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Advances in Brief

Loss of Heterozygosity Frequently Affects Chromosome 17q in Non-Small Cell Lung Cancer[1]

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Abstract

Although the short arm of chromosome 17, which contains the *p53* gene, is frequently affected by loss of heterozygosity (LOH) in lung cancer, little is known about similar changes on the long arm. We found that LOH affected one or more of six loci along chromosome 17 in 59% of 102 informative non-small cell lung cancer (NSCLC) cases. Specifically, the frequency of LOH at 17q was 42%, approaching that at 17p (54%), and two distinct 17q regions were implicated. LOH at *D17S4* on 17q was more frequent in adenocarcinomas than in squamous cell carcinomas, whereas squamous cell carcinomas had more LOH at 17p than at 17q, findings that indicate molecular genetic heterogeneity between the major NSCLC subtypes. In addition, LOH at 17q correlated with higher T stages and a significantly worse prognosis. In comparison, 25% of cases had mutations of *p53* exons 5–8 but these were not associated with stage or survival. The data suggest that independent of *p53*, there are important tumor suppressor gene(s) on 17q that may influence NSCLC pathogenesis, progression, and survival.

Introduction

In Western countries, lung cancer is the leading cause of cancer deaths in males, with a similar pattern developing in females. Oncogenic activation and the inactivation of tumor suppressor genes by mutation and allelic deletion are implicated in the pathogenesis of cancers including NSCLC.[4]

Chromosome 17 appears to be an important target for such molecular abnormalities. At region p13 is the *p53* gene, a tumor suppressor gene that is often disrupted in lung cancer (1). These changes include frequent LOH at 17p13 (2, 3) and specific *p53* mutations in 23–52% of resected NSCLC tumors (4–9) and 74% of cell lines (10).

In addition, there is functional evidence of at least one other chromosome 17 tumor suppressor gene from chromosomal transfer studies (11). Candidate genes on 17q include *NF1*, *NM23-H1 (NME1)*, and *NM23-H2 (NME2)* antimetastatic genes, the prohibitin gene, and the familial breast/ovarian (*BRCA1*) locus. LOH affecting multiple regions of 17q has been reported familial and sporadic breast (12–19), ovarian (18–23), esophageal (24), and head and neck (25), and certain cancers with a familial link (26).

In comparison, lung cancer has been much less studied, although a single 17q marker was affected by LOH in 21% of 39 informative NSCLCs in Japanese patients (27). Here, we report that LOH occurs frequently along chromosome 17q in resected NSCLC, targeting specific regions and can be independent of LOH at 17p and *p53* mutations.

Materials and Methods

DNA was obtained from 108 cases of postsurgically staged, resected NSCLC, and normal lung tissue from patients at The Prince Charles Hospital (Brisbane, Australia) with fully informed consent as described previously (28). Southern blot analysis of RFLPs was used to detect LOH at six loci along chromosome 17 (Table 1), as reported previously (28). SSCP was used to screen exons 5–8 of the *p53* gene (29). Statistical analysis was performed examining for differences between groups with χ^2 or Fisher's test, differences between means with *t* tests, and Kaplan-Meier survival curves with log-rank tests. Median follow-up duration was 23 months from time of analysis.

Results

Of the 108 cases analysed, 102 were heterozygous (informative) at one or more chromosome 17 loci. LOH involving either or both chromosomal arms affected 60 of the 102 (59%) informative NSCLC cases, with 54% showing LOH at 17p (*D17S5*) and 42% having LOH at 17q (Table 1). The frequency of 17q LOH from centromere to telomere was: *NF1*, 20%; *NM23-H1*, 27%; *D17S40*, 34%; *D17S21*, 42%; and *D17S4*, 29% (Fig. 1). LOH was independent of preoperative adjuvant treatment because it was not detected in the patients who received either radiotherapy (n = 4) or chemotherapy (n = 1).

Two patterns of LOH were identified. In 11 cases, LOH was found at all informative markers, indicating that the whole of chromosome 17 was deleted. The other pattern was of LOH apparently restricted to one chromosomal arm. For instance, there were 16 cases with LOH at 17p but retained heterozygosity at 17q (another 2 cases had 17p LOH but were uninformative at all 17q markers). In contrast, LOH was localized to the long arm in 17 cases (Table 2), with a distinct region of loss implicated between, but excluding, *D17S40* and *D17S21*. In addition, another 17q region was suggested by case 115 to lie more proximally, centered around *NM23-H1* and flanked by *NF1* and *D17S40*.

p53 mutations at exons 5–8 were detected by mobility shift of single-strand conformational polymorphism bands in 27 of 108 (25%) NSCLC cases, all of which were somatically acquired (data not shown). There were 9, 5, 7, and 6 mutations detected at exons 5–8, respectively. The clinico-pathological features are shown in Table 3, and one mutation (case 53) may have conceivably been due to preoperative adjuvant chemotherapy. As expected, *p53* mutations correlated with LOH at 17p, with LOH being found in 14 of 17 cases compared with 23 of 51 cases without mutations (P = 0.008; χ^2), implicating *p53* as the responsible tumor suppressor gene on 17p. However, as *D17S5* is actually distal to *p53*, it should be noted that LOH here is also consistent with the presence of a more distal 17p tumor suppressor gene, as has been suggested in breast (12, 30) and ovarian cancers (31).

Comparing the two major histological subtypes. LOH at *D17S4* on 17q was more common in adenocarcinomas than in SCCs [13 (38%)

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[4] The abbreviations used are: NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; LOH, loss of heterozygosity.

Table 1 *Frequency of LOH on chromosome 17 in NSCLC*

Locus	Restriction enzyme	Allele size (kb)	Probe	Location	No. of NSCLC cases with LOH/informative cases (%)		
					All subtypes	Squamous cell	Adenocarcinomas
D17S5	*Taq*I	VNTR[a]	pYNZ22	17p13.3	37/68 (54)	17/28 (61)	12/31 (39)[b]
NF1	*Taq*I	2.8/2.6	AE25	17q11.2	9/44 (20)	1/13 (8)	7/22 (32)[b]
NM23-H1	*Bgl*II	7.6/2.3	pNM23-H1	17q21.3–22	13/49 (27)	3/15 (20)	6/26 (23)[b]
D17S40	*Msp*I/*Hpa*II	15.0/7.0	pEW101	17q12–24	12/35 (34)	3/10 (30)	4/17 (24)[b]
D17S21	*Msp*I/*Hpa*II	4.3/3.9	pC63	17q23-qter	16/38 (42)	6/15 (40)	6/17 (36)[b]
D17S4	*Taq*I	VNTR	pTHH59	17q23–25.3	20/69 (29)	3/24 (12)	13/34 (38)[c]
				Overall 17q	42/99 (42)	11/38 (29)	20/44 (45)[b]

[a] VNTR, variable number of tandem repeats.
[b] $P > 0.05$ (Fisher's or χ^2 test) for the difference in LOH between squamous cell carcinomas and adenocarcinomas.
[c] $P < 0.05$ (Fisher's or χ^2 test) for the difference in LOH between squamous cell carcinomas and adenocarcinomas.

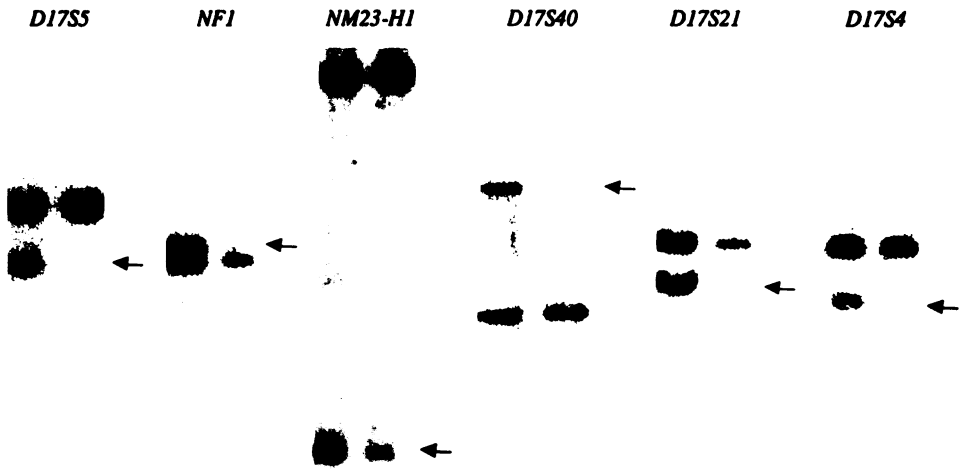

Fig. 1. Examples of LOH at chromosome 17 markers. Examples of LOH (*arrows*) at chromosome 17 loci (in each case, normal lung and tumor DNA is on the *left* and *right*, respectively).

of 34 *versus* 3 (12%) of 24] ($P < 0.05$; Fisher's test). The higher frequency of LOH at *D17S4* in adenocarcinomas could be explained if there were a third tumor suppressor region specifically for adenocarcinomas distally on 17q because D17S4 lies outside the common region of loss between *D17S40* and *D17S21*. However, because another possibility is that adenocarcinomas have more extensive 17q LOH, detailed mapping is necessary to confirm whether such a region exists in adenocarcinomas.

In contrast, SCCs had more frequent LOH at 17p than at 17q [17 (61%) of 28 *versus* 11 (29%) of 38] ($P = 0.01$, χ^2 test). Likewise, as reported previously (5), *p53* mutations were also significantly more common in SCCs than in adenocarcinomas [17 (40%) of 43 *versus* 5 (11%) of 46] ($P = 0.002$, χ^2 test) and in males compared to females [23 (30%) of 76 *versus* 4 (12%) of 32] ($P = 0.052$, χ^2). Although there were more males than females (81 *versus* 19%) in the SCC subtype, confounding was unlikely because there were still more mutations in SCCs than in adenocarcinomas in the male subset; 15 of 35 *versus* 4 of 27 ($P = 0.02$, χ^2 test). Other evidence of molecular heterogeneity between NSCLC histological subtypes comes from the finding that the adenosquamous subtype had the most frequent LOH, 6 (86%) of 7 at 17p and 7 (70%) of 10 at 17q (Table 3).

LOH at chromosome 17 appeared to be involved in tumor progression. Supporting data are the finding that 50 (68%) of 74 NSCLC cases with LOH at one or more chromosome 17 loci had advanced T_{2-4} stages compared to 10 (36%) of 28 cases without LOH ($P < 0.05$, χ^2). In addition, LOH along chromosome 17 correlated significantly with adverse survival ($P < 0.05$; data not shown). Furthermore, the SCC subset with LOH along chromosome 17 also had more nodal involvement than those without LOH [12 (54%) of 22 *versus* 4 (22%) of 18] ($P < 0.05$, χ^2).

Because this data indicated an important gene(s) on chromosome 17, the clinico-pathological significance of LOH on each chromosomal arm and *p53* mutations was examined. Although LOH at 17p correlated significantly with higher T_{2-4} stages, neither it nor *p53* mutations were associated with tumors-nodes-metastasis stage (Table 3) or survival ($P > 0.05$; data not shown). In contrast, LOH at 17q not only correlated with higher T stages (Table 3), but also with a worse survival (Fig. 2). In addition, distal 17q LOH in the adenocarcinoma subtype also correlated with a poorer survival ($P = 0.005$ and $P = 0.011$ for the *D17S21* and *D17S4* markers, respectively).

As expected, there were more smokers in group with LOH along chromosome 17 compared to those without LOH [58 (97%) of 60 *versus* 35 (83%) of 42] ($P < 0.05$, χ^2 test). LOH cases had also smoked more than those without LOH, 45.5 *versus* 31.8 pack-years ($P = 0.019$, t test). Otherwise, we found no difference in mean age, sex, or smoking history between cases with and without LOH on each individual chromosomal arm (Table 3).

Discussion

In NSCLC, we have shown LOH involving 17q to be frequent (42%), just slightly less than at 17p (54%). There were two patterns of LOH at chromosome 17 in NSCLC; one apparently involving all of chromosome 17 and the other was LOH localized on a particular chromosomal arm. LOH at 17q was similar to ovarian cancer where loss may affect the whole chromosome 17 (31) or various 17q regions

Table 2 *LOH pattern along chromosome 17 of 42 NSCLCs (18 tumors with LOH at 17p but not 17q are not included)*

Case no.	Age (yr)	Sex[a]	Subtype[b]	pTNM stage	*p53* mutation[c]	*D17S5*	*NF1*	*NM23*	*D17S40*	*D17S21*	*D17S4*
39	64	M	SCC	I	+	•[d]	ø	•	ø	ø	•
44	38	M	SCC	I	–	•	øø	ø	•	ø	
55	75	M	SCC	I	–	ø	•	ø	ø	ø	ø
61	57	F	SCC	I	–	•	ø	ø	ø	•	ø
32	45	M	SCC	II	+	•	ø	ø	•	•	○
50	58	M	SCC	II	–	•	ø	ø	ø	•	ø
112	39	F	SCC	II[e]	–	○	○	○	•	ø	ø
24	59	M	SCC	IIIa[e]	–	ø	○	•	ø	ø	○
41	71	M	SCC	IIIa[e]	+	•	ø	○	ø	•	•
97	65	M	SCC	IIIa	–	ø	ø	•	•	ø	•
104	56	F	SCC	IIIb	+	ø	ø	ø		•	○
75	54	M	BAC	I[e]	–	•	ø	○	ø	•	•
119	54	M	BAC	I	–	ø	ø	ø	•	ø	•
13	73	M	AC	I[e]	+	○	ø	○	ø	•	ø
52	55	M	AC	I	–	ø	ø	ø	ø	ø	•
66	63	M	AC	I[e]	–	ø	ø	○	ø	ø	•
73	50	M	AC	I[e]	–	○	○	ø	ø	ø	•
103	59	M	AC	I	–	•	•	ø		ø	•
117	71	M	AC	I	–	ø	•	ø	ø	•	•
6	42	F	AC	I[e]	–	•	ø	○	○	•	•
68	69	F	AC	I	–	ø	•	•	•	ø	•
76	57	F	AC	I[e]	–	ø		•	○	•	○
82	68	F	AC	I	–		•	•			○
89	48	F	AC	I[e]	+	○	ø	○	•	ø	○
81	57	M	AC	II	+	•	ø	•			ø
110	50	M	AC	II	+	•	•	•			•
14	71	M	AC	IIIa	–	•	•	ø	ø	ø	•
15	57	M	AC	IIIa	–	ø	•	ø	ø	ø	•
124	51	M	AC	IIIa[e]	–	○	ø	○	•	○	○
27	50	F	AC	IIIa[e]	–	•	○	○	○	•	•
86	54	F	AC	IIIa	–	ø	ø	•	ø	ø	ø
84	63	M	AS	I	–	•		ø	ø	ø	•
100	71	M	AS	I[e]	–	•	○	•	ø	•	ø
111	74	M	AS	I[e]	–	•	○	•	ø	ø	ø
123	61	M	AS	I[e]	–	○	○	ø	•	•	○
8	64	M	AS	II[e]	+	•	○	○	•	○	○
115	47	M	AS	II[e]	–	ø	○	•	○	•	ø
109	65	M	AS	IIIa	+	•	ø	ø	•	ø	•
45	62	M	LCC	I	+			ø	•	ø	
12	70	M	LCC	IIIa	–	•	•	ø	•	•	•
120	62	F	LCC	IIIa	–	ø	ø	•	ø	○	ø
77	63	F	A/Carc	I	+	ø	ø	ø		ø	•

[a] M, male; F, female.
[b] LCC, large cell carcinoma; AC, adenocarcinoma; BAC, adenocarcinoma, bronchioloalveolar cell subtype; AS, adenosquamous carcinoma; A/Carc, atypical carcinoid.
[c] –, normal *p53*; +, mutant *p53*.
[d] ○, heterozygous; •, LOH; ø, homozygous; blank, no information.
[e] Refers to the cases (n = 17) with LOH on 17q which was not contiguous with LOH on 17p.

either involving (23) or distinct from the *BRCA1* locus (18, 20, 22). Similarly, there is evidence of localized 17q loss, distal to the *BRCA1* locus in breast cancer (12, 14–18).

The distal 17q region of loss mapped between *D17S40* and *D17S21*, the importance of this region also being highlighted by *D17S21* having the highest LOH on 17q (42%). This region is situated within a region of loss defined in breast cancer to be centered around *D17S40* and bordered by *D17S86* and *D17S21* (16), thus, suggesting that the putative tumor suppressor gene situated here is likely to be important for lung cancer too.

A second, more proximal region of loss may lie telomeric to the *BRCA1* and *NF1* loci, encompassing the putative antimetastatic *NM23-H1* gene, the expression levels of which correlated inversely with metastases in experimental systems (32) and with some breast cancers (33). On the other hand, the situation may differ in lung cancer because NM23-H1 protein/NDP kinase levels were not of prognostic value in adenocarcinomas (34). Secondly, high *NM23-H1* mRNA levels were associated with poor differentiation and advanced tumor stage in SCCs (35). Nevertheless, apart from aberrant expression, *NM23-H1* allelic loss may influence tumor progression as it does in colon cancer (36). Such deletions have also been reported in lung cancer (37), and we show that NSCLC with LOH at *NM23-H1* had higher T_{2-4} stages than did NSCLCs without LOH [13 of 13 *versus* 20 of 36] (P = 0.002, Fisher's test). However, as LOH was not associated with nodal involvement or survival, the role of *NM23-H1* should be considered cautiously. Refined mapping with mutation analysis should help determine whether *NM23-H1* is important or merely deleted coincidentally.

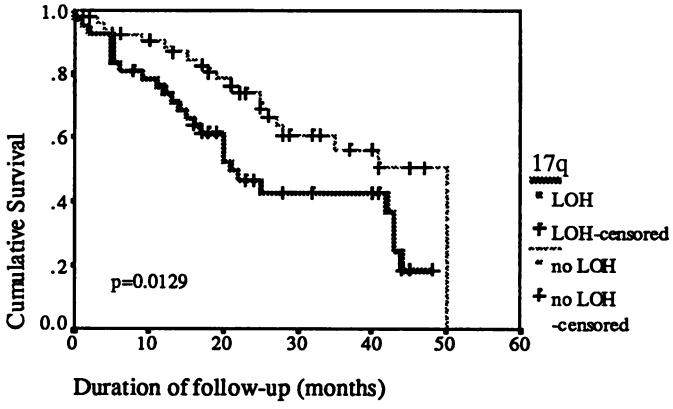

Fig. 2. Kaplan-Meier survival curves. The survival of NSCLC with LOH at 17q (n = 42) was significantly worse (P = 0.013, log-rank test) than in those without LOH (n = 57).

Table 3 *Clinical features of NSCLC cases with LOH on 17p, 17q, and p53 mutations*

	Cases with 17p LOH	Informative cases without LOH	*P* value[a,b]	Cases with 17q LOH	Informative cases without LOH	*P* value[a,b]	*p53* mutations	Normal *p53*	*P* value[a,b]
Mean age (yr)	60.1	61.3	ns	59.1	62.3	ns	62	60.7	ns
95% confidence interval	3.6	3.9		2.9	3.0		3.8	2.4	
Sex									
Male	30	19		30	38		23	53	
Female	7	12	0.07	12	19	0.614	4	28	0.052
Smoking history									
Smokers	36	27		40	50		26	73	
Nonsmokers	1	4	0.108	2	7	0.198	1	8	0.315
Mean pack-years	45.9	34.1	ns	41.8	37.8	ns	49.3	39.7	ns
95% confidence interval	10.2	9.1		8.6	7.8		11.9	6.7	
Histology									
SCC	17	11		11	27		17	26	
Adenocarcinoma	12	19	0.091	20	24	0.124	5	41	0.002
Carcinoid/malignant atypical carcinoid	1	0		1	3		2	2	
Adenosquamous	6	1		7	3		2	9	
Large cell carcinoma	1	0		3	0		1	3	
T stage									
1	6	15		5	23		7	23	
2, 3, 4	31	16	0.004	37	34	0.002	20	58	0.804
N stage									
0	18	21		27	35		14	55	
1, 2	19	10	0.113	15	22	0.77	13	26	0.133
TNM[c] stage									
I	16	19		23	30		12	49	
II, III	21	12	0.141	19	27	0.834	15	32	0.145

[a] *P* value, χ^2 test.
[b] ns, $P > 0.05$, *t* test.
[c] TNM, tumors-nodes-metastasis.

In contrast to 17q, we like others (5, 7, 10), found that *p53* mutations did not correlate with survival. This contrasts with recent reports of the prognostic significance of *p53* mutations in resected NSCLC (6, 9). These latter studies had relatively more *p53* mutations (43 and 49%), which could be due to differences in mutation frequency, sample size, study populations, methodology, or chance. For instance, our result is probably underestimated because only about 87% of *p53* mutations occur within exons 5–8 (38), and the sensitivity of SSCP analysis by using a single set of conditions is only about 80% (39).

In conclusion, this study shows for the first time that apart from *p53* mutations and 17p LOH, distinct regions of 17q may be associated with the pathogenesis, progression, and outcome in NSCLC. In addition, LOH at 17q was associated with other molecular aberrations that we have reported in NSCLC (28, 40), including LOH at 5q21 but not 11p ($P = 0.032$ and $P = 0.337$, respectively; data not shown). Thus, detailed analysis of 17q is warranted and likely to contribute to the knowledge of the molecular pathogenesis of lung cancer.

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