Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Leukaemia Section

Mini Review

t(3;7)(q27;q32)

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Clinics and pathology

Disease

Splenic Marginal Zone Lymphoma (SMZL).

Etiology

SMZL is quite rare, comprising about 1% of lymphomas. Patients typically present with splenomegaly often involving peripheral blood, liver, and bone marrow. About a third of patients have a slight monoclonal gammopathy, thus SMZL may overlap Waldenstrom's macroglobulinemia.

Epidemiology

Though rare overall, SMZL is still one of the most common small B-cell lymphoma of the spleen. It mainly affects those over 50 years.

Pathology

The histologic, immunohistochemical, and molecular heterogeneity of SMZL suggests it originates from different (centrocytic, monocytoid, lymphoplasmacytic) B-cell populations residing within normal SMZ.

Treatment

Splenectomy. Responds poorly to chemotherapy.

Evolution

May develop into large cell lymphoma.

Prognosis

Favorable: SMZL displays an indolent course: 10 year survival ≅ 70%.

Cytogenetics

Note

t(3;7)(q27;q32) may be a variant of del(7)(q32) - the main recurrent abnormality reported in SMZL.

Probes

BCL6: flanking BACs RP11-208n14 (centromeric) & RP11-67e18 (telomeric); MBR straddling BAC RP11-211g3, MBR straddling fosmid G248P81269F11 (alias WI2802L21).

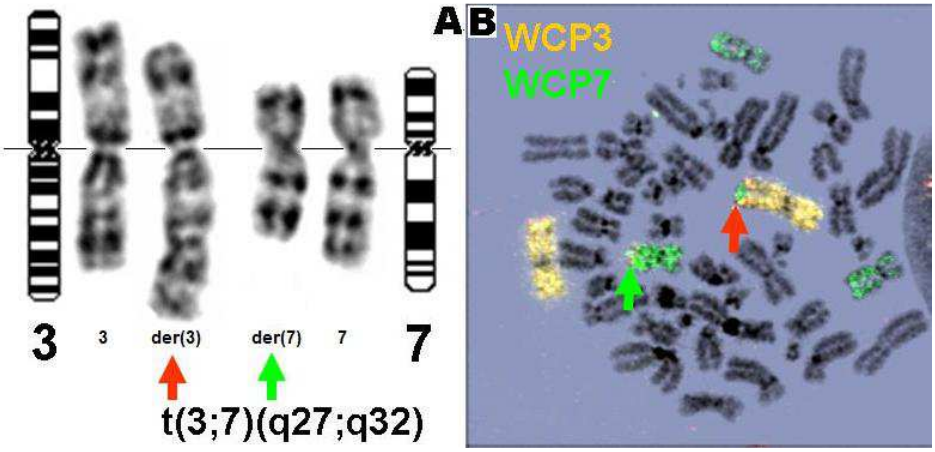

Figure 1: Cytogenetic analysis of t(3;7) in a DLBCL cell line (RC-K8). G-banding (A) and FISH (B) images show t(3;7)(q27;q32) in a DLBCL cell line RC-K8 established from a patient with DLBCL. Expression profiling shows this cell line to express a related but significantly different set of genes from other DLBCL derived cell lines.

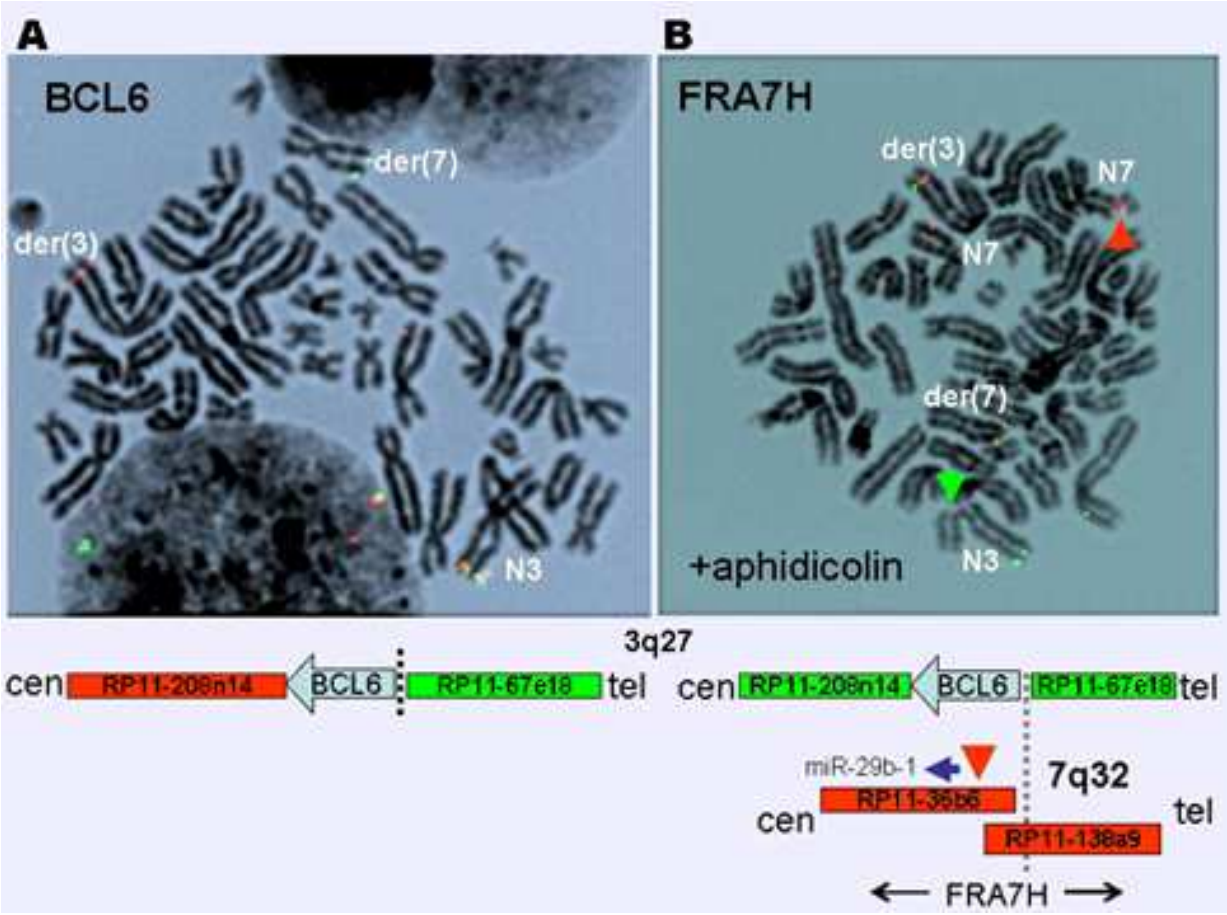

Figure 2: BCL6 and FRA7H Breakpoints in RC-K8 cells. FISH analysis showed rearrangement of BCL6 (A) with FRA7H (B). Treatment of RC-K8 cells with aphidicolin (APC) to induce expression of fragile sites revealed chromatid breaks (ctb) at FRA7H (red arrowhead) as well as elsewhere, e.g. at FRA3D (green). The break at FRA7H induced by APC (B) lies close to the translocation breakpoint present in t(3;7) as determined by LDI-PCR (see below). Interestingly, clastogenesis at FRA7H favored normal chr. 7 homologs over t(3;7) implying stabilization of FRA7H by the latter.

Genes involved and proteins

BCL6

Location
3q27

Note
Breakpoint lies outwith MBR and ABR.

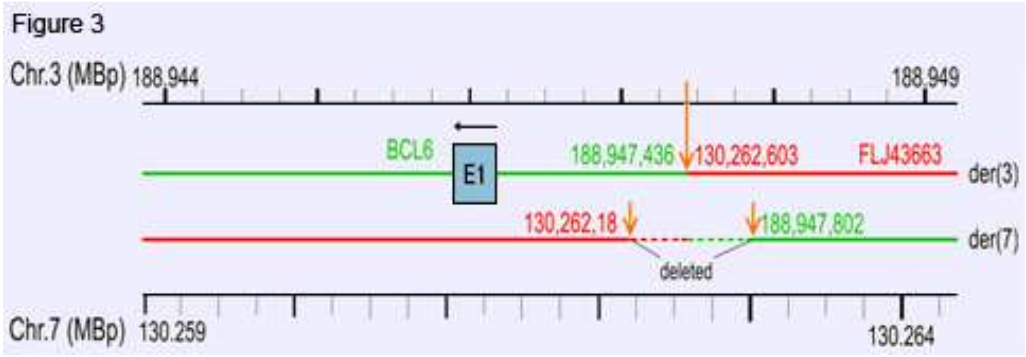

Figure 3: Molecular breakpoint analysis at 3q27 by LDI-PCR. Results of molecular breakpoint analysis by long-distance inverse (LDI)-PCR of the BCL6 and FRA7H junctions on der(3) and der(7) (arrows). Note deletions of 365 bp from chromosome 3 and 416 bp from chromosome 7 (broken lines) on der(7).

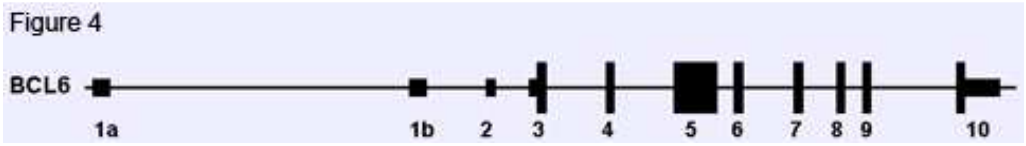

Figure 4: BCL6 protein. The BCL6 gene comprizes 10 exons. There are two alternative exons 1 (a or b). Only exons 3-10 harbor protein coding sequences.

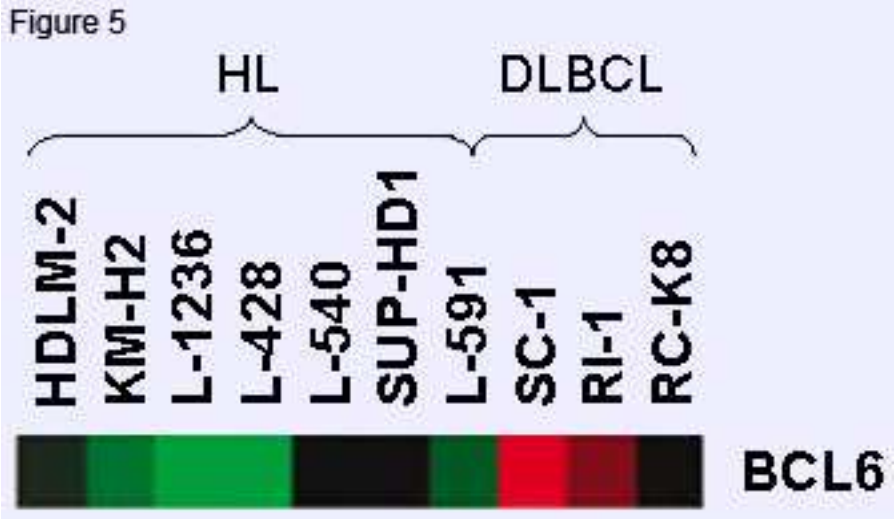

Figure 5: Expression of BCL6 in Hodgkin lymphoma and DLBCL. Note preferential expression of BCL6 in DLBCL. RC-K8 t(3;7) cells display moderately upregulated BCL6 expression typical of non-IGH BCL6 rearrangements. Heatmap shows upregulation (red), inconspicuous expression (black) and downregulation (green).

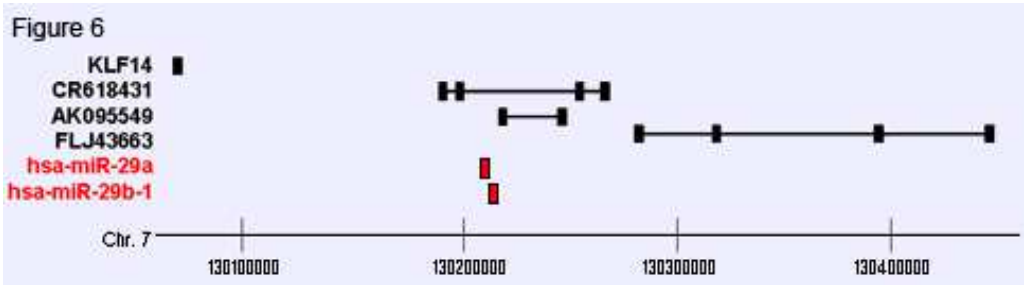

Figure 6: Putative gene targets at 7q32 in t(3;7)(q27;q32). The miR-29 sequences (miR-29a and miR-29b1) are located on chromosome 7q32 upstream of Ref.Seq. gene KLF14 which lies outside FRA7H, and within the intron of a putative uncharacterized gene CR618431.

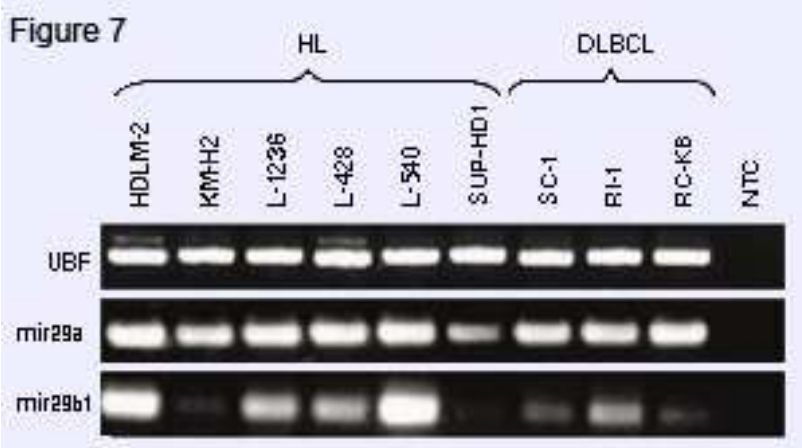

Figure 7: Expression of miR-29-a/b1 in Hodgkin lymphoma and DLBCL. Expression analysis of miR-29a and miR-29b1 was performed by RT-PCR analysis in HL and DLBCL cell lines in comparison to the control gene UBF. Data indicate low level expression of miR-29-b1 in DLBCL cell lines as compared to HL cell lines.

miR-29-a

Location
7q32

Note
miR-29-a and/or miR 29b1 (7q32). miR-29-a/b1 resides inside common fragile site FRA7H (APC inducible, cloned).

Result of the chromosomal anomaly

Hybrid gene

Note
t(3;7)(q27;q32) belongs to the emerging class of non-fusogenic BCL6 translocations. These carry upstream BCL6 breakpoints which lie closer to the transcription unit than ABR breakpoints at ≅ 250 KBp. While BCL6 is undoubtedly upregulated in such cases, expression levels lie below those carrying IGH-BCL6 translocations. In the case of t(3;7) the chromosome 7 breakpoint lies within FRA7H, the first FRA firmly associated with an hematopoietic malignant translocation (as opposed to deletion). Physiological BCL6 expression occurs in germinal centers where it is thought to permit immunological DNA breakage by suppressing apoptosis induced by the p53 damage pathway. It is tempting to suppose that BCL6 expression might also incur the risk of untoward breakage at fragile sites.
FRA7H is bereft of RefSeq genes. Apart from putative mRNA transcripts of dubious provenance (several including CR618431 shown in Figure 6 have been inadequately annotated and may be pseudogenes), miR-29-a/b1 are the only verified genes mapped to FRA7H. Deletions affecting the miR-29-a/b1 cluster have been recently linked to SMZL and previously to CLL. Interestingly, a key target of miR-29-a/b1 is TCL1 known to be upregulated in SMZL.

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