t(8;21)(q22;q22)

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Identity

Clinics and pathology

**Disease**
ANLL

**Phenotype / cell stem origin**
M2 mostly, rarely: M1 or M4.

**Epidemiology**
Annual incidence: $1/10^6$; 10% of ANLL, 40% of M2
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ANLL; the most frequent anomaly in childhood ANLL; Seen in children and adults; mean age 30 yrs, rare in elderly patients; male excess (4M/3F) is much less than sometimes claimed.

Clinics

Chloromas

Cytology

Numerous and thin Auer rods; eosinophilia of the bone marrow; CD19 (early B) and CD56 (natural killer) may be expressed; the cell involved may be an early progenitor.

Prognosis

CR in most cases (90%); but relapse is frequent, and median survival -1.5 yrs (adults) to 2 yrs (children)- in the range with other ANLL in some series, relatively long median survival, especially in the adults for others; no adverse effect of additional chromosome anomalies.

Cytogenetics

Cytogenetics, molecular

Cases with cryptic molecular translocation have been detected (similar to Ph negative CML with positive BCR-ABL) → FISH use may be relevant.

Additional anomalies

Sole anomaly in only 20%; additional anomalies: numerical in 2/3, structural in 1/3; 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).

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 - Courtesy Georges Flandrin, CD-ROM AML/MDS G. Flandrin/ICG. TRIBVN.
Genes involved and Proteins

**ETO**

*Location:* 8q22  
*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.

**AML1**  

*Location:* 21q22  
*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.

Results of the chromosomal anomaly

**Hybrid gene**

*Description*  
5' AML1 - 3' ETO; breakpoints: at the very 5' end of ETO, between exons 5 and 6 in AML1.

**Detection protocol**  
RT-PCR in cases: 1- of typical cell morphology, but apparently without the t(8;21); 2- for minimal residual disease detection.

Fusion protein

*Description*  
The N-term runt domain from AML1 is fused to the 577 C-term residues from ETO; reciprocal product not detected; probable DNA binding role; the fusion protein retains the ability to recognize the AML1 consensus binding site → negative dominant competitor with the normal AML1) and to dimerize with the CBFβ subunit.

**Oncogenesis**  
Probable altered transcriptional regulation of normal AML1 target genes.

References


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