Gene Section
Mini Review

ALK (anaplastic lymphoma kinase)
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Identity
HGNC (Hugo): ALK
Location: 2p23

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.

DNA/RNA

Transcription
6226 bp cDNA; coding sequence: 4.9 kb.
Implicated in

**Anaplastic 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**
Although 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+ anaplastic 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)(p23q21), t(2;17)(p23;q23), t(2;17)(p23q25) 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 anaplastic 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/gene 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.

**References**


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