

Leukaemia Section

Mini Review

del(13q) in myeloid malignancies

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Published in Atlas Database: September 2001

Online updated version : <http://AtlasGeneticsOncology.org/Anomalies/del13qID1096.html>

DOI: 10.4267/2042/37814

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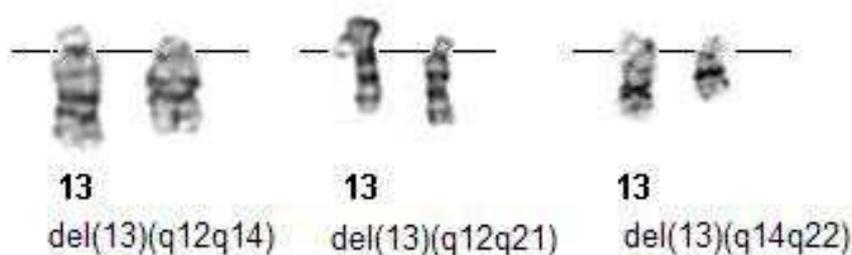
Identity

Note

Chromosomal deletions are among the most common genetic events observed in hematologic malignancies; loss of genetic material is regarded as a hallmark of putative tumor suppressor gene localization.

Deletions 13q occurs in lymphoid neoplasias: see del(13q) in non-Hodgkin's lymphoma and del(13q) in chronic lymphoproliferative diseases.

In myeloid disorders, the most frequently reported deletions affect chromosomes 5, 7 and 20 (del(5q), del(7q), and del(20q), but deletion of chromosome 13 is another relatively common aberration.



del(13q) G- banding - Courtesy Diane H. Norback, Eric B. Johnson, Sara Morrison-Delap UW Cytogenetic Services.

Clinics and pathology

Disease

Chronic myeloid leukemia (CML).

Epidemiology

Deletion of 13q is sometimes found in accelerated phase of the CML disease.

CML patients with persistent or relapsed disease following bone-marrow transplantation usually show clonal cytogenetic changes in addition to the translocation t(9;22); in a series of 22 patients with more than 50% philadelphia positive-metaphases, chromosome 13 was involved in 55% of the cases. The chromosome 13 rearrangements comprise both translocations and deletions, a common region of deletion is identified at 13q12-14. The t(12;13) as the

sole additional abnormality in CML cases with myeloid blast crisis seems to be directly related to progression of the disease.

Disease

Other chronic myeloproliferative diseases (MPD): polycythemia vera (PV), and idiopathic myelofibrosis.

Epidemiology

Polycythemia vera: del(13q) is found in 10% of the cases.

Idiopathic myelofibrosis (agnogenic myeloid metaplasia: MM): In a report of 47 cases where 15 cases have had clonal abnormalities (32%), interstitial 13q deletion occurred in three cases (6%). Molecular deletions of 13q14 is detected in a relatively large fraction of BCR/ABL negative myeloproliferative disorders and appear to be more frequent in myeloid metaplasia (MM).

Disease

Myelodysplastic syndromes (MDS).

Epidemiology

Deletion 13q is found in about 2% of cases or less.

Disease

Acute non lymphocytic leukemia (ANLL).

Epidemiology

Structural abnormalities of the RB gene (at 13q14) with absent protein expression is frequent in all types of human acute leukemia but are particularly common (between 20 and 55 % in several studies) in ANLL with monocytic differentiation (M4 and M5). The differences in the frequency of attainment of complete remission or length of survival observed between patients with normal and abnormal RB expression is controversial but the majority of published studies found low RB expression to be a negative prognostic predictor.

Disease

Therapy-related myelodysplasia and leukemia (t-MDS and t-ANLL).

Epidemiology

In a series of 137 cases of t-MDS or t-ANLL, deletion of the long arm of chromosome 13 involving band q14 is observed in three patients as single clonal abnormality (2%) and as part of a complex karyotype in four patients (3%). All seven patients have previously been treated by alkylating agents.

Cytogenetics**Cytogenetics morphological**

Abnormal metaphases carrying the 13q anomaly range from 40% to 100% of analysed cells.

Generally, the 13q anomaly was found at diagnosis, while, in rare cases, the anomaly appeared during course of the disease.

The deletion has been described as interstitial in most cases, with the following breakpoints: q13-q21 (most frequently), q13-q22, q14-q22, q12-q21.

Loss of material at band 13q14-21 is common to all cases.

Loss of 13q12-q32 appeared to be prevalent in MPD, loss of 13q12-q22 was more common in MDS, and loss of 13q21 band more frequent in ANLL.

Translocations involving chromosome 13 may also occur, sometimes with cryptic microdeletions of 13q; however, apart from the t(12;13)(p12;q14), none was yet found recurrent.

Cytogenetics molecular

Results of FISH studies show the absence of

hybridization signal of the applied probes for 13q13.3-13q14.3

The data indicate the presence of two distinct breakpoint cluster regions: centromeric of RB1 in myeloid malignancies and distal to RB1 in some lymphoid B-cell and T-cell malignancies.

The smallest deleted region common of all myeloid cases reported correspond to YAC 937C7, the RB1 gene and the YAC 745E3.

Additional anomalies

Anomaly of 13q is either the sole abnormality in half cases or as part of a complex karyotype with trisomy 8, del(5q).

Genes involved and proteins**Note**

In ANLL, the RB gene (see below) is not transcribed, whereas it is most often normally transcribed in myelodysplastic syndromes. Southern blot analysis of the RB gene detects no gross gene rearrangements but several restriction enzyme polymorphisms are observed. By western blot analysis, about 20% of patients have no detectable pRb protein and about 10% have truncated pRb bands. Discordance between the DNA and protein suggests that there may be minor deletions and point mutations in the RB gene or abnormalities in the expression of the pRb protein at the post-transcriptional level.

RB, or RB1

Location: 13q14

Note

The retinoblastoma gene, RB, is a prototype tumor-suppressor gene.

DNA/RNA

The RB-gene is divided into at least 27 exons distributed over 180 kb. Transcription: 4,7 kb mRNA, 2,7 kb open reading frame, 2 kb 3'-UTR.

Protein

The retinoblastoma protein pRb is a nuclear 110-KD phosphoprotein whose function is closely related to cell-cycle control. The activity of pRb depends on its degree of phosphorylation. The hypophosphorylated form of pRb maintains cell in quiescence by its ability to bind to transcription factors of the E2F family, whereas during the G1-S phase the hyperphosphorylated form of pRb does not bind the E2F factor who becomes active and whose target genes encode proteins (c-myc, dihydrofolate reductase, thymidine kinase, and DNA polymerase alpha, cdk kinases) necessary for progression of the cell cycle from G1 to S-phase. The protein pRb is also involved in the process of cell differentiation (high levels of RB mRNA are found during erythroid differentiation).

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This article should be referenced as such:

Boyer J. del(13q) in myeloid malignancies. *Atlas Genet Cytogenet Oncol Haematol*. 2002; 6(1):29-31.
