

## Laboratory Investigation

# Loss of Heterozygosity at 1p, 7q, 17p, and 22q in Meningiomas

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**Objective** : Allelic losses or loss of heterozygosity (LOH) at many chromosomal loci have been found in the cells of meningiomas. The objective of this study was to evaluate LOH at several loci of different chromosomes (1p32, 17p13, 7q21, 7q31, and 22q13) in different grades of meningiomas.

**Methods** : Forty surgical specimens were obtained and classified as benign, atypical, and anaplastic meningiomas. After DNA extraction, ten polymorphic microsatellite markers were used to detect LOH. Medical and surgical records, as well as pathologic findings, were reviewed retrospectively.

**Results** : LOH at 1p32 was detected in 24%, 60%, and 60% in benign, atypical, and anaplastic meningiomas, respectively. Whereas LOH at 7q21 was found in only one atypical meningioma. LOH at 7q31 was found in one benign meningioma and one atypical meningioma. LOH at 17p13 was detected in 4%, 40%, and 80% in benign, atypical, and anaplastic meningiomas, respectively. LOH at 22q13 was seen in 48%, 60%, and 60% in benign, atypical, and anaplastic meningiomas, respectively. LOH results at 1p32 and 17p13 showed statistically significant differences between benign and non-benign meningiomas.

**Conclusion** : LOH at 1p32 and 17p13 showed a strong correlation with tumor progression. On the other hand, LOH at 7q21 and 7q31 may not contribute to the development of the meningiomas.

**KEY WORDS** : Chromosome · Loss of heterozygosity · Meningiomas.

## INTRODUCTION

Since the introduction of Giemsa staining to distinguish between open and compact chromosome regions in the early 1970's, many cytogenetic approaches have been developed during the last three decades<sup>25</sup>. Loss of heterozygosity (LOH) analyses, such as fluorescence *in situ* hybridization (FISH) and comparative genomic hybridization, have been used for localizing tumor suppressor genes in different grades of meningiomas<sup>12</sup>. LOH leading to inhibition of tumor suppressor genes has been shown to be one of the mechanisms of tumor development<sup>4,34</sup>.

The allelic loss or LOH of various chromosomal regions in meningiomas, including chromosomes 1p, 3q, 6q, 10q, 17p, 18p, 18q, and 22q, has been reported<sup>12</sup>. Among them, the loss of allelic regions in the long arm of chromosome 22 was the most prominent, found in 40-70% of meningiomas<sup>1,30</sup>.

HGF/cMET signaling has been shown to play an important role in oncogenesis in many human cancers, including human papillary renal cancer, ovarian cancer, childhood hepatocellular carcinoma, and gastric cancer<sup>19</sup>. The human Met and HGF receptor genes are located at 7q21 and 7q31<sup>15</sup>. However, there have only been a few reports relating the signaling of these genes to the formation and progression of meningiomas<sup>2,17</sup>. The objectives of this study were to evaluate LOH in several chromosomes in which LOH is seen frequently 17p13 related with mutation of p53 tumor suppressor gene, 7q21, 7q31, and 22q13 in different grades of meningiomas and to correlate the findings with various clinicopathological factors<sup>9,29</sup>.

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## MATERIALS AND METHODS

This study was approved by the Institutional Research Board (number : 10-022). Patients who had undergone total resection of a meningioma (Simpson grade I or II) between January 2000 and December 2004 were selected for the study. The authors could obtain tumor specimen and normal tissue of meninges during operations. Forty paraffin-embedded surgical specimens from these patients were obtained. After pathological interpretation of hematoxylin and eosin (H&E) stained slides, all tumors were classified as benign, atypical, or anaplastic meningiomas according to World Health Organization (WHO) classification<sup>11,16</sup>. Medical and surgical records, as well as pathologic findings, were reviewed retrospectively.

### DNA extraction

All specimens were fixed in 10% formaldehyde and paraffin-embedded slices were obtained. Forty paraffin-embedded tumors were examined. Serial sections of 5 µm thickness containing tumor and non-tumor portions (normal tissue of meninges) were performed on each surgical specimen. After staining with H&E, the sections were microdissected to obtain an extract of deoxyribonucleic acid (DNA). Microdissected tissues were then deparaffinized in xylene for 1-2 hours. To extract DNA from specimens, the selected tissues were placed in 1.5 mL of digestion buffer (100 mM Tris-HCL, pH 8.0; 1% Tween 20, and 0.1 mg/mL proteinase K) at 52°C for two days. After digestion, proteinase K was inactivated by incubation at 96°C for 10 min and the samples were centrifuged at 14,000 rpm for 30 min. The extracts (about 2 µL) were used as template DNA for polymerase chain reaction (PCR).

### LOH analysis and decision

A total of ten polymorphic microsatellite markers were used : D1S193 and D1S463 for chromosome 1p32, D7S660 and D7S492 for 7q21, D7S486 and D7S655 for 7q31, D17S796 and TP53 for 17p13, and D22S193 and D22S929 for 22q13. Commercially available primers for these markers were used (GIBCO Inc., Carlsbad, CA, USA). The genomic sequences of the primers are listed in Table 1. PCR was carried out in a thermal cycler (Perkin Elmer Cetus 9700, USA). PCR amplifications were performed using 2 µL of

**Table 1.** DNA sequences of primers used to detect LOH

Chromosome	Microsatellite markers		Genomic sequences
1p32	D1S193	Sense	5'-ACTCTAGCCTGGGTGACAAG-3'
		Anti-sense	5'-AGACTGGGAAAATGCAAATG-3'
	D1S463	Sense	5'-AGCTACAANAACCTCAGTACATGGAA-3'
		Anti-sense	5'-TTGCTTTGAACTAGGAACCC-3'
7q21	D7S660	Sense	5'-TAGGCCAACACTGGGG-3'
		Anti-sense	5'-AGCITGATAGTGGGAATCAITTT-3'
	D7S492	Sense	5'-ATCITGGATTTAGGGTTGGC-3'
		Anti-sense	5'-GGCTCTGCTCCATCTTCATA-3'
7q31	D7S486	Sense	5'-AAAGGCCAATGGTATATCCC-3'
		Anti-sense	5'-GCCCAGGTGATTGATAGTGC-3'
	D7S655	Sense	5'-CAAAATAGTGGGGTATTGGTAAA-3'
		Anti-sense	5'-CCAAGTTAATCTINTGTGAAAGTGTA-3'
17p13	TP53	Sense	5'-TGGATCCTCTTGCAGCAGCC-3'
		Anti-sense	5'-AACCCITGTCTTACCAGAA-3'
	D17S796	Sense	5'-CAATGGAACCAAATGTGGTC-3'
		Anti-sense	5'-AGTCCGATAATGCCAGGATG-3'
22q13	D22S193	Sense	5'-CTGTTGGCAGCTTTGTAGGGATTG-3'
		Anti-sense	5'-CATTATATGCAGAAATCAGCCCCAT
	D22S929	Sense	5'-CTGCAGATCACAAACTCCTTG-3'
		Anti-sense	5'-GCATTTATGGAGTATCCACAG-3'

LOH: loss of heterozygosity

DNA template, 0.25 µL of each primer, 1.25 mM NTP with 1/2dCTP, 1.5 mM MgCl<sub>2</sub>, 0.6 U Taq polymerase (0.07 µL), and 10× PCR buffer. Every cycle consisted of denaturation at 94°C for 30 seconds, annealing at 55-60°C for 30s, and extension at 72°C for 40s, followed by a final extension at 72°C for 10 min. Amplified PCR products (3 µL) were analyzed by 12% polyacrylamide gel electrophoresis. Using silver staining, the gain or loss of heterozygosity was assessed. The band intensity of two alleles in each case was determined visually. For a questionable allelic loss, the intensity was measured by densitometric analysis (Pharmacia, San Francisco, CA, USA).

LOH was assigned if there was a decrease in signal intensity greater than 50% in the tumor tissue allele compared to that of the corresponding non-tumor tissue allele. In this study, specimens scored as homozygote, not amplified, or not informative were excluded.

### Statistical analysis

Statistical analysis was performed using the SAS® system. Chi-square test and Fisher's exact test were used to analyze the relationship between LOH of each chromosome and age, tumor location, grade, and histological types. A *p*-value of less than 0.05 was considered statistically significant.

## RESULTS

Of 40 patients, there were 27 females and 13 males and the

mean age was 44 years with a range of 27-67. Twenty-five benign, 10 atypical, and 5 anaplastic meningiomas were identified. The locations of tumors were 22 in the convexity, 7 in the parasagittal area, 6 in the falx, 3 in the lateral ventricle, and 2 in the sphenoidal ridge. Histological subtypes of 25 benign meningiomas consisted of 17 meningotheliomatous, 4 transitional, 3 fibrous, and 1 psammomatous type. The clinical and experimental data were described in Table 2.

**Frequency of LOH according to the grades**

LOH at loci 1p32, 7q21, 7q31, 17p13 and 22q13 was detected in 15 (37.5%), 1 (2.5%), 2 (5%), 9 (22%), and 21 (52.5%) cases of meningiomas, respectively (Table 3). Identification of LOH at 1p32 was made in 24% of benign, 60% of atypical and 60% of anaplastic meningiomas, respectively. The authors classified grades as benign and non-benign (atypical or anaplastic) to assess statistical signifi-

**Table 2.** Clinical and experimental data of LOH in 40 cases of meningiomas

Case	Age/Sex	Location	Simpson grade	WHO grade	Histological characteristics	Interval to recurrence	LOH				
							1p32	7q21	7q31	17p13	22q13
1	43/F	P	I	I	m	-	LOH				LOH
2	42/F	C	I	I	t	-					
3	35/F	C	I	I	m	-					
4	52/M	Fx	I	I	m	-					LOH
5	37/F	C	I	I	f	-	LOH				LOH
6	29/F	C	I	I	m	-					
7	33/F	V	I	I	m	-					LOH
8	36/M	C	I	I	m	58 months	LOH				
9	42/F	P	II	I	t	-					LOH
10	45/M	C	I	I	p	-					
11	65/F	C	I	I	m	-	LOH		LOH		
12	38/F	Fx	I	I	m	-					LOH
13	47/F	C	I	I	f	-					
14	41/M	C	I	I	m	47 months				LOH	
15	47/F	S	I	I	m	-					LOH
16	36/F	Fx	I	I	t	-					LOH
17	47/M	C	I	I	m	-					
18	42/F	C	I	I	m	-					LOH
19	55/F	P	I	I	m	-	LOH				
20	53/M	V	I	I	f	-					
21	39/F	C	I	I	m	-					
22	27/F	C	I	I	m	-					LOH
23	48/M	Fx	I	I	t	-	LOH				LOH
24	50/M	C	I	I	m	-					
25	44/F	C	I	I	m	-					LOH
26	52/F	C	I	II		-	LOH				LOH
27	41/F	P	II	II		28 months	LOH			LOH	LOH
28	64/M	C	I	II		-			LOH		
29	57/M	P	I	II		-					
30	42/F	P	I	II		-	LOH				LOH
31	35/F	C	I	II		36 months	LOH			LOH	
32	41/F	C	I	II		-				LOH	LOH
33	37/F	Fx	I	II		30 months	LOH				
34	44/M	S	II	II		-		LOH			LOH
35	41/M	Fx	I	II		-	LOH			LOH	LOH
36	67/F	C	I	III		-				LOH	LOH
37	46/F	C	I	III		-	LOH				LOH
38	57/M	P	I	III		-	LOH			LOH	
39	48/F	C	I	III		-				LOH	LOH
40	44/F	V	I	III		-	LOH			LOH	

C: convexity, F: female, f: fibroblastic, Fx: falx, LOH: loss of heterozygosity, M: male, m: meningotheliomatous, P: parasagittal, p: psammomatous, S: sphenoidal ridge, t: transitional, V: lateral ventricle

cance, and there was a significant relationship between benign and non-benign meningiomas and LOH at 1p32 ( $p = 0.0228$ ) (Fig. 1). Whereas LOH at 7q21 was found in only one atypical meningioma, LOH at 7q31 was seen in one benign meningioma and one atypical meningioma. No significant correlations were identified between benign and non-benign meningiomas at 7q21 and 7q31. LOH on 17p13 was detected in 4%, 40%, and 80% of benign, atypical, and anaplastic meningiomas, respectively (Fig. 1). LOH on 22q13 was detected in 48%, 60%, and 60% of benign, atypical, and anaplastic meningiomas, respectively. LOH results at 17p13 showed a statistically significant difference between benign and non-benign meningiomas ( $p = 0.0006$ ). However, there was no significance at 22q13 ( $p = 0.461$ ).

#### Frequency of LOH according to the histological subtypes

Of 25 benign meningiomas, excluding 10 atypical and 5 anaplastic meningiomas, identification of LOH at 1p32, according to histological subtypes, was seen 4 (23.5%) in meningothelial, 1 (33.3%) fibrous, and 1 (25%) in transitional type. In the case of 7q31 and 17p13, LOH was detected 1 (5.3%) in meningothelial type, respectively. Eight cases (47%) of meningothelial and 3 cases (75%) of transitional meningiomas showed LOH at 22q13 ( $p = 0.399$ ). There were no statistical correlations between subtypes and LOH in any of the chromosomal regions examined in this study.

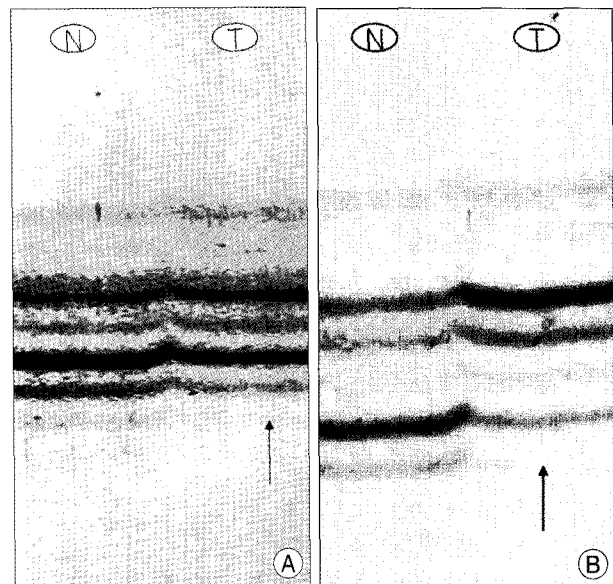
#### DISCUSSION

Since the identification of monosomy of chromosome 22, the molecular studies of meningiomas and gliomas have advanced in accordance with various cytogenetic developments<sup>13,33</sup>. LOH examined in this study led to the discovery of a tumor suppressor gene. The analysis of LOH using microsatellite probes has been reported in many tumors, especially malignant tumors<sup>32</sup>. In meningiomas, many authors have revealed deletions in various chromosomes using LOH analysis. Of them, the most common site of LOH was chromosome 22, followed by chromosome 1p.

The characteristic findings of this study were : 1) the detection of LOH was higher at 1p and 22q (24% and 48%, respectively) than that of at 7q21, 7q31 and 17p3 (0%, 4%, and 4%, respectively) in benign meningiomas, 2) LOH was most frequently detected at 22q13 and there was a significant

**Table 3.** LOH of 1p32, 7q, 17p13, and 22q13 according to the clinicopathological factors in meningiomas

Clinicopathologic parameters	1p32	7q21	7q31	17p13	22q13
Grade (n=40)					
Benign (n=25)	6 (24%)	0	1 (4%)	1 (4%)	12 (48%)
Atypical (n=10)	6 (60%)	1 (10%)	1 (10%)	4 (40%)	6 (60%)
Malignant (n=5)	3 (60%)	0	0	4 (80%)	3 (60%)
Histological subtype (n=25)					
Meningothelial (n=17)	4 (23.5%)	0	1 (5.9%)	1 (5.9%)	8 (47%)
Transitional (n=4)	1 (25%)	0	0	0	3 (75%)
Fibroblastic (n=3)	1 (33.3%)	0	0	0	1 (33.3%)
Psammomatous (n=1)	0	0	0	0	0



**Fig. 1.** LOH at chromosomes 1p32 and 17p13. Representative D1S193 at 1p32 (A) and TP53 at 17p13 (B) microsatellite analysis of normal (N) and tumor (T) samples. The bottom band of each tumor lanes shows loss appearance (arrow).

difference of LOH between benign and non-benign meningiomas at 1p32 and 17p13.

Neurofibromatosis type 2 (NF 2) is a tumor suppressor gene on chromosome 22q, which has been implicated in the development of benign meningiomas<sup>27</sup>. NF2 gene mutations occur with a similar frequency between benign and non-benign (atypical or anaplastic) meningiomas, which suggests that NF2 is associated with meningioma initiation rather than progression<sup>27</sup>. According to Weber et al.<sup>31</sup>, the initial event of meningioma formation was related to an allelic loss at 22q. LOH at 1p, 6q, 10, 14q, and 18q, and gains in 1q, 9q, 12q, 15q, 17q, and 20q were associated with atypical meningiomas. As reported by Kim et al.<sup>10</sup>, LOH at 22q was seen in 47% of benign and in 100% of anaplastic meningiomas and there was a statistically significant correlation between the two groups. In addition, Lee et al.<sup>12</sup> reported that 12.5-64% of benign meningiomas showed

LOH of 22q and anaplastic meningiomas demonstrated 100% LOH on chromosome 22. In our study, LOH at 22q13 of benign meningiomas was 48%, which was similar to the results of other studies. In anaplastic meningiomas, however, LOH at 22q was 60%, and there was no significant correlation between two groups. This finding implies that LOH at 22q is related to tumorigenesis more so than tumor progression.

LOH at 1p is the second most frequent chromosomal abnormality in meningiomas and has been shown to be associated with meningioma progression<sup>21,28</sup>. The detection rate of LOH in 1p is 21-33% in benign and 71-85% in anaplastic meningiomas<sup>14,29</sup>. Leuraud et al.<sup>14</sup> stated that LOH at 1p occurs after the loss of chromosome 22 and is more frequent in grade 2 than grade 1 meningiomas. In our study, LOH at 1p occurred more frequently in non-benign than in benign meningiomas, and in the transitional type more than in the meningothelial type. There was a significant correlation in grades, but no statistical association in histological subtypes ( $p = 0.02$  and  $p = 0.18$ , respectively).

p53 gene located on chromosome 17p is a tumor suppressor gene and has been found to have mutations in most human cancers<sup>6,22</sup>. Mutations of p53 gene in human meningiomas have been reported in 7-13% of these tumors<sup>8,23</sup>. According to the report of Pykett et al.<sup>26</sup>, however, there was lack of elevated p53 protein levels in 16 primary meningiomas. There were few reports about LOH at 17p<sup>10,18</sup>. Kim et al.<sup>10</sup> reported that LOH at 17p was identified in only two anaplastic meningiomas. In our study, LOH at 17p was seen with very low frequency in benign meningiomas (4%) and 80% of anaplastic meningiomas showed LOH. Also, there was a significant association between LOH at 17p and the grade of the tumor ( $p = 0.0006$ ). Although we do not have data about the frequency of p53 gene somatic mutation, the findings of our study suggest that LOH at 17p might be associated with tumor progression in human meningiomas.

The hepatocyte growth factor/scatter factor (HGF/SF) is a pleiotrophic protein secreted by mesenchymatous cells, which has been identified as a potent mitogen for hepatocytes<sup>3,19</sup>. The c-Met gene has been identified as a proto-oncogene in human osteogenic sarcoma and serves as a receptor for HGF/SF<sup>5,7</sup>. HGF/SF and c-MET are located on chromosome 7q<sup>15,24</sup>. HGF and c-MET are associated with oncogenesis in many human cancers and co-expressed in meningiomas<sup>19,20</sup>. A relationship between co-expression of HGF/c-MET and recurrence in meningiomas has been reported<sup>17</sup>. Accordingly, the authors wanted to identify whether or not LOH at 7q is related to meningioma recurrence. However, LOH at 7q21 and 7q31 was seen at very low frequencies in our study (2.5% and 5%, respectively).

## CONCLUSION

This study suggests LOH at 22q13 may contribute to meningeal tumorigenesis and LOH at 1p32 and 17p13 may be associated with tumor progression. However, LOH at 7q21 and 7q31 may not contribute to the development of meningiomas. Nevertheless, to determine the relationship between LOH at 7q and meningiomas, further studies are necessary.

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