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Gene Section
Review

ALK (anaplastic lymphoma receptor tyrosine kinase)

Michèle Allouche

INSERM U.563 CPTP, Bat. B, Pavillon Lefevre, CHU Purpan, BP 3028, 31024 Toulouse Cedex 3, France (MA)

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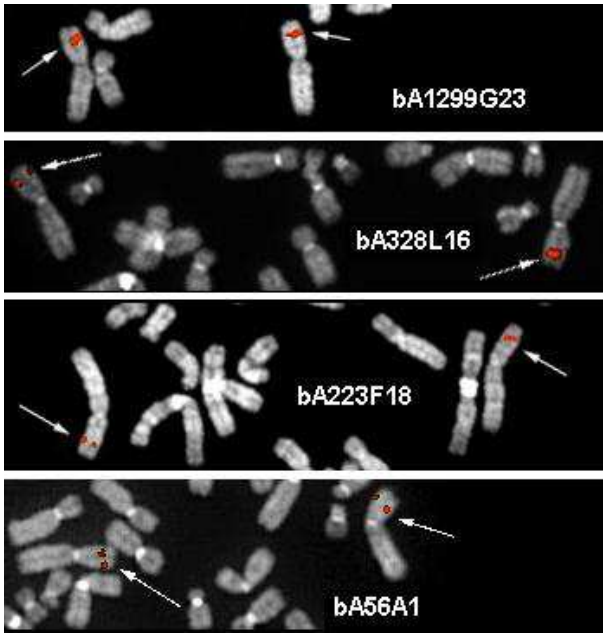
Identity

Other names: anaplastic lymphoma kinase (Ki-1); CD246

HGNC (Hugo): ALK

Location: 2p23



ALK (2p23) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

DNA/RNA

Description

The gene is composed of 29 exons spanning in a region of 728793 bp.

Transcription

6226 bp cDNA; coding sequence: 4.9 kb.

Protein

Description

1620 amino acids; 177 kDa; after glycosylation, produces a 200 kDa mature glycoprotein; type I transmembrane receptor; composed of an extracellular region (containing two MAM and one LDLa domains, and one glycin-rich region), a transmembrane, and an intracellular region (composed of a juxta-membrane domain, a tyrosine kinase domain (1122-1376), and a C-terminal domain; dimerization.

Expression

Is tissue specific; mainly in: central and peripheral nervous system during development (less in adult), and testis; not in the lymphocytes.

Localisation

Cell membrane.

Function

ALK is a membrane associated tyrosine kinase receptor of the insulin receptor superfamily. The function of the full-length ALK receptor is poorly understood. It has a probable role in the central and peripheral nervous system development and maintenance. ALK is a dependence receptor, which may exert antagonist functions, proapoptotic or antiapoptotic, depending on the absence or presence of a ligand (Mourali et al., 2006). Dependence receptors have a potential role in cancer and development (Allouche, 2007). Ligands available for this demonstration were agonist anti-ALK antibodies (Motegi et al., 2004; Moog-Lutz et al., 2005). If a specific ALK ligand (jelly belly) has been clearly identified in Drosophila, it has no homologue in vertebrates (Palmer et al., 2009). ALK is still an orphan receptor, given the high level of controversy about pleiotrophin and midkine, which have been proposed as ligands by Stoica et al. (2001, 2002) (see review by Chiarle et al., 2008).

Homology

Homologies with the insulin receptor super family: LTK (leucocyte tyrosine kinase), IGF1-R, IRb, TRKA, ROS (homolog of the drosophila Sevenless).

Implicated in

ALK+ anaplastic large cell lymphoma (ALCL)

Disease

ALCL are high grade non Hodgkin lymphomas. ALK+ ALCL are ALCL where ALK is involved in a fusion gene; systemic ALK+ ALCL (as opposed to cutaneous ALCL, which are usually ALK negative) represent 60 to 80 % of ALCL cases (they are CD30+, ALK+); 70 to 80% of ALK+ ALCL cases bear a t(2;5); the remaining ALK+ ALCL cases bear variant translocations "X-ALK", where X designates a partner gene.

Prognosis

Although presenting as a high grade tumour, an 80% five year survival is associated with this anomaly, but recurrence is a concern.

Cytogenetics

The prototype anomaly is the t(2;5)(p23;q35) generating the NPM1-ALK fusion.

Alternative anomalies involving the ALK gene in ALCL are described below as "cytoplasmic ALK+ ALCL" cases, among which the t(1;2) TPM3-ALK is found in 20% of ALK+ ALCL.

Complex karyotypes may also be found.

Hybrid/Mutated gene

5' NPM1 - 3' ALK on the der(5).

Abnormal protein

680 amino acids, 80 kDa; N-term 117 amino acids from NPM1 fused to the 563 C-term amino acids of ALK (i.e. composed of the oligomerization domain and the metal binding site of NPM1, and the entire cytoplasmic portion of ALK); no apparent expression of the ALK/NPM1 counterpart. Characteristic localisation in the cytoplasm, nucleus and nucleolus, due to heterooligomerization of NPM1-ALK and normal NPM1 whereas the normal NPM1 protein is confined to the nucleus and nucleolus; constitutive activation of the catalytic domain of ALK.

Oncogenesis

Via the kinase function activated by oligomerization of NPM1-ALK mediated by the NPM1 part.

Cytoplasmic ALK+ anaplasic large cell lymphoma (ALCL)

Prognosis

Present a favourable prognosis comparable to the one found in t(2;5) ALK+ ALCL.

Cytogenetics

Either t(X;2)(q11;p23), t(1;2)(q25;p23), inv(2)(p23q35), t(2;3)(p23;q21), t(2;17)(p23;q23), t(2;17)(p23;q25), t(2;19)(p23;p13.1) or t(2;22)(p23;q11.2).

Hybrid/Mutated gene

5' MSN, TPM3, ATIC, TFG, CLTC, ALO17, TPM4 or MYH9 - 3' ALK.

Abnormal protein

N-term amino acids from the partner gene fused to the 563 C-term amino acids (in the great majority of cases) from ALK (i.e. the entire cytoplasmic portion of ALK with the tyrosine kinase domain); cytoplasmic/membraneous localisation only.

Oncogenesis

The partner gene seems to provoke the dimerization of the fused X-ALK, which should lead to constitutive autophosphorylation and activation of the ALK tyrosine kinase, as for NPM1-ALK (see t(2;5)(p23;q35)).

Inflammatory myofibroblastic tumours with 2p23 rearrangements

Disease

Rare soft tissue tumour found in children and young adults about one third to half of inflammatory myofibroblastic tumour cases present with a 2p23 rearrangement involving ALK.

Prognosis

Good prognosis.

Cytogenetics

t(1;2)(q25;p23), t(2;2)(p23;q13) or inv(2)(p23;q11-13), inv(2)(p23;q35), t(2;4)(p23;q21), t(2;11)(p23;p15), t(2;17)(p23;q23), or t(2;19)(p23;p13.1) so far.

Hybrid/Mutated gene

5' TPM3 in the t(1;2), RANBP2 in the t(2;2) or inv(2)(p23;q11-13), 5' ATIC in inv(2)(p23;q35), 5'

SEC31L1 in t(2;4), 5' CARS in the t(2;11), 5' CLTC in the t(2;17), or 5' TPM4 in the t(2;19) - 3' ALK.

Abnormal protein
N-term amino acids from the partner gene fused to the 563 C-term amino acids from ALK (i.e. the entire cytoplasmic portion of ALK with the tyrosine kinase domain); homodimerization of the fusion protein is known or suspected.

Oncogenesis
Fused-ALK is constitutively activated.

ALK+ diffuse large B-cell lymphoma (DLBCL)

Disease
Very rare form of DLBCL (40 cases described) expressing either ALK in fusion with CLTC (cytoplasmic granular localisation) associated to t(2;17)(p23;q23) (most frequently), or (rarely) NPM1-ALK in t(2;5)(p23;q35); tumours are EMA+, CD30- and CD20-negative.

Prognosis
Poor prognosis: aggressive lymphoma with 25% five year survival.

Cytogenetics
t(2;5)(p23;q35) or t(2;17)(p23;q23).

Hybrid/Mutated gene
5' NPM1 or CLTC - 3' ALK.

Abnormal protein
N-term amino acids from the partner gene fused to the 563 C-term amino acids from ALK (i.e. the entire cytoplasmic portion of ALK with the tyrosine kinase domain); homodimerization of the fusion protein is known or suspected.

Oncogenesis
Fused-ALK is constitutively activated.

ALK+ non-small cell lung cancer (NSCLC)

Disease
1-6 % of all NSCLC present a rearrangement involving ALK fused to EML4 in an inv(2)(p21p23); studies on East Asian and American/European patients (Soda et al., 2007; Perner et al., 2008).

Prognosis
50% survival at 24 months, so far (first identification in 2007).

Cytogenetics
inv(2)(p21;p23).

Hybrid/Mutated gene
5' EML4 - 3' ALK; multiple variants of EML4-ALK noted depending on the breakpoint on the EML gene; ALK fusion starts at a portion encoded by exon 20.

Abnormal protein
N-term amino acids from the partner gene fused to the 563 C-term amino acids from ALK (i.e. the entire cytoplasmic portion of ALK with the tyrosine kinase domain); homodimerization of the fusion protein is known or suspected; protein is difficult to detect by classical immunohistochemistry methods (low expression).

Oncogenesis
Fused-ALK is constitutively activated.
Note: in a European study, EML4-ALK fusion transcript has also been found in up to 9% non-tumour lung tissue from lung tumour patients. Interestingly, the EML4-ALK transcript was not detected in matching tumour samples from the same patients (Martelli et al., 2009).

Familial neuroblastoma and sporadic neuroblastoma

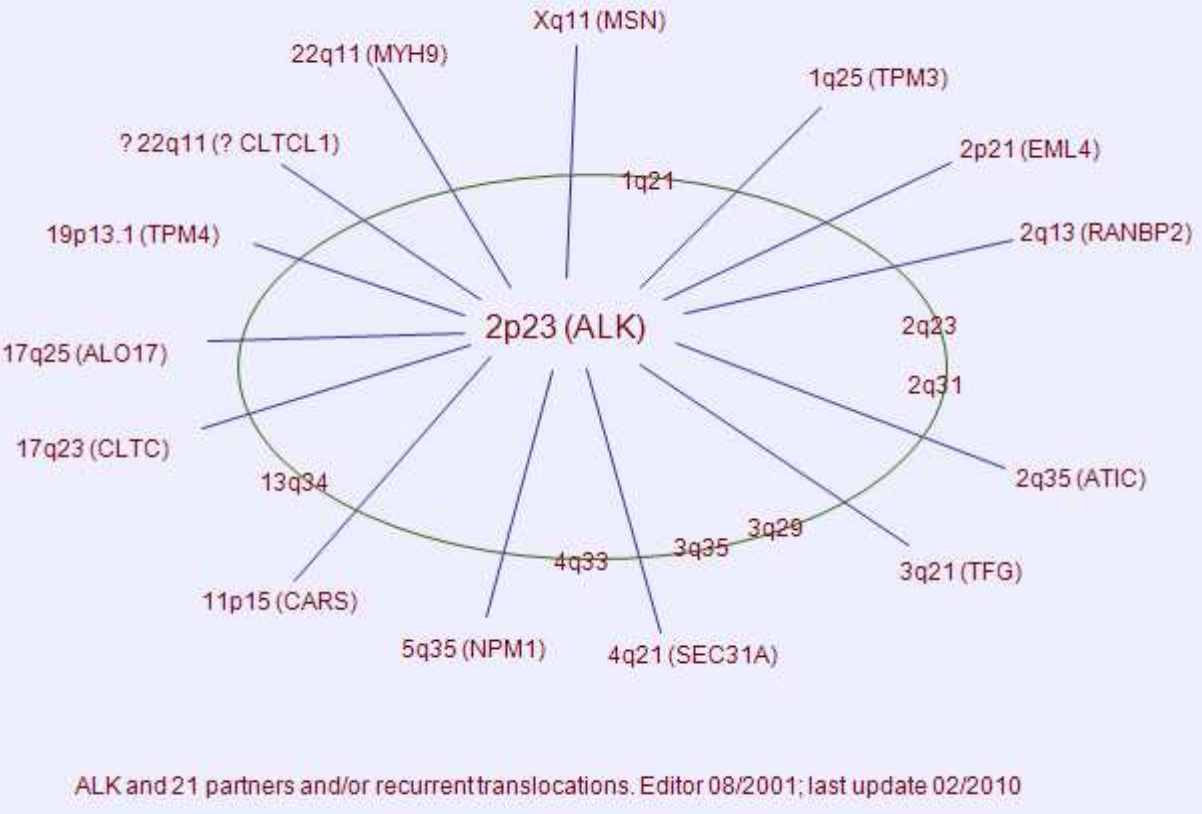
Disease
Neuroblastoma is a cancer of early childhood that arises from the developing autonomic nervous system, giving rise to peripheral tumours. It is the most common malignancy diagnosed in the first year of life and shows a wide range of clinical phenotypes, with a few patients having tumours that regress spontaneously, whereas most patients have aggressive metastatic disease. It can be transmitted in an autosomal dominant mode as a familial predisposition, or occur as a sporadic disease.

Prognosis
Aggressive neuroblastoma cases have survival probabilities of less then 40% despite intensive chemoradiotherapy, and the disease continues to account for 15% of childhood cancer mortality.

Cytogenetics
Gene amplifications or mutations of ALK;
Associated alterations: tumours from patients with an aggressive phenotype often show amplification of the MYCN oncogene, and/or deletions of chromosome arms 1p and 11q.

Hybrid/Mutated gene
Several point mutations located in the coding region of the receptor intracellular portion, mostly in the tyrosine kinase domain.

Abnormal protein
54 ALK mutations reported, affecting 12 different residues (Caren et al., 2008; Chen et al., 2008; George et al., 2008; Janoueix-Lerosey et al., 2008; Mosse et al., 2008); two hotspots: F1174 and R1275.
Most frequent germline mutations (familial cases): G1128A, R1192P, R1275Q.



Most frequent somatic mutations (sporadic cases): F1174L/I, F1245C/V.

Oncogenesis

Gene amplifications or point mutations both confer constitutive kinase activation.

Breakpoints

Note

Most of the breakpoints occur in the same intron of ALK, whichever partner is involved in the fusion protein.

To be noted

Note

ALK in fusion to several gene partners, is found implicated both in hematopoietic and non-hematopoietic solid tumours; this was a new concept in 2003, that several different types of tumour may result from the same chromosomal/genes rearrangement(s).

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