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Gene Section
Review

TACC3 (transforming, acidic coiled-coil containing protein 3)

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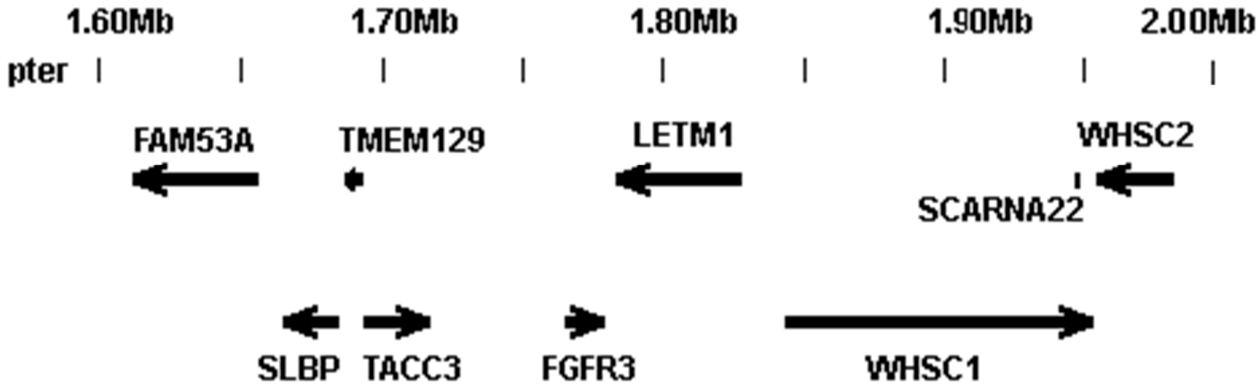
Identity

Other names: ERIC1; MGC117382; MGC133242

HGNC (Hugo): TACC3

Location: 4p16.3



DNA/RNA

Description

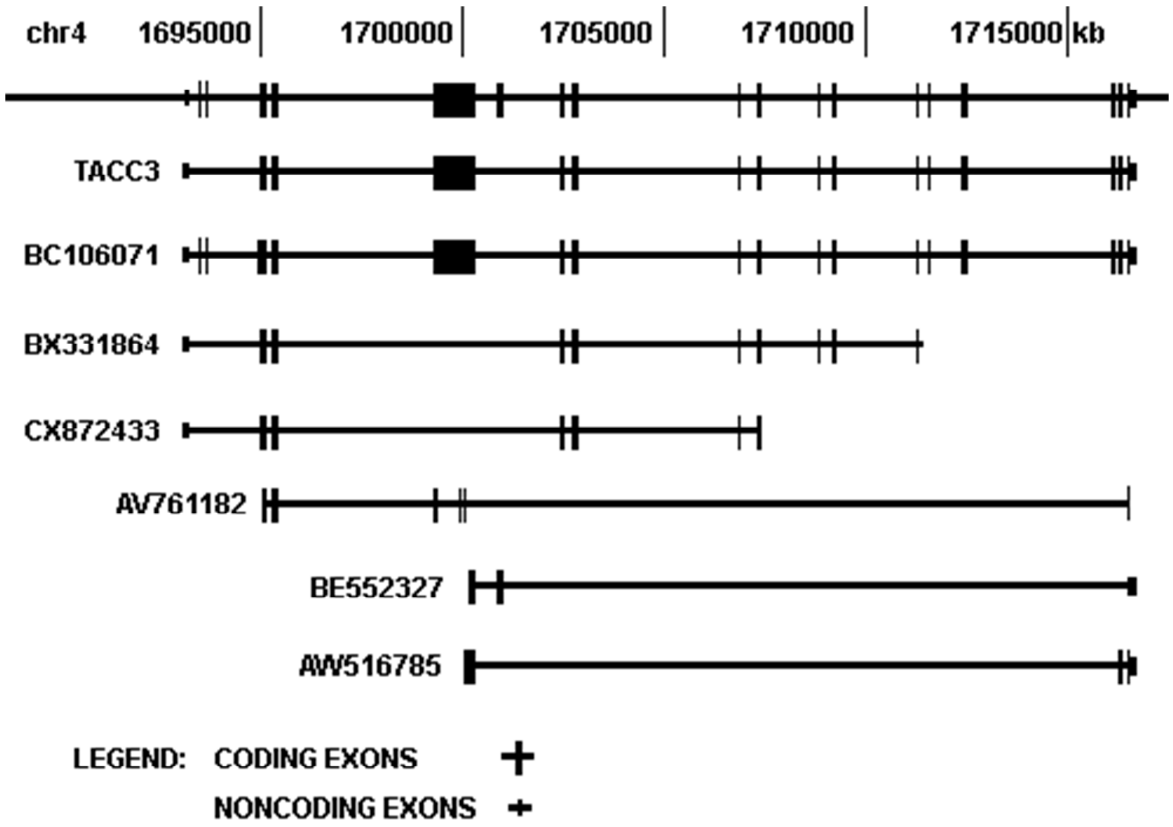
The gene is composed of 16 verified exons spanning 23.6 kb.

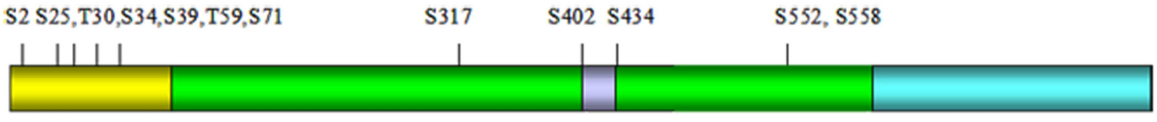
Transcription

Encodes a single confirmed 2788 nt transcript (NM_006342) (Still et al., 1999), although one additional transcript with two additional small 5' coding exons between exon 1 and the first coding exon (exon 2), based on NM_006342, is indicated based on several cDNAs that may however be from suspect cDNA libraries (see UCSC Genome Bioinformatics Site (http://genome.ucsc.edu)). Four additional transcripts variants are suggested based on singleton Expressed sequence tags in tumor cell lines (AW516785, BE552327, BX331864) and/or stem cell progenitors (AV761182, CX872433).

Pseudogene

None.





Conserved N-terminal region
SDP repeat
TACC domain

S34, S552, S558 are phosphorylation targets for Aurora A kinase
S558 is a target for TPX2 in meiotic oocytes
S25, T59, S71, S317, S434 are presumed targets for CDKs in mitotic HeLa cells
S25 is phosphorylated in nocadozole treated HeLa cells
S434 is phosphorylated in nuclear localized TACC3 in HeLa cells
S2, T30, S39, S402 are additional sites for phosphorylation

Protein

Description

TACC3 encodes a single protein of 838 amino acids with a molecular mass of 90 kDa (Still et al., 1999). The protein is heavily phosphorylated based on direct evidence and based on predictions from the Xenopus and mouse orthologs (Beausoleil et al., 2004; Beausoleil et al., 2008; Kinoshita et al., 2005; Yu et al., 2007; Cantin et al., 2008; Dephoure et al., 2008). Thus, human TACC3 migrates at approxi-mately 150 kDa in SDS-PAGE. Additional variants are suggested based on singleton cDNAs (see above) but their predicted protein isoforms have not been confirmed.

Expression

High levels during early (mouse) embryogenesis, in particular during early differentiation of specific tissues (Sadek et al., 2003). In adult tissues, expression is relatively limited, with high levels noted in hematological tissues such as the thymus, spleen and leukocytes, and reproductive tissues, especially meiotic cells of the testes and ovary (Still et al., 1999; Sadek et al., 2003).

Epithelial layers of the lung, mammary gland and ovary express TACC3 and alterations in expression are noted during tumorigenesis (see below). Expression in human adult tissues is summarized in Lauffart et al. 2006.

Localisation

Human (and mouse) TACC3 is located in the interphase nucleus and/or cytosol, depending on cell type and cancer type (Gergely et al., 2000; Aitola et al., 2003; Lauffart et al., 2005; Jung et al., 2006; Vettaikkorumakankauv et al., 2008). TACC3 does not however contain a classical nuclear localisation signal (Still et al., 1999). TACC3 associates with the centrosome in a cell cycle dependent manner (Gergely et al., 2000). Phosphorylation of TACC3 by Aurora A on key serine residues is required for this interaction (Kinoshita et al., 2005; LeRoy et al., 2007). Overexpression of TACC3 from artificial constructs can result in accumulation in the cytosol of some cells resulting in oligmerisation in punctate structures (Gergely et al., 2000).

Function

Gene knockout and knockdown studies in mouse have indicated that TACC3 is vital for embryonic development. A functionally null TACC3 mutant dies during mid to late gestation due to excessive apoptosis affecting hematopoietic and other organ systems (Piekorz et al., 2002). Hypomorphic alleles result in defects in mitosis affecting mesenchymal sclerotome and therefore the axial skeleton (Yao et al., 2007). These mutational mouse models indicate that TACC3 has a role in chromosomal alignment, separation and cytokinesis and that TACC3 can be associated with p53-mediated apoptosis.

TACC3 has a well characterized function in microtubule dynamics, particularly during mitosis, based on mutational analysis (see above) and physical interactions with Aurora A and Aurora B kinases, CKAP5 (ch-TOG/XMAP215) and AKAP9 via the TACC domain (see Peset and Vernos, 2008 for review). Interaction with CEP120 is important in interkinetic nuclear migration and maintenance of neural progenitor self-renewal during the development of the neocortex (Xie et al., 2007). Phosphorylation of Ser34, Ser552 and Ser558 by Aurora A are required for localization to centro-somes and is necessary for recruitment of CKAP5 and nucleation of microtubules (Kinoshita et al., 2005; LeRoy et al., 2007). Ser25, Thr59, Ser71, Ser317, and Ser 434 are presumed targets for cyclin dependent kinases in mitotic HeLa cells (Yu et al., 2007; Cantin et al., 2008; Dephoure et al., 2008). By homology, Ser558 phosphorylation by TPX2 is required for nucleation of microtubules in meiotic oocytes (Brunet et al., 2008).

TACC3 also has a defined role in interphase cells as a transcriptional cofactor for the aryl-nuclear translocator protein (Sadek, 2000), FOG1 (Garriga-Canut and Orkin, 2004; Simpson et al., 2004) and is a possible indirect activator of CREB via FHL family of coactivator/corepressor proteins (Lauffart et al., 2007b). Roles in transcriptional regulation

have also been proposed based on TACC3 binding to GAS41 (YEATS4) via the SDP repeat, histone acetyl transferases hGCN5L2 (KAT2A), pCAF (KAT2B), and retinoid X-receptor beta via the TACC domain (Gangisetty, 2004; Lauffart et al., 2002; Vettaikkorumakankauv et al., 2008). TACC3 functionally interacts with MBD2 bound to methylated promoters, promoting transcription by displacement of HDAC2 and recruitment of KAT2B (Angrisano et al., 2006). Human TACC3 may be involved in transcriptional termination and/or pre-mRNA splicing through TTF2 (Leonard et al., 2003). TACC3 can interact with BARD1, BRCA1 and p53 and has been shown to have some protective affects against adriamycin-mediated DNA damage in ovarian cancer cells (Lauffart et al., 2007a). Phosphorylation of the last amino acid of the SDP repeat, Ser434, is noted in nuclear extracts of HeLa (Beausoleil, 2004; Beausoleil, 2006), although its functional significance is unknown.

Homology

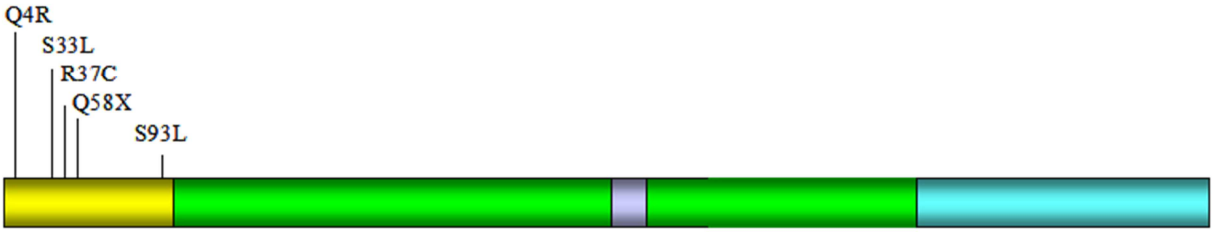
Member of the TACC family, based on the presence of the evolutionarily conserved approxi-
mately 200 amino acid carboxy terminal coiled coil domain (TACC domain) (Still et al., 1999; Still et al., 2004). TACC3 orthologues are noted in all vertebrates sequenced to date (Still et al., 2004 and Still unpublished). However, the central region between the conserved N-terminal region and the TACC domain is highly variable in size and sequence. The SDP repeats are noted within the central region in most vertebrates except mouse and rat (Still et al., 2004).

Mutations

Note

Somatic mutations noted in ovarian cancer samples (Lauffart et al., 2005; Eslinger, 2006).

Nucleotide change (based on ORF of NM_006342)	Codon Change	Detected as Somatic or germ line mutation	Amino Acid Change	Reference
c.11A>G	CAG to CGG	Somatic	Q4R	Eslinger 2006
c.98C>T	TCG to TTG	Somatic	S33L	Eslinger 2006
c.109C>T	CGT to TGT	Somatic	R37C	Eslinger 2006
c.172C>T	CAG to TAG	Somatic	Q58X	Eslinger 2006
c.278C>T	TCA to TTA	Germ line	S93L	Lauffart et al 2005



See legend for normal protein.

Implicated in

Ovarian cancer

Prognosis

Overexpression of TACC3 is associated with chemoresistance in ovarian tumors (L'Esperance et al., 2006).

Oncogenesis

Total cellular expression or nuclear localization lost in ovarian cancer (Lauffart et al., 2005).

Non-small cell lung cancer

Prognosis

High TACC3 expression is an independent prognostic indicator associated with significantly shorter median survival time. TACC3 expression was correlated with p53 expression and poor prognosis (Jung et al., 2006).

Oncogenesis

A high level of TACC3 expression was observed in 14.8% of cases of non small cell lung cancer, predominantly of the squamous cell carcinoma type (Jung et al., 2006).

Breast cancer

Prognosis

Loss of TACC3 is observed as a predictor of poor prognosis in breast cancer (Conte et al., 2002).

Oncogenesis

TACC3 protein downregulated in breast cancer (Conte et al., 2002).

Multiple myeloma

Prognosis

TACC3 overexpression correlates with the t(4;14) translocation that is associated with poor prognosis (Stewart et al., 2004).

Oncogenesis

TACC3 is located close to the MMSET gene that is rearranged in t(4;14) translocation (Still et al., 1999). This rearrangement upregulates the TACC3 gene (Stewart et al., 2004).

Thyroid cancer

Prognosis

Reduction of expression associated with increased malignancy in cell line models (Ulisse et al., 2007).

Oncogenesis

Analysis of differentiated thyroid cancers indicates that TACC3 mRNA levels were either upregulated (44%) or downregulated (56%) in tumors, in some cases correlation was observed between TACC3 and Aurora-A kinase (Ulisse et al., 2007). However protein analysis was not reported.

Breakpoints

Note

Rearrangements of the human TACC3 gene have not been described. However, translocation breakpoints in the WHSC1 gene, associated with multiple myeloma upregulate the intact TACC3 promoter (Stewart et al., 2004). Tacc3 in the mouse genome is a site of proviral integration of MoMuLV transmitted via milk from infected mothers. This leads to upregulation of the gene and leads to the development of lymphomas (Chakraborty et al., 2008).

References

Still IH, Vince P, Cowell JK. The third member of the transforming acidic coiled coil-containing gene family, TACC3, maps in 4p16, close to translocation breakpoints in multiple myeloma, and is upregulated in various cancer cell lines. Genomics. 1999 Jun 1;58(2):165-70

Gergely F, Karlsson C, Still I, Cowell J, Kilmartin J, Raff JW. The TACC domain identifies a family of centrosomal proteins that can interact with microtubules. Proc Natl Acad Sci U S A. 2000 Dec 19;97(26):14352-7

Sadek CM, Jalaguier S, Feeney EP, Aitola M, Damdimopoulos AE, Pelto-Huikko M, Gustafsson JA. Isolation and characterization of AINT: a novel ARNT interacting protein expressed during murine embryonic development. Mech Dev. 2000 Oct;97(1-2):13-26

Lauffart B, Howell SJ, Tasch JE, Cowell JK, Still IH. Interaction of the transforming acidic coiled-coil 1 (TACC1) protein with ch-TOG and GAS41/NuBI1 suggests multiple TACC1-containing protein complexes in human cells. Biochem J. 2002 Apr 1;363(Pt 1):195-200

Piekorz RP, Hoffmeyer A, Duntsch CD, McKay C, Nakajima H, Sexl V, Snyder L, Rehg J, Ihle JN. The centrosomal protein TACC3 is essential for hematopoietic stem cell function and genetically interfaces with p53-regulated apoptosis. EMBO J. 2002 Feb 15;21(4):653-64

Aitola M, Sadek CM, Gustafsson JA, Pelto-Huikko M. Aint/Tacc3 is highly expressed in proliferating mouse tissues during development, spermatogenesis, and oogenesis. J Histochem Cytochem. 2003 Apr;51(4):455-69

Leonard D, Ajuh P, Lamond AI, Legerski RJ. hLodestar/HuF2 interacts with CDC5L and is involved in pre-mRNA splicing. Biochem Biophys Res Commun. 2003 Sep 5;308(4):793-801

Sadek CM, Pelto-Huikko M, Tujague M, Steffensen KR, Wennerholm M, Gustafsson JA. TACC3 expression is tightly regulated during early differentiation. Gene Expr Patterns. 2003 May;3(2):203-11

Beausoleil SA, Jedrychowski M, Schwartz D, Elias JE, Villén J, Li J, Cohn MA, Cantley LC, Gygi SP. Large-scale characterization of HeLa cell nuclear phosphoproteins. Proc Natl Acad Sci U S A. 2004 Aug 17;101(33):12130-5

Gangisetty O, Lauffart B, Sondarva GV, Chelsea DM, Still IH. The transforming acidic coiled coil proteins interact with nuclear histone acetyltransferases. Oncogene. 2004 Apr 1;23(14):2559-63

Garriga-Canut M, Orkin SH. Transforming acidic coiled-coil protein 3 (TACC3) controls friend of GATA-1 (FOG-1) subcellular localization and regulates the association between GATA-1 and FOG-1 during hematopoiesis. J Biol Chem. 2004 May 28;279(22):23597-605

Simpson RJ, Yi Lee SH, Bartle N, Sum EY, Visvader JE, Matthews JM, Mackay JP, Crossley M. A classic zinc finger from friend of GATA mediates an interaction with the coiled-coil of transforming acidic coiled-coil 3. J Biol Chem. 2004 Sep 17;279(38):39789-97

Stewart JP, Thompson A, Santra M, Barlogie B, Lappin TR, Shaughnessy J Jr. Correlation of TACC3, FGFR3, MMSET and p21 expression with the t(4;14)(p16.3;q32) in multiple myeloma. Br J Haematol. 2004 Jul;126(1):72-6

Still IH, Vettaikkorumakankauv AK, DiMatteo A, Liang P. Structure-function evolution of the transforming acidic coiled coil genes revealed by analysis of phylogenetically diverse organisms. BMC Evol Biol. 2004 Jun 18;4:16

Jacquemier J, Ginestier C, Rougemont J, Bardou VJ, Charafe-Jauffret E, Geneix J, Adélaïde J, Koki A, Houvenaeghel G, Hassoun J, Maraninchi D, Viens P, Birnbaum D, Bertucci F. Protein expression profiling identifies subclasses of breast cancer and predicts prognosis. Cancer Res. 2005 Feb 1;65(3):767-79

Kinoshita K, Noetzel TL, Pelletier L, Mechtler K, Drechsel DN, Schwager A, Lee M, Raff JW, Hyman AA. Aurora A phosphorylation of TACC3/maskin is required for centrosome-dependent microtubule assembly in mitosis. J Cell Biol. 2005 Sep 26;170(7):1047-55

Lauffart B, Vaughan MM, Eddy R, Chervinsky D, DiCioccio RA, Black JD, Still IH. Aberrations of TACC1 and TACC3 are associated with ovarian cancer. BMC Womens Health. 2005 May 26;5:8

Angrisano T, Lembo F, Pero R, Natale F, Fusco A, Avvedimento VE, Bruni CB, Chiariotti L. TACC3 mediates the association of MBD2 with histone acetyltransferases and relieves transcriptional repression of methylated promoters. Nucleic Acids Res. 2006;34(1):364-72

Beausoleil SA, Villén J, Gerber SA, Rush J, Gygi SP. A probability-based approach for high-throughput protein phosphorylation analysis and site localization. Nat Biotechnol. 2006 Oct;24(10):1285-92

Eslinger MR.. Molecular Analysis of TACC3 in ovarian cancer. MS thesis, Department of Natural Science, Roswell Park Division, SUNY Buffalo 2006. 106p.

Jung CK, Jung JH, Park GS, Lee A, Kang CS, Lee KY. Expression of transforming acidic coiled-coil containing protein 3 is a novel independent prognostic marker in non-small cell lung cancer. Pathol Int. 2006 Sep;56(9):503-9

Lauffart B, Dimatteo A, Vaughan MM, Cincotta MA, Black JD, Still IH. Temporal and spatial expression of TACC1 in the mouse and human. Dev Dyn. 2006 Jun;235(6):1638-47

L'Espérance S, Popa I, Bachvarova M, Plante M, Patten N, Wu L, Têtu B, Bachvarov D. Gene expression profiling of paired ovarian tumors obtained prior to and following adjuvant chemotherapy: molecular signatures of chemoresistant tumors. Int J Oncol. 2006 Jul;29(1):5-24

Lauffart B, Gangisetty O, Still IH.. Evolutionary conserved interaction of TACC2/TACC3 with BARD1 and BRCA1: potential implications for DNA damage response in breast and ovarian cancer. Cancer Therapy. 2007a Dec;5(2):409-416.

Lauffart B, Sondarva GV, Gangisetty O, Cincotta M, Still IH. Interaction of TACC proteins with the FHL family: implications for ERK signaling. J Cell Commun Signal. 2007 Jun;1(1):5-15

LeRoy PJ, Hunter JJ, Hoar KM, Burke KE, Shinde V, Ruan J, Bowman D, Galvin K, Ecsedy JA. Localization of human TACC3 to mitotic spindles is mediated by phosphorylation on Ser558 by Aurora A: a novel pharmacodynamic method for measuring Aurora A activity. Cancer Res. 2007 Jun 1;67(11):5362-70

Ulisse S, Baldini E, Toller M, Delcros JG, Guého A, Curcio F, De Antoni E, Giacomelli L, Ambesi-Impiombato FS, Bocchini S, D'Armiento M, Arlot-Bonnemains Y. Transforming acidic coiled-coil 3 and Aurora-A interact in human thyrocytes and their expression is deregulated in thyroid cancer tissues. Endocr Relat Cancer. 2007 Sep;14(3):827-37

Xie Z, Moy LY, Sanada K, Zhou Y, Buchman JJ, Tsai LH. Cep120 and TACCs control interkinetic nuclear migration and the neural progenitor pool. Neuron. 2007 Oct 4;56(1):79-93

Yao R, Natsume Y, Noda T. TACC3 is required for the proper mitosis of sclerotome mesenchymal cells during formation of the axial skeleton. Cancer Sci. 2007 Apr;98(4):555-62

Yu LR, Zhu Z, Chan KC, Issaq HJ, Dimitrov DS, Veenstra TD. Improved titanium dioxide enrichment of phosphopeptides from HeLa cells and high confident phosphopeptide identification by cross-validation of MS/MS and MS/MS/MS spectra. J Proteome Res. 2007 Nov;6(11):4150-62

Brunet S, Dumont J, Lee KW, Kinoshita K, Hikal P, Gruss OJ, Maro B, Verlhac MH. Meiotic regulation of TPX2 protein levels

governs cell cycle progression in mouse oocytes. PLoS One. 2008 Oct 3;3(10):e3338

Cantin GT, Yi W, Lu B, Park SK, Xu T, Lee JD, Yates JR 3rd. Combining protein-based IMAC, peptide-based IMAC, and MudPIT for efficient phosphoproteomic analysis. J Proteome Res. 2008 Mar;7(3):1346-51

Chakraborty J, Okonta H, Bagalb H, Lee SJ, Fink B, Changanamkandat R, Duggan J. Retroviral gene insertion in breast milk mediated lymphomagenesis. Virology. 2008 Jul 20;377(1):100-9

Dephoure N, Zhou C, Villén J, Beausoleil SA, Bakalarski CE, Elledge SJ, Gygi SP. A quantitative atlas of mitotic phosphorylation. Proc Natl Acad Sci U S A. 2008 Aug 5;105(31):10762-7

Peset I, Vernos I. The TACC proteins: TACC-ling microtubule dynamics and centrosome function. Trends Cell Biol. 2008 Aug;18(8):379-88

Vettaikkorumakankauv AK, Lauffart B, Gangisetty O, Cincotta MA, Hawthorne LA, Cowell JK, Still IH.. The TACC proteins are coregulators of the Retinoid-X Receptor Beta. Cancer Therapy. 2008 Dec;6(2):805-816.

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