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 10⁹/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, hiding 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 (phosphatidylinositol 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 indistinguishable from true ALL with t(9;22) and P210 BCR/ABL hybrid.

**References**

*This article should be referenced as such:*