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Gene Section

Review

ETS2 (v-ets erythroblastosis virus E26 oncogene homolog 2 (avian))

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Identity

Other names: Ets2; Ets-2; LOC114; ETS2IT1

HGNC (Hugo): ETS2

Location: 21q22.2

Local order: Chr 12: 39099101 - 39118749 on the direct strand.

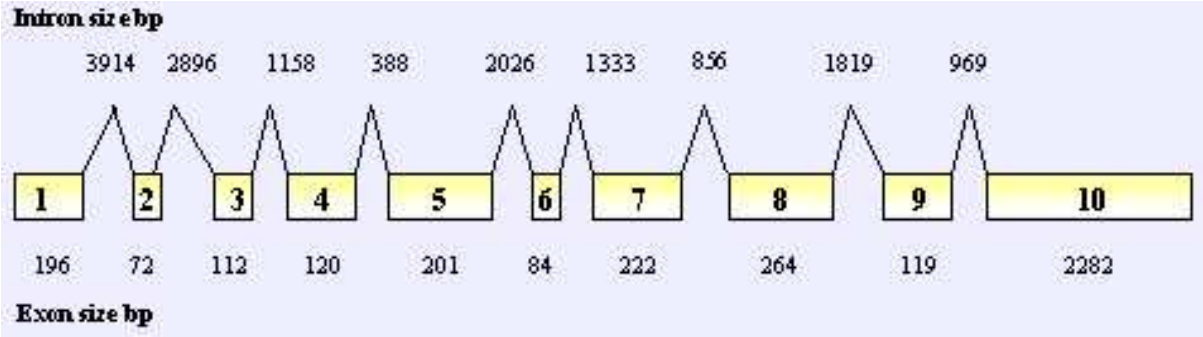
DNA/RNA

Description

Ets-2 is a functioning gene comprising 10 exons and spanning 19.6 kb of genomic DNA. It encodes three mRNA transcripts: 4.7 kb, 3.6 kb and 2.7 kb, respectively (Watson et al., 1988). This suggests the existence of three functionally distinct proteins, potentially translated from these transcripts.

Transcription

Structural analysis of the Ets2 promoter has revealed the absence of TATA and CAAT boxes, thus allowing transcription initiation from multiple start sites (Papas et al., 1990a). The first Intron of Ets2 also contains transcriptional initiation sequences, facilitating transcription. These sequences may compensate for the absence of TATA and CAAT sites within the promoter (Begue et al., 1997). The three RNA transcripts are thought to arise from alternative splicing by a number of different promoter polyadenylation signals (Watson et al., 1990). All Ets genes, including Ets2, are characterised by a region of conserved sequence known as the Ets domain (GGAA/T). This comprises an 85 amino acid region which forms the winged helix-turn-helix DNA binding domain (Watson et al., 1990).



Exon-Intron structure of human ETS2.

Schematic representation of the Ets2 protein.
The pointed domain, the transactivation domain and the Ets DNA binding domain are all shown.

Protein

Description

1-469 amino acids.
Pointed domain: 87-170 amino acids.
DNA binding domain: 363-443 amino acids.
The Ets2 protein consists of 469 amino acids, a pointed domain, a transactivation domain and the Ets DNA binding domain (Watson et al., 1988). The protein is thought to exist in two forms: a 52 kDa, thought to be the full length protein (Watson et al., 1988) and a 54 kDa protein, believed to be a phosphorylated protein (Ma et al.,1996). The Ets2 protein is phosphorylated by Ca2+- dependent mitogenic signaling (Fisher et al., 1989; Fujiwara et al., 1990).

Expression

Ets2 has previously been shown to play a role in cell proliferation and differentiation (Kilpatrick et al., 1999). Early studies demonstrated that overexpression of Ets2 results in cellular transformation and proliferation in vitro (Seth et al.,1989). Furthermore, transfection of non-tumourigenic cell lines with Ets2 results in increased cell adhesion and enhanced invasiveness. Increased Ets2 expression has been observed in breast (Buggy et al., 2006; Galang et al., 2004), prostate (Foos et al., 2000; Turner et al., 2007b), esophageal (Li et al., 2003) and hepatocellular (Liao et al., 1996) carcinomas.

Localisation

The Ets2 protein is located in the nucleus.

Function

Ets-2 has a number of important functions defined in mammalian systems. Ets genes are thought to act as positive or negative regulators of gene expression involved in various biological processes (Papas et al., 1989; Sapi et al., 1998). Ets-2 is thought to be involved in the regulation of cell proliferation and differentiation in certain cell types (Kilpatrick et al., 1999). In T-cells, Ets-2 expression is induced upon mitogenic stimulation (Bhat et al., 1987). It has been demonstrated that Ets-2 overexpression in myeloid progenitor cells stimulates the development of mature macrophages (Aperlo et al., 1996). Yamamoto et al., showed that deleting the Ets-2 gene in mice resulted in growth retardation and often embryonic death (Yamamoto et al.,1998). This may be due to a disruption in the transcriptional regulation of the epidermal growth factor and transforming growth factor-BETA.
Ets-2 expression has long been associated with Down's Syndrome. In 1990, Papas et al., identified and mapped two members of the Ets family of transcription factors - Ets-2 and Erg to the portion of chromosome 21 believed to be involved in Down's Syndrome (Papas et al., 1990 b). The Ets-2 gene is found in three copies in partial trisomies associated with the syndrome phenotype (Sacchi et al., 1988).
In the liver, Ets-2 expression has been associated with hepatic cell regeneration and also with the development of hepatocellular carcinoma (Bhat et al., 1996; Liao et al., 1996). Ets-2 expression has also been found in 30% of rheumatoid arthritis patients (Sun et al., 2001). Ets-2 expression was reported in the synovial cells, suggesting an intrinsic activation mechanism of this immediate early gene in the disease process (Dooley et al., 1996).
A distinct role for Ets-2 in malignant transformation has been established. Seth et al., demonstrated that Ets-2 expression in NIH3T3 cells stimulates growth in the absence of serum growth factors (Seth et al., 1989). This group also showed that cell lines producing high levels of Ets-2 were capable of proliferating in the absence of serum. The Ets-2 transformed cells also exhibited anchorage-independent cell growth in agar suspension and tumourigenesis in nude mice. This study provides the first evidence of the transforming ability and mitogenic activity of Ets-2. Similar findings have been obtained by Sapi et al., using BT20 breast carcinoma cells (Sapi et al., 1998). Using these cells, colony formation was abolished following transfection with a dominant negative construct of Ets-2. Induction of Ets-2 has also been shown to be necessary for thyroid cell transformation (Sapi et al., 1998).

Implicated in

Human malignancies

Note

A growing number of human malignancies have been associated with Ets2 overexpression. Early studies have demonstrated overexpression of Ets2 results in cellular transformation (Seth et al., 1989). Ets2 has been shown to act as both a negative and positive regulator of gene expression in biological processes, including metastasis, angiogenesis, tissue remodeling and apoptosis (Papas et al., 1990a).

Breast cancer

Disease

Deregulation of Ets2 has been shown in human breast cancer (Turner et al., 2007a). Buggy et al., showed that both Ets2 mRNA and protein are overexpressed in human breast cancer compared with normal breast tissue (Buggy et al., 2006). Multiple studies in animal models and cell lines suggest that Ets2 is causally involved in breast cancer formation and progression (Buggy et al., 2006; Watabe et al., 1998). Transfection of the non-tumourigenic immortalized MCF-12A breast cancer cells with Ets2 resulted in serum growth factor independent proliferation, growth in soft agar and enhanced invasiveness (Sapi et al., 1998). In addition, Ets2 plays an important regulatory role in controlling expression of the breast tumour promoting protein, parathyroid hormone-related protein (Lindemann et al., 2003).

Esophageal carcinoma

Disease

Overexpression of Ets2 has been observed in human esophageal carcinoma (Li et al., 2003). Compared with normal tissue expression of both Ets2 mRNA and protein are upregulated in tumour tissue, suggesting a role in the pathology of esophageal carcinoma.

Prostate cancer

Disease

Increased expression of Ets2 has been shown in human prostate cancer (Foos et al., 2000; Turner et al., 2007b). Inhibition of Ets2 by antisense oligonucleotides or dominant negative constructs reduces anchorage-independent growth of prostate cancer cells, significantly reduces the ability of cells to form colonies in soft agar and reduces tumour formation in nude mice. Furthermore, Ets2 has been associated with the transcriptional upregulation of uPA and matrix metalloproteinase's (Man et al., 2003; Trojanowska, 2000), which are associated with prognosis in prostate cancer.

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