

Gene Section

Review

IGF2BP1 (insulin-like growth factor 2 mRNA binding protein 1)

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Identity

Other names: CRD-BP; CRDBP; IMP-1; IMP1; VICKZ1; ZBP1

HGNC (Hugo): IGF2BP1

Location: 17q21.32

Local order: The IGF2BP1 gene is located on the plus strand on chromosome 17, at 17q21.32. This gene starts at 47074774 and ends at 47133507 bp from pter, encompasses 58734 bp and lies 5' of the gene B4GALNT2, encoding beta-1,4-N-acetylgalactosaminyl transferase 2.

Note

The IGF2BP1 gene encodes a member of the IGF-II mRNA-binding protein (IMP) family (RRM IMP/VICKZ family).

DNA/RNA

Description

There are 4 probable alternative promoters driving transcription of IGF2BP1 and two of them have been experimentally confirmed (Gu et al., 2008). The

upstream (promoter) region contains binding sites for the following transcription factors: delta CREB, CREB, NF-kappaB1, NF-kappaB, AP-1, HNF4 alpha2, FOXO1a, MZF-1, Max and c-Myc. Beta-catenin/TCF4 binding and activation of transcription has been experimentally confirmed (Gu et al., 2008).

Transcription

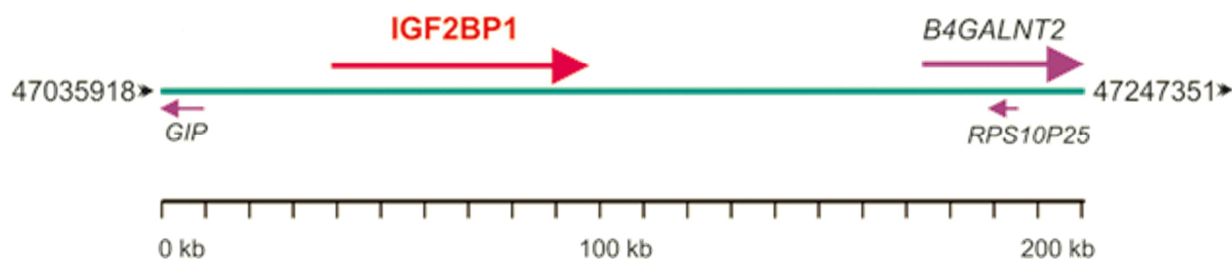
Two protein coding transcripts exist resulting from alternative splicing:

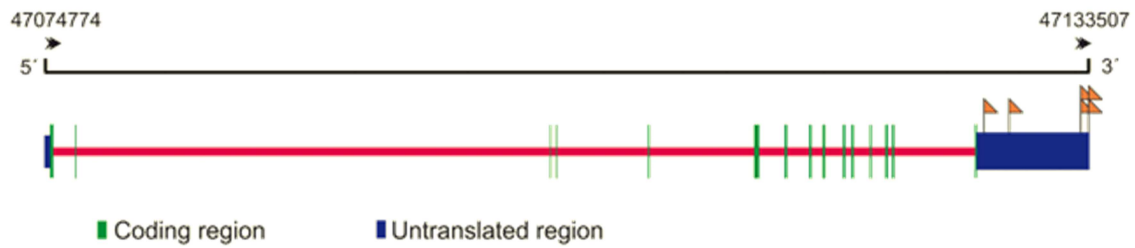
Transcript variant 1 (NM_006546). The length of this transcript is 8769 nt and encompasses all 15 exons (exon 1: 509 bp, exon 2: 60 bp, exon 3: 48 bp, exon 4: 51 bp, exon 5: 63 bp, exon 6: 281 bp, exon 7: 134 bp, exon 8: 122 bp, exon 9: 135 bp, exon 10: 122 bp, exon 11: 119 bp, exon 12: 74 bp, exon 13: 131 bp, exon14: 113 bp, exon 15: 6973 bp).

Several alternative 3' ends (polyadenylation sites) exist at exon 15 3'-UTR (marked by flags in the figure above). Translation starts at +335 and ends at +2068.

Transcript variant 2 (NM_001160423.1). It encompasses 8352 bp and lacks two consecutive in-frame exons (6 and 7).

Other spliced variants have been reported without corresponding protein product recorded.





Protein

Description

The IGF2BP1 protein translated from the transcript variant 1 consists of 577 aa (63,48 kD) and has 2 highly conserved RRM motifs belonging to the RNA recognition motif (RRM) superfamily and 4 KH domains (NP_006537.3). The third and fourth KH domains constitute both the protein dimerization motif and the RNA binding domain. The four KH domains promote granule formation and stress granule targeting (Stöhr et al., 2006). Two nuclear export signals (NES) exist within the second and fourth KH domains (Nielsen et al., 2003). The KH domains have been implicated in the suppression of HIV-1 infectivity (Zhou et al., 2008). Phosphorylation sites are marked (Bennetzen et al., 2010; Dephoure et al., 2008). Phosphorylation of Tyrosine 396 prevents RNA binding and translation inhibition of beta-actin mRNA (Hüttelmaier et al., 2005).

The IGF2BP1 protein translated from transcript 2 variant is predicted to consist of 438 aa (48.597 kD) and contain 2 RRM and 3 KH domains (NP_001153895.1).

Expression

IGF2BP1 is widely expressed in fetal tissues (liver, lung, kidney, thymus, etc), placenta and CD34+ cord blood cells (Nielsen et al., 1999; Ioannidis et al., 2001; Ioannidis et al., 2005). Postnatally it is expressed in ovary (oocytes and granulosa cells), in testis

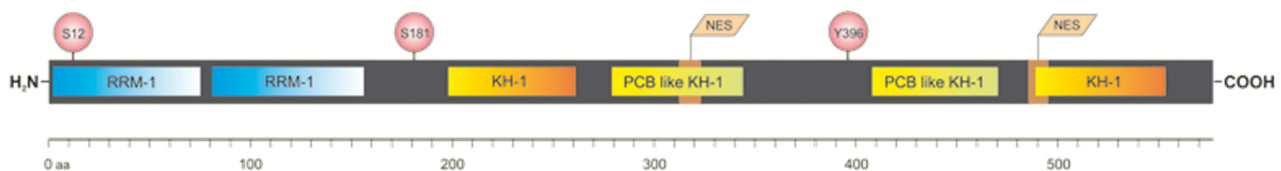
(spermatogonia), in semen (Hammer et al., 2005) and in intestinal crypts (Nielsen et al., 1999; Dimitriadis et al., 2007). It is expressed de novo in kidney, prostate, trachea, testis, ovarian and lung cancer, melanoma, mesenchymal and brain tumors. At protein level, it is expressed in testicular, lung and colon cancer.

Localisation

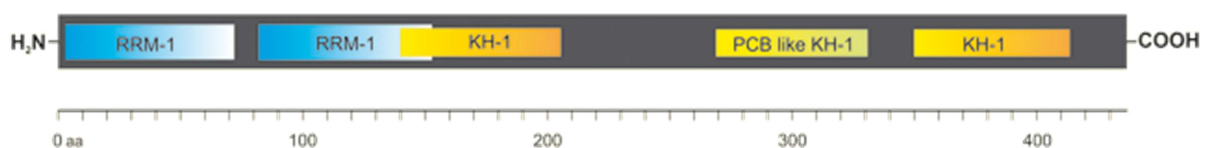
IGF2BP1 has been detected in the nucleus, cytoplasm, cytoplasmic mRNPs, granules (Nielsen et al., 2002; Nielsen et al., 2003). In stress granules IGF2BP1 co localizes with G3BP1 and TIAL1 (Stöhr et al., 2006). It has also been detected in lamellipodia (Yaniv et al., 2003), growth cones and the leading edge of developing axons (Eom et al., 2003).

Function

mRNA translation: IGF2BP1 regulates translation by binding the 5'-UTR of the mRNA of certain genes, including insulin-like growth factor 2 (Nielsen et al., 1999), and beta actin (Hüttelmaier et al., 2005). It has been identified in a HCV IRES-mediated translation complex along with EIF3C and RPS3, enhancing translation of the Hepatitis C virus (HCV) RNA-replicon via the internal ribosome entry site (IRES), without affecting 5'cap-dependent translation (Weinlich et al., 2009). IGF2BP1 binds the adenine-rich autoregulatory sequence (ARS) of the 5'-UTR of the PABPC1 mRNA in collaboration with CSDE1 and PABPC1 proteins and causes translational repression (Patel and Bag, 2006; Patel et al., 2005).



IGF2BP1 protein translated from transcript 1 variant.



IGF2BP1 protein translated from transcript 2 variant.

mRNA stabilization: IGF2BP1 binds to the coding region mRNA stability determinant (CRD) of c-myc mRNA and protects it from endonucleolytic cleavage (Doyle et al., 1998; Lemm and Ross, 2002). It protects MDR-1 mRNAs from endonucleolytic cleavage by binding to a coding region element (Sparanese and Lee, 2007). Also binds to the coding region of betaTrCP1 mRNA and stabilizes it by disrupting miRNA-dependent interaction with AGO2 (Noubissi et al., 2006; Elcheva et al., 2009). Binds and stabilizes GLI1 mRNA causing an elevation of GLI1 expression and transcriptional activity (Noubissi et al., 2009). IGF2BP1 binds to multiple elements in the 3'-UTR of the CD44 mRNAs and stabilizes this mRNA (Vikesaa et al., 2006). Binds to the 3'-UTR of Microphthalmia associated transcription factor mRNA and prevents the binding of miR-340 to its target sites, resulting in stabilization of the transcript, elevated expression and activity of this transcription factor (Goswami et al., 2010).

mRNA transportation: IGF2BP1 binds to the fourth and fifth exons of the oncofetal H19 RNA (Runge et al., 2000) and with ELAVL4 and G3BP to 3'-UTR of the neuron-specific TAU mRNA (Atlas et al., 2004; Atlas et al., 2007) and regulates their localization. In collaboration with IGF2BP2, IGF2BP1 binds to the conserved 54-nucleotide element in the 3'-UTR of the beta actin mRNA, known as the 'zip code'. IGF2BP1 promotes the localization of the beta-actin mRNA to dendrites (Eom et al., 2003). IGF2BP1 may act as a regulator of mRNA transport to activated synapses in response to synaptic activity.

Protein binding: IGF2BP1 interacts through the third and fourth KH domains with PABPC1 in a RNA-independent manner (Patel and Bag, 2006) and can form homo- and heterodimers with IGF2BP2 or IGF2BP3 (Nielsen et al., 2004). It interacts with fragile X metal retardation protein isoform 18 (Rackham and Brown, 2004). It interacts with DHX9, ELAVL2, HNRNPA2B1, HNRNPC, HNRNPH1, HNRNPU, IGF2BP2, IGF2BP3, ILF2 and YBX1 (Weindensdorfer et al., 2009). IGF2BP1 was identified in a mRNP granule complex, with hnRNP A1, hnRNP A2/B1, hnRNP D, hnRNP L, hnRNP Q, hnRNP R, hnRNP U, YB1/major core protein, interleukin enhancer-binding factor 2 and 3, PABP1, PABP2, PABP4, nucleolin, RNA helicase A, a series of 40 S ribosomal proteins, and the nuclear cap-binding protein CBP80 (Jønson et al., 2007). IGF2BP1 associates with HIV-1 particles. It interacts (via KH3 and KH4 domains) with HIV-1 GAG protein and diminishes viral RNA packaging, thwarts GAG processing to the cellular membranes, and impedes HIV-1 assembly (Zhou et al., 2008).

Homology

The identity of human IGF2BP1 over an aligned region in UniGene is as follows:

- Pan troglodytes: 99.83%
- Canis lupus familiaris: 90.93%
- Bos taurus: 91.05%
- Mus musculus: 89.43%
- Rattus norvegicus: 89.43%

Implicated in

Lung cancer

Disease

IGF2BP1 is expressed in lung cancer and its expression correlates with adverse histological and clinical features and is an indicator of poor prognosis. Suppression of its expression with siRNA suppresses growth of NSCLC cells in vitro (Ioannidis et al., 2004; Kato et al., 2007).

Ovarian cancer

Disease

Increased expression of IGF2BP1 mRNA is associated with an advanced clinical stage and poor prognosis in patients with ovarian cancer (Köbel et al., 2007).

Testicular cancer

Disease

Detected in testicular carcinomas even in early stage carcinoma in situ (Hammer et al., 2005).

Melanoma

Disease

IGF2BP1 is highly expressed in primary human malignant melanomas and melanoma cell line (Elcheva et al., 2008).

Breast cancer

Disease

The IGF2BP1 gene is amplified in breast cancer (Doyle et al., 2000). Significant associations are detected between IGF2BP1 expression and the absence of estrogen receptors. IGF2BP1 collaborates with c-myc amplification to render tumours more aggressive (Ioannidis et al., 2003). Tissue specific induced expression in transgenic mice promotes tumor formation (Tessier et al., 2004).

Colon cancer

Disease

IGF2BP1 is scarce or absent from normal colon but is over expressed in colorectal cancer. IGF2BP1 positive tumours associate with metastasis/recurrence and shorter survival (Ross et al., 2001; Dimitriadis et al., 2007).

Hepatocellular carcinoma

Disease

IGF2BP1 is detected as an autoantigen in hepatocellular carcinoma (Himoto et al., 2005).

Oncogenesis

Note

The oncogenic action of IGF2BP1 is effected through the stabilization of the mRNA of oncogenes such as c-myc, betaTrCP1, Gli and upregulation of their expression. IGF2BP1 expression may promote metastasis by shuttling requisite RNAs to the lamellipodia of migrating cells (Vikesaa et al., 2006; Vainer et al., 2008).

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