Leukaemia Section
Short Communication

t(2;11)(p23;q12.3) EEF1G/ALK

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Published in Atlas Database: March 2019

Online updated version: http://AtlasGeneticsOncology.org/Anomalies/t0211p23q12EEF1G-ALKID1841.html
DOI: 10.4267/2042/70660

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Abstract

Review on the translocation t(2;11)(p23;q12.3) EEF1G/ALK involving EEF1G (alias, eukaryotic translation elongation factor 1 gamma) gene and ALK (alias, anaplastic lymphoma kinase) gene. The novel fusion gene and correspondent chimeric protein were observed in pediatric anaplastic large cell lymphoma (ALCL) patients. EEF1G/ALK translocation carries an unfavorable prognosis.

Keywords
Chromosome 2; chromosome 11; EEF1G; eukaryotic translation elongation factor 1 gamma; EF1G, GIG35, PRO1608, EF1γ, EF1By, EF-1B gamma, EF-1-gamma, elongation factor 1-gamma, translation elongation factor EF-1 gamma chain, pancreatic tumor-related protein; ALK; anaplastic lymphoma kinase; anaplastic lymphoma receptor tyrosine kinase; CD246; NBLST3; (2;11)(p23;q12.3); anaplastic large cell lymphoma

Clinics and pathology

Disease
Anaplastic large cell lymphoma (ALCL), CD30-positive, ALK-positive

Note
Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma, alias ALK+ ALCL, is a T-cell peripheral lymphoma characterized by many genomic aberrations and chromosomal rearrangements that make the cellular karyotype much complicated. It consists of a proliferation of usually large, pleomorphic, T-lymphocytes with strong expression of the cytokine receptor CD30 (CD30+), with abundant cytoplasm and the presence of some translocation and rearrangements involving the ALK gene with 2p23/ALK aberrations well know, such as the classic t(2;5)(p23;q35) NPM1/ALK rearrangement, and others less know. These multiple partner fusion genes are transcribed and also translated in several fusion protein variants (Palacios et al., 2017; van der Krogt et al., 2017; van Krieken, 2017; Stein et al., 2000; http://codes.iarc.fr).

Epidemiology

ALK+ ALCL predominantly affects young male patients and in one study 28 pediatric patients were tested for the presence of the chimeric EEF1G/ALK fusion gene and is emerged that only four of them (4/28, i.e. 14.29%) shown a different variant by common NPM1/ALK rearrangement (that represent instead 85.71% of samples) and only two of whom (2/28, i.e. 7.14%) shown the chimeric EEF1G/ALK fusion (Palacios et al., 2017; Stein et al., 2000).

Prognosis

The prognosis is very poor. In fact, patients expressing EEF1G/ALK fusion gene have shown an unfavorable clinical course with fatal outcome.

Cytogenetics

Cytogenetics molecular

In ALK+ ALCL was observed that the major fusion partner of ALK is nucleophosmin 1 (NPM1) which results in the translocation t(2;5)(p23;q35) and aberrant production of the fusion protein NPM1/ALK (Morris et al., 1994; Palacios et al., 2017) but other different partners has been identified, such as TMP3, TFG, ATIC, CLTCL, MSN, MYH9, TRAF1 and EEF1G (Hallberg and Palmer, 2013; Stein et al., 2000).

Atlas of Genetics and Cytogenetics in Oncology and Haematology. 2020; 24(2)
Remarkingly, any fusion with an alternative partner leads to an aberrant constitutive activation of the catalytic domain of ALK through homodimerization (Palacios et al., 2017; Bischof et al., 1997).

**Genes involved and proteins**

**EEF1G**

**Location 11q12.3**

**Note**

Alias: Eukaryotic translation elongation factor 1 gamma, EF1G, GIG35, PRO1608, EF1γ, EF1Bγ, EEF-1B Gamma, EF-1-Gamma, Elongation Factor 1-Gamma, Translation Elongation Factor EEF-1 Gamma Chain, Pancreatic Tumor-Related Protein 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).

**ALK**

**Location 2p23.2**

**Note**

Alias: anaplastic lymphoma receptor tyrosine kinase, anaplastic lymphoma kinase (Ki-1), CD246, NBLST3

**DNA/RNA**

ALK (anaplastic lymphoma kinase) gene is composed by 29 exons (RefSeq NC_000002) and its transcript is 6240 nt long (RefSeq NM_004304).

**Protein**

ALK is formed by 1620 amino acids (RefSeq NP_004295) and it has a molecular weight of 177 kDa. It is a transmembrane receptor tyrosine kinase of the insulin receptor superfamily and it is
composed of several domains, i.e. an extracellular region (with meprin, A5 protein, and receptor protein-tyrosine phosphatase mu domains, alias MAM domains), a transmembrane domain and an intracellular region with a tyrosine kinase domain (Allouche M, 2010). The native ALK protein is found to be expressed during the development and at a weaker level in adult central and peripheral nervous system, but it cannot be detected in hematopoietic cells (Iwahara et al., 1997). The function of ALK receptor is poorly understood but it is supposed that it may have a role in the development and maintenance of central and peripheral nervous system (Allouche M, 2010; Allouche M, 2007).

**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**

It was observed in some ALK+ ALCL pediatric patients the presence of an in-frame fusion transcript between an intronic region among exons 8 and 9 of EEF1G with the middle part of exon 20 of ALK. The resulting novel fusion chimeric gene 5'EEF1G/3'ALK was revealed to be a coding-gene (van der Krogt et al., 2017).

On the contrary, other authors found EEF1G/ALK transcripts in a tumor sample originated by the genomic fusion of the exon 6 of EEF1G with the exon 20 of ALK. The presence of the chimera EEF1G/ALK was not observed in vitro in the corresponding cancer SupM2 (NPM1/ALK positive ALCL) cell line (Palacios et al., 2017).

**Fusion protein**

**Description**

The EEF1G/ALK fusion gene encodes a chimeric protein of 780 amino acids with a molecular mass of 87 kDa. Its amino acidic structure include the N-terminal GST-like domain of EEF1G (residues 1-225) and the intracellular tail containing the protein tyrosine kinase (PTK) domain of ALK (resides 226-780) (Palacios et al., 2017). In another study by other authors the chimeric eEF1G/ALK protein was described with some structural differences and it was reported that it is 857 amino acids long (van der Krog et al., 2017). The chimeric protein eEF1G/ALK is a constitutively active protein as demonstrated by analysis and this is due to its own probable homodimerization followed by the kinase activation (Palacios et al., 2017; van der Krog et al., 2017; van Krieken, 2017; Allouche M, 2007).

Figure 2 Schematic representation of the eEF1G, ALK and eEF1G/ALK protein structures. In the upper side of the image there are the structures with also the main structural domains both eEF1G protein and ALK protein. In the bottom side of the image are reported two proposed structures by different authors: (1) eEF1G/ALK fusion protein with complete GST C-terminal domain and GST N-terminal domain of eEF1G fused with the kinase domain of ALK (Palacios et al., 2017) and (2) eEF1G/ALK fusion protein with complete C-terminal domain, GST C-terminal domain and with a partial GST N-terminal domain of eEF1G fused with the kinase domain of ALK (van der Krogt et al., 2017) (reworked by Palacios et al., 2017; van der Krogt et al., 2017).
Furthermore, was revealed that expression of EEF1G/ALK can give a cytokine-independent growth to the cancer cells. However, its biological activities, its oncogenic potential and its roles in proliferation and cancer aggressiveness are still poor understood although it is supposed that eEF1G-ALK fusion protein has a cell-transforming activity due to the activation of ALK kinase by the GST domain of EEF1G (Palacios et al., 2017).

Expression / Localisation
EEF1G/ALK was found only in the cytoplasm (Palacios et al., 2017).

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This article should be referenced as such:

Cristiano L. t(2;11)(p23;q12.3) EEF1G/ALK. Atlas Genet Cytogenet Oncol Haematol. 2020; 24(2):87-90.