## t(1;19)(q23;p13) TCF3/PBX1

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### Identity

**Note**

Balanced form: -1, -19, +der(1), +der(19); unbalanced form: -19, +der(19).

**Disease**

B Lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1); mostly found in ALL, L1/L2 type; exceptionally found in L3-like ALL, T-ALL, NHL, or AML.

**Phenotype/cell stem origin**

Most cases: ‘pre B’ (clg+) ALL; may be clg- or sIg+.

CD45dim, CD19pos, CD34neg, CD22pos/dim, CD20dim/pos, CD24pos, TdTpos, CD10neg/dim, clgMpos, CD9pos, CD15neg, CD65neg, CD66cneg, CD13neg, CD33neg.

**Epidemiology**

5% of ALL, or 20% of pre B ALL; found in children and young adults (1-60 yrs, median: 10 yrs --> one of the most frequent ALL in childhood (4-6%)); 3 male/4 female patients.

**Clinics**

Moderate organomegaly; frequent CNS involvement; blood data: high WBC (median 20 x 10^9/L); high LDH.
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c-PBX1 at 1q23 in normal cells: PAC 1146N1 - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics. Laboratories willing to validate the probes are welcome: contact M Rocchi.

Treatment
Treatment should be adapted to biological features at the moment of diagnosis and also to early chemotherapy response and risk group stratification should not be based on TCF3-PBX1 detection.

Prognosis
Although this chromosomal abnormality usually discloses adverse prognostic features (WBC, SNC), it is associated with good prognosis with modern intensive protocols. Median 5 yr-event free survival probability in childhood ALL: 85(6)%: no age or blood data prognostic significance; there are no differences between the prognosis of balanced or unbalanced forms. Prognosis in adults is not different between TCF3-PBX1 positive and negative cases (pEFS: 40 vs. 44%).

Cytogenetics
Cytogenetics morphological
Breakpoint is in 19p13.3; two different forms (see diagrams above): - the balanced t(1;19), one fourth of cases, with a der(1) and a der(19); - the unbalanced form, found in 3/4 cases, with 2 normal chromosomes 1, a der(19), and 1 normal chromosome 19: --> partial trisomy for 1q23-1qter and monosomy for 19p13.3-pter; the 2 forms can be in mosaic; note: 19p13 and 19q13 may be confused (e.g. literature reports). A subset of ALL usually hyperdyploid B-ALL has an identical t(1;19) that lack the expected phenotype probably do not represent TCF3-PBX1 B-ALL.

Additional anomalies
t(17;19)(q22;p13) is not stricto sensu a variant, but, so far, an equivalent, with HLF (hepatic leukemia factor), on 17q22, involved in the translocation. Additional anomalies are found in half of the cases, mostly partial dup (1q), +6, del(6q), +8, i(9q), +17, i(17q), +21.

Genes involved and proteins

Note
The following are (most often) involved, except in some cases lacking the elg expression:

PBX1 (pre-B-cell leukemia homeobox 1)
Location 1q23.3
Note
Previously known as "pre-B-cell leukemia transcription factor 1".

DNA/RNA
Alternate splicing (variants 1, 2 and 3) (Acc Numbers: NM_001204963.1, NM_001204961.1 and NM_002585.3).

Protein
Nuclear protein that belongs to the PBX homeobox family of transcriptional factors. Contains a homeodomain to bind to DNA.

TCF3 (transcription factor 3)
Location 19p13.3
Note

DNA/RNA
Alternate splicing 2 isoforms --> E12 and E47. Alternatively spliced transcript variants encoding multiple isoforms have been observed for this gene, and a pseudogene of this gene is located on the short arm of chromosome 9.
Protein
Contains transcriptional activation domains and a basic helix-loop-helix DNA binding site; binds specifically to an immunoglobulin enhancer; nuclear localization; transcription factor.

Result of the chromosomal anomaly

Hybrid gene
Description
5' TCF3 exons fused to 3' PBX1; breakpoints are clustered on both genes; the reciprocal 5' PBX1 - 3' E2A is not transcribed.

Transcript
Most cases present fusion of exons 1-16 in TCF3 to exons 4-9 in PBX1. Alternative breakpoint in intron 4 of PBX1, not detectable by standardized RT-PCR primers, has been reported.

Fusion protein
Description
550 amino acids; 85 kDa; N-term transcriptional activation domains from TCF3 fused to the Hox cooperativ motif and homeodomain of C-term PBX1; potent transcriptional activator.

Expression / Localisation
Nuclear localisation.

Oncogenesis
Pleiotropic transforming activity.
The resulting fusion protein (TCF3-PBX1), in which the DNA binding domain of E2A is replaced by the DNA binding domain of TCF3, transforms cells by constitutively activating transcription of genes regulated by PBX1 or by other members the PBX protein family.

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