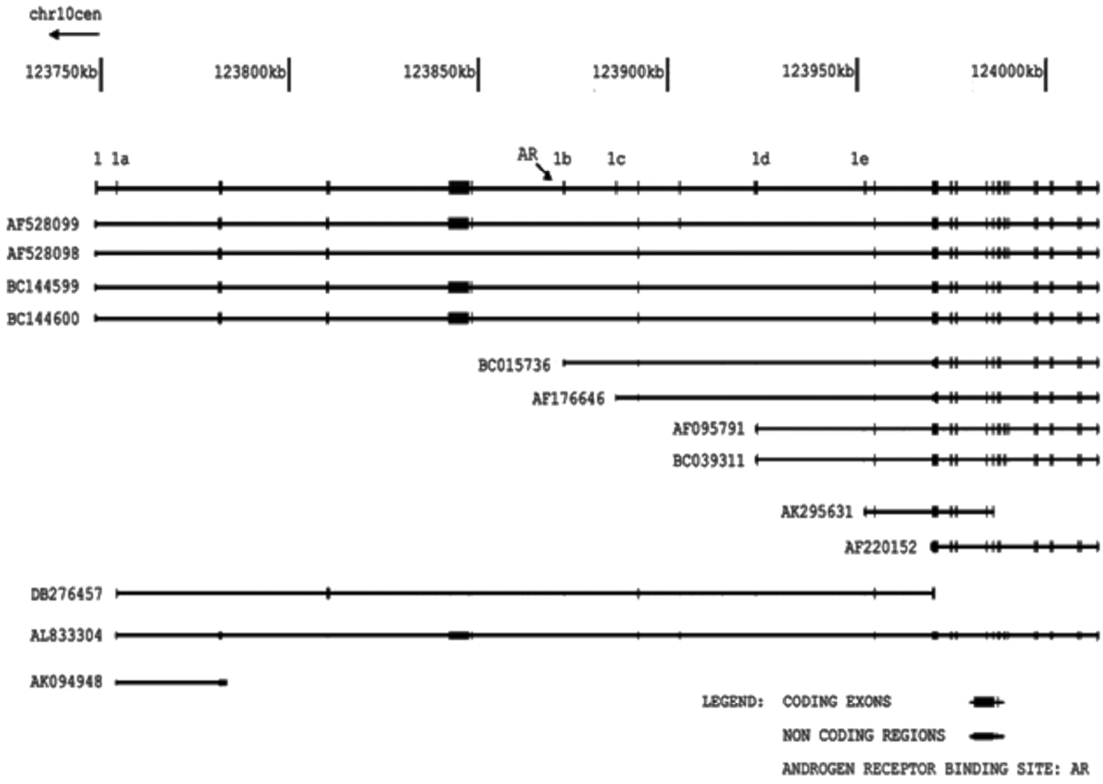
The gene is composed of 28 exons spanning 265369 bp.

Transcription

Transcripts depicted above encompass most transcripts evident in AceView and USGC genome browsers.

Most other AceView "transcripts" appear to be subsets of those shown or unspliced. AF176646 represents the published "Azu-1" variant (Chen et al., 2000); although no other cDNAs support the 5' end as a transcriptional start site (123886229 bp), a H3K27 acetylation cluster is noted in this region (ENCODE Project Consortium, 2011).



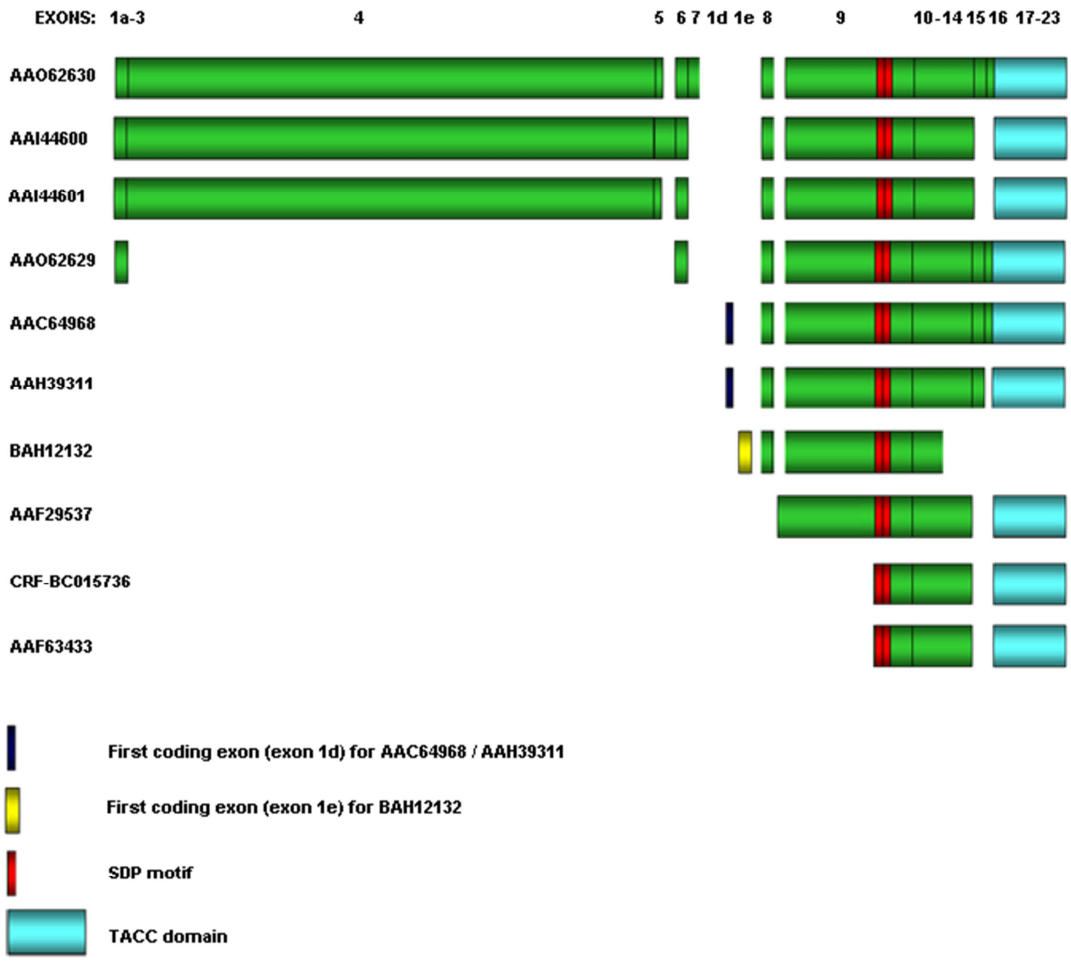


AF220152 represents the "ECTACC variant" (Pu et al., 2001), first 13 bases of which do not match the genomic DNA and no other cDNAs support its 5' end as a transcriptional start site.
Transcription start site at 123754142 bp identified in a global search for alternative promoters (Kimura et al., 2006) and supported by three cDNAs (AL833304, DB276457 and AK094848). AL8333304 does not encode a protein as it appears to use a "non canonical" splice site at 123781503, 4 nucleotides after initiator codon for the TACC2 "long isoforms". DB276457 appears to be incomplete at the 3' end due to the nature of its isolation (Kimura et al., 2006).

Protein

Description

Ten isoforms are predicted based on published cDNA sequences. Features will be referenced to their location in the largest AAO62630 isoform (2948 amino acids, 309403,40 Da). The nine other isoforms are: AAI44600, 2875 amino acids, 302586,86 Da; AAI44601, 2826 amino acids, 296742,08 Da; AAO62629, 1094 amino acids, 119330,60 Da; AAC64968, 1026 amino acids, 112110,91 Da; AAH39311, 996 amino acids, 108703,96 Da; BAH12132, 601 amino acids, 64367,07 Da; AAF29537, 906 amino acids, 99590,14 Da; ORF-BC015736 (longest open reading frame of GB:BC015736), 575 amino acids, 64675,57 Da; AAF63433, 571 amino acids, 64156,01 Da.
ORF-BC015736 and AAF63433, beginning at an "internal" AUG present in exon 9, are identical except for 4 amino acids missing in AAF63433 (amino acid 2429-2432). BAH12132 prematurely terminates due to a C-T mutation in the cDNA generating a nonsense codon; the partial cDNA coding this open reading frame is identical to other TACC2 isoforms downstream of the nonsense codon, suggesting the mutation is a cloning artefact.
Western blot analysis confirms the large ≈ 300 kDa isoforms and those of ≈ 100 kDa. Western blot often shows species 65-70 kDa (corresponding in size to ORF-BC015736 and AAF63433 isoforms), however the variability in intensity in different preparations from the same cell type suggests that these species could also arise as a product of degradation (PEST sequences support that TACC2 is subject to regulated degradation).
PSORT II predicts multiple nuclear localisation signals between amino acid 2128 and 2420 (http://psort.hgc.jp/form2.html). Multiple phosphorylation sites have been identified throughout the protein sequence by mass spectrometry (summarized at PhosphoSitePlus (Hornbeck et al., 2012)).



The following lysine modifications are noted: lysine trimethylation at K1339 and K1346 (Cao et al., 2013); ubiquitylation at K2542 in HCT116 colon cancer cells (Kim et al., 2011); acetylation at K2884 in A549 lung cancer cells (Choudhary et al., 2009), K2736 in a resected liver cancer, K2927 and K2928 in NCI H2228 non small cell lung cancer cells (Hornbeck et al., 2012).

Expression

Short isoforms (100-120 kDa) widely expressed in fetal and adult tissue, but large isoforms (≈ 300 kDa) expressed at high levels in muscle tissue (Lauffart et al., 2003). Short form(s) expression is upregulated by erythopoietin in human microvascular endothelial cells (Pu et al., 2001) and androgens in prostate cancer cells (Takayama et al., 2012). Induction of large forms occurs as development proceeds in the tissues that express them (Still et al., unpublished).

Localisation

TACC2 short isoforms can be located in the nucleus and/or cytosol of interphase cells (Chen et al., 2000; Gergely et al., 2000; Lauffart et al., 2003). TACC2 interacts with the centrosome and mitotic spindle during mitosis (Gergely et al., 2000).

In some cells, overexpression can result in accumulation of the protein into cytoplasmic punctate structures due to oligmerisation (Gergely et al., 2000). The oligomerisation motif is located between amino acid 2740 and 2815 (Tei et al., 2009).

Function

TACC2 plays a role in microtubule dynamics during mitosis based upon interactions with Aurora C kinase (Tien et al., 2004) and CKAP5 (ch-TOG/XMAP215) via the TACC domain (see Peset and Vernos, 2008 for Review). TACC2 is implicated in G2/M progression (Takayama et al., 2012) and its ability to function in the maintenance of normal mitotic spindle dynamics is targeted by SV40 T-antigen (Tei et al., 2009).

TACC2 is an effector of a mitotic checkpoint control kinase, TTK, with disruption of TTK activity preventing phosphorylation of 100-120 kD TACC2 short isoforms, subsequent recruitment of the TACC2 to the centrosome, leading to reduction of centrosome-centrosome distance in mitotic cells

(Dou et al., 2004). TACC2 also interacts with mitotic regulatory proteins Haus 1, Haus 4 and PRC1 (Hutchins et al., 2010).
Alternative functions have been ascribed in transcription through direct interaction with coregulators FHL2 and FHL3 proteins (Lauffart et al., 2007b), YEATS4 (GAS41) and the SWI/SNF chromatin remodeling complex (Lauffart et al., 2002), histone acetyltransferases KAT2A (hGCN5L2)/KAT2B (pCAF)/Ep300/CREBBP (Gangisetty et al., 2004), a core component of a histone deacetylase complex, HMG20B (BRAF35) (Stelzl et al., 2005) and the retinoid-X receptor (Vettaikkorumakankauv et al., 2008).
TACC2 enhances transcriptional regulation from a cAMP response element (Lauffart et al., 2007b), and retinoid-X-receptor responsive genes (Vettaikkorumakankauv et al., 2008).
Interaction with nucleoporin NUP155 has been identified by mass throughput technologies (Havugimana et al., 2012).
TACC2 is found in complexes containing BRCA1, BARD1, p53 and Ku70 and may therefore also have a role in DNA damage/repair (Lauffart et al., 2007a).
TACC2 is phosphorylated during mitosis (Dephoure et al., 2008; Olsen et al., 2010) and in response to activation of EGFR and oncogenic signaling pathways (Rikova et al., 2007; Chen et al., 2009; Moritz et al., 2010).
Tumour suppressive properties of TACC2 are thought to function through the PLCγ pathway (Cheng et al., 2011). PPP1CC, protein phosphatase 1 may be involved in dephosphorylation of TACC2 (Esteves et al., 2013).
Acetylation, ubiquitylation and trimethylation of TACC2 may also impact TACC2's function (Choudhary et al., 2009; Kim et al., 2011; Hornbeck et al., 2012; Cao et al., 2013).

Homology

Member of the TACC family, based on the presence of the conserved approximately 200 amino acid carboxy terminal coiled coil domain (TACC domain) (Still et al., 1999; Still et al., 2004).
Both TACC1 and TACC2 contain a 16 amino acid SFP motif SSDSE-X2- FETPE-X2-TP, and a conserved string of nine amino acids, HATDEEKLA.
These two motifs are specific to TACC1 and 2 only.
Additionally, TACC2 contains two copies of the 33 amino acid SDP repeat, which is conserved between the members of the vertebrate TACC family (Lauffart et al., 2002).
In TACC1, the SDP repeat serves as the binding site for the SWI/SNF component/accessory factor, YEATS4 (Lauffart et al., 2002).

Mutations

Note
To date, no mutations in the TACC2 gene have been detected.

Implicated in

Infant acute lymphoblastic leukemia

Prognosis
In a gene array analysis of 97 patients, increased expression was correlated with an intermediate or high risk for a poorer outcome, independent of patient age (Kang et al., 2012). Results were not confirmed at the protein level.

Oncogenesis
Upregulation of TACC2 may be triggered by the underlying alteration in the MLL gene in patients, resulting in recruitment of histone methylases to target genes.
Proposed mechanism based on previous identification of the regulation of the TACC2 gene by the histone methylase SMYD2 (Abu-Farha et al., 2008).

Neuroblastoma

Prognosis
Identified as a marker of minimal residue disease based on Affymetrix U-95 gene chip expression array analysis of 48 stage 4 tumours and 9 remission bone marrows.
Expression of TACC2 in tumour as compared to marrow was superior to that of tyrosine hydroxylase, however, TACC2 expression failed to be of prognostic value for progression-free survival (Cheung et al., 2008).

Intracranial ependymoma

Prognosis
Single allele deletion detected by high-resolution matrix-based CGH in 11/68 intracranial ependymoma (Mendrzyk et al., 2006), not linked to clinicopathologic subgroups.

Oncogenesis
Apparent overexpression from remaining allele in the tumours observed by qRT-PCR (Mendrzyk et al., 2006).

Breast cancer

Prognosis
Decreased expression of TACC2 was noted in a survey of breast cancer samples by immunohistochemistry of tumour microarrays derived from 552 breast cancer patients (Jacquemier et al., 2005). In another study, "increased" levels of TACC2 were reported, based on quantitative rt-PCR and analysis of protein

levels in "macro-dissected" tumours, to be associated with poorer prognosis, grade and short disease-free survival (Cheng et al., 2010). However, the intensity of immunohistochemical staining of the tumour cells appeared to be the same as in normal breast epithelium used in the study. Thus, in this study, TACC2 staining may only reflect the percentage of the resected tumour tissue occupied by tumour cells and may reflect retention of expression of TACC2 at normal levels seen in the precursor mammary epithelial cells (Cheng et al., 2010).

Oncogenesis

The TACC2 transcript AF176646 (AZU1) is downregulated in the more malignant derivatives of the HMT-3522 tumour progression cell model (Chen et al., 2000). Expression of exogenous TACC2 short isoforms (AF176646, AF095791 or AF528098) reduces malignant potential of breast tumour cells (Chen et al., 2000; Lauffart et al., 2003). Tumor suppressor properties may operate through PLCγ (Cheng et al., 2011).

Prostate cancer

Prognosis

Positive correlation between Gleason score and immunohistochemical staining for TACC2 noted in a survey of 103 prostate cancer samples (Takayama et al., 2012).

Oncogenesis

The TACC2 gene is androgen responsive, with two confirmed androgen receptor binding sites in intron 4*; at 123870283-123870871 (Takayama et al., 2012).

TACC2 promotes cell proliferation in androgen sensitive and androgen-independent prostate cancer cells.

A single-nucleotide polymorphism, rs3763763, inside an estrogen response element is associated with prostate cancer-specific mortality and "all-cause mortality" after androgen-deprivation therapy (Huang et al., 2012) suggesting that hormonally regulated expression of TACC2 is important in the oncogenic process.

It has been noted that TACC2 interacts with androgen receptor regulator FHL2 (Lauffart et al., 2007b), a protein of known importance in attainment of androgen independence in prostate cancer (McGrath et al., 2013), suggesting potential positive feedback on TACC2 expression.

*designated based on genomic structure of the AF528099 long form (see genomic model).

Breakpoints

Note

No translocation or deletions within the TACC2 gene have been identified.

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