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in Oncology and Haematology

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Leukaemia Section
Mini Review

inv(7)(p15q34), t(7;7)(p15;q34)

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Clinics and pathology

Disease

T cell acute lymphoblastic leukemia (T-ALL) and non-Hodgkin lymphoma (T-NHL).

Phenotype / cell stem origin

T lineage; occurs at early stage of T cell development (CD2-, CD4+, CD8-).

Epidemiology

3.5 % of T-ALL or T-NHL.

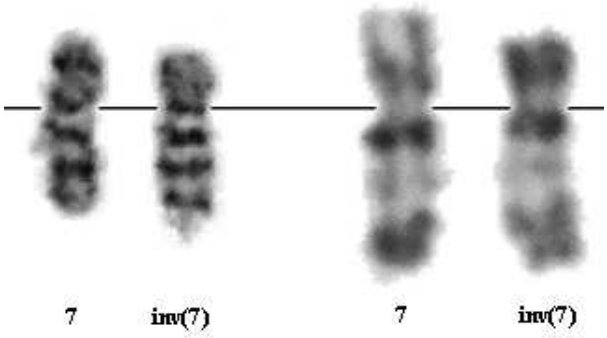
Clinics

Hepato and/or splenomegaly, lymphadenopathy, mediastinal mass, moderate WBC count (15 to 100 X 10^9l).

Cytology

FAB L1 or L2.

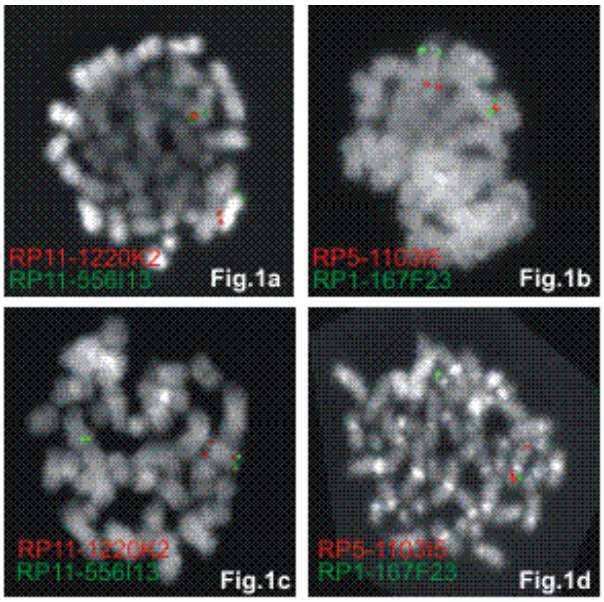
Cytogenetics



inv(7)(p15q34) G- banding (left) and R- banding (right).

Cytogenetics morphological

This rearrangement remains undetected in poor quality metaphases. In less condensed, well banded metaphases, the abnormality may be suspected as del(7)(p15) or clearly as an inv(7)(p15q34).



FISH results of inv(7) (Fig.1a and b) and t(7;7) (Fig.1c and d) case using TRB flanking (Fig.1a and 1c) and HOXA (Fig.1b and 1d) flanking probes.

Cytogenetics molecular

inv(7)(p15q34) and t(7;7)(p15;q34) can be detected by FISH using either TRB and HOXA flanking probes which gives a split signal of both probes in these cases. A fusion signal will be detected when combining the proximal TCR/distal HOXA flanking or the distal TCR/proximal HOXA flanking FISH probe.

Probes

TRB flanking probes: RP11-1220K2 and RP11-556I13
HOXA flanking probes: RP1-167F23 and RP5-1103I5

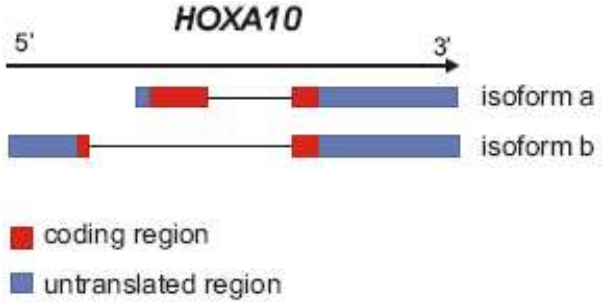
Additional anomalies

Most patients show no additional karyotypic abnormalities.

Genes involved and Proteins

Note: Chromosomal disruption of the HOXA gene cluster (7p15) following chromosomal rearrangement, leads to upregulation of HOXA gene expression, which are normally weakly expressed in T-ALL. Further studies are needed to determine the various patterns of HOXA gene upregulation but from present data, HOXA10 seems most consistently involved in keeping with the breakpoint position near HOXA9. The upregulation of HOXA10 expression is thought to result from enhancers embedded within the TRB locus, which is translocated upstream from these genes. Upregulation of HOXA genes has also been described for other subgroups of T-ALL i.e. the CALM-AF10 and MLL rearranged T-ALLs indicating a more general role for HOXA genes in T-ALL development.
HOXA, together with HOXB, HOXC and HOXD, belongs to the class I homeobox genes and compromises 11 HOXA cluster genes: HOXA1, HOXA2, HOXA3, HOXA4, HOXA5, HOXA6, HOXA7, HOXA9, HOXA10, HOXA11, HOXA13. Given the breakpoint position 5' to HOXA10 and its consistent overexpression in all TRB-HOXA rearranged cases, we currently assume that this gene exerts a specific oncogenic effect in this subgroup of T-ALLs.

HOXA10 (alias: PL, HOX1.8, HOX1H, HOX1)



Location: 7p15

Note: DNA-binding transcription factor which regulates gene expression, morphogenesis, and differentiation. More specifically, it may function in fertility, embryo viability, and regulation of hematopoietic lineage commitment. Two transcript variants encoding different isoforms have been found for this gene. HOXA10 expression is normally present in hematopoietic stem cells and developing T-cells with decreasing expression as T-cells mature.

DNA / RNA

2 transcripts:
- transcript variant 1 (isoform a): 2 exons, transcript 2618 bp, protein 393 amino-acids.
- transcript variant 2 (isoform b): 2 exons, transcript 2241 bp, protein 94 amino-acids.

Protein

DNA binding, transcription factor activity.

TRB

Location: 7q34

Note: The human TRB locus at 7q34 spans 620 kb and consists of 82-85 genes. Enhancer sequences have been characterized 5.5kb 3' from TRBC2.

Protein

Proteins encoded by the TRB locus are the T-cell receptor beta chains.

Results of the chromosomal anomaly

Fusion protein

Description

No fusion protein, but ectopic expression of HOXA10.

Oncogenesis

Little is known about the target genes for HOXA10. Cyclin-dependent kinase inhibitor p21 (alias CDKN1A, CIP1, WAF1) was shown to be a transcriptional target of HOXA10 in differentiating myelomonocytic cells. However, a potential role of p21 in HOXA10 driven oncogenesis has not been proved so far. In vitro transfection experiments with HOXA9 and HOXA10 showed upregulation of several genes of the Wnt pathway (Wnt10b, Frizzled1, Frizzled5) which are essential in hematopoietic stem cell renewal.

To be noted

Translocations involving the TRB genes frequently result from errors of the recombinase enzyme complexe (RAG1, RAG2, etc.), responsable of the Immunoglobulin and T cell receptor V-J and V-D-J rearrangements.

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