Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Short Communication

EHF (ets homologous factor)

Giuseppina M Carbone, Carlo V Catapano, Domenico Albino

Institute of Oncology Research (IOR) and Oncology Institute of Southern Switzerland (IOSI), Via Vela 6, Bellinzona, 6500 Switzerland (GMC, CVC, DA)

Published in Atlas Database: April 2012

Online updated version : http://AtlasGeneticsOncology.org/Genes/EHFID40421ch11p13.html
DOI: 10.4267/2042/48140

Identity

Other names: ESE3, ESE3B, ESEJ

HGNC (Hugo): EHF

Location: 11p13

Note
This gene encodes a protein that belongs to the ETS family of transcription factor.
This gene belongs to the ETS subfamily defined as Epithelial Specific ETS (ESE) characterized by prevalent expression in epithelial cells.
The encoded protein acts as a transcriptional repressor and/or activator.

It is expressed in normal epithelium and may be involved in epithelial differentiation. Reduced expression of this gene is associated with tumorigenesis.

DNA/RNA

Note
Tumor suppressor gene.

Description

DNA Size: 39,72 kb, 9 exons.

Transcription

See below figure B.

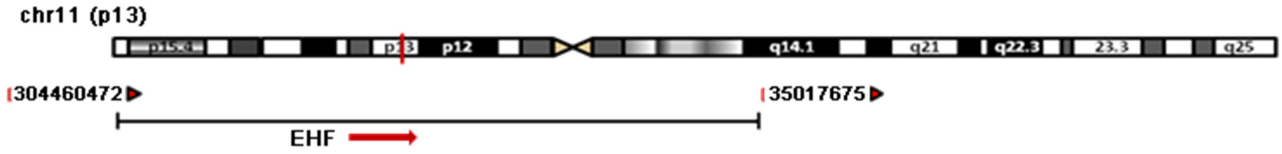

Fig.A

Fig. B

			Transcripts messenger RNA		
identification	type	bp	kDa	AA	Pubmed
ESE3A	splicing	2853	32,3	277	Kas, 2000.
ESE3B	splicing	3617	34,9	300	Kas,2000; Cangemi, 2008.

Schematic diagram of the EHF gene comprising 9 exons (in red). The sizes in base pairs (bp) of exons (below) are shown. **B. Transcripts.**

Sequence	Length	Mass (Da)
Isoform 1 (ESE-3A) FASTA	277	32345

```
          10         20         30         40         50         60
MILEGGGVMN LNPGNNLLHQ PPAWTDSYST CNVSSGFFGS QWHEIHPQYW TKYQVVWEWLQ

          70         80         90        100        110        120
HLLDTNQLDA NCIPFQEFDI NGEHLCSMSL QEFTRAAGTA GQLLYSNLQH LKWNGQCSSD

         130        140        150        160        170        180
LFQSTHNVIV KTEQTEPSIM NTWKDENYLY DTNYGSTVAE SPDMKKEQDP PAKCHTKKHN

         190        200        210        220        230        240
PRGTHLWEFI RDILLNPDKN PGLIKWEDRS EGVFRFLKSE AVAQLWGKKK NNSSMTYEKL

         250        260        270
SRAMRYYYKR EILERVDGRR LVYKFGKNAR GWRENEN
```

Sequence	Length	Mass (Da)
Isoform 2 (ESE-3B) FASTA	300	34892

```
          10         20         30         40         50         60
MILEGGGVMN LNPGNNLLHQ PPAWTDSYST CNVSSGFFGS QWHEIHPQYW TKYQVVWEWLQ

          70         80         90        100        110        120
HLLDTNQLDA NCIPFQEFDI NGEHLCSMSL QEFTRAAGTA GQLLYSNLQH LKWNGQCSSD

         130        140        150        160        170        180
LFQSTHNVIV KTEQTEPSIM NTWKDENYLY DTNYGSTVDL LDGKTFCRVQ ISMTTTSHLP

         190        200        210        220        230        240
VAESPDMKKE QDPPAKCHTK KHNPRGTHLW EFIRDILLMP DMKPGLIKWE DRSEGVFRFL

         250        260        270        280        290        300
KSEAVAQLWG KKKNNSSMTY EKLSRAMRYY YKREILERVD GRRLVYKFGK NARGWRENEN
```

Protein

Description

As reported by Kas et al., (J Biol Chem. 2000) sequence analysis revealed an open reading frame of 277 amino acids and a predicted molecular mass of 32,3 kDa for ESE-3a and an open reading frame encoding a 300-amino acid protein with a predicted molecular mass of 34,9 kDa for ESE-3b.
In addition, several potential phosphorylation sites are present in ESE-3b including two potential protein kinase C phosphorylation sites, three casein kinase II phosphorylation sites, and one potential JNK/p38/ ERK kinase phosphorylation sites ((S/T)P) in the central region of ESE-3, just behind the alternatively spliced exon.

Expression

Normal epithelium.

Localisation

Nuclear.

Function

Transcription factor that binds to DNA sequences containing the ETS factor consensus nucleotide core sequence GGAA. May act as a repressor for a specific subset of ETS/AP-1-responsive genes and as a modulator of the nuclear response to RAS and mitogen-activated protein kinase (MAPK) signaling cascades.
Involved in negative regulation of the expression of EZH2 through ETS binding sequences on the EZH2 promoter in normal prostate epithelial cells, prostate cancer cells and prostate tumors.
Involved in positive regulation of NKX3.1 in normal prostate epithelial cells through ETS binding site in the gene promoter.
Involved in the regulation of the expression of caspase-3 through ETS binding sequences on the caspase-3 promoter in prostate cancer cells.
Involved in regulation of TNFRSF10B/DR5 expression through ETS binding sequences on the TNFRSF10B/DR5 promoter.
May play a role in regulating epithelial cell differentiation and contribute to development and tumorigenesis by acting as a tumor suppressor gene.

Mutations

Note

Unknown.

Germinal

Unknown.

Somatic

Unknown.

Schematic representation of the two ESE3 protein isoforms. The pointed domain (PNT) and the Ets binding site (Ets DNA binding) domain are shown. PNT: (Pointed domain); EBS: (Ets binding site).

Implicated in

Human malignancies

Note

Albino et al. (Cancer Research, 2012) showed that ESE3, an endogenously expressed ETS transcription factor, controls prostate epithelial cell differentiation and stem-like potential. Stable ESE3 knockdown in prostate epithelial cells induced epithelial-to-mesenchymal transition (EMT), stem-like features, tumour-initiating and metastatic properties. Conversely, re-expression of ESE3 in prostate cancer cells reduced stem-like and tumorigenic potential. Mechanistically, ESE3/EHF maintains in a repressive state key EMT and Cancer stem cells (CSC) genes, including TWIST1, ZEB2, BMI1 and POU5F1, by directly binding to novel ETS binding sites identified in their promoters. Analysis of human tissue microarrays showed that reduced ESE3 expression was an early event and frequently independent of other ETS gene alterations. Analyses of multiple microarray datasets linked loss of ESE3/EHF expression to a distinct group of prostate tumors. ESE3 ^{low} tumors displayed distinctive molecular and biological characteristics, including increased expression of EMT and CSC genes and close similarity to ESE3 knockdown prostate epithelial cells. Low ESE3 expression was associated with increased biochemical recurrence and reduced overall survival after prostatectomy.

Prostate cancer

Note

The ESE3 expression is reduced in prostate tumors.

Disease

Prostate cancer (possibly implicated in other solid tumors of epithelial origin).

Oncogenesis

Cangemi et al. (Oncogene 2008) and Albino et al. (Cancer Research, 2012) propose a tumor suppressor role in prostate cancer for ESE3. Albino et al. (Cancer Research, 2012) propose the possibility to identify molecularly defined tumour subgroups based on the exclusive loss of ESE3 expression level.

References

Kleinbaum LA, Duggan C, Ferreira E, Coffey GP, Butticè G, Burton FH. Human chromosomal localization, tissue/tumor expression, and regulatory function of the ets family gene EHF. Biochem Biophys Res Commun. 1999 Oct 14;264(1):119-26

Kas K, Finger E, Grall F, Gu X, Akbarali Y, Boltax J, Weiss A, Oettgen P, Kapeller R, Libermann TA. ESE-3, a novel member of an epithelium-specific ets transcription factor subfamily, demonstrates different target gene specificity from ESE-1. J Biol Chem. 2000 Jan 28;275(4):2986-98

Tugores A, Le J, Sorokina I, Snijders AJ, Duyao M, Reddy PS, Carlee L, Ronshaugen M, Mushegian A, Watanaskul T, Chu S, Buckler A, Emtage S, McCormick MK. The epithelium-specific ETS protein EHF/ESE-3 is a context-dependent transcriptional repressor downstream of MAPK signaling cascades. J Biol Chem. 2001 Jun 8;276(23):20397-406

Silverman ES, Baron RM, Palmer LJ, Le L, Hallock A, Subramaniam V, Riese RJ, McKenna MD, Gu X, Libermann TA, Tugores A, Haley KJ, Shore S, Drazen JM, Weiss ST. Constitutive and cytokine-induced expression of the ETS transcription factor ESE-3 in the lung. Am J Respir Cell Mol Biol. 2002 Dec;27(6):697-704

Appel S, Bringmann A, Grünebach F, Weck MM, Bauer J, Brossart P. Epithelial-specific transcription factor ESE-3 is involved in the development of monocyte-derived DCs. Blood. 2006 Apr 15;107(8):3265-70

Lim JH, Cho JY, Park YB, Park JW, Kwon TK. ESE-3 transcription factor is involved in the expression of death receptor (DR)-5 through putative Ets sites. Biochem Biophys Res Commun. 2006 Nov 24;350(3):736-41

Taylor TD, Noguchi H, Totoki Y, Toyoda A, Kuroki Y, Dewar K, Lloyd C, Itoh T, Takeda T, Kim DW, et al.. Human chromosome 11 DNA sequence and analysis including novel gene identification. Nature. 2006 Mar 23;440(7083):497-500

Cangemi R, Mensah A, Albertini V, Jain A, Mello-Grand M, Chiorino G, Catapano CV, Carbone GM. Reduced expression and tumor suppressor function of the ETS transcription factor ESE-3 in prostate cancer. Oncogene. 2008 May 1;27(20):2877-85

Kunderfranco P, Mello-Grand M, Cangemi R, Pellini S, Mensah A, Albertini V, Malek A, Chiorino G, Catapano CV, Carbone GM. ETS transcription factors control transcription of EZH2 and epigenetic silencing of the tumor suppressor gene Nkx3.1 in prostate cancer. PLoS One. 2010 May 10;5(5):e10547

Albino D, Longoni N, Curti L, Mello-Grand M, Pinton S, Civenni G, Thalmann G, D'Ambrosio G, Sarti M, Sessa F, Chiorino G, Catapano CV, Carbone GM. ESE3/EHF controls epithelial cell differentiation and its loss leads to prostate tumors with mesenchymal and stem-like features. Cancer Res. 2012 Jun 1;72(11):2889-900

This article should be referenced as such:

Carbone GM, Catapano CV, Albino D. EHF (ets homologous factor). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(10):692-694.