Submicroscopic deletions in the 7q region are associated with recurrent chromosome abnormalities in acute leukemia

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Background and Objectives. Loss of heterozygosity (LOH) on the long arm of chromosome 7 (7q) has been frequently reported in several types of human cancer including hematologic malignancies. Moreover, monosomy of chromosome 7 and 7q deletions have been associated in acute myeloid leukemia (AML) with aggressive disease and poor prognosis.

Design and Methods. Using a panel of 11 polymorphic microsatellite markers at bands 7q21-q36, we investigated fifty patients (acute myeloid leukemia [AML], n=33 and acute lymphoid leukemia [ALL], n=17) for LOH, a hallmark of possible involvement of tumor suppressor genes. In parallel, the same acute leukemia (AL) cases were studied by conventional cytogenetics.

Results. A total of 48 spots of allelic loss were observed in 16 (32%) out of 50 patients (AML, n=11 and ALL, n=5). Among LOH^{+ve} cases 3 showed chromosome 7 monosomies, whereas no cytogenetically detectable abnormalities were observed in chromosome 7 in the remaining 13.

Interpretation and Conclusions. Comparison with karyotypic results indicated that presence of LOH at 7q21-q36 was significantly associated with other chromosomal aberrations. In fact, an altered karyotype was detectable in 87% of LOH^{+ve} and in 52% of LOH^{-ve} AL cases (p=0.024). In addition, LOH at 7q was prevalently associated with *unfavorable* cytogenetic lesions (p=0.013). Our study represents the first report of a significant association between LOH and recurrent chromosomal abnormalities in AL patients suggesting that the 7q21–q36 region may be an unstable area prone to chromosome breakage in patients with an abnormal karyotype.

Key words: LOH, 7q region, acute leukemia, recurrent chromosomal aberrations.

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Monosomy and deletions of the long arm of chromosome 7 (7q) are among the most common *non random* chromosomal aberrations described in acute myeloid leukemia (AML) and myelodysplastic syndromes.[1-4] Both terminal and interstitial deletions of 7q have been reported with variable breakpoints among patients.[5,6] Chromosome 7 aberrations are consistently recognized indicators of poor prognosis in adult acute myeloid leukemia.[7,8] Analogous significance seems to be associated with acute lymphoid leukemia (ALL).[9,10] Patients exhibiting –7/7q- normally show a more aggressive disease, characterized by low response to chemotherapy, high susceptibility to infections, and short survival.[11] Moreover, interstitial deletions of 7q have been reported in a variety of solid tumors in which distinct segments of loss have been identified.[12-15]

The delineation of the critical region of loss at 7q has been the focus of intense investigation both in solid tumors and hematologic malignancies. These studies led to identification of two distinct critical regions at bands 7q22 and 7q31.[16-20] Chromosomal deletions are indicative of loss of function, and it has been hypothesized that chromosome 7 harbors one or more putative tumor suppressor genes. Some critical genes located at this region have been suggested to be implied in the molecular pathogenesis of 7q malignancies.[21-27] but definitive evidence for their role has not been provided.

The advent of high resolution linkage maps provides densely spaced highly polymorphic microsatellite markers useful for dissecting genetic imbalances in order to identify patients who have submicroscopic deletions in various chromosomal regions. To investigate the incidence of 7q microsatellite loss of heterozygosity (LOH) and its relationship with karyotype we performed an allelotype assay based on fluorescence-polymerase chain reaction (PCR) in 50 patients with acute leukemia.

Design and Methods

Patients and samples

Patients were enrolled into the study by sequential admission in the last two years to our institution; they were, therefore, not selected on the basis of any phenotypic or genotypic criteria. A total of 50 consecutive patients with acute leukemia (AML, n=33; ALL, n=17) were analyzed. The diagnoses were established according to the criteria of the French-American-British (FAB) classification by standard morphologic, cytochemical and immunophenotypic methods. Patients included in

the study were predominantly adult and their median age was 41 years (range 12-78). The male/female ratio was 0.92. Bone marrow and/or peripheral blood specimens were collected at the time of diagnosis and used for molecular and cytogenetic studies. Diagnostic samples containing a high proportion of leukemic cells (>80% in most cases), which minimized contamination by normal cells, were used to obtain leukemic DNA. As a source of normal control DNA, we used epithelial cells from buccal mucosa or positive-immunoselected T-lymphocytes from peripheral blood, using a magnetic cell separation technique (MiniMacs; Miltenyi Biotec Bergish Gladbach, Germany).

Cytogenetic studies

Cytogenetic studies on pre-treatment bone marrow or unstimulated blood samples were performed according to standard procedures. Specimens were processed using direct methods and unstimulated short-term (24, 48, and 72 hours) cultures. For each case a minimum of 20 GTG-banded metaphases was karyotyped. Images were captured and processed in the Ikaros System (Zeiss, Germany). Chromosomal abnormalities were classified according to the International System for Cytogenetic Nomenclature 1985.[28]

Fluorescence in situ hybridization (FISH) analysis

FISH analysis was performed using the commercially available LSI D7S486 Spectrum Orange / CEP 7 Spectrum Green Dual Color probe (Vysis, Downers Grove, IL, USA) according to the manufacturer's instructions. Improvements were obtained by incubating bone marrow slides at room temperature overnight before digestion with proteinase K (stock solution 1mg/mL) for 6' at 37°C. After washing twice with phosphate buffer solution 1×, slides were fixed in a 1% formaldehyde solution; they were then denatured in a 70% formamide/2×SSC solution for 5' at 74°C. The probe was denatured at 74°C for 5'. Hybridization was performed overnight at 37°C in a humidified chamber. Post-hybridization washing was done in 4×SSC NP 40 for 2' at 74°C first and then for 2' at room temperature. Slides were counterstained with DAPI. A total of 500 nuclei were analyzed using Vysis scoring criteria.

Microsatellite analysis

LOH was assessed by using a first set of 11 primers for polymorphic repeat markers chosen from among those encompassing bands 7q21-7q36: D7S630, D7S657, D7S515, D7S518, D7S658, D7S2459, D7S486, D7S530, D7S640, D7S684, and D7S636 (Figure 1). All primers but D7S518 and D7S658 were purchased (Applied Biosystem, CA, USA). Forward primers were labeled with fluorescent dye phosphoramidites FAM, TET or NED. Genomic DNA from each patient was isolated from whole EDTA blood by salt extraction. Each 25 mL PCR mixture contained 50-100ng of genomic DNA, 2.5 units of AmpliTaq GOLDTM DNA polymerase, 1 µM of each primer, 100 µM each dNTP, 1.5 mM $MgCl_2$, and PCR GOLD Buffer at a 1× final concentration (Applied Biosystem, CA, USA). Thirty cycles of PCR were performed in a DNA-thermal cycler (model 9700 Applied Biosystem). Each cycle consisted of denaturing at 94°C for 30", annealing at 55°C for 30", and extension at 72°C for 1'. A final extension cycle consisted of 5 min at 72°C. PCR products were diluted 25-fold in formamide (Eurobio Biotechnology), denatured for 3 minutes at 94°C and run along with 1 µL internal size standard (Genescan ROX 500 labeled with 6-carboxy-N,N,NI, NI-tetramethylrhodamine; Applied Biosystems) on an ABI Prism 310 DNA Genetic Analyzer (Applied Biosystem). Locus-specific PCR products were detected by capillary electrophoresis with a 47×50 µm capillary using Performance Optimized Polymer 4 (Applied Biosystem). Samples were run electrophoretically following the GS STR POP4 (1 mL) D Module (injection second: 5; injection KV: 15.0; run KV: 15.0; run C°: 60; run time: 30 min) in association with the GS Matrix D (Applied Biosystem). Collected data were visualized on a fluorescent histogram and analyzed by using ABI GeneScan software (Applied Biosystem). Only heterozygous loci were regarded to be informative. LOH was scored as positive when the degree of reduction in allelic signal intensity was greater than 70% in one of

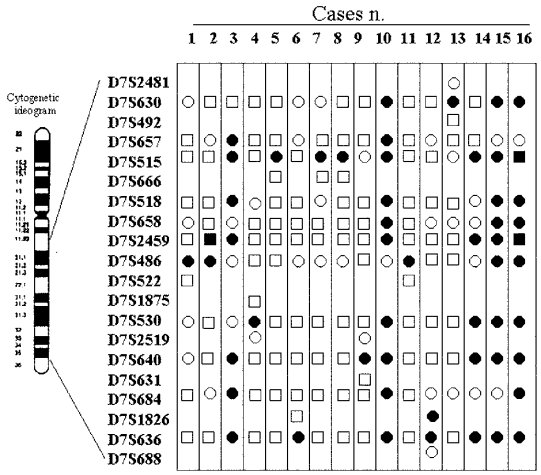

Figure 1. Diagramatic representation of microsatellite markers chosen at bands 7q21-q36 in patients with genetic imbalances. Black dots indicate LOH events, white dots indicate non-informative loci, white squares indicate heterozygous loci and black squares indicate genomic amplification.

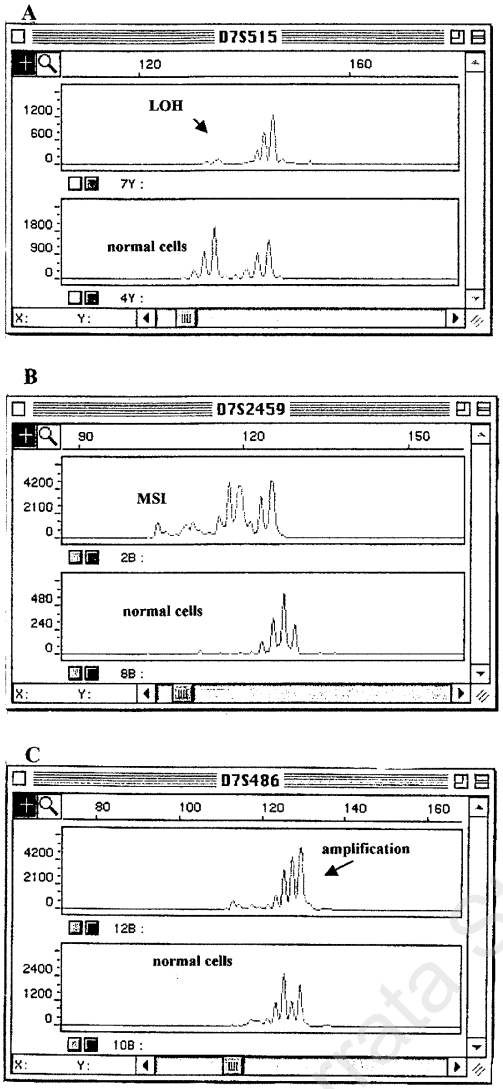

Figure 2. Examples of allelotyping results visualized on a fluorescent histogram and analyzed using GeneScan software (Applied Biosystem). A) loss of heterozygosity; B) microsatellite instability; C) genomic amplification.

the alleles of the blast population compared with control DNA. The presence of novel alleles in leukemic cells combined with their absence in normal cells was referred to as microsatellite instability (MSI), whereas an increased intensity signal of one of the markers in tumor cells indicated a further allelic imbalance and was defined genomic amplification. Examples of LOH, MSI and amplification are shown in Figure 2.

All samples showing LOH were subjected to repeat amplification. A second set of primers was selected to amplify the same loci where restricted LOH was occurring (D7S630, D7S515, D7S486, D7S530, D7S640, and D7S636), and the most proximal flanking markers (D7S2481, D7S492, D7S666, D7S522, D7S1875, D7S2519, D7S631, D7S1826, and D7S688). Sequences for D7S518, D7S658, for the second set of primers and for flanking markers were retrieved from the Genome Database (*http://www.gdb.org*). Primers are listed in Table 3.

Results

Cytogenetic analysis

Conventional cytogenetic characterization was successful in 44 cases (88%); the results are summarized in Table 1. Twenty-eight patients (63%) showed clonal chromosomal abnormalities, while 16 (36%) patients exhibited a normal karyotype. Among the cases with clonal abnormalities, there were 8 patients (18%) with *favorable* cytogenetics, such as t(8;21), t(15;17), and inv(16); 13 cases (29,5%) with *unfavorable* karyotypes such as –7/del(7q), 11q23 and 3q abnormalities , t(6;9), t(9;22), hyperdiploidy and complex karyotypes, while the remaining 7 cases (16%) carried miscellaneous clonal abnormalities.

Identification of LOH and MSI at 7q

DNA from leukemic blasts and normal samples from 50 patients were analyzed for LOH by using 11 highly polymorphic microsatellite repeat markers mapping at bands 7q21-q36 (Figure 1). Informative allelotypes were found in 420 of 550 examined loci (76%). All samples were informative for at least 7 of the 11 microsatellite markers. Balanced allelotypes were observed in 30 cases (60%), LOH was detected in 16 cases (32%), microsatellite instability was evident in 2 cases (4%) at the D7S636 and the D7S2459 loci, and two other patients (4%) showed genomic amplification at D7S486 and D7S640 (Figure 2). Thirteen out of 16 LOH^{+ve} cases did not exhibit abnormalities in chromosome 7. We found a total of 48 LOH events; 25 of them were related to -7/7q- patients (cases #10, 15 and 16, Table 1) and the remaining 23 events were related to 12 cases with no chromosome 7 involvement and one case in which karyotype was not available. A slight prevalence of LOH at D7S515 and D7S636, both identified in 7 cases, was observed. To further ensure that allelic loss did not depend on potential technical pitfalls, such as the preferential amplification of particular alleles, restricted LOH in cases #1, 2, 4, 5, 6, 7,8, 9, 11, 12, and 13 was confirmed by using a different set of primers. Furthermore, we extended our analysis to the most proximal flanking markers and we found in case #12 that LOH involved the closest locus D7S1826 too. The deletion map shown in Figure 1 indicates the distribution of LOH events relating to the patients with genetic imbalances.

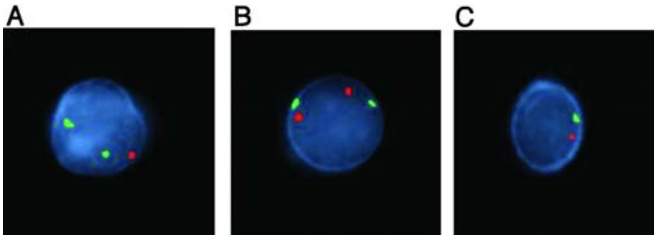

Figure 3. Analysis of the D7S486 locus by FISH. Green signals indicate chromosome 7 centromere and red signals indicate D7S486 locus. Nuclei are counterstained with DAPI. A) Interphase cell with LOH (case #11); B) normal interphase cell; C) interphase cell with chromosome 7 monosomy (case #15).

Table 1. Patients' characteristics.

Patient	*Age (years)*	*Sex*	*Disease*	*Cytogenetic findings*	*Genetic imbalance location*
Patients with LOH identified					
1	36	F	AML	46,XX,dup(1),t(17;18)	D7S486
2	74	F	AML	46,XX,-20,+mar	D7S486
3	75	M	AML	NA	From D7S657 to 636
4	52	F	AML	46,XX	D7S530
5	57	F	AML	46,XX,del(11)(q23)	D7S515
6	18	F	AML	45,X,-X,t(8;21)(q22;q22)	D7S636
7	20	M	AML	47,XY,+8,inv(16)(p13q22)	D7S515
8	16	F	AML	46,XX,t(6;9)(p23;q34)	D7S515
9	76	F	AML	Hyperdiploidy	D7S640
10	38	M	AML	46,XY,del(7)(q22q36)	Extensive
11	54	M	ALL	46,XY,t(9;22)(q34;q11)	D7S486
12	35	M	ProT-ALL	46,XY,t(1;3)(p32;q11)	D7S1826, 636
13	13	M	Common-ALL	46,XY	D7S630
14	32	F	ALL	47,XX,+18	D7S515, 2459,530,640,636
15	45	F	PreB-ALL	45,XX,-7	Extensive
16	61	F	AML D7S2459	45,XX,inv(3)(q21q26),del(5)(q13),-7	Extensive and amplification at D7S515,
Parients with MSI identified					
17	23	M	T-ALL	46,XY,14q+	D7S636
18	21	M	T-ALL	46,XY,del(6)(p21pter)	D7S2459
Parients with amplification identified					
19	38	M	AML	NA	D7S640
20	62	M	AML	46,XY	D7S486

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Pts without 7q genetic imbalances					
21	33	M	AML	Hyperdiploidy	–
22	55	M	AML	46,XY	–
23	53	F	AML	45,XX,-X,t(8;21)(q22;q22),del(9)(q13q22)	–
24	18	M	AML	46,XY,t(1;7)(q32;q32),t(10;11)(p11;q23)	–
25	57	M	AML	46,XY	–
26	78	F	AML	NA	–
27	62	F	AML	46,XX	–
28	48	F	AML	46,XX	–
29	16	F	AML	46,XX	–
30	67	M	AML	45,X,-Y,t(8;21)(q22;q22)	–
31	73	F	AML	46,XX	–
32	41	M	AML	46,XY	–
33	69	F	AML	46,XX	–
34	30	M	AML	46,XY,t(15;17)(q22;q11)	–
35	12	F	AML	46,XX,t(15;17)(q22;q11)	–
36	13	M	AML	46,XY,inv(16)(p13q22)	–
37	38	F	AML	46,XX, t(9;11)(p22;q23)	–
38	67	F	AML	47,XX,+der(3)	–
39	46	M	AML	NA	–
40	14	M	Pre T-ALL	46,XY	–
41	16	M	Pre T-ALL	NA	–
42	18	M	T-ALL	46,XY	–
43	16	F	T-ALL	46,XX	–
44	54	M	T-ALL	Hyperdiploidy	–
45	20	F	Pre B-ALL	46,XX	–
46	22	F	Pro B-ALL	NA	–
47	33	F	B-ALL	46,XX	–
48	52	F	B-ALL	Hyperdiploidy, t(9;22)(q34;q11)	–
49	56	F	L3-ALL	46,XX,t(8;14)(q24;q32)	–
50	42	M	AML	46,XY,t(8;21)(q22;q22)	–

LOH: loss of heterozigosity; MSI: microsatellite instability; AML: acute myeloid leukemia; ALL; acute lymphoid leukemia; NA; not available.

Correlation between LOH and FISH analysis

To corroborate LOH data we performed FISH analysis on samples for which a commercially probe was available. In particular we analyzed all samples in which LOH at D7S486 had been observed (cases #1, 2 and 11). For each sample 500 interphase cells were analyzed for loss of D7S486 signal. The patients had a significant loss of signals ranging from 4% and 8.7% of interphase nuclei. No significant loss of signal was observed in the negative control and a 90% of loss was detected in a patient with chromosome 7 monosomy (case n. 15). Representative examples of FISH results are shown in Figure 3.

The percentage of cells with loss of D7S486 signal may be underrepresented because the probe is

designed to detect a 200 kb deletion and it is less efficient at revealing shorter deletions. In fact its annealing capability may be partially lost when part of the covered region is missing.

Comparison of genotype and karyotype

The correlation of LOH with karyotype is summarized in Table 2. Karyotype information was available in 15/16 LOH^{+ve} cases and in 29/34 LOH^{-ve} cases. An altered karyotype was detected in 13/15 (87%) of LOH^{+ve} cases and in 15/29 (52%) of LOH^{-ve} cases (p=0.024). In addition, LOH at 7q was prevalently associated with *unfavorable* cytogenetic lesions (p=0.013). In particular among LOH^{+ve} patients, 8 (53%) had *unfavorable* cytogenetics, including 3 ALL patients with –7 (case #15), t(9;22) (q34;q11) (case #11) and t(1;3)(p32;q11) (case #12); and 5 AML patients with del(7q) (case #10), del(11)(q23) (case #5), t(6;9)(p23;q34) (case #8), hyperdiploidy (case #9) and a complex karyotype (case #16). LOH was also detected in 2 AML patients (13%) with *favorable* cytogenetic markers such as t(8;21) and inv(16) (cases #6 and 7, respectively), in 3 AML patients (20%) showing miscellaneous chromosomal abnormalities (cases #1,2 and 14), and in 2 patients with diploid karyotype (cases #4 and 13). LOH^{-ve} patients showed a higher frequency of diploid karyotypes (p=0.024).

Of the 4 patients carrying chromosome 7 abnormalities, two showed LOH extended to all tested loci (cases #10 and #15); one with a 46,XX,inv(3)(q21q26),del(5)(q13),-7 complex karyotype (case #16) exhibited LOH in 8 loci and both allelic retention and amplification in two distinct markers D7S515 and D7S2459; and finally, the fourth carrying a balanced t(1;7)(q32;q32) translocation (case #24) showed allelic retention.

Discussion

To detect submicroscopic deletions at bands 7q21-q36 we conducted an evaluation of microsatellite allelic loss in 50 patients with acute leukemia. LOH analyses are uniquely suited for identifying such events. LOH may be a hallmark of loss of gene function and most investigations have concentrated on defining the minimal region of loss at band 7q22 in various tumors in an effort to identify the putative tumor suppressor genes (TSG). Several genes localized in this region have been suggested as TSG in myeloid disorders, such as PIK3CG,[26] ORC5L,[27] MLL5[25] and a human homolog of the *Drosophila* homeobox gene cut (CUTL1) which is considered the best candidate. The deletion of CUTL1 has been documented in different types of tumor,[24,29] in myeloid disorders with del(7q) and in an apparently balanced t(7;7) described by Tosi *et al.*[23] in a patient with acute myeloid leukemia. We found 48 LOH events in 16 patients and the deletion map shown in Figure 1 indicates their distribution. We could not delineate a commonly deleted segment but a slight prevalence of LOH was observed at D7S515 and D7S636, both identified in 7 cases. Furthermore we found that LOH at D7S518, a marker located within the CUTL1 gene, was restricted to patients with 7q monosomies.

Table 2. Correlation of LOH with cytogenetics findings.

	LOH+ve (pts= 16)	*LOH-ve (pts=34)*	*p*
Clonal abnormalities	87%	52%	0.024
Unfavorable cytogenetics	53%	17%	0.013
Favorable cytogenetics	13%	21%	ns
Normal karyotype	13%	48%	0.024
Miscellaneous cytogenetics	20%	10%	ns
Not valuable	1	5	

p values were obtained by the χ^2 test.

The incidence of LOH in acute leukemia remains a controversial issue. Genome-wide screening studies on childhood AML reported LOH in 17 of 53 samples (32%),[30] whereas a much higher rate of LOH has been found in adult leukemia.[31,32] On the other hand allelotype studies focused on 7q markers provide conflicting results in patients lacking chromosome 7 cytogenetic abnormalities. In fact, no evidence of LOH was observed by some authors[19,33] whereas others found an incidence of LOH ranging from 15% to 27%.[34,35] We found LOH in 16 (32%) out of 50 analyzed cases; 13 of these LOH^{+ve} cases did not exhibit abnormalities on chromosome 7. No significant difference in LOH distribution between patients with AML (33%) and those with ALL (29%) was found (p=NS). We found a high incidence of genetic imbalances in elderly patients (>60 years), as suggested by other recently published data,[36] although this result did not have a significant value (p=NS). The relatively low rate of MSI we found, together with genomic amplification, is consistent with the notion that MSI is more frequently present in solid tumors than in hematologic malignancies.[37-40] Because of the resolution limits of cytogenetic analysis, we did expect to find 7q LOH mostly in diploid patients.

We unexpectedly found that LOH was significantly associated with other recurrent chromosomal alterations; in fact an altered karyotype was detected in 87% of LOH^{+ve} and in 52% of LOH^{-ve} AL cases (p=0.024). Moreover, we found a striking correlation between *unfavorable* cytogenetics and LOH occurrence (p=0.013). Only 2 cases out of the LOH^{+ve} group exhibited a diploid karyotype, consistent with the finding that occult chromosome deletions affecting chromosome 5q, 7q and 17p are not

Table 3. Sequences of PCR primers.

Probe designation	*Sequence 5'- 3'*	*Size*	*GenBank Accession*
D7S518	CAGTAGGCAGGGGTGG GGGTGTGTCTGTGTGACAAC	179-201bp	Z17029
D7S658	CATCACACACCAGGGC AACAGAAGGACTGAACTTCATC	263-272bp	Z23925
D7S630	TCCATTCTGAGGTTTGATGT CCATGGTCTTTTCAATGAAC	198-222bp	Z23423
D7S515	GGGAGTTACTACCCTCACTTAATG GGACTGGGCAGCAAAG	128-190bp	Z16999
D7S486	AATCTGTTCTGGCAATGG GCCCAGGTGATTGATAGTGC	114-146bp	Z16567
D7S530	TGCATTTTAGTGGAGCACAG CAGGCATTGGGAACTTTG	106-118bp	Z17136
D7S640	GTCTTCCAGCCCACCC GCACATCACCAACAACG	113-144bp	Z23671
D7S636	GAGGAGAGACTCAGAATTGGA CTTAGCATCTCCCTTTCCAT	136bp	Z23585
D7S2481	TTTGACATTATTATCCAGCAGG ATCATTGTAGACTCCCACCAGTAG	203-217 bp	Z53262
D7S492	TGTGTGTATCCAGAATCTCAGA TCTGCTCCATCTTCATATGG	231bp	Z16704
D7S666	GCCTTCTCAAGCAAATTGAT TGAGGTAATGAAAGAGGCA	158bp	Z24028
D7S522	GCCAAACTGCCACTTCTC ACGTGTTATGCCACTCCC	217-229bp	Z17100
D7S1875	AGCTCTTGGCAAACTCACAT GCCTAAGGGAATGAGACACA	186-226bp	Z52964
D7S2519	TTAGGAACTTGTGGTCCAG GCTGTGGTGTATCCTGTG	104-132bp	Z54039
D7S631	ACTCAACCACATGCCAGTTT CTTGCCTCAGTTGTCACATT	167bp	Z23439
D7S1826	CATCCATCTATCTCTGTAATCTCTC TATTTAACACACCTGTCTCAATCC	142-162bp	G08622
D7S688	AAGGGATGCATTTCATGATT AGAGAACAGGAAACGATTGC	130bp	Z24402

Primers are given in forward and reverse order.

found in *de novo* adult AML with normal karyotype reported by Cuneo *et al.* (*personal communication*). Our study represents the first report of a significant association between LOH and recurrent *unfavorable* chromosomal abnormalities in AL.

Submicroscopic deletions have already been shown to accompany some primary translocations in hematologic malignancies.[41,42] For example, deletions at 5' of ABL and 3' of BCR often accompany BCR/ABL rearrangement in Ph+ chronic myeloid leukemia and ALL patients, conferring a poor prognosis.[43,44] Frequent deletions have been documented in both 3' of MYH11 at 16p13 and at band 16q22 involving the breakpoint cluster region in leukemia patients with inv(16).[45-47] Corral *et al.*[48] showed deletions 3' to the MLL gene in association with translocations involving chromosome 11. However, all these additional deletions were always proximal to the translocation breakpoints suggesting that the underlying mechanism is likely to be associated with the translocation process itself and may be dependent on the flanking sequences. The deletions detected in our patients, although associated with recurrent chromosomal abnormalities, were not proximal to primary breakpoint regions, suggesting that alternative mechanisms should be considered. Unfortunately, we are

unable to identify a specific mechanism underlying these abnormalities, although it is conceivable that multiple molecular events, including defects in the repair-recombination machinery, illegitimate and homologous recombination, fragile sites, and translin activity, may lead to these rearrangements.[49-51] It is still currently unknown whether secondary molecular lesions result from genomic instability as a consequence of the primary events or, alternatively, whether submicroscopic deletions represent a primary event which increases the likelihood of subsequent rearrangements.

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Pre-Publication Report & Outcomes of Peer Review

Contributions

RB and AS: conception and design, analysis and interpretation of data, drafting the article; RP, GC: cytogenetic and molecular analyses; FF, SM, SM: clinical support. MP, LC: technical support. All authors : final approval of the version to be published FLC: revising the manuscript critically for important intellectual content.

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Manuscript processing

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In the following paragraphs, the Associate Editor summarizes the peer-review process and its outcomes.

What is already known on this topic

Conventional cytogenetics definitively proved the occurrence of 7q deletions in acute leukemias. Moreover AML with complex karyotypes and poor prognosis frequently show 7q deletion. LOH is a successful approach to identify microdeletions which escape cytogenetics.

What this study adds

LOH is helpful to refine information on microdeletions as compared to conventional cytogenetics or FISH, and to reveal losses undetected by other technologies. LOH microdeletions at 7q are associated with unfavorable changes.

Caveats

This new information may be important to characterize primary and secondary genomic events in acute leukemias.