

Leukaemia Section

Mini Review

12p abnormalities in myeloid malignancies

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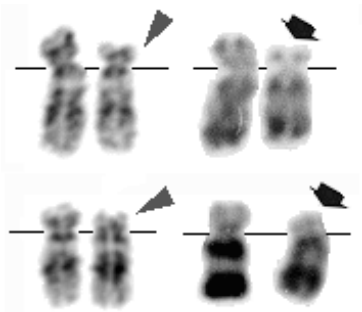
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Identity



del(12)(p11p13) G-banding (left) Courtesy Jean-Luc Lai and Alain Vanderhaegen; R-banding (right) - Editor (below); Courtesy Jean-Luc Lai (above).

Clinics and pathology

Epidemiology

12p abnormalities are common in a broad spectrum of haematological malignancies (acute lymphoblastic (ALL) or acute myeloid (ANLL) leukaemias, myelodysplastic (MDS) or chronic myeloproliferative syndromes, non-Hodgkin's lymphomas; observed in about 5% of acute non lymphocytic leukaemias and myelodysplastic syndromes; characteristic of secondary leukaemia after prior mutagenic exposure (10%) and associated with a poor prognosis (karyotypes mostly complex)).

Cytogenetics

Cytogenetics, morphological

- Sole anomaly in 20%; numerical and structural rearrangements of chromosomes 5 and 7 frequently associated (found in 50% in de novo cases).
- del(12p): due to the very heterogeneous breakpoints in 12p (assigned to all chromosome bands), no

cytogenetic subgroups are defined; deletion in 12p is generally associated with a poor prognosis; however, different clinical courses are defined concerning the magnitude of 12p; a group with small deletions has a better prognosis than patients with 12p abnormalities in general and a lower tendency to additional chromosomal rearrangements; submicroscopic deletions of 12p are much more common in lymphoid than in myeloid malignancies; a minimal interstitial deletion region is described, involving ETV6 and CDKN1B genes; homozygous deletion of CDKN1B is rare (the other wild allele never found mutated); none of the malignancies with disease specific changes displayed submicroscopic 12p deletions.

- dup(12)(p11.2p13) described in one MDS case after benzole agent exposure.

- Additions are frequent, considered as imbalanced translocations.

- Translocations: translocations or dicentrics involving 12p are mostly associated with loss of 12p material; a lot of partner bands are described; chromosome 12 breakpoint is most often localized in 12p13, involving ETV6 gene, with fusion of 5' end of ETV6 with 3' end of the partner, and sometimes accompanied with a concomitant deletion of the other ETV6 allele:

- t(3;12)(q23;p12.3): described as reciprocal and recurrent, involving ETV6 (heterogeneous breakpoints described) and EVI1, and associated with a poor prognosis.

- t(4;12)(q11q13;p12;p13): associated with specific clinical features: CD7-positive ANLL, three-lineage dysplasia, blood and bone marrow basophilia.

- t(5;12)(q33;p13): recurrent, described in chronic myelomonocytic leukemia: fusion between HLH domain of ETV6 and transmembrane and cytoplasmic domains of PDGFRb; a variant t(10;12)(q24;p13) is described in MDS in progression with eosinophilia and monocytosis.

- t/dic(12;13): representing up to 20% of 12p rearrangements in one study, associated with a poor prognosis.
- t(12;22)(p13;q11): resulting in MN1-ETV6 fusion gene (where breakpoint, 5' of, or in, ETV6 HLH domain, is the sole exception), and reported in myeloid malignancies (ANLL and MDS).
- other translocations involving ETV6: t(5;12)(q31;p12) in 'atypical CML', t(6;12)(p21;p13) in MDS, t(7;12)(p15;p13), t(7;12)(q36;p13) in ANLL, t(9;12;14)(q34;p13;q22) in ANLL,... and the never-up-to-date following list: t(6;12)(q23;p13), t(12;17)(p11.2;q11), t/dic(12;20)(p12-p13;p11.2-q13), i(12p) where implication of ETV6 gene is not yet proven.

Probes

From telomere to centromere:
 Corresponding to D12S1455: PAC9015;
 To CCND2: C139C5, C140H4, C146H1, C213C1;
 To PRB: CPRB;
 To ETV6: yacs 958B8, 964C10, cosmids: C5OF4, C163E7, C179AB(5'), C148B6(3');
 To CDKN1B: 123C12, 142C5;
 To KRAS2: 153F12.

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