American Journal of Pathology, Vol. 154, No. 5, May 1999

7q31-32 Allelic Loss Is a Frequent Finding in Splenic Marginal Zone Lymphoma

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Splenic marginal zone lymphoma (SMZL) has been recognized as an entity defined on the basis of its morphological, phenotypic, and clinical characteristic features. Nevertheless, no characteristic genetic alterations have been described to date for this entity, thus making an exact diagnosis of SMZL difficult in some cases. As initial studies showed that chromosome region 7q22-32 is deleted in some of these cases, we analyzed a larger group of SMZL and other lymphoproliferative disorders that may partially overlap with it. To better define the frequency of 7q deletion in SMZL and further identify the deleted region, polymerase chain reaction analysis of 13 microsatellite loci spanning 7q21-7q36 was performed on 20 SMZL and 26 non-SMZL tissue samples. The frequency of allelic loss in SMZL (8/20; 40%) was higher than that observed in other B-cell lymphoproliferative syndromes (2/26; 7.7%). This difference was statistically significant ($P < 0.05$). The most frequently deleted microsatellite was D7S487 (5/11; 45% of informative cases). Surrounding this microsatellite the smallest common deleted region of 5cM has been identified, defined between D7S685 and D7S514. By comparative multiplex polymerase chain reaction analysis, we detected a homozygous deletion in the D7S685 (7q31.3) marker in one case. These results suggest that 7q31-q32 loss may be used as a genetic marker of this neoplasia, in conjunction with other morphologic, phenotypic, and clinical features. A correlation between 7q allelic loss and tumoral progression (death secondary to the tumor or large cell transformation) in SMZL showed a borderline statistical significance. The observation of a homozygous deletion in this chromosomal region may indicate that there is a tumor suppressor gene involved in the pathogenesis of this lymphoproliferative neoplasia. *(Am J Pathol 1999, 154:1583–1589)*

Although specific pathological and phenotypic traits are gradually being recognized for splenic marginal zone lymphomas (SMZL),[1–3] the distinction in comparison other lymphoproliferative disorders is frequently blurred by the lack of specific molecular markers for this neoplasia. Cytogenetic analysis of SMZL cases has showed diverse abnormalities at chromosomes 1, 3, 7, and 8,[4–5] chromosome 7 being the most frequently altered (3/19 cases).[4] Some SMZL cases showed del 7q as the only cytogenetic abnormality, this chromosome loss being found in 7q22 as well as in 7q32.[4] 7q abnormalities have been previously published in studies of other chronic lymphoproliferative disorders by cytogenetic techniques.[6–10] Most reports center on tumors that may at least partially overlap SMZL, such as immunocytoma and splenic lymphoma with circulating villous lymphocytes (SLVL). In these series the most common deletions identified were also 7q22 and 7q32.[6–10]

Some of the uncertainties in genetic studies of SMZL arise from the fact that cases with this diagnosis have been lumped in larger groups together with other lymphoproliferative disorders, as there is no requirement to confirm the diagnosis by study of a splenectomy specimen.[8–10] Here we have chosen a more conservative approach, exclusively studying cases in which the diagnosis of SMZL has been performed after histological study of a splenectomy specimen. At the same time, we have refined the molecular techniques used. Thus previous studies on SMZL were performed using mainly standard cytogenetic techniques, which do not detect the entire spectrum of chromosomal changes, including microdeletions. In this study loss of heterozygosity (LOH) analysis was used because it is a sensitive molecular method to screen for changes involving allele loss.[11–12]

To clarify the frequency of 7q deletion in SMZL and define the deleted region, we analyzed 7q LOH specifically on 7q22-32 using a panel of highly polymorphic markers on 7q21-qter, in a series of SMZL cases defined on the basis of the splenic histology, and in a control series of lymphoproliferative processes whose morphology may mimic SMZL, such as B-chronic lymphocytic leukemia (B-CLL), mucosa-associated lymphoid tissue (MALT) lymphoma, follicular lymphoma (FL), and mantle cell lymphoma (MCL).

Supported by a grant (96/1382) from the Fondo de Investigaciones Sanitarias, Ministerio de Sanidad y Consumo, Spain.

Accepted for publication February 4, 1999.

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Table 1. Summary of Markers, Map Positions, and Frequency of 7q Allelic Loss in 20 Cases of SMZL

Marker	Map Position	No. of cases studied (informative cases)	No. of cases with LOH (%)
D7S460	7p	18 (14)	0
D7S492	7q21.1	19 (14)	0
D7S518	7q22.1	19 (16)	0
D7S471	7q22-31.1	18 (11)	1 (8%)
D7S466	7q22-31.1	18 (12)	4 (33%)
D7S486	7q31.1	20 (12)	4 (33%)
D7S522	7q31.1	20 (12)	3 (25%)
D7S2847	7q31.3	20 (18)	5 (27%)
D7S480	7q31.3	19 (17)	6 (35%)
D7S685	7q31.3	14 (10)	3 (30%)
D7S487	7q31.3	19 (11)	5 (45%)
D7S514	7q31.3-32	20 (13)	4 (30%)
D7S530	7q32.2	19 (10)	3 (33%)
D7S550	7q36	15 (12)	2 (16%)

Materials and Methods

Tissue Samples

Twenty SMZL cases were included in this study. They were consecutive cases obtained from the routine and consultation files of the Pathology Laboratory of the Virgen de la Salud Hospital (Toledo, Spain). These cases were diagnosed on the basis of splenic morphology according to the criteria established by Isaacson[3,13] and Mollejo.[2,14] The only criterion for a case to be included in the series was the availability of control DNA extracted from oral swabs.

A control series of 26 lymphoproliferative disorders, including 7 B-CLL, 4 MCL, 9 MALT, and 6 FL cases, was also included. All of them were consecutive routine cases in which control DNA could be extracted either from oral swabs or microdissected nontumoral areas in the surgical specimens.

In all of the SMZL cases, a clinical follow-up was performed over a median range of 37 months. Large cell transformation was diagnosed if the patient presented a histology of large B-cell lymphoma in a different location after the initial diagnosis. Deaths secondary to the tumor were classified as attributable either to the tumor itself or to the consequences of the treatment.

Thirteen of the SMZL cases were previously analyzed by conventional cytogenetic means. Chromosome analysis was carried out on the spleen (six patients), lymph node (one case), and peripheral blood (six patients) by standard procedure. The cytogenetic findings of some cases (S1, S4, S74 and S149) have already been reported.[4]

DNA Extraction

Tumoral DNA was extracted from fresh frozen tissue, paraffin-embedded tissue, or peripheral blood lymphocytes in non-SMZL cases with high tumoral lymphocyte counts. Fresh frozen tissue was treated with sodium dodecyl sulfate buffer and proteinase K, followed by phenol-chloroform purification and precipitation with ethanol, according to standard procedures.

Paraffin-embedded tissue sections were dewaxed in xylene and hydrated with ethanol. The samples were air-dried, incubated with buffer (100 mmol/L Tris, pH 8.5; 500 mmol/L KCl; 15 mmol/L Cl_2Mg; 0.5% Tween 20) and heated for 7 minutes in a microwave oven. Peripheral blood lymphocytes were isolated by Histopaque gradient (Sigma, St. Louis, MO) and DNA was extracted using a standard procedure.

Normal DNA was obtained from oral swabs in 20 SMZL and 22 non-SMZL cases, or from microdissected nontumoral areas in surgical specimens in 4 cases of non-SMZL. Oral swabs were incubated for 2 hours in double distilled H_2O at room temperature, centrifuged, and treated with sodium dodecyl sulfate buffer and proteinase K (200 μg/ml) at 37°C for 6 hours.

The quality of the extracted DNA was assessed using primers for the p53 gene, exon 8 (249 pb).

Microsatellite Analysis

Fourteen pairs of microsatellite markers on chromosome 7 were used (1 for the short arm and 13 for the long arm), all of which were obtained from Research Genetics (Huntsville, AL). The markers used in this study were D7S460, D7S492, D7S518, D7S471, D7S466, D7S486, D7S522, D7S2847, D7S480, D7S685, D7S487, D7S514, D7S530, and D7S550 (Table 1). All microsatellite markers were previously published in studies of LOH in 7q, where they were found to be frequently deleted.[15–18] The location and linear order of the microsatellites used are based on the map release by Généthon.[19] A tetranucleotide repeat polymorphism in chromosome 7p (D7S460) was also tested.[20] The markers analyzed for non-SMZL cases were the most frequently deleted and informative for SMZL cases (D7S518, D7S466, D7S522, D7S480, D7S487, and D7S530).

Each microsatellite repeat was amplified using polymerase chain reaction (PCR). PCR reactions were performed in a final volume of 20 μl containing 50–100 ng of DNA template, 10 pmol of each primer, 200 mmol/L dNTPs, 1.5 mmol/L Cl_2Mg, 1 μCi of [α-^{32}P] dCTP, and 1 U of Taq polymerase (Boehringer Mannheim, Mannheim,

Germany). Twenty-five cycles were performed, each consisting of 30 seconds at 94°C, with annealing temperatures at 57°C and 30 seconds at 72°C, using a Perkin Elmer 2400 GeneAmp PCR system (Norwalk, CT). The products of PCR reactions were mixed with an equal volume of formamide loading buffer (95% formamide, 20 mmol/L EDTA, 0.05% bromophenol blue, 0.05% xylencyanol), then denatured at 95°C for 5 minutes and cooled on ice. Approximately 2 μl of each sample were loaded onto 6% denaturing polyacrylamide gel containing 7 mol/L urea. Gels were fixed in 10% acetic acid, air-dried, and exposed to X-ray films.

Allelic Loss Determination

Cases were considered to be informative when heterozygosity was detected in normal tissue samples. LOH was determined visually by two different examiners, as complete loss of one allele or as quantified by densitometric analysis (1-D Analysis and Hand Scanner Settings, Biomed Instruments, Zeineh Programs (Fullerton, CA). By densitometric analysis a tumor was scored as LOH when the allelic ratio of the tumor tissue compared to the normal control tissue was >3. Allelic imbalance was considered to be present when this allelic ratio was >1.5 and <3.[15,21–24] Homozygous alleles in the normal tissue samples were considered uninformative.

In an attempt to distinguish whether allelic imbalance was due to gain or loss, comparative multiplex PCR was performed.[15,25,26] Microsatellite markers (D2S1360 and D7S550) without allelic imbalance were selected as internal controls. The intensity of the control alleles was compared with the intensity of the locus showing allelic imbalance by means of visual inspection and densitometric image analysis.

All cases of allelic loss were confirmed by three separate experiments with two different examiners.

Statistical Analysis

A χ^2 test was used to compare the frequency of tumoral progression between cases with and without 7q allelic losses. Differences were considered significant when $P < 0.05$.

Results

Allelic Loss 7q in SMZL

A set of 13 microsatellite markers spanning the region from 7q21 to 7q36 (Figure 1) were used to perform allelic loss analysis in 20 SMZL and 26 non-SMZL cases. Figure 1 summarizes the results obtained, and representative cases are illustrated in Figure 2. As is shown in the deletion map in Figure 1, all markers analyzed were highly informative (Table 1).

Allelic losses were detected in 8 of 20 (40%) SMZL. In the analysis of allelic loss we differentiated between allelic imbalances and LOH according to previous works.[15,21–24] In three tumors (S254, S274, and S74) LOH involved all the markers with allelic loss (Figures 1 and 2). In addition, one tumor (S1) showed either LOH or allelic imbalances, whereas the other four tumors displayed only allelic imbalances (Figures 1 and 2). To determine whether the observed allelic imbalances were gains or losses, cytogenetic analysis was used to confirm the existence of allelic loss in all three cases with allelic imbalances (S1, S220, and S221) (Figure 1). In cases S4 and S5, comparative multiplex PCR analysis was performed, confirming the existence of allelic loss (Figure 3). All cases were considered to demonstrate genuine LOH according to the criteria of previous works.[15,21–24]

A 7q31.3-q32 homozygous deletion was observed in one case (S5). Multiplex PCR with primers for both D7S685 and D7S550 show that when the D7S550 alleles in the normal and tumor DNA lanes were of equal intensity, the signal for D7S685 in the tumor lane was absent or very weak (Figure 4).

The results of the cytogenetic studies performed in a subset of these cases are shown in Figure 1. Deletion 7q detectable by karyotype was seen in five cases, all of which were confirmed in this LOH analysis. Additionally, one case (S4) without cytogenetic 7q alterations showed LOH after molecular study (Figure 1).

The frequency of allelic loss at each locus is shown Table 1. The locus that showed the highest percentage of LOH was D7S487 (5 of 11 informative cases, 45%). The lowest incidence of allelic loss was found in microsatellites D7S518 and D7S471 (0% and 8%, respectively), spanning the 7q22 band.

Five of the eight cases with allelic loss showed LOH in all the informative loci of band 7q31-32, as analyzed here. In contrast with this finding, case S74 showed just a small deletion, thereby making it possible to delimit the smallest commonly deleted region (SCDR) (Figures 1 and 2). The localization of the SCDR was inferred from the pattern of allelic loss in these tumors, defined by flanking markers D7S685 and D7S514, as demonstrated by tumor samples S74 and S5, respectively (Figure 1). This region is located in bands 7q31-32.

7q Allelic Loss in Non-SMZL

Two of 26 (7.7%) non-SMZL cases showed allelic loss. Positive 7q LOH cases were 1/4 MCL and 1/5 FL. When comparing the frequency of 7q allelic loss between SMZL and non-SMZL cases, a statistically significant difference was found ($P < 0.008$; Fisher's Exact Test) (Table 2).

Correlation between del(7q) and Tumoral Progression in SMZL

To explore the relationship between tumoral aggressiveness and 7q LOH, we selected a group of cases with morphological or clinical evidence of tumoral progression, and compared their frequency of 7q LOH to that in other cases. Four of eight (50%) SMZL cases with 7q LOH showed either death attributable to the tumor or large cell transformation, whereas a similar clinical aggressiveness was found only in 1/12 cases without 7q

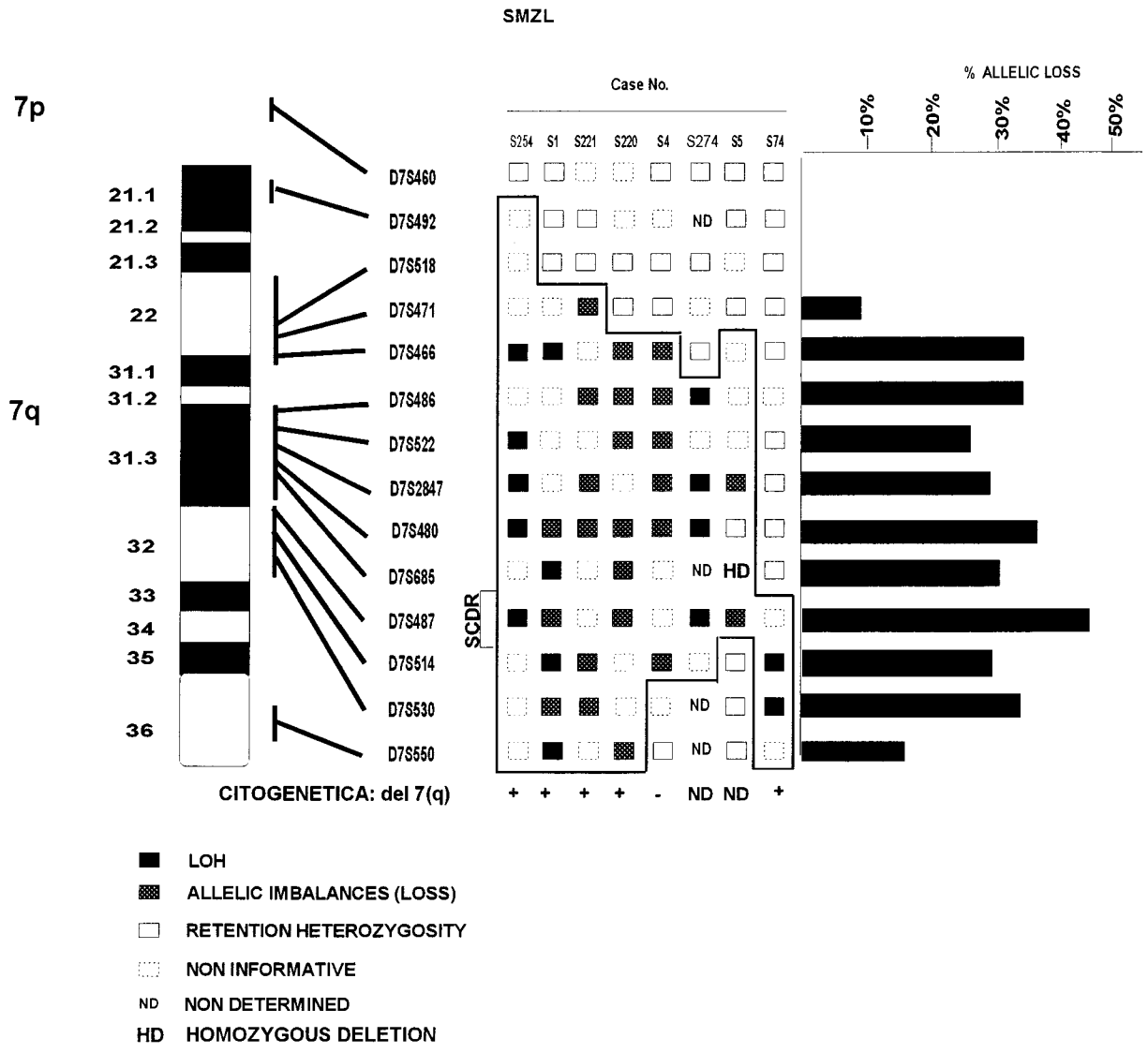

Figure 1. Summary of allelic loss data for 7q in SMZL. Graphic representation of the 13 microsatellite markers in 7q21-qter, giving the approximate position of each locus. Only cases showing LOH or allelic imbalance are illustrated. The results of the cytogenetic study are also included. Smallest common deletion region (SCDR) in the eight cases with allelic loss is shown, and spans about 5cM, from markers D7S685 to D7S514. A histogram shows the frequency of allelic loss for each of these markers in the informative samples.

LOH. This had a borderline statistical significance ($P < 0.05779$, Fisher's Exact Test) (Table 3).

Discussion

In this study we used 13 dinucleotide repeats spanning the 7q21-q36 band to deduce the frequency of deletion and draw a deletion map for this LOH. In these tumors we detected 8/20 (40%) cases of SMZL with allelic losses, as opposed to a frequency of 2/26 (7.7%) in non-SMZL B-cell lymphoproliferative disorders. Cytogenetic studies and comparative multiplex PCR excluded the possibility that the allelic imbalance found here in some cases could be attributable to allelic gains. These results indicate that 7q31-32 allelic loss is a characteristic finding in SMZL, which, in conjunction with other features of the tumor, may be used in differential diagnosis of SMZL *versus* other types of lymphoma.

Chromosome 7 abnormalities in non-Hodgkin's lymphomas (NHLs) have been described in different studies using cytogenetic, fluorescent *in situ* hybridization and comparative genomic hybridization techniques.[4–8,27–32] Although in some studies no significant incidence of 7q loss in NHLs was found,[27,30,31] other studies have shown increased frequency in some specific lymphoproliferative processes.[8,9,32] Thus, two consecutive studies performed by the same group[9,32] showed that, in spite of an overall 7q loss incidence of 3.6% in NHLs, 26–31% of the cases with a diagnosis of SLVL display different abnormalities of chromosome 7 including del(7)(q22-32), del(7)(q34-36), and t(7q22). Other comprehensive studies on NHLs confirm that the overall incidence of 7q loss

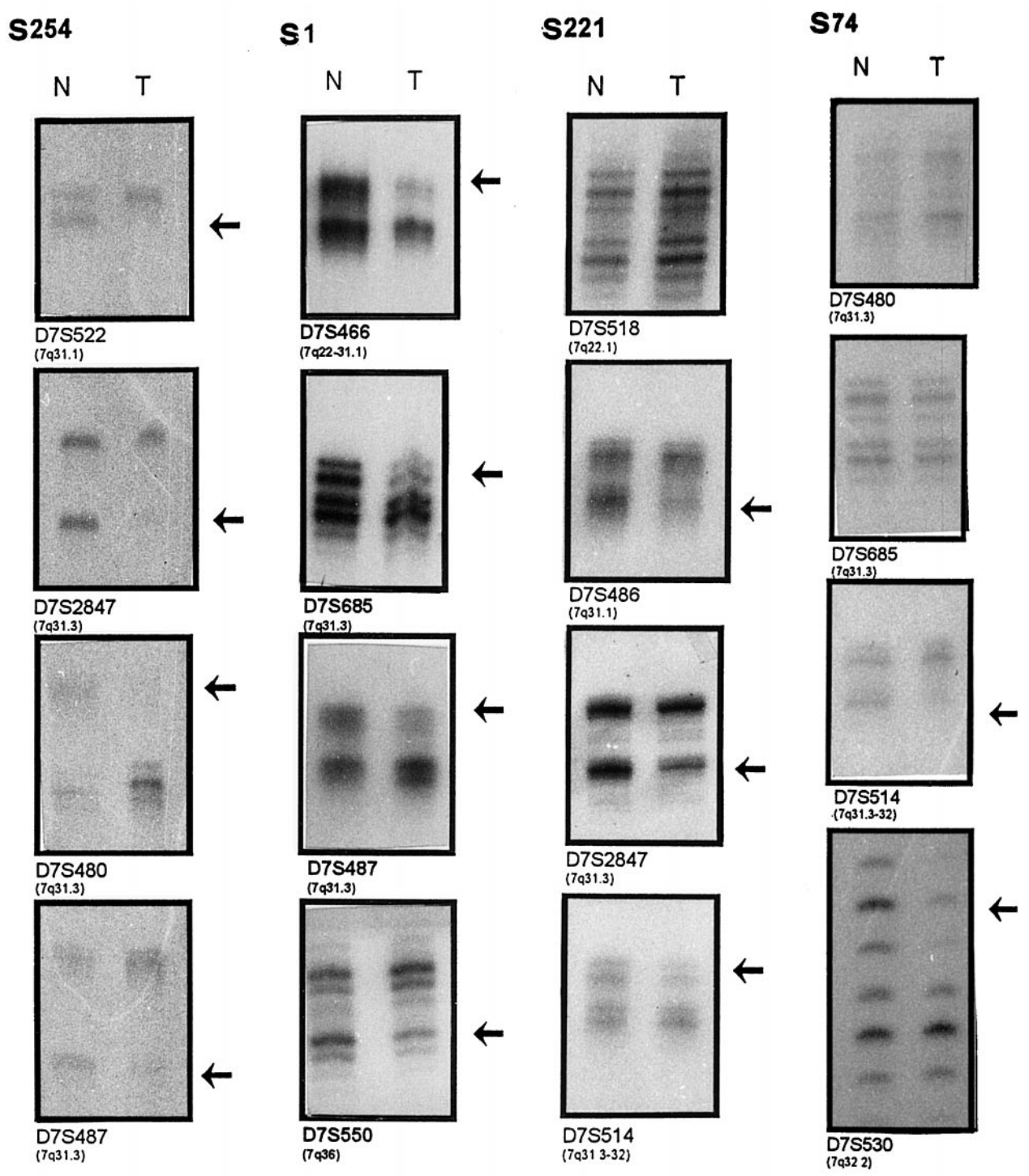

Figure 2. Representative examples of allelic loss in chromosome 7q. The presence of allelic losses in tumor (T) in comparison with matched normal (N) DNA is shown by arrows. Case S254 shows allelic loss in all informative loci. Case S1 shows loss of alleles for the loci mapping the 7q31-qter region (band intensity ratios of 3.1, 3.5, 1.6, and 2.7, respectively). Case S221 shows loss of alleles for loci D7S486, D7S2847, and D7S514 (band intensity ratios are 2.1, 2.8, 1.9 respectively) and retention of alleles for loci D7S518 mapped to 7q22. Case S74 shows loss of alleles for loci mapped to 7q32 (D7S514 and D7S530) and retention of alleles for loci D7S685 and D7S480, situated at the 7q31 band.

is low in the group of NHLs as a whole, 24/558 cases (4.3%).[8] This frequency is higher when only small lymphocytic lymphoma is considered.

The data so far described are therefore consistent with those reported here, because the histological types where a higher incidence of 7q loss has been found are those which overlap SMZL. Different reports agree that the splenic histology of SLVL cases is similar to that described for SMZL,[6] although some differences between these two groups have also been stated to exist,

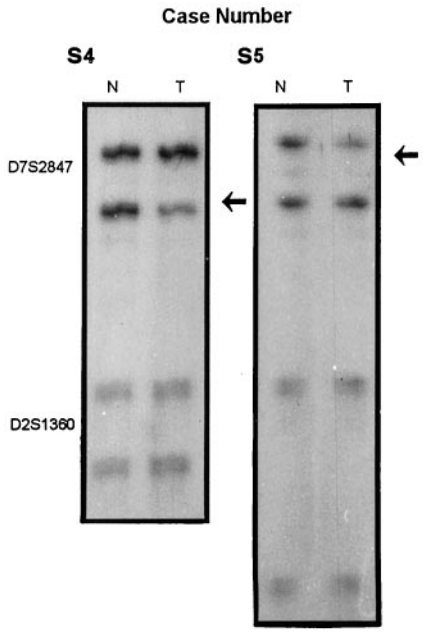

Figure 3. Example of comparative multiplex PCR in cases S4 and S5. An internal control marker (D2S1360) shows the amount of tumor (T) and normal (N) DNA amplified. Case S5 shows a loss of the upper band, whereas case S4 has a loss of the lower band, as shown by arrows.

such as the reported presence of t(11;14) in a subset of SLVL cases (this has never been found in SMZL) and the occasional lack of peripheral blood involvement in cases of SMZL.[4,6] The selection of cases used here, taking splenic histology into account together with the other features of the tumors, made it possible to restrict the

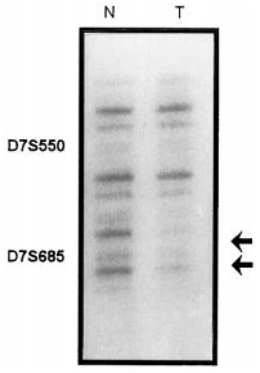

Figure 4. Case number S5, showing homozygous deletion of microsatellite D7S685 (arrows). Autoradiography of multiplex PCR products showed that primer sets D7S550 and D7S685 amplified products from the normal (N) DNA, whereas only D7S550 amplified a product from the corresponding tumor (T) DNA. (The signal for D7S685 in the tumor lane was absent or very weak)

Table 2. Frequency of Allelic Loss at 7q in the Different Types of Lymphoma

Diagnosis	Allelic loss at 7q(%)
non-SMZL	2/26 (7.7%)
SMZL	8/20 (40 %)

$P < 0.008$

Table 3. Correlation between Features at Diagnosis, Neoplastic Progression, and 7q Allelic Loss in SMZL Cases

	7q allelic loss		
	Yes	No	*P*
Progression			
Large cell transformation	1/8	0/12	0.05779
Death secondary to the tumor	3/8	1/12	

cases included to a relatively homogeneous histological type, thus avoiding any bias arising from the selection of the sample.

The relevance of this genetic abnormality in the pathogenesis of SMZL is underlined by the fact that in different descriptions it appears as a single cytogenetic alteration.[4,7,8,10] The exact region of genetic loss seems to be closer to microsatellite D7S487, where the highest incidence of LOH (45%) has been identified. This region is situated between the D7S685 and D7S514 markers, which define the smallest commonly deleted region observed by Hernandez and colleagues in a previous study of a group of NHL.[33]

The data reported here confirm and expand initial observations made by Sole et al[4] using cytogenetic and fluorescence *in situ* hybridization techniques pointing to 7q alterations as a significant cytogenetic finding in SMZL defined on the basis of splenic histology. It now appears after LOH analysis that the incidence of this genetic loss is more frequent than initially expected and that, additionally, it seems to be associated with a more aggressive course.

Loss of this chromosome region is not restricted to lymphoproliferative disorders,[8–10] but has also been described in other solid tumor and myeloid disorders.[15–18,23,26,34–37] This recurrent abnormality suggests that these regions contain a novel tumor suppressor gene that has yet to be identified. In several studies of other types of tumors it has been observed that genetic alterations at 7q31 may participate in tumor progression.[15,34] The existence in one of these cases of a biallelic deletion in the D7S685 locus, as detected by the use of comparative multiplex PCR analysis, offers additional evidence in favor of the existence of a tumor suppressor gene in this location.

To summarize, this study shows that 7q31-q32 loss is a relatively specific genetic marker of SMZL, which may be used in the differential diagnosis of this entity in conjunction with other clinical, morphological, and phenotypic traits of the neoplasia. The data obtained here seem to show, additionally, that the loss of this genetic region causes these tumors to display more aggressive behavior and thereby supplying data that is potentially useful in the treatment of these patients. Further genetic studies could make progress towards the identification of a tumour suppressor gene that may be located in this area.

Acknowledgments

We thank Dr. Jose Fernandez Piqueras of Laboratory Human Molecular Genetic, Department of Biology (Uni-

versity Autonoma, Madrid, Spain) for his critical review of the manuscript and technical advice, and Drs. T. Flores, L. Bernardo, M. Morente, and P. Gonzalvo from the pathology departments at hospitals in Salamanca, Gerona, Guadalajara, and Asturias, Spain, for kindly providing the cases included in this series.

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