

Leukaemia Section

Review

t(15;17)(q24;q21) PML/RARA

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Abstract

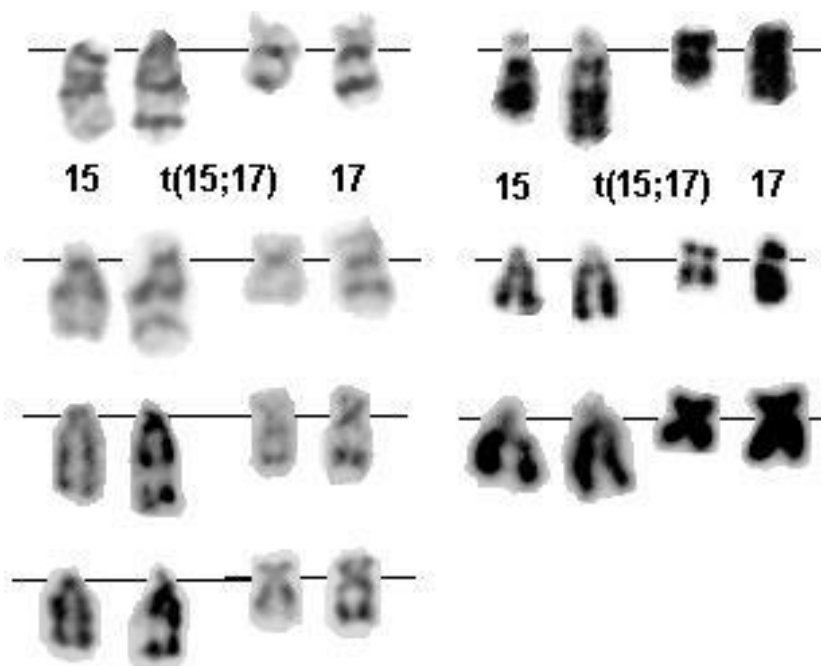
Review on t(15;17)(q24;q21), with data on clinics, and the genes involved.

Keywords

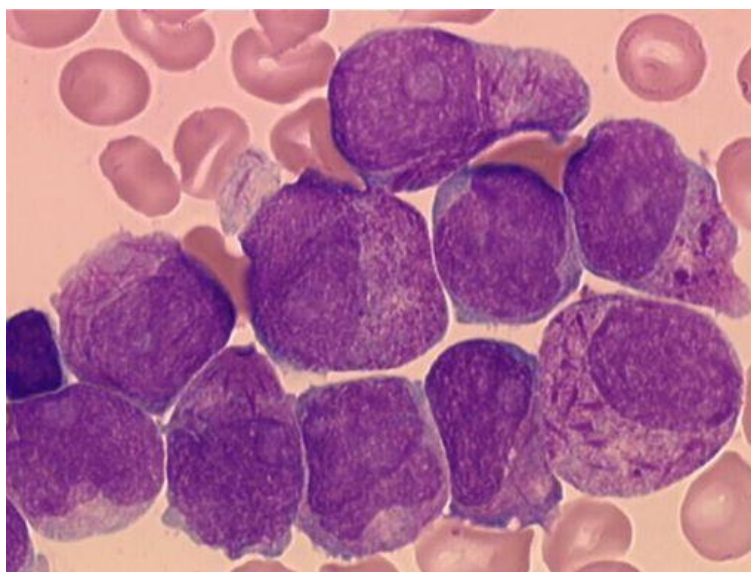
chromosome 15; chromosome 17; PML; RARA; acute promyelocytic leukaemia

Identity

The translocation, formerly known as t(15;17)(q22;q21) or t(15;17)(q22;q12), has been renamed t(15;17)(q24;q21), since PML is located in chromosome band 15q24, and RARA in chromosome band 17q21.



t(15;17)(q24;q21) G- banding (left) - 2 top left: Courtesy Jean-Luc Lai and Alain Vanderhaegen, 2 bottom left: Courtesy Roland Berger ; R-banding (right) - top: Editor, middle: Courtesy Christiane Charrin, bottom: Courtesy Roland Berger.



t(15;17)(q24;q21) is associated consistently with AML M3. This chromosomal abnormality first appeared to be confined to the characteristic or morphologically typical M3 AML or "hypergranular promyelocytic leukemia", defined by bone marrow replacement with highly granulated blast cells. The nuclear size and shape is irregular and highly variable; they are often kidney-shaped or bilobed. The cytoplasm is completely occupied by densely packed or even coalescent large granules, staining bright pink, red or purple by MGG. In some cells the cytoplasm is filled with fine dust-like granules. Characteristic cells containing bundles of Auer rods ("faggot cells") randomly distributed in the cytoplasm, although frequent, are not present in all cases. Auer rods in M3 are usually larger than in other AML and they may have a characteristic morphology at the ultrastructural level. In some cases, the cytoplasmic granules are so large and/or numerous that they totally obscure the cell, rendering the nuclear cytoplasmic limit indistinct. In M3 AML, MPO is always strongly positive in all blast cells, with the reaction product covering the whole cytoplasm and often the nucleus too - Text and iconography Courtesy Georges Flandrin 2001.

Clinics and pathology

Disease

Acute promyelocytic leukaemia (APL), subtype of acute myeloid leukaemia (AML). Mostly de novo; a very few cases of t(15;17) in therapy-related leukaemia (t-APL) have been reported. In sporadic cases the t(15;17) can be present in chronic myelogenous leukemia (CML) in myeloid blast crisis as an additional abnormality to the t(9;22)(q34;q11.2).

Phenotype/cell stem origin

t(15;17) is quasi pathognomonic of APL. Both hypergranular or "typical" APL and microgranular (hypogranular) types exist.

Epidemiology

Found in 10% of adult AML; annual incidence: 1 per 106, similar to the incidence of the t(8;21)(q22;q22). The disease can occur at any age, but patients are predominantly adult in mid-life; sex ratio 1M/1F (WHO 2008).

Clinics

Typical and microgranular APL are frequently associated with disseminated intravascular coagulation (DIC). In microgranular APL, unlike typical APL, the leukocyte count is very high, with rapid doubling time. WBC and platelets may be lower than in other AMLs.

Cytology

Large cells with myeloperoxidase positive cytoplasmic granulations (microgranular forms are called variant or hypogranular APL, and are often hyperleucocytic); bundles of Auer rods.

The typical morphology shows abnormal, usually bilobed hypergranular promyelocytes.

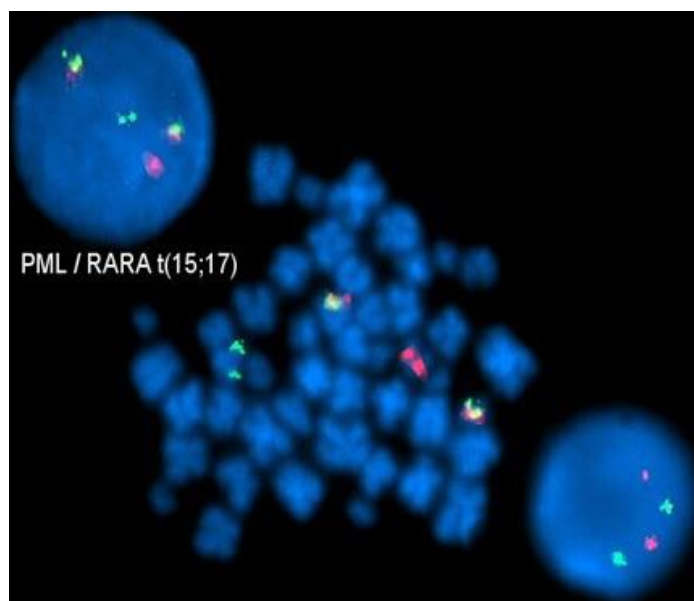
Sudan Black (SB) is always strongly positive in all blast cells (WHO 2008).

Treatment

One of the rare leukaemias where treatment is an emergency, as intra vascular coagulation is prominent, causing a high rate (10 to 40%) of early mortality, mainly due to cerebral haemorrhage. With the recent differentiation therapy using all-trans retinoic acid ATRA (with combined cytotoxic chemotherapy or arsenic trioxide (ATO)), complete remission (CR) is obtained in more than 90% of cases; this is the only cancer which, to date, can be treated by differentiation therapy.

Prognosis

The prognosis in APL, treated optimally with ATRA and an anthracycline, is more favourable than for any other AML cytogenetic subtype, and cases of relapsed or refractory APL show a generally good response with arsenic trioxide therapy.



FISH with the LSI PML/RARA Dual Color Dual Fusion Translocation Probe (Abbott) on a bone marrow cell sample, showing a metaphase spread and one interphase nucleus with two PML-RARA fusion signals (arrows), and one normal interphase cell with two red and two green signals. Courtesy Hossein Mossafa.

Expression of DC56 is associated with a less favourable prognosis, (Ferrara et al 2000) while the prognostic significance of FLT3 -ITD mutations in this disease remains unclear (Kuchenbauer et al 2005). Survival at 1 yr and at 3 yrs are stable at 70%, instead of a 30 to 40% 3 yr survival previously.

Cytogenetics

Cytogenetics morphological

Classic translocation t(15;17)(q24;q21). The translocation may be overlooked in traditional karyotyping. Interphase FISH is indicated, preferably urgent (within 8 hours) on bone marrow aspirate cells (see Figure 1).

Although primary anomaly in most cases, t(15;17) can also occur in rare occurrences at acutisation (of promyelocytic type, of course) of a CML with the usual t(9;22).

Additional anomalies

Secondary cytogenetic abnormalities are noted in about 40% of cases, +8 most frequent (10-15%); del(7q) ; del(9q) rare.

Genes involved and proteins

Note

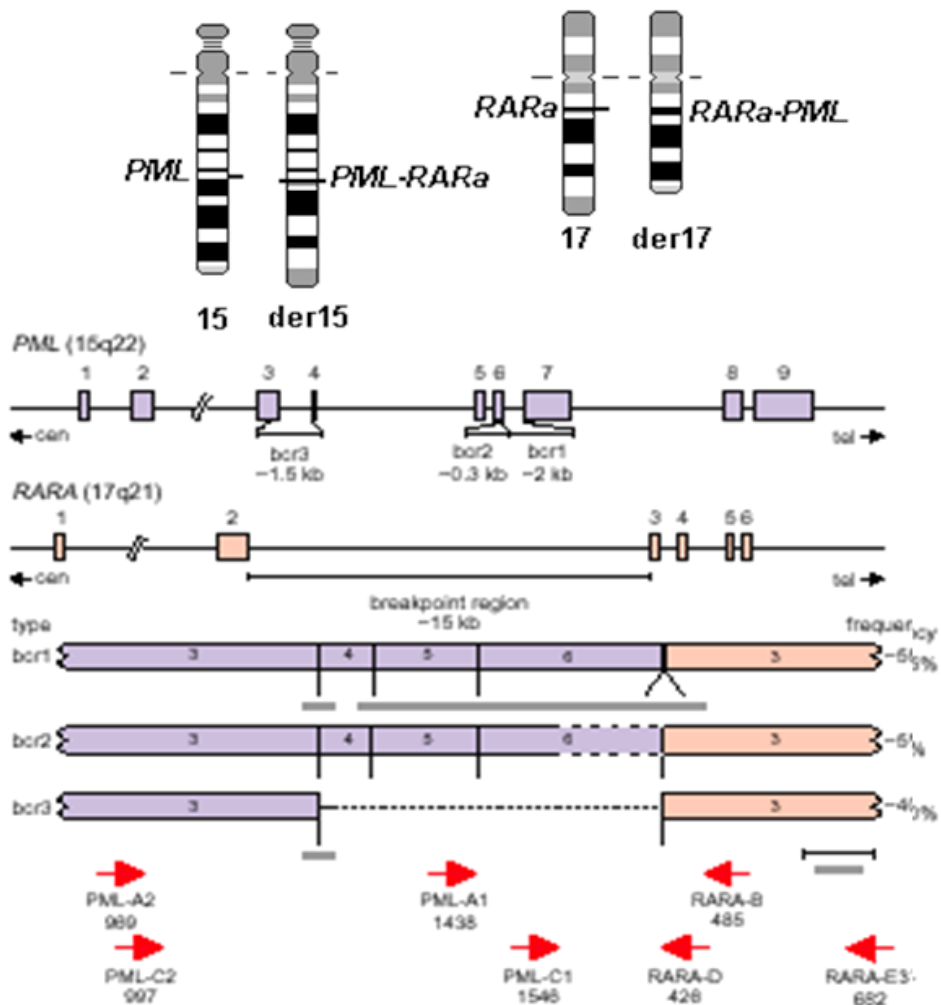
The sensitivity of APL cells (both hypergranular and hypogranular forms) to ATRA has led to the discovery that the retinoic acid receptor alpha

(RARA) gene on chromosome band 17q21 fuses with a nuclear regulatory factor gene on chromosome band 15q24 (PML gene) giving rise to a PML-RARA fusion gene product.

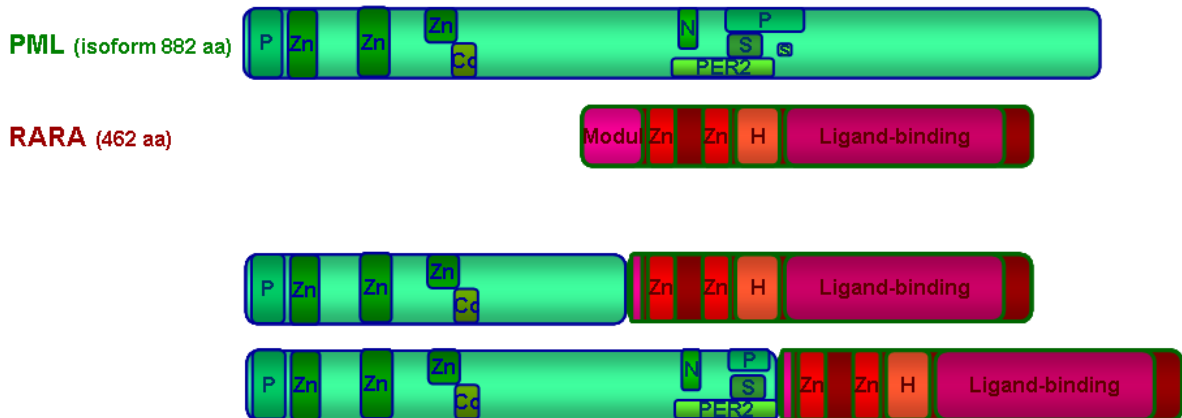
Rare cases of APL lacking the classic translocation in routine cytogenetic studies have been described with complex variant translocations (true variants) involving both chromosomes 15 and 17 with an additional chromosome (three way translocations) or with submicroscopic insertion of RARA into PML leading to the expression of the PML-RARA transcript; these latter cases are considered as cryptic or masked t(15;17)(q24;q21). Morphological analysis shows no major differences between the t(15;17)(q24;q21) positive group and the PML-RARA positive patients without t(15;17)(q24;q21). Three way translocations demonstrated that the crucial event lies on der(15), which receives the end part of chromosome 17.

A subset of patients, often with morphological features resembling APL, show variant translocations involving RARA (17q21). These variant fusion partners include ZBTB16 (previously known as PLZF at 11q23) in t(11;17)(q23;q21), NPM1 at 5q35 in t(5;17)(q32;q12), and NUMA1 at 11q13 in t(11;17)(q13;q21) ID: 1126> and STAT5B at 17q11.2 in dup(17)(q12q21). Some APL variants, including t(11;17)(q23;q12) with ZBTB16-RARA and cases with STAT5B-RARA fusions are resistant to ATRA.

Mutations involving FLT3 occur in 34-45% of APL.



PML and RARA breakpoints in the t(15;17) / 5' PML - 3' RARA fusion gene - Courtesy Hossein Mossafa.



P: Pro-rich; Zn: Zinc fingers; Cc: Coiled coil; Interaction with PER2; N: Nuclear localization signal; P: Pro-rich; S: Ser-rich
 Breakpoint after aa 395 or, alternatively, after aa 552, Junction with aa 61:
 Zn fingers; H: Hinge; Ligand binding region

t(15;17)(q24;q21) PML/RARA (796 or 954 aa)
 Jean Loup Huret 2014

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PML (promyelocytic leukemia)

Location

15q24.1

DNA/RNA

Numerous splices in 3'.

Protein

Nuclear protein; contains zinc fingers and a leucine zipper; transcription factor.

RARA (Retinoic acid receptor, alpha)

Location

17q21.2

Protein

Wide expression; nuclear receptor; binds specific DNA sequences: HRE (hormone response elements); ligand and dimerization domain; role in growth and differentiation.

Result of the chromosomal anomaly

Hybrid gene

Description

Variable breakpoint in PML between intron 3 and exon 7a; constant breakpoint in intron 2 of RARA.

Transcript

5' PML -3' RARa transcript is found in all cases, and 5' RARa - 3' PML transcript is detected in 2/3 of cases.

Fusion protein

Description

Variable, as breakpoints in PML are variable; e.g.: 932 amino acids; 103 kDa; N-term PML, with the DNA binding and the dimerization domains fused to most of RARA with the DNA and retinoid binding regions.

Oncogenesis

Abnormal retinoic acid receptor with a dominant effect over RARA, antagonizing differentiation.

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