Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Leukaemia Section

Mini Review

Amplified NUP214/ABL1

Nathalie Nadal

Laboratoire d'hématologie (niveau 1), Pavillon de Biologie, CHU Hôpital Nord, 42055 St Etienne Cedex 2, France

Published in Atlas Database: September 2005

Online updated version: http://AtlasGeneticsOncology.org/Anomalies/ampNUP214ABL1ID1397.html
DOI: 10.4267/2042/38298

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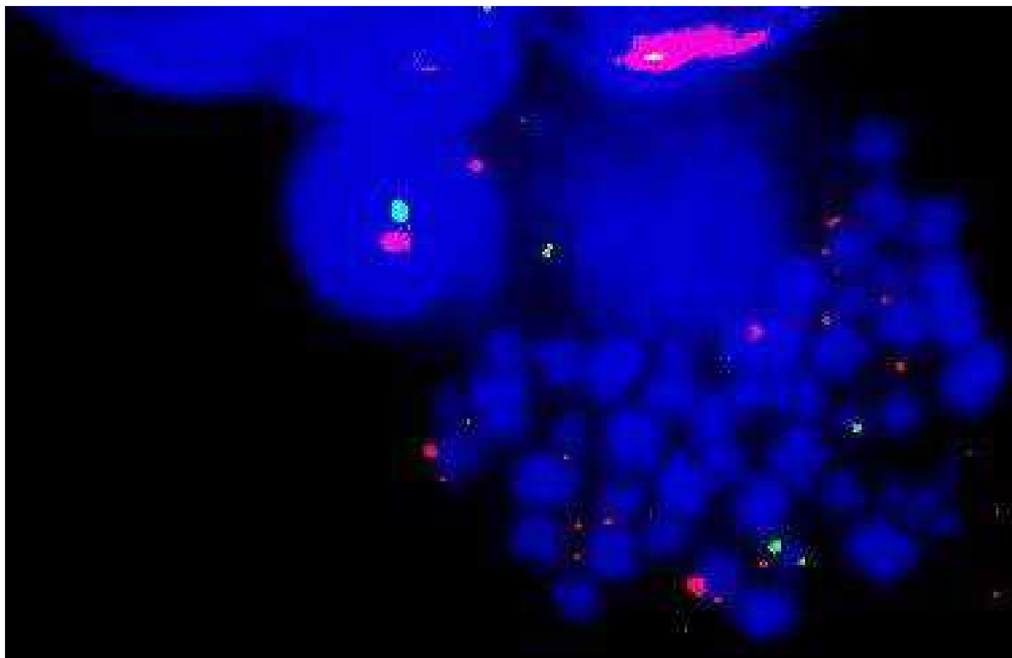
Identity

Other names: NUP214/ABL1 fusion gene on amplified episomes.



Episomal amplification of ABL detected by FISH with the commercial probe LSI BCR-ABL ES.

Clinics and pathology

Disease

T-cell acute lymphoblastic leukemia (T-ALL).

Phenotype / cell stem origin

Immature T-cell leukemia (CD3+, CD2+ and CD7+). Not seen in B-cell ALL.

Epidemiology

In about 6% of T-ALL. Mainly observed in T-ALL associated with the mutually exclusive overexpression of the oncogenes HOX11 and HOX11L2. Found in pediatric T-ALL and adults T-ALL.

Cytology

Lymphoblasts.

Prognosis

Present data suggests that NUP214-ABL1 fusion gene amplification in T-ALL is associated with poor outcome. NUP214-ABL1 is sensitive to the tyrosine kinase inhibitor imatinib mesylate. Targeting therapies may improve outcome.

Cytogenetics

Note: Mechanism of gene amplification.
The main hypothesis for genomic amplification mechanism is that it is a dynamic process. Molecular chronology of genomic amplification has been schematically described as follows. The first step is the production of submicroscopic, acentric, circular, extrachromosomal DNA molecules which replicate autonomously, called episomes. These DNA molecules are made of amplified genes. 2 mechanisms for the formation of episomes have been proposed: Conservative which preserves the original DNA sequence at the native chromosomal locus and non conservative which leads to the deletion of the original sequence at the native locus. The second step corresponds to an increase in copy number resulting from unequal mitotic segregation and an increase in size. They enlarge over time to form progressively heterogeneously sized structures, microscopically visible, called double minutes (dmin). In a later step they may integrate into chromosomes to generate intrachromosomally amplified structures (HSR). In some cases dmins or HSRs may form directly without precursors.

Cytogenetics morphological

Cryptic extrachromosomal amplification of the fusion NUP214-ABL. Rearrangement invisible by conventional cytogenetics. No dmins observed.

Cytogenetics molecular

FISH using commercially available ABL1 probe shows multiple extrachromosomal sites on metaphases and multiple signals in interphase nuclei. The extrachromosomal amplification of ABL1 appears to be pathognomonique for the presence of NUP214-ABL1 fusion in T-ALL.
There may be a corresponding deletion of the ABL1 probe on one of the chromosomes 9 (see note below concerning mechanisms of gene amplification).

Additional anomalies

Associated with an apparently normal karyotype with banding techniques or variable additional abnormalities.

Genes involved and Proteins

ABL1

Location: 9q34.1

DNA / RNA

Alternate splicing. mRNA of 6 and 7 kb.

Protein

145 kDa; Localization: nuclear and cytoplasmic; Tyrosine kinase; Ubiquitously expressed.

NUP214 (nuclear pore complex protein 241 kDa) or CAN, CAIN, Nucleoporin

Location: 9q34.3, more telomeric than ABL1.

DNA / RNA

7.5 kb mRNA.

Protein

214 kDa; dimerization domains (2 leucine zippers) and a repeated motif; forms homodimers. Nuclear membrane localisation. Component of the Nuclear Pore Complex. Mediate nucleocytoplasmic transport.

Results of the chromosomal anomaly

Hybrid gene

Description

Molecular analysis delineated the amplicon as a 500 kb region from chromosome band 9q34 containing the genes ABL1, LAMC3 and NUP214. The genomic region from ABL1 to NUP214 circularizes to generate the NUP214-ABL1 fusion gene = New mechanism for generation of a fusion gene. The breakpoint within ABL1 occurs in intron1 (coincides with ABL1 breakpoint in the Philadelphia chromosome). Whilst the breakpoint in NUP214 is variable (ranging from intron 23 to intron 34).

Detection protocole

RT-PCR

Fusion protein

Description

The NUP214-ABL transcript encodes a 239-333 kDa protein. NUP214-ABL retains the N-terminal region of NUP 214 which includes the predicted coiled-coil domains that serve as oligomerisation motifs. NUP214-ABL contains SH3, SH2 and kinase domains of ABL1. NUP214-ABL is a constitutively activated tyrosine kinase that activates similar pathways as BCR-ABL1.

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This article should be referenced as such:

Nadal N. Amplified NUP214/ABL1. Atlas Genet Cytogenet Oncol Haematol.2006;10(2):107-109.