Molecular characterization of the *MLL-SEPT6* fusion gene in acute myeloid leukemia: identification of novel fusion transcripts and cloning of genomic breakpoint junctions

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ABSTRACT

One of the *MLL* fusion partners in leukemia is the *SEPT6* gene, which belongs to the evolutionarily conserved family of genes of septins. In this work we aimed to characterize at both the RNA and DNA levels three acute myeloid leukemias with cytogenetic evidence of a rearrangement between 11q23 and Xq24. Molecular analysis led to the identification of several *MLL-SEPT6* fusion transcripts in all cases, including a novel *MLL-SEPT6* rearrangement (*MLL* exon 6 fused with *SEPT6* exon 2). Genomic DNA breakpoints were found inside or near Alu or LINE repeats in the MLL breakpoint cluster region, whereas the breakpoint junctions in the *SEPT6* intron 1 mapped to the vicinity of GC-rich low-complexity repeats, Alu repeats, and a topoisomerase II consensus cleavage site. These data suggest that a non-homologous end-joining repair mechanism may be involved in the generation of *MLL-SEPT6* rearrangements in acute myeloid leukemia.

Key words: *MLL-SEPT6*, fusion oncogene, fusion transcript, genomic breakpoint, acute myeloid leukemia.

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Introduction

Abnormalities of 11q23, resulting in fusion of the mixed lineage leukemia (*MLL*) gene with numerous translocation partners, are found in primary acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), as well as in secondary, topoisomerase II inhibitor–related leukemia.[1] The MLL gene codes for a multi-domain protein that is a major regulator of class I homeobox (*HOX*) gene expression.[2] *HOX* genes play a key role in the regulation of hematopoietic development and altered patterns of MLL activity might cause abnormal *HOX* gene expression in hematopoietic stem cells, resulting in blockage of hematopoietic maturation and, eventually, leukemia.[3]

To date, more than 50 *MLL* fusion partners have been cloned.[4] Five of these, *SEPT2*, *SEPT5*, *SEPT6*, *SEPT9*, and *SEPT11*, code for septins[4,5] and belong to an evolutionarily conserved family of genes with 13 members identified so far.[6] As a consequence, the septins are the protein family most frequently involved in rearrangements with *MLL*, suggesting that their involvement in *MLL*-related leukemia is anything but a chance event.[5,6] Septins are conserved GTP-binding proteins that assemble into homo- and hetero-oligomers and filaments with key roles in cell division cytoskeletal dynamics and secretion.[6]

To our knowledge, the fusion between *MLL* and *SEPT6* has so far only been described in 10 AML patients.[7-13] However, the genomic breakpoint junction was only characterized in 2 patients.[9,10] We present a detailed RNA and DNA analysis in 3 new AML patients with the *MLL-SEPT6* rearrangement, one of them showing a novel in-frame fusion transcript.

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The online version of this article contains a supplementary appendix.

Design and Methods

The study comprised three cases of childhood AML in which Xq24 and 11q23 rearrangements were detected by karyotyping and/or molecular cytogenetic analyses of the leukemic cells. Molecular studies involved RT-PCR, LD-PCR, HN-PCR, sequencing, and bioinformatic analyses. For detailed information on patients, methods and results see *Online Supplementary Appendix*.

Results and Discussion

Karyotyping and molecular cytogenetics

The 3 AML patients showed cytogenetic evidence of a rearrangement involving the long arm of chromosome 11 (11q23), the first with additional material of unknown origin in 11q23 and Xp11 (patient 1), the second as a translocation between 11q23 and Xq24, and the third as an insertion of 11q13q23 into Xq24 (Table 1, Figure 1). FISH analysis on leukemic metaphases was performed, demonstrating in all cases a break in *MLL* (Figure 1) and the presence of *MLL* sequences in Xq (cytogenetically cryptic in case 1). The known localization of *SEPT6* in Xq24 prompted further analysis with BACs mapped to this band in patients 2 and 3. In patient 2, the breakpoint was mapped to clone CTD-2334F19, suggesting a breakpoint in or near the 5' region of the *SEPT6* gene. In patient 3, the breakpoint was mapped to the overlapping region of the two BAC clones RP11-379J1 and CTD-2334F19, which suggested that the break occurred in the 5' region of the *SEPT6* gene. In patient 1, BAC analysis could not be performed due to lack of material. Rearrangements recombining 11q23 and Xq24 resulting in *MLL-SEPT6* fusions are usually complex as a result of the opposite orientation of *MLL* and *SEPT6* on the respective chromosome arms. At least four different types of chromosomal rearrangements have been described that can generate the *MLL-SEPT6* in-frame fusion.[7-10] The combined chromosome banding and molecular cytogenetic investigations of our 3 patients confirm that complex, sometimes cryptic, chromosome rearrangements are common in AML patients with *MLL-SEPT6* rearrangements (Table 1).

Characterization of MLL-SEPT6 fusion transcripts

RT-PCR followed by sequencing analysis led to the identification of *MLL-SEPT6* fusion transcripts in all 3 cases. In patient 1, two major PCR fragments of 719 bp and 605 bp were detected (*Online Supplementary Figure 1A*). Sequencing analysis revealed a fusion of *MLL* exon 7 and *MLL* exon 8 with *SEPT6* exon 2. In addition, a minor band of 541 bp detected in this patient (*Online Supplementary Figure S1A*) was shown by sequencing analysis to correspond to an out-of-frame fusion between *MLL* exon 7 and *SEPT6* exon 2 with splicing of 74 bp corresponding to *MLL* exon 6. RT-PCR analysis of patient 2 revealed one major band of 473 bp and a minor band of 399 bp (*Online Supplementary Figure S1B*). Sequencing analysis revealed the presence of two

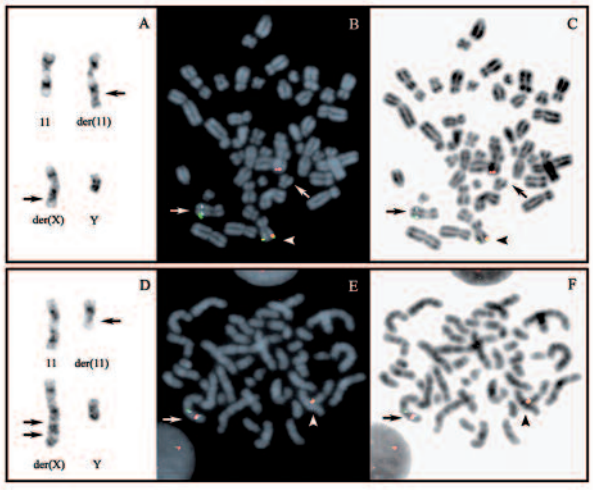

Figure 1. G-banding and FISH analyses of the leukemic cells of patients 2 and 3. (A) Partial karyotype of case 2, with arrows indicating breakpoints of rearranged chromosomes. (B) FISH and (C) inverted DAPI images of metaphase plate from case 2. The hybridization was performed using a locus-specific, break-apart probe for *MLL* (green and red signals) and the BAC clone CTD-2334F19 (blue signal). The blue signal has moved to the derivative chromosome 11, indicating that the breakpoint is in the 5' of the *SEPT6* gene. Arrows indicate derivative chromosomes, arrow heads are pointing to the normal chromosome 11. (D) Partial karyotype of case 3. (E) FISH and (F) inverted DAPI images of a metaphase plate from case 3. Hybridization was performed using the *MLL* probe and the clone CTD-2334F19. The BAC clone (blue colour) splits giving two signals on the rearranged X chromosome, indicating that the breakpoint is inside that clone.

novel *MLL-SEPT6* chimeric transcripts: an in-frame fusion between *MLL* exon 6 and *SEPT6* exon 2 and an out-of-frame fusion of *MLL* exon 5 to *SEPT6* exon 2 (*Online Supplementary Figure S1D*). The novel *MLL-SEPT6* in-frame fusion variant is expected to give rise to a chimeric fusion protein, where the N terminus of *MLL* fused to almost the entire open reading frame of *SEPT6*, except for the first nine amino acids.

In patient 3, RT-PCR analysis showed the presence of two PCR fragments of 605 bp and 541 bp (*Online Supplementary Figure S1C*). Sequencing analysis demonstrated fusions between *MLL* exon 7 and *SEPT6* exon 2, with the smaller fragment showing, as in patient 1, an out-of-frame splicing of *MLL* exon 6. The 10 cases of *MLL-SEPT6* rearrangement described so far showed fusions between *SEPT6* exon 2 and *MLL* exon 7 (3 cases), *MLL* exon 8 (3 cases), both *MLL* exons 7 and 8 (3 cases), or *MLL* exon 9 (one case).[8-13] The novel *MLL-SEPT6* chimeric transcript we here describe between *MLL* exon 6 and *SEPT6* exon 2 may be called type IV, after the three fusion types previously identified (Table 1).

SEPT6 belongs to an evolutionarily conserved family of genes that encode a P loop-based GTP-binding domain flanked by a polybasic domain and, in most cases, a coiled-coil-region.[6] The SEPT6 protein possesses all the three domains and, as previously reported in cases of gene fusion involving *MLL* and other septins (*MLL-SEPT2, MLL-SEPT5, MLL-SEPT9*, and *MLL-*

SEPT11), almost the entire open reading frame of *SEPT6*, containing all the three septin function-defining domains, is fused with the N-terminal moiety of *MLL*. A relevant role of septins in *MLL*-related leukemia, besides activation of the *MLL* protein by dimerization, is therefore a possibility that should not be ruled out.[5,6] Additional support for this hypothesis comes from the observation that all 13 patients reported so far with *MLL-SEPT6* rearrangement were children (age range; 0-29 months) with AML (the FAB-typed included one M1, five M2, four M4 and one M5; Table 1). Since the majority (65%) of pediatric patients with *MLL* rearrangements have ALL,[4] we hypothesize that the SEPT6 domains of the MLL-SEPT6 chimeric protein contribute to myeloblastic leukemogenesis in children. In fact, the *MLL* fusion with the other septins (*SEPT2, SEPT5, SEPT9*, and *SEPT11*) is also preferentially associated with myeoloblastic rather than lymphoblastic leukemogenesis.[4,5,14] In all 3 cases studied we observed the presence of out-of-frame alternative splicing variants, something that has not been previously reported[7-13] and whose biological relevance is not clear.

Characterization of MLL-SEPT6 genomic breakpoints

The genomic breakpoints in all cases occurred in the *MLL* 8.3 kb breakpoint cluster region (BCR) and in *SEPT6* intron 1 (*Online Supplementary Figure 2*). In patient 1, a total of six suggestive HN-PCR fragments were gel extracted and sequenced. Sequencing of the amplification products showed that the breakpoint was located 231 bp downstream of *MLL* exon 8 and 476 bp downstream of *SEPT6* exon 1 (*Online Supplementary Figure 2D*). The HN-PCR study of case 2 revealed a total of 11 suggestive HN-PCR fragments that were gel extracted and sequenced. Sequencing analysis showed that the genomic breakpoints were located 629_634 bp downstream of *MLL* exon 6 and 14410_14415 bp upstream of *SEPT6* exon 2 (*Online Supplementary Figures 2B and 2E*). In this case, the exact position of the genomic breakpoint could not be determined due to the presence of an identical 5-bp microhomology sequence (TGGGA) at the *MLL-SEPT6* genomic junction. In patient 3, an LD-PCR fragment of 2179 bp was detected (*Online Supplementary Figure 2C*). Interestingly, partial direct sequencing of the amplification product revealed the

Table 1. Clinical, karyotyping, FISH and RT-PCR data on all known acute myeloid leukemia-patients with *MLL-SEPT6*, and classification of the fusion variants.

Patient	*Age (mo.)*	*Sex*	*Diagnosis*	*Karyotype*	*FISH*	*RT-PCR (MLL/SEPT6 fusion)*	*Type*	*Reference*
1	17	F	AML-M2	47,X,add(X)(p11),+6,add(11)(q23)[20]	MLL	exon 7/exon 2 exon 8/exon 2 exon 5-7/exon 2	Type II Type I Out-of-Frame	Present study
2	12	M	AML	46,Y,t(X;11)(q24;q23)[11])/46,XY[9]	MLL	exon 6/exon 2 exon 5/exon 2	Type IV Out-of-Frame	Present study
3	0	M	AML	46,Y,ins(X;11)(q24;q13q23)[11]	MLL	exon 7/exon 2 exon 5-7/exon 2	Type II Out-of-Frame	Present study
4	6	F	AML-M2	46,X,ins(X;11)(q24;q23)	MLL	exon 8/exon 2	Type I	8
5	20	F	AML-M4	47,X,der(X)t(X;11)(q22;q23)t(3;11)(p21;q12), der(3)t(3;11)(p21;q23)t(X;11)(q22;q25), +6,der(11)del(11)(q12?qter)	MLL	exon 7/exon 2	Type II	9
6	10	M	AML-M2	46,Y,t(X;11)(q22;q23)[25]/46,XY[5]	Not done	exon 8/exon 2	Type I	9
7	3	F	AML-M2	46,XX,t(5;11)(q13;q23)[6]/46, idem,add(X)(q22)[12]	MLL	exon 7/exon 2 exon 8/exon 2	Type II Type I	7
8	7	M	AML-M2	46,XY[20]	MLL	exon 7/exon 2	Type II	7
9	6	F	AML-M1	46,X,add(X)(q2?),del(11q?)[20]	MLL	exon 7/exon 2 exon 8/exon 2	Type II Type I	7
10	29	M	AML-M5	46,Y,ins(X;11)(q24;q23q13)[13]/46,XY[7]	MLL	exon 7/exon 2	Type II	11
11	8	M	AML-M4	46,XY	Not done	exon 8/exon 2	Type I	10
12	13	M	AML-M4	46,Y,ins(11;X)(q23;q24q22) [14]/46,idem,i(10)(q10)[6]	MLL	exon 9 / exon 2	Type III	12
13	26	F	AML-M4	46,XX,t(11;17)(q23;q?25)[20]	MLL	exon 7/exon 2 exon 8/exon 2	Type II Type I	13

same genomic breakpoint junction as detected in patient 1, with fusion of nucleotide 231 downstream of *MLL* exon 8 with nucleotide 476 downstream of *SEPT6* exon 1 (*Online Supplementary Figure 2D*).

We searched for topoisomerase II consensus cleavage sites in the vicinity of the breakpoint regions in *MLL* introns 6 and 8 and *SEPT6* intron 1. We found one sequence with 100% homology with the topoisomerase II consensus cleavage site located in *SEPT6* intron 1 (GTTTTCCTGTTGTTGTTT), nucleotide position 9533_9550 bp downstream of *SEPT6* exon 1. We also searched the breakpoint junctions (15 bp either side) for repetitive DNA sequence elements and motifs known to be associated with site specific recombination, cleavage, and gene rearrangement, but none could be found. Translocations may or may not involve gain or loss of genetic material at the genomic breakpoint junctions. Patients 1 and 3, as well as the two previously reported cases, showed no nucleotide(s) deletion or duplication at the breakpoint junction.[9,10] In our patient 2, the exact position of the genomic breakpoint could not be determined due to an identical 5-bp microhomology region at the *MLL-SEPT6* genomic junction, so it is unknown whether duplications and/or deletions occurred in this particular patient. The identification of identical microhomologies at genomic junctions suggests that the non-homologous DNA end-joining (NHEJ) pathway may be involved in this rearrangement.[15] In patients 1 and 3, the genomic junction mapped near a 484 bp LINE1 repeat in *MLL* intron 8, whereas the genomic breakpoint in *SEPT6* intron 1 mapped near two GC-rich low complexity repeats. In patient 2, the *MLL* intron 6 genomic breakpoint occurred inside a 298 bp Alu repeat, whereas the breakpoint junction in the *SEPT6* intron 1 mapped near a 300 bp Alu repeat. Although repetitive sequences may occur near or spanning breakpoint junctions by chance, it is plausible that introns with a high density of repetitive sequences, such as *SEPT6* intron 1, are vulnerable to breaking and non-homologous pairing that can lead to gene fusions such as *MLL-SEPT6*. Strikingly, although the breakpoints in the large *SEPT6* intron 1 seem to be distributed all over the intronic region (our patient 2, and cases 6 and 11 in the literature; Table 1), patients 1 and 3 showed exactly the same genomic breakpoint both in *MLL* and *SEPT6*. Since the genomic breakpoint junctions in these 2 patients were cloned by different methods (HN-PCR and LD-PCR), on separate occasions, and taking the strictest anti-contamination measures, these findings can only be explained by the presence of a hot-spot for recombination at the said sites. Supporting this hypothesis, in addition to the above-mentioned high density of repetitive sequences in *SEPT6* intron 1, is the detection of a topoisomerase II consensus site-specific cleavage in the same intron. Identical genomic breakpoints or breakpoint clustering within very narrow regions have been reported before, namely in *MLL-AF4*,[16] *MLL-AF9*,[17] and *TCF3-PBX1*[18] leukemias. Interestingly, the presence of an *MLL* intron 8 genomic breakpoint in patient 3 does not seem to translate into fusion transcripts that include *MLL* exon 8, since the only in-frame fusion transcript detected showed a fusion between *MLL* exon 7 and *SEPT6* exon 2. Splicing of *MLL* exon 8, which includes the first of the four zinc fingers of the first zinc finger domain of the *MLL* gene, has been previously described in acute leukemia with *MLL* rearrangements, both in cases with translocation [(t(4;11), t(9;11), and t(11;19)][19,20] and tandem duplication,[21] changing the structural and possibly the functional features of the first zinc finger region of the MLL protein.

The *MLL* genomic breakpoints in *MLL-SEPT6* AML patients seem to occur preferentially in the telomeric half (between introns 7 and 11) of the *MLL* BCR. This is characteristic of infant AML (the *MLL-SEPT6* cases with genomic breakpoint characterization have an age at diagnosis from 0 to 17 months) and topoisomerase II inhibitor-related secondary leukemia, and a putative association with *in utero* exposure to topoisomerase II inhibitors has been hypothesized.[22] The detection of a topoisomerase II recognition sequence in *SEPT6* intron 1 also supports the hypothesis that exposure to topoisomerase II inhibitors, can result in double-strand DNA breaks that trigger the error-prone non-homologous end-joining pathway, which in turn can lead to formation of the *MLL-SEPT6* fusion oncogene.

Authorship and Disclosures

NC designed and performed the research, analyzed the data and wrote the paper. FM and JS performed the research, analyzed the data and wrote the paper. MP, CC, SL, and SB performed the research and analyzed the data. LN, AG, and AEA clinically assessed the patients. SH and MRT analyzed the data and wrote the paper. The authors reported no potential conflicts of interest.

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