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Gene Section

Review

EFEMP1 (EGF containing fibulin-like extracellular matrix protein 1)

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Identity

Other names: DHRD, DRAD, FBLN3, FBNL, FIBL-3, MLVT, MTLV, S1-5
HGNC (Hugo): EFEMP1
Location: 2p16.1

DNA/RNA

Transcription

The EFEMP1 coding region extends over a genomic interval of 56485 bp and comprises 10 exons.
EFEMP1 proximal promoter lacks TATA or CAAT regulatory boxes and is rich with CG residues. EFEMP1 expression is repressed by promoter methylation in several cancer types and cancer cell lines. Primers used to detect EFEMP1 promoter methylation are show in figures 2 and 3.

Protein

Note
The two transcription variants encode the same EFEMP1 protein of 493-amino acids with a molecular mass of ~ 55 kDa. Consecutive exons from 4 to 9 encode tandem arrays of epidermal growth-factor (EGF)-like domains.
There is no EFEMP1 ortholog in non-mammalian species, indicating its recent evolution in higher vertebrates with intragenic exon duplications.
There are 92-94% similarity at protein level among EFEMP1 of human, rat and mouse.

Description

EFEMP1 belongs to seven-member family of secreted glycoproteins characterized by a N-terminal signal peptide, a tandem repeat of EGF-like domains and a unique C-terminal fibulin-type module.

Expression

EFEMP1 is broadly expressed throughout the body during development and in adult tissues. It is highly expressed by epithelial and endothelial cells.

Localisation

Extracellular matrix.

Function

EFEMP1 is one member of fibulins that serve to modulate cellular behavior and functions by connecting and integrating multiple partner molecules in extracellular compartment. EFEMP1 is likely to contribute the integrity of basement membrane zones and anchor other extracellular matrix structures such as elastic fibers to basement membranes. Studies based on Efemp1 knock-out mouse implicate EFEMP1 function in withholding tissue integrity by stimulating the expression of Timp1 and Timp3 and inhibiting the expression and activities of matrix metalloproteinase Mmp2, and Mmp9 (Rahn et al., 2009). EFEMP1 interacts with TIMP3 (Klenotic et al., 2004) and hepatitis B virus X antigen (Sun et al., 1998). EFEMP1 suppresses endothelial cell spouting and antagonizes angiogenesis in vivo (Albig et al., 2006). EFEMP1 interacts with EGFR (Camaj et al., 2009).

Human *EFEMP1* gene exon/intron structure				
	Variant 2		Variant 3	
#	Exon	Intron	Exon	Intron
1	453	771	453	1263
2	41	451		
3	88	4092	88	4092
4	49	167	49	167
5	387	35926	387	35926
6	123	3746	123	3746
7	120	1003	120	1003
8	120	1558	120	1558
9	120	3822	120	3822
10	124	85	124	85
11	196	3486	196	3486
12	1273		1273	
Exons for CDS in red. Sequence length in base pair				

Figure 1. Three transcripts were reported in Genebank for variant 1 (NM_004105), variant 2 (NM_001039348), and variant 3 (NM_001039349). NM_004105 has been permanently suppressed because currently there is insufficient support for the transcript. Variant 3 originates from alternative splicing of exon 2 in variant 2.

Location relative to transcription initiation site		Forward primer (5' to 3')	Reverse primer (5' to 3')	Product (bp)	Reference (cancer)
	Genomic	GAGCAGCTCCAGGGGACCGCCGCG	TCCCCGACACGCTACCTTCG		Yue et al. 2007 (CRC, NSCLC, NPC)
420 to 577	MSP (M)	GTAGTTTTAGGGGATCGTCGC	TCCCCGACACGCTACCTTCG	158	
418 to 577	MSP (U)	GAGTAGTTTTAGGGGATTGTTGT	TCCCCAACACACTACCTTCA	160	
-139 to -20	Genomic	CGCCGGGCTCGCAACGCTGG	GGCAGCGGCCGCGGCGGCAG	120	Nomoto et al. 2010 (HCC)
	MSP (M)	CGTCGGGTTCGTAACGTTGG	GACAACGACCGCGACGACAA		
-254 to -152	Genomic	GGCGTGGGGTCCCCGCGAGTCTG	CGCAGCGAGGTCCGCGCCCCCTG	103	
	MSP (U)	GGTGTGGGGTTTTTGTGAGTTTG	CACAACAAAATCCACACCCCCTA		
378 to 600	Genomic	CACCTGGATTCCATAGGAGCTGGTTAGA	CTCTTTTGTCTTATCAGTCTGGGTCCC	223	Sadr-Nabavi et al. 2009 * (SBC)
	BGS	TATTTGGATTTTATAGGAGTTGGTTAGA	CTCTTTTATCTTATCAATCTAAATCCC		
208 to 471	Genomic	AGGGAGGTGGAGGTGTGCAGCCT	ATGAGGTCCCCTTTCTTAACAGCAAGC	264	
	BGS	AGGGAGGTGGAGGTGTGTAGTTT	ATAAAATCCCCTTTCTTAACAACAAAC		
1028 to 1206	Genomic	GCAGCCTGCTTTGTAGGTGCAG	CCAATCTGCTTTCTCATCTCCC	179	Kim et al. 2010 (PCa)
	BGS	GtAGttTGtTTTGTAGGTGtAG	CCAATCTaCTTTCTCATCTCCC		

* Corrections have been made in primer sequence shown in red according to GenBank AC096549.1

Figure 2. Primers used to detect methylation of EFEMP1 promoter in cancer.

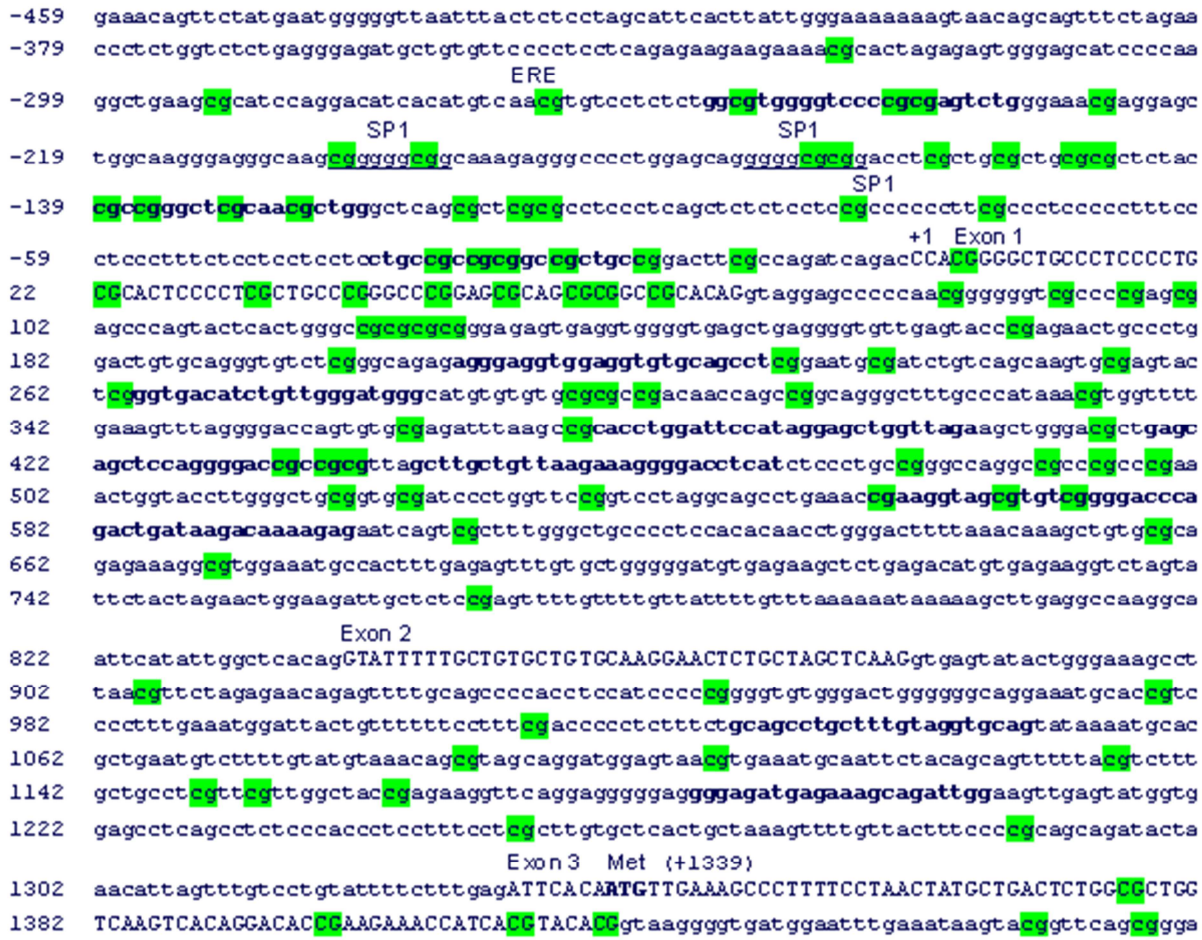

Figure 3. EFEMP1 proximal promoter and sequence upstream of translation start site. Three SP1-binding sites and an estrogen response element (ERE) binding site are underscored, CG residues are marked in green, exons in uppercase, and MSP/BGS primer locations in boldface with sequences shown in B.

However, opposing effects from EFEMP1 on EGFR-AKT signaling activity were reported in different cancer cells, to promote (Camaj et al., 2009) or suppress (Hu et al., 2011; Hwang et al., 2010; Kim et al., 2012) cancer cell migration/invasion and/or in vivo tumor growth.

A Delta-Serrate-Lag motif in EGF-like module with insertion has been revealed to be responsible for EFEMP1-mediated activation of Notch signaling in glioma cells (Hu et al., 2012).

Homology

EFEMP1 shares homology with the other members of fibulin family on (EGF)-like domains and fibulin-type module.

Mutations

Germinal

A single mutation of EFEMP1 gene at R345W was identified in patients with Malattia Leventinese (ML) and Doyne honeycombe retinal dystrophy (DHRD) (Stone et al., 1999).

Severe atropy of the retina was observed in patients with this mutation, including absence of photoreceptor and RPE cells, and large fibrous scars in the macular region.

This mutation was reported to cause protein misfolding, so that it is secreted inefficiently and retained within cells (Marmorstein et al., 2002).

Comparison of pathological features of Efemp1 knockout and R345W knock-in mice suggests R345W mutation in causing macular degeneration is not due to loss of EFEMP1, so it is likely that the mutation has an added detrimental effect that alters Bruch's membrane to a greater extent than other structures (Fu et al., 2007; McLaughlin et al., 2007).

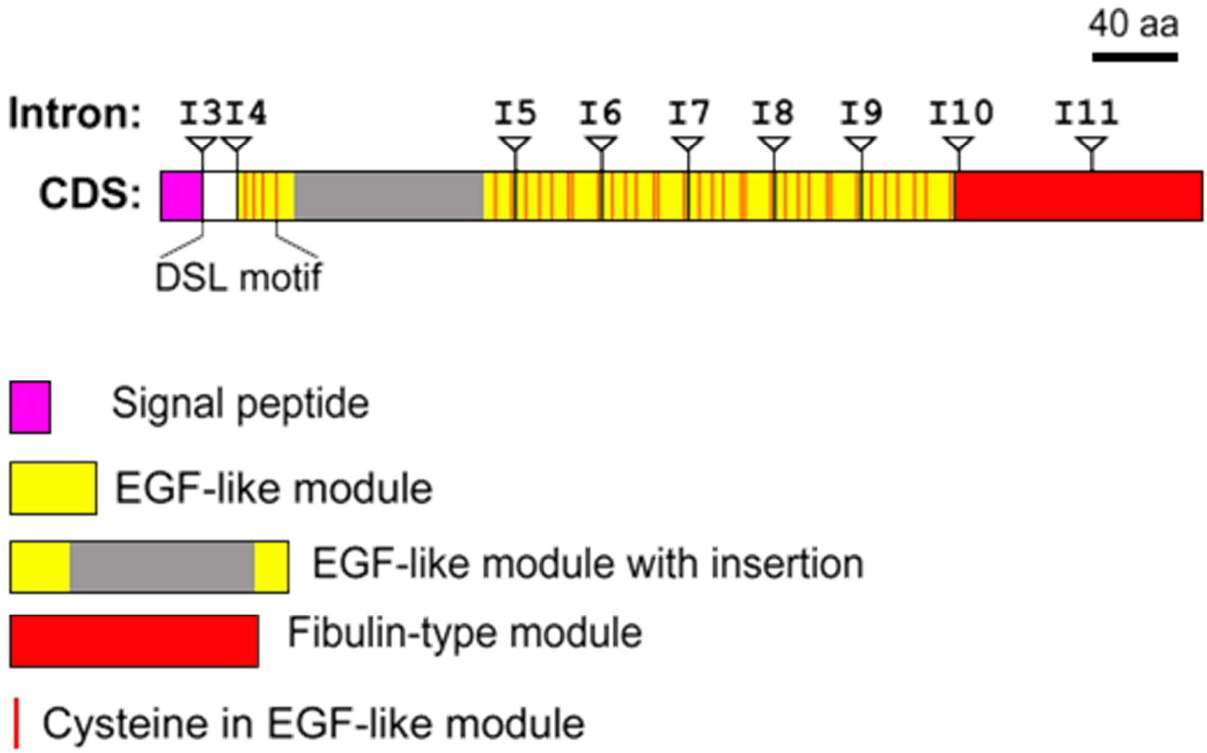

Figure 4. Domain structures of EFEMP1 and modular gene structure for EGF-like domains based on variant 2. DSL, Delta-Serrate-Lag (DSL) motif is a motif unique to Delta/Serrate/LAG-2 proteins in addition to repeated copies of EGF motif (Lissemore and Starmer, 1999).

Implicated in

Brain cancer

Note

EFEMP1 was found to be highly expressed in malignant gliomas and in glioma cells with activation of Notch signaling (Hu et al., 2012; Hu et al., 2009). However, EFEMP1 expression is positively associated with survival of patients with the highest grade of glioma - glioblastoma multiforme (GBM) and consistently, EFEMP1 was shown to suppress highly proliferative GBM cell growth in vivo by attenuation of EGFR-AKT signaling activities and VEGFA-induced angiogenesis (Hu et al., 2011). Along with activation of Notch pathway, EFEMP1 was shown to enhance migration/invasion and growth in vivo by glioma cells high in Notch signaling and stem-like feature (Hu et al., 2012). The contradictory roles of EFEMP1 to the growth of different glioma cells suggest EFEMP1 context-dependent function, thus could be an interesting gene to study glioma initiation, progression and tumor heterogeneity.

Breast cancer

Note

Hypermethylation of EFEMP1 promoter was found to be the major cause of EFEMP1 expression down-regulation in 50-60% sporadic breast cancer (SBC). Tumor suppressive function of EFEMP1 is implicated in SBC by a favorable prognosis effect of EFEMP1 expression to survival, particularly node-positive patients who received adjuvant anthracycline-based chemotherapy, but not in those treated by either cyclophosphamide-methotrexate-5-fluorouracil (CMF) or tamoxifen (Sadr-Nabavi et al., 2009).

Cervical cancer

Note

EFEMP1 protein expression was found to be significantly higher in cervical carcinoma with lymph node metastasis and correlates with poor patient survival (En-lin et al., 2010). Tumor-promoting effect of EFEMP1 in cervical cancer is supported by its function in promoting growth in vivo and in vitro invasion by cervical cancer cell line Hela (Song et al., 2011).

Colorectal cancer

Note

Hypermethylation of EFEMP1 promoter was reported in 38,8% colorectal cancer (CRC), which is correlated with downregulation of EFEMP1 expression and cancer progression to advanced pathological stage with lymph node metastasis. Tumor suppressive function of EFEMP1 is implicated in CRC by a favorable prognosis effect of EFEMP1 expression to overall survival and disease-free survival (Tong et al., 2011).

Liver cancer

Note

Hypermethylation of EFEMP1 promoter was reported in 50% hepatocellular carcinoma (HCC), which is correlated with downregulation of EFEMP1 expression. Tumor suppressive function of EFEMP1 is implicated in liver cancer by unfavorable prognosis from promoter methylation of EFEMP1 (Nomoto et al., 2010).

Lung cancer

Note

Hypermethylation of EFEMP1 promoter was independently reported by two laboratories in 36% and 43% of non-small cell lung carcinoma (NSCLC), while it was rarely found in the matched normal samples (Wang et al., 2010; Yue et al., 2007; Zhang et al., 2011).

It is correlated with downregulation of EFEMP1 expression and cancer progression to advanced pathological stage and lymph node metastasis.

Tumor suppressive function of EFEMP1 in lung cancer cell is demonstrated by its suppression effect on anchorage independent growth and in vitro invasion via suppression the expression of matrix metalloproteinase, including MMP2, MMP7, and MMP9 (Kim et al., 2012).

Nasopharyngeal carcinoma

Note

Hypermethylation of EFEMP1 promoter has been revealed in nasopharyngeal carcinoma (NPC) tumours compared with normal tissues. Downregulation of EFEMP1 expression was found in NPC at advanced lymph node-metastasis stages and a poor 5-year survival rate.

Tumor suppressive function of EFEMP1 in NPC is revealed by suppressing migration and invasion of NPC-derived cells and correspondingly decreasing the AKT phosphorylation (Hwang et al., 2010).

Pancreatic cancer

Note

EFEMP1 was reported to bind EGFR and activate MAPK and AKT pathways in pancreatic carcinoma cells and promote in vivo tumor growth with a stimulation of VEGFA production by tumors (Camaj et al., 2009; Seeliger et al., 2009).

Prostate cancer

Note

Hypermethylation of EFEMP1 promoter was reported in 95,3% of prostate cancer (PCa) but 13,4% of benign prostate hyperplasia (BPH), and EFEMP1 expression was significantly higher in tissue samples from patients with BPH than in those with PCa (Kim et al., 2011).

Werner syndrome

Note

S1-5 mRNA is overexpressed in Werner syndrome and senescent human diploid fibroblasts (Lecka-Czernik et al., 1995).

Adult height

Note

The EFEMP1 locus is one of 20 loci identified in a genome-wide association analysis that influence adult height (Okada et al., 2010).

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