

Leukaemia Section

Mini Review

11q23 rearrangements in leukaemia

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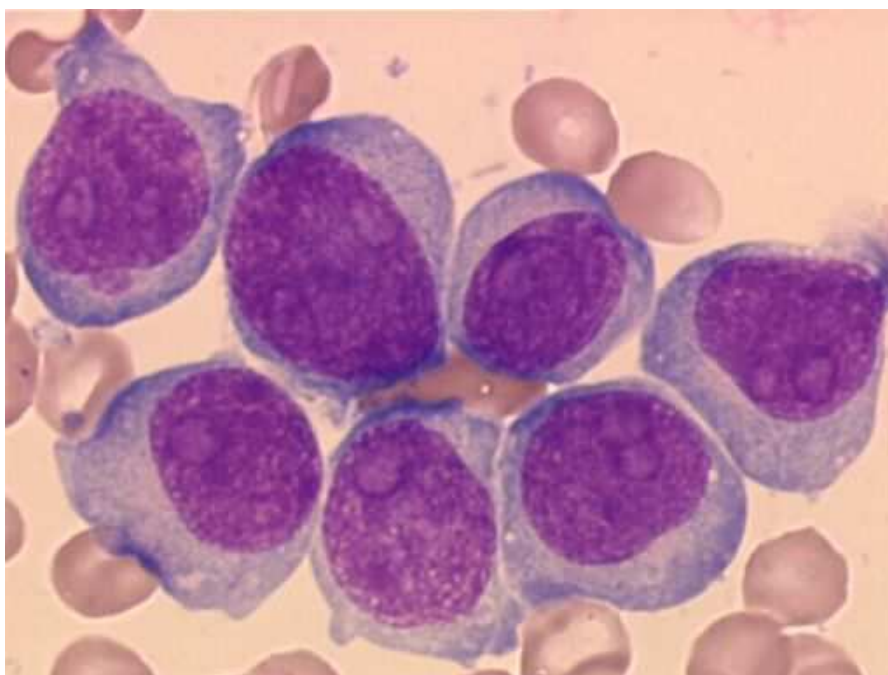
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Clinics and pathology



Molecular studies have identified a human homologue of the drosophila trithorax gene (designed HRX or MLL). MLL is a developmental regulator and is structurally altered in leukemia associated translocations that show an abnormality at band 11q23. The MLL gene on 11q23 is involved in a number of translocations with different partner chromosomes. The most common translocations observed in childhood AML are the t(9;11)(p21;q23) and the t(11;19)(q23;p13.1); other translocations of 11q23 involve at least 30 different partners chromosomes. Molecular studies have shown that MLL is rearranged more frequently than is revealed by conventional cytogenetic studies. A partial tandem duplication of MLL gene has also been reported in the majority of adult patients whose leukemic blast cells have a +11 and in some with normal karyotype. There is a strong association between AML M5/M4 and deletion and translocations involving 11q23. Sometimes cases of 11q23 M5B and M4, and occasionally M2 or M1 also show MLL rearrangement. Two clinical subgroups of patients have a high frequency of 11q23 aberration and M5 subtypes: one is AML in infants with MLL rearrangement in about 50% of cases; the other group is "secondary leukemia" (sAML) potentially after treatment with DNA topoisomerase II inhibitors. In general the translocations in these leukemia are the same as those occurring in "de novo" leukemia i.e. t(9;11), t(11;19) - Courtesy Georges Flandrin, CD-ROM AML/MDS G. Flandrin/ICG. TRIBVN

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 antitopoisomerase 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 (See also 11q23 rearrangements in childhood acute lymphoblastic leukemia: Clinical aspects and congenital leukemias).

Clinics

Organomegaly; frequent CNS involvement (5%); high WBC (> 50 X 10⁹/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: 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 < 4 yrs (1M/2F); children represent half cases (infants <1 yr) accounting for 1/3 of all cases); children aged 2-9 yrs appear to have a much better prognosis; the gene involved in 4q21 is AF4, a transcription activator.

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 <1 yr) accounting for 15% of all cases); the gene involved in 9p22 is AF9, a transcription activator.

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 Septin6

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)(p11.2;q23); 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 P300 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).

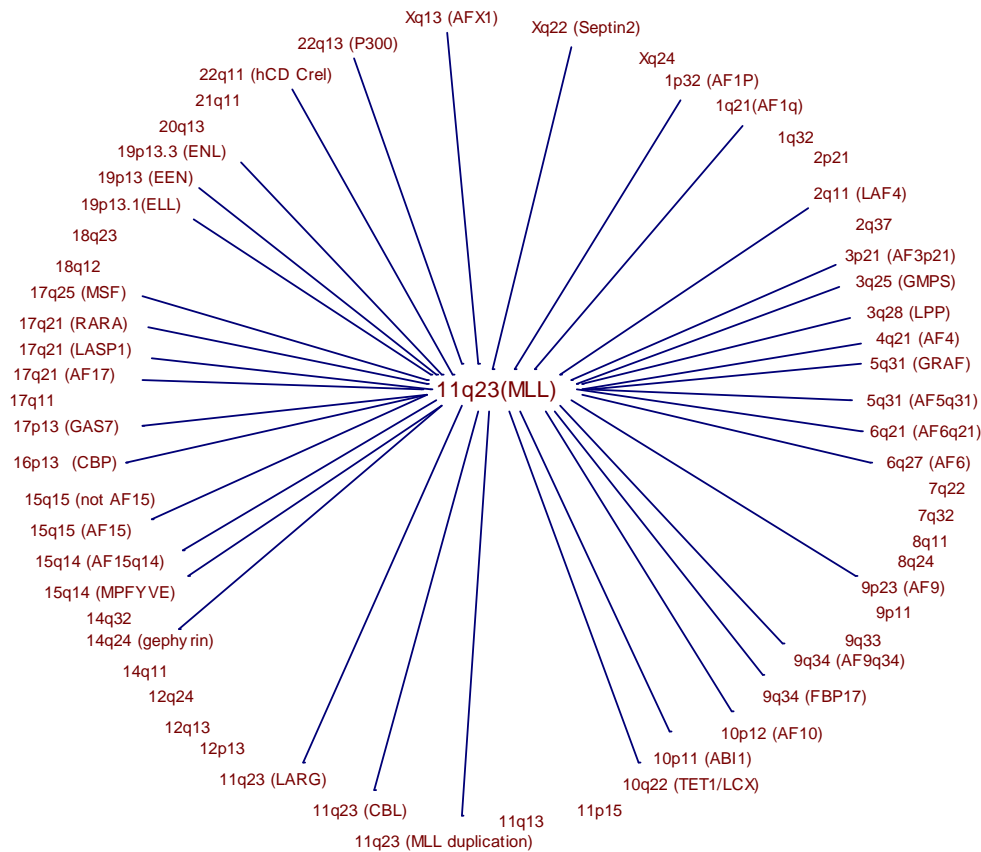
Variable gene, from a variable chromosome partner (see above)

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



MLL and partners - Editor, 06/2000, last update 09/2001. We implore researchers not to discover further MLL partners: there is no more room.

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.

To be noted**Note**

Cases with MLL involvement in rare translocations are yet poorly known; additional cases are needed to delineate the entities; we propose that detailed cases reports are herein collected and published; if you have a case with iconography, please, contact us

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