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Deletions at 14q in malignant mesothelioma detected by microsatellite marker analysis

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Summary Previous molecular cytogenetic studies by comparative genomic hybridization (CGH) on primary tumours of human malignant mesothelioma have revealed that loss of genetic material at chromosome 14q is one of the most frequently occurring aberrations. Here we further verify the frequency and pattern of deletions at 14q in mesothelioma. A high-resolution deletion mapping analysis of 23 microsatellite markers was performed on 18 primary mesothelioma tumours. Eight of these had previously been analysed by CGH. Loss of heterozygosity or allelic imbalance with at least one marker was detected in ten of 18 tumours (56%). Partial deletions of varying lengths were more common than loss of all informative markers, which occurred in only one tumour. The highest number of tumours with deletions at a specific marker was detected at 14q11.1–q12 with markers D14S283 (five tumours), D14S972 (seven tumours) and D14S64 (five tumours) and at 14q23–q24 with markers D14S258 (five tumours), D14S77 (five tumours) and D14S284 (six tumours). We conclude from these data that genomic deletions at 14q are more common than previously reported in mesothelioma. Furthermore, confirmation of previous CGH results was obtained in all tumours but one. This tumour showed deletions by allelotyping, but did not show any DNA copy number change at 14q by CGH. Although the number of tumours allelotyped was small and the deletion pattern was complex, 14q11.1–q12 and 14q23–q24 were found to be the most involved regions in deletions. These regions provide a good basis for further molecular analyses and may highlight chromosomal locations of tumour suppressor genes that could be important in the tumorigenesis of malignant mesothelioma.
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Keywords: microsatellite marker analysis; loss of heterozygosity; allelic imbalance; malignant mesothelioma

Malignant mesothelioma, a tumour frequently linked to past occupational exposure to asbestos, arises from mesothelial cells of the pleura, peritoneum or pericardium (Wagner et al, 1960). Mesothelioma is characterized by a long latent period (35–40 years) (Browne, 1986; Yates et al, 1997) and due to the lack of efficient treatment, its prognosis is very poor. From 1975 to 1990 there was an increasing trend in the incidence of mesotheliomas in Finland, but since 1990 it has slowed down. Based on observations from 1985 to 1995, by 2010 the annual incidence of mesotheliomas among men and women is expected to be around 40–50 and 10–20 cases respectively (Karjalainen et al, 1997).

Previous cytogenetic and molecular genetic studies have indicated several chromosomal locations with frequent alterations in mesothelioma (Tiainen et al, 1989; Hagemeijer et al, 1990; Taguchi et al, 1993; Cheng et al, 1994; Lu et al, 1994; Zeiger et al, 1994; Bianchi et al, 1995; Sekido et al, 1995). However, no aberration specific to mesothelioma has been detected. Comparative genomic hybridization (CGH) analyses on primary mesothelioma tumours and cell lines have revealed that loss of genetic material at chromosome 14q is one of the most frequently occurring aberrations (Kivipensas et al, 1996; Björkqvist et al, 1997, 1998; Balsara et al, 1999). In this study we further verify the frequency and pattern of deletions at 14q in primary mesothelioma tumours using polymerase chain reaction (PCR) and 23 microsatellite markers spanning the whole of the long arm of chromosome 14.

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MATERIALS AND METHODS

Tumours and clinical characteristics of patients

Eighteen primary tumours of patients with malignant mesothelioma were included in the microsatellite marker analysis. All of the patients had undergone surgery at the Helsinki University Central Hospital during years 1995–1997. Three of the patients were females and 15 males. The mean age at diagnosis was 57 years (range 44–72 years). Thirteen patients had a clear history of asbestos exposure. Three tumour samples were from patients with stage 2 disease, whereas eight and seven samples were from patients with stage 3 and 4 disease respectively. The median survival of the patients was 16 months. The histological classification of the tumours was performed by the Finnish Mesothelioma Panel. Fourteen tumours were epithelial (nos 1–14), two mixed (nos 15 and 16), one fibromatous (no. 17) and in one case the histological subtype could not be determined (no. 18). CGH analyses had previously been performed on eight of the tumours (Table 1).

Tumour DNA was extracted from paraffin-embedded tissues (nos 1–13 and 15–18) by a salting out procedure (Miller et al, 1988) or from fresh-frozen material (no. 14) according to standard protocols. The proportion of malignant cells in the tumour samples

Table 1 Pattern and frequency of loss of heterozygosity (LOH) and allelic imbalance (AI) detected with 23 microsatellite markers at 14q in 18 primary mesothelioma tumours

Marker[b]	Tumour[a]																		Tumours with LOH or AI/total informative	LOH or AI (%)	cM[k]
	1[c]	2[d]	3[e]	4[f]	5	6	7	8	9	10[g]	11	12	13[h]	14[i]	15[j]	16	17	18			
D14S72	■	■	■	□	□	□	—	ND	X	ND	□	□	□	□	□	□	□	■	4/14	29	1.4
D14S1003	◨	—	□	—	□	■	□	—	—	□	□	□	□	—	□	—	□	—	2/11	18	4.0
D14S283	■	■	■	◨	□	□	□	—	—	□	□	□	□	□	□	□	□	■	5/16	31	7.6
D14S972	■	◨	◨	□	◨	◨	□	X	□	ND	□	□	□	X	◨	□	X	■	7/14	50	1.2
D14S64	■	◨	■	□	□	—	—	◨	ND	ND	—	□	□	□	ND	□	—	■	5/11	45	4.3
D14S80	□	X	□	—	◨	—	—	□	□	□	—	□	□	□	—	□	X	■	2/11	18	7.4
D14S1060	□	—	—	—	□	□	□	□	—	□	□	□	□	□	□	□	□	■	1/14	7	8.3
D14S75	■	■	—	—	□	□	—	□	—	□	□	□	—	□	■	□	—	■	4/12	33	6.6
D14S269	■	■	ND	—	—	□	ND	X	X	□	□	□	□	X	—	□	X	■	3/9	33	7.1
D14S66	■	—	□	◨	□	□	□	◨	□	—	□	□	□	□	□	—	□	—	3/14	21	9.0
D14S63	■	□	□	◨	□	□	□	◨	X	□	□	□	□	□	□	□	X	■	4/16	25	6.8
D14S258	■	—	■	□	—	□	■	◨	X	—	—	□	ND	□	■	□	□	—	5/11	45	2.2
D14S277	—	X	◨	—	—	□	□	X	□	—	□	□	—	□	X	□	X	—	1/8	13	1.8
D14S77	□	□	■	◨	■	□	□	□	X	□	□	□	□	□	■	□	ND	■	5/16	31	1.7
D14S71	X	X	□	□	□	—	—	X	□	—	□	□	□	□	ND	□	X	—	0/9	0	1.7
D14S284	■	□	■	—	—	■	◨	◨	—	□	—	—	—	□	◨	—	□	—	6/10	60	0.5
D14S76	—	□	—	—	◨	□	—	◨	—	□	—	□	□	□	◨	□	□	—	3/11	27	2.7
D14S74	—	□	◨	□	□	□	—	◨	X	□	—	—	—	□	—	□	—	■	3/10	30	9.9
D14S68	■	ND	□	□	■	■	□	□	□	—	□	□	□	—	—	□	ND	■	4/13	31	12.5
D14S81	■	ND	□	—	□	□	■	ND	□	ND	□	□	ND	□	□	□	□	■	3/13	23	9.3
D14S65	■	□	□	□	□	□	□	◨	□	—	□	□	□	□	□	—	□	ND	2/15	13	8.2
D14S78	■	□	□	—	□	□	□	□	□	□	□	□	□	□	ND	□	—	■	2/15	13	12.3
D14S1007	—	□	■	—	□	—	□	X	□	—	—	□	□	□	□	□	—	■	2/11	18	0.0

[a]Tumours 1–14 are epithelial, 15 and 16 mixed, 17 fibromatous and 18 could not be determined; [b]microsatellite markers are placed in the predicted order from cen-qter; [c,d,e,f,g,h]cases 9, 21, 23, 11, 20 and 6 in Björkqvist et al (1998) respectively; [i,j]cases 4 and 14 in Björkqvist et al (1997) respectively; [k]genetic distance between markers in cM; □ = Retained heterozygosity; ■ = LOH; ◨ = AI; — = Uninformative; ND = Not determined; X = no data

was at least 60%. Normal DNA from each patient was isolated from peripheral blood samples according to standard methods.

Microsatellite marker analysis

A total of 23 dinucleotide microsatellite markers were used in the analysis. The samples were first screened using 15 microsatellite markers: D14S72, D14S283, D14S80, D14S1060, D14S75, D14S269, D14S66, D14S63, D14S77, D14S74, D14S68, D14S81, D14S65, D14S78 and D14S1007. These spanned the whole q-arm with an average genetic distance of 9 cM (range 5.4–13.1 cM) between the markers. To further refine the locations with the highest number of tumours with loss of heterozygosity (LOH) or allelic imbalance (AI), eight additional microsatellite markers (D14S1003, D14S972, D14S64, D14S258, D14S277, D14S71, D14S284 and D14S76) were analysed. The relative order of markers and genetic distances between them were obtained from the Généthon genetic linkage map (http: //www.genethon.fr) (Dib et al, 1996). Cytogenetic locations of the markers were based on the Genome Database (The Johns Hopkins University BioInformatics Web Server) at http: //www.bis.med.jhmi.edu/.

The PCR reactions were carried out in an MJ Research PTC-200 Peltier Thermal Cycler. The reaction was done in a 20 μl volume containing 50 ng DNA, 10 mM Tris–HCl (pH 8.3), 50 mM potassium chloride, 1.5 mM magnesium chloride, 0.001% gelatin (w/v), 1% dimethyl sulphoxide (w/v), 0.5 μM of each primer, 200 μM each of dATP, dCTP, dGTP and dTTP, and 0.6 unit of *AmpliTaq* DNA Polymerase (Perkin-Elmer, Branchburg, NJ, USA). The following amplification programme was used: an initial denaturation at 94°C for 4 min followed by 28 cycles of 30 s at 94°C, 1 min 15 s at 55°C, and 15 s at 72°C and then by a 6-min extension at 72°C. The annealing temperature for different microsatellite markers varied between 55°C and 65°C. For some of the samples the extension time was increased from 15 to 45 s. The amplification product was diluted 1:1 in a 95% formamide gel-loading buffer, denatured at 93°C for 3 min, after which 5 μl was loaded on a 6% denaturing polyacrylamide sequencing gel (National Diagnostics Inc., Atlanta, GA, USA). After the gel was fixed in 10% citric acid, the PCR products were visualized by silver staining. The gels were scanned using a UMAX Power Look 2000 (UMAX Data Systems Inc., Hsinchu, Taiwan).

The analysis was done visually and independently by two observers by comparing the intensities between the alleles in tumour DNA to those in normal DNA. Tumours homozygous for a specific locus were defined as uninformative. LOH was observed in heterozygous samples when one of the alleles in the tumour

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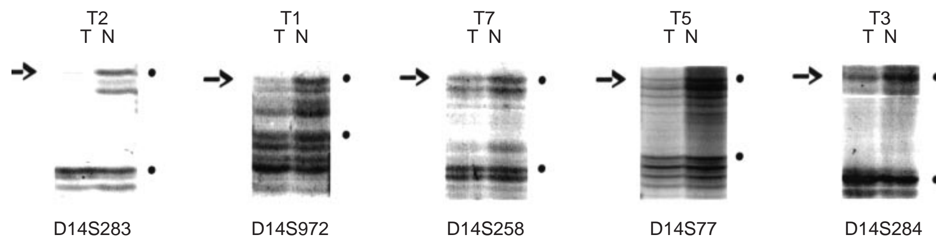

Figure 1 Representative results of microsatellite markers D14S283, D14S972, D14S258, D14S77, and D14S284. Tumour numbers are shown at top. Locations of alleles are indicated with a dot. Arrowheads, LOH. Faint signals in the tumour lanes may result from normal cell contamination or intratumour heterogeneity. T, primary tumour DNA; N, normal DNA from peripheral blood

DNA was reduced in intensity relative to the remaining allele and the alleles in the normal DNA. Other intensity differences were interpreted merely as AIs. All reactions displaying LOH or AI were repeated. If the allele pattern was interpreted as LOH in one experiment and as AI in the other, it was considered to be an AI. However, the reason some of the observed AIs were not determined as LOHs could be that tumour DNA was amplified more efficiently than normal DNA. Moreover, previous CGH data of, for instance, tumour no. 4 confirm the presence of loss of DNA sequences at 14q, although allelotyping was interpreted as AI. Therefore we refer to deletion for both LOH and AI.

RESULTS

Ten of 18 (56%) mesothelioma tumours displayed LOH or allelic imbalance with at least one microsatellite marker at 14q (Table 1). Eight of these were epithelial tumours, one a mixed tumour and one a tumour with undetermined histology. Partial deletions of varying lengths, detected as LOH or AI of some loci and as retention of heterozygosity of others, were more common than loss of the entire q-arm. Deletions of all informative markers, revealing deletion of the whole long arm which indicates monosomy 14, were found in only one tumour (no. 18). In four tumours deletions of several adjacent markers were observed, whereas the remaining five tumours displayed deletions of two adjacent markers or only at one marker. In some of these the marker that showed deletion was, however, flanked by an uninformative marker or a marker, whose status could not be determined.

Based on the results of the first 15 microsatellite markers analysed, the highest number of tumours carrying a deletion was found for markers D14S283 (five tumours) and D14S77 (five tumours) (Table 1). The density of mapping was increased around these markers by analysing additional eight markers. Based on the results from all 23 markers, 14q11.1–q12 and 14q23–q24 were found to be the most involved regions in deletions. Representative results of some markers are presented in Figure 1. The highest number of tumours displaying deletions at 14q11.1–q12 was detected with markers D14S283 (five tumours; frequency: 31%), D14S972 (seven tumours; frequency: 50%) and D14S64 (five tumours; frequency: 45%). Four tumours had deletions with all three markers. The highest number of tumours displaying deletions at 14q23–q24 was observed with markers D14S258 (five tumours; frequency: 45%), D14S77 (five tumours; frequency: 31%) and D14S284 (six tumours; frequency: 60%). Only one tumour (frequency: 13%) displayed a deletion with marker D14S277 (between D14S258 and D14S77) and no deletions were detected with marker D14S71 (between D14S77 and D14S284; Table 1).

Eight tumours displayed deletions at both 14q11.1–q12 and 14q23–q24 with at least one marker. Tumour no. 2, which displayed deletions only in the proximal part of 14q, was uninformative at D14S258 but contained both alleles at loci detected with markers D14S77 and D14S284. Tumour no. 7, which displayed deletion at 14q23–q24 but not at 14q11.1–q12, was uninformative at D14S64 but displayed retention of heterozygosity at both D14S283 and D14S972 (Table 1).

Patients, in whose tumour DNA we detected deletions at 14q, had a shorter median survival (12 months) than those without deletions at 14q in their tumours (20 months). Five of the eight patients with no detectable deletion at 14q in their tumours survived more than 1.5 years compared to only two of the ten with a deletion at 14q in their tumours. However, the difference in survival between these two groups, analysed using log-rank and Wilcoxon tests, was not statistically significant. Nine out of 11 patients with stage 2 or 3 disease had deletions at 14q in their tumours, as compared to only one of the seven patients with stage 4 disease (P = 0.013, Fisher's exact test, two-tailed). In nine of the 13 tumours from patientswith a clear history of asbestos exposure, deletions at 14q were detected, as compared to only one of the five patients with no known exposure to asbestos (not statistically significant). The small number of samples analysed does not allow decisive conclusions to be drawn from the statistical analyses.

DISCUSSION

Eighteen primary malignant mesothelioma tumours were analysed using 23 microsatellite markers spanning the whole long arm of chromosome 14 in order to characterize the frequency and pattern of deletions at 14q. Fifty-six per cent of the tumours displayed a deletion. The percentage is much higher than that (24%) observed in primary tumours by CGH (Kivipensas et al, 1996; Björkqvist et al, 1997, 1998). However, this is not unexpected due to the small partial deletions observed by allelotyping in some of the tumours and because of the resolution limitation of the CGH method (Kallioniemi et al, 1994). Recent allelotyping analyses at 1p and 6q on primary mesothelioma tumours have revealed frequencies of 61% (11/18) and 38% (6/16) for allelic loss respectively (Lee et al, 1996; Bell et al, 1997).

In eight of the tumours (nos 1, 2, 3, 4, 10, 13, 14 and 15) we were able to compare the allelotyping results with previous CGH data of 14q (Björkqvist et al, 1997, 1998). Loss of genetic material at 14q was found by CGH in tumour nos 1, 3, 4 and 15. In all of these we found deletions for several markers. Tumour nos 10, 13 and 14, which did not show any loss of DNA sequences at 14q by CGH, did not display any deletion by allelotyping either. However, tumour no. 2, whose CGH profile of 14q did not exceed the

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threshold for loss of genetic material, displayed deletions at the proximal part of 14q by allelotyping.

In earlier cytogenetic analyses deletions at chromosome 14 have not been among the most frequently observed chromosomal aberrations in mesothelioma. However, monosomy 14 has been detected (Tiainen et al, 1989; Taguchi et al, 1993). The deletion pattern that we observed in the present allelotyping analysis was very complex. Only one of the tumours displayed deletion of all informative markers revealing a loss of the whole chromosome. Partial deletions of varying lengths were more common, suggesting a complex mechanism, which perhaps involves both chromosomal deletions and rearrangements, for inactivation of tumour suppressor genes. Such complexity at the chromosomal level was evident in a recent mesothelioma tumour analysed in our diagnostic laboratory (data not shown). By G-banding a chaotic karyotype was observed with a hypodiploid modal chromosome number and seven unidentified marker chromosomes. Both copies of chromosome 14 were missing. Chromosome painting analysis using a chromosome 14-specific library probe revealed one of the smaller markers to be composed of material from chromosome 14 [del(14q)] and part of chromosome 14 to be translocated to two unidentified marker chromosomes. As a result there was a net loss of genetic material from chromosome 14. This loss was further mapped by CGH to 14qcen–q21. Taken together these results manifest the complexity and suggest possible impact of deletions at 14q in mesothelioma. Thus, it would appear that profound chromosomal instability accumulates aberrant cells, of which some exhibit genetic changes advantageous in tumorigenesis.

Although the deletion pattern in the present study was complex, and most probably induced by chromosomal aberrations, 14q11.1–q12 and 14q23–q24 were found to be the most involved regions in deletions. 14q11.1–q12 overlaps those regions that have been found deleted in ovarian carcinoma and bladder cancer (14q12–q13 and 14q12 respectively). However, the critical markers in these studies, in contrast to ours, were all located distal to D14S64 (Chang et al, 1995; Bandera et al, 1997). In lung carcinoma the highest frequency of LOH was found with marker D14S261 at 14q11.1–q11.2 (centromeric to D14S72) (Abujiang et al, 1998). We observed deletions at 14q23–q24 by microsatellite markers D14S258, D14S77 and D14S284 in five, five and six tumours respectively. Interestingly, Schwerdtle et al have found that marker D14S258 also exhibits frequent allelic loss in renal oncocytomas, implicating a locus for a tumour suppressor gene possibly involved in different tumours (Schwerdtle et al, 1997). Furthermore, 14q24–q32 has been found to be the smallest overlapping segment of deletions in both nonpapillary renal cell carcinoma and meningiomas (Simon et al, 1995; Herbers et al, 1997).

No tumour suppressor genes have so far been assigned to 14q. However, the *APEX* gene located at 14q11.2–q12 falls into one of the regions that we found to be most involved in deletions. This gene encodes a DNA repair enzyme called APEX nuclease or apurinic endonuclease (APE), which initiates the repair of abasic sites caused by mutagens such as free oxygen radicals (Demple et al, 1991; Harrison et al, 1992). Such oxygen radicals, with DNA-damaging properties, are known to be released by macrophages exposed to asbestos (Hansen and Mossman, 1987; Goodglick and Kane, 1990). Inactivation of enzymes involved in DNA repair, including *APEX*, would prevent their functions and leave the damaged DNA uncorrected, thereby causing mutations. The expression level of APEX in mesothelioma has, as far as we know, not been studied. However, increased production of APEX has been detected in rat pleural mesothelial cells, but not in Met5A cells (an immortalized human mesothelial cell line), as a response to asbestos exposure (Fung et al, 1998).

In conclusion, the present microsatellite marker analysis suggests that genomic losses at 14q are more frequent in mesothelioma than previously recognized by other methods. Partial deletions were more common than loss of the whole arm and sometimes included only a small chromosomal segment. Although the deletion pattern seems to be complex, deletion at both 14q11.1–q12 and 14q23–q24 was observed in eight of the ten tumours exhibiting losses. The two remaining tumours had deletion either at 14q11.1–q12 or 14q23–q24.

These chromosomal regions provide a good basis for further fine-mapping and can help in pinpointing the locations of genes, which may be important in the tumorigenesis of malignant mesothelioma.

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