Gene Section
Review

EEF1D (eukaryotic translation elongation factor 1 delta)

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Abstract

Eukaryotic translation elongation factor 1 delta, alias EEF1D, is a protein-coding gene that plays a role in the elongation step of translation and 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 EEF1D is involved.

Keywords

EEF1D; Eukaryotic translation elongation factor 1 delta; Translation; Translation elongation factor; protein synthesis; cancer; oncogene; cancer marker

Identity

Other names: EF-1D, EF1D, FLJ20897, FP1047
HGNC (Hugo): EEF1D
Location: 8q24.3

Figure 1. EEF1D gene and splicing variants/isoforms. The figure shows the locus on chromosome 8 of the EEF1D gene (reworked from https://www.ncbi.nlm.nih.gov/gene; http://grch37.ensembl.org; www.genecards.org)
| Name   | Variant | RefSeq (1) | Transcript ID | Exons | Type            | Lenght (bp) | Isoform | Alias          | RefSeq (2) | Lenght (aa) | MW (kDa) | pI   |
|--------|---------|------------|---------------|-------|-----------------|-------------|----------|----------------|-------------|-------------|----------|-----|
| EEF1D-204 | Var.3   | NM_001130053 | ENST00000423316.6 | 9     | protein coding  | 2356        | Isoform 1 | -              | NP_001123525 | 647         | 71.42    | 6.02 |
| EEF1D-205 (EEF1D-001) | Var.1   | NM_032378   | ENST00000442189.6 | 10    | protein coding  | 2473        | Isoform 1 | -              | NP_115754 | 647         | 71.42    | 6.02 |
| EEF1D-201 | Var.6   | NM_001130057 | ENST00000317198.10 | 8     | protein coding  | 1458        | Isoform 2 | -              | NP_001123529 | 281         | 31.12    | 4.90 |
| EEF1D-203 | Var.5   | NM_001130055 | ENST00000419152.6 | 9     | protein coding  | 1427        | Isoform 2 | -              | NP_001123527 | 281         | 31.12    | 4.90 |
| EEF1D-225 (EEF1D-006) |       |             | ENST00000529272.5 | 8     | protein coding  | 1311        | -        | -              | -           | 281         | -        | -    |
| EEF1D-202 (EEF1D-002) | Var.9   | NM_001289950 | ENST00000395197.7 | 8     | protein coding  | 1428        | Isoform 2 | -              | NP_001279679 | 281         | 31.12    | 4.90 |
| EEF1D-207 (EEF1D-053) | Var.2   | NM_001960   | ENST00000524624.5 | 8     | protein coding  | 1084        | -        | -              | -           | 257         | -        | -    |
| EEF1D-218 (EEF1D-005) | Var.8   | NM_001195203 | ENST00000526838.5 | 8     | protein coding  | 1194        | Isoform 5 | -              | NP_001182132 | 262         | 29.07    | 4.91 |
| EEF1D-223 (EEF1D-004) | Var.7   | NM_00130056 | ENST00000528610.5 | 7     | protein coding  | 1179        | Isoform 4 | -              | NP_001123528 | 257         | 28.56    | 4.81 |
| EEF1D-223 (EEF1D-004) | Var.10  | NM_001317743 | ENST00000528610.5 | 7     | protein coding  | 1176        | Isoform 4 | -              | NP_001304672 | 257         | 28.56    | 4.81 |
| EEF1D-211 (EEF1D-005) | Var.11  | NM_001330646 | ENST00000521001.5 | 7     | protein coding  | 1386        | Isoform 4 | -              | NP_001317575 | 257         | 28.56    | 4.81 |
| EEF1D-246 (EEF1D-007) |       |             | ENST00000532741.5 | 8     | protein coding  | 2387        | -        | -              | -           | 697         | -        | -    |
| EEF1D-256 |       |             | ENST00000618139.2 | 10    | protein coding  | 2238        | -        | -              | -           | 631         | -        | -    |
| EEF1D-232 (EEF1D-017) |       |             | ENST00000530445.5 | 5     | protein coding  | 1217        | -        | -              | -           | 166         | -        | -    |
| EEF1D-253 (EEF1D-048) |       |             | ENST00000534380.5 | 8     | protein coding  | 1001        | -        | -              | -           | 261         | -        | -    |
| EEF1D-256 (EEF1D-040) |       |             | ENST00000526710.1 | 1     | protein coding  | 996         | -        | -              | -           | 300         | -        | -    |
| EEF1D-239 (EEF1D-034) |       |             | ENST00000531670.5 | 3     | protein coding  | 926         | -        | -              | -           | 179         | -        | -    |
| EEF1D-230 (EEF1D-032) |       |             | ENST00000530191.5 | 5     | protein coding  | 853         | -        | -              | -           | 204         | -        | -    |
| EEF1D-247 |       |             | ENST00000533204.5 | 7     | protein coding  | 842         | -        | -              | -           | 204         | -        | -    |
| Protein ID | Description | Transcript ID | Start | End | Protein Coding | Score | Description |
|------------|-------------|---------------|-------|-----|----------------|-------|-------------|
| EEF1D-238  | Eukaryotic translation elongation factor 1 delta | ENST0000053 1621.5 | 7    | 840 | protein coding | 238   | -           |
| EEF1D-208  | Eukaryotic translation elongation factor 1 delta | ENST0000052 4883.1 | 2    | 828 | protein coding | 180   | -           |
| EEF1D-237  | Eukaryotic translation elongation factor 1 delta | ENST0000053 1281.1 | 2    | 813 | protein coding | 257   | -           |
| EEF1D-244  | Eukaryotic translation elongation factor 1 delta | ENST0000053 2543.1 | 2    | 791 | protein coding | 39    | -           |
| EEF1D-236  | Eukaryotic translation elongation factor 1 delta | ENST0000053 1218.5 | 7    | 787 | protein coding | 198   | -           |
| EEF1D-215  | Eukaryotic translation elongation factor 1 delta | ENST0000052 6340.5 | 6    | 770 | protein coding | 63    | -           |
| EEF1D-245  | Eukaryotic translation elongation factor 1 delta | ENST0000053 2596.5 | 3    | 761 | protein coding | 190   | -           |
| EEF1D-248  | Eukaryotic translation elongation factor 1 delta | ENST0000053 3494.5 | 7    | 758 | protein coding | 168   | -           |
| EEF1D-234  | Eukaryotic translation elongation factor 1 delta | ENST0000053 0616.5 | 6    | 749 | protein coding | 210   | -           |
| EEF1D-249  | Eukaryotic translation elongation factor 1 delta | ENST0000053 3749.5 | 5    | 633 | protein coding | 137   | -           |
| EEF1D-252  | Eukaryotic translation elongation factor 1 delta | ENST0000053 4377.5 | 5    | 617 | protein coding | 187   | -           |
| EEF1D-233  | Eukaryotic translation elongation factor 1 delta | ENST0000053 0545.5 | 3    | 616 | protein coding | 84    | -           |
| EEF1D-241  | Eukaryotic translation elongation factor 1 delta | ENST0000053 1931.1 | 2    | 614 | protein coding | 35    | -           |
| EEF1D-210  | Eukaryotic translation elongation factor 1 delta | ENST0000052 5223.1 | 2    | 610 | protein coding | 39    | -           |
| EEF1D-228  | Eukaryotic translation elongation factor 1 delta | ENST0000052 9832.5 | 3    | 600 | protein coding | 146   | -           |
| EEF1D-231  | Eukaryotic translation elongation factor 1 delta | ENST0000053 0306.5 | 3    | 583 | protein coding | 129   | -           |
| EEF1D-211 (EEF1D-031) | - | - | ENST0000052 5261.5 | 3 | protein coding | 559 | - | - | 81 | - | - |
| EEF1D-220 (EEF1D-026) | - | - | ENST0000052 8303.5 | 4 | protein coding | 558 | - | - | 21 | - | - |
| EEF1D-255 (EEF1D-029) | - | - | ENST0000053 4804.5 | 4 | protein coding | 555 | - | - | 68 | - | - |
| EEF1D-222 (EEF1D-036) | - | - | ENST0000052 8519.1 | 2 | protein coding | 553 | - | - | 157 | - | - |
| EEF1D-254 (EEF1D-030) | - | - | ENST0000053 4475.5 | 4 | protein coding | 538 | - | - | 31 | - | - |
| EEF1D-214 (EEF1D-038) | - | - | ENST0000052 6135.5 | 3 | protein coding | 535 | - | - | 53 | - | - |
| EEF1D-229 (EEF1D-014) | - | - | ENST0000053 0109.5 | 3 | protein coding | 533 | - | - | 156 | - | - |
| EEF1D-242 (EEF1D-021) | - | - | ENST0000053 1953.5 | 3 | protein coding | 506 | - | - | 49 | - | - |
| EEF1D-226 (EEF1D-019) | - | - | ENST0000052 9516.5 | 6 | protein coding | 473 | - | - | 139 | - | - |
| EEF1D-227 (EEF1D-015) | - | - | ENST0000052 9576.5 | 3 | protein coding | 424 | - | - | 119 | - | - |
| EEF1D-243 (EEF1D-016) | - | - | ENST0000053 2400.1 | 4 | protein coding | 419 | - | - | 99 | - | - |
| EEF1D-213 (EEF1D-022) | - | - | ENST0000052 6133.1 | 2 | protein coding | 367 | - | - | 36 | - | - |
| EEF1D-209 (EEF1D-044) | - | - | ENST0000052 4900.1 | 3 | protein coding | 343 | - | - | 62 | - | - |
| EEF1D-221 (EEF1D-013) | - | - | ENST0000052 8382.1 | 3 | protein coding | 308 | - | - | 36 | - | - |
| EEF1D-206 | - | - | ENST0000052 4397.5 | 8 | nonsense md | 957 | - | - | - | - | - |
| EEF1D-224 | - | - | ENST0000052 9007.5 | 8 | nonsense md | 861 | - | - | - | - | - |
| EEF1D-250 | - | - | ENST0000053 3833.5 | 7 | nonsense md | 831 | - | - | - | - | - |
**DNA/RNA**

**Description**

EEF1D (Eukaryotic Translation Elongation Factor 1 delta) is a protein-coding gene that starts at 143,579,722 nt and ends at 143,597,675 nt from pter. It has a length of 17,954 bp and the current reference sequence is NC_000008.11.

It is proximal to the NAPRT (nicotinate phosphoribosyl-transferase domain containing 1) gene and TIGD5 (tigger transposable element derived 5) gene. Around the genomic locus of EEF1D there are different promoter or enhancer transcriptional elements.

Two strong of these elements are closer to the sequence of EEF1D gene and are located at +1.6 kb and at -1.2 kb respectively.

**Transcription**

Several alternative splicing transcript variants for EEF1D were observed and they encode multiple eEF1D isoforms. Their main characteristics are reported in Table 1. The main reference sequence is NM_032378.5 that corresponds to the variant 1 of EEF1D mRNA, alias EEF1D-205 or EEF1D-001, and it is 2,473 bp long. The 5'UTR counts 459 nt, the CDS is extended from 460 to 2,403 nt, while the 3'UTR covers the last 70 nt.

**Pseudogene**

According to Entrez Gene, the analysis of the human genome revealed the presence of several pseudogenes for EEF1D (Table 2) classified as processed pseudogenes and probably originated by retrotransposition.

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.

Little more characterized are EEF1DP3 and EEF1DP4 pseudogenes respect the others. What is known is that these two pseudogenes are probably involved in human cancers or in other diseases. Especially EEF1DP3 was found in some genomic rearrangements with the formation of hybrid genes among which the most studied is EEF1DP3/FRY (Kim et al., 2015).

**Protein**

**Description**

The eukaryotic translation elongation factor 1 delta (alias eEF1D, eEF1delta; eEF1Bdelta;) is a subunit of the macromolecular eukaryotic translation elongation factor-1 complex (alias eEF1, also called eEF1H), a high-molecular-weight form made up of an aggregation of different protein subunits: EEF1A (alias eEF1α), EEF1B2 (alias eEF1B, eEF1β, eEF1B2), EEF1G (alias eEF1γ, heEF1γ, eEF1βγ), EEF1D and valyl t-RNA synthetase (VARS).

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.

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 mediated the GTP hydrolysis. Thus eEF1BGD-complex acts as a guanine nucleotide exchange factor (GEF) regenerating eEF1A-GTP for the successive elongation cycle.

The physiological role of eEF1D in the translation context is still not well defined, however eEF1D seems to strictly collaborate with eEF1B 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).
### EEF1D (eukaryotic translation elongation factor 1 delta)

**Cristiano L.**

| Gene | Gene name | Gene ID | RefSeq | Locus | Location | Start | End | Length (nt) | Main diseases/diagnosis | Reference |
|------|-----------|---------|--------|-------|----------|-------|-----|-------------|--------------------------|-----------|
| EEF1D P1 | EEF1D pseudogene 1 | 126037 | NC_000019.10 | Chromosome 19 | 19p13.1 | 14070325 | 14071304 | 980 | Large B-cell lymphoma (?) | - |
| | | | | | | | | | Myeloid leukemia (?) | - |
| EEF1D P2 | EEF1D pseudogene 2 | 442429 | NC_000009.12 | Chromosome 9 | 9q22.31 | 92836766 | 92837741 | 976 | Melanoma (?) | - |
| | | | | | | | | | Prostate carcinoma | Erho et al., 2012 |
| | | | | | | | | | Breast carcinoma | Kim et al., 2015 |
| | | | | | | | | | Ankylosing spondylitis | Shahba et al., 2018 |
| | | | | | | | | | Melanoma (?) | - |
| | | | | | | | | | Non-small cell lung cancer (?) | - |
| | | | | | | | | | Multiple sclerosis (?) | - |
| | | | | | | | | | Large B-cell lymphoma cell lines (SUDHL4, Toledo, OCI-Ly3) (?) | - |
| | | | | | | | | | Lung adenocarcinoma (?) | - |
| | | | | | | | | | Epidermolysis Bullosa Simplex (?) | - |
| EEF1D P3 | EEF1D pseudogene 3 | 196549 | NC_000013.11 | Chromosome 13 | 13q13.1 | 31846783 | 31959584 | 112802 | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| EEF1D P4 | EEF1D pseudogene 4 | 442325 | NC_000007.14 | Chromosome 7 | 7q11.21 | 64862951 | 64864450 | 1500 | Glioma (?) | - |
| | | | | | | | | | | Breast carcinoma (?) | - |
| | | | | | | | | | | Primary myelofibrosis (?) | - |
| | | | | | | | | | | Osteosarcoma (?) | - |
| EEF1D P5 | EEF1D pseudogene 5 | 442258 | NC_000006.12 | Chromosome 6 | 6q22.33 | 128580065 | 128580952 | 888 | Breast carcinoma | Stefansson et al., 2011 |
| EEF1D P6 | EEF1D pseudogene 6 | 644357 | NC_000001.11 | Chromosome 1 | 1p36.32 | 4175463 | 4175899 | 437 | - | - |
| EEF1D P7 | EEF1D pseudogene 7 | 100422656 | NC_000017.11 | Chromosome 17 | 17q23.3 | 63636601 | 63637110 | 510 | - | - |
| EEF1D P8 | EEF1D pseudogene 8 | 283236 | NC_000011.10 | Chromosome 11 | 11q12.3 | 62169219 | 62169827 | 609 | - | - |

**Table 2 EEF1D pseudogenes** (reworked from https://www.ncbi.nlm.nih.gov/gene/1937; https://www.targetvalidation.org; https://www.ncbi.nlm.nih.gov/geoprofiles/) [ (?) ] uncertain; [ - ] no reference

There are known four isoforms produced by alternative splicing: the isoform 1 (RefSeq NP_001123525 or NP_115754), also called eEF1DL or eEF1BdeltaL, is the longest isoform that also has been chosen as the canonical sequence and it is formed by 647 residues.

It is found in the eEF1H protein complex and it shows many domains: in the carboxyl half terminal there are an acidic region and an EF-1 guanine nucleotide exchange domain (EF1-GNE domain / GEF) while in the amino half terminal there are a highly-conserved leucine-rich zipper-like region (aa 184-225), a basic region (aa 272-294) and a nuclear localization signal (NLS)(Kaitsuka et al., 2015; Kaitsuka et al., 2011; Sanders et al., 1993). The basic region seems to be involved in DNA binding while the leucine zipper region may be a protein interaction domain.

However, the exact functional role of these regions is unclear (Kaitsuka et al., 2015).
The N-terminal domain of eEF1D interacts with the NT-eEF1G domain of eEF1G (Cao et al., 2014; Mansilla et al., 2002; Janssen et al., 1994) but there are no interactions between eEF1D and eEF1B (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).

The long isoform of eEF1D (eEF1DL) interacts with HSF1 and NFE2L2 (NRF2) proteins into the nucleus (Kaitsuka et al., 2011; https://www.genecards.org) and regulates induction of heat-shock-responsive genes, such as HSPA6, CRYAB, DNAJB1 and HO-1, through the association with the heat shock transcription factors and with a direct DNA-binding at heat shock promoter elements (HSE) (Kaitsuka et al., 2015; Kaitsuka et al., 2011; https://www.uniprot.org/uniprot/P29692).

The isoform 2, with 281 amino acids, is smaller and, as the isoform 1, it is a multi-domain protein which consists of three main domains: from the amino to carboxyl half terminal there are an N-terminal leucine zipper domain, a C-terminal acidic region and a C-terminal domain that shows GDP/GTP exchange activity (GEF) (Kaitsuka et al., 2015; Kaitsuka et al., 2011). The roles of the isoform 4 and isoform 5 are still undefined.

All isoforms have many interaction surface points with the eukaryotic translation elongation factor 1 alpha (eEF1A) protein (https://www.ncbi.nlm.nih.gov/protein/NP_001123525) and interact with the valyl -tRNA synthetase (Val-RS) (Le Sourd et al., 2006; Bec et al., 1994).

EEF1D interacts with SIAH1, an E3 ubiquitin protein ligase involved in the regulation of cell cycle, tumorigenesis and also in the initiation of neurodegenerative diseases. Is reported that the overexpression of EEF1D is linked with an increase in SIAH-1 levels due to the inhibition of its autoubiquitination and thus of its degradation (Wu et al., 2011).

In addition, EEF1D is an interaction partner of kinectin that function as the membrane anchor for EEF1D on the endoplasmic reticulum (Ong et al., 2003).

Post-translational modifications. Some post-translational modifications are observed, such as phosphorylation, acetylation and succinylation (https://www.ncbi.nlm.nih.gov). eEF1D can be hyperphosphorylated and the phosphorylations are made by some protein kinases, including casein kinase 2 (Gyenis et al., 2011; Browne and Proud, 2002) and cyclin-dependent kinase 1 (CDK1) (Kawaguchi et al., 2003). In particular, CDK1 phosphorlates EEF1D at Ser-133 (Kawaguchi et al., 2003).

In addition, eEF1D can be found hyperphosphorylated by viral protein kinases after alpha-, beta-, and gammaherpesviruses infections (Kawaguchi et al., 2003).
**Expression**
eEF1D is expressed widely in human tissues and high levels of protein are reported in bone marrow stromal cells (https://www.geneCards.org). The long form of eEF1D (eEF1DL) is found to be highly expressed in brain and testis (Kaitsuka et al., 2011).

**Localisation**
eEF1D is located mostly in the cytoplasm but it is also found in the nucleus, especially its long form (Kaitsuka et al., 2011), and also in relation with the endoplasmic reticulum (Sanders et al., 1996).
**Function**

eEF1D has shown to cover an important role in normal brain functioning and development and some experiments on KO mice lacking the expression of its long isoform (eEF1DL) have done emerging its implication for normal physiology of the brain. In fact, in these KO mice were observed severe seizures in response to loud sounds and also significant brain structure alterations such as a decrease in brain weight, atrophy of the hippocampus and midbrain and a reduction of cortical layer thickness (Kaitsuka et al., 2018).

eEF1D shows canonical functions and multiple non-canonical roles (moonlighting roles) inside the cell. **Canonical function:** eEF1D binds to eEF1B and eEF1G in the eEF1BDG macromolecular complex and contributes to catalyze the exchange of GDP/GTP for eEF1A during the translation elongation cycle.

**Non-canonical roles:** eEF1D seems to have other functions inside the cell besides its involvement in translation. At least two other non-canonical roles have been detected, i.e. its role as a transcriptional factor and its involvement in the stress response. These roles are closely connected to each other. In fact, it was demonstrated that heat shock induces the splicing-dependent expression change from the short eEF1D isoform (isoform 2) to the eEF1DL long isoform (isoform 1)(Kaitsuka et al., 2015). The silencing of eEF1DL inhibits the stress responses suggesting its role in the modulation of stress response in the cell (Hensen et al., 2013). In fact, EEF1D is a heat shock transcription factor that can bind to the heat shock element (HSE) in the promoter of the HSPA6 and HO-1 genes and activate their transcription (Kaitsuka et al., 2011).

**Homology**
eEF1D is highly conserved and its homology between the species is reported in Table.3

| Organism       | Species          | Symbol | DNA Identity (%) | PROT Identity (%) |
|----------------|------------------|--------|------------------|-------------------|
| Human          | H.sapiens        | EEF1D  | 100              | 100               |
| Chimpanzee     | P.troglodytes    | EEF1D  | 99.6             | 99.3              |
| Macaco         | M.mulatta        | EEF1D  | 95.7             | 95.7              |
| Wolf           | C.lupus          | LOC475115 | 85.2         | 85.5              |
| Cattle         | B.taurus         | EEF1D  | 92.1             | 88.3              |
| Mouse          | M.musculus       | Eef1d  | 85.2             | 84.3              |
| Rat            | R.norvegicus     | Eef1d  | 86.8             | 84.5              |
| Chicken        | G.gallus         | EEF1D  | 57.7             | 61.6              |
| Xenopus tropical| X.tropicalis     | eef1d  | 67.8             | 69.7              |
| Zebrafish      | D.rerio          | eef1db | 65.8             | 66.3              |
| Fruit fly      | D.melanogaster   | eEF1delta | 55.6           | 57.0              |

**Mutations**

**Note**
A great number of mutations in the genomic sequence and in the amino acid sequence for EEF1D 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 fusion genes.

Figure 5. Circos plot for fusion events involving eEF1D. The picture summarizes all fusion events concerning eEF1D and its fusion partners (from https://fusionhub.persistent.co.in/search_genewise.html).

**Implicated in**

**Top note**
EEF1D is a cellular proto-oncogene (Joseph et al., 2002) and it is involved in many and heterogeneous genomic translocations in different kind of tumors with also the creation of numerous fusion gene (Table.4). An increase of its expression level has an oncogenic potential with resulting in cell transformation (Lei et al., 2002) and this was observed in many cancer types (Hassan et al., 2018). In addition, the use of antisense mRNA to block EEF1D translation can revert its oncogenic potential (Lei et al., 2002). These data could suggest its role as a potential diagnostic indicator and prognostic marker in tumors (Joseph et al., 2002).
| Name                  | 5' end       | 3' end       | Loc1       | Loc2       | Description         | Type                      | Disease | Organ   | Code | Ref.       |
|-----------------------|--------------|--------------|------------|------------|---------------------|---------------------------|---------|---------|------|------------|
| ACSF2/EEF1D           | ACSF2        | EEF1D        | 17q21.33   | 8q24.3     | t(8;17)(q24;q21)    | Translocation             | (?)     | -       | -    |            |
| AGO2/EEF1D            | AGO2         | EEF1D        | 8q24.3     | 8q24.3     | t(8;8)(q24;q24)     | Fusion gene               | (?)     | -       | -    |            |
| ASAPI/EEF1D           | ASAPI        | EEF1D        | 8q24.21    | 8q24.3     | t(8;8)(q24;q24)     | Fusion gene               | (?)     | -       | -    |            |
| ASB8/EEF1D            | ASB8         | EEF1D        | 12q13.11   | 8q24.3     | t(8;12)(q24;q13)    | Translocation             | (?)     | -       | -    |            |
| ATXN1/EEF1D           | ATXN1        | EEF1D        | 6p22.3     | 8q24.3     | t(6;8)(p22;q24)     | Translocation             | (?)     | -       | -    |            |
| B2M/EEF1D             | B2M          | EEF1D        | 15q21.3    | 8q24.3     | t(8;15)(q24;q21)    | Translocation             | (?)     | -       | -    |            |
| BOD1L1/EEF1D          | BOD1L1       | EEF1D        | 4p15.33    | 8q24.3     | t(4;8)(p15;q24)     | Translocation             | (?)     | -       | -    |            |
| C19ORF10/EEF1D        | C19ORF10     | EEF1D        | 19p13.3    | 8q24.3     | t(8;19)(q24;p13)    | Translocation             | (?)     | -       | -    |            |
| CAPN15/EEF1D          | CAPN15       | EEF1D        | 16p13.3    | 8q24.3     | t(8;16)(q24;p13)    | Translocation             | (?)     | -       | -    |            |
| CBX7/EEF1D            | CBX7         | EEF1D        | 22q13.1    | 8q24.3     | t(8;22)(q24;q13)    | Translocation             | (?)     | -       | -    |            |
| CHN2/EEF1D            | CHN2         | EEF1D        | 7p14.3     | 8q24.3     | t(7;8)(p14;q24)     | Translocation             | (?)     | -       | -    |            |
| CLPS/EEF1D            | CLPS         | EEF1D        | 6p21.31    | 8q24.3     | t(6;8)(p21;q24)     | Translocation             | (?)     | -       | -    |            |
| CLTB/EEF1D            | CLTB         | EEF1D        | 5q35.2     | 8q24.3     | t(5;8)(q35;q24)     | Translocation             | (?)     | -       | -    |            |
| CMSS1/EEF1D           | CMSS1        | EEF1D        | 3q12.1     | 8q24.3     | t(3;8)(q12;q24)     | Translocation             | (?)     | -       | -    |            |
| COLGALT1/EEF1D        | COLGALT1     | EEF1D        | 19p13.11   | 8q24.3     | t(8;19)(q24;p13)    | Translocation             | (?)     | -       | -    |            |
| CRY1/EEF1D            | CRY1         | EEF1D        | 12q23.3    | 8q24.3     | t(8;12)(q24;q23)    | Translocation             | (?)     | -       | -    |            |
| CTDPI/EEF1D           | CTDPI        | EEF1D        | 18q23      | 8q24.3     | t(8;18)(q24;q23)    | Translocation             | (?)     | -       | -    |            |
| CTTN/EEF1D            | CTTN         | EEF1D        | 11q13.3    | 8q24.3     | t(8;11)(q24;q13)    | Translocation             | (?)     | -       | -    |            |
| DDX23/EEF1D           | DDX23        | EEF1D        | 12q13.12   | 8q24.3     | t(8;12)(q24;q13)    | Translocation             | (?)     | -       | -    |            |
| DDX5/EEF1D            | DDX5         | EEF1D        | 17q23.3    | 8q24.3     | t(8;17)(q24;q23)    | Translocation             | (?)     | -       | -    |            |
| EEF1D/ANKRD19P        | EEF1D        | ANKRD19P     | 8q24.3     | 9q22.31    | t(8;9)(q24;q22)     | Translocation Adenocarcinoma | Stomach | STD     | MCFI0 | Babice anu et al.,2016 |
| EEF1D/CALR            | EEF1D        | CALR         | 8q24.3     | 19p13.1    | t(8;19)(q24;p13)    | Translocation - Cell line | -       | -       | -    | Babice anu et al.,2016 |
| EEF1D/CKB             | EEF1D        | CKB          | 8q24.3     | 14q32.33   | t(8;14)(q24;q32)    | Translocation             | (?)     | -       | -    |            |
| EEF1D/DUSP28          | EEF1D        | DUSP28       | 8q24.3     | 2q37.3     | t(2;8)(q37;q24)     | Translocation             | (?)     | -       | -    |            |
| EEF1D/EEF1DP1         | EEF1D        | EEF1DP1      | 8q24.3     | 19p13.1    | t(8;19)(p24;13)    | Translocation             | (?)     | -       | -    |            |
| EEF1D/EEF1DP5         | EEF1D        | EEF1DP5      | 8q24.3     | 6q22.33    | t(6;8)(q22;q24)     | Translocation             | (?)     | -       | -    |            |
| EEF1D/GSDMB           | EEF1D        | GSDMB        | 8q24.3     | 17q12      | t(8;17)(q24;q12)    | Translocation             | (?)     | -       | -    |            |
| EEF1D/KRT4            | EEF1D        | KRT4         | 8q24.3     | 12q13.13   | t(8;12)(q24;q13)    | Translocation - Esophagus | -       | -       | -    | Babice anu et al.,2016 |
| EEF1D/KRT5            | EEF1D        | KRT5         | 8q24.3     | 12q13.13   | t(8;12)(q24;q13)    | Translocation Squamous Cell Carcinoma | Head and Neck | HNSC | Klijn et al.,2015 |
| EEF1D/KRT6A           | EEF1D        | KRT6A        | 8q24.3     | 12q13.13   | t(8;12)(q24;q13)    | Translocation Squamous Cell Carcinoma | Head and Neck | HNSC | Klijn et al.,2015 |
| EEF1D/KRT10           | EEF1D        | KRT10        | 8q24.3     | 17q21.2    | t(8;17)(q24;q21)    | Translocation - Skin      | -       | -       | -    | Babice anu et al.,2016 |
| EEF1D/KRT14           | EEF1D        | KRT14        | 8q24.3     | 17q21.2    | t(8;17)(q24;q21)    | Translocation Squamous Cell Carcinoma | Uterine cervix | CESC | Alaeri-Mahabadi et al.,2016 |
| EEF1D       | LSP1      | LSP1     | 8q24.3 | 11p15, 5 | t(8;11)(q24;p15) | Translocation (?) | - | - | - |
|-------------|-----------|----------|--------|----------|-----------------|------------------|---|---|---|
| EEF1D       | MAN2C1    | MAN2C1   | 8q24.3 | 15q24.2  | t(8;15)(q24;q24) | Translocation (?) | - | - | - |
| EEF1D       | NAPRT     | NAPRT    | 8q24.3 | 8q24.3   | Readthrough transcription | Fusion gene | - | - | - |
| EEF1D       | NFKB1B    | NFKB1B   | 8q24.3 | 19q13.2  | t(8;19)(q24;q13) | Translocation (?) | - | - | - |
| EEF1D       | PARK2     | PARK2    | 8q24.3 | 6q26     | t(6;8)(q26;q24) | Translocation (?) | - | - | - |
| EEF1D       | PNLIP     | PNLIP    | 8q24.3 | 10q25.3  | t(8;10)(q24;q25) | Translocation (?) | - | - | - |
| EEF1D       | PUFS60    | PUFS60   | 8q24.3 | 8q24.3   | t(8;8)(q24;q24) | Fusion gene     | - | - | - |
| EEF1D       | RNF2      | RNF2     | 8q24.3 | 1q25.3   | t(1;8)(q24;q13) | Translocation (?) | - | - | - |
| EEF1D       | RYR1      | RYR1     | 8q24.3 | 19q13.2  | t(8;19)(q24;q13) | Translocation (?) | - | - | - |
| EEF1D       | SDC4      | SDC4     | 8q24.3 | 20q13.12 | t(8;20)(q24;q13) | Translocation     | - | - | - |
| EEF1D       | SFTPC     | SFTPC    | 8q24.3 | 8p21.3   | t(8;8)(q24;p21) | Fusion gene     | (?) | - | - |
| EEF1D       | SPIB      | SPIB     | 8q24.3 | 19q13.33 | t(8;19)(q24;q13) | Translocation     | - | - | - |
| EEF1D       | TG        | TG       | 8q24.3 | 8q24.22  | t(8;8)(q24;q24) | Fusion gene      | - | - | - |
| EEF1D       | TSNARE1   | TSNARE1  | 8q24.3 | 8q24.3   | t(8;8)(q24;q24) | Fusion gene      | - | - | - |
| EEF1D       | TSTA3     | TSTA3    | 8q24.3 | 8q24.3   | t(8;8)(q24;q24) | Fusion gene      | - | - | - |
| EEF1D       | UBE2L3    | UBE2L3   | 8q24.3 | 22q11.2  | t(8;22)(q24;q11) | Translocation     | (?) | - | - |
| EEF1D       | ZBTB7A    | ZBTB7A   | 8q24.3 | 19p13.3  | t(8;19)(q24;p13) | Translocation     | (?) | - | - |
| EEF1D       | ZC3H3     | ZC3H3    | 8q24.3 | 8q24.3   | t(8;8)(q24;q24) | Fusion gene     | (?) | - | - |
| FAM104A/EEF1D | FAM104A  | FAM104A  | 17q25.1| 8q24.3   | t(8;17)(q24;q25) | Translocation     | - | - | - |
| FAM222B/EEF1D | FAM222B  | FAM222B  | 17q11.2| 8q24.3   | t(8;17)(q24;q11) | Translocation     | (?) | - | - |
| FLCN/EEF1D  | FLCN      | FLCN     | 17p11.2| 8q24.3   | t(8;17)(q24;p11) | Translocation     | (?) | - | - |
| HDAC5/EEF1D | HDAC5     | HDAC5    | 17q21.3| 8q24.3   | t(8;17)(q24;q21) | Translocation     | - | - | - |
| Locus | Gene | Chromosome | Translocation | Cell line | OVTO KO | Reference |
|-------|------|------------|---------------|-----------|--------|-----------|
| HIF1A/EEF1D | HIF1A | 1q23.2 | 8q24.3 | Translocation | (?) | - | - |
| HIF3A/EEF1D | HIF3A | 1q13.32 | 8q24.3 | Translocation | (?) | - | - |
| HRH1/EEF1D | HRH1 | 3p25.3 | 8q24.3 | Translocation | (?) | - | - |
| IGL5/EEF1D | IGL5 | 22q11.22 | 8q24.3 | Translocation | (?) | - | - |
| IL4R/EEF1D | IL4R | 16p12.1 | 8q24.3 | Translocation | (?) | - | - |
| IRF3/EEF1D | IRF3 | 19q13.33 | 8q24.3 | Translocation | (?) | - | - |
| KRT13/EEF1D | KRT13 | 17q21.2 | 8q24.3 | Translocation | (?) | - | - |
| LGR6/EEF1D | LGR6 | 1q32.1 | 8q24.3 | Translocation | (?) | - | - |
| METRNL/EEF1D | METRNL | 17q25.3 | 8q24.3 | Translocation | (?) | - | - |
| MGRN1/EEF1D | MGRN1 | 16p13.3 | 8q24.3 | Translocation | (?) | - | - |
| NCAM1/EEF1D | NCAM1 | 11q23.2 | 8q24.3 | Translocation | (?) | - | - |
| NID1/EEF1D | NID1 | 1q42.3 | 8q24.3 | Translocation | (?) | - | - |
| OAZ1/EEF1D | OAZ1 | 19p13.3 | 8q24.3 | Translocation | (?) | - | - |
| OGG1/EEF1D | OGG1 | 3p25.3 | 8q24.3 | Translocation | (?) | - | - |
| OPLAH/EEF1D | OPLAH | 8q24.3 | 8q24.3 | Fusion gene | Adenocarcinoma | Stomach | STAD |
| PL2G6/EEF1D | PL2G6 | 22q13.1 | 8q24.3 | Translocation | Adenocarcinoma | Breast | BRCA |
| PLINS/EEF1D | PLINS | 19p13.3 | 8q24.3 | Translocation | (?) | - | - |
| PMF1/EEF1D | PMF1 | 1q22 | 8q24.3 | Translocation | - | Esophagus | - |
| POLI/EEF1D | POLI | 18q21.2 | 8q24.3 | Translocation | (?) | - | - |
| POU2F1/EEF1D | POU2F1 | 1q24.2 | 8q24.3 | Translocation | (?) | - | - |
| PSMB7/EEF1D | PSMB7 | 9q33.3 | 8q24.3 | Translocation | (?) | - | - |
| PTPA3/EEF1D | PTPA3 | 8q24.3 | 8q24.3 | Fusion gene | Adenocarcinoma | - | - |
| RAB3GAP1/EEF1D | RAB3GAP1 | 2q21.3 | 8q24.3 | Translocation | (?) | - | - |
| RAB40C/EEF1D | RAB40C | 16p13.3 | 8q24.3 | Translocation | (?) | - | - |
| RCC1/EEF1D | RCC1 | 1p35.3 | 8q24.3 | Translocation | (?) | - | - |
| RILPL2/EEF1D | RILPL2 | 12q24.31 | 8q24.3 | Translocation | (?) | - | - |
| RNF14/EEF1D | RNF14 | 5q31.3 | 8q24.3 | Translocation | (?) | - | - |
| RPL30/EEF1D | RPL30 | 8q22.2 | 8q24.3 | Fusion gene | Adenocarcinoma | Breast | BRCA |
| RPL36AL/EEF1D | RPL36AL | 14q21.3 | 8q24.3 | Fusion gene | (?) | - | - |
| RPS9/EEF1D | RPS9 | 19q13.42 | 8q24.3 | Translocation | Burkit lymphoma | Blood | BL |
| RSAD1/EEF1D | RSAD1 | 17q21.33 | 8q24.3 | Translocation | (?) | - | - |
| SCYLI/EEF1D | SCYLI | 8q24.3 | 8q24.3 | Fusion gene | Serous Cystadenocarcinoma | Ovary | OVSC |

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**Amyotrophic lateral sclerosis (ALS)**

EEF1D is a potential candidate gene associated with ALS (Wain et al., 2009) but more studies are needed to clarify its effective contribution.

**Bladder cancer**

There are no data about EEF1D expression alterations in bladder cancer. However, it was reported the translocation t(1;8)(q22;q24) PMF1/EEF1D (Klijn et al., 2015).

**Hybrid/Mutated gene**

The t(1;8)(q22;q24) PMF1/EEF1D was detected in bladder transitional-cell carcinoma RT4 cell line (Klijn et al., 2015). This rearrangement is originated by the fusion of "polyamine modulated factor 1" (PMF1) gene at 5’-end with EEF1D gene at 3’-end. There are no data about its chimeric transcript or protein and the role of this genomic alteration is poorly understood.

**Brain and central nervous system (CNS) cancers**

EEF1D is found to be overexpressed in astrocytoma and in glioblastoma samples and also in low-risk patients. This may associate its expression to favourable survival outcome (Hassan et al., 2018).

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| SH2B2/EEF1D | SH2B2 | EEF1D | 7q22.1 | 8q24.3 | t(7;8)(q22;q24) | Translocation | Burkitt lymphoma | Blood | BL |
|-------------|-------|-------|--------|--------|----------------|---------------|-----------------|-------|----|
| SMYD3/EEF1D | SMYD3 | EEF1D | 1q44   | 8q24.3 | t(1;8)(q44;q24) | Translocation | (?)             | -     | -  |
| SORB1/EEF1D | SORB1 | EEF1D | 10q24.1| 8q24.3 | t(8;10)(q24;q24) | Translocation | (?)             | -     | -  |
| SORT1 /EEF1D | SORT1 | EEF1D | 1p13.3 | 8q24.3 | t(1;8)(p13;q24) | Translocation | (?)             | -     | -  |
| SPIB/EEF1D  | SPIB | EEF1D | 19q13.3| 8q24.3 | t(8;19)(q24;q13) | Translocation | Burkitt lymphoma | Blood | BL |
| ST3GAL1 /EEF1D | ST3GAL1 | EEF1D | 8q24.22| 8q24.3 | t(8;8)(q24;q24) | Fusion gene   | (?)             | -     | -  |
| TATDN1 /EEF1D | TATDN1 | EEF1D | 8q24.13| 8q24.3 | t(8;8)(q24;q24) | Fusion gene   | Adenocarcinoma | Breast | BRCA |
| TMEM99 /EEF1D | TMEM99 | EEF1D | 17q21.2| 8q24.3 | t(8;17)(q24;q21) | Translocation | (?)             | -     | -  |
| TMLHE /EEF1D | TMLHE | EEF1D | Xq28   | 8q24.3 | t(X;8)(q28;q24) | Translocation | (?)             | -     | -  |
| TOP2B /EEF1D | TOP2B | EEF1D | 3p24.2 | 8q24.3 | t(3;8)(p24;q24) | Translocation | (?)             | -     | -  |
| TP53I3 /EEF1D | TP53I3 | EEF1D | 2p23.3 | 8q24.3 | t(2;8)(p23;q24) | Translocation | (?)             | -     | -  |
| TP53TG5 /EEF1D | TP53TG5 | EEF1D | 20q13.12| 8q24.3 | t(8;20)(q24;q13) | Translocation | (?)             | -     | -  |
| TTC21B /EEF1D | TTC21B | EEF1D | 2q24.3 | 8q24.3 | t(2;8)(q24;q24) | Translocation | (?)             | -     | -  |
| TTLL3 /EEF1D | TTLL3 | EEF1D | 3p25.3 | 8q24.3 | t(3;8)(p25;q24) | Translocation | Carcinoma       | Esophagus | ESCA |
| UBA2P2 /EEF1D | UBA2P2 | EEF1D | 9p13.3 | 8q24.3 | t(8;9)(q24;p13) | Translocation | (?)             | -     | -  |
| UBE2G1 /EEF1D | UBE2G1 | EEF1D | 17p13.2| 8q24.3 | t(8;17)(q24;p13) | Translocation | (?)             | -     | -  |
| UFM1 /EEF1D  | UFM1 | EEF1D | 13q13.3| 8q24.3 | t(8;13)(q24;q13) | Translocation | Adenocarcinoma | Colon | COAD |
| XNR2 /EEF1D | XNR2 | EEF1D | 20p11.23| 8q24.3 | t(8;20)(q24;p11) | Translocation | (?)             | -     | -  |
| ZC3H3 /EEF1D | ZC3H3 | EEF1D | 8q24.3 | 8q24.3 | t(8;8)(q24;q24) | Fusion gene   | -                | Bone marrow | Babice et al., 2016 |
| ZG16B /EEF1D | ZG16B | EEF1D | 16p13.3| 8q24.3 | t(8;16)(q24;p13) | Translocation | (?)             | -     | -  |
| ZNF146 /EEF1D | ZNF146 | EEF1D | 19q13.12| 8q24.3 | t(8;19)(q24;q13) | Translocation | (?)             | -     | -  |
| ZNF232 /EEF1D | ZNF232 | EEF1D | 17p13.2| 8q24.3 | t(8;17)(q24;p13) | Translocation | (?)             | -     | -  |
| ZNF429 /EEF1D | ZNF429 | EEF1D | 19p12 | 8q24.3 | t(8;19)(q24;p12) | Translocation | (?)             | -     | -  |
| ZNF608 /EEF1D | ZNF608 | EEF1D | 5q23.2 | 8q24.3 | t(5;8)(q23;q24) | Translocation | (?)             | -     | -  |

**Table 4** EEF1D rearrangements: translocations and fusion genes (reworked from ps://www.ncbi.nlm.nih.gov/homologene; http://www.tumorfusions.org; https://cgap.nci.nih.gov/Chromosomes; http://quiver.archerdx.com; http://atlasgeneticsoncology.org//Bands/8q24.html#REFERENCES; https://fusionhub.persistent.co.in/home.html; https://ccsm.ut.edu/FusionGDB/index.html) [ (?) unknown; [ ] no reference]
Breast cancer

EEF1D is involved in breast cancer (Jurca et al., 2016). In fact, was detected an EEF1D gene copy number gain in BT483, EFM19, HCC1143, HCC1395, HCC1569, HCC1806, HCC1937, HCC2157, HCC2218, HDQ1, MDAMB436 and UACC893 breast cancer cell lines and in about 10% of breast invasive carcinoma donor samples (http://www.oasis-genomics.org/). EEF1D was found overexpressed in T-47, MCF-7, MDA-MB-361 and MDA-MB-453 breast cancer cell lines (Joseph et al., 2004). It is also overexpressed in breast cancer samples and this predicted worse relapse-free survival (RFS) in luminal A subtype patients and poor overall survival (OS) and RFS in basal subtype (Hassan et al., 2018).

Some authors have found an EEF1D downregulation in ER+/ER- cancer cell lines and in human breast cancer samples when high levels of bone morphogenetic protein-6 ( BMP6) are expressed (Yang et al., 2007). This seems to be linked with the prevention of eEF1D-induced breast cancer metastasis. In fact, EEF1D is a candidate protein marker of human brain metastasis in primary breast tumors (Sanz-Pamplona et al., 2011; van’t Veer et al., 2002). In addition, some fusion genes and genomic translocations were reported (https://fusionhub.persistent.co.in/home.html).

Hybrid/Mutated gene

The translocation t(8;22)(q24;q13) PLA2G6/EEF1D was found in breast carcinoma (BRCA) and consists with the fusion of ‘phospholipase A2 group VI’ (< CC: TXT: PLA2G6 ID: 45836>) gene at 5' end with EEF1D gene at 3' end. In addition, other uncharacterized and rare rearrangements due to the translocation t(8;8)(q24;q24) are reported, i.e. the RPL30 /EEF1D and TATDN1/EEF1D fusion genes (https://fusionhub.persistent.co.in/home.html). In particular, the t(8;8)(q24;q24) RPL30 /EEF1D brings to the formation of a transcript composed by the exons 1 to 3 of RPL30 joined with exons 2 to 7 of EEF1D (http://203.255.191.229:8080/chimerdbv31/chimers eq_link.cdb?gene_pair=RPL30_EEF1D), while the t(8;8)(q24;q24) TATDN1/EEF1D brings to the formation of a transcript composed by the exon 1 of TATDN1 joined with exons 2 to 7 of EEF1D (http://203.255.191.229:8080/chimerdbv31/chimers eq_link.cdb?gene_pair=TATDN1_EEF1D). Despite what has just been said, these genomic alterations are still poorly understood.

Chondrosarcoma

The human chondrosarcoma cells are able to respond to mechanical stimuli, like cellular stretching, with different phosphorylation events. Increase of phosphorylations impacts also on the EEF1D protein. It is unclearly the significance or the effect on the cell of these phosphorylations as also if these changes may affect the level or speed of protein synthesis (Pitti et al., 2008).

Colorectal cancer

It was detected an EEF1D gene copy number gain in LS123 and RKO colorectal cancer cell lines and in about 5% of colon adenocarcinoma donor samples (http://www.oasis-genomics.org/). In addition, EEF1D transcript is found to be significantly overexpressed (Hassan et al., 2018), especially in the right-sided colon cancer (RSCC) respect left-sided colon cancer (LSCC) samples (Shen et al., 2013). It was reported the translocation t(8;13)(q24;q13) UFM1/EEF1D (https://fusionhub.persistent.co.in/home.html).

Hybrid/Mutated gene

The t(8;13)(q24;q13) UFM1/EEF1D was found in colon adenocarcinoma. This rearrangement is originated by the fusion of ‘ubiquitin modifier 1’ ( UFM1) gene at 5'end with EEF1D gene at 3' end. There are no data about the respective chimeric transcript or protein and the role of this genomic alteration is unknown.

Gastric cancer

It was detected an EEF1D gene copy number gain in 2313287, LMSU, MKN1, SNU5, SNU216, SNU601 and SNU668 gastric cancer cell lines (http://www.oasis-genomics.org/) but it was found down-expressed in gastric cancer samples (Hassan et al., 2018). Some fusion genes and genomic translocation are reported (Klijn et al., 2015; https://fusionhub.persistent.co.in/home.html).

Hybrid/Mutated gene

The t(8;22)(q24;q11) IGLL5/EEF1D was found in gastric adenocarcinoma samples (Klijn et al., 2015) and consists by the fusion of ‘immunoglobulin lambda-like polypeptide 5' ( IGLL5) gene at 5'-end with EEF1D gene at 3' end. In addition, other uncharacterized and rare rearrangements are reported, i.e. OPLAH/EEF1D fusion gene and t(8;9)(q24;q24) EEF1D/ANKRD19P (https://fusionhub.persistent.co.in/home.html). In particular, the t(8;9)(q24;q24) RPL30 /EEF1D brings to the formation of a transcript composed by the exons 1 to 3 of RPL30 joined with exons 2 to 7 of EEF1D (http://203.255.191.229:8080/chimerdbv31/chimers eq_link.cdb?gene_pair=RPL30_EEF1D), while the t(8;9)(q24;q24) TATDN1/EEF1D brings to the formation of a transcript composed by the exon 1 of TATDN1 joined with exons 2 to 7 of EEF1D (http://203.255.191.229:8080/chimerdbv31/chimers eq_link.cdb?gene_pair=TATDN1_EEF1D). Despite what has just been said, these genomic alterations are still poorly understood.
**Head and neck squamous cell carcinoma (HNSC)**

EEF1D gene was found up-regulated in head and neck squamous cell carcinoma (HNSC) (Hassan et al., 2018; Han et al., 2009). In particular, Flores and colleagues (Flores et al., 2016) detected its overexpression in oral squamous cell carcinoma (OSCC) respect to oral healthy mucosa. It could have a critical role both in cell proliferation and in epithelial-mesenchymal transition (EMT). In fact, EEF1D knockdown shown a decrease in cell cycle rate and proliferation. Some fusion genes and genomic translocation are reported (Klijn et al., 2015).

In addition, EEF1D was found up-regulated in human laryngeal cancer (Peyvandi et al., 2018) and was found an intrachromosomal translocation with the formation of a chimeric fusion gene between EEF1D and NAPRT1 genes in laryngeal cancer (Tao et al., 2018).

**Hybrid/Mutated gene**

The t(8;12)(q24;q13) EEF1D/KRT5 and the t(8;12)(q24;q13) EEF1D/KRT6A were found in head and neck squamous cell carcinoma (HNSC) samples with the production of chimeric genes originated by the fusion of EEF1D at 5'-end with 'keratin 5' (KRT5) or 'keratin 6A' (KRT6A) genes at 3' end (Klijn et al., 2015). In addition, it was detected in laryngeal cancer the fusion gene 5'-EEF1D - 3' NAPRT (Tao et al., 2018) that is probably originated by readthrough transcription, a known mechanism into the cell (He et al., 2018). In fact, EEF1D and NAPRT1 are two neighboring genes on the same chromosome. The roles of all these genomic alterations are unknown.

**Kidney cancer**

High EEF1D mRNA levels were found in renal Wilms tumor and in clear cell carcinoma (Hassan et al., 2018). Some authors have detected missense mutations of EEF1D in papillary renal cell carcinoma (PRCC)(Liu et al., 2015). These mutations could contribute to the pathogenic mechanism for PRCC but more studies are necessary.

**Liver cancer**

EEF1D was found overexpressed in moderately to poorly differentiated (M/P-) primary human hepatocellular carcinoma (HCC) tissues (Hassan et al., 2018; Shuda et al., 2000). In addition, it was found the EEF1D/NAPRT fusion gene (https://fusionhub.persistent.co.in/home.html; https://ccsm.uth.edu/FusionGDB/index.html).

**Hybrid/Mutated gene**

The EEF1D/NAPRT fusion gene was found in hepatocellular carcinoma (LIHC). This rearrangement is originated by the fusion of EEF1D gene at 5'-end with 'nicotinate phosphoribosyltransferase domain containing 1' (NAPRT) gene at 3' end and it is probably due to readthrough transcription. In fact, EEF1D and NAPRT1 are two neighboring genes on the same chromosome. There are no data about the respective chimeric transcript or protein and the role of this genomic alteration is unknown.

**Lung cancer**

EEF1D was found to be down-expressed in lung carcinoid tumor and not shows any correlation with survival parameters (Hassan et al., 2018). It was also found down-expressed in adriamycin-resistant variants of DLKP squamous lung cancer cell line (Keenan et al., 2009). On the contrary, other authors found overexpression of EEF1D mRNA in some adenocarcinoma of the lung and squamous lung cell carcinoma tissue samples (Varemieva et al., 2014). In addition, EEF1D was found both on the cytoplasm and in the nucleus of lung adenocarcinoma A549 cell line (Varemieva et al., 2014) and the EEF1D/TSTA3 fusion gene was reported for lung adenocarcinoma (LUAD)(Yoshihara et al 2015).

**Hybrid/Mutated gene**

The EEF1D/TSTA3 fusion gene was found in lung adenocarcinoma (LUAD) samples (Yoshihara et al. 2015). This rearrangement is originated by t(8;8)(q24;q24) i.e. from the fusion of EEF1D gene at 5'-end with 'tissue specific transplantation antigen P35B' (TSTA3) gene at 3' end. In particular, this rearrangement brings to the formation of a transcript composed by the exon 1 of EEF1D joined with exons 4 to 11 of TSTA3 (http://203.255.191.229/8080/chimeredb31/chimeres_eq_link.cdb?gene_pair=EEF1D_TSTA3). Despite what has just been said, this genomic alteration is still poorly understood.

**Lymphoma and other blood cancers**

EEF1D is significantly overexpressed in different lymphoma subtypes, i.e. ALK-negative/ALK positive anaplastic large cell lymphomas, Hodgkin's lymphoma, acute adult T-cell leukaemia/lymphoma, Burkitt's lymphoma, follicular lymphoma and diffuse large B-cell lymphoma (Hassan et al., 2018). Some fusion genes and genomic translocation were reported (Klijn et al., 2015; https://fusionhub.persistent.co.in/home.html; https://ccsm.uth.edu/FusionGDB/index.html).

**Cytogenetics**

The t(8;19)(q24;q13) EEF1D/ SPIB, t(8;17)(q24;21) HDAC5/EEF1D, t(8;19)(q24;q13) RPS9/EEF1D, t(7;8)(q22;q24) SH2B2/EEF1D, t(8;19)(q24;q13) SPIB/EEF1D translocations and EEF1D/NAPRT fusion gene were reported for Burkitt's lymphoma (BL). In addition, the
t(8;22)(q24;q11) IGLL5/EEF1D was observed in multiple myeloma MOLP-8 cell line (Klijn et al., 2015). There are no data about the respective chimeric transcripts or proteins and the role of these genomic alterations is unknown.

**Medulloblastoma / Ependymoma**

EEF1D is overexpressed in medulloblastoma samples and it is adversely associated with overall and progression-free survival regardless of cytogenetic profile (De Bortoli et al., 2006). In addition, EEF1D was found highly expressed in ependymoma and this is related to poor outcome (de Bont et al., 2008).

**Melanoma**

EEF1D was found overexpressed in human chemoresistant melanoma cell lines (Sinha et al., 2000) and it was reported the translocation t(8;17)(q24;q25) FAM104A/EEF1D (Klijn et al., 2015).

**Hybrid/Mutated gene**
The t(3;8)(p25;q24) TTLL3/EEF1D, t(8;17)(q24;q21) KRT13/EEF1D, t(8;12)(q24;q13) EEF1D/KRT4 translocations and ZC3H3/EEF1D fusion gene were reported in oesophageal carcinoma (ESCA).

In particular, the t(3;8)(p25;q24) TTLL3/EEF1D brings to the formation of a transcript composed by the exons 1 to 3 of "tubulin tyrosine ligase like 3" (TTLL3) joined with exons 2 to 7 of EEF1D (http://203.255.191.229:8080/chimerdbv31/chimeres eq_link.cdb?gene_pair=TTLL3_EEF1D), while the t(8;8)(q24;q24) ZC3H3/EEF1D brings to the formation of a transcript composed by the exon 1 of "zinc finger CCCH-type containing 3" (ZC3H3) joined with exons 4 to 7 of EEF1D (http://203.255.191.229:8080/chimerdbv31/chimeres eq_link.cdb?gene_pair=ZC3H3_EEF1D). Despite what has just been said, these genomic alterations are still poorly understood.

**Osteosarcoma**

EEF1D may play an important role in osteosarcoma tumorigenesis because it is overexpressed in osteosarcoma tissues samples respect to adjacent non-tumor tissues and this enhances the Akt-mTOR and Akt-Bad signalling pathways. In fact, knockdown of EEF1D in MNNG/HOS and U2OS cells (both osteosarcoma cell lines) shows a slight decrease in the phosphorylation of Akt, mTOR and BAD. In addition, the high expression of EEF1D has a positive correlation with recurrences and its expression levels are higher in patients in advanced Enneking stage than in the early stage ones (Cheng et al., 2018). It was reported the translocation t(3;8)(p25;q24) OGG1/EEF1D (Klijn et al., 2015).

**Hybrid/Mutated gene**
The t(3;8)(p25;q24) OGG1/EEF1D was detected in sarcoma ES2-TO cell line (Klijn et al., 2015). This rearrangement is originated by the fusion of "8-oxoguanine DNA glycosylase" (OGG1) gene at 5'-end with EEF1D gene at 3' end. There are no data about the respective chimeric transcript or protein and so this genomic alteration is still poorly understood.

**Ovarian cancer**

It was detected an EEF1D gene copy number gain in COV362, KURAMOCHI, OVCAR4, OVCAR8 and SNU119 ovarian cancer cell lines, in about 26% of ovarian serous cystadenocarcinoma donor samples (http://www.oasis-genomics.org/) and also in metastasis and this correlates with poor prognosis (Ogawa et al., 2004). Some fusion genes and genomic translocation are reported (Babiceanu et al., 2016; https://fusionhub.persistent.co.in/home.html; https://ccsm.uth.edu/FusionGDB/index.html).

**Hybrid/Mutated gene**
The t(3;8)(p25;q24) TTLL3/EEF1D, t(8;17)(q24;q21) KRT13/EEF1D, t(8;12)(q24;q13) EEF1D/KRT4 translocations and ZC3H3/EEF1D fusion gene were reported in oesophageal carcinoma (ESCA). In particular, the t(3;8)(p25;q24) TTLL3/EEF1D brings to the formation of a transcript composed by the exons 1 to 3 of "tubulin tyrosine ligase like 3" (TTLL3) joined with exons 2 to 7 of EEF1D (http://203.255.191.229:8080/chimerdbv31/chimeres eq_link.cdb?gene_pair=TTLL3_EEF1D), while the t(8;8)(q24;q24) ZC3H3/EEF1D brings to the formation of a transcript composed by the exon 1 of "zinc finger CCCH-type containing 3" (ZC3H3) joined with exons 4 to 7 of EEF1D (http://203.255.191.229:8080/chimerdbv31/chimeres eq_link.cdb?gene_pair=ZC3H3_EEF1D). Despite what has just been said, these genomic alterations are still poorly understood.

**Neurological and neurodevelopmental disorders**

Mutations of EEF1D are involved in neurodevelopmental abnormalities, severe intellectual disability (ID) and microcephaly (McLachlan et al., 2018; Reuter et al., 2017). In particular, some authors identified a pathogenic variant of EEF1DL that could be a candidate for the autosomal recessive ID (ARID) due to its loss of function (Ugur Iseri et al., 2019). In addition, also the interaction between eEF1D and SIAH1 could impact on the initiation of neurodegenerative diseases when eEF1D is overexpressed (Wu et al., 2011).

**Ovarian cancer**

It was detected an EEF1D gene copy number gain in COV362, KURAMOCHI, OVCAR4, OVCAR8 and SNU119 ovarian cancer cell lines, in about 26% of ovarian serous cystadenocarcinoma donor samples (http://www.oasis-genomics.org/) and also in
ovarian clear cell adenocarcinomas and other ovarian cancer samples (Zhang et al., 2015; Sung et al., 2013). Some fusion genes and genomic translocation are reported (Klijn et al., 2015; https://fusionhub.persistent.co.in/home.html; https://ccsm.uth.edu/FusionGDB/index.html).

Hybrid/Mutated gene

The EEF1D/ PUF60, EEF1D/ TSNARE1 and SCRIB/EEF1D fusion genes originated by t(8;8)(q24;q24) were found in ovarian serous cystadenocarcinoma (OVSC) samples. In addition, the t(8;14)(q24;q23) HIF1A/EEF1D was reported for ovarian clear cell adenocarcinoma OVTOKO cell line (Klijn et al., 2015). This rearrangement is originated by the fusion of "hypoxia inducible factor 1 subunit alpha" ( HIF1A) gene at 5'end with EEF1D gene at 3' end. The roles of these genomic alterations are still unknown.

Pancreatic cancer

EEF1D mRNA is found to be down-regulated in pancreatic cancer tissue samples (Hassan et al., 2018).

Parkinson’s disease

Some rare mutated variants of eEF1D are considered potential candidates in Parkinson's disease. These mutated variants differ from the amino acid sequence of EEF1D for some amino acids substitutions, i.e. in position 290 (Gly/Arg), 325 (Ala/Thr), 549 (Ala/Val) and 601 (Pro/Ser) (Schulte et al., 2014).

Prostate cancer

EEF1D mRNA is found to be up-regulated in prostate cancer tissue samples (Hassan et al., 2018). In addition, it was found the translocation t(8;20)(q24;q13) EEF1D/SDC4 (Wu et al., 2012).

Hybrid/Mutated gene

The t(8;20)(q24;q13) EEF1D/SDC4 was found in prostate adenocarcinoma (PRAD). This rearrangement is originated by the fusion of EEF1D gene at 5'-end with "syndecan 4" ( SDC4) gene at 3' end. There are no data about the respective chimeric transcript or protein and the role of this genomic alteration in prostate cancer is unknown.

Thyroid cancer

There are no data about EEF1D expression alterations in thyroid cancers. However, it was reported the EEF1D/TG fusion gene (https://fusionhub.persistent.co.in/home.html; https://ccsm.uth.edu/FusionGDB/index.html).

Hybrid/Mutated gene

The EEF1D/TG fusion gene was reported in thyroid Carcinoma (THCA). This rearrangement is originated by the fusion of EEF1D gene at 5'-end with "thyroglobulin" ( TG) gene at 3' end due to the translocation t(8;8)(q24;q24). There are no data about its chimeric transcript or protein and the role of this genomic alteration is unknown.

Uterine cancer

It was detected an EEF1D gene copy number gain in about 14% of uterine carcinosarcoma donor samples (http://www.oasis-genomics.org/). It was found the translocation t(8;17)(q24;q21) EEF1D/KRT14 (Alaei-Mahabadi et al., 2016).

Hybrid/Mutated gene

The t(8;17)(q24;q21) EEF1D/KRT14 was found in cervical squamous cell carcinoma (CESC). This rearrangement is originated by the fusion of EEF1D gene at 5'-end with "keratin 14" ( KRT14) gene at 3' end. There are no data about the respective chimeric transcript or protein and the role of this genomic alteration is unknown.

To be noted

Role of eEF1D in viral replication and pathogenesis. Have discovered some interactions between some human immunodeficiency virus type 1 (HIV-1) proteins, such as HIV-1 Tat, and eEF1D and its recruitment for the viral mRNAs translation (Milev et al., 2012). In addition, eEF1D can be found hyperphosphorylated by viral protein kinases after alpha-, beta-, and gammaherpesviruses infections. In particular, the viral protein kinases involved in eEF1D phosphorylation include UL13 of herpes simplex virus type 1 (HSV-1), UL97 of human cytomegalovirus and BGLF4 of Epstein-Barr virus (EBV) (Kawaguchi et al., 2003). Apart from that, in general, this brings a reduction of cellular proteins biosynthesis efficiency instead privileging the viral proteins translation process (Milev et al., 2012).

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