t(11;17)(q23;q21)
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Clinicals and Pathology

Disease
Specifically observed in acute promyelocytic leukemia (APL), or M3 ANLL; in the vast majority of cases, M3 ANLL is characterized by a t(15;17)(q25;q21); the t(11;17) represents a rare variant translocation with characteristic clinicopathologic features concerning presentation, response to treatment with all-trans retinoic acid (ATRA) and prognosis.

Phenotype / cell stem origin
Promyelocytic (M3) acute leukaemia; a number of patients express an unusual morphologic spectrum intermediate between M2 and M3 AML.

Epidemiology
Less than 1% of morphologic M3 ANLL.

Clinics
High incidence at diagnosis of disseminated intravascular coagulation; poor response to ATRA at induction therapy, in contrast with the classical M3 ANLL with t(15;17).

Cytology
High rate of normal or dystrophic promyelocytes in peripheral blood and in bone marrow; no intracytoplasmic Auer rods; myeloperoxidase reaction positive; immunocytochemical detection with an anti-PLZF shows a distinct punctate nuclear distribution of the protein, suggesting its compartmentalization in the nucleus.

Prognosis
Distinctly worse prognosis than M3 ANLL with t(15;17), mainly because the patients fail to respond to the maturation effect of ATRA.

Cytogenetics

Cytogenetics, molecular
Fusion of distal PLZF probe with RARa on 17q21.

Probes
Whole chromosome 11 and 17 paintings; or painting with unique sequence probes for PLZF and RARa.

Additional anomalies
No recurrent additional anomalies are known.

Variants
3 related translocations observed in M3 ANLL; the first is the common translocation (15;17) and the two others are extremely rare; all these translocations involve a breakpoint at 17q21, in RARa, which fuses with different partners:
1- t(15;17)(q22;q21), fusion with PML in 15q22;
2- t(5;17)(q32;q21), fusion with NPM1 in 5q32, encoding for a RNA processing protein;
3- t(11;17)(q13;q21), fusion with NUMA in 11q13, involved in the control of mitosis.

Genes involved and Proteins

PLZF
Location: 11q24
DNA / RNA
Krüppel-like zinc finger gene.

Protein
Transcription factor associated with myeloid maturation.

RARa
Location: 17q21
Protein
Nuclear receptor with DNA binding and transcriptional properties.
In patients with t(11;17)(q23;q21), t(5;17)(q35;q21), and t(11;17)(q13;q21) where RARα is fused to the PLZF (promyelocytic leukemia zinc finger), NPM (nucleophosmin) and NuMA (nuclear mitotic apparatus) genes respectively, chromosome 17 and RARα but not PML are involved. Patients were initially reported as having M3 morphology. Interestingly, the t(11;17)(q23;q21) PLZF/RARα subgroup showed a clearly morphological differences with predominance of cells with regular nuclei, many granules, usually no Auer rods, increased number of pseudo Pelger-Huet cells and a strong MPO activity. These particular characteristics could allow the definition of a separate morphological entity among APL. Patients with t(5;17)(q35;q21) are too rares to draw any morphological correlation - Courtesy Georges Flandrin, CD-ROM AML/MDS G.Flandrin/ICG. TRIBVN.

### Results of the chromosomal anomaly

#### Hybrid gene

**Description**
The translocation involves a breakpoint in the zinc finger region of PLZF, with fusion of two zinc fingers to the RARα B region to form a 5' PLZF - 3' RARα fusion gene; the reciprocal 5' RARα - 3' PLZF gene fuses seven zinc fingers to the RARα region; RARα's breakpoint occurs in intron 2, as is in classical t(15;17).

**Transcript**
Both 5' PLZF-3' RARα and 5' RARα - 3' PLZF transcripts are detected by RT-PCR, and both fusion partners would be implicated in leukemogenesis; four chimeric transcripts are produced, due to alternative splicing of PLZF gene and to transcription of either A1 or A2 domain of RARα gene.

### Fusion protein

**Description**
1- As a result of the alternative splicing of PLZF gene, two forms of PLZF-RARα protein can be detected:
   a) PLZF(A)-RARα (735 amino acids; 81 kDa) composed of the N-term part of PLZF including POZ domain and two of the nine zinc fingers, fused to the DNA and ligand binding domains of RARα.
   b) PLZF(B)-RARα (858 amino acids; 93 kDa) differing from form A by the inclusion of a 123 amino acid prolin rich segment of PLZF; PLZF-RARα protein is an abnormal retinoic acid receptor with reduced and modified DNA-binding and transcriptional activities.
2- Two forms of RARα-PLZF protein are also detected, due to involvement of alternative promoters of the RARα gene: RARα(A1)-PLZF (277 amino acids; 31 kDa) and RARα(A2)-PLZF (274 amino acids; 31 kDa), composed of A1 or A2 transcriptional activation
domain of RARα linked to the seven C-terminal zinc fingers of PLZF.

References


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