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Gene Section
Mini Review

TBX2 (T-box 2)

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Identity

Other names: FLJ10169

HGNC (Hugo): TBX2

Location: 17q23

Local order: Genes flanking TBX2 in centromere to telomere direction on 17q23 are:
APPBP2, 17q21-q23, amyloid beta precursor protein (cytoplasmic tail) binding protein 2.
TBX2, 17q23, T-box2.
PPM1D, 17q23, protein phosphatase 1D magnesium-dependent, delta isoform.
LOC440450, 17q23.2 LOC440450.
LOC388407, 17q23.2, hypothetical gene supported by BC046200.
LOC388406, 17q23.2, hypothetical LOC388406.
MGC71999, 17q23.2, alpha-NAC protein.

Note: T-box proteins contain a T-domain that has roles in dimerization and DNA binding. TBX2 belongs to the Tbx2 subfamily of T-box transcription factors. Other subfamilies of T-box genes are Brachyury, T-brain1, Tbx1 and Tbx6.

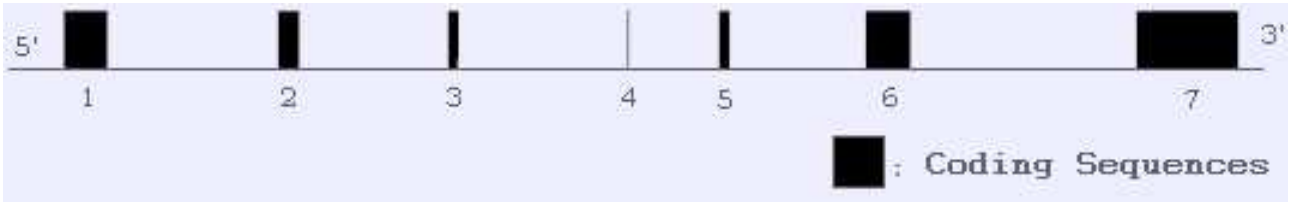
TBX2, TBX3, TBX4 and TBX5 belong to the Tbx2 subfamily. TBX2 and TBX3 are the only mammalian T-box factors with reported transcriptional repressor functions.

DNA/RNA

Note
Genes of the same T-box subfamily are thought to have arisen from duplication and recombination of a single ancestor gene. TBX2 is most closely related to TBX3 (12q24), whereas the other members of the subfamily, TBX4 and TBX5, are more closely related to one another. It is postulated that genes of the same subfamily may have redundant expression patterns and thus potential functional redundancy.

Description

TBX2 gene spans 9,5kb. TBX2 gene has 7 exons and the sizes of the exons 1 to 7 are 676, 268, 147, 77, 164, 635, 1413 bps. Exon/intron boundaries of TBX2 and a polymorphism within intron 2 of the gene have also been reported.



The alignment of TBX2 mRNA (3396 bp) to its genomic sequence.

Transcription

TBX2 mRNA is 3396 bp. TBX2 mRNA is expressed in a wide variety of tissues including fetal kidney and fetal lung as well as multiple adult tissues, kidney, lung, placenta, ovary, prostate, spleen, testis and breast. Relatively reduced expression of TBX2 can be detected in heart, white blood cells, small intestine and thymus. Transcript size heterogeneity has been detected for TBX2, possibly due to alternative polyadenylation. Increased TBX2 mRNA is observed within 2 hours after addition of retinoic acid in B16 mouse melanoma cells due to the presence of a degenerate retinoic acid response element (RARE) between -186 and -163 in the promoter region of the TBX2 gene.
Transcript localisation: Human and mouse TBX2, TBX3, and TBX5 transcripts detected by riboprobes are found asymmetrically across the embryonic neural retina, with highest levels of transcripts within dorsal and peripheral retina. The dorsoventral gradient of TBX2 expression cannot be detected before the ganglion cell layer (GCL) forms and expression is found to be restricted to the inner neuroblastic retina and later to the GCL and inner nuclear layer. TBX2 transcript is also detected in the optic and otic vesicles at 9.5 dpc, and in the naso-facial mesenchyme, and later in the developing limbs and other internal organ primordia (of lungs and genitalia). Later at around 8 and 10 dpc, TBX2 is detected in allantois, inflow tract (IFT), outflow tract (OFT) and atrio-ventricular canal (AVC) of the developing mouse heart. Chick heart development is also consistent in terms of similar TBX2 expression patterns. During mammary development, TBX2 expression is detected at 11.5 dpc in the mesodermal milk lines.

Pseudogene

No pseudogenes have been reported for TBX2.

Protein

Description

Protein consists of 702 amino acids and is 74.2 kDa. Protein has the T-box DNA binding domain (corresponds to amino acids 96-279) of the T-box family of transcriptional regulators.

Function

In an evolutionarily diverse group of organisms including chick, Xenopus, mouse, and human, TBX2 is involved during development of widely diverse organs and tissues including limbs, kidneys, lungs, mammary glands, heart and craniofacial structures.
In order to identify genes that may be regulated by Tbx2, mouse cDNA microarrays were used to analyze differential gene expression profiles, comparing stably transfected NIH3T3 cells
overexpressing Tbx2 with vector-transfected controls. 107 genes were up-regulated (more than or equal to 2-fold) and 66 genes were down-regulated (more than or equal to 2-fold). Among the upregulated genes in the Tbx2-overexpressing cells were: Caveolin, Pleiotrophin, Osteoblast-specific factor-2 and Collagen Type I alpha. Cadherin 3, Tenascin C, and Insulin-like Growth Factor Binding Protein 10/CYR61 (IBP10) were among the genes that are downregulated. In vitro reporter assays and transgenic mice studies suggest that TBX2 represses the transcription of certain cardiac genes (e.g. Connexin 40, Connexin 43, and Natriuretic Peptide Precursor A) during heart development. TBX2 and TBX3 are also thought to be regulating one another in Hedgehog related signaling pathways during chick limb development.
In addition to developmental functions, evidence suggest that TBX2 also has important roles in cell cycle regulation through repressing the expression of CDKN1A (p21, cyclin-dependent kinase inhibitor) and CDKN2A (p19ARF). In BMI oncogene deficient murine embryonic fibroblasts, TBX2 is shown to repress the CDKN2A promoter and also attenuate the induction of CDKN2A by E2F1, MYC, and HRAS, providing senescence bypass and suggesting TBX2 as a potent immortalizing gene.

Homology

C.familiaris: Tbx2, T-box 2 transcription factor.
M.musculus: Tbx2, T-box 2.
R.norvegicus: Tbx2_predicted, T-box 2 (predicted)
D.melanogaster: bi, bifid.
A.gambiae: 1280927, Anopheles gambiae str. PEST ENSANGG00000011542 gene.
C.elegans: tbx-2, T-box family member (47.0 kD).

Mutations

Germinal

Despite the high frequency T-box family gene mutations identified as causes of congenital developmental disorders, there have been no mutations reported for TBX2 that cause congenital anomalies. Germline segregation of TBX2 mutations with human diseases has not been identified.

Somatic

CGH (comparative genomic hybridization), Southern blot, FISH, PCR based techniques and microarray analyses suggest amplification and overexpression of TBX2 in certain cancer cells.

Implicated in

Breast cancer

Note
TBX2 has been found to be amplified and overexpressed in breast cancer cell lines and primary tumors. TBX2 resides on the chromosomal band 17q23

that is frequently amplified in breast cancer cells. Evidence suggests presence of distinct proximal and distal amplicons on 17q23 with defined boundaries. TBX2 seems to be at the center of the distal amplicon. In addition to breast cancer cell line data, a study of tissue microarray of 372 primary tumors found TBX2 amplification in 8.6% of the cases. Moreover, preferential amplification and overexpression of TBX2 have been detected in BRCA1 and BRCA2 mutated breast tumors compared to sporadic controls.

Pancreatic Cancer

Note

TBX2 amplification has been detected in 50% of 20 pancreatic cancer cell lines detected by interphase FISH.

Melanomas

Note

TBX2 overexpression in melanoma cell lines is thought to target histone deacetylase 1 to the CDKN1A initiator. Expression of a dominant-negative Tbx2 leads to displacement of histone deacetylase 1 with up-regulation of CDKN1A expression and the induction of replicative senescence in CDKN2A-null B16 melanoma cells. In human melanoma cells, expression of the same dominant negative TBX2 results with reduced growth and induction of senescence-associated heterochromatin foci.

Note

Analysis of TBX2 in other tumor types has not been widely reported.

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