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Leukaemia Section

Mini Review

t(9;22)(q34;q11) in ALL

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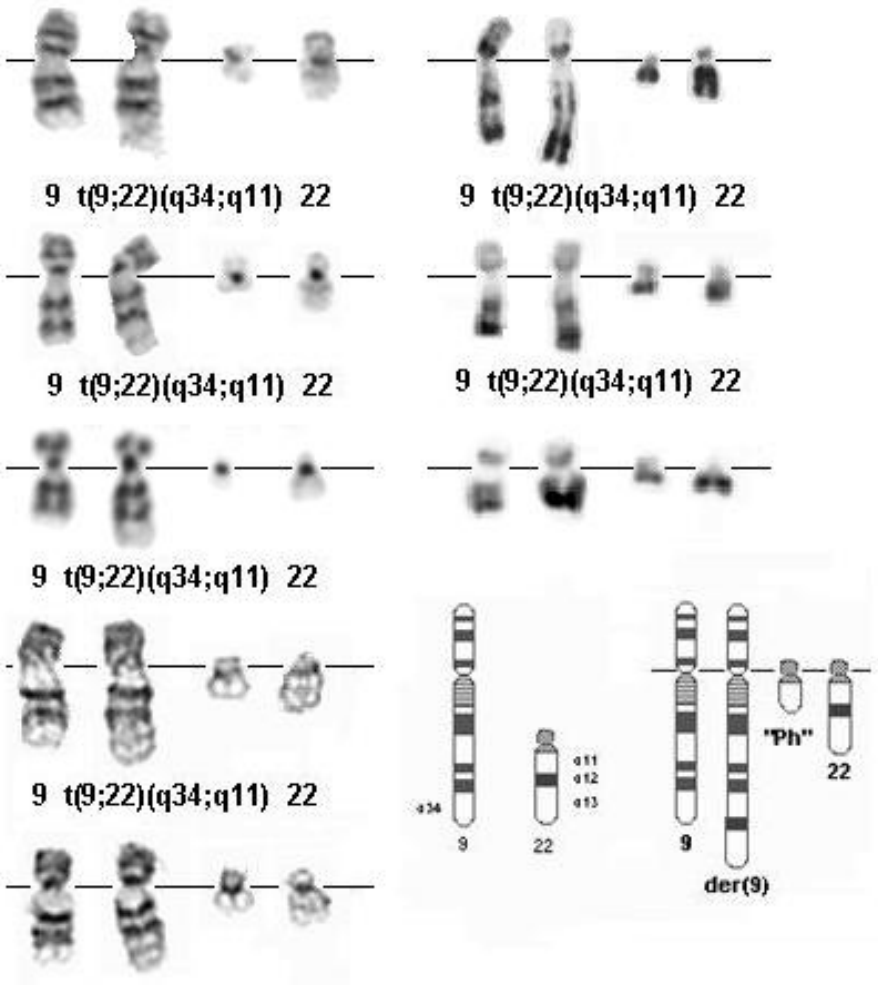
Identity

Note: Although the same hybrid genes issued from ABL and BCR are the hallmark of the t(9;22) translocation, this translocation may be seen in the following diseases: CML, ANLL, and ALL, and will therefore be described in the 3 different situations: t(9;22)(q34;q11) in CML, t(9;22)(q34;q11) in ALL, t(9;22)(q34;q11) in ANLL.
t(9;22)(q34;q11) in ALL is herein described.



t(9;22)(q34;q11) G-banding (left) - Courtesy Jean-Luc Lai and Alain Vanderhaegen (3 top) and Diane H. Norback, Eric B. Johnson, and Sara Morrison-Delap, UW Cytogenetic Services (2 bottom); R-banding (right) top: Editor; 2 others Courtesy Jean-Luc Lai and Alain Vanderhaegen); diagram and breakpoints (Editor).

Clinics and Pathology

Disease

ALL

Phenotype / cell stem origin

L1 or L2 ALL; most often with B-cell phenotype, rare T-cell cases; heterogeneity of lineage involvement: may either be a multipotent stem cell, or a lymphoid-committed progenitor.

Epidemiology

20% of adult ALL, 2-5% of children ALL.

Clinics

Frequent CNS involvement, even at diagnosis; blood data: high WBC (50-150 X 10^9/l).

Cytology

CD10+ in most cases, sometimes CD19+ CD10-.

Treatment

BMT is indicated.

Prognosis

Is very poor, especially in lymphoid-committed progenitor cases; the breakpoint in M-bcr or in m-bcr (see below) does not seem to have impact on prognosis.

Cytogenetics

Cytogenetics, morphological

The chromosomal anomaly disappears during remission, in contrast with BC-CML cases when treated with conventional therapies.

Cytogenetics, molecular

Is useful to uncover a 'masked Philadelphia' chromosome, where chromosomes 9 and 22 all appear to be normal, but where cryptic insertion of 3' ABL within a chromosome 22 can be demonstrated.

Additional anomalies

Found in 50 to 80% of cases: +der(22), -7, del(7q) most often, +8, but not an i(17q), in contrast with CML and ANLL cases; complex karyotypes, often hyperploid, are frequent.

Variants

t(9;22;V) and apparent t(V;22) or t(9;V), where V is a variable chromosome, may be found, as in CML.

Genes involved and Proteins

ABL

Location: 9q34

DNA / RNA

Alternate splicing (1a and 1b) in 5'.

Protein

Giving rise to 2 proteins of 145 kDa; contains SH (SRC homology) domains; N-term SH3 and SH2 - SH1 (tyrosine kinase) - DNA binding motif - actin binding domain C-term; widely expressed; localisation is mainly nuclear; inhibits cell growth.

BCR

Location: 22q11

DNA / RNA

Various splicings.

Protein

Main form: 160 kDa; N-term Serine-Threonine kinase domain, SH2 binding, and C-term domain which functions as a GTPase activating protein for p21rac; widely expressed; cytoplasmic localisation; protein kinase; probable role in signal transduction.

Results of the chromosomal anomaly

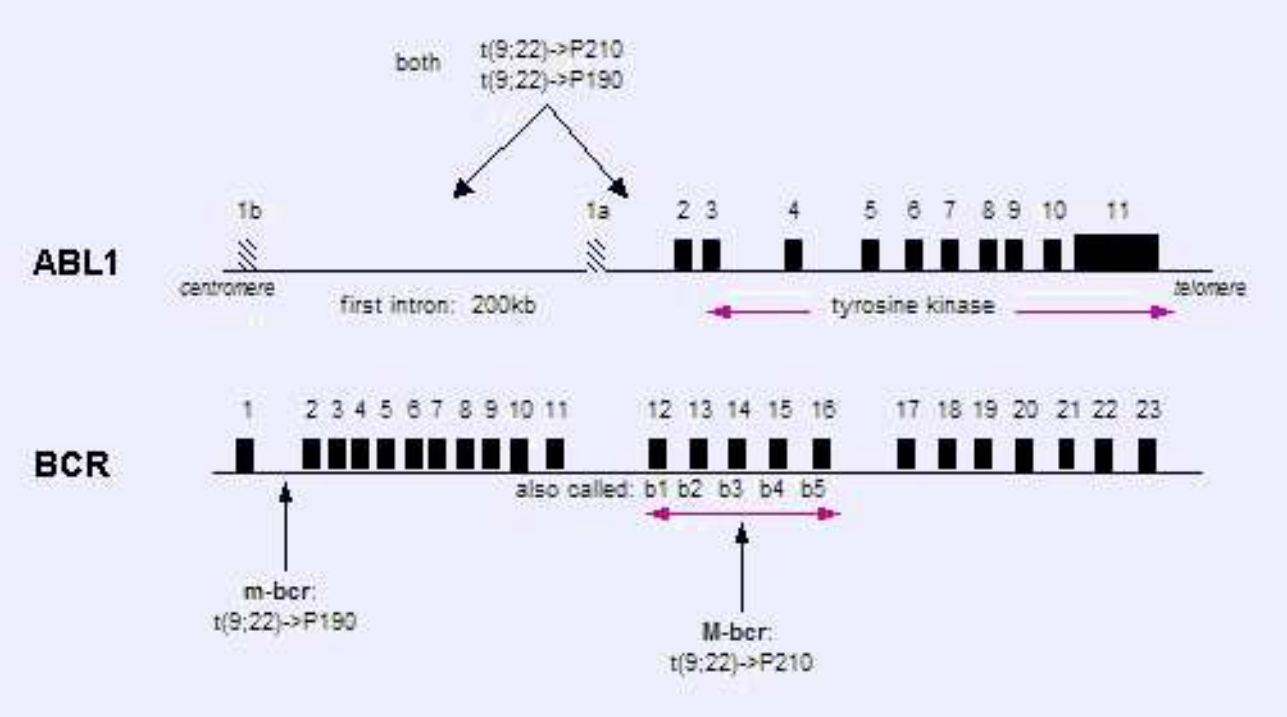
Hybrid gene

Description

The crucial event lies on der(22), id est 5' BCR/3' ABL hybrid gene is pathogenic, while ABL/BCR may or may not be expressed;
- breakpoint in ABL is variable over a region of 200 kb, often between the two alternative exons 1b and 1a, sometimes 5' of 1b, or 3' of 1a, but always 5' of exon 2;
- breakpoint in BCR is either:
1- in the same region as in CML, called M-bcr (for major breakpoint cluster region), a cluster of 5.8 kb, between exons 12 and 16, also called b1 to b5 of M-bcr; most breakpoints being either between b2 and b3, or between b3 and b4; transcript is 8.5 kb long; this results in a 210 kDa chimeric protein (P210), with the first 902 or 927 amino acids from BCR;
2- in a 35 kb region between exons 1 and 2, called m-bcr (minor breakpoint cluster region), → 7 kb mRNA, resulting in a 190 kDa protein (P190), with the 427 N-terminal amino acids from BCR.

Transcript

7 or 8.5 kb.



Fusion protein

Description

190 or 210 kDa (see diagram);
BCR/ABL has a cytoplasmic localization, in contrast with ABL, mostly nuclear; this may have a carcinogenetic role.
The hybrid protein has an increased protein kinase activity compared to ABL: 3BP1 (binding protein) binds normal ABL on SH3 domain, which prevents SH1 activation; with BCR/ABL, the first (N-terminal) exon of BCR binds to SH2, hidding SH3 which, as a consequence, cannot be bound to 3BP1; thereof, SH1 is activated.

Oncogenesis

1-Proliferation is induced: there is activation by BCR/ABL of Ras signal transduction pathway via it's linkage to son-of-sevenless (SOS), a Ras activator; PI3-K (phosphatidyl inositol 3' kinase) pathway is also activated; MYC as well;
2-BCR/ABL inhibits apoptosis;
3-BCR/ABL provokes cell adhesive abnormalities: impaired adherence to bone marrow stroma cells, which allows unregulated proliferation of leukaemic progenitors.

To be noted

Blast crisis is sometimes at the first onset of CML, and those cases may be undistinguishable from true ALL with t(9;22) and P210 BCR/ABL hybrid.

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