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Gene Section
Mini Review

ALK (anaplastic lymphoma kinase)

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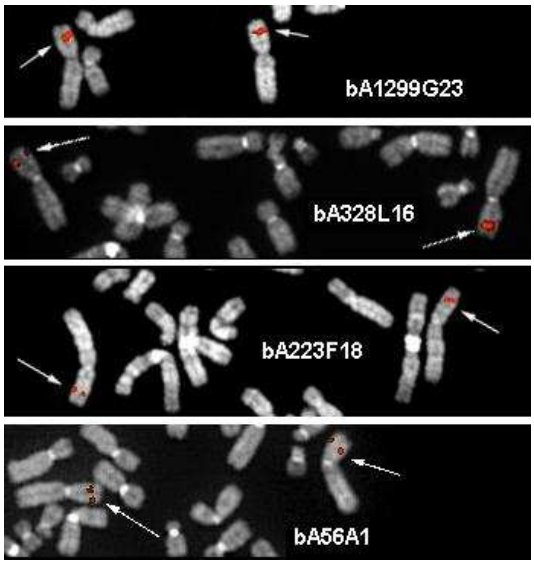
Identity

HGNC (Hugo): ALK

Location: 2p23



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

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 intracyto-plasmic 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+;); 70 to 80% of ALK+ ALCL cases bear a t(2;5); the remaining ALK+ ALCL cases bear variant translocations described below and are called "cyto-plasmic ALK+" cases, of which is the t(1;2) TPM3/ ALK, found in 20% of ALK+ ALCL.

Prognosis
Althouth presenting as a high grade tumour, a 80% five year 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 562 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 expres-sion 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 oligomeri-zation 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
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) or t(2;22)(p23;q11.2); hidden translocation is frequently found.

Hybrid/Mutated gene
5' MSN, TPM3, ATIC, TFG, CLTC, ALO17 or MYH9 - 3' ALK.

Abnormal protein
N-term amino acids from the partner gene fused to the 562 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-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), 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), CARS in the t(2;11), 5' CLTC in the t(2;17), or 5' TPM4 in the t(2;19)- 3' ALK.

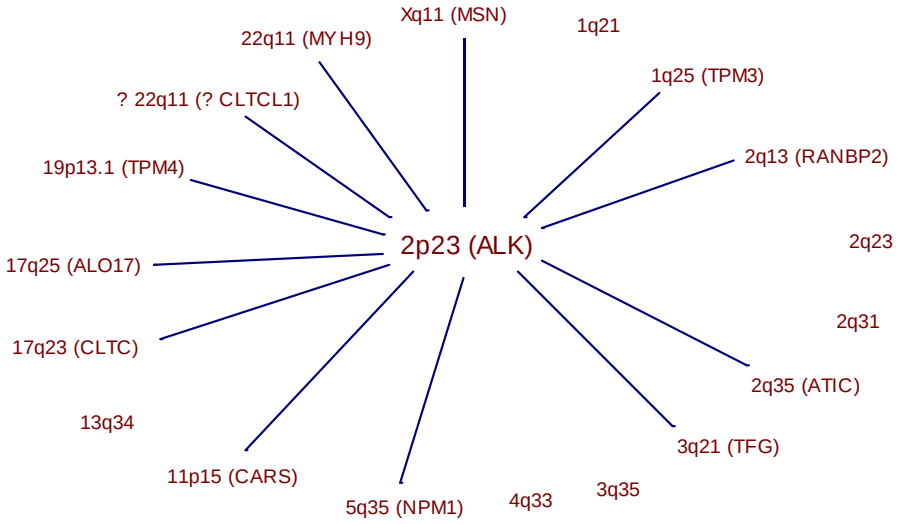
Abnormal protein
N-term amino acids from the partner gene fused to the 562 C-term amino acids from ALK (i.e. the entire cytoplasmic portion of ALK with the tyrosine kinase domain); homodimerization of the fusion protein is known or suspected.

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 both in anaplasic large cell lymphoma and in Inflammatory myofibroblastic tumours; 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; last update 08/2003.

Note

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

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