11q23 rearrangements in leukaemia

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Clinics and pathology

Disease
De novo and therapy related leukaemias; acute non lymphocytic leukaemia (ANLL) and acute lymphocytic leukaemia (ALL) grossly represent half cases each; myelodysplasia (MDS) in the remaining 5%; biphenotypic leukaemia at times (likely to be more frequent with more investigations); 11q23 rearrangements in treatment related leukaemias (5-10% of 11q23 cases) are found mainly following a treatment with anti-topoisomerase II, or an intercalating topoisomerase II inhibitor, but also after alkylating agents treatment and/or radiotherapy; the prior cancer is variable.

Phenotype/cell stem origin
ANLL: M5a in half cases, M4 (20%), M1 or M5b (10% each), M2 (5%); ALL: B-cell mostly, L1 or L2, CD19+ in 60% of B-ALL cases, CD10+ 35%; T-ALL in rare cases (<1%); MDS: most often RA or RAEB1T.

Epidemiology
25% are infant (<1 yr) cases; children and adults each represent 50% of cases; M/F=0.9 (NS).

Clinics
Organomegaly; frequent CNS involvement (5%); high WBC (>50 X 10^9/l in 40%).

Prognosis
Very poor in general; variable according to the translocation, the phenotype, the age, and whether the leukaemia is de novo or treatment related.

Cytogenetics

Cytogenetics morphological
I-The most frequent are:
- Normal karyotype: a partial tandem duplication (in situ) of MLL is present in a percentage of ANLL with a normal karyotype; LARG, in 11q23, has been found fused to MLL;
+11: 1% of ANLL and MDS as well; M1, M2, and M4 ANLL; therapy related ANLL; MDS evolving towards ANLL; partial tandem duplication (in situ) of MLL; visible dup(11q) also occur;
- t(4;11)(q21;q23): represent 1/3 of cases; found mainly (95%) in B-ALL (CD19+ in 75%, CD10+ in 15%); treatment related ALL in 5%; unbalanced sex ratio - t(6;11)(q27;q23): 5% of cases; mostly; children and young adults; male predominance; the gene involved in 6q27 is AF6; role in signal transduction;
-t(9;11)(p23;q23): represent 1/4 of cases; found in ANLL mainly in M5a (70%), or M4 (10%); in ALL in 10%; de novo and therapy related AL: children represent half cases (infants - t(10;11)(p12;q23): 5% of cases; M4 or M5 ANLL; ALL at times; from infants and children to (rare) adult cases; the gene involved in 10p12 is AF10, a transcription activator;
- t(11;19)(q23;p13.1): 5% of cases; M4 or M5 ANLL most often; de novo and therapy related AL: adults mainly; the gene involved in 19p13.1 is ELL, a transcription activator;
-t(11;19)(q23;p13.3): 5% of cases; ALL, biphenotypic AL and ANLL (M4/M5 mainly); therapy related AL; T-cell ALL at times, these T-cell cases are the only cases of t(11;19) with an excellent prognosis, a rather...
rare feature in this page!!; mostly found in infants (half cases), and other children (altogether: 70%), or young adults (cases > 40 yrs are 4%; 23 unpublished cases and a review of 90 cases); the gene involved in 19p13.3 is ENL, a transcription activator.

II-Various other 11q23 rearrangements have been described; these are rare, some are even poorly known, but the ones listed below are recurrent and/or with ascertainment of a partner gene to MLL:  
- inv(11)(p15q23): ANLL and MDS;  
- del(11q): one case (t-ANLL) showed involvement of GAS7, a gene sitting in 17p13; del(11q) with MLL rearrangement is likely to be heterogeneous, as MLL shows multiple possible partners, and, not rarely, complex translocations;  
- t(X;11)(q13;q23): ANLL; the gene involved in Xq13 is AFX1, a transcription regulator;  
- t(X;11)(q22;q23): the gene in Xq22 is Septin2;  
- t(1;11)(p32;q23): ALL and ANLL; the gene involved in 1p32 is AF1P;  
- t(1;11)(q21;q23): mostly M4 ANLL; the gene involved in 1q21 is AF1q;  
- t(2;11)(p21;q23): ANLL and MDS; may be found associated with del(5q);  
- t(2;11)(q11;q23): the gene in 2q11 is LAF4;  
- t(3;11)(p21;q23): the gene involved in 3p21 is AF3p21;  
- t(3;11)(q25;q23): the gene in 3q25 is GMPS;  
- t(5;11)(q31;q23) and ins(5;11)(q31;q13q23): the latter involve AF5q31 in 5q31; very rare;  
- t(5;11)(q31;q23): the gene in 5q31 is GRAF;  
- t(6;11)(q21;q23): ANLL; the gene in 6q21 is AF6q21, a transcription regulator;  
- t(9;11)(q34;q23): the gene in 9q34 is AF9q34;  
- t(10;11)(p11.2q23): the gene in 10p11.2 is ABI1;  
- t(10;11)(q22;q23);  
- t(11;11)(q13;q23);  
- t(11;12)(q23;q13);  
- t(11;14)(q23;q24): the gene in 14q24 is h-gephyrin;  
- t(11;15)(q23;q14): the gene in 15q14 is AF15q14;  
- t(11;15)(q23;q15);  
- t(11;16)(q23;p13): treatment related ANLL/MDS; most cases are children cases; the gene involved in 16p13 is CBP, a transcriptional adaptor/coactivator;  
- t(11;17)(q23;p13): the gene in 17p13 is GAS7;  
- t(11;17)(q23;q12): the gene in 17q12 is RARA;  
- t(11;17)(q23;q21): ANLL; the gene involved in 17q21 is AF17; not to be confused with the in M3 ANLL variant, with involvement of PLZF in 11q23 and RARA in 17q21;  
- t(11;17)(q23;q25): ANLL and MDS; the gene in 17q25 is MSF/AF17q25;  
- t(11;18)(q23;q23);  
- t(11;19)(q23;p13): ANLL; the gene in 19p13 is EEN;  
- t(11;21)(q23;q11);  
- t(11;22)(q23;q13): ANLL; the gene in 22q13 is P000;  
- t(11;22)(q23;q11.2): ANLL; the gene in 22q11.2 is hCDCRel.

III-Finally, various other breakpoints with 11q23 have been described, but without gene ascertainment: Xq24, 1q32, 2q37, 7q22, 7q32, 8q11, 9p11, 9q33, 12p13, 12q24, 14q11, 14q32, 17q11, 18q12, 20q13...

Additional anomalies  
+X and i(7q) in the t(4;11); +8, +19, +21 in the t(6;11);  
+8 and +19 in the t(9;11); inv(11) in the t(10;11); +X, +6 and +8 in the 19p13.3; +8 in the 19p13.1.

Genes involved and proteins

MLL  
Location: 11q23  
DNA/RNA  
21 exons, spanning over 100 kb; 13-15 kb mRNA; coding sequence: 11.9 kb.  
Protein  
431 kDa; contains two DNA binding motifs (a AT hook, and Zinc fingers), a DNA methyl transferase motif, a bromodomain; transcriptional regulatory factor; nuclear localisation; wide expression; homology with trithorax (drosophila).  
Variable gene, from a variable chromosome partner (see below)  
DNA/RNA  
These genes appear to have, in most cases, no apparent homology to each other; for DNA and protein description of each, refer to their gene entry.

Result of the chromosomal anomaly  
Hybrid gene  
Description  
5’ MLL-3’ partner; highly variable breakpoints on the partner.  
Fusion protein  
Description  
N-term AT hook and DNA methyltransferase from MLL fused to (little or most of) the partner C-term part; the reciprocal (partner-MLL) may or may not be expressed.
References


