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Advances in Brief

Loss of Heterozygosity at Chromosome 11q in Lung Adenocarcinoma: Identification of Three Independent Regions[1]

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Abstract

We examined the pattern of allelic loss in 76 adenocarcinomas of the lung using 14 highly informative microsatellite markers on the long arm of chromosome 11. Loss of heterozygosity was found in 48 of 76 tumors (63%). Three distinct regions of deletion were identified. The first region, the most centromeric, lies between markers *D11S940* and *CD3D*; the second, delimited by markers *D11S924* and *D11S925*, is estimated to be 4 Mb in length, and has never been previously described; a third, more telomeric region, the length of which is also estimated to be in the range of 4 Mb, is bracketed by loci *D11S1345* and *D11S1328*. These findings suggest the presence of at least three tumor suppressor genes on the long arm of chromosome 11, and confirm the relevance of 11q22–24, a region frequently deleted in carcinomas of the breast, ovary, uterine, cervix, colon, and malignant melanoma in the pathogenesis of solid tumors. The characterization of minimal regions of loss could provide the basis for the identification and cloning of the critical genes.

Introduction

Lung cancer is the leading cause of cancer-related death for both men and women in the industrialized countries. In 1993, more than 140,000 people died of lung cancer in the United States, and the incidence of this disease is rising (1). In the past 15 years, adenocarcinoma has replaced squamous cell carcinoma as the most common histological type of lung cancer (2). Understanding the molecular and biological characteristics of this tumor could improve the management of this still incurable disease.

Cytogenetic studies have shown complex chromosome alterations in lung cancer (3, 4), and molecular genetic analysis has pointed to the role of chromosomes 1q, 2q, 3p, 5q, 8p, 9p, 11p, 13q, and 17p as possible tumor suppressor-carrying regions (5–8). The involvement of regions 11p13 and 11p15 in lung cancer has been reported by several investigators (9–11), but only very recently LOH[3] at 11q14–24 (12) has been documented for the first time.

Functional studies have shown that introduction of normal human chromosome 11 into the A549 lung adenocarcinoma cell line is capable of suppressing tumorigenicity in nude mice (13, 14). A549 carries an 11q-chromosome, suggesting that the deletion may be indicative of the location of a putative tumor suppressor gene in this cell line. In addition, suppressive functions on the long arm of chromosome 11 were demonstrated to affect the tumorigenic phenotype of the MCF-7 breast cell line (15). We have recently found two independent regions of LOH at 11q22–23 in breast carcinomas (16), and we have now investigated whether the same regions could be affected by loss of genetic material in lung cancer. Our data indicate that LOH on chromosome 11q22–24 is frequent in lung adenocarcinomas, and loss of genetic material on the long and short arms of this chromosome are independent events. Three distinct regions at 11q that could potentially harbor genes with tumor suppressor function have been identified, and the boundaries of these regions have been assessed.

Materials and Methods

Tumor Samples. Seventy-six primary tumors of the lung and matched normal lung tissue were excised and snap-frozen in liquid nitrogen. All cases were identified histopathologically as lung adenocarcinoma. None of the patients had received chemotherapy or radiotherapy. The mean age of the lung cancer patients was 62 years (range, 40–78). Genomic DNAs were isolated using established procedures (17).

LOH Analyses. Microsatellite primers were obtained from information available through the Genome Data Base, William Welch Library, Johns Hopkins University (Baltimore, MD), and exact locations are based on the recently developed radiation hybrid map for human chromosome 11 (18). PCRs were performed using 50 ng of template in 25 μl of volume using 0.5 unit of Taq DNA polymerase; 20 μM each of dATP, dGTP, and dTTP; 2.0 μM of dCTP; and [α^{30}P]dCTP at 0.5 μCi/reaction. PCR conditions were optimized for each primer. In general, PCR reactions were carried out for 20 s at 94°C, 20 s at 54–63°C, and 30 s at 72°C, for a total of 19–22 cycles. PCR products were separated on a 6% acrylamide sequencing gel and exposed for visualization by autoradiography on Kodak X-AR5 film.

Assessment of LOH. LOH for the informative cases was assessed by two independent observers by visual inspection. However, cases that were uncertain or where the mapping information was crucial were analyzed by densitometric film scanning using a computerized Molecular Dynamics system (Personal Densitometer). Quantification was performed using the ImageQuant software. The relative ratio of tumor alleles and normal alleles was determined, normalized, and then compared. LOH was assigned if the allele ratio in tumor DNA differed more than 30% from the allele ratio in normal DNA.

Results

Paired normal and tumor DNAs from 76 previously untreated patients with histologically confirmed adenocarcinoma of the lung were analyzed for LOH using 14 polymorphic microsatellite markers spanning chromosome 11q22–24. Results of LOH analyses performed on all the tumor samples are shown in Fig. 1. Cases defining the minimal regions of loss are shown in Fig. 2 and summarized in Fig. 3.

Forty-eight of 76 tumors (63%) showed LOH for at least one locus of region 11q22–24. Whereas 21 tumors exhibited LOH at all the informative markers used, and thus were not helpful in defining any minimal region of loss, several cases had restricted areas of LOH. The overall picture indicates that a complex array of deletions occurred in the various tumor samples. In Fig. 3, three minimal regions of loss that do not overlap each other are pointed out by sample 59, which shows loss for a region bracketed by loci *D11S940* and *CD3D*; samples 20, 30, and 51, which define an area delimited by loci *D11S924* and *D11S925*; and samples 2, 25, 38, 42, 43, and 57, which indicate the existence of a third, more telomeric region of loss distal to *D11S1345*

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[3] The abbreviations used are: LOH, loss of heterozygosity; A-T, ataxia-telangiectasia.

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	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	27	28	29	30	31	32	33	35	36	38	40	41	42	
D11S922	a/b	a/b	a/b	a/-	a/-	a/-	a/b	a/b	a/b	a/b	a/b	a/b	a/b	a/-	a/b	a/b	a/b	a/b	a/b	m.i.	a/b	a/-	o	a/-	a/b	o	o	a/-	a/-	a/-	o	a/-	a/b	a/b	o	a/-	a/-	a/b	D11S922
D11S35	a/-	a/b	a/b	o	a/-	o	a/b	a/b	a/b	a/-	a/-	a/-	a/-	o	a/b	a/b	o	a/b	a/b	a/-	a/-	a/b	a/-	m.i.	o	a/-	a/b	a/b	a/-	a/b	o	o	a/-	o	o	a/-	a/-	o	D11S35
D11S940		a/b		o			o							a/b								a/b					a/b												D11S940
D11S1818	a/-	o	a/b	o	a/-	a/b	o	o	o	a/-	a/-	o	a/-	o	a/b	o	a/b	a/b	o	o	a/-	a/-	o	a/b	a/b	a/-	a/-	o	a/-	a/b	a/-	o	a/b	a/b	a/b	o	a/-	o	D11S1818
D11S29		a/b		a/-			a/-					a/b	a/-	a/b						a/b											a/-	o							D11S29
CD3D	o	a/b	o	a/-	a/-	o	a/-	a/b	a/b	a/-	o	a/b	o	a/b	o	a/b	a/b	a/b	a/b	o	a/-	a/-	a/-	o	a/b	a/-	a/-	a/b	a/-	a/b	o	a/b	a/b	a/b	a/b	a/-	a/-	a/b	CD3D
D11S924		a/b												a/b				o		a/b		o				o	o		a/b		a/-				o	a/-	o		D11S924
D11S528	a/-	a/b	a/b	a/-	a/-	a/b	o	a/b	a/b	a/-	a/-	a/b	a/-	o	a/b	a/b	o	o	a/b	a/-	a/-	m.i.	a/-	a/b	o	a/-	o	a/b	a/-	a/b	a/-	a/b	a/b	a/b	a/b	o	o	o	D11S528
D11S925	a/-	a/b	o	a/-	o	a/b	a/-	a/b	a/b	o	a/-	o	a/-	o	a/b	a/b	a/b	o	a/b	o	a/-	o	a/-	a/-	a/b	a/b	a/b	a/b	a/-	a/b	a/-	a/b	a/b	a/b	a/b	a/-	o	a/b	D11S925
D11S1345		a/-	o			a/b	a/-	a/b	a/b			o		a/b		o		o		a/b				a/-	a/-	a/-	o		a/b	a/b				o	a/-			a/-	D11S1345
D11S1284		a/-	a/b			o	o	o	o			o	a/-	o	a/b	o	a/b	o	o	a/b		a/-		o	a/-	a/-	o		o	a/b		o	o	o	a/-	a/-	o	a/-	D11S1284
D11S1328		a/b																a/b		o		a/-		a/-	o	a/-	a/b		a/b	a/b				a/b	a/b				D11S1328
D11S689		a/b	a/b			a/b		a/b	a/b			o	a/-	o	a/b	a/b	a/b	o	a/b	a/b		o			o	a/-	a/b	a/b	n.d.	o		a/b	a/b	a/b	a/b	a/-	o	a/-	D11S689
D11S990	a/-	a/b	a/b	a/-	a/-	a/b	a/-	a/b	o	a/-	a/-	o	a/b	a/b	a/b	o	a/b	a/-	a/b	a/b	a/-	o	a/-	a/-	a/b	o	a/b	o	o	a/b	a/-	a/b	a/b	a/b	a/b	a/b	o	a/-	D11S990
D11S934																		o		a/b				o	a/b	a/-			a/-	a/b								a/-	D11S934

	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	
D11S922	a/b	o	a/b	a/-	a/b	a/-	a/b	a/-	a/b	o	o	a/b	a/-	a/b	a/b	a/b	a/b	o	o	a/-	a/b	o	a/b	a/-	a/b	a/b	a/b	a/b	a/b	m.i.	a/b	a/-	a/b	a/b	a/b	a/-	a/-	a/b	D11S922
D11S35	a/b	a/b	a/b	a/-	a/-	a/-	a/b	a/-	a/b	a/-	a/b	a/-	a/-	a/b	a/b	o	a/b	a/b	a/-	a/-	a/b	a/-	a/b	o	a/b	a/b	a/-	a/b	a/b	a/-	a/b	a/-	a/b	a/b	o	a/-	o	a/b	D11S35
D11S940																	a/b	a/b					a/b			o		a/b								a/-			D11S940
D11S1818	a/b	a/b	a/b	a/-	a/-	m.i.	o	a/-	a/b	o	a/b	a/-	a/b	a/b	a/b	a/b	a/-	a/-	a/-	a/-	o	a/b	a/-	a/b	o	a/-	a/-	a/b	m.i.	m.i.	a/b	a/-	a/b	a/b	a/b	a/-	o	a/b	D11S1818
D11S29	o							a/-	a/b	a/-	a/b	o	a/b		a/b	a/b	a/-					a/-	a/-					a/b		m.i.							a/-		D11S29
CD3D	a/b	a/b	a/b	a/-	a/-	a/-	a/b	a/-	a/-	o	a/b	o	o	a/b	o	o	a/b	a/-	a/-	a/-	o	o	o	a/b	a/b	a/-	a/-	a/-	a/b	o	a/b	a/-	a/b	o	a/b	a/-	o	o	CD3D
D11S924	a/b							a/-	a/-	a/-	a/b	o			a/b		a/-		a/b																				D11S924
D11S528	a/b	o	a/b	a/-	a/-	a/-	a/b	o	a/-	a/-	o	o	o	o	a/b	a/b	a/-	a/-	o	a/-	a/b	o	a/-	a/b															D11S528
D11S925	a/b	a/b	a/b	a/-	a/-	a/-	a/b	o	a/b	a/-	o	a/-	a/-	a/b	o	a/b	o	o	a/-	a/-	o	a/-	a/-	a/b	a/b	a/-	a/-	o	a/b	m.i.	a/b	o	o	a/b	a/b	a/-	a/-	o	D11S925
D11S1345	a/b													a/b	a/b				a/-																				D11S1345
D11S1284	o	o	a/b	a/-			a/b	o	a/b	a/-	o	o	o	a/b	a/-	a/b	a/-	o	o	n.d.	a/b	a/-	a/-	a/b	a/b	o	o	o	o	m.i.	a/b	o	a/b	o	o	a/-	a/-	o	D11S1284
D11S1328	a/-			a/-					o						a/-			a/-	a/-			a/b	a/-					o		m.i.									D11S1328
D11S689	a/-	a/b	o	o			o		o		o			o	a/-			o	o			a/b	m.i.			m.i.		o	a/b			o		a/b	m.i.			m.i.	D11S689
D11S990	o	a/b	a/b	o	a/-	a/-	a/b	a/-	a/b	a/-	o	a/-	a/-	a/b	a/-	a/b	a/-	a/-	a/b	a/-	a/b	a/b	a/b	a/b	a/b	a/b	a/-	a/b	a/b	m.i.	a/b	o	a/b	a/b	a/b	a/-	a/-	o	D11S990
D11S934	a/b												o		a/-		a/-																						D11S934

Fig. 1. Schematic representation of LOH on chromosome 11q in all tumor samples. Cases designated by numbers are shown at the *top*. Microsatellite markers, used to detect LOH, are shown at the *right* and *left*. *Shaded areas*, regions of LOH. *Dark shadowing*, region of secure LOH; *light shadowing*, region of uncertainty; *unshadowed*, retained heterozygosity. *a/b*, locus maintaining heterozygosity; *a/–*, LOH; *o*, a homozygous locus; *m.i.*, microsatellite instability; *n.d.*, not determined.

and proximal to *D11S1328*. Because of the relative proximity of the various loci analyzed, many of the regions of deletion overlap. Samples 59, 61, 64, and 70 show areas of deletion that overlap more than one potential minimal common region of LOH, making it impossible to assess the relevance of the deletion for one specific region.

By analysis and comparison of samples with LOH at these regions, the minimal overlapping areas of LOH were defined as follows: case 59 defines the limits of the most centromeric region at loci *D11S940* and *CD3D*, which are estimated to be approximately 20 cM apart (19). Case 28 confirms *D11S940* as proximal boundary but, being homozygous for loci *D11S924* and *D11S528*, sets the telomeric boundary of this case at *D11S925*. Therefore, the minimal region remains defined between loci *D11S940* and *CD3D*. Included within this area is marker *D11S1818*, for which 25 of 53 informative tumors (47%) displayed LOH.

A second, more telomeric minimal region of loss is pointed out by cases 20, 30, and 51. The area of deletion shown by cases 20 and 30 is delimited by loci *D11S924* and *D11S1345* and includes markers *D11S528* and *D11S925*. Case 51, heterozygous for *D11S29*, displays LOH at *CD3D*, *D11S924*, and *D11S528*, and regains heterozygosity at locus *D11S925*. By comparing the two sets of data, we conclude that the minimal area of loss lies between markers *D11S924* and *D11S925*, in a region of approximately 4 Mb of length. This region includes locus *D11S528*, for which 21 of 44 (48%) informative tumors exhibited LOH.

A third common region of LOH is defined by cases 2, 24, 25, 27, 38, 42, 43, and 57. In particular, cases 2 and 38 show loss for markers *D11S1345* and *D11S1284*, whereas case 43 retains heterozygosity at *D11S1345*, is homozygous, and thus not informative for *D1S1284*, and shows LOH for the next two markers. The areas of deletion exhibited by these tumors reveal an overlapping region, bracketed by loci *D11S1345* and *D11S1328*, that appears to be commonly lost, the size of which is estimated to be about 4 Mb. Within this region lies locus *D11S1284*, for which 16 of 31 (52%) informative tumors displayed genetic loss.

All of the tumors were analyzed for LOH at locus *D11S922* at 11p15 to determine whether the alterations leading to loss of genetic material on chromosome 11 were restricted to this chromosomal arm. LOH was found in 21 of 76 adenocarcinomas (28%), and only 13 of the tumors showing allelic imbalance in the short arm of the chromosome showed it also in the long arm. Because 5 of the cases that had LOH at 11q were not informative at 11p, we should conclude that for at least 30 of 48 tumors (62%), LOH was restricted to the long arm of the chromosome.

Microsatellite instability was detected in some samples; 9 tumors (12%) displayed microsatellite instability for only one of the markers used, and only sample 72 showed microsatellite instability for most of the markers (7 of 9).

Discussion

We studied the pattern of allelic loss in 76 adenocarcinomas of the lungs with markers spanning 11q22–24, a region frequently deleted in breast carcinomas (16, 20, 21), cervical carcinomas (22), ovarian carcinomas (23), colorectal carcinomas (24), and melanomas (25, 26). Areas of genetic loss at 11p13 and 11p15.5 in lung cancer have been reported by several investigators; however, evidence of the involvement of the long arm of chromosome 11 is less compelling. Only recently, Iizuka *et al.* (12) reported LOH at 11q in about 40% of non-small cell lung cancer.

Our results show high frequency (63%) of LOH at region 11q22–24 in lung adenocarcinoma and indicate the presence of three distinct regions that could potentially harbor tumor suppressor genes. The first, more centromeric region, is bracketed by loci *D11S940* and

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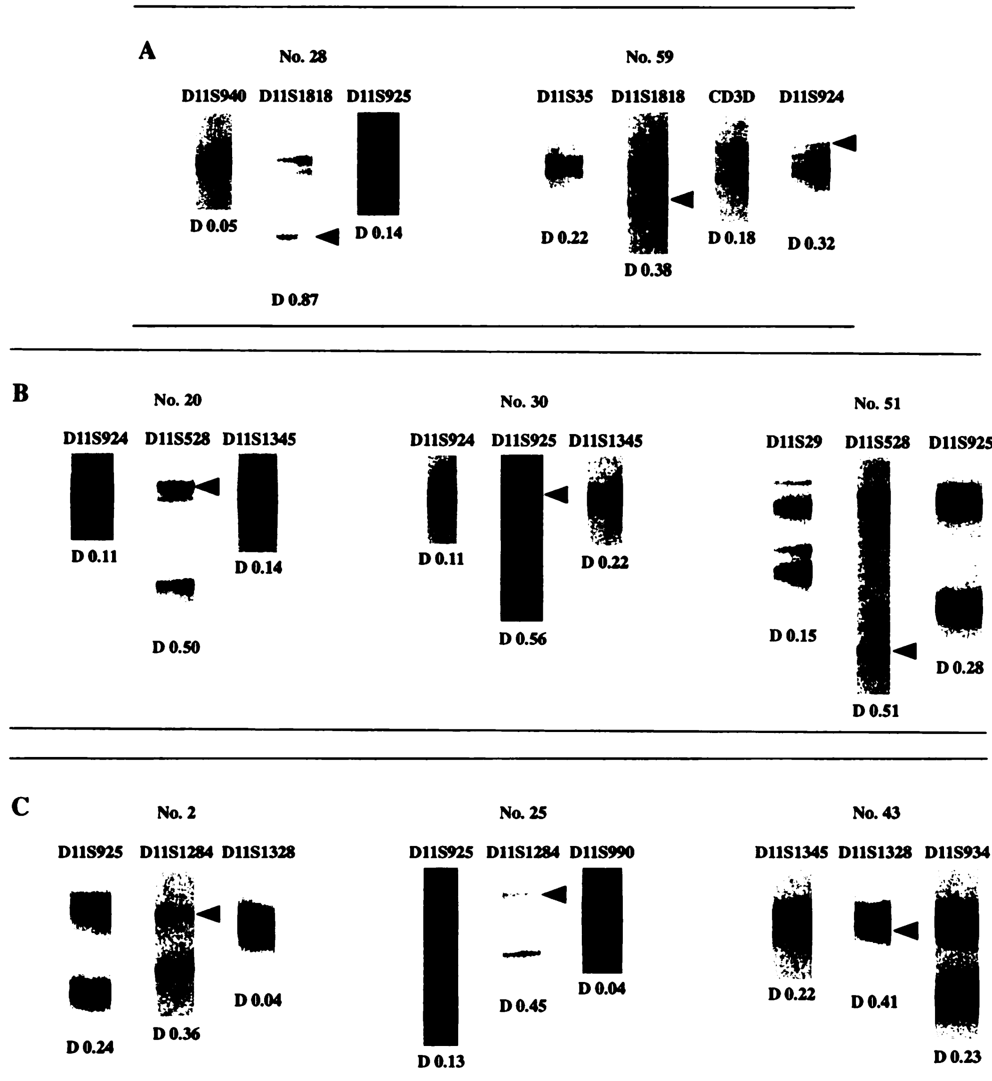

Fig. 2. Selection of tumors that define the minimal regions of LOH. *A*, *B*, and *C*, critical cases for each of the regions of LOH identified in the study, with the most centromeric region in *A* and the most telomeric in *C*. Each autoradiograph includes normal (*left*) and tumor (*right*) DNA from the same patient. Case number and locus are shown at the *top* of each autoradiograph. At the *bottom*, the calculated difference in the ratio between tumor and normal allele is shown. A value more than 0.3 was taken to indicate LOH. *Arrowheads*, allele lost in tumor DNA.

CD3D and includes markers *D11S1818*, for which 25 of 53 informative tumors (47%) showed LOH, and *D11S29*, where LOH was detected in 10 of 20 (50%) informative cases. *D11S1818* comprises the 5-Mb yeast artificial chromosome contig of the A-T locus (27) and lies in the same region reported to be deleted in breast cancer (16, 20, 21). The A-T carrier state has been correlated with a 5-fold increase probability of breast cancer development (28, 29), and elevated risk of cancer of the lung, pancreas, gallbladder, and stomach has been associated with the heterozygous state in one study (28). The recent identification of the gene responsible for the A-T phenotype (30) may help to determine whether the same gene is also implicated in the pathogenesis of sporadic cancers with LOH at 11q23. LOH for *D11S29* has been reported with high frequency in melanomas (67%; Refs. 25, 26) and colon carcinomas (50%; Ref. 24), but it is not possible to determine whether the same region is involved because a detailed analysis of the minimal region of genetic deletion in melanoma and colon carcinoma was not performed.

Iizuka *et al.* (12) reported LOH in lung cancer in a region of 3 cM, bracketed by loci *D11S938* and *D11S939*, which lies in the telomeric portion of the area that we described. In breast cancer, the minimal region of LOH appears to be more centromeric (between loci *D11S2000* and *D11S897*) (16). At present, we cannot exclude whether loci centromeric to *D11S938* are targets of genetic deletion in lung cancer.

Cases 20, 30, and 51 set the limits of a second region of deletion between markers *D11S924* and *D11S925*. The region of loss delimited by cases 20 and 30 includes marker *D11S925*, while heterozygosity for *D11S925* is retained at the densitometric analysis of case 51. The difference in the ratio between tumor and normal alleles for this sample is 0.28, thus differing only slightly from the minimal value established for the assignment of LOH (0.30). Because we used the results of the scanning laser densitometry to assess LOH, we could not include *D11S925* in the region of loss reported by case 51, although the assignment of this locus as telomeric boundary of the region needs further validation. This minimal area of approximately 4 Mb of length has not been reported previously as a possible target of genetic loss in lung cancer or in other types of neoplasms, and the involvement of this region should be confirmed by analysis of additional samples.

A third region of deletion, also in the range of 4 Mb in length, lies between loci *D11S1345* and *D11S1328* and includes locus *D11S1284*, for which 52% of informative tumors showed LOH. This minimal region of LOH is included within an area of deletion that we recently

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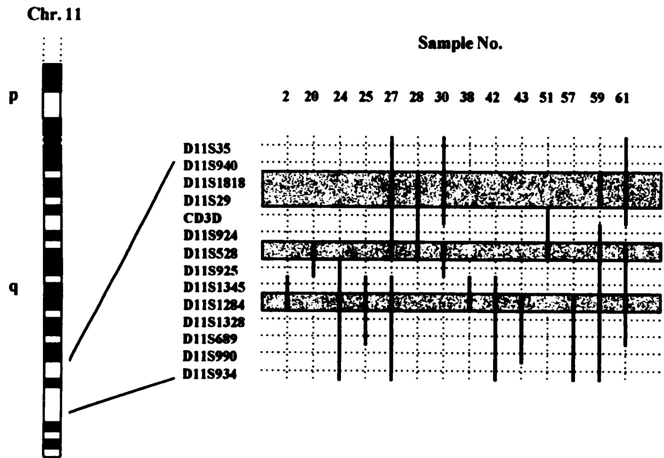

Fig. 3. Ideogram of the long arm of chromosome 11 (*Chr. 11*) showing the position of polymorphic markers used. Marker positions are based on Ref. 18. Selected cases that allow the definition of the minimal overlapping regions of LOH are shown at *right*. Only representative samples and loci are shown. *Vertical thick lines*, regions of LOH for each umor specimen. *Horizontal shadowed bars*, minimal regions of LOH.

described in breast carcinomas (16) and may define an area of loss also reported by Iizuka *et al.* (12) in lung cancer, although the boundaries of allelic deletion in this work have not been assessed.

Microsatellite instability at more than one locus was detected only in case 72, suggesting that a potential mutation in one of the genes involved in replication repair is not frequent in the pathogenesis of sporadic adenocarcinomas of the lung.

These studies, together with the reports of LOH in cervical carcinoma at 11q22–24, ovarian carcinoma at 11q23.3–qter, colorectal carcinoma at 11q22–23, and the before mentioned malignant melanoma and breast carcinoma, are pointing to the importance of the long arm of chromosome 11 in the pathogenesis of solid tumors. Multiple potential tumor suppressive genes appear to map to this chromosomal region, and only recently the definition of the minimal areas of LOH have begun to be elucidated.

This work confirms the finding of high frequency of LOH at 11q22–24 in lung cancer and identifies three distinct regions of loss that potentially harbor gene(s) important in the maintenance of the normal phenotype. The overall picture of the region is complex, suggesting that multiple genes linked to tumor suppressive molecular pathways are located in this area. A new region of loss bracketed by loci *D11S924* and *D11S925* has been identified, and the boundaries of a second region have been narrowed down to 4 Mb of length. The size of these two regions may allow us to approach the identification of the critical genes by a positional cloning strategy.

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