Frequent Allelic Loss at 7p14-15 Associated with Aggressive Histologic Types of Breast Cancer

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We examined 142 primary human breast cancers to determine their patterns of loss of heterozygosity (LOH) at 19 microsatellite markers over the entire length of chromosome 7. Allelic loss at one or more loci on the short arm of chromosome 7 was observed in 37 of the tumors (26%). We found a new target region of allelic loss on 7p between D7S1802 and D7S817 at 7p14-15. LOH on 7p was found more frequently in tumors of the invasive solid tubular and scirrhous type (31 of 87; 36%) than in other less aggressive types (2 of 27; 7%) (*P*=0.0047). The results suggest that inactivation of putative tumor suppressor gene(s) located at 7p14-15 may play a role in the development and/or progression of primary breast cancers, particularly those of the invasive solid tubular and scirrhous type. Allelic loss was also found in 56 of 142 tumors on the long arm, and a commonly deleted region was defined between D7S522 and D7S1801 at 7q31.

Key words: Breast cancer — Loss of heterozygosity — Tumor suppressor gene — Chromosome 7

Breast cancer is the most common malignancy in women. One in nine Caucasian women and one in 40–50 Japanese women will develop breast cancer in their lifetimes, and the incidence has been increasing worldwide. Human solid tumors are now believed to develop through a multistep process involving activation of oncogenes and inactivation of tumor suppressor genes.[1–3] Many tumor suppressor genes are inactivated by intragenic mutations in one allele accompanied by the loss of a chromosomal region containing the other allele, termed loss of heterozygosity (LOH). In primary breast cancers frequent LOH in many chromosome arms, including 1p, 3p, 6q, 13q, 16q, 17, 18q, and 22q,[4–17] suggests that many putative tumor suppressor genes may influence the development and/or progression of breast cancer.

Allelic loss on the long arm of chromosome 7, especially at 7q31, has also been described in several previous LOH studies of breast cancers, with a frequency varying from zero to 41%.[4, 8, 18–20] Zenklusen *et al.*[21] showed that transfer of human chromosome 7 by microcell fusion to a murine squamous cell carcinoma cell line (CH72) suppressed the tumorigenicity of the cells; the tumorigenic phenotype was restored after loss of the introduced human chromosome 7. In similar experiments, Ogata *et al.*[22] found that insertion of an intact human chromosome 7 into nontumorigenic immortalized human fibroblast cell lines with LOH at 7q31-q32 (KMST-6 and SUSM-1)

restored the senescence properties of the cells. However, no breast cancer-specific allelic losses on the short arm of chromosome 7 have been described to date.

To determine the role of genetic alterations on chromosome 7 in the development and/or progression of this common disease, we performed LOH analysis on 142 primary breast cancers using 19 microsatellite markers distributed along the entire length of the chromosome, and looked for correlations between LOH and certain clinicopathological parameters.

MATERIALS AND METHODS

Samples and DNA preparation   Specimens were obtained from 142 primary breast tumors and corresponding noncancerous tissues surgically removed from patients at the Cancer Institute Hospital; none of the patients had undergone previous radiotherapy or chemotherapy. Immediately following surgery, tissues were frozen and stored at −80°C. High-molecular-weight DNAs were extracted from frozen tissues as described previously.[4] Tumors were classified by pathologists according to the histologic TNM classification and the histologic typing scheme of the Japanese Breast Cancer Society into the following types: noninvasive tubular (1a), invasive papillotubular (a1), invasive solid tubular (a2), invasive scirrhous carcinoma (a3), and other specific types (b Group). This classification is essentially the same as the World Health Organization scheme for typing breast tumors. Estrogen

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receptor (ER) and progesterone receptor (PgR) were measured by radioreceptor assay according to a standard dextran-coated charcoal method, using [^{125}I]estradiol as the labeled ligand, with homogenates of fresh-frozen tissue (Otsuka Pharmaceutical). All samples containing >5 fmol of ER or PgR per mg protein were considered receptor-positive.

The χ^2 test and Fisher's exact test were used for statistical analysis of the results. One-tailed P values of <0.05 were considered statistically significant.

LOH analysis Chromosome 7 LOH was assessed using 19 polymorphic microsatellite markers along the entire length of chromosome 7: (7pter)-D7S2201-D7S1802-D7S817-D7S1830-D7S820-D7S1799-D7S496-D7S523-D7S522-D7S1801-D7S2544-D7S500-D7S2450-D7S1824-D7S2195-D7S498-D7S1826-D7S2447-D7S559-(7qter). All primers were obtained from the MapPairs collection (Research Genetics, Huntsville, AL). Polymerase chain reaction (PCR) experiments, electrophoresis, and autoradiography were carried out as described elsewhere.[13]

Definition of LOH Signal intensities of polymorphic alleles were quantified by a Hoefer GS-300 scanning densitometer; peak areas corresponding to each signal were calculated by electronic integration using the GS-370 electrophoresis data system (Hoefer Scientific Instruments, San Francisco, CA). The signal intensities of

alleles of tumor-tissue DNAs were compared with those of normal-tissue DNAs. A reduction in signal intensity of more than 50% was judged to demonstrate LOH. LOH was distinguished from chromosome multiplication by normalizing each signal to the signal obtained when the same DNA was analyzed with markers for loci on other chromosomes; thus, we compared the PCR-detected band intensities of alleles of each chromosome 7 marker in normal DNA and tumor DNA with the PCR-detected bands representing two control markers, IL1B on 2q and LDLR on 19q. Chromosomal loss or gain has been observed only rarely in these "control" regions by cytogenetic analysis, fluorescence *in situ* hybridization (FISH) analysis, or restriction fragment length polymorphism analysis in breast cancers. A preliminary comparison of the microsatellite-PCR method with FISH for detection of 1p loss and

Table I. Frequencies of LOH at 19 Loci on Chromosome 7

| Name	Informative cases	LOH	LOH/Informative cases (%)
D7S2201	69	14	20.3
D7S1802	90	21	23.3
D7S817	103	19	18.4
D7S1830	103	18	17.5
7p Total	142	37	26.1
D7S820	68	14	20.6
D7S1799	111	26	22.5
D7S496	102	23	23.4
D7S523	97	28	28.9
D7S522	59	13	22.0
D7S1801	103	30	29.1
D7S2544	91	22	24.2
D7S500	109	23	21.1
D7S2450	95	19	20.0
D7S1824	81	19	23.5
D7S2195	98	17	17.3
D7S498	65	14	21.5
D7S1826	63	10	15.9
D7S2447	63	12	19.0
D7S559	97	20	20.6
7q Total	142	56	39.4
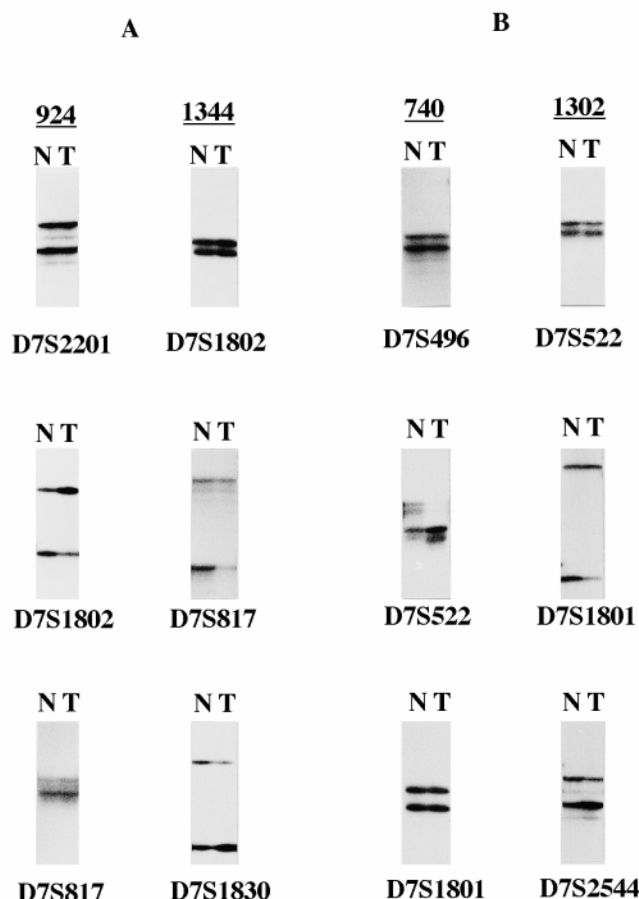
Fig. 1. Representative autoradiograms of LOH analysis (A: 7p region, B: 7q region). Case numbers are shown at the top of each lane; T and N, matched DNA samples isolated from tumor and normal tissues, respectively.
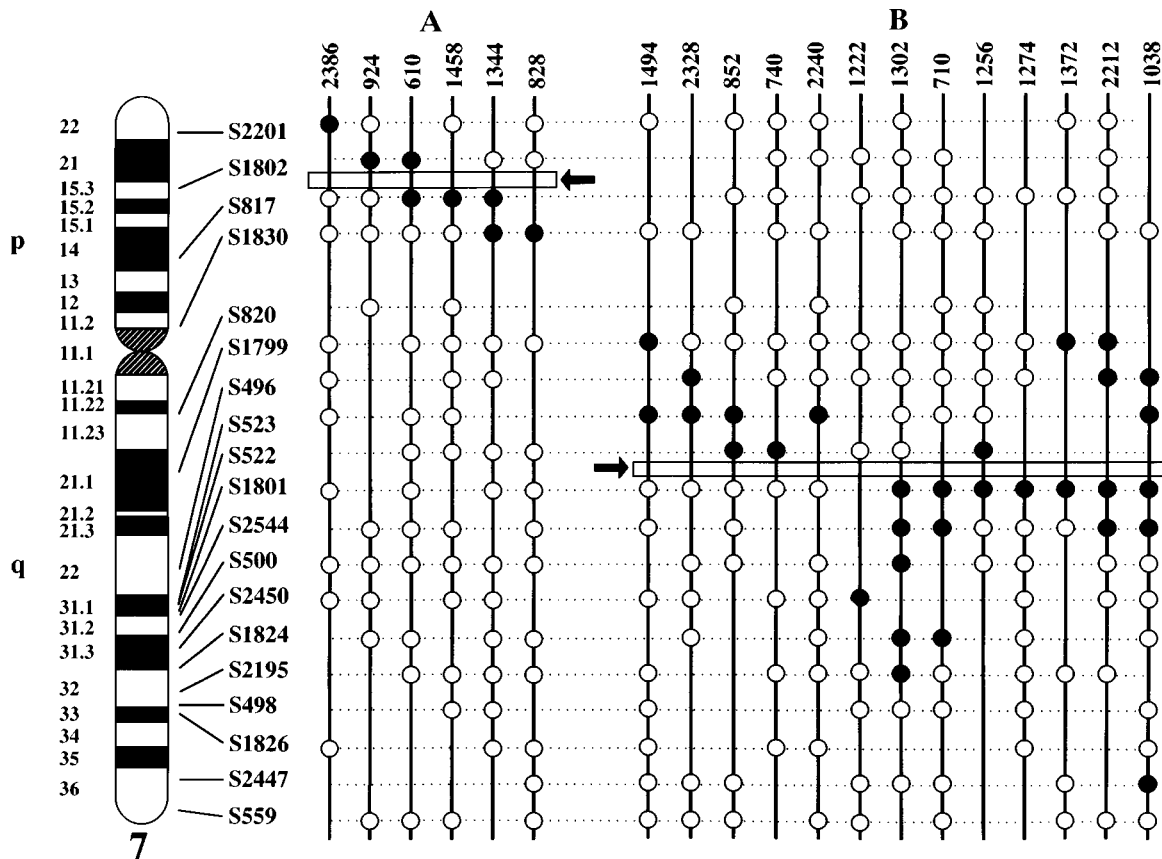
Fig. 2. Schematic representation of deletion mapping in tumors that showed partial or interstitial deletions on chromosome 7 in breast cancers (A: 7p region, B: 7q region). Case numbers are shown above each column; marker names appear on the linkage map at the left. White circles indicate retention of heterozygosity, black circles indicate LOH, and gaps reflect uninformativeness for specific markers. Commonly deleted regions (arrows) are outlined by rectangles superimposed on the maps.

1q gain in the same series of breast cancer specimens confirmed the reliability of our microsatellite-PCR method for the detection of allelic loss and multiplication.[23]

RESULTS

All patients in our study were informative, and LOH at one or more loci on the short arm of chromosome 7 was detected in 37 (26.1%) of the 142 tumors examined. The marker loci and their frequencies of LOH in our panel of patients are listed in Table I in descending order from 7pter to the centromere. Representative autoradiograms for cases with partial or interstitial loss of 7p are shown in Fig. 1A. Tumor 924 showed LOH at D7S1802, but retention of alleles at D7S2201 and D7S817. Tumor 1344 showed LOH at D7S817 and D7S1830, but retention of alleles at D7S1802. Of the 13 tumors with partial or interstitial deletions, six were critical in defining a novel com-

monly deleted region at 7p14-15, within a 19-cM interval flanked by D7S1802 and D7S817 (Fig. 2A).

We investigated potential relationships between the presence of LOH at 7p14-15 and clinicopathological parameters including tumor size and infiltration, lymph node metastasis, ER status, PgR status, and histopathologic classification (Table II). LOH at 7p14-15 was more frequent in tumors of the invasive solid tubular and scirrhous types (31 of 87; 36%) than in less aggressive types (2 of 27; 7%) (P=0.0047). We found no significant association with any of the other parameters.

On the long arm of chromosome 7, LOH was detected in 56 of 142 tumors (39%). The frequency of LOH at each 7q locus is shown in Table I. Fig. 1B shows autoradiograms representative of cases that exhibited partial or interstitial deletions of 7q. Tumor 740 showed LOH at D7S522, but retention of alleles at D7S496 and D7S1801. Tumor 1302 showed LOH at D7S1801 and D7S2544, but retention of alleles at D7S522. Of the 37 tumors with par-

Table II.   Correlation between LOH on Chromosome 7 and Clinicopathological Parameters

	7p14-15		7q31	
	LOH/Informative cases (%)	Statistical significance	LOH/Informative cases (%)	Statistical significance
Tumor size[a]				
t1	3/18 (17)		5/20 (25)	
t2	25/88 (28)	NS	34/93 (37)	NS
t3	5/17 (29)		9/20 (45)	
Lymph node metastasis				
(−)	13/49 (27)	NS	20/53 (38)	NS
(+)	20/75 (27)		28/81 (35)	
Hormone receptor				
ER (−)	9/47 (19)	NS	13/50 (26)	NS
(+)	18/57 (32)		26/62 (42)	
PgR(−)	10/31 (32)	NS	13/34 (38)	NS
(+)	17/74 (23)		27/79 (34)	
Histologic type[b]				
1a: Intraductal carcinoma	1/2 ⎤ 2/27 (7)	⎤	1/2 (50)	
a1: Papillotubular carcinoma	1/25 ⎦	[c]*P*=0.0047	5/25 (20)	NS
a2: Solid tubular carcinoma	17/46 ⎤ 31/87 (36)	⎦	18/49 (37)	
a3: Scirrhous carcinoma	14/41 ⎦		21/47 (45)	

a) t1: tumor≤2 cm, t2: 2 cm<tumor≤5 cm, t3: tumor>5 cm.
b) Histologic classification of the Japanese Breast Cancer Society.
c) 1a+a1 vs. a2+a3 (*P*=0.0047).

tial or interstitial deletions, 13 were critical in defining the commonly deleted region indicated in Fig. 2B, a 7-cM interval at 7q31 flanked by D7S522 and D7S1801. No significant association was found between LOH at 7q31 and any of the clinicopathological parameters.

DISCUSSION

When a particular type of cancer exhibits frequent LOH in a specific chromosomal region, one can infer that a tumor suppressor gene important in the genesis of that tumor is present in the deleted region. This theory received experimental support when LOH studies revealed 5q21 and 17p13 as targets of frequent LOH in colon cancers[24] and further investigations led to identification of the *APC* gene[25] and the *p53* gene[26] as the mutated tumor suppressor genes in the indicated regions. Observation of frequent LOH at multiple chromosomal regions in breast cancers revealed in previous LOH studies by us and others suggested that multiple tumor suppressor genes play roles in breast carcinogenesis.[4–6, 9–11, 13, 14, 27] Frequent LOH at 7p14-15 observed in the present study indicates that this chromosomal region is another candidate locale for a putative suppressor gene for breast cancer.

Among 142 primary breast cancers examined for LOH with 19 microsatellite markers for chromosome 7, we identified one commonly deleted region within the 19-cM interval between D7S1802 and D7S817 (7p14-15) on the

short arm, and another in the 7-cM interval between D7S522 and D7S1801 at 7q31. To our knowledge, LOH on 7p has not been reported before in breast cancers.

LOH at frequencies of less than 10% (3–8%) was observed using the same panel of breast cancers when we studied it with markers from several other chromosomal regions; such as, 1q21-32, 2q13-21, 19q13, 20p12-13, etc. (unpublished data). Frequent LOH (26%) observed on 7p in the present study therefore reflects non-random genetic alterations associated with breast carcinogenesis.

In the present study, we observed frequent allelic loss at 7p14-15 in tumors of the invasive solid-tubular and scirrhous types. We have previously observed associations between genetic alterations at certain chromosomal regions and specific histologic types of breast carcinoma, such as frequent allelic loss at 18q21 and solid-tubular type carcinoma,[16] frequent allelic loss at 22q13 and scirrhous type carcinoma,[17] and frequent multiplication of 1q and papillotubular type carcinoma.[23] Together, these results imply that genetic alterations at some specific chromosomal regions are associated with distinct histologic types of breast carcinoma, rather than reflecting the complexity of the karyotypes in each tumor.

The allelic loss we observed at 7p14-15 in a substantial number of breast cancers suggests that a putative tumor suppressor gene is present in that region. Since LOH at 7p14-15 appeared to be more frequent in tumors of aggressive histologic types (solid tubular and scirrhous;

31 of 87, 36%) than in less aggressive histologic types (noninvasive and papillotubular; 2 of 27, 7%) (P=0.0047), inactivation of the putative tumor suppressor gene(s) at 7p14-15 may play a role in acquisition of an aggressive phenotype in breast cancer.

LOH at 7q31 is observed frequently in cancers originating in a variety of tissues in addition to the breast: colon, ovary, prostate, head and neck (squamous cell), and pancreas.[19, 28–35] Furthermore, functional assays via chromosome transfer have shown that chromosome 7q31-32 possesses tumor-suppression activity.[22] We detected LOH at several marker loci on 7q31, at frequencies of 20–30%. Zenklusen et al.[30] claimed to have detected LOH at 7q31 in >80% of breast cancers, whereas Kerangueven et al.,[36] Champème et al.,[33] and Lin et al.[37] reported frequencies of 10–38%. Our results are in agreement with data from the latter three groups, which have been confirmed by an international consortium that reported the 7q31 LOH frequency as less than 40% in breast cancers.[38] The commonly deleted region we defined lies within a 7-cM interval between D7S522 and D7S1801 at 7q31, and overlaps the regions described by Zenklusen et al.,[30] Champème et al.,[33] and Lin et al.[37]

Champème et al.[33] observed similar frequencies of LOH at 7q31 between primary breast tumors and recurrent or metastatic tumors, and suggested that LOH at 7q31 is an early event in tumor progression. The Breast Cancer International Collaborating Group similarly found no association between 7q LOH and t-size, nodal status, distant metastasis, or lymph-node involvement.[38] The results of the present study support those observations and conclusions.

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