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Gene Section

Review

GREB1 (growth regulation by estrogen in breast cancer 1)

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Identity

HGNC (Hugo): GREB1

Location: 2p25.1

DNA/RNA

Description

The GREB1 gene is located on the short arm of chromosome 2, at 2q25.1, between the genomic sites for E2F transcription factor 6 and neurotensin receptor 2 (Entrez gene 9687). It is encoded on the plus strand covering 108.68 kb from 11674242 to 11782912 (UCSC). The gene structure consists of 60 exons/alternative exons and 40 distinct introns.

Transcription

The GREB1 gene contains a distal enhancer 20 kb upstream of the transcription start site containing 3 estrogen response elements (EREs), which bind estrogen receptor α (ERα) in the presence of estrogen. In breast cancer cells, the steroid receptor co-activator SRC-3, phosphorylated RNA polymerase II and actylated histones are also bound in the presence of estrogen. Chromatin loops link the three distal EREs and the transcription start site, indicating the distal enhancer plays a potent role in GREB1 estrogen responsiveness (Deschênes et al., 2007; Sun et al., 2007).

Three primary representative complete cDNA clones have been isolated from an MCF7 (ER+ breast cancer cell line) cDNA library, designated GREB1a, GREB1b and GREB1c respectively (Ghosh et al., 2000).

The longest transcript variant is GREB1a, consisting of 8482 bp spliced from 33 exons. GREB1b is 2521 bp in length and is spliced from 11 exons, whilst GREB1c is 2432 bp long spliced from 10 exons.

All three variants differ in their 5' and 3' UTRs and contain distinct c-terminus regions.

In addition, up to 10 additional splice variants have been identified amongst clones from breast, uterus, prostate and brain (Dias Neto et al., 2000; Nagase et al., 1998).

Expression of GREB1 variants have also been detected in the ovary, prostate and pancreas (NCBI).

Protein

Description

GREB1 protein has 7 isoforms containing a transmembrane domain and/or N-myristoylation domain. The three well documented isoforms of GREB1 protein, GREB1a, GREB1b and GREB1c contain 1949, 457 and 409 amino acids, respectively (Table 1).

They share N-terminus end region and containing diverging C-terminus end.

The divergence between 1a and 1b start from 450 aa. GREB1c shares first 386 amino acids with GREB1a and differs from 387 to 409 amino acids (Ghosh et al., 2000).

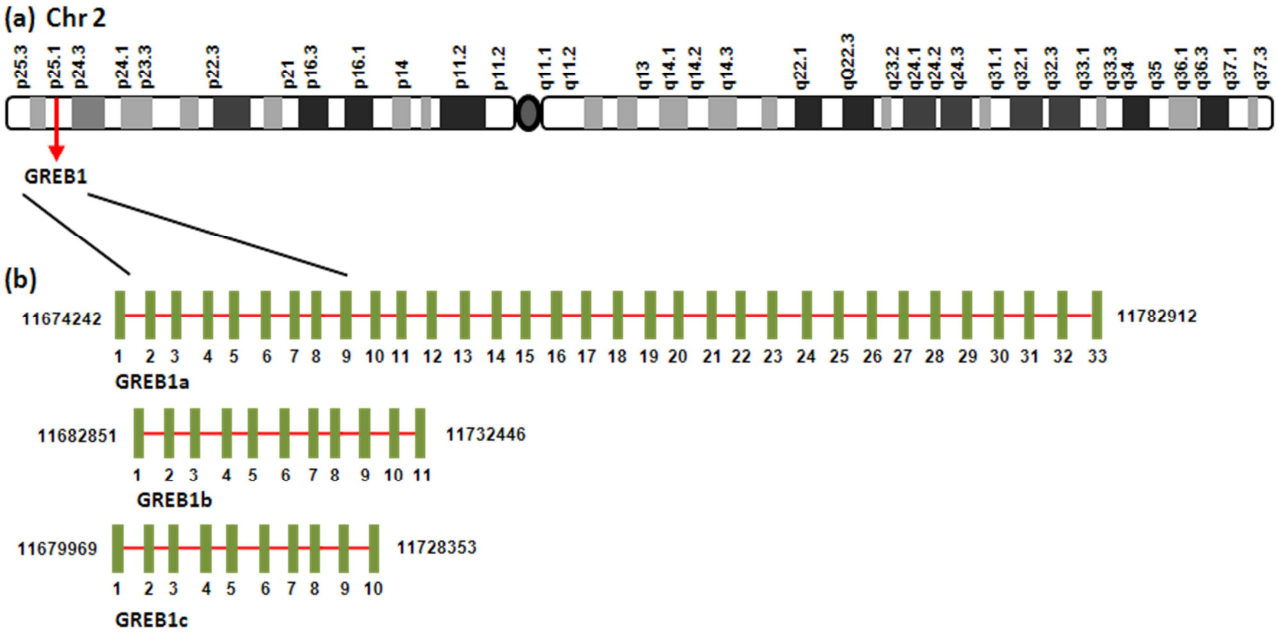

Figure 1. (a) The genomic location of GREB1 on the short arm of chromosome 2. **(b)** The 3 primary splice variants of GREB1, GREB1a, GREB1b and GREB1c. Green boxes represent exons, red lines introns. Numbers below exons indicate exon number. Numbers either side of variant indicate genomic location of the start and end of each transcript.

Expression

GREB1 protein expression is found in both normal and cancerous tissues. Its regulation is not only correlated with the presence of a subset of nuclear receptors such as ERα (Deschênes et al., 2007; Hnatyszyn et al., 2010; Lin et al., 2004; Pellegrini et al., 2012), androgen receptor (AR) (Rae et al., 2006) and Liver receptor Homolog 1 (LRH-1) (Chand et al., 2012) but also depends on their activation.

In breast cancers, GREB1 protein is detected in ERalpha+ but not ERalpha-negative breast tumour tissue (Hnatyszyn et al., 2010).

In addition GREB1, regulated by androgens is expressed in proliferating prostatic tissue and prostate cancer (Rae et al., 2006).

Localisation

GREB1 protein expression is predominantly nuclear with some cytoplasmic appearance (Hnatyszyn et al., 2010).

Function

The role of GREB1 is emerging as a hormone-dependent mediator of tumour cell proliferation.

It has been reported to elicit estrogen and androgen-stimulated cell proliferation in breast and prostate tumours (Rae et al., 2006; Rae et al., 2005; Antunes et al., 2012).

Whether the three variants have the same cellular function is unclear and its precise mechanistic action within the cell has still not been demonstrated.

The exact roles that GREB1 have in normal tissue are poorly defined.

Homology

GREB1 protein together with his paralogue GREB1-like located on chromosome 18 belong to the GREB1 family (Nagase et al., 2000). The GREB1 gene sequence is conserved in chimpanzee, dog, cow, mouse, chicken and monkey (HomoloGene).

Isoform	Accession	Length (aa)	Molecular mass (kDa)	Transmembrane domain	N-myristoylation domain
GREB1-1a	NP_055483	1949	216.5	1	1
GREB1-1b	NP_149081	457	48.9	0	1
GREB1-1c	NP_683701	409	43.2	0	1

Table 1. Isoforms of GREB1. 1=present, 0=absent.

Implicated in

Breast cancers

Note

A family of estrogen responsive genes discovered in MCF7 cells were designated GREB (genes regulated by estrogen in breast cancer) (Ghosh et al., 2000). Of these novel genes, GREB-1 was identified to have a strong correlation with ERα in breast cancer cells (Ghosh et al., 2000; Rae et al., 2005). Interestingly, GREB-1 was significantly induced by E_2 in MCF-7 cells and its suppression blocked E_2 induced growth (Rae et al., 2005). Furthermore, the GREB-1 regulatory region was found to possess three crucial estrogen response elements (EREs) (Lin et al., 2004). In addition, ChIP analysis revealed the binding of ERα, the steroid receptor coactivator-3, acetylated histones and phosphorylated RNA polymerase II to all three EREs in the presence of E_2 (Deschênes et al., 2007). Subsequently, GREB-1 is now a well characterised estrogen responsive gene used to identify ERα activity (Cai et al., 2011; Chand et al., 2012; Gupta et al., 2012; Liu et al., 2012; Rae et al., 2005; Sun et al., 2007; Woodfield et al., 2010). Hnatyszyn, et al developed a novel GREB-1 antibody which was used to detect GREB-1 protein expression in $ERα^{+ve}$ breast cancer cells and tissue (Hnatyszyn et al., 2010).

This positive correlation of GREB1 expression with ERα expression is validated in clinical cohorts (Ghosh et al., 2000). Another cohort of ER positive breast cancers in postmenopausal women (n=104) has shown a strong correlation of GREB-1 gene expression with plasma E_2 levels (Dunbier et al., 2010). In a cohort of breast cancer patients (n=64) compared to healthy women (n=79) GREB-1 gene expression correlated positively with serum E_2 levels (Haakensen et al., 2011). Furthermore in-vivo studies involving the transplantation of human breast tissue into female athymic mice (Balb/c nu/nu mice) has also demonstrated the induction of GREB-1 in response to E_2 treatment (Wilson et al., 2006).

Prostate cancer

Note

High levels of GREB1 mRNA ,comparable to levels in breast cancer MCF-7 cells, were found in prostatic tissues and prostate tumours (Rae et al., 2006). GREB1 was found to be also expressed in the AR-positive cell line LNCaP but absent in the AR-negative cell line PC-3 (Rae et al., 2006). GREB1 expression was responsive to androgens via androgen response elements (ARE) located ~3.3 kb upstream of the promoter. Knock-down of GREB1 in LNCaP cells led to the suppression of hormone-induced growth. Using microarray and qRT-PCR analysis of 33 prostate cancer patients, GREB1 was found to be over-expressed 13-fold compared to normal (Antunes et al., 2012). GREB1 transcript was significantly higher among patients with later stage prostate cancers.

Lung cancer

Note

Following exposure to 2R4F tobacco mainstream smoke (MSS), GREB1 expression was elevated in normal human bronchial epithelial (NHBE) cells (Parsanejad et al., 2008). Using human saliva samples from 42 lung cancer patients and 74 healthy control subjects, transcriptomes were analyzed by gene microarray and revealed that GREB1 was one of five biomarkers found to be elevated in lung cancer patients (Zhang et al., 2012).

Ovarian cancer

Note

To identify epigenetic changes associated with progression-free interval of ovarian cancer, 20 samples of advanced ovarian cancer with a predominantly serous papillary histological subtype were subjected to DNA methylation profiling. GREB1 promoter hypomethylation was associated with longer survival (Bauerschlag et al., 2011).

Hypertension

Note

A SNP, 45718A>G, was significantly associated with hypertension and blood pressure level in men, and this SNP was in linkage disequilibrium with a SNP present at the 3' splice site of intron 11 (Kamide et al., 2005).

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