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Gene Section
Review

EEF1B2 (eukaryotic translation elongation factor 1 beta 2)

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Abstract

Eukaryotic translation elongation factor 1 beta 2, alias EEF1B2, is a protein-coding gene that plays a role in the elongation step of translation:
In fact, it mediates GDP/GTP exchange on eEF1A. Considering its importance it is found frequently overexpressed in human cancer cells.
This review collects the data on DNA/RNA, on the protein encoded and on the diseases where EEF1B2 is involved.

Keywords
EEF1B2; Eukaryotic translation elongation factor 1 beta 2; Translation; Translation elongation factor; protein synthesis; cancer; oncogene; cancer marker

Identity

Other names: EEF1B1; EEF1B; EF1B; eEF1β; eEF1Bα; EF-1-beta

HGNC (Hugo): EEF1B2

Location: 2q33.3

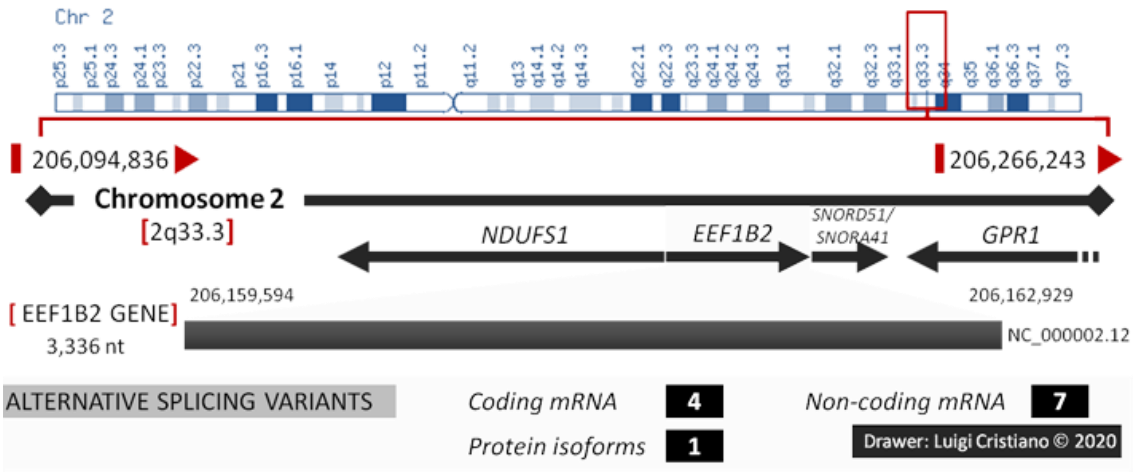

Figure. 1. EEF1B2 gene and splicing variants/isoforms. The figure shows the locus on chromosome 2 of the EEF1B2 gene (reworked from https://www.ncbi.nlm.nih.gov/gene; http://grch37.ensembl.org; www.genecards.org)

DNA/RNA

Description

EEF1B2 (eukaryotic translation elongation factor 1 beta 2) was identified for the first time by Sanders and colleagues in 1991 (Sanders et al, 1991) and afterwards, its gene location was described by Pizzuti and colleagues in 1993 (Pizzuti et al, 1993). EEF1B2 is a protein-coding gene that starts at 206,159,594 nt and ends at 206,162,929 nt from pter. It has a length of 3,336 bp and the current reference sequence is NC_000002.12. It is proximal to SNORA41 (small nucleolar RNA, H/ACA box 41) gene, SNORD51 (small nucleolar RNA, C/D box 51) gene and NDUFS1 (NADH: ubiquinone oxidoreductase core subunit S1) gene. Near to the genomic sequence of EEF1B2 there is a strong promoter transcriptional element that is located at – 0.2 kb.

Transcription

Three main alternative splicing transcript variants for EEF1B2 were detected although several others were reported. The three main transcript variants differ from each other only in the 5' UTR. In addition, it was speculated the presence of four protein isoforms, one main isoform of 225 amino acids and other three minor isoforms of 123 residues, 68 residues and 29 residues respectively. However, only the protein with the highest number of amino acids was detected. The main characteristics of the alternative splicing transcript variants are reported in Table.1. The main mRNA reference sequence is NM_001959.4 and it is 808 bp long. The 5'UTR counts 85 nt, the CDS is extended from 86 to 763 nt, while the 3'UTR covers the last 45 nt.

Name	Variant	RefSeq (1)	Transcript ID	Exons	Type	Length (bp)	Isoform	Alias	RefSeq (2)	Length (aa)	MW (kDa)	pI
EEF1B2-201 (EEF1B2-001)	Var.2	NM_021121.3	ENST00000236957.9	7	protein coding	844 (854)	-	P24534	NP_066944.1	225	24.76	4.50
EEF1B2-202 (EEF1B2-201)	Var.3	NM_001037663.1	ENST00000392221.5	7	protein coding	880 (900)	-	P24534	NP_001032752.1	225	24.76	4.50
EEF1B2-203 (EEF1B2-003)	Var.1	NM_001959.4	ENST00000392222.7	6	protein coding	808	-	P24534	NP_001950.1	225	24.76	4.50
EEF1B2-204 (EEF1B2-005)	-	-	ENST00000415904.1	4	nonsense md	649	-	-	-	68	-	-
EEF1B2-205 (EEF1B2-007)	-	-	ENST00000429769.5	8	nonsense md	912	-	-	-	68	-	-
EEF1B2-206 (EEF1B2-009)	-	-	ENST00000435123.1	3	nonsense md	389	-	-	-	29	-	-
EEF1B2-207 (EEF1B2-004)	-	-	ENST00000445505.5	5	protein coding	515	-	-	-	123	-	-
EEF1B2-208 (EEF1B2-010)	-	-	ENST00000455150.1	6	nonsense md	670	-	-	-	68	-	-
EEF1B2-209 (EEF1B2-008)	-	-	ENST00000460760.1	2	retained intron	1025	-	-	-	-	-	-
EEF1B2-210 (EEF1B2-006)	-	-	ENST00000479587.1	3	retained intron	701	-	-	-	-	-	-
EEF1B2-211 (EEF1B2-002)	-	-	ENST00000482103.1	2	retained intron	587	-	-	-	-	-	-

Table.1 Alterative splicing variants and isoforms of EEF1B2. (reworked from http://grch37.ensembl.org; https://www.ncbi.nlm.nih.gov; https://web.expasy.org/protparam/; https://www.uniprot.org). ncRNA = non-coding RNA; nonsense md = nonsense mediated decay;(?) = undetermined; MW = molecular weight; pI = theoretical pI.

Gene	Gene name	Gene ID	RefSeq	Locus	Location	Start	End	Lenght (nt)	Main diseases	Reference
EEF1B2P1	EEF1B2 pseudogene 1	1932	NC_000015.10	Chromosome 15	15q21.2	52505029	52505908	880	-	-
EEF1B2P2	EEF1B2 pseudogene 2	1934	NC_000005.10	Chromosome 5	5q13.1	68159175	68159977	803	-	-
EEF1B2P3	EEF1B2 pseudogene 3	644820	NC_000023.11	Chromosome X	Xp22.11	24788347	24789110	764	-	-
EEF1B2P4	EEF1B2 pseudogene 4	100130631	NC_000012.12	Chromosome 12	12q23.3	106901238	106902398	1161	-	-
EEF1B2P5	EEF1B2 pseudogene 5	442227	NC_000006.12	Chromosome 6	6q12	63480050	63481926	1877	-	-
EEF1B2P6	EEF1B2 pseudogene 6	647030	NC_000007.14	Chromosome 7	7q32.3	131661900	131662665	766	-	-
EEF1B2P7	EEF1B2 pseudogene 7	100421756	NC_000002.12	Chromosome 2	2q37.1	232729478	232730276	799	-	-
EEF1B2P8	EEF1B2 pseudogene 8	100421774	NC_000003.12	Chromosome 3	3q26.31	175059315	175060110	796	-	-

Table.2 EEF1B2 pseudogenes (reworked from https://www.ncbi.nlm.nih.gov/gene/1933; https://www.targetvalidation.org; https://www.ncbi.nlm.nih.gov/geoprofiles/)
[(?)] uncertain; [-] no reference

Pseudogene

According to Entrez Gene, the analysis of the human genome revealed the presence of several pseudogenes for EEF1B2 (Table.2), which are perhaps related to recent retrotransposition events (Chambers et al, 2001).
The alternative forms EEF1B3 and EEF1B4 previously designated for EEF1B2 (Pizzuti et al, 1993) have instead proved to
be pseudogenes: i.e. EEF1B2P2 and EEF1B2P3 respectively.
If these elements have any regulatory role in the expression of the respective gene as described for others (Hirotsune et al., 2003), is only speculation in the absence of experimental evidence.
Currently, there is no evidence about the involvement of these pseudogenes in human cancers or in other diseases.

Protein

Description

The eukaryotic translation elongation factor 1 beta 2 (alias eEF1B2, eEF1β, eEF1Bα) is the smallest subunit of the macromolecular eukaryotic translation elongation factor-1 complex (alias eEF1, also called eEF1H)(Cao et al, 2014), a high-molecular-weight form made up of an aggregation of different protein subunits: EEF1A1 (alias eEF1α), EEF1B2, EEF1G (alias eEF1γ, heEF1γ, eEF1Bγ), EEF1D (alias eEF1δ, eEF1Bδ) and VARS2 (valyl t-RNA synthetase val-RS). eEF1H protein complex plays a central role in peptide elongation during eukaryotic protein biosynthesis, in particular for the delivery of aminoacyl-tRNAs to the ribosome mediated by the hydrolysis of GTP.

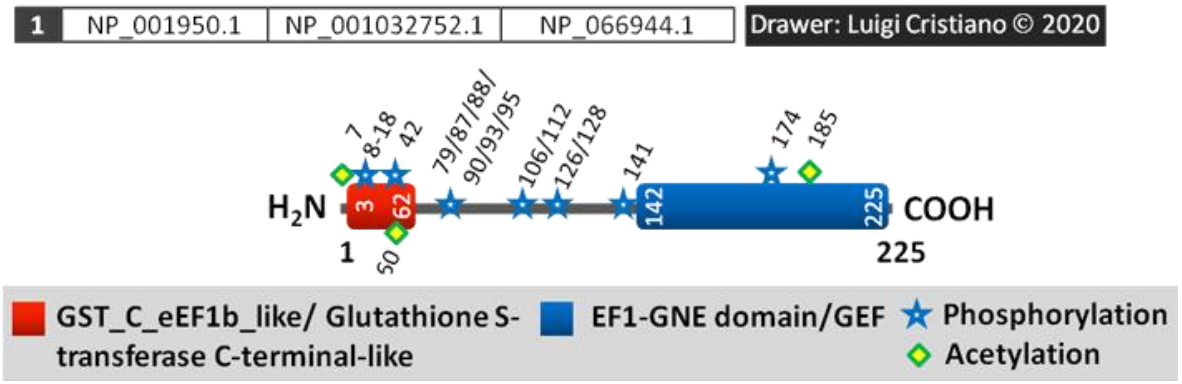

Figure.2 eEF1B2 protein. Graphical representation of eEF1B2 protein with the evidence of the main verified post-translational modifications (reworked from Le Sourd et al., 2006; http://grch37.ensembl.org; https://www.ncbi.nlm.nih.gov; http://bioinf.umbc.edu/dmdm/gene_prot_page.php; http://www.hprd.org/ptms?hprd_id=02804isoform_id=02804_1isoform_name=Isoform_1).

In fact, during the translation elongation step, the inactive GDP-bound form of eEF1A (eEF1A-GDP) is converted to its active GTP-bound form (eEF1A-GTP) by eEF1BGD-complex through GTP hydrolysis.
Thus eEF1BGD-complex acts as a guanine nucleotide exchange factor (GEF) for the regeneration of eEF1A-GTP for the next elongation cycle. The physiological role of eEF1B2 in the translation is fundamental to permit the conversion of the inactive form eEF1A-GDP into its corresponding active form eEF1A-GTP. In particular, eEF1B2 strictly collaborate with eEF1D and eEF1G in the conversion of eEF1A from its inactive GDP-bound form to its active GTP-bound form and so it covers a role as a guanine nucleotide exchange factor (GEF) for eEF1A (Le Sourd et al., 2006; Browne and Proud, 2002).
It was shown that the nucleotide exchange reaction by eEF1B2 is inhibited by Mg2+ that binds on K205 residue. Only after the displacing of Mg2+ from its binding site eEF1B2 can function correctly (Pittmann et al, 2006).
In prokaryotes, the homolog of eEF1B2 is known as EF-Ts, while in eukaryotes it is known only one functional protein form with the reference sequence NP_001950.1 by 225 residues. It is found in the eEF1H protein complex and it shows many domains: in the carboxyl half terminal there is an EF-1 guanine nucleotide exchange domain (EF1-GNE domain / GEF) while in the amino half terminal there is a region called GST-C-eEF1b-like domain (Glutathione S-transferase C-terminal-like domain)(see figure.2).
The fold of the C-terminal domain of eEF1B2 is found very similar to that many ribosomal proteins, i.e. it shows two so-called split b-a-b motifs (Andersen et al, 2003).
This region possesses nucleotide exchange activity and interacts with eEF1A (Le Sourd et al., 2006).
The non-catalytic N-terminal domain of eEF1B2, that interacts with the N-terminal domain of eEF1G (Le Sourd et al., 2006; van Damme et al, 1991), has a regulatory role on the eEF1B2 itself because it can interfere with the guanine nucleotide exchange activity located on the C-terminal domain. In fact, the non-catalytic N-terminal domain of eEF1B2 brings to the reduction in the overall rate of the guanine nucleotide exchange reaction mediated by eEF1B2. It is only thanks to the bond of eEF1B2 with eEF1G that this inhibitory effect is abolished (Trosiuk et al, 2016). EEF1B2 interacts primarily with eEF1A1/ EEF1A2 and eEF1G but also with valyl -tRNA synthetase (Val-RS)(Le Sourd et al., 2006; Bec et al., 1994). Seems that there are no direct interactions between eEF1B2 and eEF1D (Cao et al, 2014; Sheu and Traugh, 1997), although different interactional models were proposed (Le Sourd et al., 2006; Jiang et al.,2005; Sheu and Traugh, 1999; Minella et al., 1998).

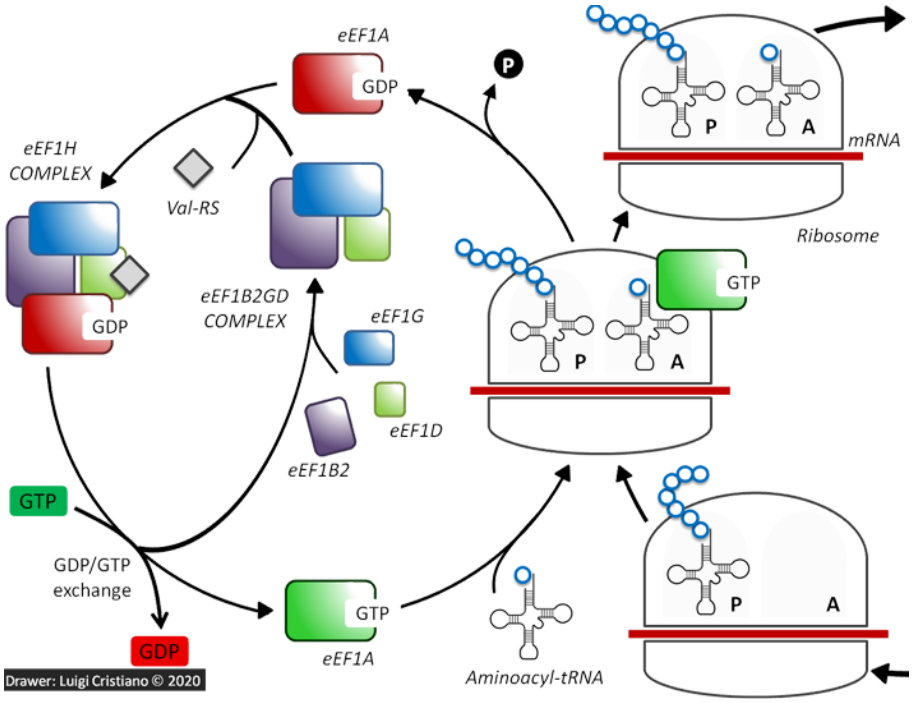

Figure 3. The translation elongation mechanism. The active form of eukaryotic translation elongation factor 1 alpha (eEF1A) in complex with GTP delivers an aminoacylated tRNA to the A site of the ribosome. Following the proper codon-anticodon recognition the GTP is hydrolyzed and the inactive eEF1A-GDP is released from the ribosome and then it is bound by eEF1B2GD complex forming the macromolecular protein aggregate eEF1H. eEF1H is formed previously by the binding of three subunits: eEF1B2, eEF1G and eEF1D. This complex promotes the exchange between GDP and GTP to regenerate active form of eEF1A (reworked from Li et al., 2013; Ejiri, 2002; Riis et al, 1990; https://reactome.org)

In addition, eEF1B2 interact with translationally controlled tumor protein (TCTP) but the nature of this interaction is still poorly understood (Wu et al, 2015).

Post-translational modifications. Some post-translational modifications are observed, such as phosphorylation and acetylation (https://www.ncbi.nlm.nih.gov). Phosphorylations of eEF1B2 are made by some protein kinases, including casein kinase 2 (CK2) (Browne and Proud, 2002).

Expression

eEF1B2 is expressed widely in human tissues (https://www.genecards.org) although its expression is not uniform in either tissues or cell lines (Cao et al, 2014).

Localisation

eEF1B2 is located mostly in the cytoplasm but it was also found in the nucleus (https://www.genecards.org/cgi-bin/carddisp.pl?gene=EEF1B2). It shows a perinuclear distribution (Sanders et al, 1996) and it is found on the endoplasmic reticulum (Cho et al, 2003; Sanders et al, 1996).

Function

eEF1B2 plays a fundamental role in the cell, in particular in the translation elongation step. In fact, eEF1B2 shows canonical functions and multiple non-canonical roles (moonlighting roles) inside the cell.

Canonical function: eEF1B2 binds to eEF1D and eEF1G in the eEF1B2DG macromolecular complex and contributes to catalyze the exchange of GDP/GTP for eEF1A during the translation elongation cycle. It was shown that eEF1B2 has the ability to disrupt eEF1A-induced actin organization and so engage eEF1A for protein synthesis (Pittman et al, 2009).

Non-canonical roles: eEF1B2 seems to have other functions inside the cell besides its involvement in translation. Together with eEF1D and eEF1G, it controls the translation fidelity (Le Sourd et al, 2006) and in response to stressors such as heat shock, oxidative stress, and toxins, it mediates the inhibition of protein synthesis. In addition, it seems to have interaction with the cytoskeleton (Khudhair et al., 2014), but the effect of eEF1B2 on actin filaments is still poorly understood (Sasikumar et al, 2012).

Homology

eEF1B2 is highly conserved and its homology between the species is reported in Table.3

Mutations

A great number of mutations in the genomic sequence and in the amino acid sequence for EEF1B2 were discovered in cancer cells that are obviously genetically more unstable respect normal ones.

The genomic alterations observed include the formation of novel fusion genes.

However, there are no sufficient experimental data yet to understand the repercussions on cellular behaviour and so the implications in cancer of these alterations.

Organism	Species	Symbol	DNA Identity (%)	PROT Identity (%)
Human	H.sapiens	EEF1B2	100	100
Chimpanzee	P.troglodytes	EEF1B2	99.9	100
Macaco	M.mulatta	EEF1B2	97.6	99.6
Wolf	C.lupus	EEF1B2	93.0	98.2
Cattle	B.taurus	EEF1B2	91.1	97.8
Mouse	M.musculus	Eef1b2	89.2	95.6
Rat	R.norvegicus	Eef1b2	89.2	94.7
Chicken	G.gallus	EEF1B2	82.0	93.3
Xenopus tropicalis	X.tropicalis	eef1b2	78.1	85.3
Zebrafish	D.rerio	eef1b2	73.8	82.6
Fruit fly	D.melanogaster	Ef1beta	58.7	58.8
Mosquito (Anopheles)	A.gambiae	AgaP_AGAP010612	60.2	62.0
Caenorhabditis	C.elegans	eef-1B.1	55.1	53.1

Table.3 EEF1B2 homology (reworked from htpps://www.ncbi.nlm.nih.gov/homologene)

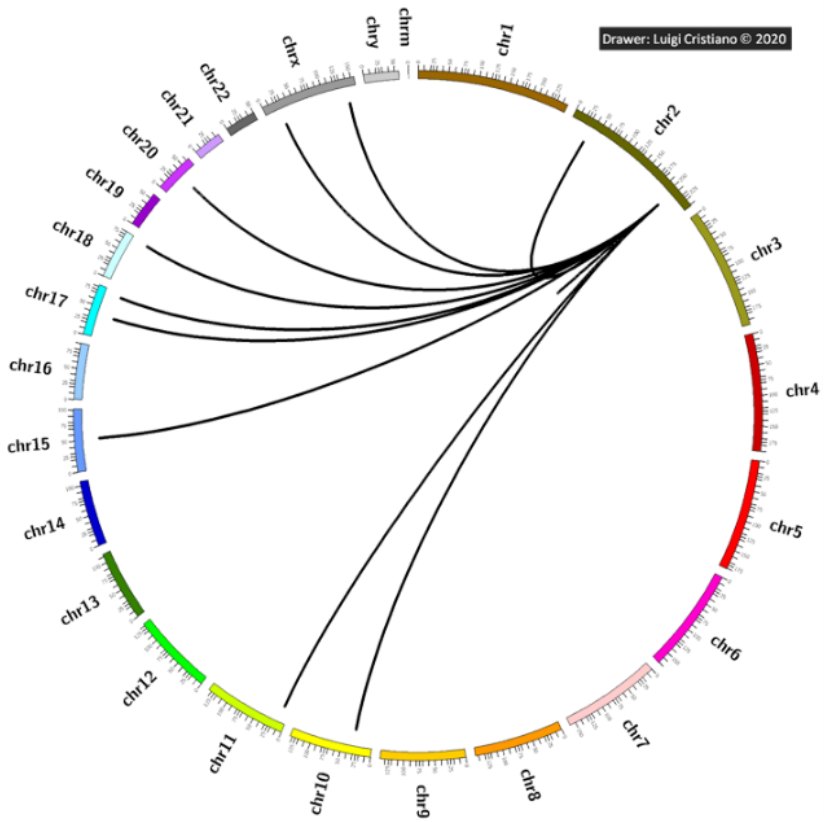

Figure 4. Circos plot for fusion events involving eEF1B2. The picture summarizes all fusion events concerning eEF1B2 and its fusion partners (from https://fusionhub.persistent.co.in/search_genewise.html).

Implicated in

A different expression level of EEF1B2 was observed in many cancer types, i.e. some cancer types show an increase of its expression levels, whereas others show a significant reduction of its expression level, compared to noncancerous control tissue. Therefore, eEF1B2 seems to be involved in tumorigenesis like the other members of eEF1H complex (Hassan et al., 2018; Le Sourd et al., 2006) but not only: it was revealed that all subunits of eEF1B2GD complex, included eEF1B2, can function separately from the eEF1B2GD complex or the eEF1H complex in cancer tissues (Veremieva et al, 2011).
In addition, eEF1B2 is involved in some genomic translocations with the creation of numerous fusion genes (Table.4).

Brain and central nervous system (CNS) cancers

Significative high expression levels for eEF1B2 were observed in atypical teratoid/rhabdoid tumor and oligodendroglioma (Hassan et al, 2018).

Prognosis

Lower protein levels of eEF1B2 were correlated with poor survival in glioma patients (Biterge-Sut, 2019; Hassan et al, 2018)

Breast cancer

It was reported that eEF1B2 is overexpressed in breast carcinoma (Al-Maghrebi et al, 2005). On the contrary, Hassan et colleagues reported that eEF1B2 expression levels are reduced both in invasive ductal breast carcinoma and invasive lobular breast carcinoma (Hassan et al, 2018).
In addition, it is downregulated in IR-induced senescence in MCF7 breast cancer cell line (Byun et al, 2009).

Prognosis

According to Hassan et colleagues, elevated levels of eEF1B2 expression predict a better overall survival (OS) in luminal B subtype breast cancer, a better overall survival (OS) and distant metastasis free survival (DMFS) in luminal A subtype breast cancer, but a worse DMFS in basal type (Hassan et al, 2018).

Colorectal cancer

In colorectal cancer the involvement of eEF1B2 is controversial.
Although there are no significant difference in expression levels of eEF1B2 in tumor samples respect normal ones, it is believed that a reduction of its expression level in colorectal cancer can be related to poor patients survival (Hassan et al, 2018)

Name	5' end	3' end	Loc1	Loc2	Description	Type	Disease	Organ	Code	Ref.
ACACA/EEF1B2	ACACA	EEF1B2	17q12	2q33.3	t(2;17)(q33;q12)	Translocation	(?)	-	-	-
BLCAP/EEF1B2	BLCAP	EEF1B2	20q11.23	2q33.3	t(2;20)(q33;q11)	Translocation	(?)	-	-	-
CRIM1/EEF1B2	CRIM1	EEF1B2	2p22.3	2q33.3	t(2;2)(p22;q33)	Translocation	Adenocarcinoma	Kidney	KIRC	Yoshihara et al 2015
EEF1B2/CDR1	EEF1B2	CDR1	2q33.3	Xq27.1	t(X;2)(q27;q33)	Translocation	(?)	-	-	-
EEF1B2/EEF1B2P1	EEF1B2	EEF1B2P1	2q33.3	15q21.2	t(2;15)(q33;q21)	Translocation	(?)	-	-	-
EEF1B2/EEF1B2P3	EEF1B2	EEF1B2P3	2q33.3	Xp22.11	t(X;2)(p22;q33)	Translocation	(?)	-	-	-
EEF1B2/H3F3B	EEF1B2	H3F3B	2q33.3	17q25.1	t(2;17)(q33;q25)	Translocation	(?)	-	-	-
EEF1B2/MBP	EEF1B2	MBP	2q33.3	18q23	t(2;18)(q33;q23)	Translocation	(?)	-	-	-
MICAL2/EEF1B2	MICAL2	EEF1B2	11p15.3	2q33.3	t(2;11)(q33;p15)	Translocation	(?)	-	-	-
NDUFS1/EEF1B2	NDUFS1	EEF1B2	2q33.3	2q33.3	Readthrough transcription	Fusion gene	-	Cell line (urinary bladder)	BFTC-905	Klijn et al., 2015
ZEB1/EEF1B2	ZEB1	EEF1B2	10p11.22	2q33.3	t(2;10)(q33;p11)	Translocation	(?)	-	-	-
ZNF620/EEF1B2	ZNF620	EEF1B2	3p22.1	2q33.3	t(2;3)(q33;p22)	Translocation	(?)	-	-	Klijn et al., 2015

Table.4 EEF1B2 rearrangements: translocations and fusion genes (reworked from: http://www.tumorfusions.org; https://mitelmandatabase.isb-cgc.org/; http://quiver.archerdx.com; http://atlasgeneticsoncology.org//Bands/2q33.html#REFERENCES; https://fusionhub.persistent.co.in/home.html; https://ccsm.uth.edu/FusionGDB/index.html) [(?)] unknown; [-] no reference

Gastric cancer

It is found that eEF1B2 is expressed at levels about three times higher in gastric cancer tissues compared with respective normal ones and that the high expression of eEF1B2 seems to be significantly associated with histological type, TNM stage, tumor size, and distant metastases (Jia et al, 2019). This could suggest that eEF1B2 participate in gastric tumorigenesis and progression and so it may a possible prognostic biomarker for gastric cancer. On the contrary, a previous study reported that eEF1B2 levels in gastric cancer were significantly downregulated (Hassan et al, 2018).

Prognosis

High expression levels for eEF1B2 in gastric cancer patients predict poor overall survival (Jia et al, 2019). On the contrary, Hassan and colleagues, reported that its elevated transcript levels may predict better overall survival (OS) and better first progression (FP) (Hassan et al, 2018).

Head and neck squamous cell carcinoma (HNSC)

eEF1B2 expression levels are significantly lower in tongue squamous cell carcinoma, salivary gland adenoid cystic carcinoma, and hypopharyngeal squamous cell carcinoma respect normal ones (Hassan et al, 2018).

Kidney cancer

EEF1B2 mRNA levels were found to be upregulated in cancer samples, in particular in kidney clear cell carcinoma (Hassan et al., 2018). In addition, the yet poorly understood translocation t(2;2)(p22;q33) CRIM1/EEF1B2 was reported in kidney clear cell carcinoma (Yoshihara et al, 2015).

Liver cancer

There is not much data on the expression levels of eEF1B2 in liver tumors however lower protein levels for eEF1B2 seems to be correlated with better survival in hepatocellular carcinoma patients (Biterge-Sut, 2019; Hassan et al, 2018).

Lung cancer

eEF1B2 expression levels seem to not show any significant difference between tumor and normal tissue (Hassan et al, 2018) although other research revealed that it is overexpressed in 8% of cancer samples examined (Veremieva et al, 2014).

Prognosis

An overexpression of EEF1B2 predicts poor prognosis in lung cancer, in particular in adenocarcinoma (Hassan et al, 2018).

Lymphoma and other blood cancers

High expression levels of eEF1B2 were detected in follicular lymphoma, diffuse large B-Cell lymphoma and Burkitt's lymphoma (Hassan et al, 2018).

Neurological and neurodevelopmental disorders

Loss of function of EEF1B2 brings to defects in the elongation process and it is involved in autosomal recessive intellectual disability (ID) (Larcher et al., 2019).

Oesophageal carcinoma

It was detected that eEF1B2 is overexpressed in about 20% of cardioesophageal carcinoma samples examined respect noncancerous ones (Veremieva et al., 2014).

Pancreatic cancer

EEF1B2 mRNA is found to be down-regulated in pancreatic cancer tissue samples and this can be correlated to a better survival (Hassan et al., 2018).

Prostate cancer

There are no significant differences in expression levels of eEF1B2 in prostate cancer respect normal one (Hassan et al, 2018).

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