

Leukaemia Section

Mini Review

t(5;14)(q35;q32.2)

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Clinics and pathology

Disease

T cell acute lymphoblastic leukemia (T-ALL)

Phenotype/cell stem origin

Cortical T cell leukemia (CD1a+, CD10+).

Epidemiology

Restricted to T-ALL. Relatively frequent in pediatric T-

ALL (approximately 20%); less frequent in adult T-ALL.

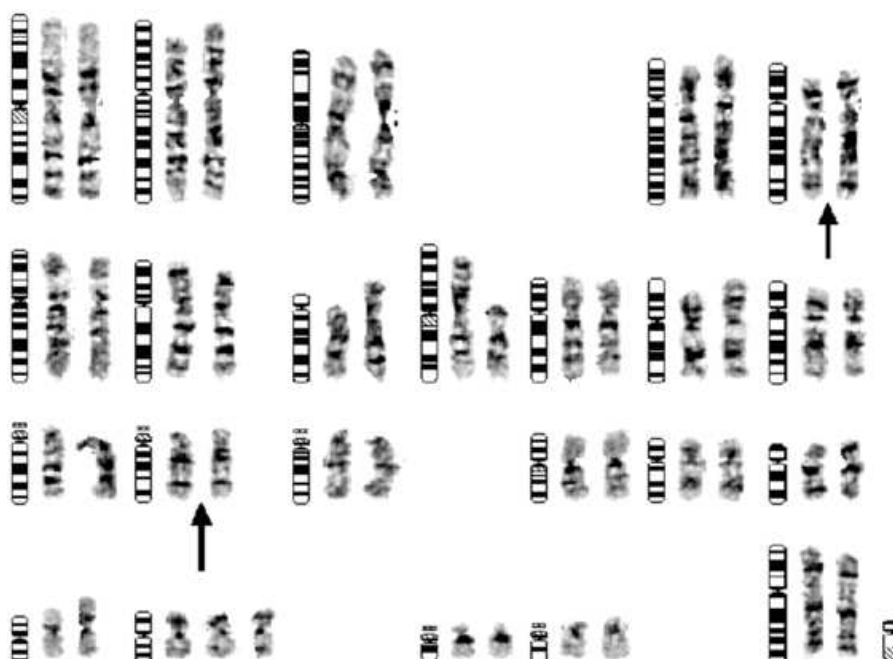
Cytology

FAB nomenclature: L1 or L2 ALL.

Prognosis

TLX3 expression - presumably due to t(5;14)(q35.1;q32) or its congeners - has been reported to confer poor prognosis.

Cytogenetics



G-banding of t(5;14)(q35;q32.2) in a pediatric T-ALL leukemia cell line (CCRF-CEM) illustrating the cryptic nature of this rearrangement. Hence normal and rearranged homologs are indistinguishable by G-banding, as are standard and rare variant t(5;14) subtypes. In chromosome painting images only a minority of cells in even superior preparations show the t(5;14).

Cytogenetics morphological

t(5;14), like other cryptic chromosomal aberrations, was discovered relatively recently and most subsequent studies have focused on molecular and clinical aspects of this entity to the exclusion of cytogenetics. This gap is aggravated by the uniquely large breakpoint cluster region (bcr) of the 14q32 partner gene, BCL11B (alias CTIP2, RIT1). Hence, detailed documentation of this interesting rearrangement is largely based on data obtained using t(5;14) T-ALL cell lines which hitherto all carry submicroscopic insertions, both ins(5;14) and ins(14;5), instead of conventional reciprocal translocations. If verified in patient material, detailed analysis of such configurations may reveal neighboring genes or regulators inimical to the oncogenic activity of t(5;14), and therefore excluded by the more selective insertional rearrangements.

Cytogenetics molecular

The proximities of the 14q32.2, and of both standard and variant 5q35 breakpoints to their respective telomeres, impairs FISH detection using chromosome painting probes except in optimal preparations. The tendency of t(5;14) to involve microinsertions (in both directions), together with the sheer magnitude of the BCL11B bcr, impedes detection by specific BAC/PAC combinations.

Probes

The widespread involvement of cryptic rearrangements, notably microinsertions, plus the sheer length of the 14q32.2 breakpoint cluster complicates diagnostic probe design. Sensitive molecular cytogenetic diagnosis requires a BAC contig-battery covering bcr at both 5q35 and 14q32. Given the ectopic - all or none - nature of TLX3 expression in affected cells, screening t(5;14) is probably better performed by RT-PCR.

Variants

A microscopically synonymous variant, t(5;14)(q35.2;q32.2), whereby the closely related and neighboring NKX2-5 is juxtaposed to BCL11B, has proved frustratingly difficult to identify clinically despite occurring in two widely used T-ALL cell lines, CCRF-CEM and PEER. NKX2-5 is ectopically activated in t(5;14)(q35.2;q11.2) where it is juxtaposed with TRAD. The diagnostic caveats for the standard translocation also apply: detection of variant t(5;14) by RT-PCR is likely to pose fewer technical difficulties than cytogenetic detection by FISH.

Genes involved and proteins

Note

The breakpoints at 14q32.2 are located in the

downstream region of BCL11B and are widely distributed along an almost unprecedentedly long stretch of about 1 Mbp in extent. So far there is no hint of deregulation of BCL11B by t(5;14)(q35;32). The t(5;14) aberration results in the juxtaposition of either TLX3 or NKX2-5 homeobox genes with enhancer elements located downstream of BCL11B inside a "genomic desert" region. TLX3 and NKX2-5 are located at 5q35.1 and 5q35.2, respectively, about 2 Mbp apart.

The centromeric neighbour of TLX3, RANBP17, may undergo truncation by the translocation, although this may not be significant as RANBP17 is not expressed in T-cells. While both, TLX3 and NKX2-5 have been described to be activated by translocations involving the T-cell receptor genes, aberrations targeting NKX2-5 seem to be very rare in T-ALL. Together with TLX1/HOX11 both homeobox genes, TLX3 and NKX2-5, are members of the NK-like family of homeobox genes, implicating similar activities in T-cell leukemogenesis. However, differences in the prognostic outcome may indicate functional differences between TLX1 and TLX3. A couple of dysregulated targets of these NK-like homeobox genes have been described, including PP2A for TLX1 and MEF2C for NKX2-5. Physiologically, TLX3 and NKX2-5 are involved in organogenesis of the spleen. Additionally, TLX3 is expressed in neuronal cells of the periphery and NKX2-5 in the heart. Therefore, their expression in T-cells is ectopic and serves as a solid diagnostic marker detectable by (quantitative) RT-PCR. However, no standard assay for TLX3, as described for other mutated genes in leukemia/lymphoma by BIOMED, has been published so far.

TLX3

Location

5q35.1

Note

Alias: HOX11L2.

Protein

Homeodomain; member of the NK-like family of homeobox genes.

NKX2-5

Location

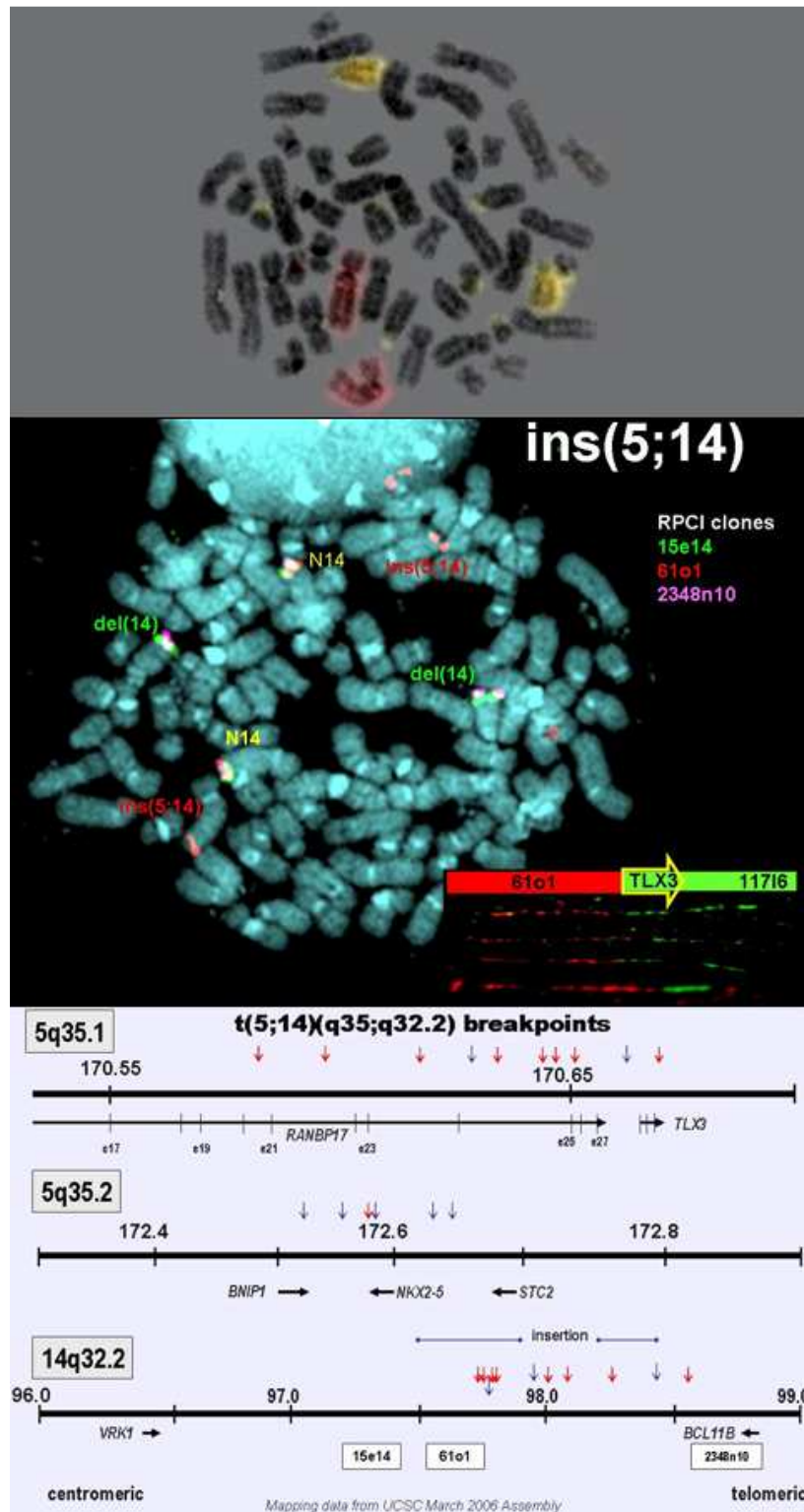
5q35.2

Note

Alias: CSX.

Protein

Homeodomain; member of the NK-like family of homeobox genes.



Upper image depicts results of chromosome painting in an above average T-ALL cell (CCRF-CEM) with t(5;14) and concurrent ins(14;5). Note absence of visible signs betraying reciprocal exchange. Chromosome painting was performed using Cambio probes (Cambridge, UK) for chromosomes 5 (TexasRed), and 14 (Cy3). **Middle image** depicts standard t(5;14)(q35.1;q32.2) as represented by ins(5;14)(q35.1;q32.2q32.2) in cell line DND-41 which activates TLX3 transcription by juxtaposition with part of the noncoding region of BCL11B (clones shown below). Insert shows fiber-FISH confirming the regions juxtaposed. **Lower image** summarizes breakpoint data for t(5;14)(q35;q32) in T-ALL at three loci: TLX3 (standard translocation), NKX2-5 (variant translocation), and BCL11B (both translocations). Patient and cell line breakpoints are shown red and blue, respectively, together with insertion data from cell line DND-41. The NKX2-5 patient breakpoint included for comparison is from a t(5;14)(q35.2;q11.2) patient where TRAD is the activating partner. Coordinates are given in Mbp. Note the circa 1 Mbp 14q32.2 bcr which effectively covers the 3'-BCL11B regulatory region, while TLX3 breakpoints cover a "modest" 90 Kbp. NKX2-5 cases are too rare to allow bcr delineation.

Result of the chromosomal anomaly

Hybrid gene

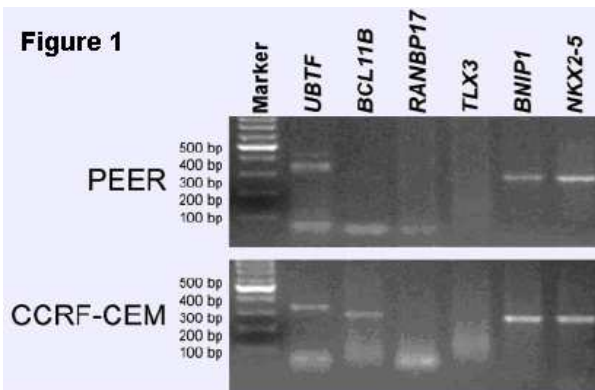


Figure 1 shows RT-PCR analysis of genes involved in t(5;14)(q35;q32) in T-ALL cell lines PEER and CCRF-CEM, both expressing NKX2-5 instead of TLX3.

Figure 2 shows expression array data converted into a heatmap and demonstrate gene activities in five T-ALL cell lines: ALL-SIL (TRAD/TLX1), CCRF-CEM (NKX2-5/BCL11B), HPB-ALL (TLX3/BCL11B), PEER (NKX2-5/BCL11B), JURKAT (negative control). Red indicates high, green low, and black medium expression level. Note expression of homeobox genes is restricted to presence of corresponding translocation.

Fusion protein

Description

No fusion protein, but ectopic expression of either TLX3 or NKX2-5.

Oncogenesis

Due to the chromosomal translocation, transcription factor binding sites for PU.1 and HMGA1, located near 5'-TLX3/NKX2-5 (5q35) and 3'-BCL11B (14q32.2), respectively, are juxtaposed. PU.1 and HMGA1 proteins are thus able to interact across the boundaries of the juxtaposed regions and form enhanceosomal complexes mediating transcriptional activity. Furthermore, BCL11B enhancer regions at 14q32 aggregate with acetylated histones recruited to open chromatin at DNaseI hypersensitive sites and contact the nuclear matrix - a region favorable to transcription. Altogether, these data indicate the existence of potent enhancer regions at 14q32 downstream of BCL11B responsible for homeobox gene activation in

participating translocations. The precise physiological mechanism(s) underlying the normal activity of presumptive BCL11B enhancers awaits clarification: although these enhancers may be involved in the developmental control of BCL11B activity - a gene demanding exquisite regulation in T-cells - little supporting data are as yet available.

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