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Loss of Heterozygosity at 11q22–q23 in Breast Cancer[1]

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ABSTRACT

Studies of loss of heterozygosity (LOH) in breast tumor DNA suggest that several tumor suppressor genes participate in the pathogenesis of breast cancer. Although the short arm of chromosome 11 has been implicated in breast cancer development, no previous LOH studies have indicated the involvement of a suppressor gene on 11q in breast carcinoma. To this end, tumor samples and corresponding normal tissue were collected from 62 unselected patients with primary breast cancer, and the extracted DNA was analyzed by polymerase chain reaction using microsatellite markers on chromosome 11. We found that 39% of the tumors (22 of 57 informative cases) revealed allelic loss in the region 11q22–23, and this loss was independent of LOH found to occur on 11p15. Interestingly, more than 90% of the tumors showed concordant loss of alleles at both 11q and 17p. The marker *D11S528*, showing LOH in 39% of informative cases, had the highest frequency of LOH among the markers that were used. The data presented indicate that the common overlapping region of LOH is between the loci *D11S35* and *D11S29*, suggesting that this area contains a tumor suppressor gene frequently lost in breast cancer.

INTRODUCTION

The development of breast cancer, as well as that of other tissues, is associated with multiple genetic abnormalities resulting in alterations of normal mechanisms of growth control. In breast cancer, most genetic changes are not inherited but rather are somatically acquired in breast epithelial cells. The involvement of tumor suppressor genes in the pathogenesis of solid tumors may be inferred by studies which detect allelic losses in tumor DNA (1). LOH[3] studies, which determine loss of alleles at specific loci in tumor DNA, have demonstrated that a significant number of primary breast cancers show loss of heterozygosity of chromosomal regions 1p, 1q, 3p, 6q, 7q, 11p, 13q, 16q, 17p, 17q, and 18q (2–11). These data suggest that several different tumor suppressor genes may participate in the development and/or progression of breast cancer.

Although no reported studies have shown high frequency loss of genetic information on the long arm of chromosome 11 in primary breast cancers, cytogenetic studies have found that abnormalities of the long arm of chromosome 11 are evident in a significant number of breast cancers (12). Further evidence of a tumor suppressor gene in this region has been suggested by studies in which the transfer of a portion of the long arm of a normal human chromosome 11 into the breast cancer cell line MCF-7 significantly inhibited the tumorigenicity of the cell line (13). LOH from the long arm of chromosome 11 has been detected at region 11q12–q13 in neoplasms associated with multiple endocrine neoplasia type 1 (14) and at 11q22–q24 in ovarian, colorectal, and cervical carcinomas and malignant melanomas (15–18).

In this study we analyzed DNA from 62 unselected breast tumors for LOH in the long arm of chromosome 11. We performed comparisons of each tumor with normal DNA from the same patient, using microsatellite markers. Three markers were used in the 11q22–23 region, one marker at 11q13 and three markers on 11p. Since previous LOH studies have shown that 11p15 likely contains a tumor suppressor gene (4, 7, 19), we wanted to demonstrate that the loss that occurs in the 11q arm is independent of that which is at 11p15.

MATERIALS AND METHODS

Patient Materials. Tumors and corresponding normal tissue and/or peripheral blood samples were obtained from 62 consenting patients with primary breast cancer at the time of surgery. Tumors and tissues were snap-frozen in liquid nitrogen and stored at −70°C. Cell pellets from the peripheral blood samples were made and also stored at −70°C. Each tumor specimen was histopathologically characterized to confirm its diagnosis. DNA was extracted from the tumors, normal tissues, and peripheral blood using described techniques (20). Whenever necessary, following a histopathological examination of the frozen samples, neoplastic tissue was enriched by microdissection of the tumor specimens. Histopathological examination of tumor specimens revealed that the studied samples consisted of more than 80% of neoplastic cells; however, a significant infiltration of lymphocytes in some of the samples was revealed. Thus, enrichment for neoplastic tissue was not possible by further microdissection of the anatomical samples. The presence of infiltrating lymphocytes could have, in some instances, produced a tumor:normal cell ratio approaching 50:50. In these cases, the establishment of LOH might have been difficult, resulting in a final estimation of LOH at 11q22–23 slightly lower than the real LOH percentage.

DNA Analysis. Microsatellite oligonucleotide primers were selected, based on information obtained from the Genome Data Base, William Welch Library at Johns Hopkins University, at the following loci: *TH* at 11p15.5 (primers TH.PCR3.1/3.2); *D11S860* at 11p15.5 (primers BS48L/R); *WT-1* at 11p13 (primers WT1.PCR2.1/2.2); *FGF-3* at 11q13.3 (primers FGF3.PCR1.1/1.2); *D11S35* at 11q22 (primers 780/781); *D11S528* at 11q23.3 (primers 42026/42027); and *D11S29* at 11q23.3 (primers 7.1/7.2) (21). Polymerase chain reactions were performed with 100 ng of DNA in a 50-μl volume using 1.0 unit of Taq DNA polymerase (from Boehringer-Mannheim) with 50 μM concentrations each of dATP, dGTP, and dTTP and 2.5 μM dCTP, in addition to [α-^{32}P]dCTP at 1.0 μCi/reaction. Reaction conditions were optimized for each primer. After optimization of the specific annealing temperature, the reaction produced a single band detectable by ethidium bromide staining, in a nondenaturating agarose gel; then, the optimal number of cycles was determined. Too many cycles may produce allelic bands which do not differ in intensity because the reaction is at saturation, and no quantitative differences can be distinguished between the two alleles. Thus the number of cycles was optimized by reducing them to a number that allowed the differences in allelic band intensity to remain detectable, reflecting real differences in allelic ratio. In general, each PCR reaction was carried out for 30 s at 95°C, 45 s at 57°C or 58°C and 1 min at 72°C for 18–25 cycles. PCR products were separated on a 6% acrylamide sequencing gel and exposed for visualization by autoradiography on Kodak X-AR5 film.

Southern blotting was carried out by genomic DNA digestion and separation on a 0.8% agarose gel and blotting onto Hybond-N plus filters (Amersham, Arlington Heights, IL) through the capillary blotting method. Plasmid probes were obtained from American Tissue Culture Collection and chosen to include various loci on chromosome 11:phins214 (*IGF-2* at 11p15.5); pHBI59 (*D11S146* at 11q12–13.1); pHE5.4 (*ETS-1* at 11q23); and pCIII-606 (*APOC-3* at 11q23-qter), while probe B859 (*ALL-1* at 11q23) was generated in our laboratory (22). Probe YNZ22 (*D17S30* at 17p13.3) was obtained from Dr. Y. Nakamura (Tokyo, Japan); probe pPL8 (*CCND-1* at 11q13) was from Dr. A.

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[3] The abbreviations used are: LOH, loss of heterozygosity; PCR, polymerase chain reaction; AT, ataxia-telangiectasia.

Arnold (Boston, MA), and probe SS6 (*FGF-3* at 11q13) was from Dr. C. Dickson (London, England). Probes were radiolabeled using a random priming DNA labeling kit (Stratagene, La Jolla, CA). Filters were hybridized overnight and washed to a stringency of 0.2× SSC, 0.1% SDS at 65°C.

Assessment of LOH. LOH for tumor samples was determined by comparing the intensities of the alleles in a heterozygote of the matched tumor with normal DNA. The intensity signals of the two alleles in the normal DNA were consistently approximately equal, and a tumor was assessed to have a loss of one of the alleles when their signals in the tumor samples differed from each other at least twice as much as those in the normal samples. To discriminate between LOH and amplification of one of the alleles, Southern blot analysis was performed using several probes for chromosome 11. In some of the cases, PCR amplification of alleles deriving from normal tissue contaminating tumor samples made the detection of LOH difficult. In these cases, however, a reduction of the number of cycles for the PCR often optimized the difference in the allele intensities, and a definite determination could be made. The cases which exhibited a loss of heterozygosity were repeated to verify the results.

RESULTS

DNA samples from 62 unselected patients with primary breast cancer were analyzed by PCR using microsatellite markers from chromosome 11 to detect LOH. Representative results of the LOH studies are shown in Fig. 1. Loss was assessed by the reduction of one of the allele signals. The variability in the intensities of the allelic loss in tumor DNA is likely due either to cellular heterogeneity in tumor cells or to normal tissue "contamination." As mentioned in "Materials and Methods," different tumors have different ratios of tumor cells to normal stromal cells and infiltrating lymphocytes. The high "noisy" signal seen in some samples, *e.g.*, 4 and 39 in Fig. 1, is likely due to lymphocytes infiltration of the neoplastic tissue, as revealed by histological examination.

Allelic data for each of the matched DNA pairs are depicted in Table 1 and summarized in Table 2. From the 62 tumors analyzed, 25% (7 of 28) showed LOH at *D11S35*, 32% (15 of 47) showed LOH at *D11S29*, and 38% (16 of 42) showed LOH at *D11S528* for their respective informative cases. In total, 42% (26 of 62) of the tumors had LOH somewhere on chromosome 11 and 39% (22 of 57 informative cases) had LOH in the 11q22–23 region. The 27% LOH rate found on 11p15 (*D11S860*) is consistent with previously reported data of 33.3 and 30% (7, 19). Although there are some samples (*e.g.*, 5, 15, 43, 47, 51) which exhibit LOH in all the markers on both the long and short arms of chromosome 11, thus indicating probable loss of the entire chromosome in these particular tumors, other samples (*e.g.*, 13, 17, 18, 27, 28, 49) demonstrate allelic loss only on the long arm and not on the short arm. Furthermore, several tumors (*e.g.*, 4, 14, 24) show LOH on the short arm as well as in the 11q22–23 region but do not have loss in 11q13, suggesting that two independent loci may participate in the pathogenesis of breast cancer.

To confirm that the intensity differences in the alleles were due to allelic loss and not to DNA amplification of one allele, the tumor samples were tested on Southern blots for possible amplification by utilizing probes for various loci on the chromosome including *IGF-2* (11p15.5), *D11S146* (11q12–13.1), *ALL-1* (11q23), *ETS-1* (11q23), and *APOC-3* (11q23–qter) (not shown). Partial study of gene amplification at region 11q13 using *CCND-1* and *FGF-3* probes revealed that samples 4 and 13 had amplification of *CCND-1* and sample 15 had amplification of both *CCND-1* and *FGF-3*, while other cases with LOH at 11q23 did not show amplification at 11q13. Except patient 15, in whom amplification of *FGF-3* was detectable (Fig. 1), none of the patients who had a demonstrable allelic imbalance by microsatellite analysis showed evidence of amplification, indicating that the allelic imbalance was due to LOH and not to DNA amplification and that LOH at 11q22–23 and amplification at 11q13 are independent events in breast cancer etiopathogenesis.

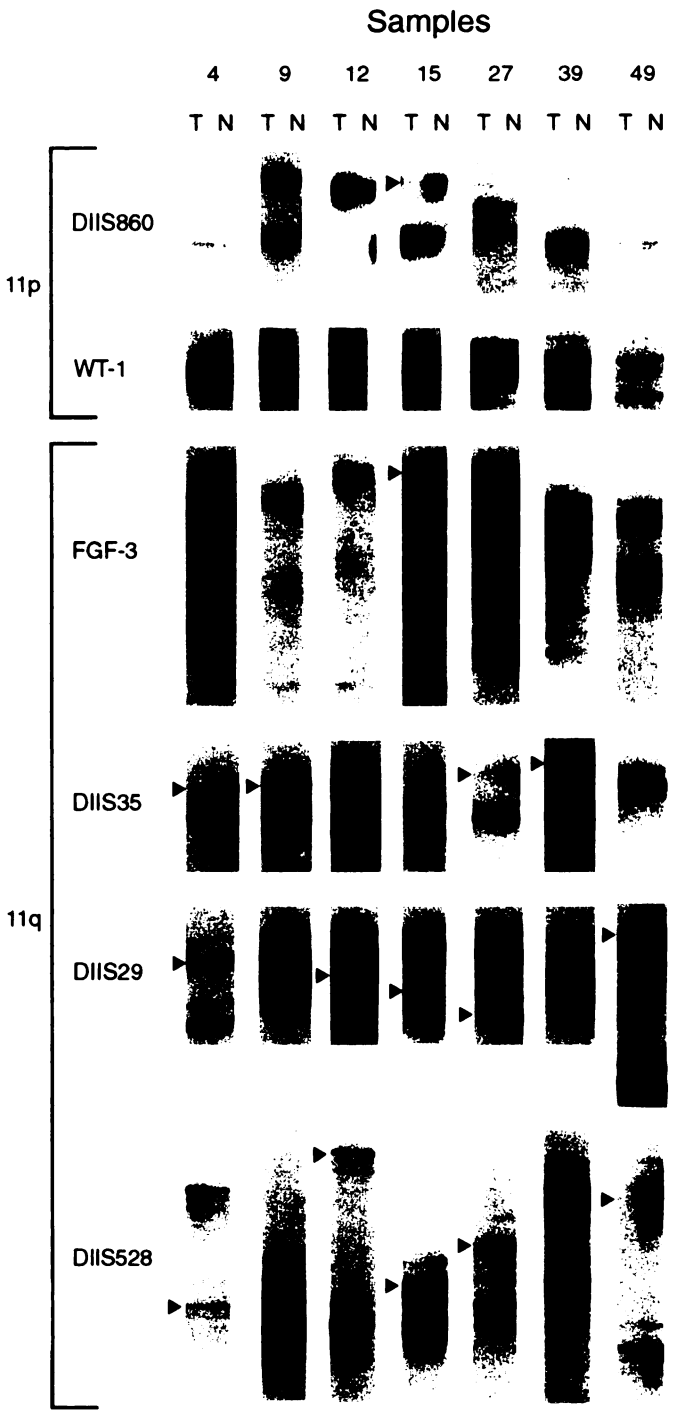

Fig. 1. Examples of LOH at chromosome 11 in representative breast tumors. Analysis of tumor (*T*) and normal tissue (*N*) DNA from patients 4, 9, 12, 15, 27, 39, 49. *Arrows*, alleles showing LOH. Tumors 4 and 39 show partial LOH due to cellular heterogeneity, from the presence of stromal cells and lymphocytes infiltrating the tumor samples from which DNA was purified. The allelic imbalance shown at the *FGF-3* locus in sample 15 is due to gene amplification at 11q13, detected by Southern blot analysis using *CCND-1* and *FGF-3* probes (data not shown).

The localization of a common area of LOH is inferred by the pattern of loss in some of the cases. For example, while tumors 12, 14, and 55 have LOH at *D11S29* and/or *D11S528*, but not at *D11S35*, tumors 9 and 39 have LOH only at *D11S35*, and not at *D11S29* or *D11S528*. Furthermore, tumor 24 has loss only at *D11S29*. Unfortunately, the location of *D11S528* with relation to *D11S35* or *D11S29* is not known at this time but appears to be relatively close to *D11S29*.

Table 1 *Allelic data for markers of chromosome 11 for each matched DNA pairs*

Tumor sample	*D11S528*[a] 11q23	*D11S29* 11q23.3	*D11S35* 11q22	*FGF-3* 11q13	*WT-1* 11p13	*D11S860* 11p15.5	*TH* 11p15.5
1	o	o	o	A/B		A/B	
2	A/B	o	o	o		A/B	
3	o	A/B	o	A/B		o	
4	A/–	A/–	A/–	A/B	o	o	A/–
5	A/–	o	o	A/–	A/–	A/–	A/–
6	A/–	A/–	o	o	o	o	A/B
7	A/B	o	A/B	A/B		o	
8	o	A/B	A/B	A/B	o	o	A/B
9	A/B	A/B	A/–	A/B	A/B	A/B	o
10	o	A/B	A/B	o		o	
11	o	o	o	nd		A/B	
12	A/–	A/–	A/B	A/B	A/B	o	o
13	A/–	A/–	A/–	A/B	o	A/B	o
14	A/–	o	A/B	o	o	A/–	o
15	A/–	A/–	o	A/–	o	A/–	A/–
16	A/B	o	A/B	A/B		A/B	
17	A/–	A/–	o	A/B	A/B	o	o
18	A/–	A/–	A/–	A/B	A/B	A/B	A/B
19	o	A/B	A/B	A/B		o	
20	A/B	A/B	A/B	A/B		A/B	
21	A/B	A/B	o	A/B		o	
22	A/B	A/B	A/B	A/B		o	
23	A/B	o	o	A/B		o	
24	A/B	A/–	A/B	nd		A/–	
25	o	A/B	o	nd		o	
26	o	o	o	A/B		o	
27	A/–	A/–	A/–	A/B	o	A/B	A/B
28	A/–	A/–	o	A/B	A/B	o	A/B
29	A/B	A/B	A/B	A/B		A/B	
30	A/B	A/B	A/B	A/B		A/B	
31	A/B	o	o	A/B		A/B	
32	A/B	A/B	o	A/B		A/B	
33	o	A/B	A/B	A/B		A/B	
34	A/B	A/B	A/B	A/B		o	
35	A/B	A/B	o	o		o	
36	A/B	A/B	o	A/B		o	
37	o	A/B	A/B	A/B		o	
38	A/–	o	o	o	o	o	A/B
39	A/B	A/B	A/–	A/B	A/B	o	o
40	A/–	A/–	nd	nd		nd	
41	A/–	A/–	o	o		A/–	
42	A/B	A/B	o	o		A/B	A/B
43	o	o	A/–	o	A/–	A/–	o
44	o	A/B	o	o		A/–	
45	A/B	A/B	A/B	o		o	
46	A/B	A/B	A/B	o		A/B	
47	o	A/–	o	A/–		A/–	
48	o	o	o	o		o	
49	A/–	A/–	o	A/B	A/B	A/B	A/B
50	A/B	A/B	o	A/B	A/B	A/B	A/B
51	A/–	o	o	A/–	A/–	A/–	A/–
52	A/B	A/B	o	A/B		A/B	
53	o	A/B	o	o	A/–	o	o
54	o	A/B	o	A/B	o	A/–	o
55	o	A/–	A/B	nd	A/B	A/B	A/B
57	nd	A/B	A/B	nd		A/B	
58	A/B	A/B	o	A/B		A/B	
59	A/B	A/B	o	A/B		A/B	
60	A/B	A/B	A/B	A/B		A/B	
61	A/B	A/B	o	A/B		A/B	
62	nd	A/B	A/B	nd		A/B	

[a] Allelic composition of tumor DNA was indicated as follows: A/B, retention of heterozygosity; A/–, loss of heterozygosity; o, homozygosity, noninformative; nd, not determined. A and B do not specify any particular allele, but only the presence of two distinguishable alleles.

These data do suggest, however, that a putative tumor suppressor gene maps distal to *D11S35* and proximal to *D11S29*.

Many of the patient samples were also evaluated for LOH at 17p13.3 using the plasmid probe YNZ22, and we found that 41% (11 of 27) of informative cases showed genetic loss at this locus (Table 3). Comparisons of our data identifying tumors with LOH revealed that 90% (9 of 10) of the tumors with DNA loss at 11q22–23 also had loss at 17p13.3, whereas 93% (14 of 15) of the tumors without loss at 11q did not show loss at 17p either. Thus there exists a significant association between loss of genetic material at 11q and loss at 17p in these tumors ($\chi^2 = 17.4$, $P < 0.001$). Whether the *TP53* or the putative tumor suppressor gene distal to *TP53* are lost or mutated in association with LOH at 11q23 remains to be established.

DISCUSSION

The genetic etiology of breast cancer is complex and appears to involve a number of mutations at several loci on different chromosomes. That tumor suppressor genes are involved in tumorigenesis has been evidenced by the elucidation of regions and specific genes which are found to be altered in a significant number of cancers; in breast cancer a number of these regions have been identified. In this study,

Table 2 *Percentage of LOH at different markers of chromosome 11 in breast cancer samples*

Locus	Chromosome location	Informative cases	LOH cases	% of LOH
D11S860	11p15.5	36	10	28
FGF-3	11q13	40	4	10
D11S35	11q22	28	7	25
D11S29	11q23.3	47	15	32
D11S528	11q23.3	42	16	38

Table 3 *Association of LOH at 11q23 with LOH at 17p13*[a]

	LOH[b] at 11q22–23	ROH at 11q22–23
LOH at 17p13	9	1
ROH at 17p13	1	14

[a] Only cases where either YNZ22 (17p13) and markers at 11q22–23 were heterozygous were considered.
[b] LOH, loss of heterozygosity; ROH, retention of heterozygosity.

data indicate that another locus at 11q22–23 is involved in the pathogenesis of breast cancer.

Allelic losses and deletions have been demonstrated at 11q22–24 in colorectal, ovarian, and cervical carcinomas and malignant melanomas in more than 50% of the cases (15–18). Although cytogenetic studies have indicated that this region may also be involved in a significant number of primary breast carcinomas (12, 23), only a limited number of cases have been previously studied by LOH analysis (24). By utilizing microsatellite markers as a means of identifying LOH, we were able to show that 39% of an unselected group of breast cancers exhibit LOH at 11q22–23. It is possible that the same region and eventually the same gene is altered in these different epithelial neoplasms.

The short arm of chromosome 11 has been implicated in breast cancer by previous LOH studies (4, 7, 19), and our results concur that approximately 30% of breast cancer cases have LOH in this chromosome region. We have further identified, however, an area of LOH in 11q that is independent of that on the short arm, suggesting that a tumor suppressor gene located at 11q22–23 is involved in approximately 40% of breast cancers. This conclusion is consistent with findings of an earlier study in which transfer of a normal chromosome 11, and specifically the region 11q13–23, into the MCF-7 breast cancer cell line, significantly reduced the tumorigenicity of the cell line in nude mice (13).

Microsatellites are highly polymorphic markers, which are relatively easy to analyze by PCR. However, LOH is evidenced by variation in the ratio between intensities of the bands corresponding to the two alleles and only rarely by complete disappearance of one of the bands. The presence of normal DNA contaminating tumor DNA is the most frequent reason for the presence of this "noisy" signal from the lost allele, which can occasionally make the interpretation difficult. Many of the breast tumor specimens were highly infiltrated by lymphocytes, which may have contributed a significant amount of normal DNA contaminating the neoplastic DNA. Alternatively, neoplastic cells may be heterogeneous and only a fraction of them may carry a specific genetic alteration, such as LOH at one particular locus. Histopathological examination of the tumor specimens indicated that they consisted mainly of carcinoma tissue, except for the infiltration of lymphocytes, indicating that tumor cells heterogeneity cannot be ruled out. The possibility of preferential allele amplification seems unlikely, because it was never detected in the normal paired controls. Because of possible failure to detect LOH for the presence of significant amount of nonneoplastic DNA in the tumor specimens or heterogeneity in tumor cell genotype, it is possible that the 40% LOH that we detected may be approximate by defect to the correct LOH percentage.

We noted that a significant correlation exists between the LOH at 11q22–23.3 and LOH at 17p13.3 in these breast tumors. It is well documented that a locus at 17p is involved in breast tumors and that allele losses in this region occur in more than 50% of breast cancers and are associated with a more aggressive tumor phenotype (10). Our data suggest that the genetic mutations in chromosomal region 17p involved in breast cancer may have a close temporal relationship with those in 11q, the two events occurring in combination with each other or one occurring as the result of the other. The participation of certain genetic alterations in a cascade of events leading to cancer development and/or progression has been suggested in colorectal carcinomas (25) and is beginning to be described for breast cancer as well. Losses of 17p material, specifically *TP53* and that at the *YNZ22* locus, are presumed to participate in early steps in breast cancer progression, while losses at 13q occur at later stages (26, 27), and studies have demonstrated an association existing between RB1 on 13q and pYNZ22 on 17p (28). Because of its close association with 17p, then, a loss of a gene in 11q may occur in the early stages of breast cancer and may provide important prognostic information.

Our findings suggest that the gene lies distal to the marker *D11S35* and proximal to *D11S29*, as evidenced by tumor samples in which one marker, but not the other, shows LOH. The distance between these two markers is approximately 20–30 cM. The AT gene, which lies between these two markers, has been implicated in breast cancer, and women who are heterozygous for AT have been shown to have an approximately 5-fold increased risk of developing breast cancer (29). Although there are studies which provide evidence against genetic linkage between chromosome 11 markers linked to the AT locus and breast cancer in breast cancer families (30, 31), we have shown through the use of microsatellite markers that chromosomal region 11q22–23, which contains the AT gene, is involved in LOH in breast cancer and the role of the AT gene in breast cancer must be further investigated. Since we have detected LOH at 11q22–q23 by using the *D11S528* marker, additional studies with a larger patient population are necessary to determine its position in relation to the other markers in this chromosomal region, as well as to more accurately localize the position of the putative tumor suppressor gene. Eventually the cloning of the critical gene and its identification could provide insight into the genetic mechanism by which breast cancers develop and progress.

While our manuscript was under review, Hampton *et al.* (32) independently identified a 43% LOH at region 11q22–23 in sporadic breast cancer. The identification of the same region of LOH by two independent laboratories supports the importance of region 11q22–23 in breast cancer etiopathogenesis.

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