The pseudogenes of eukaryotic translation elongation factors (EEFs): Role in cancer and other human diseases

Luigi Cristiano

R&D Division, Prestige, 18 via Vecchia, Terranuova Bracciolini, AR 52028, Italy

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Abstract: The eukaryotic translation elongation factors (EEFs), i.e. EEF1A1, EEF1A2, EEF1B2, EEF1D, EEF1G, EEF1E1 and EEF2, are coding-genes that play a central role in the elongation step of translation but are often altered in cancer. Less investigated are their pseudogenes. Recently, it was demonstrated that pseudogenes have a key regulatory role in the cell, especially via non-coding RNAs, and that the aberrant expression of ncRNAs has an important role in cancer development and progression. The present review paper, for the first time, collects all that published about the EEFs pseudogenes to create a base for future investigations. For most of them, the studies are in their infancy, while for others the studies suggest their involvement in normal cell physiology but also in various human diseases. However, more investigations are needed to understand their functions in both normal and cancer cells and to define which can be useful biomarkers or therapeutic targets.

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Introduction

The eukaryotic translation elongation factors (EEFs) play a central role in the proteins biosynthesis during the elongation step of translation (Fig. 1). They include the eukaryotic translation elongation factor 1 alpha 1 (EEF1A1), eukaryotic translation elongation factor 1 alpha 2 (EEF1A2), eukaryotic translation elongation factor 1 beta 2 (EEF1B2), eukaryotic translation elongation factor 1 delta (EEF1D), eukaryotic translation elongation factor 1 gamma (EEF1G), eukaryotic translation elongation factor 1 epsilon 1 (EEF1E1), and eukaryotic translation elongation factor-2 (EEF2). These genes, and related proteins, can be grouped into two large subfamilies, namely non-alpha EEFs and alpha EEFs. Many published studies reported their biological significance as well as their involvement in cancer and other human diseases.
other human diseases. Nevertheless, the role and biological function of their pseudogenes in normal and pathological states are still poorly studied.

Until recently, pseudogenes were believed to be junk DNA, i.e. relics, non-functional versions, of parental protein-coding genes no longer able to encode a protein and devoid of any biological significance or usefulness. Recent transcriptomic and proteomic analyses have shown that both pseudogene-derived transcripts and pseudogene-derived proteins can be found in new locations on different chromosomes than their gene from which it derives. Furthermore, they can be expressed or in other cellular compartments. The role of a protein produced by a pseudogene can also be revealed only in a pathologic condition such as cancer.6

The expression profile of pseudogenes has been reported to vary in different tissues, under different conditions, both physiologically than pathological,11 but it cannot be excluded that it varies over time, i.e. during embryogenesis12 and/or childhood or adulthood, as well as it can be acquired systematically, as shown during cancer development.13

Pseudogenes are classified into three main categories: processed pseudogenes, unprocessed pseudogenes, and unitary pseudogenes.14,15 Processed pseudogenes (PPs) are pseudogenes devoid of introns and other regulatory elements (such as enhancers and promoter) and derive from the reverse transcription of mRNA followed by the reinsertion of respective DNA (cDNA) into the genome (retrotransposition) and therefore are often also called retro-pseudogenes. In this regard, the copy number of a retroseupseudogene could be related to the expression level of the gene from which it derives. Furthermore, they can be found in new locations on different chromosomes than their parental coding-gene and many of them have been reported to be actively transcribed.16,17

The unprocessed pseudogenes, on the other hand, can contain introns and regulatory sequences. They result from gene duplication during unequal crossing-over and are generally found on the same chromosome of the parental protein-coding gene. The subcategory of transcribed pseudogenes, both unprocessed and processed, shows one or more transcripts. Finally, the unitary pseudogenes (orphans) are considered to be previously active genes that become inactive due to mutations and genomic alterations and have no homologous active gene in the genome.

This review paper, for the first time, collects and summarizes all that are known and currently published on EEFs pseudogenes to create a state of the art from which to build further research and insights.

Materials and methods

A list of annotated pseudogenes by each EEF gene was obtained from NCBI:Gene (https://www.ncbi.nlm.nih.gov/gene/) by typing the official symbol of the parental gene and then searching for annotated pseudogenes on its profile on the “General gene information” sub-tab.

Each pseudogene is searched for published papers by typing its official symbol on Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Academia (https://www.academia.edu/),
Pseudogenes of non-alpha eukaryotic translation elongation factors

Non-alpha EEFs collect nearly all components of the eukaryotic translation elongation factor-1 macromolecular complex (eEF1H), namely eEF1B2, eEF1D and eEF1G, as well as a component of multiaminoacyl-tRNA synthetase macromolecular complex (MARS), that is eEF1E1, and eEF2. All of these genes encode at least one protein, but more frequently several protein isoforms, which play a central role in peptide elongation during protein biosynthesis.

eEF1B2, eEF1D, and eEF1G join the valyl t-RNA synthetase (valRS) to form the macromolecular complex eEF1BGD which is involved in the regeneration of the active form of eEF1A, i.e. converts the inactive GDP-bound form of eEF1A into its active GTP-bound form (eEF1A-GTP).\(^\text{19}\)

eEF1E1 interacts with different aminoacyl-tRNA synthetases\(^\text{20}\) and could contribute to the anchoring of the macromolecular aminoacyl-tRNA synthetases complex (MARS) to the EF1H complex in the translation elongation step.\(^\text{21}\) Finally, eEF2 is required for translocation of the peptidyl-tRNA from A-site to P-site of the ribosome.

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**Figure 1** The elongation step of translation. The active form of eEF1A (eEF1A-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 eEF1H protein complex. eEF1H is formed previously by the binding of eEF1B2, eEF1G, eEF1D and Val-RS. This complex promotes the exchange between GDP and GTP to regenerate the active form of eEF1A. eEF1E1 collaborates to anchor MARS complex to eEF1H. eEF2 is subsequently involved for ribosome translocation. A box is added to each EEFs indicating the number of pseudogenes known so far.\(^\text{1}\)
All these factors exhibit canonical functions and multiple non-canonical roles (moonlight roles) within the cell and are frequently altered in expression, gene amplification and genomic rearrangements in many cancers and other diseases. All have at least one pseudogene, but more frequently more than one, dispersed in the human genome (Fig. 2) with the exception of EEF2 for which no pseudogenes in humans are known.

The pseudogenes reported for non-alpha EEFs are classified into processed pseudogenes, unprocessed pseudogenes and transcribed unprocessed pseudogenes. These pseudogenes are listed in Table 1A (more detail in the T1ASuppl supplementary material). All non-alpha EEF coding genes, briefly, and their pseudogenes, more extensively, will be treated individually.

Figure 2  Localization of EEFs pseudogenes. The figure shows the locations of each pseudogene and its respective parental gene in the human genome. The data have been extracted from Gene (NCBI).
Table 1A  Pseudogenes of non-alpha EEFs. List of all non-alpha EEFs pseudogenes so far discovered and the correlation with diseases where they are reported or there is evidence about them (see also supplementary table TA1SUPPL).

| RFG   | PS          | Description                  | Status                  | CHR  | Location | Length (nt) | Main diseases                                                                                          |
|-------|-------------|------------------------------|-------------------------|------|----------|-------------|--------------------------------------------------------------------------------------------------------|
| EEF1B2 | EEF1B2P1    | EEF1B2 pseudogene 1          | Processed pseudogene    | 15   | 15q21.2  | 880         | Non-squamous non-small cell lung cancer (NSCLC) (?)26, Human bone osteosarcoma epithelial cell line (U2OS) (?), acute myeloid leukemia (AML) cell lines (KG-1, MOLM-14) (?), Hepatocellular carcinoma (?), HIV-1 reverse transcription cofactor (?)29,32 |
|       | EEF1B2P2    | EEF1B2 pseudogene 2          | Unprocessed pseudogene  | 5    | 5q13.1   | 803         | —                                                                                                      |
|       | EEF1B2P3    | EEF1B2 pseudogene 3          | X                       | Xp22.11 | 764      | —           | —                                                                                                      |
|       | EEF1B2P4    | EEF1B2 pseudogene 4          | Processed pseudogene    | 12   | 12q23.3  | 1161        | —                                                                                                      |
|       | EEF1B2P5    | EEF1B2 pseudogene 5          | Unprocessed pseudogene  | 6    | 6q12     | 1877        | —                                                                                                      |
|       | EEF1B2P6    | EEF1B2 pseudogene 6          | Processed pseudogene    | 7    | 7q32.3   | 766         | —                                                                                                      |
|       | EEF1B2P7    | EEF1B2 pseudogene 7          | Transcribed unprocessed pseudogene | 2    | 2q37.1   | 799         | —                                                                                                      |
|       | EEF1B2P8    | EEF1B2 pseudogene 8          | Transcribed unprocessed pseudogene | 3    | 3q26.31  | 796         | —                                                                                                      |
| EEF1D  | EEF1DP1     | EEF1D pseudogene 1           | Processed pseudogene    | 19   | 19p13.12 | 980         | Acute myeloid leukemia cell lines (HL-60, MOLM-14, THP-1, U937) (?), diffuse large B-cell lymphoma cell lines (DHL4, DHL6) (?), hepatocellular carcinoma cell line (Huh-7) (?), Human bone osteosarcoma epithelial cell line (U2OS) (?), melanoma (?)50, Melanoma (?) |
|       | EEF1DP2     | EEF1D pseudogene 2           |                          | 9    | 9q22.31  | 976         | Prostate carcinoma, breast carcinoma, ankylosing spondylitis, adenocortical carcinoma (ACC), pheochromocytoma and Paraganglioma (PCPG), brain lower-grade glioma (LGG), rectum adenocarcinoma (READ), cervical squamous cell carcinoma, endocervical adenocarcinoma (CESC), uterine carcinosarcoma (UCS), head and neck squamous cell carcinoma (HNSC), hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), mesothelioma, acute myeloid leukemia (AML), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), skin cutaneous melanoma (SKCM), pancreatic adenocarcinoma (PAAD), sarcoma (SARC), bladder urothelial carcinoma (BLCA), chromophobe renal cell carcinoma (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), synucleinopathy and Parkinson’s disease (?), non-small cell lung cancer (?), multiple sclerosis (?), large B-cell lymphoma cell lines (SUDHL4, Toledo, OCI-Ly3) (?), epidermolysis bullosa simplex (?)17-45 |
|       | EEF1DP3     | EEF1D pseudogene 3           | Transcribed unprocessed pseudogene | 13   | 13q13.1  | 575         | (continued on next page)                                                                                      |
Pseudogenes of EEF1B2

EEF1B2, also known as eEF1β or eEF1Bα, is a coding-gene located on Chromosome 2 (2q33.3). Several alternative splicing transcript variants have been observed but to date only one protein has been detected. Like the other members of the eEF1H complex, it is involved in the elongation step of translation and collaborates closely with eEF1D and eEF1G in the conversion of eEF1A from its inactive GDP-bound form to its active GTP-bound form.

Analysis of the sequences reported in the human genome revealed the presence of eight pseudogenes for EEF1B2 which are mostly classified as processed pseudogenes and probably related to recent retrotransposition events. The alternative forms EEF1B3 and EEF1B4, previously designated for EEF1B2, instead have shown to be pseudogenes namely EEF1B2P2 and EEF1B2P3 respectively. However, the pseudogenes of EEF1B2 are poorly studied and publications have been made only for some of them.

The EEF1B2 pseudogene 1, alias EEF1B2P1, was first reported in 1991. It was first referred to as a gene parologue...
of EEF1B2, named EEF1B1, but was latter better described as a processed pseudogene. It has been studied as a baseline putative marker for the prediction of overall patient survival in advanced non-squamous non-small cell lung cancer (NSCLC) but its biological significance in this cancer is unknown.

The EEF1B2 pseudogene 2, alias EEF1B2P2, was first reported in 1993 as an isof orm of EEF1B2 called EF-105a but it has subsequently been classified as a processed pseudogene. A transcript of this pseudogene was found in the human brain and muscle where this isof orm replaces the transcription of EEF1B2.

The EEF1B2 pseudogene 3, alias EEF1B2P3, was first reported in 1993 and later in an analysis of gene cluster in the human bone osteosarcoma epithelial cell line (U2OS) and in hepatocellular carcinoma, but its significance in these diseases is unknown. Some studies report differences in its expression levels: in particular, it has been found to be upregulated during HIV-1 infection, so it may be a critical reverse transcription cofactor of HIV-1. However, it is not clear why. Furthermore, the expression levels of EEF1B2P3 decrease after the use of a dihydroorotate dehydrogenase inhibitor in KG-1 and MOLT-14 acute myeloid leukaemia (AML) cell lines. The EEF1B2 pseudogene 6, alias EEF1B2P6, was first reported in 2007 but no other studies have been conducted.

The others, i.e. the EEF1B2 pseudogene 4 (alias EEF1B2P4) the EEF1B2 pseudogene 5 (alias EEF1B2P5), the EEF1B2 pseudogene 7 (alias EEF1B2P7) and the EEF1B2 pseudogene 8 (alias EEF1B2P8), are predicted by genome sequence analysis but are not yet supported by experimental evidence.

**Pseudogenes of EEF1D**

EEF1D, alias eEF1b or eEF1bo, is a coding gene with several alternative splicing variants that encode several protein isoforms. Like the other members of the eEF1H complex, it is involved in the elongation step of translation and closely collaborates with eEF1B in the conversion of eEF1A from its inactive GDP-bound form to its active GTP-bound form. Analysis of the human genome revealed the presence of eight pseudogenes. Some are poorly characterized while others are better known, especially EEF1DP3.

The EEF1D pseudogene 1, alias EEF1DP1, was first reported in 2001 and in datasets on some cancer cell lines of hepatocellular carcinoma, acute myeloid leukemia, diffuse large B-cell lymphoma, human bone osteosarcoma (U2OS) and melanoma without specific information, so its significance in these diseases is unclear. The same happens for EEF1D pseudogene 2, alias EEF1DP2, that is reported in datasets on melanoma. It is not entirely clear whether it is expressed or expressed even at a low level.

The EEF1D pseudogene 3, alias EEF1DP3, is the most studied pseudogene compared to the others of EEF1D and, in general, of all non-alpha EEFs pseudogenes. First reported in 2005 but also later by other authors, it is found on chromosome 13. To note that chromosome 13 is known to carry some putative oncogenes involved in cancer, including breast cancer type 2 (BRCA2) and retinoblastoma (RB1) genes.

EEF1DP3 is classified as a transcribed unprocessed pseudogene and the genomic sequence contains four non-coding exons. It is not yet known it undergoes post-transcriptional modifications, however it is transcribed and produces a long non-coding RNA (lncRNA) of 575 nt. It is known that lncRNAs, like other ncRNAs, can modulate gene expression both at the transcriptional level, interacting with the parental gene promoter, and at the post-transcriptional level, acting as microRNA decoys and thus may play key roles in cellular biological processes. Nowadays, the exact role of EEF1DP3 in healthy tissues is still unknown, however, it has been reported to be overexpressed in the heart, particularly in the left ventricle and is also expressed in the normal trachea, liver, testis, kidney, bladder and brain. Conversely, a low expression is found in the adrenal gland, colon and pituitary gland.

Numerous mutations and alterations in the genomic sequence for EEF1DP3 have been discovered which include copy number variations, translocations and interchromosomal translocations with the formation of novel fusion genes. These have been found in many kinds of cancer, such as breast cancer and Burkitt’s lymphoma, but also non-neoplastic disorders.

The most reported of these alterations is the EEF1DP3/FRY fusion originating from the read-through transcription between EEF1DP3 and FRY gene. EEF1DP3/FRY is a recurrent read-through fusion transcript that was first detected in vitro in KPL4 breast carcinoma cell-line and then was also detected in vivo in breast cancer samples but cannot be detected in breast normal tissues counterparts or blood samples from EEF1DP3/FRY positive patients. It has been detected in some types of non-neoplastic disorders and in some cancers such as malignant melanoma, Burkitt’s lymphoma, lung cancer and breast cancer.

EEF1DP3 is abnormally expressed in a very large list of cancers and diseases. It has been reported to be highly expressed in adrenal carcinomas i.e. adrenocortical carcinoma (ACC) and pheochromocytoma and paraganglioma (PCPG), brain lower-grade glioma (LGG), rectum adenocarcinoma (READ), gynaecological cancers such as cervical squamous cell carcinoma, endocervical adenocarcinoma (CESC) and uterine carcinosarcoma (UCS), head and neck squamous cell carcinoma (HNSC), hepatocellular carcinoma samples (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), mesothelioma, acute myeloid leukemia (AML) and lymphoid neoplasm diffuse large B-cell lymphoma (DLBCL), skin cutaneous melanoma (SKCM), pancreatic adenocarcinoma (PAAD), sarcoma (SARC) and urinary tract cancers such as urothelial bladder carcinoma (BLCA), chromophobe renal cell carcinoma (KICH), kidney renal clear cell carcinoma (KIRC) and kidney renal papillary cell carcinoma (KIRP). Furthermore, it is also overexpressed in prostate adenocarcinoma (PRAD) while its loss by deletion has been associated with an increased risk and predisposition for ankylosing spondylitis (AS).

It was also reported in datasets on various neurodegenerative disorders such as synucleinopathy and Parkinson’s disease, but also in non-small cell lung cancer, multiple sclerosis and epidermolysis bullosa simplex. However, its role in these diseases is unclear.
The *EEF1D* pseudogene 4, alias *EEF1DP4*, was first described in 1998. It was reported in datasets on glioma, breast cancer, primary myelofibrosis, colon cancer and osteosarcoma. However, its significance in these diseases is still unknown. A similar situation is also for the *EEF1D* pseudogene 5, alias *EEF1DP5*, which is not clearly reported in breast cancer and in a gene cluster analysis in the human bone osteosarcoma epithelial cell line (U2OS). Furthermore, this pseudogene exhibits frequent genomic deletions whose role is completely unknown.

The *EEF1D* pseudogene 6 (*EEF1DP6*) is reported in datasets on acute myeloid leukemia, systemic juvenile idiopathic arthritis and neuropathy in Charcot-Marie-Tooth disease type 1A, but like other pseudogenes, its significance is unknown. The last ones foreseen by the analysis of the genome are *EEF1D* pseudogene 7 (*EEF1DP7*) and *EEF1D* pseudogene 8 (*EEF1DP8*). However, they are not yet supported by any experimental evidence.

**Pseudogenes of EEF1G**

*EEF1G*, alias *EEF1γ* or *EEF1βγ*, is a coding gene located on Chromosome 11 (11q12.3). At least five alternative splicing variants have been observed, of which two are protein-coding while the others are ncRNA sequences. Like the other components of the eEF1H complex, it is involved in the elongation step of translation and most likely stimulates the activity of eEF1B2 and guarantees stability to the entire eEF1H complex. Analysis of the human genome revealed the presence of nine pseudogenes for *EEF1G* classified as processed pseudogenes. These pseudogenes are studied very marginally.

The *EEF1G* pseudogene 1, alias *EEF1GP1*, was first reported in 1998 and later in a gene cluster analysis dataset on human bone osteosarcoma epithelial cell line (U2OS) but its involvement is unclear.

*EEF1G* pseudogene 4, alias *EEF1GP4*, was reported by some studies on the sequencing of the human genome. *EEF1G* pseudogene 5, alias *EEF1GP5*, is not clearly reported with regard to prostate cancer and Duchenne muscular dystrophy thus its significance in these diseases is unknown. It is also reported in a gene cluster analysis dataset on human bone osteosarcoma epithelial cell line (U2OS). Similar considerations can be made for *EEF1GP1* pseudogene 9, alias *LOC729998*, which appears in datasets on some cancer cell lines of hepatocellular carcinoma, acute myeloid leukaemia, and diffuse large B-cell lymphoma.

The others, i.e. the *EEF1G* pseudogene 2 (alias *EEF1GP2*), the *EEF1G* pseudogene 3 (alias *EEF1GP3*), the *EEF1G* pseudogene 6 (alias *EEF1GP6*), the *EEF1G* pseudogene 7 (alias *EEF1GP7*) and the *EEF1G* pseudogene 8 (alias *EEF1GP8*), are predicted by genome sequence analysis but are not yet supported by any experimental evidence.

**Pseudogenes of EEF1E1**

*EEF1E1* is known under some names such as aminoaacyl tRNA synthetase complex-interacting multifunctional protein 3 (AIMP3) and P18 and was first identified by Mao and colleagues in 1998. *EEF1E1* plays a role as an auxiliary component of the macromolecular aminoacyl-tRNA synthetases complex (MARS) in the elongation step of translation, in particular, it interacts with several aminoaacyl-tRNA synthetases and could contribute to the anchoring of the MARS complex to the EF1H complex. Its expression is frequently found altered in human cancer cells and is considered a putative tumor suppressor gene.

Sequence analysis of the human genome revealed the presence of only one pseudogene related to *EEF1E1* on chromosome 2, precisely in the location 2q13. This pseudogene has been named eukaryotic translation elongation factor 1 epsilon 1 pseudogene 1, alias *EEF1E1P1*, and is classified as a processed pseudogene. It shows 93.47% identity with the alternative splicing transcript variant 1 mRNA of *EEF1E1* (*RefSeq* NM_004280.5) but no sequence identity or homology was found with the transcript variant 2 mRNA of *EEF1E1*, so it can be assumed that the origin of *EEF1E1P1* is due to a probable retrotransposition event from the *EEF1E1* variant 1 mRNA alone. It is reported in a study on genetic loci related to coronary artery disease but its significance in this disease is unclear. Until now, no one has studied this pseudogene on cancers.

**Pseudogenes of alpha eukaryotic translation elongation factors**

Alpha EEFs collect the remaining components of the eEF1H complex, i.e. *eEF1A1* and its isoform *eEF1A2*. These genes are found in different locations in the human genome and encode at least one protein that plays a central role in peptide elongation during protein biosynthesis, like the other members of eEF1H. In particular, *eEF1A1* allows the delivery of aminoaacyl-tRNAs to the ribosome mediated by the hydrolysis of GTP. Indeed, 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 by GTP hydrolysis, thus acting as a guanine nucleotide exchange factor (GEF), generating eEF1A-GTP for the successive elongation cycle. Both *eEF1A1* and *eEF1A2* exhibit canonical functions and multiple non-canonical roles (moonlight roles) within the cell and, like other EEFs, are often altered in expression, gene amplification and genomic rearrangements in many types of cancers and other diseases.

The pseudogenes reported for alpha EEFs, in particular *EEF1A1*, are very numerous and are mostly considered retropseudogenes. They are classified into processed pseudogenes, unprocessed pseudogenes and transcribed unprocessed pseudogenes. These pseudogenes are listed in Table 1B (more detail in the T1ASuppl supplementary material). Below are described in detail, one by one, the pseudogenes of the alpha EEFs (see also Fig. 2).

**Pseudogenes of EEF1A1**

*EEF1A1* is a coding gene of 5283 nt long located on Chromosome 6 (6q13) with several alternative splicing transcript variants and protein isoforms of which most studied are the prostate tumor-inducing gene-1, alias *PTI-1* or EEF 1-alpha 1-like 14 (*EEF1A1L14*), and cervical cancer suppressor 3 (*CCS-3*). Today it is one of the most studied proteins both
| RFG | PS         | Description          | Status              | CHR | Location  | Length (nt) | Main diseases                                                                 |
|-----|------------|----------------------|---------------------|-----|-----------|-------------|-------------------------------------------------------------------------------|
| EEF1A1 | EEF1A1P1 | EEF1A1 pseudogene 1  | Processed pseudogene | 21  | 21q21.2   | 1034        | Celiac disease (?), oral squamous cell carcinoma, osteosarcoma (?)          |
|      | 72        |                      |                     |     |           |             | Bladder cancer (?), Uterine cancer (?), Colorectal cancer (?)                |
| EEF1A1 | EEF1A1P2 | EEF1A1 pseudogene 2  |                     | 14  | 14q31.1   | 1912        |                                                                             |
|      | 70,76     |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P3 | EEF1A1 pseudogene 3  |                     | 13  | 13q12.2   | 1623        |                                                                             |
|      | 70        |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P4 | EEF1A1 pseudogene 4  |                     | 12  | 12p12.3   | 1659        |                                                                             |
|      | 70        |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P5 | EEF1A1 pseudogene 5  |                     | 9   | 9q34.13   | 1747        | Hepatocellular carcinoma (?), nasopharyngeal carcinoma (?), oral squamous cell carcinoma, hepatitis E virus cofactor 31,74,82,83 |
|      | 70,77−81  |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P6 | EEF1A1 pseudogene 6  |                     | 7   | 7p15.3    | 1746        | Rectum cancer (?), schizophrenia (?), multiple myeloma (?), hepatocellular carcinoma (?) 31,84,85 |
|      | 70,78     |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P7 | EEF1A1 pseudogene 7  |                     | 19  | 19q13.12  | 2142        | Hepatocellular carcinoma (?), breast cancer (?) 31,86,87                     |
|      | 70        |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P8 | EEF1A1 pseudogene 8  |                     | 3   | 3q27.1    | 1644        |                                                                             |
|      | 70        |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P9 | EEF1A1 pseudogene 9  |                     | 4   | 4q24      | 1751        | Duchenne muscular dystrophy (DMD) (?), acute lymphoblastic leukemia (?), metastatic prostate cancer (?), prostate adenocarcinoma cell line (LNCaP) (?), melanoma (?), kidney cancer (?), osteosarcoma (?), hepatocellular carcinoma (?), glioma, cervical cancer (?), autism spectrum disorders (?), 31,79,88−92 |
|      | 70        |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P10| EEF1A1 pseudogene 10 |                     | 7   | 7q35      | 1650        |                                                                             |
|      | 70        |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P11| EEF1A1 pseudogene 11 |                     | 1   | 1p21.3    | 1748        | Osteosarcoma (?), lung cancer (?), colon cancer, type 2 diabetes mellitus 75,94,95 |
|      | 70,93     |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P12| EEF1A1 pseudogene 12 |                     | 2   | 2q12.2    | 1698        | Hepatocellular carcinoma (?), osteosarcoma (?), multiple myeloma (?), oral squamous cell carcinoma, epilepsy (?) 31,74,75,85,96 |
|      | 70        |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P13| EEF1A1 pseudogene 13 |                     | 5   | 5p15.2    | 1747        |                                                                             |
|      | 70,97−98  |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P14| EEF1A1 pseudogene 14 |                     | 1   | 1q31.3    | 1666        | Liver cancer (?), rectum cancer (?), ovarian cancer (?), oral squamous cell carcinoma, breast cancer (?) 74,103 |
|      | 70,99     |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P15| EEF1A1 pseudogene 15 |                     | X   | Xq21.33   | 1689        |                                                                             |
|      | 70        |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P16| EEF1A1 pseudogene 16 |                     | 12  | 12p12.3   | 1635        | Gastric cancer, Glioma (?) 101,102                                           |
|      | 70        |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P17| EEF1A1 pseudogene 17 |                     | 12  | 12q12    | 1413        |                                                                             |
|      | 70        |                      |                     |     |           |             |                                                                             |
| EEF1A1 | EEF1A1P18| EEF1A1 pseudogene 18 |                     | 11  | 11q13.1   | 467         |                                                                             |

(continued on next page)
| RFG             | PS       | Description                  | Status                   | CHR | Location | Length (nt) | Main diseases                                                                 |
|-----------------|----------|------------------------------|--------------------------|-----|----------|-------------|-----------------------------------------------------------------------------|
| EEF1A1P19       | EEF1A1   | pseudogene 19                | 5                        | 5p12| 1645     |             | Hepatocellular carcinoma (?)[^31]                                           |
| EEF1A1P20       | EEF1A1   | pseudogene 20                | 5                        | 5q21.1| 1644     |             | Nonalcoholic fatty liver disease (?)[^104]                                   |
| EEF1A1P21       | EEF1A1   | pseudogene 21                | 4                        | 4p15.1| 1339     |             | Oral squamous cell carcinoma[^74]                                           |
| EEF1A1P22       | EEF1A1   | pseudogene 22                | 15                       | 15q21.3| 1639     | Multiple myeloma (?)[^85]                                                   |
| EEF1A1P23       | EEF1A1   | pseudogene 23                | Transcribed processed pseudogene | 3 | 3q29 | 658 | — |
| EEF1A1P24       | EEF1A1   | pseudogene 24                | Processed pseudogene     | 3 | 3p22.1 | 1638 | Acute lymphoblastic leukemia (?) |
| EEF1A1P25       | EEF1A1   | pseudogene 25                | 3                        | 3q22.3| 1471     | — |
| EEF1A1P26       | EEF1A1   | pseudogene 26                | 7                        | 7p21.2| 1383     | Oral squamous cell carcinoma, type 2 diabetes mellitus (?)[^74,105]         |
| EEF1A1P27       | EEF1A1   | pseudogene 27                | 7                        | 7p21.1| 1151     | Oral squamous cell carcinoma[^74]                                           |
| EEF1A1P28       | EEF1A1   | pseudogene 28                | 7                        | 7q21.13| 1671    | EBV-positive T/NK-cell lymphoma (?)[^106]                                    |
| EEF1A1P29       | EEF1A1   | pseudogene 29                | X                        | Xq21.2| 1443     | Breast cancer (?), lung cancer (?), prostate cancer (?), colorectal cancer (?), leukemia (?)[^87,107] |
| EEF1A1P30       | EEF1A1   | pseudogene 30                | X                        | Xq24 | 2354     | — |
| EEF1A1P31       | EEF1A1   | pseudogene 31                | Unprocessed pseudogene   | X  | Xq28 | 10,389 | — |
| EEF1A1P32       | EEF1A1   | pseudogene 32                | 1                        | 1q31.3| 2156     | Oral squamous cell carcinoma[^74]                                           |
| EEF1A1P33       | EEF1A1   | pseudogene 33                | Processed pseudogene     | 12 | 12q23.1 | 1662 | — |
| EEF1A1P34       | EEF1A1   | pseudogene 34                | 20                       | 20p11.23| 1464    | — |
| EEF1A1P35       | EEF1A1   | pseudogene 35                | 4                        | 4q28.3| 1646     | — |
| EEF1A1P36       | EEF1A1   | pseudogene 36                | 6                        | 6q23.2| 1431     | — |
| EEF1A1P37       | EEF1A1   | pseudogene 37                | 8                        | 8q23.3| 557      | Oral squamous cell carcinoma[^74]                                           |
| EEF1A1P38       | EEF1A1   | pseudogene 38                | Processed pseudogene     | 16 | 16p12.1 | 1937 | Gastric cancer, oral squamous cell carcinoma[^74,104] |
| EEF1A1P39       | EEF1A1   | pseudogene 39                | 10                       | 10p11.23| 250     | Oral squamous cell carcinoma[^74]                                           |
| EEF1A1P40       | EEF1A1   | pseudogene 40                | X                        | Xq22.3| 573      | — |
| EEF1A1P41       | EEF1A1   | pseudogene 41                | Y                        | Yp11.2| 374      | — |
| EEF1A1P43       | EEF1A1   | pseudogene 43                | Unprocessed pseudogene   | 17 | 17p11.2 | 3871 | Smith-Magenis syndrome (?)[^109] |
| EEF1A2P42       | EEF1A1   | pseudogene 42                | Processed pseudogene     | 6  | 6p12.3 | 2214 | Hepatocellular carcinoma cell line (Huh-7) (?), Diffuse large B-cell lymphoma cell lines (DHL4, DHL6) (?), Acute myeloid leukemia cell lines (HL-60, MOLM-14, THP-1, U937) (?), Melanoma cell line (FEMX-I) (?) |
| LOC401677       | EEF1A2   | pseudogene                   | Transcribed unprocessed  | 11 | 11p14.1 | 931 | — |

[^31]: Hepatocellular carcinoma (?)
[^104]: Nonalcoholic fatty liver disease (?)
[^74]: Oral squamous cell carcinoma
[^85]: Multiple myeloma (?)
[^106]: EBV-positive T/NK-cell lymphoma (?)
[^107]: Breast cancer (?), lung cancer (?), prostate cancer (?), colorectal cancer (?), leukemia (?)
[^109]: Smith-Magenis syndrome (?)
[^74]: Oral squamous cell carcinoma
for its fundamental role in the cell and for its involvement in many human diseases, especially cancer. In fact, it plays a key role in the elongation step of translation in which it is responsible for the enzymatic delivery of aminoacyl tRNAs to the ribosome. Furthermore, it is expressed in all tissues except the brain, heart and skeletal muscles where it is replaced by the isoform EEF1A2.83 Furthermore, it interacts with Hepatitis E virus (HEV) nonstructural protein 7, a mitochondrial protein encoded in many human diseases, especially cancer.23 In fact, it was first reported in 199670 and is highly expressed in human primary monocytes.78 Subsequently, it is reported in a study on schizophrenia,84 hepatocellular carcinoma,85 multiple myeloma,85 and in a dataset on rectum cancer. The contribution of EEF1A1P6 in these diseases is unknown.

The EEF1A1 pseudogene 7 (EEF1A1P7), the EEF1A1 pseudogene 9 (EEF1A1P9) and the EEF1A1 pseudogene 12 (EEF1A1P12) were first reported in 199670 and subsequently in a study on hepatocellular carcinoma.31 Furthermore, EEF1A1P7 was also reported in two studies on breast cancer both as such65 and as aberrant transcript fused with EEF1A1P2.97

EEF1A1P9 is reported in familiar melanoma (FM) where it was found upregulated after UV-exposure of FM cultured fibroblasts.56 It is also reported in kidney cancer,59 osteosarcoma57 and autism spectrum disorders, in which copy gain of a genomic region that includes EEF1A1P92 is shown. In glioma it has been reported that it is a protective factor: in fact, patients with a high expression for EEF1A1P9 had a favorable prognosis so it can play an important role in the onset and progression of glioma.90 EEF1A1P9 is shown to be downregulated in cervical cancer71 and is reported in datasets on Duchenne muscular dystrophy (DMD), acute lymphoblastic leukaemia, metastatic prostate cancer and in the LNCap prostate adenocarcinoma cell line. EEF1A1P12 is reported in osteosarcoma,75 multiple myeloma,85 oral squamous cell carcinoma (with copy gain)85 and epilepsy.96

Table 1B (continued)

| RFG     | PS            | Description                | Status   | CHR | Location | Length (nt) | Main diseases |
|---------|---------------|----------------------------|----------|-----|----------|-------------|--------------|
| LOC441880 | EEF1A2        | pseudogene                 | pseudogene | 1   | 1p35.2   | 1383        | –            |
| LOC642791 | EEF1A2        | pseudogene                 | pseudogene | 11  | 11q14.3  | 2001        | –            |
| LOC729856 | Elongation    | factor 1-alpha-like        | Unprocessed pseudogene | 1   | 1p36.11  | 468         | –            |
| LOC100421798 | EEF1A2     | pseudogene                 | Processed pseudogene | 5   | 5q31.1   | 1148        | –            |
| LOC100421817 | EEF1A2     | pseudogene                 | pseudogene | 3   | 3q25.1   | 1344        | –            |
| LOC100421840 | EEF1A2     | pseudogene                 | pseudogene | 1   | 1q32.1   | 1329        | –            |
| LOC100421842 | EEF1A2     | pseudogene                 | pseudogene | 1   | 1q42.13  | 554         | –            |

Abbreviations: RFG, related functional gene; PS, pseudogene; CHR, Chromosome; [ (?) ], uncertain; [ - ], unknown.
| Disease list | Solid tumors and cell cultures | Lip, oral cavity and pharynx | Nasopharyngeal carcinoma | Pseudogenes |
|-------------|--------------------------------|-------------------------------|--------------------------|-------------|
| Cancer (included tissues and cell cultures) | | | Oral squamous cell carcinoma | EEF1A1P5, EEF1A1P1, EEF1A1P5, EEF1A1P12, EEF1A1P14, EEF1A1P21, EEF1A1P26, EEF1A1P27, EEF1A1P32, EEF1A1P37, EEF1A1P38, EEF1A1P39, EEF1A1P16, EEF1A1P38 |
| Digestive organs | Gastric cancer/stomach adenocarcinoma (STAD) | Rectum adenocarcinoma (READ) | Colon adenocarcinoma (COAD) | EEF1A1P6, EEF1A1P14, EEF1A1P12, EEF1A1P14, EEF1A1P11, EEF1A1P29 |
| | Liver hepatocellular carcinoma (LIHC) | | | EEF1B2P2, EEF1DP3, LOC729998, EEF1A1P5, EEF1A1P6, EEF1A1P7, EEF1A1P9, EEF1A1P12, EEF1A1P14, EEF1A1P19, EEF1A1P42 |
| Respiratory system and intrathoracic organs | Pancreatic adenocarcinoma (PAAD) | Lung adenocarcinoma (LUAD) | Lung squamous cell carcinoma (LUSC) | EEF1DP3, EEF1A1P11, EEF1A1P29 |
| | Mesothelioma (MESO) | Non-squamous non-small cell lung cancer (NSCLC) | Skin cutaneous melanoma (SKCM) | EEF1DP3, EEF1DP1, EEF1DP2, EEF1DP3, EEF1A1P9, LOC401677 |
| Skin | | | | EEF1B2P2, EEF1DP1, EEF1DP4, EEF1DP5, EEF1GP1, EEF1GP5, EEF1A1P1, EEF1A1P9, EEF1A1P11, EEF1A1P12 |
| Bones, joints and articular cartilage | | Bone osteosarcoma | | EEF1DP3 |
| Connective, subcutaneous and other soft tissues | | Sarcoma (SARC) | | |
| Eye, brain and other parts of central nervous system | | Glioma | | EEF1DP3, EEF1DP4, EEF1A1P9, EEF1A1P16 |
| Peripheral nerves and autonomic nervous system | | Primary myelofibrosis | | EEF1DP4 |
| Breast | | Breast carcinoma (BRCA) | | EEF1DP3, EEF1DP4, EEF1DP5, EEF1A1P7, EEF1A1P14, EEF1A1P29, EEF1A1P14 |
| Female genital organs | | Ovarian cancer | | EEF1A1P2, EEF1DP3 |
| System                                      | Cancer Type                                                                 | EEFs                                                                 |
|---------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------|
| Male genital organs                         | Cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC)      | EEF1DP3, EEF1A1P9                                                    |
|                                             | Prostate carcinoma (PRAD)                                                  | EEF1DP3, EEF1GP5, EEF1A1P9, EEF1A1P29                               |
| Urinary tract                               | Adrenocortical carcinoma (ACC)                                             | EEF1DP3                                                             |
|                                             | Bladder cancer/urothelial carcinoma (BLCA)                                 | EEF1A1P2, EEF1DP3                                                    |
|                                             | Chromophobe renal cell carcinoma (KICH)                                     | EEF1DP3                                                             |
|                                             | Kidney renal clear cell carcinoma (KIRC)                                   | EEF1DP3, EEF1A1P9                                                   |
|                                             | Kidney renal papillary cell carcinoma (KIRP)                               | EEF1DP3                                                             |
| Thyroid and other endocrine glands          | Pheochromocytoma and Paraganglioma (PCPG)                                 | EEF1DP3                                                             |
| Other and ill-defined sites                 | Head and neck squamous cell carcinoma (HNSC)                               | EEF1DP3                                                             |
| Hematological malignancies                 | Lymphoid neoplasm diffuse large B-cell lymphoma (DABC)                    | EEF1DP1, EEF1DP3, LOC729998, EEF1A1P42                              |
|                                             | Acute lymphoblastic leukemia                                               | EEF1A1P9, EEF1A1P24, EEF1A1P29                                      |
|                                             | Leukemia                                                                   |                                                                      |
|                                             | Multiple myeloma                                                           | EEF1A1P6, EEF1A1P12, EEF1A1P22                                      |
|                                             | Acute myeloid leukemia                                                     | EEF1B2P2, EEF1DP1, EEF1DP3, EEF1DP6, LOC729998, EEF1A1P42           |
| Other human diseases                        | EBV-positive T/NK-cell lymphoma                                            | EEF1A1P28                                                           |
| Infectious Agents                           | HIV-1 reverse transcription cofactor                                       | EEF1B2P2                                                           |
| Mental, behavioural or neurodevelopmental disorders | Hepatitis E virus cofactor                                               | EEF1A1P5                                                           |
| Developmental anomalies                     | Schizophrenia                                                              | EEF1A1P6                                                           |
|                                             | Neuropathy in Charcot-Marie-Tooth disease type 1A                          | EEF1DP6                                                            |
| Diseases of the musculoskeletal system or connective tissue | Smith-Magenis syndrome                                                    | EEF1A1P43                                                          |
|                                             | Ankylosing spondylitis                                                    | EEF1DP3                                                            |
| Diseases of the nervous system              | Systemic juvenile idiopathic arthritis                                     | EEF1DP6                                                            |
|                                             | Synucleinopathy and Parkinson’s disease                                    | EEF1DP3                                                            |
|                                             | Multiple sclerosis                                                         | EEF1DP3                                                            |
|                                             | Duchenne muscular dystrophy                                                | EEF1GP5, EEF1A1P9                                                  |
| Diseases of the skin                        | Epilepsy                                                                   | EEF1A1P12                                                          |
| Diseases of the digestive system            | Celiac disease                                                             | EEF1A1P1                                                           |
|                                             | Nonalcoholic fatty liver disease                                           | EEF1A1P20                                                          |
| Endocrine, nutritional or metabolic diseases | Type 2 diabetes mellitus                                                   | EEF1A1P11, EEF1A1P26                                               |
| Diseases of the circulatory system          | Coronary artery disease                                                    | EEF1E1P1                                                           |
ovarian cancer and rectal cancer, but no other studies have been conducted.

EEF1A1 pseudogene 16 (EEF1A1P16) and EEF1A1 pseudogene 38 (EEF1A1P38) are both upregulated in gastric cancer patient samples. Furthermore, EEF1A1P16 is also reported on glioma while EEF1A1P38 is reported on oral squamous cell carcinoma (with copy gain). EEF1A1 pseudogene 19 (EEF1A1P19) is reported in hepatocellular carcinoma, while EEF1A1 pseudogene 20, alias EEF1A1P20, is reported in a study concerning single nucleotide polymorphisms associated with the pathology of non-alcoholic fatty liver disease. EEF1A1 pseudogene 21 (EEF1A1P21) is reported in oral squamous cell carcinoma (with copy gain). EEF1A1 pseudogene 22 (EEF1A1P22) is reported in multiple myeloma, while EEF1A1 pseudogene 24, alias EEF1A1P24, is reported in datasets on acute lymphoblastic leukaemia.

EEF1A1 pseudogene 26, alias EEF1A1P26, is reported in type 2 diabetes mellitus and oral squamous cell carcinoma (with copy gain), while EEF1A1 pseudogene 27 (EEF1A1P27) is reported in oral squamous cell carcinoma (with copy gain). EEF1A1 pseudogene 28 (EEF1A1P28) shows copy number gain in EBV-positive T/NK-cell lymphoma and EEF1A1 pseudogene 29 (EEF1A1P29) is reported in breast cancer, prostate cancer, colorectal cancer and leukaemia. EEF1A1 pseudogene 31 (EEF1A1P31) was first reported in 2018 while EEF1A1 pseudogene 32 (EEF1A1P32) is reported in oral squamous cell carcinoma (with copy gain). EEF1A1 pseudogene 37 (EEF1A1P37) and EEF1A1 pseudogene 39 (EEF1A1P39) are reported together on oral squamous cell carcinoma with copy loss for the former and a copy gain for the latter. EEF1A1 pseudogene 43, alias EEF1A1P43 or formerly known as EEF1A3, was first reported in 1998 and later in Smith-Magenis syndrome where, however, it is not considered important because it does not show significant physiological effects.

The EEF1A1 pseudogene 4 (EEF1A1P4), the EEF1A1 pseudogene 8 (EEF1A1P8), the EEF1A1 pseudogene 10 (EEF1A1P10) and the EEF1A1 pseudogene 15 (EEF1A1P15) are first described in 1996 but no other studies have been done. Lastly, the remaining ones, i.e. EEF1A1 pseudogene 2 (alias EEF1A1P2), EEF1A1 pseudogene 17 (EEF1A1P17), EEF1A1 pseudogene 18 (EEF1A1P18), EEF1A1 pseudogene 23 (EEF1A1P23), EEF1A1 pseudogene 25 (EEF1A1P25), EEF1A1 pseudogene 30 (EEF1A1P30), EEF1A1 pseudogene 33 (EEF1A1P33), EEF1A1 pseudogene 34 (EEF1A1P34), EEF1A1 pseudogene 35 (EEF1A1P35), EEF1A1 pseudogene 36 (EEF1A1P36), EEF1A1 pseudogene 40 (EEF1A1P40) and EEF1A1 pseudogene 41 (EEF1A1P41), are predicted by genome sequence analysis but are not yet supported by experimental evidence, so they are very little known.

Pseudogenes of EEF1A2

EEF1A2 is a coding gene located on Chromosome 20 (20q13.33) and at the same time it is an isofom of EEF1A1 that performs the same function in the translation elongation step. The switch between the two isoforms occurs only in the brain, heart and skeletal muscle. EEF1A2 shows expression alterations and various genomic anomalies in many cancers. Analysis of the human genome revealed nine poorly studied pseudogenes for EEF1A2 listed below. EEF1A1 pseudogene 42, alias EEF1A1P42, is associated with EEF1A2 pseudogenes instead with EEF1A1 pseudogenes and is reported in datasets on some cancer cell lines of hepatocellular carcinoma, acute myeloid leukaemia and diffuse large B-cell lymphoma without any other type of study.

LOC401677 is reported in some papers and in datasets on melanoma, in particular in the FEMX-I melanoma cell line.

LOC642791 and LOC729856 are reported in some studies but not much more is known about them.

The other EEF1A2 pseudogenes, namely LOC441880, LOC100421798, LOC100421817, LOC100421840 and LOC100421842, are predicted by genome sequence analysis but are not yet supported by experimental evidence, so they are unknown.

Conclusion and perspective

All the coding genes belonging to EEFs play an important role in the cell and undergo important alterations in cancer. Similarly, even if still in its infancy, the studies available so far on the respective pseudogenes highlight at least two important aspects: first, they certainly have one or more roles in the cell, most likely via ncRNAs, but the possibility of other forms of regulation is not excluded, including through proteins or peptides still unknown, and second that they certainly have a role in human pathologies, first of all in cancer.

EEFs pseudogenes discovered to date are very numerous, especially for EEF1A1, and this could not only be a simple result of chance, a consequence of errors or evolution, but could reflect a complex system of genomic regulation that is still poorly understood today. EEF1A1, for example, is very conserved in the evolution of the species, so much so that its counterpart is also known in bacteria with the name of EF-Tu. Therefore, it is the oldest gene in the EEFs and has certainly been the subject of many events during the evolution of the species. However, it may be equally true that the abundance of its pseudogenes in the human genome is not only entirely linked to evolution but could also be related to other factors, including the high transcription of its parental gene. Indeed, in some cases there is a positive correlation between high levels of gene expression, especially for housekeeping genes, and the increase in the number of related pseudogenes in the human genome. This is true, apart for EEF1A1, also for GAPDH and RPL21 (for more details see supplementary table TAI SUPPL), both of which are highly transcribed.

The other members of the EEFs, among them, have a similar number of pseudogenes and this is less than ten except for EEF1E1 which has only one pseudogene. On an evolutionary level, the latter could certainly be the most recent, but it is also significant that its parental gene is considered a putative tumor suppressor gene that is often downregulated in cancer. In fact, EEF1E1 also has the least number of genomic rearrangements.

It is currently not known whether the pseudogenes of EEFs have a regulatory role in the expression of the
respective parental gene as described for others and for many there is still no evidence of their involvement in the development and/or progression of human cancers or other human diseases because there is no sufficient knowledge about them to understand their repercussions on cellular behavior. Furthermore, EEFs pseudogenes could theoretically produce non-coding transcripts, but there is currently no firm evidence for this.

The studies in which EEFs pseudogenes have most appeared concern oral squamous cell carcinoma, hepatocellular carcinoma, osteosarcoma, breast cancer and acute myeloid leukaemia (Table 2). However, their exact role in these cancers is not yet defined while the most studied pseudogenes are EEF1DP3 and EEF1A1P9, although they must be well characterized and understood. More work is needed for all these pseudogenes, especially for those that are currently less known, to achieve two very important goals, in addition to general knowledge about them, which are their role as possible biomarkers, both diagnostic and prognostic, and their possible role as therapeutic targets.

In conclusion, EEFs pseudogenes may play a role in the cell, probably in gene regulation, and are involved in many human diseases, including cancer. In the future, it will be important to characterize them and explore their ability to modulate parental gene expression under different cellular conditions, their precise mechanisms of function and the possibility of using them as new biomarkers or therapeutic targets for cancer management and treatment or other human diseases.

Conflict of interests

The author has no conflict of interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2021.03.009.

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