Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Leukaemia Section
Short Communication

t(8;21)(q22;q22) RUNX1/RUNX1T1

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Published in Atlas Database: May 2016
Online updated version : http://AtlasGeneticsOncology.org/Anomalies/t0821ID1019.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/68158/05-2016-t0821ID1019.pdf
DOI: 10.4267/2042/68158

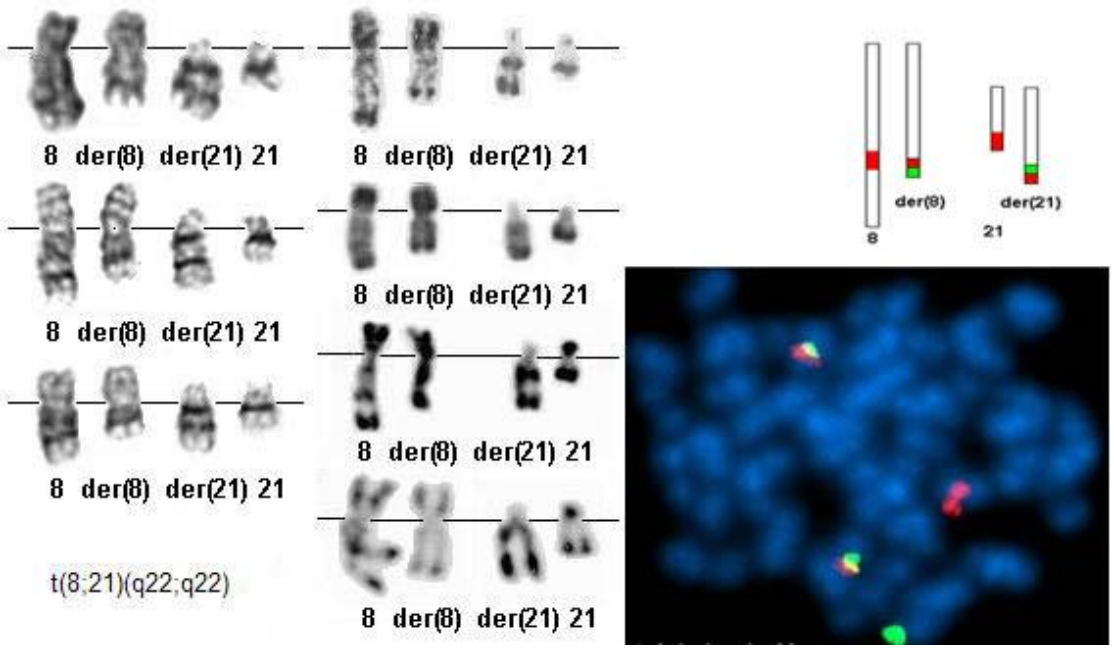
This article is an update of :
Huret JL. t(8;21)(q22;q22). Atlas Genet Cytogenet Oncol Haematol 1997;1(1)

Abstract

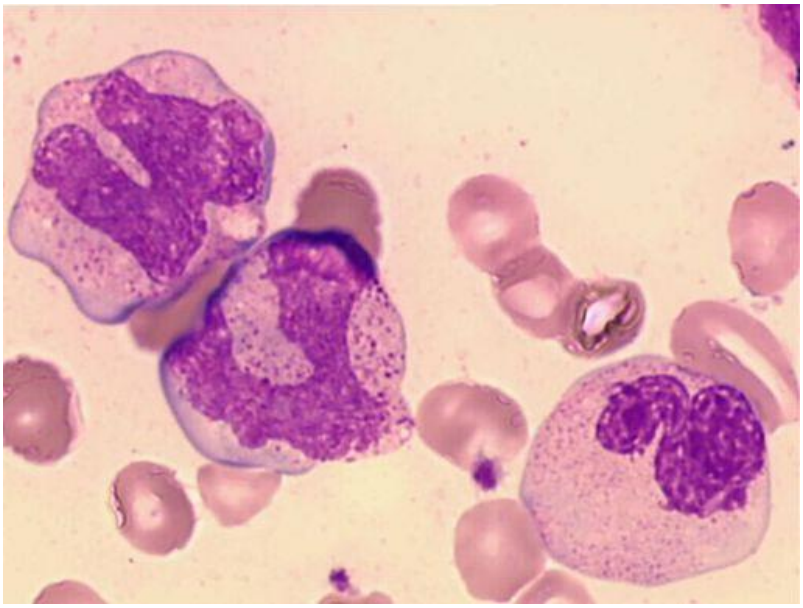
Review on t(8;21)(q22;q22) RUNX1/RUNX1T1, with data on clinics, and the genes involved.

Identity

See figure below.



t(8;21)(q22;q22) G- banding (left) - Courtesy Jean-Luc Lai and Alain Vanderhaegen (top) and Diane H. Norback, Eric B. Johnson, Sara Morrison-Delap; R- banding (middle) - above: Jean Loup Huret; 2nd row: - Courtesy Christiane Charrin; 3rd and 4th row: - Courtesy Roland Berger. Right: FISH - Courtesy Hossein Mossafa.



Translocation t(8;21) is found in 5-12% of AML. Among the non-random chromosomal aberrations observed in AML, t(8;21)(q22;q22) is one of the best known and usually correlates with AML M2, with well defined and specific morphological features. The common morphological features include the presence of large blast cells with abundant basophilic cytoplasm, often containing numerous azurophilic granulations; few blasts in some cases show very large granules (pseudo-Chediak-Higashi granules), suggesting abnormal fusion. Auer rods are frequently found. In addition to the large blast cells, there are also some smaller blasts, predominantly found in the peripheral blood. Promyelocytes, myelocytes and mature granulocytes with variable dysplasia are seen in the bone marrow. These cells may show abnormal nuclear segmentation and/or cytoplasmic staining defects including homogeneous pink colored cytoplasm - Text and iconography Courtesy Georges Flandrin 2001.

Clinics and pathology

Disease

Acute myeloid leukemia (AML) with t(8;21)(q22;q22) is part of the Group of AML with recurrent genetic abnormalities.

Phenotype/cell stem origin

M2 mostly, rarely: M1 or M4

Epidemiology

Annual incidence: $1/10^6$; 5% of AML, 10% of prior AML M2 (FAB classification). The most frequent anomaly in chilhood AML; seen in children and adults: mean age 30yrs, rare in elderly patients.

Clinics

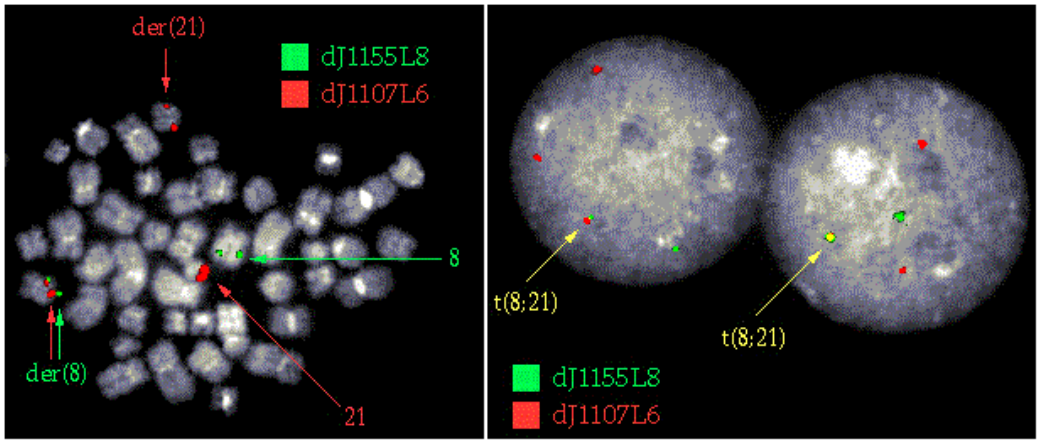
Myeloid sarcomas may be present at presentation.

Prognosis

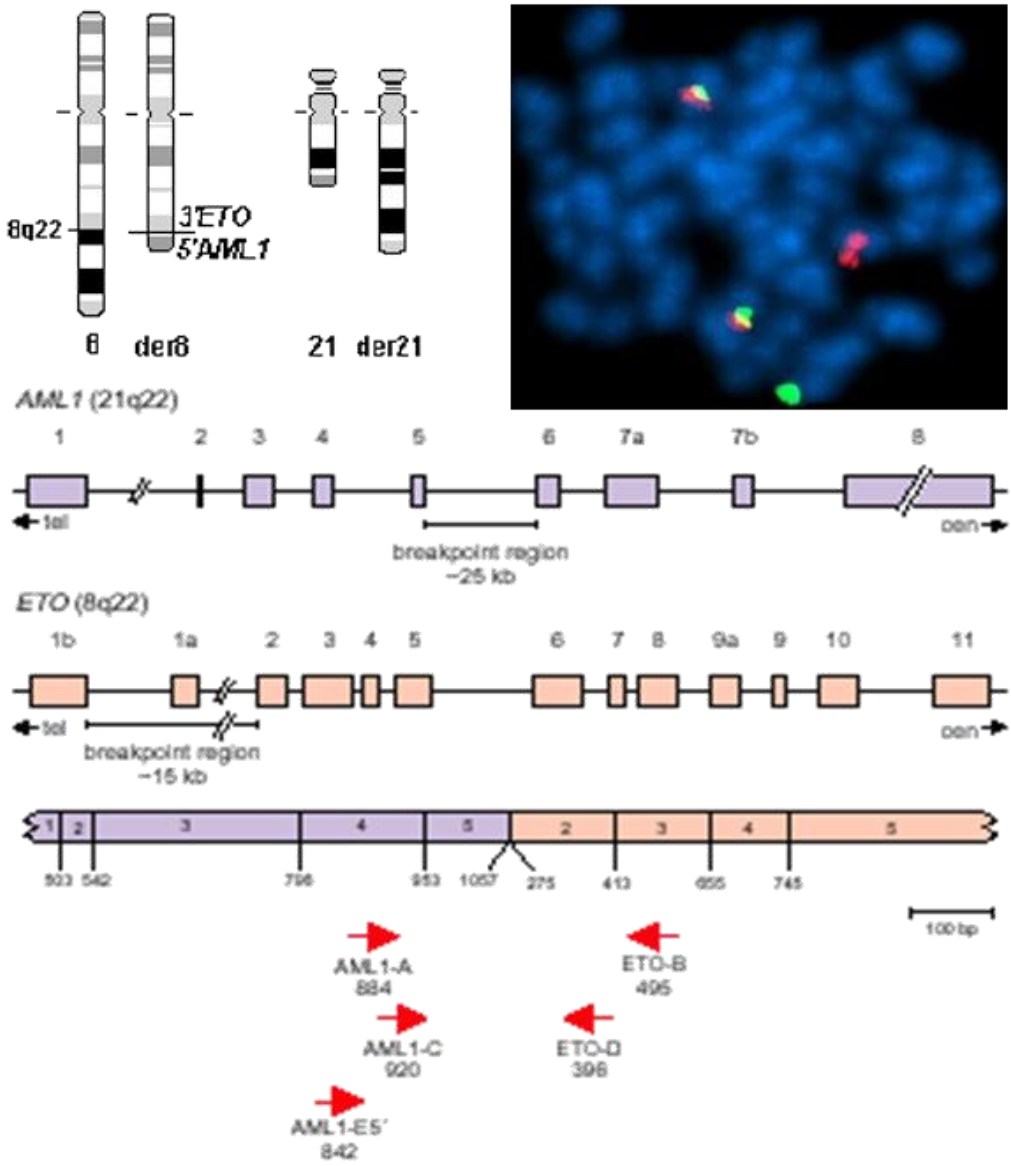
Complete remission (CR) in most cases (90%) with relatively long disease-free survival when treated with high dose chemotherapy.

Cytology

See figure and legend.



t(8;21)(q22;q22): cohybridization experiments using dJ155L8 (RUNX1T1) and dJ1107L6 (RUNX1); note the splitting of RUNX1 and colocalization on der(8) with RUNX1T1 - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.



RUNX1 and RUNX1T1 breakpoints in the t(8;21) / 5' RUNX1 - 3' RUNX1T1 fusion gene, and FISH - Courtesy Hossein Mossafa.

Cytogenetics

Cytogenetics molecular

Cases with cryptic molecular translocation have been detected --> FISH use may be relevant.

Additional anomalies

Sole anomaly in only 20-30%; additional anomalies: loss of Y or X chromosome in half cases (1 X must be present), del(7q) or -7, +8, del (9q): 10% each.

Variants

Complex t(8;21;Var) involving a (variable) third chromosome have been described in 3%; part from chromosome 21 goes on der(8), part of the 8 on der (Var), and part of Var on der(21); therefore, the

crucial event lies on der(8).

Genes involved and proteins

RUNX1T1 (runt-related transcription factor 1; translocated to, 1 (cyclin D-related))

Location

8q21.3

DNA/RNA

Transcription is from telomere to centromere.

Protein

3 proline rich domains, 2 Zn fingers, and in C-term, a PEST region; tissue restricted expression; nuclear localisation; putative transcription factor.

RUNX1 (runt-related transcription factor 1 (acute myeloid leukemia 1; aml1 oncogene))

Location
21q22.12

DNA/RNA
Transcription is from telomere to centromere.

Protein
Contains a Runt domain and, in the C-term, a transactivation domain; forms heterodimers; widely expressed; nuclear localisation; transcription factor (activator) for various hematopoietic-specific genes.

Result of the chromosomal anomaly

Hybrid gene

Description
5' RUNX1 - 3' RUNX1T1; breakpoints: at the very 5' end of RUNX1T1, between exons 5 and 6 in RUNX1.

Detection
Karyotyping, RT-PCR and FISH for cases of typical cell morphology, but apparently without the t(8;21); RT-PCR for minimal residual disease detection

Fusion protein

Description
The N-term runt domain from RUNX1 is fused to the 577 C-term residues from RUNX1T1; reciprocal product not detected; probable DNA binding role; the fusion protein retains the ability to recognize the RUNX1 concensus binding site (--> negative dominant competitor with the normal RUNX1) and to dimerize with the CBFb subunit.

Oncogenesis
Probable altered transcriptional regulation of normal RUNX1 target genes.

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This article should be referenced as such:

Kroes W, Stevens-Kroef M. t(8;21)(q22;q22) RUNX1/RUNX1T1. Atlas Genet Cytogenet Oncol Haematol. 2017; 21(2):52-55.