

# Leukaemia Section

## Short Communication

## dup (11q) in myeloid malignancies

Adriana Zamecnikova, Soad Al Bahar

Kuwait Cancer Control Center, Department of Hematology, Laboratory of Cancer Genetics, Kuwait  
annaadria@yahoo.com

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### Abstract

Partial gain of the long arm of chromosome 11, containing the unrearranged mixed lineage leukaemia (MLL) gene (KMT2A; lysine (K)-specific methyltransferase 2A) is a rare but recurrent anomaly in myeloid malignancies, and is often associated with an older age and a highly complex karyotype.

#### Keywords

gene amplification, intrachromosomal KMT2A duplication, karyotype complexity, acute myeloid leukemia.

### Identity

A different mode of duplication is the internal partial tandem duplication (PTD) of KMT2A (MLL) (MLL-PTD), repeating the 5' part of the gene leading to its self-fusion. MLL-PTD occurs in approximately 10% of cytogenetically normal acute myeloid leukemias (AML) and in the majority of AML cases with trisomy 11 as a sole abnormality.

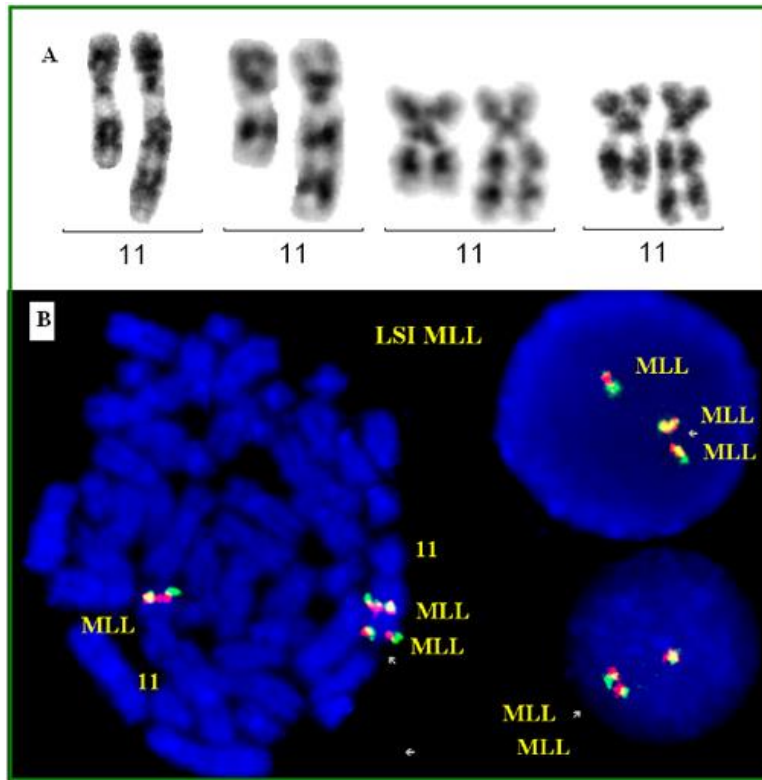
### Clinics and pathology

#### Disease

Chronic myeloproliferative neoplasms and acute myeloid leukemia (AML).

### Phenotype/cell stem origin

Phenotype / cell stem origin 25 of the 29 cases presented were AML, 3 were diagnosed with myelodysplasia (MDS) (Werner et al., 1992; Harrison et al., 1998; MacGrogan et al., 2004) and 1 with chronic myeloid leukemia (CML) (Pedersen et al., 2000). While the most common phenotype of AML cases with MLL translocations is AML-M4/M5, the phenotype of AML cases was AML-M1 (7 patients) mainly (Soni et al., 1996; Green et al., 1999; Cuthbert et al., 2000; Brezinova et al., 2002; Mrozek et al., 2002; Arnaud et al., 2005; Babicka et al., 2007). In addition, there were 1 AML-M0 (Van Limbergen et al., 2002), 5 AML-M2 (Soni et al., 1996; Mauritzson et al., 2002; Van Limbergen et al., 2002; Rucker et al., 2006), 1 AML-M4 (Harrison et al., 1998), 4 AML-M5 (Kaneko et al., 1982; Harrison et al., 1998; Xu et al., 2001), 1 AML-M7 (Dastugue et al., 2002) and 6 AML not specified cases (Smadja et al., 1989; Lai et al., 1995; Andersen et al., 2005; Babicka et al., 2007; Lessard et al., 2007; Huh et al., 2013). Among the 29 patients, 1 patient developed AML after therapy for multiple myeloma (Soni et al., 1996), 2 after therapy for adenocarcinoma (Mauritzson et al., 2002; Andersen et al., 2005) and 1 after chemotherapy for diffuse large B-cell lymphoma (Huh et al., 2013) (Table 1).



Légend (A) Partial karyotypes with 11q duplication. (B) Fluorescence in situ hybridization (FISH) with LSI MLL (Vysis/Abott, USA) showing intrachromosomal duplication of MLL (KMT2A) (2 fusion signals on 11q+) on metaphase and interphase cells.

	Sex/ Age	Diagnosis	Karyotype
1	F/0	AML- M5	51,XX,+1,del(1)(p22)x2,+3,+6,+9,add(10)(p13),dup(11)(q11q21),+19/52,idem,+18
2	F/60	AML	44,XX,der(1)t(1;4)(q11;p11),+der(1)t(1;7)(p11;p11),-4,del(5)(q14q34),der(7)t(7;17)(q11;q11),dup(11)(q12q13),-12,-17,-20,+mar
3	M/84	RAEB	46,XY,dup(11)(q13q25)
4	M/53	AML	44-45,XY,-3,-5,-10,dup(11)(q12q13),add(12)(p12),add(14)(q32),der(17)t(5;17)(p11;p11),i(18)(q10),+1-2mar
5	M/59	AML-M1	49-52,XY,+1,+der(2)t(2;11)(q27;q11),der(3)t(3;3)(q23;p23),del(6)(q23),+10,del(11)(q21q23),+dup(11)(q23),+13,add(14)(p13),add(16)(p23),-17,-17,-18,der(19)t(17;19)(q21;p13),inc
6	F/83	AML- M2	44-47,XX,-5,der(6)t(6;13)(p22;q21),+der(11)ins(11;11)(q24;q?12q14),+dup(11)(q23q25),+i(11)(q10),del(13)(q?),der(16)t(13;16)(q?q;13),del(17)(p?),-18,der(22)t(13;22)(q?p11) multiple myeloma, chemotherapy
7	M/45	AML- M5a	46,XX,dup(11)(q23q23)
8	F/15	AML-M4	49,XX,+8,+8,+8,dup(11)(q14q23)/50,idem,+mar
9	M/77	AML- M5b	45,XY,-10,dup(11)(q23q24)
10	M/63	RA	43,X,-Y,del(5)(q13q33),der(7)t(7;13)(p22;q1?),-9,der(11)add(11)(p15)dup(11)(q14q23),-13
11	M	AML-M1	43,XY,del(5)(q15q33),-7,-11,dup(11)(q13q23),-17,der(18)t(7;18)(q22;q23)/44, idem,+mar
12	F/76	AML-M1	45,XX,del(5)(q13q33),del(7)(q?11q36),dup(11)(q23q23),-16,add(16),der(18)t(16;18)(?;p11)
13	F/66	CML	45,XX,-7,-9,t(9;22),add(10)(q26),dup(11)(q22q23),der(19),+del(22)(q?)
14	M/23	APL/ AML- M5a	46,XY,dup(11)(q?),t(15;17)(q22;q21)

15	F/66	AML-M1	46,XX,del(5)(q13q33),dup(11)(q13q23),t(17;20)(q12;q11)/46,XX,del(5),del(7)(q21q31),+8,dup(11)(q23q23), -14,der(17)t(14;17)(q21;q12),der(20)t(17;20)/46,XX,del(5),del(7),+8,der(11)t(11;11)(q23;p?),-14,der(17)t(14;17),der(20)t(17;20)
16	M/1	AML-M7 DS	44,XY,t(9;15)(p11;q11),dup(11)(q11q13),-13,-15,-16,der(17)t(16;17)(q11;p11),+21c,der(21)t(13;21)(q21;p11)
17	F/61	MDS AML-M2	46,XX,t(6;9)(p11;p11),t(6;13)(p25;q14),ins(17;1)(q25;q21q25),del(19)(q12)/47,idem,+21 46,XX,t(6;9),t(6;13),-13,+mar/46,XX,del(1)(p11p32),-4,-5,add(7)(q31-32),-9,+dup(11)(q13q23),-12,del(14)(q22),-16,-17,ins(17;1),+der(?)t(?)2)(?)q?), +2mar adenocarcinoma, chemotherapy, radiotherapy
18	M/80	AML-M1	44,X,-Y,del(5)(q13q33),der(5)t(5;11)(q35;q13),-7,der(21)t(7;21)(?:q2?1)t(7;21)t(7;21)t(7;21)t(7;21)/44,X,-Y,del(5),-7,der(16)t(11;16)(q13;q24),der(21)/44,X,-Y,del(5),-7,dup(11)(q23q25),der(21)
19	F/68	AML- M2	43,XX,-4,del(5)(q12q34),der(10)t(1;10)(p13;q26),dup(11)(q?24q?),-17,-18
20	M/63	AML-M0	45,XY,der(2)t(2;18)(p13;p11),del(5)(q13q33),der(7)t(7;11),der(11;12)(q10;q10),dup(11)(q?24q?),+13,der(13)t(7;13)(q?;q21)x2,-16,der(17)t(2;17)(p13;q21),der(17)t(7;17)(?:q24),der(18)t(18;20)(q?;p11),der(20)t(7;20)
21	M/76	AML- M2	46,XY,der(1;19)t(1;19)(p13;p12)t(1;19)(p36;q13),der(5)t(5;17)(q13;q11-22),dup(11)(q?24q?),der(17)r(5;17) -19,+22,i(22)(q10)x2
22	M	RAEB	44-49,XY,+Y,del(1)(q32),add(2)(p25),del(5)(q15q31),der(6)t(2;6)(q21;q13),del(7)(q22),+9,add(9)(q34)x2, add(11)(p13),dup(11)(q13q23),-17,add(17)(p11), add(19)(p13),-20,i(21)(q10),+2mar
23	F/86	AML	44,XX,dic(5;17)(q11;p11),-7,der(10)t(10;11)(q25;q22)/43,idem,del(3)(p21),dic(4;7)(q11;q11),+7,der(8)t(4;8)(q21;p21),-12,der(12)t(12;21)(p13;q22),der(21)t(12;21)(q?;q21)/43,idem,del(3),dic(4;7),+7,der(8)(4;8),dup(11)(q23q23),-12,der(12)t(12;21),der(21)t(12;21) adenocarcinoma, chemotherapy
24	F/60	AML-M1	46,XX,der(3)t(3;11)(q29;q11)/46,XX,dup(11)(q14q23)
25	F/64	AML-M2	44,XX,del(2)(q31q35),-4,del(5)(q13q33),-11,dup(11)(q21q23),-14,del(17)(q21),del(18)(q21),+mar
26	M/62	AML	45,XY,del(5)(q13q33),del(7)(q22q35),dup(11)(q?),der(17)t(17;21)(p11;?),der(20)t(20;21)(q12;?),-21/44,XY, del(4)(q32),del(5),der(7)t(3;7)(q?;q21),-15,der(16)t(15;16)(?:q22),der(17)t(17;21),der(20)t(20;21),-21
27	F/66	AML-M1	46,XX,del(5)(q13q33),del(7)(q21q33),dup(11)(q13q23),-17,der(20)t(17;20)(q12;q11)/46,XX,del(5),del(7),+8, dup(11),-14,der(17)t(14;17)(?:q12),der(20)t(17;20)
28	M/60	AML	46,XY,del(5)(q13q33),dup(11)(q23q23)/43,idem,-4,-17,-18/42,idem,del(2)(q21),-6,-dup(11),add(12)(p11), del(12)(p11),-16,-17,-18
29	M/63	AML	42,X,-Y,del(1)(q32),add(2)(q13),-4,add(4)(q31),del(5)(q15q33), add(6)(p25),add(6)(q13),der(7;16)(p10;q10), -8,add(10)(p13),dup(11)(q23q25),add(13)(p11),-16,-17,add(18)(q12),add(20)(q13),+2mar diffuse large B-cell lymphoma, chemotherapy

**Abbreviations:** F., female; M., male; AML., acute myeloid leukemia; AML-M5., acute monoblastic leukemia; RAEB., refractory anemia with excess of blasts; AML-M1., acute myeloblastic leukemia without maturation; AML-M2., acute myeloblastic leukemia with maturation; AML-M5a., acute monoblastic leukemia without differentiation; AML-M4., acute myelomonocytic leukemia; AML-M5b., acute monocytic leukemia; RA., refractory anemia; CML., chronic myeloid leukemia; APL., acute promyelocytic leukemia; DS., Down's syndrome; MDS., myelodysplastic syndrome; AML-M0., acute myeloblastic leukemia with minimal differentiation.

1. Kaneko et al., 1982; 2. Smadja et al., 1989; 3. Werner et al., 1992; 4. Lai et al., 1995; 5-6. Soni et al., 1996; 7-10. Harrison et al., 1998; 11. Green et al., 1999; 12. Cuthbert et al., 2000; 13. Pedersen et al., 2000; 14. Xu et al., 2001; 15. Brezinova et al., 2002; 16. Dastugue et al., 2002; 17. Mauritzson et al., 2002; 18. Mrozek et al., 2002; 19-21. Van Limbergen et al., 2002; 22. MacGrogan et al., 2004; 23. Andersen et al., 2005; 24. Arnaud et al., 2005; 25. Rucker et al., 2006; 26-27. Babicka et al., 2007; 28. Lessard et al., 2007; 29. Huh et al., 2013.

## Prognosis

The over-representation of complex karyotypes in association with unbalanced rearrangements and/or chromosome 5 and 7 anomalies may reflect genomic instability and correlate with an unfavorable outcome in patients with 11q duplications.

## Epidemiology

16 male and 13 female patients with median age of 63 years (range 0 to 86 years), among them 2 were infants (aged 0 and 1 years) and a single pediatric case aged 15 years. The ages of the adult patients ranged from 23 to 86 years, with a mean age of 63 years.

## Cytogenetics

### Note

Fluorescence in situ hybridisation (FISH) allows identification of genes included in the amplified regions such as duplicated copies of MLL located together on the same chromosome arm without gene splitting.

### Cytogenetics morphological

Identified as add(11)(q) with cytogenetically heterogeneous breakpoints by conventional cytogenetic analysis. The involved region was within the 11q13 to 25 bands in the majority of patients, clustering within the 11q13 to 23 and 11q23 to 25 regions and within the 11q11 to 21 bands in 4 cases.

### Additional anomalies

Significantly associated with complex karyotypes; sole anomaly only in 2 patients: 1 with refractory anemia with excess of blasts (Werner et al., 1992) and 1 AML case (Harrison et al., 1998), associated with monosomy 10 in 1 (Harrison et al., 1998), pentasomy 8 in 1 (Harrison et al., 1998) and found in an unrelated clone in 1 AML case (Harrison et al., 1998). Highly complex anomalies in the remaining cases including dicentric chromosomes, highly rearranged chromosome derivatives and unbalanced structural aberrations; loss or deletion of chromosome 5 was found in 10 patients (Smadja et al., 1989; Lai et al., 1995; Soni et al., 1996; Harrison et al., 1998; Mauritzson et al., 2002; Van Limbergen et al., 2002; Van Limbergen et al., 2002; Rucker et al., 2006; Lessard et al., 2007; Huh et al., 2013), while simultaneous loss or deletion of chromosomes 5 and 7 was found in 7 (Green et al., 1999; Cuthbert et al., 2000; Brezinova et al., 2002; Mrozek et al., 2002; MacGrogan et al., 2004; Babicka et al., 2007; Babicka et al., 2007).

Loss or deletion of chromosomes 5 and 7 was accompanied with -17 or 17p rearrangements in 11 cases (Smadja et al., 1989; Lai et al., 1995; Soni et al., 1996; Green et al., 1999; Mauritzson et al., 2002; Van Limbergen et al., 2002; MacGrogan et al., 2004; Babicka et al., 2007; Babicka et al., 2007; Lessard et al., 2007; Huh et al., 2013).

## Result of the chromosomal anomaly

### Fusion protein

#### Oncogenesis

The MLL gene, located at 11q23, is frequently rearranged in acute leukaemia as either gene fusions or partial tandem duplications, but 11q duplication is a relatively rare anomaly in myeloid malignancies. In the majority of cases it is found as a part of a

highly complex karyotype representing clonal evolution that plays a role in disease progression. Chromosome duplications occur in a broad spectrum of malignancies and typically leads to inappropriate activation or overexpression of one or more oncogenes located within the amplicon. FISH and expression analyses confirmed MLL as a prominent target within 11q23 copy gain or amplification, providing further evidence for an etiologic role for MLL gain of function in myeloid malignancies. However, as varying and often large parts of 11q are involved in chromosome duplication, it is possible that gains of other genes such as DDX6, ETS1, and FLI1 may contribute to leukemogenesis as a gain-of-function mutation (Pope et al., 2004).

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