

Leukaemia Section

Short Communication

t(8;14)(q24;q32) / t(2;8)(p12;q24) / t(8;22)(q24;q11)

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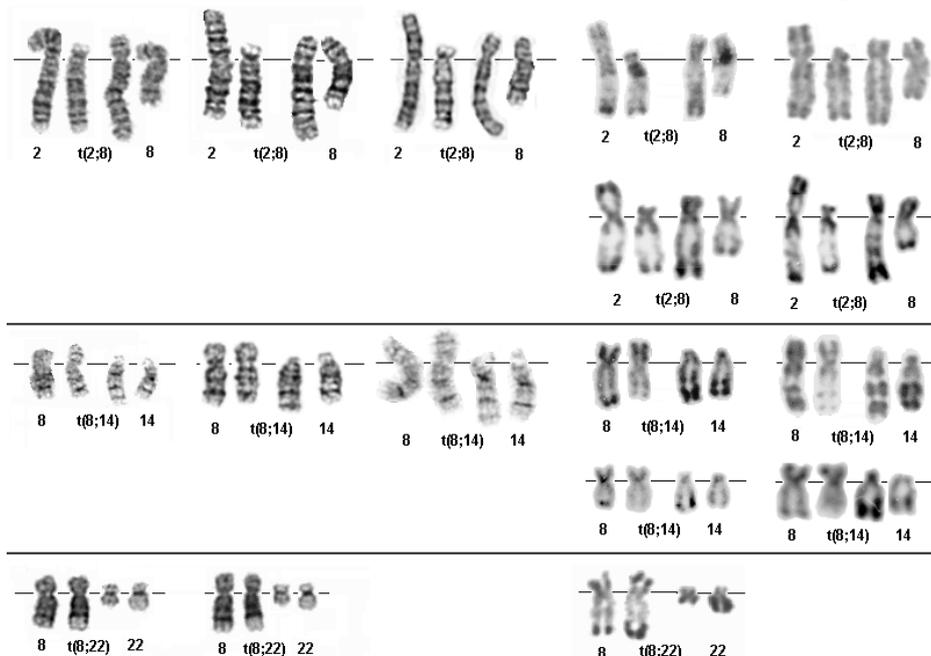
Abstract

Review on t(8;14)(q24;q32) / t(2;8)(p12;q24) / t(8;22)(q24;q11), with data on clinics, and the genes involved.

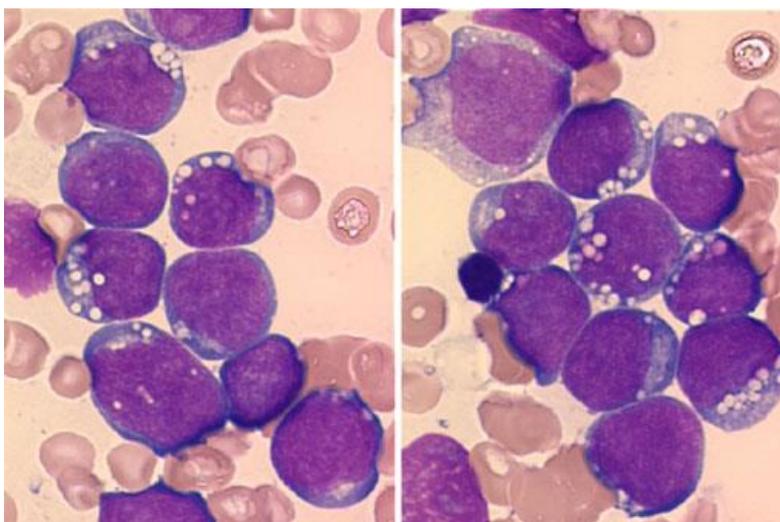
Identity

Note

The 3 translocations are variants of each other, and they share the same clinical significance.



Top row: t(2;8)(p12;q24) G- banding - Courtesy Diane H.Norback, Eric B. Johnson, Sara Morrison-Delap; R- banding - (middle right) Courtesy Jean-Luc Lai; (right) Courtesy Hossein Mossafa; below: Courtesy Roland Berger. Middle rows: t(8;14)(q24;q32) G- banding - (left, middle left, center) Courtesy Diane H. Norback, Eric B. Johnson, Sara Morrison-Delap; R- banding - middle right Courtesy Jean-Luc Lai; right: Jean Loup Huret; below: Courtesy Roland Berger. Lower row: t(8;22)(q24;q11) G- banding (left and center) - Courtesy Diane H. Norback, Eric B.Johnson, Sara Morrison-Delap UW Cytogenetic Services; R- banding - (right) Courtesy Jacques Boyer.



Bone marrow sample: the medium-sized cells show a diffuse monotonous pattern of infiltration. The nuclei are round, cytoplasm deeply basophilic and usually contain vacuoles. The morphological feature in this bone marrow smear (Giemsa), quite similar to tumor cells as seen in tissue imprints, is highly characteristic of Burkitt lymphoma - Text and iconography Courtesy Georges Flandrin 2005.

Clinics and pathology

Disease

described both in B-cell acute lymphoblastic leukemia (ALL) and in non-Hodgkin lymphomas (NHL), especially in the Burkitt lymphoma, and 'double-hit' diffuse large B-cell lymphomas (DLBCL).

Phenotype/cell stem origin

The postulated normal counterpart is the germinal centre or post-germinal centre B-cell.

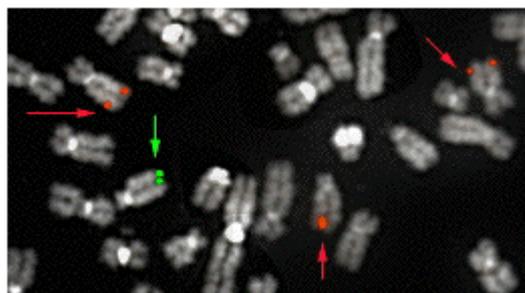
Epidemiology

Most Burkitt lymphoma cases show the t(8;14)(q24;q32) MYC/IGH and less commonly the t(8;22)(q24;q11) or t(2;8)(p12;q24). The translocation is present in both the endemic African Burkitt lymphoma and in the non endemic tumor type (Europe, America, and Japan). In case the Burkitt lymphoma infiltrated the bone marrow (leukemic phase) the MYC-translocation can be demonstrated in the bone marrow or blood as well. If no immunophenotyping results are available, it is good practice to exclude a BCL2 rearrangement because a t(8;14) can be observed in other B cell neoplasms (such as double hit DLBCL see below). Some DLBCL ('double-hit') cases contain the t(8;14) translocation. In some clinical studies patients with DLBCL and MYC rearrangement will receive more aggressive treatment. The disease defines the prognosis. Given the correct treatment regime Burkitt lymphoma patients do well, while the outcome in double-hit DLBCL patient is totally different.

Cytology

ALL : L3 morphology according to the FAB classification, very occasionally L1 or L2 cytology reported.

Cytogenetics



The figure illustrates the translocation of the c-Myc gene (probe 944B18, red) to 14q32.3 - Courtesy Mariano Rocchi.

Cytogenetics morphological

t(8;14) is described in 75-85% of the cases, t(2;8) in 5%, and t(8;22) in the remaining 10%; high-quality metaphases are required to detect t(8;14) and t(8;22).

Additional anomalies

Reported in 70% cases in Burkitt lymphoma and DLBCL, especially: t(14;18)(q32;q21) in double-hit DLBCL lymphoma's, structural rearrangements of the long arm of chromosome 1 (30% cases) resulting in a partial trisomy 1q, rearrangements of 13q34 (15% cases).

Variants

t(2;8)(p12;q24) and t(8;22)(q24;q11) are variants of



the t(8;14)(q24;q32); three-way rearrangements and translocations of submicroscopic chromosome fragments have also been described

Genes involved and proteins

Note

On the molecular point of view, in all these three translocations, the oncogene C-MYC is juxtaposed either with the immunoglobulin heavy chain locus IGH (14q32), the kappa light-chain locus IGK (2p12), or the lambda light-chain locus IGL (22q11); all these translocations share a breakpoint in 8q24 (C-MYC locus). The MYC breakpoints are diverse and distributed over a 2Mb region. Therefore it has to be noted that not all MYC-rearrangements can be detected by FISH.

MYC

Location

8q24

DNA/RNA

The human C-MYC oncogene is the cellular homologue of an avian retrovirus; in vertebrates, it belongs to a small gene family with closely related members (MYC, N-MYCN, MYCL); C-MYC has three exons; two promoters P1 and P2 control the C-MYC transcription; the choice of the promoter depends on the myc protein level. P2 promoter is considered as the most active promoter, generating a 2.25 kb transcript, whereas P1 promoter encodes a 2.4 kb transcript; the main part of 5' first exon corresponds to an untranslated region, MYC1 translation starting at a CUG codon near its 3' end, having 14 additional N-terminal amino-acids compared with MYC2 translation site localized 5' near the second exon beginning

Protein

Myc protein is a transcription factor of the helix-loop-helix/leucine zipper family that activates transcription as obligate heterodimer with a partner protein, MAX.

Immunoglobulin genes:

IGH, IGK, IGL

Location

in 14q32, 2p12 and 22q11 respectively.

Result of the chromosomal anomaly

Hybrid gene

Note

No hybrid transcript.

The translocation leads to the MYC gene under direct regulation of the enhancer of the IGH (or IGK/IGL genes), thereby causing high level transcription of the MYC gene.

Description

MYC is translocated to der(14) in the t(8;14), whereas it remains on der(8) in the variant translocations; t(8;14) leads to a head-to-head fusion of MYC with the heavy chain immunoglobulin locus : 8q24 is close to the 5' extremity of C-MYC exon 2, leading the all translated gene region to 14q32; the 8q24 breakpoint region is variable, scattered over a 190 Kb region, 5' far from MYC or within MYC; the 14q32 breakpoint region is mainly located in the constant region, very close within the switch or joining regions; MYC juxtaposed to the immunoglobulin constant regions and enhancer is overexpressed, shutting down the normal remaining MYC; in both t(2;8) and t(8;22), the breakpoint is in 3' of or distal to the MYC gene which always remains on der(8); the rearrangement with respectively Igk or Igl and C-MYC is head-to-tail.

Fusion protein

Note

The protein MYC resulting from the translation of the second and third exons, through DNA-binding properties, plays a role in regulating cell growth and differentiation

Oncogenesis

Constitutive expression of c-myc induces proliferation even in the absence of growth factors.

To be noted

Case Report

Translocation t(8;14)(q24;q32) as a clue for the diagnosis of B cell prolymphocytic leukemia

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