Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Short Communication

ALK (anaplastic lymphoma kinase)

Jean-Loup Huret

Genetics, Dept Medical Information, UMR 8125 CNRS, UMR 8125 CNRS, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH)

Published in Atlas Database: August 2001

Online updated version : http://AtlasGeneticsOncology.org/Genes/ALK.html
DOI: 10.4267/2042/37775

This article is an update of: Huret JL. ALK (anaplastic lymphoma kinase). Atlas Genet Cytogenet Oncol Haematol.1997;1(1):4.

Identity

HGNC (Hugo): ALK

Location: 2p23

DNA/RNA

Transcription

6226 bp cDNA; coding sequence: 4.9 kb.

Protein

Description

1620 amino acids; 177 kDa; after glycosylation, produces a 200 kDa mature glycoprotein; composed of an extracellular domain, a transmembrane domain, a tyrosine kinase domain, and an intracytoplasmic domain in C-term; dimerization.

Expression

Is tissue specific; mainly in: brain, gut and testis; not in the lymphocytes.

Localisation

Cell membrane.

Function

Membrane associated tyrosine kinase receptor; probable role in the nervous system development and maintenance.

Homology

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

Implicated in

Anaplasic large cell lymphoma (ALCL) with t(2;5)(p23;q35) --> NPM1/ALK

Disease

ALCL are high grade non Hodgkin lymphomas; ALK+ ALCL are ALCL where ALK is involved in a fusion gene; ALK+ ALCL represent 50 to 60% of ALCL cases (they are CD30+, ALK+); 80% of ALK+ ALCL cases bear a t(2;5); the remaining ALK+ ALCL cases bear variant translocations described below and are called "cytoplasmic ALK+" cases.

Prognosis

Althouth presenting as a high grade tumour, a 80% five yr survival is associated with this anomaly.

Cytogenetics

Additional anomalies and complex karyotypes are most often found.

Hybrid/Mutated gene

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

Abnormal protein

680 amino acids, 80 kDa; N-term 116 amino acids from NPM1 fused to the 563 C-term aminoacids 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 both in the cytoplasm and in the nucleus, due to heterooligomerization of NPM-ALK and normal NPM whereas the normal NPM protein is confined to the nucleus; 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

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

Cytogenetics
Hidden translocation is frequently found; either t(X;2)(q11;p23), or t(1;2)(q25;p23), or inv(2)(p23q35), or t(2;3)(p23;q21), or t(2;22)(p23;q11.2).

Hybrid/Mutated gene
5' MSN, TPM3, ATIC, TFG, or CLTCL1 - 3' ALK.

Abnormal protein
N-term amino acids from the partner gene fused to the 562 C-term amino acids 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-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;17)(p23;q23), or t(2;19)(p23;p13.1) so far.

Hybrid/Mutated gene
5' TPM3 in the t(1;2), or 5' CLTC in the t(2;17), or 5' TPM4 in the t(2;19)- 3' ALK.

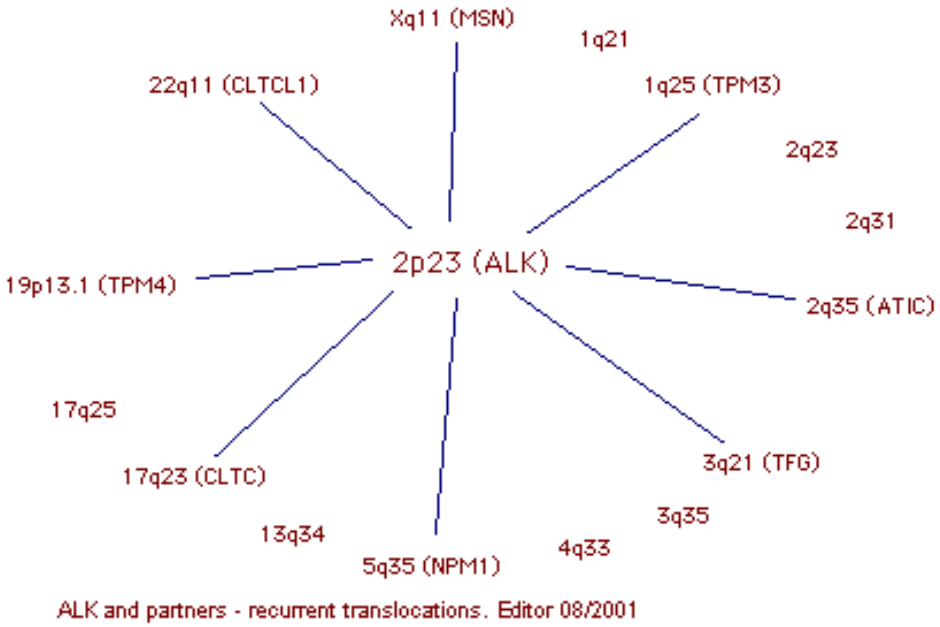
Abnormal protein
N-term amino acids from the partner gene fused to the 562 C-term amino acids from ALK (i.e. the entire cytoplasmic portion of ALK with the tyrosine kinase domain); homodimerization of the fusion protein is known or suspected.

Oncogenesis
Fused-ALK is contitutively activated.

To be noted

Note
ALK and some of the above ALK partners, or closely related genes, are found implicated in anaplasic large cell lymphoma; this is a new concept, that 2 different types of tumour may result from the same chromosomal/genes rearrangement.

Breakpoints



ALK and partners - recurrent translocations. Editor 08/2001

References

Morris SW, Kirstein MN, Valentine MB, Dittmer K, Shapiro DN, Look AT, Saltman DL. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science. 1995 Jan 20;267(5196):316-7

Bischof D, Pulford K, Mason DY, Morris SW. Role of the nucleophosmin (NPM) portion of the non-Hodgkin's lymphoma-associated NPM-anaplastic lymphoma kinase fusion protein in oncogenesis. Mol Cell Biol. 1997 Apr;17(4):2312-25

Iwahara T, Fujimoto J, Wen D, Cupples R, Bucay N, Arakawa T, Mori S, Ratzkin B, Yamamoto T. Molecular characterization of ALK, a receptor tyrosine kinase expressed specifically in the nervous system. Oncogene. 1997 Jan 30;14(4):439-49

Morris SW, Naeve C, Mathew P, James PL, Kirstein MN, Cui X, Witte DP. ALK, the chromosome 2 gene locus altered by the t(2;5) in non-Hodgkin's lymphoma, encodes a novel neural receptor tyrosine kinase that is highly related to leukocyte tyrosine kinase (LTK) Oncogene. 1997 May 8;14(18):2175-88

Griffin CA, Hawkins AL, Dvorak C, Henkle C, Ellingham T, Perlman EJ. Recurrent involvement of 2p23 in inflammatory myofibroblastic tumors. Cancer Res. 1999 Jun 15;59(12):2776-80

Hernández L, Pinyol M, Hernández S, Beà S, Pulford K, Rosenwald A, Lamant L, Falini B, Ott G, Mason DY, Delsol G, Campo E. TRK-fused gene (TFG) is a new partner of ALK in anaplastic large cell lymphoma producing two structurally different TFG-ALK translocations. Blood. 1999 Nov 1;94(9):3265-8

Lamant L, Dastugue N, Pulford K, Delsol G, Mariamé B. A new fusion gene TPM3-ALK in anaplastic large cell lymphoma created by a (1;2)(q25;p23) translocation. Blood. 1999 May 1;93(9):3088-95

Siebert R, Gesk S, Harder L, Steinemann D, Grote W, Schlegelberger B, Tiemann M, Wlodarska I, Schemmel V. Complex variant translocation t(1;2) with TPM3-ALK fusion due to cryptic ALK gene rearrangement in anaplastic large-cell lymphoma. Blood. 1999 Nov 15;94(10):3614-7

Colleoni GW, Bridge JA, Garicochea B, Liu J, Filippa DA, Ladanyi M. ATIC-ALK: A novel variant ALK gene fusion in anaplastic large cell lymphoma resulting from the recurrent cryptic chromosomal inversion, inv(2)(p23q35). Am J Pathol. 2000 Mar;156(3):781-9

Drexler HG, Gignac SM, von Wasielewski R, Werner M, Dirks WG. Pathobiology of NPM-ALK and variant fusion genes in anaplastic large cell lymphoma and other lymphomas. Leukemia. 2000 Sep;14(9):1533-59

Lawrence B, Perez-Atayde A, Hibbard MK, Rubin BP, Dal Cin P, Pinkus JL, Pinkus GS, Xiao S, Yi ES, Fletcher CD, Fletcher JA. TPM3-ALK and TPM4-ALK oncogenes in inflammatory myofibroblastic tumors. Am J Pathol. 2000 Aug;157(2):377-84

Ma Z, Cools J, Marynen P, Cui X, Siebert R, Gesk S, Schlegelberger B, Peeters B, De Wolf-Peeters C, Wlodarska I, Morris SW. Inv(2)(p23q35) in anaplastic large-cell lymphoma induces constitutive anaplastic lymphoma kinase (ALK) tyrosine kinase activation by fusion to ATIC, an enzyme involved in purine nucleotide biosynthesis. Blood. 2000 Mar 15;95(6):2144-9

Stein H, Foss HD, Dürkop H, Marafioti T, Delsol G, Pulford K, Pileri S, Falini B. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood. 2000 Dec 1;96(12):3681-95

Touriol C, Greenland C, Lamant L, Pulford K, Bernard F, Rousset T, Mason DY, Delsol G. Further demonstration of the diversity of chromosomal changes involving 2p23 in ALK-positive lymphoma: 2 cases expressing ALK kinase fused to CLTCL (clathrin chain polypeptide-like). Blood. 2000 May 15;95(10):3204-7

Trinei M, Lanfrancone L, Campo E, Pulford K, Mason DY, Pelicci PG, Falini B. A new variant anaplastic lymphoma kinase (ALK)-fusion protein (ATIC-ALK) in a case of ALK-positive anaplastic large cell lymphoma. Cancer Res. 2000 Feb 15;60(4):793-8

Bridge JA, Kanamori M, Ma Z, Pickering D, Hill DA, Lydiatt W, Lui MY, Colleoni GW, Antonescu CR, Ladanyi M, Morris SW. Fusion of the ALK gene to the clathrin heavy chain gene, CLTC, in inflammatory myofibroblastic tumor. Am J Pathol. 2001 Aug;159(2):411-5

Delsol G, Ralfkiaer E, Stein H, Wright D, Jaffe E.. Anaplastic large cell lymphomas, Primary systemic (T/Null cell type). World Health Organization (WHO) Classification of Tumors. Pathology and Genetics of tumours of Haematopoietic and Lymphoid Tissues. 2001 pp 230-235.

Morris SW, Xue L, Ma Z, Kinney MC. Alk+ CD30+ lymphomas: a distinct molecular genetic subtype of non-Hodgkin's lymphoma. Br J Haematol. 2001 May;113(2):275-95

Tort F, Pinyol M, Pulford K, Roncador G, Hernandez L, Nayach I, Kluin-Nelemans HC, Kluin P, Touriol C, Delsol G, Mason D, Campo E. Molecular characterization of a new ALK translocation involving moesin (MSN-ALK) in anaplastic large cell lymphoma. Lab Invest. 2001 Mar;81(3):419-26

This article should be referenced as such:

Huret JL. ALK (anaplastic lymphoma kinase). Atlas Genet Cytogenet Oncol Haematol. 2001; 5(4):249-251.