Solid Tumour Section
Short Communication

EEF1G/PPP6R3 (11q12-13)

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Abstract

Analysis of the EEF1G/PPP6R3 fusion involving EEF1G (alias, eukaryotic translation elongation factor 1 gamma) gene and PPP6R3 (alias, protein phosphatase 6 regulatory subunit 3) gene. It was detected in lung squamous cell carcinoma.

Keywords
Chromosome 11; EEF1G; eukaryotic translation elongation factor 1 gamma, EF1G, GIG35, PRO1608, EEF1 gamma, EEF-1B gamma, EF-1-gamma, elongation factor 1-gamma, translation elongation factor EEF-1 gamma chain, pancreatic tumor-related protein; PPP6R3, protein phosphatase 6 regulatory subunit 3, PPP6R3, chromosome 11 open reading frame 23, C11orf23, SAPS domain family member 3, SAPS3, EEF1G/PPP6R3, lung squamous cell carcinoma

Clinics and pathology

Disease
Lung squamous cell carcinoma

Note
Lung squamous cell carcinoma (lung SqCC) shows very complex genomic alterations with abundant exonic mutations, genomic rearrangements and gene copy number alterations.

Some authors detected the presence of the EEF1G/PPP6R3 fusion deriving by the genomic translocation of a part of EEF1G gene with a portion of PPP6R3 gene, both located on chromosome 11 (Hammerman et al., 2012). Other fusion genes or abnormal chromosomal translocations detected for PPP6R3 in this cancer type are t(7;11)(q21;q13) CCDC132/PPP6R3, t(7;11)(q34;q13) PPP6R3/MGAM, t(7;11)(q34;q13)SSBP1/PPP6R3, and fusion genes PPP6R3/ARHGAP1, PPP6R3/CNTN5, and PPP6R3/LRP5 (Yoshihara et al., 2015; Hammerman et al., 2012; http://www.tumorfusions.org)

Prognosis
There is no evidence of the impact of the EEF1G/PPP6R3 fusion gene on the tumour behaviour and so its contribution in the prognosis of lung squamous cell carcinoma is still unknown.

Genes involved and proteins

EEF1G
Location 11q12.3

Note
Eukaryotic translation elongation factor 1 gamma, alias eEF1G, is a protein that play a main function in the elongation step of translation process but also cover numerous moonlighting roles.
It is expressed ubiquitously in human tissues and often it is found over-expressed in human cancer samples and cancer cell lines.

DNA / RNA
EEF1G (Eukaryotic Translation Elongation Factor 1 Gamma) is a protein coding gene with 10 exons and a length of 14388 bp (RefSeq NC_000011.10). Its transcript is 1446 bp long (RefSeq NM_001404.5) but was observed five splice variants and nine pseudogenes probably originated by retrotransposition.
**Protein**
eEF1G is formed by 437 amino acids (RefSeq NP_001395.1), it has a molecular weight of 50.12 kDa and it is a multi-domain protein which consist of three main domains: from the amino to carboxyl half terminal there are a glutathione S-transferase (GST)-like N-terminus domain (NT-eEF1G), a glutathione S-transferase (GST)-like C-terminus domain (CT-eEF1G) and a conserved C-terminal domain (CD-eEF1G)(Achilonu et al., 2014).
eEF1G is a subunit of the eukaryotic elongation factor-1 complex named eEF1H that result by the aggregation of different proteins that play a central role in peptide elongation during eukaryotic protein biosynthesis. The physiological role of eEF1G is still not well defined, however eEF1G seems to be necessary for guarantee the stability to entire eEF1H complex and to stimulate the activity of the eEF1B2 subunit during the elongation step of translation (Mansilla et al., 2002). However, are known that it has multiple non-canonical roles (moonlighting roles) inside the cell such as the interaction with cytoskeleton and binding with various mRNA and several proteins, comprise membrane-bound receptors (Coumans et al., 2014; Corbi et al., 2010; Cho et al., 2003).

**PPP6R3**

**Location** 11q13.2

**DNA / RNA**

PPP6R3 is a protein coding gene of 154617 nt long (RefSeq NC_000011.10) and with an abundant number of alternative splicing variants, i.e. 38 coding mRNA and 24 non-coding mRNA.

**Protein**

PPP6R3 counts 24 protein isoforms and is one of the three regulatory subunits of protein phosphatase 6 (PP6) complex (York et al., 2014; Guergnon et al., 2009) and has a sit4-associated protein domain, alias SAPS domain (Stefansson and Brautigan, 2006). It plays a role, as member of PP6 holoenzyme, in the turnover of serine and threonine phosphorylation events during mitosis acting as a regulatory element of the complex.

**Result of the chromosomal anomaly**

**Hybrid Gene**

The result of chromosomal anomaly is the EEF1G/PPP6R3 fusion with the formation of a novel but not still characterized fusion gene 5' EEF1G - 3' PPP6R3. Hammerman and colleagues (Hammerman et al., 2012) found it in patients with lung squamous cell carcinoma (lung SqCC), but there are no data or evidence about its mRNA and/or its protein. So, in this review, with the use of Ensembl (http://www.ensembl.org), will be predicted the result of this rearrangement. However, the data collected and showed are hypothesis and have to be experimentally verified.

![Figure 1. Schematic representation of the EEF1G gene, PPP6R3 gene and the EEF1G-PPP6R3 fusion.](https://www.genecards.org)
Description
A EEF1G/PPP6R3 fusion was found in lung squamous cell carcinoma (lung SqCC) (Hammerman et al., 2012). Hammerman and colleagues (Hammerman et al., 2012) identified two DNA breakpoints that cause the EEF1G/PPP6R3 fusion: the first is located at the position 62,332,148 of the EEF1G gene, while the second is located at the position 68,368,269 of PPP6R3 (alias, SAPS3) gene, both upstream of the respective genes involved. In addition, Hammerman and colleagues (Hammerman et al., 2012) identified a novel fusion gene 5'EEF1G - 3'PPP6R3 derived by this abnormal translocation thus formed: at 5' fusion end there is a sequence starting from 4 kb before EEF1G gene while at 3' fusion end there is a sequence starting from 303 bp after exon 19 of PPP6R3 gene. However, the nucleotide sequence of this novel chimeric gene is not reported or registered anywhere and so it remains uncharacterized.

From the direct analysis of the gene sequences and the respective DNA breakpoints using Ensembl (http://www.ensembl.org), could be advanced the hypothesis that the chromosomal rearrangement where EEF1G and PPP6R3 are involved, although it was described as an intra-chromosomal translocation, it seems more similar to an inversion. Moreover the first breakpoint is located 236,453 nt before EEF1G gene while the second breakpoint is located just before PPP6R3 gene, i.e. 92,441 nt before PPP6R3 gene (Figure.1). This chromosomal rearrangement permits to bring near EEF1G to PPP6R3, reducing the long distance between them, i.e. from 5,886,730 nt (about 5,886 kb) to only 328,894 nt (about 328 kb). The reason of this rearrangement is unknown.

Transcript
There is no evidence about the mRNA of the EEF1G/PPP6R3 fusion gene or other transcript resulting from the EEF1G/PPP6R3.

Fusion Protein
Description
There is no evidence of protein from the EEF1G/PPP6R3 fusion gene.

Oncogenesis
The role in oncogenesis of the EEF1G/PPP6R3 fusion is unclear, and there is no evidence about its effective transcription and/or translation. Hammerman and colleagues (Hammerman et al., 2012) have supposed the presence of a fusion gene 5'EEF1G - 3'PPP6R3 but actually there are poor data about it and thus it is unclearly the role of this fusion gene, i.e. if is effectively translated into a functional protein or instead it plays a regulatory role. What it is clear is that PPP6R3 is involved in many and heterogeneous genomic translocations in different kind of tumors as EEF1G that is involved in numerous genomic alterations such as translocations and in novel fusion genes. Both genes are important for cell biology and it is normal that they are subjected to rearrangements in cancer cells. In addition, this could happens also for the characteristics of their promoters because at least for PPP6R3 it is known that it possess a potent promoter activity (Guo et al., 2016). However, the truly oncogenic potential of EEF1G/PPP6R3 in proliferation and cancer aggressiveness needs to be better elucidated.

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