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Deletion mapping of the short arm of chromosome 1 identifies a common region of deletion distal to *D1S496* in human meningiomas

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Abstract We have studied a series of 63 meningiomas, including 47 benign meningiomas (World Health Organization, WHO, grade I), 13 atypical meningiomas (WHO grade II) and 3 anaplastic meningiomas (WHO grade III), using microsatellite and restriction fragment length polymorphism analysis for loss of heterozygosity (LOH) at 21 polymorphic loci on chromosome 1 (19 loci on 1p and 2 loci on 1q). LOH on 1p was found in 9 of 13 atypical meningiomas (70%) and in 3 of 3 (100%) anaplastic meningiomas, but only in 6 of 47 (13%) benign meningiomas. In 13 tumors allelic loss was observed at all informative loci on 1p. Terminal deletions with retention of heterozygosity at one or more proximal 1p loci were found in 5 tumors. The region commonly deleted in all tumors was located distally to the *D1S496* locus, i.e., at cytogenetic bands 1p34 – 1pter, and included the chromosomal segment which is frequently deleted in neuroblastoma, malignant melanoma, and different types of carcinoma.

Key words Chromosome 1 · Loss of heterozygosity · Meningioma · Progression · Tumor suppressor gene

Introduction

Meningiomas are among the most common neoplasms of the central nervous system and comprise up to 15% of intracranial and 25% of intraspinal neoplasms [26, 35]. Histologically, most meningiomas are benign and correspond to grade I of the World Health Organization (WHO) classification of tumors of the central nervous system [14]. However, a subset of meningiomas exhibits an increased tendency to recur after operation. These tumors, which are designated as atypical meningiomas (WHO grade II), are histologically characterized by increased mitotic activity, high cellularity, small cells with high nuclear cytoplasmic ratios and/or prominent nucleoli, uninterrupted patternless or sheet-like growth and foci of necrosis [14]. Finally, rare cases of meningioma may show histological features of frank anaplasia including gross brain invasion. Such tumors are classified as anaplastic (malignant) meningiomas (WHO grade III) and are associated with an adverse prognosis.

Previous studies have shown that the *NF2* (neurofibromatosis type 2) tumor suppressor gene located on 22q12 is mutated in a significant percentage of sporadic meningiomas irrespective of tumor grade [4, 27, 34]. Genetic alteration of *NF2* thus represents a major early genetic abnormality in meningiomas which is particularly frequent in fibroblastic and transitional but less frequent in meningothelial variants [28, 34]. A number of cytogenetic studies have shown that atypical and anaplastic meningiomas, in addition to 22q deletions, usually show abnormalities of several other chromosomes [5, 8, 17, 21, 24]. According to these studies and recent molecular genetic investigations [1, 18, 32] the short arm of chromosome 1 represents the second most frequently deleted chromosomal arm after 22q in meningiomas. In contrast to loss of heterozygosity (LOH) on 22q, allelic loss on 1p was found predominantly in atypical and anaplastic meningiomas but only rarely in benign meningiomas [1, 18, 32]. Thus, it is likely that a tumor suppressor gene is located on 1p that is of importance in the progression of meningiomas.

To map the location of the suspected tumor suppressor gene on 1p more precisely, we have performed a detailed deletion mapping of this chromosomal arm on a series of 63 meningiomas, including 13 atypical and 3 anaplastic meningiomas. We confirm the high frequency of 1p deletion in WHO grade II and III meningiomas. By determining the region commonly deleted in all tumors, we were able to assign the location of the putative tumor suppressor gene associated with meningioma progression to the chromosomal segment 1p34 – pter, i.e., telomeric to the anonymous locus *D1S496*. This region includes the chro-

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Table 1 Summary of the 63 investigated meningiomas including selected clinical data, neuropathological diagnoses, proliferative activity (Ki-67), and allelic status on chromosome 1p (*m* male, *f* female, *men* meningothelial, *fib* fibroblastic, *trans* transitional, *psam* psammomatous, *secr* secretory, *ang* angiomatous, *atyp* atypical, *anapl* anaplastic, *rec* recurrence, *LOH* loss of heterozygosity, + LOH on 1p, – no LOH on 1p)

Case no.	Age (years)	Sex	Localization	Subtype	WHO grade	Note	Ki-67 (%)	LOH 1p
MN 1	65	m	Parasagittal	men	I	2. rec	2	–
MN 2	42	m	Tentorium	fib	I		< 1	–
MN 3	70	m	Parasagittal	fib	I		< 1	–
MN 4	70	m	Falx	atyp	II	1. rec	5.1	+
MN 5	76	f	Thoracical	psam	I		< 1	–
MN 6	52	f	Tentorium	fib	I		< 1	–
MN 7	50	f	Fronto-basal	fib	I		< 1	+
MN 8	55	m	Tentorium	ang	I		1.5	–
MN 9	52	m	Occipital	trans	I		5	–
MN10	38	f	Convexity	trans	I		6	–
MN11	49	m	Intraventricular	trans	I		< 1	–
MN12	74	m	Temporal	men	I		< 1	+
MN13	58	f	Tentorium	men	I		< 1	–
MN14	66	f	Fronto-parietal	atyp	II		8.5	+
MN15	69	f	Fronto-temporal	men	I	1. rec	< 1	–
MN16	78	f	Frontal	atyp	II		9.9	+
MN17	55	f	Frontal	fib	I		1.3	+
MN18	35	m	Tuberculum sellae	men	I		< 1	–
MN19	52	f	Intraventricular	fib	I		< 1	+
MN20	44	m	Frontal	atyp	II		3.1	+
MN21	59	f	Sphenoidal	men	I		< 1	–
MN22	71	f	Fronto-basal	atyp	II		16	–
MN23	76	m	Fronto-temporal	fib	I		2.1	–
MN24	36	m	Olfactory groove	men	I		3.9	–
MN25	61	f	Parasagittal-central	trans	I		1.7	–
MN26	58	m	Parieto-occipital	men	I		0.9	–
MN27	73	f	Sphenoidal	trans	I		< 1	+
MN28	72	f	Parieto-occipital	men	I		1.8	–
MN29	73	m	Fronto-basal	psam	I		< 1	–
MN30	57	f	Sphenoidal	men	I		< 1	–
MN31	47	m	Falx	ang	I		< 1	–
MN32	54	f	Convexity	men	I		1.3	–
MN33	66	f	Sphenoidal	secr	I		< 1	–
MN34	55	m	Parieto-occipital	anapl	III	3. rec	22	+
MN35	49	f	Frontal	men	I		< 1	–
MN36	53	f	Parietal	fib	I		< 1	–
MN37	71	f	Parietal	fib	I		< 1	–
MN38	53	m	Olfactory groove	trans	I		2.1	–
MN39	57	m	Fronto-parietal	men	I		1.1	–
MN40	71	f	Parietal	atyp	II		13	+
MN41	55	f	Tentorium	fib	I		< 1	–
MN42	58	f	Temporal	atyp	II		3.4	–
MN43	56	m	Occipital	men	I	1. rec	2.4	+
MN44	54	m	Frontal	trans	I		< 1	–
MN45	65	f	Parasagittal	trans	I		5.5	–
MN46	56	m	Suprasellar	men	I		< 1	–
MN47	81	f	Fronto-basal	atyp	II		10.5	–
MN48	70	f	Tentorium	trans	I		< 1	–
MN49	55	f	Temporo-basal	anapl	III	1. rec	8.9	+
MN50	62	f	Frontal	trans	I		4.5	–
MN51	63	m	Planum sphenoidale	psam	I		1.1	–
MN52	65	f	Falx	men	I		< 1	–
MN53	73	m	Atlanto-occipital	secr	I		< 1	–
MN54	64	f	Parietal	trans	I		2.2	–

Table 1 (continued)

Case no.	Age (years)	Sex	Localization	Subtype	WHO grade	Note	Ki-67 (%)	LOH 1p
MN55	63	m	Olfactory groove	men	I		< 1	–
MN56	44	m	Falx	atyp	II	3. rec	16	+
MN57	59	m	Planum sphenoidale	men	I		2	–
MN58	59	f	Sphenoidal	men	I		< 1	–
MN59	72	m	Fronto-temporal	atyp	II	2. rec	5.7	+
MN60	72	f	Frontal	atyp	II		4.8	–
MN61	74	f	Convexity	atyp	II		6	+
MN62	74	f	Sphenoidal	atyp	II	1. rec	4.1	+
MN63	78	f	Fronto-basal	anapl	III	3. rec	10.5	+

mosomal sites where one or more tumor suppressor gene(s) involved in neuroblastomas and other frequent types of human tumors are suspected to be located (for review see [30]).

Materials and methods

Tumor material

A series of 63 meningiomas (including 47 benign, 13 atypical and 3 anaplastic meningiomas) was investigated (Table 1). The tumors were from 63 patients (27 male, 36 female, mean age at operation: 61 years, range 35–81 years) operated at the neurosurgical clinic of the Heinrich-Heine University in Düsseldorf and the neurosurgical clinic of the Evangelische-und-Johanniter-Krankenanstalten in Duisburg-Nord/Oberhausen; 53 tumors were primary tumors, while 10 tumors were recurrences (Table 1). None of the primary and none of the recurrent tumors had been treated by irradiation or chemotherapy prior to operation. All tumors were histopathologically classified according to the WHO classification of tumors of the central nervous system [14]. Parts of the tumor tissue and a blood sample from each patient were frozen immediately after operation and stored at –80°C. To assure that the tumor pieces taken for molecular genetic analysis contained a sufficient proportion of tumor cells, histological evaluation of a representative part of each of these pieces was performed. Only samples with a tumor cell content of more than 80% were included in this study.

Immunocytochemistry

All tumors were immunocytochemically evaluated on formalin-fixed paraffin sections for the expression of the proliferation-associated nuclear antigen Ki-67 using the indirect avidin-biotin peroxidase method as described [22]. To enhance immunoreactivity, sections were pretreated by microwave heating in 10 mM citrate buffer pH 6.0, three times for 10 min. As primary antibody the mouse monoclonal IgG_1 antibody MIB-1 (Dianova, Hamburg, Germany) was used at a concentration of 2 µg/ml for an incubation period of 16 h at room temperature. This was subsequently followed by biotinylated rabbit anti-mouse-immunoglobulin antiserum (Dako, Copenhagen, Denmark) for 30 min and by avidin-biotin-peroxidase complex (Dako) for 30 min. 3′3-Diaminobenzidine (Sigma, Deisenhofen, Germany) was used as chromogenic substrate. Between each pair of steps, sections were washed in phosphate-buffered saline twice for 10 min. Negative controls were performed by omission of the primary antibody and its substitution with an irrelevant mouse monoclonal IgG_1 antibody. Immunoreactivity was quantified by counting positive and negative tumor cells in five representative microscopical fields at high-power magnification (× 400). Thus, about 1000–5000 tumor cells were counted for each case and the results were calculated as percentage of positive cells (Table 1).

DNA extraction and analysis

The preparation of high molecular weight DNA from tumor tissue and peripheral blood leukocytes was carried out as described by Ichimura et al. [11]. Primers for polymerase chain reaction (PCR) amplification of microsatellite markers were selected from the Généthon microsatellite map [9] and synthesized by MWG-Biotech, Ebersbach, Germany. The following 18 microsatellite loci were studied: *D1S235* and *D1S305* (both located on 1q), *D1S239*, *D1S207*, *D1S224*, *D1S515*, *D1S438*, *D1S473*, *D1S200*, *D1S211*, *D1S496*, *D1S482*, *D1S478*, *D1S507*, *D1S228*, *D1S503*, *D1S214*, and *D1S468* (all located on 1p) (for details concerning the precise mapping of these markers see [7, 9, 33]). PCR amplification was performed on an automated thermocycler (MWG-Biotech, Munich, Germany) in 20-µl sample volumes with 100 ng of genomic DNA as template in 20 mM TRIS-HCl (pH 8.4), 50 mM KCl, 1.5 mM $MgCl_2$, 200 µM of each dNTP, 0.5 µM of each primer, and 5% formamide with 1 U Taq polymerase (Gibco-BRL, Eggenstein, Germany). PCR amplifications of *D1S482* and *D1S496* were performed without formamide in the PCR mixture. An initial denaturation of 4 min at 94°C was followed by 30 cycles of 1 min at 94°C, 1 min at 56°C and 1 min at 72°C, and a 10-min final elongation step at 72°C. PCR products were electrophoresed on denaturing (8 M urea) 10% polyacrylamide gels and visualized by silver staining. The band patterns produced from each blood and tumor pair were visually assessed for allelic imbalances in the tumor DNA. In case of suspected allelic imbalance the silver-stained gels were scanned with a GS-700 imaging densitometer and the densitometric profiles were evaluated using the Molecular Analyst version 2.1 software (Bio-Rad Laboratories, Hercules, Calif.).

For the analysis of restriction fragment length polymorphisms (RFLP), tumor and blood DNA were digested with the restriction enzyme *Taq*I or *Pvu*II, electrophoresed on 0.8% agarose gels, and alkali blotted to Hybond-N^+ membranes (Amersham-Buchler, Braunschweig, Germany) as described previously [23]. The membranes were sequentially hybridized with [^{32}P]dCTP-labeled plasmid probes for the polymorphic loci *D1S80* (pMCT118), *D1S76* (pCMM12), *D1S57* (pYNZ2), and the control locus *D2S44* (pYNH24). All plasmids were obtained from American Type Culture Collection (ATCC). Quantitative densitometric evaluation of the RFLP bands was performed with the Molecular Analyst version 2.1 software after scanning the autoradiograms with a GS-700 imaging densitometer (Bio-Rad Laboratories).

Results

Among the 63 meningial tumors investigated, 47 were histopathologically classified as benign meningioma (WHO grade I) and corresponded to the following subtypes: 19 meningothelial, 10 fibroblastic, 11 transitional, 3 psammomatous, 2 angiomatous, and 2 secretory (Table 1). Thir-

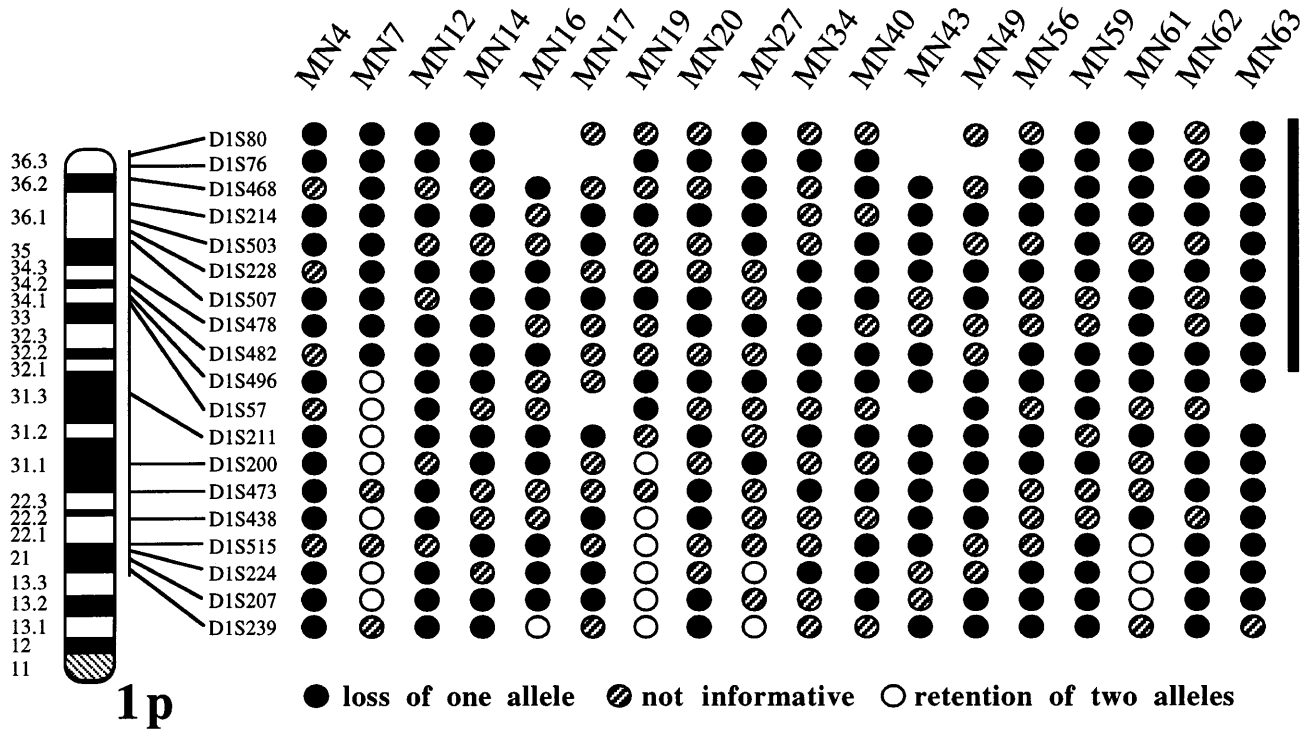

Fig. 1 Graphic representation of loss of heterozygosity (LOH) patterns in 18 meningiomas with loss on 1p; *top abscissa* represents case numbers, *ordinate* schematic drawing of 1p with approximate locations of the microsatellite and restriction fragment length polymorphism (RFLP) loci studied (for details concerning the mapping of the analyzed loci see [7, 9, 33]). *Black circles* Loss of one allele, *white circles* retention of two alleles, *hatched circles* not informative (constitutional homozygosity). The *black bar* on the *right* indicates the region commonly deleted in all 18 tumors which is located distally to *D1S496*

teen meningiomas were classified as atypical (WHO grade II) and 3 tumors as anaplastic meningioma (WHO grade III).

Immunocytochemical determination of the Ki-67 labeling index was performed for all 63 tumors and revealed values ranging from less than 1% to 22%. The mean Ki-67 labeling index increased with WHO grade, i.e., benign meningiomas showed a mean index of 1.3% (range: < 1–6%), atypical meningiomas of 8% (range: 3–16%), and anaplastic meningiomas of 13.8% (range: 8.9–22%). The correlation between mean Ki-67 labeling index and WHO grade was statistically significant ($P < 0.001$, Spearman correlation coefficient).

Only one meningioma (MN4) showed LOH at the *D1S235* locus which is located on the long arm of chromosome 1. None of the other tumors showed allelic loss at either *D1S235* or *D1S305*, indicating that deletions of 1q are rare events in meningiomas. In contrast, a total of 18 of 63 tumors (28%) showed LOH on 1p. Allelic loss on 1p was found in 9 of 13 atypical meningiomas (70%) and in 3 of 3 anaplastic meningiomas (100%). In contrast, only in 6 of 47 benign meningiomas (13%), including 2 of 19 (11%) meningothelial, 3 of 10 (30%) fibroblastic, and 1 of 11 (9%) transitional variants, showed LOH on 1p (Table 1). The association of 1p loss with increasing grade of malignancy was highly significant ($P < 0.001$, Pearson χ^2 test). Loss of 1p also correlated with increased proliferative activity. The mean Ki-67 labeling index of meningiomas with LOH on 1p was 6.6% (range: < 1–22%), while the mean Ki-67 labeling index of meningiomas without LOH on 1p was 2.0% (range; < 1–16%) ($P < 0.001$, Mann-Whitney U test). However, comparison of benign meningiomas with and without LOH on 1p revealed no significant difference in Ki-67 mean indices (0.95% vs 1.4%, $P = 0.68$, Mann-Whitney U test). Similarly, in the group of atypical meningiomas proliferative activity in tumors with LOH on 1p did not significantly differ from tumors without 1p loss (8.0% vs 8.7%, $P = 0.94$, Mann-Whitney U test).

In 13 tumors all informative loci on 1p demonstrated LOH, indicating that the entire arm or most of it had been lost. Five meningiomas showed evidence of terminal deletions with retention of heterozygosity at one or more proximal 1p markers (Fig. 1). The extend of these terminal deletions varied from case to case. Tumor MN16 for example showed LOH at all informative loci except for *D1S239* (mapped to 1p21) (Fig. 2). In contrast, MN7 had the smallest deletion with the breakpoint being located between *D1S496* and *D1S482* at 1p34 (Fig. 2). The LOH pattern of tumor MN7 was crucial in defining the chromosomal region commonly deleted in all tumors to the area located distally to *D1S496*, which corresponds to the cytogenetic segment 1p34 – 1pter (Fig. 1).

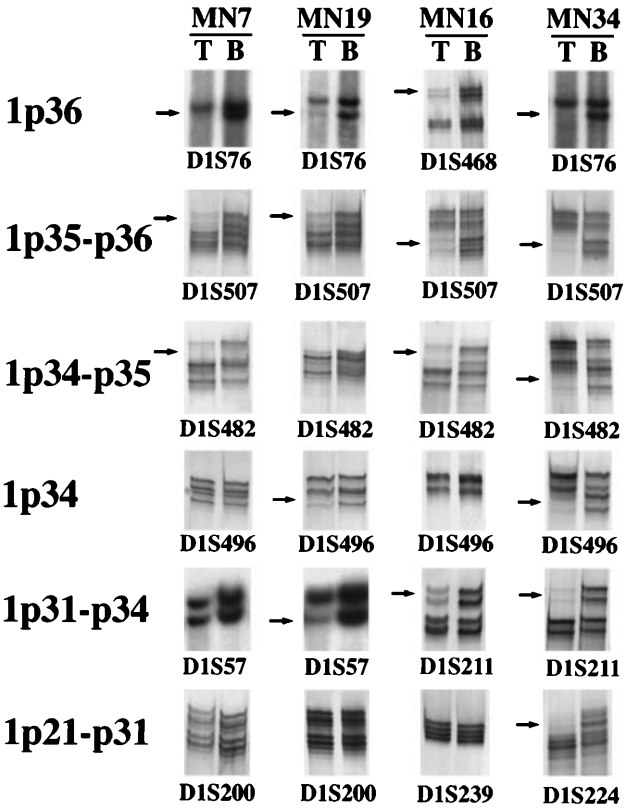

Fig. 2 Examples of LOH at different loci from 1p in four selected meningiomas; *top abscissa* represents case numbers of the meningiomas (*T* tumor DNA, *B* blood DNA). *Ordinate* represents approximate chromosomal location of the represented loci. Tumor MN7 shows the smallest terminal deletion with a breakpoint at 1p34 between *D1S496* and *D1S482*. Allelic loss in tumors MN16 and MN19 extends further to the centromer with *D1S200* (in MN19) and *D1S239* (in MN16) being the most distal loci retaining heterozygosity. Tumor MN34 shows LOH at all informative loci from 1p. Loci *D1S482* and *D1S496* are not informative in MN19 and MN16, respectively. *Arrows* indicate lost alleles in tumor DNA

Discussion

In the present study we have analyzed a set of 19 highly polymorphic markers on the short arm of chromosome 1 in 63 meningiomas, and thus performed the most comprehensive deletion mapping of 1p in these tumors so far. Allelic loss on 1p was found in 13% (6/47) of benign meningiomas, 70% (9/13) of atypical and 100% (3/3) of anaplastic meningiomas. These frequencies are similar to those reported by Bello et al. [1] who investigated three RFLP markers on 1p and found LOH in 3% (1/33) of benign, 67% (10/15) of atypical, and 100% (2/2) of anaplastic meningiomas. A more recent study analyzed 3 microsatellite markers on 1p and found LOH in 11% (2/18) of benign, 40% (6/15) of atypical, and 70% (7/10) of anaplastic meningiomas [32]. Lindblom et al. [18] allelotyped 16 anaplastic meningiomas and found allelic loss on 1p in 58% of the tumors (7 of 12 informative cases). Taken together, our results and the data from the literature clearly show that the frequency of 1p loss in meningiomas significantly increases with advancing grade of malignancy and indicate that 1p contains a tumor suppressor gene involved in meningioma progression.

With respect to the mapping of the suspected tumor suppressor gene on 1p, we could assign the region commonly deleted in all tumors to 1p34 – pter, i.e., telomeric to the *D1S496* locus. This region was defined by tumor MN7 which showed the smallest deletion in our series with the breakpoint being located between *D1S496* and *D1S482*. Our data thus considerably narrow the region of common deletion in meningiomas determined by Simon et al. [32] and move the proximal boundary from 1p22 (telomeric to *D1S188*) to 1p34 (telomeric to *D1S496*). In our study as well as in the paper by Simon et al. [32] no interstitial deletions were found. In contrast, Bello et al. [2] analyzed 81 meningiomas for LOH at 4 loci on 1p and found a total of 12 tumors with interstitial deletions. In addition, 2 tumors of Bello's series had evidence of monosomy 1 and 11 tumors demonstrated terminal 1p deletions. Since the authors were unable to define a region commonly deleted in all tumors they suggested that 1p may contain two distinct meningioma-associated tumor suppressor gene loci, i.e., one distal at 1p36 (between *D1S7* and *D1Z2*) and one proximal at 1p32-p35 (between *D1S17* and *D1S7*) [2]. The region commonly deleted in our tumor series overlaps with the distal region as well as partially with the proximal region of Bello et al. [2]. Thus, the data of both studies would be compatible, although our results do not provide further evidence in support of the existence of two independent meningioma-associated suppressor gene loci on 1p.

In addition to meningiomas, frequent loss of 1p has been reported in a wide spectrum of other tumors including most notably neuroblastomas, malignant melanomas, various types of benign and malignant epithelial tumors, and a number of hematological malignancies (for review see [30, 33]). In neuroblastomas, the location of the suspected tumor suppressor gene on 1p has been narrowed to an estimated 10-cM segment at 1p36.2–1p36.3 between the markers *D1S244* and *D1S47* (for review see [30]). This region is overlapped by the commonly deleted region determined in our study for meningiomas and is also spanned by the deletions found in hepatocellular carcinomas [16], pheochromocytomas [13, 19], parathyroid adenomas [3], malignant melanomas [6], and oligodendroglial tumors [2, 23]. Thus, there is convincing evidence that a yet-unknown tumor suppressor gene maps to 1p36 and this gene is possibly altered in a number of different tumor types.

The histopathological grading of meningiomas may be difficult in some cases because histopathological signs of increased growth potential are either too discrete or restricted to focal areas that may escape detection due to sampling errors. A number of recent studies have, therefore, searched for new methods that, in addition to conventional histopathology, could be useful for meningioma grading. So far, the methods found to be of potential value for meningioma grading include immunocytochemical

detection of proliferation-associated antigens, such as Ki-67 [20, 25], proliferating cell nuclear antigen [10] and bromodeoxyuridine [12, 31], morphometric evaluations [15, 29], and cytogenetics [15, 21]. In the present study we found a significant correlation between Ki-67 index and tumor grade. The mean labeling indices were 1.3% in benign, 8% in atypical, and 13.8% in anaplastic meningiomas. These data confirm previous studies [15, 20, 25] and support the usefulness of Ki-67 as supplementary tool for meningioma grading.

The significant association between LOH on 1p and atypical or anaplastic meningiomas also indicates a possible role for this aberration as prognostic parameter for meningioma patients. However, a small fraction of tumors in our series showed LOH on 1p but neither histopathological signs of anaplasia nor enhanced proliferative activity. Follow-up data were, unfortunately, not available for these patients. Thus, the prognostic significance of LOH on 1p remains to be evaluated in further clinicopathological studies. Nevertheless, the presence of LOH on 1p in a subset of histologically benign meningiomas indicates that this alteration alone is probably not sufficient to cause meningioma progression. Indeed, cytogenetic studies have shown that atypical and anaplastic meningiomas frequently have complex karyotypic alterations involving several other chromosomes in addition to 22q and 1p [5, 8, 17, 21]. Molecular genetic studies have revealed that LOH at loci from 10q and 14q are nearly as frequent as LOH on 1p in these tumors [32]. Thus, it is likely that multiple chromosomal and genetic aberrations contribute to the enhanced cell proliferation in atypical and anaplastic meningiomas.

In conclusion, our study shows that loss of alleles on 1p is a very frequent abnormality in atypical and anaplastic meningiomas. By analyzing multiple polymorphic markers from this chromosomal arm we could considerably narrow the location of the suspected tumor suppressor gene to the chromosomal segment 1p34 – pter distal to the microsatellite locus *D1S496*. However, this region is still quite large and covers an estimated 48–82 cM of genetic distance [7]. Therefore, further LOH studies on even larger numbers of tumors are necessary to confine this region to a genetic distance suitable for positional cloning.

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