

## Gene Section

### Review

# YBX1 (Y box binding protein 1)

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Published in Atlas Database: November 2010

Online updated version : <http://AtlasGeneticsOncology.org/Genes/YBX1ID46554ch1p34.html>

DOI: 10.4267/2042/45987

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## Identity

**Other names:** BP-8; CSDA2; CSDB; DBPB; MDR-NF1; MGC104858; MGC110976; MGC117250; NSEP-1; NSEP1; YB-1; YB1

**HGNC (Hugo):** YBX1

**Location:** 1p34.2

**Local order:** The human YBX1 gene maps on 1p34 between the PPIH and the LOC100287607 loci.

## DNA/RNA

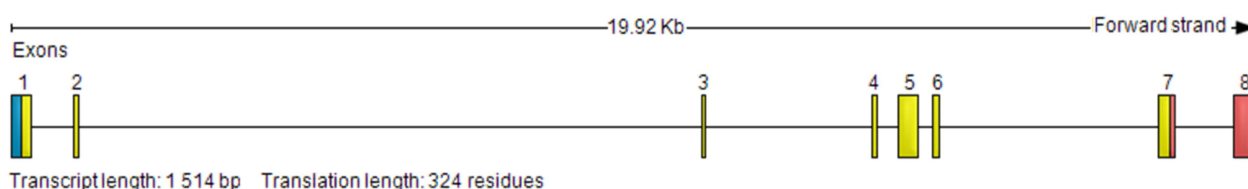
### Description

The human YBX1 gene consists of 8 exons and 7 introns spanning a 19.2-kb genomic region. Intron number 1 is phase 1 (between 1st and 2nd base of codon). Introns number 2 and 6 are phase 2 (between 2nd and 3rd base of codon). Introns number 3, 4, 5 are phase 0 (between codons). According to the SNP source (dbSNP NCBI), non-synonymous polymorphism has been reported for the codons 30 (rs11558135), 237 (rs3887881), 251 (rs55676223), and 261 (rs3887879). The YBX1 promoter region contains no typical TATA or CCAAT box, but has multiple E-

boxes located between -1855 and -422 nucleotides (relative to the start of exon 1) and several GT and GC boxes. The gene also contains a large and highly conserved CpG island at the immediate 5' promoter region which extends to the first exon encoding 5' UTR of YBX1 mRNA. The region between nucleotides -119 to +127 was shown to be essential for transcriptional activity in the reporter assays (Makino et al., 1996). YBX1 is constitutively expressed in multiple human tissues and its expression can be further induced by the E-box-binding transcription factors such as c-myc (Uramoto et al., 2002), Twist (Shiota et al., 2008) and Math2 (Ohashi et al., 2009).

### Transcription

The main processed mRNA is 1514 bp. It encompasses exons 1-8. The 70-amino acid cold-shock domain (CSD) is encoded separately by exons 2-5. Four additional splice variants in human were predicted (Ensembl), two of which (YBX1-004 and YBX1-201) preserve exons 2 and 3 coding for core elements of the CSD, the RNP1 and RNP2 motifs, respectively. An alternative transcript for ctYB-1, the YBX1 homologous gene in *C. tentans*, has been reported (Nashchekin et al., 2007).



Genomic organization of YBX1. Box = exon (blue = 5'UTR, yellow = CDS, light red = 3'UTR). Line = intron.

## Pseudogene

Description	Symbol	NCBI gene ID	Position	Introns/exons	ORF	Identity with YBX1	Gaps
nuclease sensitive element binding protein 1 pseudogene	bA327L3.4	158373	9p13.1	Intronless	Stops after E88	1477/1515 (97%)	2/1515 (0%)
Y box binding protein 1 pseudogene 1	YBX1P1	50631	4q23.3	Intronless 1496 bp	-	1488/1531 (97%)	20/1511 (1%)
Y box binding protein 1 pseudogene 2	YBX1P2	646531	7q22.3	2 exons, 1 intron, 1553 bp	Stops after E88	1431/1529 (93%)	43/1529 (2%)
Y box binding protein 1 pseudogene	LOC100131012	100131012	7q36.1	Intronless, 820 bp	-	287/353 (81%)	26/353 (7%)

## Protein

### Description

The YBX1 gene encodes the Y-box protein 1 (YB-1) which consists of 324 amino acid residues and has the isoelectric point 10.3. Theoretical MW is 35924, however YB-1 is known to migrate as a ~45-50 kDa protein in SDS-polyacrylamide gels due to its anomalous electrophoretic mobility. YB-1 belongs to the family of multifunctional DNA/RNA binding proteins that are highly conserved throughout evolution and found in eukaryotes, prokaryotes and archaea. The most conserved region in YB-1 is the 80 amino acid CSD which exhibits >40% identity and >60% similarity to the major E. coli cold shock protein CspA (Matsumoto and Wolffe, 1998; Sommerville, 1999). The CSD possesses RNP1 and RNP2-like consensus motifs and is represented by a five-stranded beta-barrel structure which creates a surface rich in aromatic and basic amino acids that may act as a large nucleic acid-binding site (Wolffe et al., 1992; Wolffe, 1994). The CSD has a preference for binding single-stranded pyrimidine-rich sequences. The N-terminal AP domain of YB-1 is similar to that found in several other transcription factors and may thus be important for its transcriptional activity. This region is also essential for interaction with p53 and modulation of p53-mediated transcription (Okamoto et al., 2000), and for association with actin microfilaments and mRNA compartmentalization (Ruzanov et al., 1999).

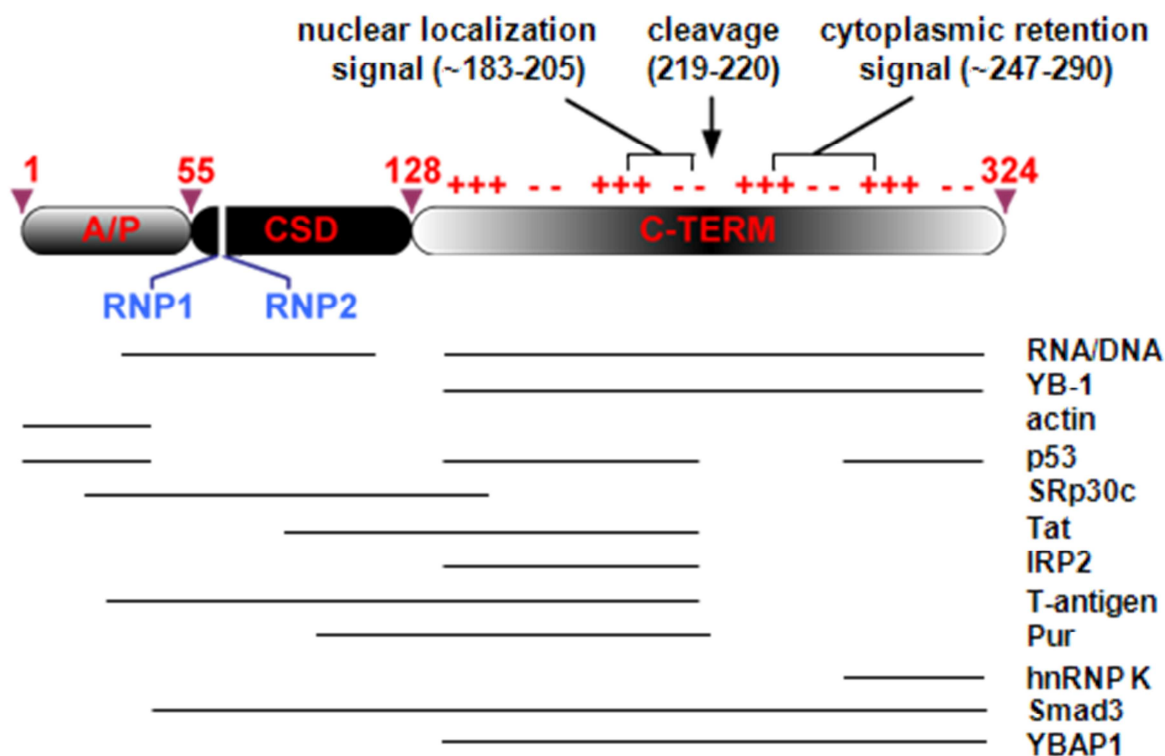
The C-terminal region of YB-1 is responsible for sequence-nonspecific binding to DNA and RNA and mediation of protein-protein interactions (Wolffe, 1994; Sommerville and Lodomery, 1996). An inverted CCAAT-box found in HLA class II gene promoters, a so-called Y-box, was originally determined as the YB-1 binding motif (Didier et al., 1988). Later studies have concluded that YB-1 rather recognizes the DNA structure than a defined nucleotide sequence, making prediction of its target genes not feasible with conventional *in silico* analyses (Swamynathan et al., 1998). YB-1 is also capable of unwinding DNA and RNA duplexes, especially those containing mismatches, thereby promoting strand exchange and formation of perfectly matched duplex structures (Skabkin et al., 2001; Gaudreault et al., 2004).

### Expression

According to Human Protein Atlas, YB-1 is variably expressed in most normal human tissues. Its expression is elevated in multiple cancer types (Kohno et al., 2003).

### Localisation

Mostly cytosolic. Shuttles between cytoplasm and nucleus. Localized in cytoplasmic stress granules and processing bodies containing untranslated mRNAs (Kedersha and Anderson, 2007). Nuclear translocation is induced in response to various stresses, including adenoviral infection (Holm et al., 2002), hyperthermia (Stein et al., 2001), DNA damage (Kohno et al., 2003) and activation of



**Structural and functional organization of YB-1.** YB-1 is composed by three domains: N-terminal Ala/Pro rich (AP) domain, cold shock domain (CSD) and the C-terminal domain (CTD) containing clusters of positively and negatively charged amino acids. Indicated are some known molecular partners of YB-1 and sites of their interactions (from Sorokin et al., 2005). The arrow indicates proteasomal cleavage sites.

PI3K-Akt signaling (Sutherland et al., 2005).

**Function**

The diverse biological functions of YB-1 appear to arise from its broad nucleic acid binding properties. YB-1 has been implicated in pre-mRNA splicing, transcriptional regulation, mRNA translation and stability as well as in chromatin remodelling, DNA repair and environmental stress responses (Kohno et al., 2003; Matsumoto and Bay, 2005).

**Splicing.** YB-1 regulates splice site selection via direct binding to splicing recognition motifs in pre-mRNA, including A/C-rich exon enhancers (Stickeler et al., 2001) or via interaction with splicing factors from the SR family (Li et al., 2003; Raffetseder et al., 2003).

**Transcription.** YB-1 is capable of binding to promoters of many genes, many of which lack the Y-box, and either activates or represses transcription. Among the genes activated by YB-1 are thymidine kinase, proliferating cell nuclear antigen (PCNA), cyclin A and cyclin B1, DNA topoisomerase II alpha, gelatinase A, matrix metalloproteinase 2, multidrug resistance 1 (MDR1), EGFR and protein tyrosine phosphatase 1B. Genes that are transcriptionally repressed by YB-1 include MHC class II, collagen alpha1, granulocyte-macrophage colony-stimulating factor (GM-CSF), etc (reviewed in Ladomery and Sommerville, 1995; Kohno et al., 2003; Kuwano et al.,

2003). Overall, YB-1 is considered as an important regulator of growth- and stress-associated genes.

**mRNA translation and stability.** YB-1 (p50) is known as a major structural component of messenger ribonucleoprotein particles (mRNPs) which exerts positive or negative effects on translation, depending on the amount bound to mRNA (Evdokimova and Ovchinnikov, 1999). YB-1 regulates translational activity of many growth- and differentiation-associated mRNAs, including Snail1, and selectively protects capped mRNAs against degradation (Evdokimova et al., 2001; Evdokimova et al., 2006; Evdokimova et al., 2009). YB-1 appears to play a role in stabilization of short-lived mRNAs, including IL-2 (Chen et al., 2000), GM-CSF (Capowski et al., 2001) and VEGF (Coles et al., 2004).

**DNA repair and stress response.** YB-1 is involved in base excision and mismatch repair pathways via interaction with multiple DNA repair proteins including glycosylase NEIL2, DNA polymerase beta and delta, DNA ligase III, APE1, MSH2, Ku80, WRN, endonuclease III, etc (Marenstein et al., 2001; Gaudreault et al., 2004; Das et al., 2007). YB-1 also directly binds and promotes separation of DNA strands that contain mismatches or are modified by cisplatin (Ise et al., 1999; Skabkin et al., 2001; Gaudreault et al., 2004). Various stresses, including DNA damage, adenovirus infection and hyperthermia, induce nuclear

translocation of YB-1 (Ohga et al., 1996; Kohno et al., 2003) and its proteasomal cleavage (Sorokin et al., 2005). Accumulation of the full-length and/or truncated YB-1 proteins in the nucleus is associated with increased survival and multidrug resistance (Kohno et al., 2003; Sorokin et al., 2005). YB-1 knock-out in mice is lethal (Lu et al., 2005; Lu et al., 2006). Fibroblasts derived from YB-1(-/-) embryos exhibit a reduced ability to respond to oxidative, genotoxic and oncogene-induced stresses, further implicating YB-1 in stress responses and embryonic development.

**Tumorigenesis.** YB-1 is frequently overexpressed in multiple human cancers (reviewed in Kohno et al., 2003; Kuwano et al., 2003). In many cases, YB-1 levels are elevated in the nucleus, positively correlating with multiple drug resistance and poor patient outcome (Bargou et al., 1997; Janz et al., 2002). Ectopic expression of YB-1 in breast cancer cells and mouse models stimulated tumor growth (Bergmann et al., 2005; Sutherland et al., 2005). Yet, the role of YB-1 in tumorigenesis is controversial. YB-1 overexpression blocked oncogenic transformation caused by PI3K or Akt (Bader et al., 2003). These apparently contradictory results were proposed to be due to differential localization of YB-1; its interference with oncogenic transformation is associated with cytosolic localization and a consequent function in translational control (Bader and Vogt, 2004; Bader and Vogt, 2005).

### Homology

YB-1 is highly homologous to human DbpA (12p13; expressed predominantly in heart and muscle) and DbpC/contrin (17p11; expressed exclusively in germ cells). They share greater than 90% identity within the CSD and a high degree of similarity in the N- and C-terminal domains, including C-terminal clusters of basic and acidic amino acids. Mouse orthologues are YB-1 (encoded by *Ybx1*; 99% overall amino acid identity with human YB-1), *MSY2* (*Ybx2*; ~93% identity with contrin) and *MSY4* (~86% identity with DbpA).

## Mutations

### Note

Mutations in YBX1 are not reported.

## Implicated in

### Breast cancer

#### Note

Elevated expression and nuclear localization of YB-1 is associated with increased proliferation, multidrug resistance and tumor aggressiveness across all tumor subtypes. Nuclear localization positively correlates with increased expression of MDR1/P-gp and HER2/ErbB2 (Bargou et al., 1997; Saji et al., 2003; Fujii et al., 2008; Habibi et al., 2008). Enforced YB-1 expression in mammary glands of transgenic mice

induced chromosomal instability and tumorigenesis (Bergmann et al., 2005). YB-1 effects on tumorigenesis are likely dependent on cellular signaling. It blocks oncogenic transformation induced by Akt or PI3K but not by Src, Jun or Qin oncoproteins (Bader et al., 2003), and decreases proliferation of tumor cells with activated MAPK-Ras signaling, while inducing their metastatic ability (Evdokimova et al., 2009).

### Prognosis

Nuclear YB-1 is considered as a marker of poor clinical outcome. Patients with high YB-1 levels are likely to benefit from dose-intensified chemotherapy regimens (Gluz et al., 2009).

### Prostate cancer

#### Note

YB-1 is upregulated during prostate cancer tumor progression and is reported to increase P-glycoprotein activity (Giménez-Bonafé et al., 2004).

### Lung cancer

#### Note

Nuclear YB-1 is associated with poor survival and expression of HER2/ErbB2 and HER3/ErbB3 in non-small cell lung cancer (Kashihara et al., 2009).

### Prognosis

Patients with nuclear YB-1 expression and p53 mutations appear to have the worst prognosis (median survival 3 months), while best outcome was found in patients with no nuclear YB-1 and wild-type p53 (Gessner et al., 2004).

### Colon cancer

#### Note

YB-1 expression levels are elevated in colorectal carcinoma and positively correlate with DNA topoisomerase II alpha and PCNA expression but not with P-gp (Shibao et al., 1999). In colon cancer cells, YB-1 accumulates in the nuclei in response to vinblastin and is associated with development of vinblastin resistance and elevated expression of P-gp (Vaiman et al., 2007).

### Ovarian cancer

#### Note

YB-1 levels are elevated in the nuclei of cisplatin-resistant cancer cell lines and cancer patients, indicating that nuclear YB-1 may be associated with acquired cisplatin resistance in ovarian cancers (Yahata et al., 2002).

### Prognosis

Co-expression of YB-1 and P-gp is indicative of unfavourable prognosis in ovarian cancer (Huang et al., 2004).

### Haematopoietic malignancies

#### Disease

Large B-cell lymphoma, multiple myeloma.

Nuclear expression of YB-1 is associated with P-gp expression and poor response to chemotherapy in large B-cell lymphoma (Xu et al., 2009). YB-1 is strongly expressed in normal plasma cell precursor blasts as well as in a multiple myeloma tumor specimens and cell lines but not in normal bone marrow or plasma cells. Its expression is associated with an immature morphology, a highly proliferative phenotype and doxorubicin resistance, indicating its involvement in drug resistance and disease progression in multiple myeloma (Chatterjee et al., 2008).

### **Bone and soft tissue tumors**

#### **Disease**

Rhabdomyosarcoma, synovial sarcoma and osteosarcoma.

Nuclear expression of YB-1 protein positively correlates with P-gp expression and a higher proliferative index in embryonal (ERMS) but not in alveolar rhabdomyosarcoma (ARMS) (Oda et al., 2008), synovial sarcoma (Oda et al., 2003) and osteosarcoma (Oda et al., 1998).

### **Melanoma**

#### **Note**

YB-1 expression is increased in melanoma cells compared to benign melanocytes, and nuclear YB-1 is found in invasive and metastatic melanoma cells. YB-1 expression is associated with increased proliferation, tumor invasion and chemoresistance (Schitteck et al., 2007).

### **Nervous system tumors**

#### **Disease**

Glioblastoma, neuroblastoma.

YB-1 levels are elevated in pediatric glioblastoma (Faury et al., 2007) and neuroblastoma (Wachowiak et al., 2010).

#### **Prognosis**

In neuroblastoma, no correlation of YB-1 expression with survival, risk factors or stage of the disease was found.

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*This article should be referenced as such:*

Evdokimova V, Sorokin A. YBX1 (Y box binding protein 1). *Atlas Genet Cytogenet Oncol Haematol*. 2011; 15(7):598-604.

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