Teratogenesis, Carcinogenesis, and Mutagenesis 22:217–225 (2002)

Evaluation of Relationship Between Chromosome 22 and p53 Gene Alterations and the Subtype of Meningiomas by the Interphase-FISH Technique

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In this study, we investigated the relationship between genetic alterations such as chromosome 22 aneuploidy and p53 gene deletion, and the pathological types of meningioma of typical and aggressive forms. Thirty-four meningiomas (23 typical and 11 aggressive) were examined by application of fluorescence in situ hybridization (FISH) with chromosome 22 specific alpha satellite probe and a combination of p53 locus specific and chromosome 17 centromere specific alpha satellite probes, to evaluate the chromosome 22 aneuploidy and gain or loss of p53 gene along with chromosome 17. The results showed that, although chromosome 22 aneuploidy was seen in 7 out of 23 typical (30.4%) and 4 out of 11 aggressive meningiomas (36.3%), no p53 deletion was detected in typical meningiomas, and p53 deletion was detected in 3 out of 11 aggressive meningiomas (1 atypical and 2 malignant), which had recurrence. There were no simultaneous occurrences of p53 gene deletions between typical and aggressive meningiomas. The present findings indicate that the loss of chromosome 22 may be involved with tumorogenesis of typical and aggressive meningiomas, while p53 gene deletions may be involved with malignant progression and recurrence in the aggressive meningiomas. *Teratogenesis Carcinog. Mutagen. 22:217–225, 2002.* © 2002 Wiley-Liss, Inc.

Contract grant sponsor: Research Foundation of Uludag University; Contract grant number: 99/39.

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Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/tcm.10013

Key words: meningioma; FISH; chromosome 22; p53 gene

INTRODUCTION

Meningiomas are common intracranial tumors that arise from cells of the meninges and account for 15–25% of all primary intracranial tumors. Although generally considered benign, in studies with long-term follow-up, meningiomas have shown significant rates of recurrence, morbidity, and mortality [1,2]. The World Health Organization (WHO) classifies meningiomas into three histologic grades: benign or typical (grade1), atypical (grade 2), and malignant or anaplastic (grade 3) in accordance with clinical prognosis [3]. Atypical and malignant ones that can be named as aggressive meningiomas tend to recur and to invade adjacent brain, bone, and skin [3,4]. Meningiomas are cytogenetically characterized by loss of one chromosome 22 in addition to loss of one chromosome 14 [5–13]. The genetic differences and their roles in the typical and higher grade meningiomas are not well characterized and molecular pathogenesis is poorly understood [14,15]. It is widely accepted that p53 protein expression, which is detectable by immunohistochemistry, is probably used as a surrogate for p53 mutations [16,17]. Abnormal p53 expression was associated with mutations of p53 gene and has shown correlation with neoplastic development and progression [18–20]. Association of p53 gene abnormalities with tumor progression and prognosis of many neoplasms has been demonstrated but little is known about the clinical significance of p53 abnormalities in typical and aggressive meningiomas [21–25]. Although there were a number of immunohistochemical studies in the literature that showed abnormal p53 expression in aggressive meningiomas, there were a limited number of molecular studies that showed association with p53 mutations in meningiomas [26–28]. With recent developments, molecular and molecular cytogenetic techniques have became more sensitive than immunohistochemical ones to detect genetic alterations. Fluorescence in situ hybridization (FISH), a molecular cytogenetic method, using chromosome specific DNA probes, allows the detection of chromosomal aberrations and gene deletions and/or gains, even in interphase nuclei in a large number of human solid tumor cells without any cultivation step [2,3,29–31].

In this study, we investigated chromosome 22 aneuploides and p53 deletions by application of FISH in typical and aggressive meningiomas to assess the correlation between genetic alterations and the type of meningiomas.

MATERIAL AND METHODS

A total of 34 fresh brain tumor samples were studied from the different patients who had undergone neurosurgery, between the beginning of 1998 and April 2001. The age range of the patients was from 37 to 71. Because of the rarity of the malignant phenotype [1,3], we obtained all of the aggressive meningiomas (11 cases) during this period, and 23 of the typical ones were selected. Two patients with aggressive meningioma (cases 26 and 32) had undergone surgery for meningioma at least twice and we studied their tumor tissues when they had undergone the second surgery. Three patients with aggressive meningiomas showed recurrence and we performed FISH on their tumor tissues (cases 24, 30, and 31). None of the patients had received any preoperative irradiation or chemotherapy except for two patients with aggressive meningiomas (cases 26 and 32). All samples were classified according to the WHO

classification of tumors of the central nervous system. Peripheral blood of ten normal persons were studied as a control group.

Slide Preparation From Tumor Tissue

Tumor tissues were divided into two pieces. One piece was examined for pathology to diagnose the histologic classification. The other part in RPMI 1640 medium 1X containing penicillin/streptomycin was immediately transported for FISH preparation. To obtain a suspension of single cells, the tissues were minced with a scissors in Petri dish under sterile conditions. The single cell suspension was placed into 10 ml sterile tubes by glass pipette and was washed twice with RPMI 1640 medium 1X. After centrifugation, the cells were treated with 0.075 M KCI solution for 20 min. Centrifugation was repeated at 1,000 revolutions per min for 10 min. The cell pellet was dispersed and was treated with methanol/acetic acid (3:1) solution three times and the fixed samples were dropped onto glass slides. Slides were checked for cell distribution under a light microscope before applying FISH. Slides were placed into 0.02 mg/ml pepsin in 0.01 N HCL solution at 37°C for 10 min. The slides were washed in 2×SSC solution and then treated with an ascending alcohol series (70, 85, and 100%) and air-dried.

FISH Analysis

Two types of probe mixture were used. The first one was a centromere specific DNA probe for chromosome 22 labeled-digoxigenin (Boehringer-Mannheim Biochemicals, Indianapolis, IN). The second one was a combination of a centromere specific DNA probe for chromosome 17 labeled- biotin (D17Z1, Oncor, Inc., Gaithersburg, MD) and a p53 locus specific DNA probe labeled-digoxigenin (Oncor, Inc). The probes were denatured at 70°C for 10 min, meanwhile interphase nuclei spreads were denatured in 70% formamide /2×SSC at 70°C for 2–3 min. The slides were dehydrated through an ascending alcohol series (70, 85, and 100%) and air-dried. The denatured combination of chromosome 17 of centromere specific probe (biotine-labeled) and locus specific p53 probe (digoxigenin-labeled) in hybridization buffer were mixed in an eppendorf tube.

For the chromosome 22 centromere specific probe and the combination of chromosome 17 centromere specific and p53 locus specific probe mixture, two slides were used for each tumor sample. These denatured probe mixtures were applied on the slides, overlaid with a coverslip and sealed with cow gum. After overnight incubation at 38°C, a post hybridization wash was performed according to the method described by Reid et al. [32] with some modifications, with 2×SSC for 3 min, 50% formamide for 4 min, and 2×SSC for 3 min at 40°C. The chromosome 17 centromere specific probe was detected with avidin-fluoresceinated, the p53 locus specific probe was detected with antidigoxigenin-rodamine, and also the chromosome 22 centromere specific probe was detected with antidigoxigenin-rodamine. The same method was applied on control samples. Slides were counterstained with DAPI (4,6 diamino-2-phenyl-indole) in mounting solution and examined on a Quips Imaging System (Applied, UK) equipped with Nikon E 600 (Japan) standard conventional epifluorescence microscope and a filter set (triple, dapi/red/green; dual color, red/green, single red; and single green; Vysis, USA). A total of 200 interphase nuclei were scored for each sample and each control. The number of cells with 0, 1, 2, 3, and 4 hybridization signals was recorded for each probe from each cell. The results were given in per-

centages. Juxtaposed or split same color signals were considered as one signal. Mean values for the percentages of two clearly identifiable signals for each probe and each nucleus were calculated separately for specimens from control and tumor tissues. Color photomicrographs were taken with a Cool Snap camera of Photometriks equipped with a computerized system.

RESULTS

For controls, interphase nuclei of peripheral blood samples (n = 10) were examined to determine the sensitivity and specificity of the uni and dual-color FISH technique. The mean percentages of nuclei showing two signals were 93%, 92%, and 94% for chromosome 22 specific centromteric and p53 locus specific probes (Table I) and chromosome 17 specific centrometric probe, respectively. Based on the results obtained from these control groups we estimated that loss of chromosome 22 and 17 and deletion of p53 could be diagnosed in the tumor tissue samples when present in a minimum of 7%, 6%, and 8% of nuclei respectively and trisomy in a minimum of 7%, 6% and 8% of nuclei, respectively. Hybridization signals on meningioma cells were analyzed under the epifluorescence microscope. Two hundred interphase nuclei were scored for each sample. The simultaneous use of chromosome 17 specific centrometric probe and the p53 locus specific probe was for verifying p53 gene deletion or gain in interphase nuclei. The results showed that there was no chromo-

TABLE I. Interphase FISH Results of Typical Meningiomas

			FISH signals (%)									
			For chromosome 22					For p53 gene				
Case	Age/sex[a]	Histopathology	0	1	2	3	4	0	1	2	3	4
1	43 F	Fibroblastic	0	4	91	1	4	2	4	89	4	1
2	54 F	Fibroblastic	1	3	93	2	1	2	6	91	1	0
3	50 M	Fibroblastic	2	42	49	1	6	1	3	92	1	3
4	45 F	Fibroblastic	1	3	88	1	7	3	2	87	2	6
5	66 M	Fibroblastic	1	0	96	0	3	2	4	90	3	1
6	50 M	Fibroblastic	4	68	21	1	5	0	5	90	0	5
7	61 M	Fibroblastic	0	2	97	0	1	0	3	94	1	2
8	58 F	Fibroblastic	0	94	2	1	3	2	2	93	0	3
9	48 M	Fibroblastic	2	2	91	1	4	0	3	89	1	7
10	61 F	Fibroblastic	0	1	95	2	2	2	1	93	1	3
11	49 M	Fibroblastic	2	3	90	1	4	1	2	96	0	1
12	37 F	Fibroblastic	0	92	4	0	4	2	2	91	1	4
13	42 F	Mix	0	2	97	0	1	0	3	95	2	0
14	70 M	Mix	1	3	91	1	5	2	2	93	0	2
15	54 F	Mix	2	48	41	3	6	1	3	92	2	4
16	37 F	Meningothelial	1	95	2	1	1	3	4	90	0	3
17	40 M	Meningothelial	1	91	5	2	1	1	2	95	1	1
18	51 F	Meningothelial	1	0	96	1	2	3	0	92	0	5
19	71 F	Meningothelial	0	2	93	2	3	1	2	89	1	7
20	47 F	Meningothelial	2	3	90	1	4	4	3	90	0	3
21	63 M	Meningothelial	0	6	90	1	3	2	1	95	0	2
22	48 F	Meningothelial	1	2	93	2	2	2	2	93	1	2
23	59 F	Meningothelial	1	3	94	2	0	1	3	92	2	2
Controls (mean values for 10 controls)			2	3	93	1	3	1	2	92	1	4

[a]F, female; M, male.

some 17 aneuploidy in 34 samples. In seven cases of 23 benign meningiomas, FISH results showed monosomy 22 (30.4%). Four of these were regular (cases 8, 12, 16, and 17) and three were the mosaic monosomy 22 (cases 3, 6, and 15). None of these showed recurrency before and in this study period. Monosomy 22 was detected in four of eleven aggressive (2 of atypical and 2 of malignant) meningioma (36.3%). The percentages of cells bearing one signal for chromosome 22 were 58%, 82%, 69%, and 91% (cases 26, 27, 29, and 33) (Table II). In the aggressive meningioma group, the application of dual-color FISH on interphase nuclei by using a combination of chromosome 17 specific centrometric and p53 locus specific probes showed the presence of the deletion of p53 gene in three cases (cases 26, 30, and 31) (Fig. 1). One of these cases (case 26), who was taken for a second operation because of recurrence, was an atypical meningioma with monosomy 22 (Fig. 2). In this case, the percentage of cells having a p53 deletion was 38%. The other two cases (cases 30 and 31) were malignant meningioma. The percentages of cells having a single p53 signal were 88% and 64%, respectively. Recurrence was observed in five cases of aggressive meningiomas (cases 24, 26, 30, 31, and 32). Two of these cases (cases 26 and 32) had showed recurrence before this study. FISH analysis was performed on their recurrent tumor samples in the second operation. Recurrence also occurred in three other patients (cases 24, 30, and 31) after FISH analysis was done.

DISCUSSION

There are a number of studies that suggest that frequent entire or partial losses of chromosome 22 are commonly encountered findings in meningiomas [1,5–12,33,34]. Additionally, some reports have pointed out that similar structural changes were also found in some benign tumor types such as neurofibromatosis type 2 [8,35,36]. However, a variety cytogenetic abnormalities have been attributed to aggressive meningiomas like the loss of chromosomes 1p arm, 10 and 14, and at the different ratios, there are few data proving the association of these abnormalities with the recurrences or malignant tendencies of meningiomas [3,6,14].

Accordingly we may assume that there could be some other criteria for meningio-

TABLE II. Interphase FISH Results of Aggressive Meningiomas

			FISH signals (%)									
			For chromosome 22					For p53 gene				
Case	Age/sex[a]	Histopathology	0	1	2	3	4	0	1	2	3	4
24[b]	43 M	Atypical	2	1	91	2	4	1	3	93	1	2
25	52 M	Atypical	0	3	93	0	4	1	4	90	0	5
26[b]	66 M	Atypical	1	58	28	2	11	2	38	52	7	1
27	71 F	Atypical	3	82	9	5	1	0	6	89	0	5
28	62 M	Atypical	0	2	94	1	3	3	2	94	0	1
29	49 M	Malignant	2	69	21	7	1	2	1	96	0	1
30[b]	60 M	Malignant	0	6	90	3	1	1	88	3	7	1
31[b]	66 F	Malignant	1	3	94	1	1	1	64	19	8	7
32[b]	68 F	Malignant	1	2	93	0	5	2	3	92	1	4
33	58 M	Malignant	1	91	6	1	0	2	2	93	2	1
34	53 M	Malignant	1	1	91	1	6	1	0	91	2	6

[a]F, female; M, male.
[b]Patient with recurrence.

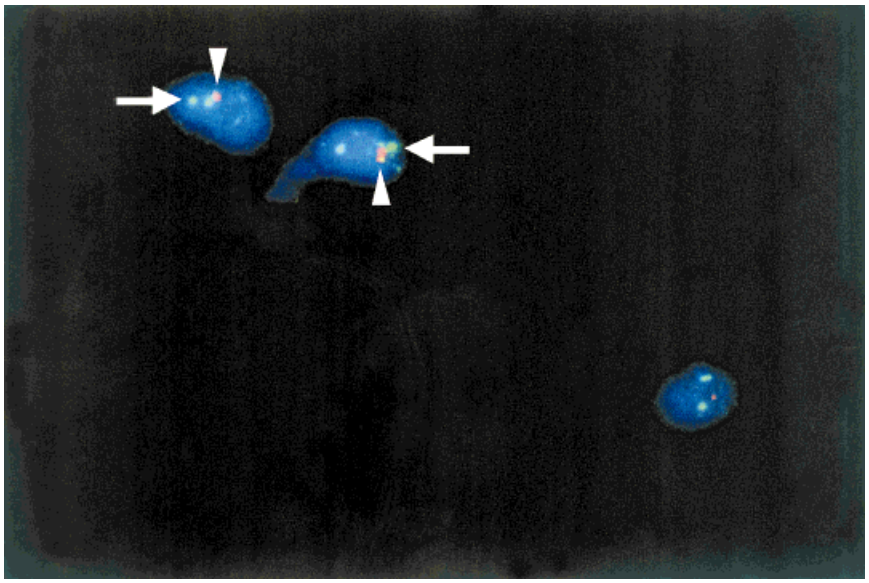

Fig. 1. p53 deletion in malign meningioma. Green signals (arrows) show centromere 17 and red signals (arrowheads) show p53 gene probes. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

mas leading to recurrence and atypical or malignant process. Although there are a number of studies that show entire or partial loss of chromosome 22 in all histologic types of meningiomas (benign, atypical, and malignant) with variety ratio, a large number of these studies have not shown certain difference rates among the benign, atypical,

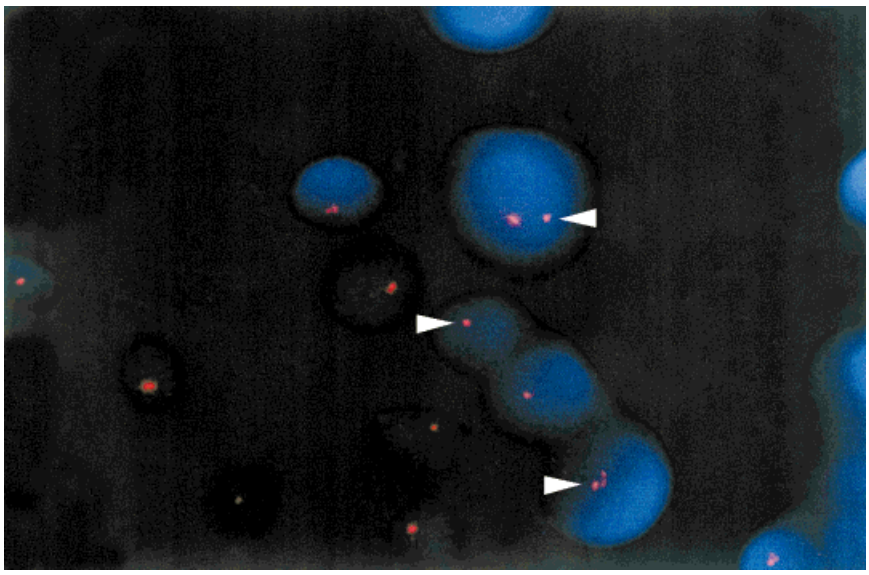

Fig. 2. Monosomy 22 in atypical meningioma. Red signals (arrowheads) show centromere 22 probes. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

and malignant meningiomas for the loss of chromosome 22, which could reveal a close association with the malignant process or recurrency [37,38]. A number of studies pointed out that p53 abnormalities are associated with malignant behaviors of some other tumor types such as leukemia, colon, or lung cancers [39–44]. On the other hand, immunohistochemical studies showed a close association between p53 over expression and malignant and recurrent behavior of meningiomas, and also there are a few molecular study that detected p53 mutations in malign and recurrent meningiomas but not in benign ones in a variety of comparative studies among all types of meningiomas. However, the place of the p53 abnormalities in recurrent or aggressive meningiomas is not fully understood [4,16–20,26–28,45,46]. The FISH technique, which is a highly valuable adjunct in cytogenetic studies, is consistently informative and has a high efficiency for detecting chromosomal abnormalities and gene alterations [22].

Shinsuke et al. [3] hypothesized that the existence of tumor suppresser genes on chromosome 1p was associated with malignant progression of meningioma and suggested that detection of the allelic status of chromosome 1p by FISH may help the clinician in predicting the prognosis of patients with meningiomas. The existence of monosomy 22 in both benign (typical) and aggressive (atypical or malignant) meningiomas at similar proportions [benign meningiomas (30.4%) vs. aggressive meningiomas (36.3%)] may support the fact that monosomy 22 is not a discriminating factor between benign and malign meningiomas. On the other hand, although there were no p53 deletions in all of 23 typical meningiomas that were benign and had not recurred, 3 out of 11 aggressive meningiomas with recurrence had p53 deletions. This may support the association of p53 deletion with recurrence and malignancy. Even though monosomy 22 was detected in one case (case 26) with recurrent aggressive meningiomas, there was also a p53 deletion in this tumor tissue. This does not support with certainty the association of monosomy 22 with recurrence, because three other aggressive meningiomas (cases 27, 29, and 33) with monosomy 22, but without p53 deletion, did not recur. Because this study has been performed in fresh tissues over a period of 3 years, it may be expected that aggressive meningiomas have not recurred yet but would probably recur later, and it could be assumed that there could be other factors leading to recurrence of the malignant process in meningiomas besides p53 deletion; there could be loss of chromosomes 10, 14, and 1p arm or others that were published in previous studies [3,6,14]. The ratio of monosomy 22 did not differ significantly between 23 benign and 11 aggressive meningiomas, and no p53 deletion was seen in 23 benign meningiomas but it was seen in 3 of 11 aggressive meningiomas (one atypical meningioma and two malignant meningiomas). In conclusion, our findings suggest that loss of chromosome 22 may be associated with tumorogenesis but not with malignant progression and recurrence, whereas p53 deletions may be associated with malignant progression and recurrence in meningiomas. To clarify this issue, more comparative studies should be done with a larger series of benign and aggressive meningiomas.

REFERENCES

1. Arie P, Robert BJ, Richard JD, Cheryl AM, Bernd, WS. Cytogenetic analysis of aggressive meningiomas. Am Cancer Soc 1996;72:2567–2573.
2. Arie P, Scott LS, Bernd WS, Vera JS, Christine ML. The prognostic significance of MIB-1, p53, and DNA Flow Cytometry in completely resected primary meningiomas. Am Cancer Soc 1998;82:2262–2269.
3. Shinsuke I, Naoya H, Shinji F, Kousei D, Toshiki M, Masahito F, Yoshio N, Satoshi U, Tatsuo A,

Johji I. Loss of material from chromosome arm 1p during malignant progression of meningioma revealed by fluorescent in situ hybridization. Am Cancer Soc 1998;83:360–366.
4. Ahmed R, Soomro IN, Aziz SA, Hasan SH. P53 and PCNA expression in benign, atypical and malignant meningiomas. JPMA 1999;49:241–243.
5. Schneider BF, Shashi V, von Kap-Herr C, Golden WL. Loss of chromosomes 22 and 14 in the malignant progression of meningiomas: a comparative study of fluorescence in situ hybridization (FISH) and standard cytogenetic analysis. Cancer Genet Cytogenet 1995;85:101–104.
6. Simon M, Deimling A, Larson JJ, Wellenreuther R, Kaskel P, Waha A, Warnick RE, Tew JM Jr, Menon AG. Allelic losses on chromosomes 14, 10, and 1 in atypical and malignant meningiomas: a genetic model of meningioma progression. Cancer Res 1995;55:4696–4701.
7. Lekanne DRH, Riegman PH, van Drunen E, Warringa UL, Groen Na, Stefanko SZ, Koper JW, Avezaat CJ, Mulder PG, Zwarthooff EC. Cytogenetic, molecular genetic and pathological analyses in 126 meningiomas. J Neuropathol Exp Neurol 1995;54:224–235.
8. Ruttlege MH, Xie Yg, Peyrard M, Collins Vp, Nordenskjold M, Dumanski JP. Deletions on chromosome 22 in sporadic meningioma. Genes Chromosom Cancer 1994;10:122–130.
9. Griffin CA, Hruban RH, Long PP, Miller N, Volz P, Carson B, Brem H. Chromosome abnormalities in meningeal neoplams: do they correlate with histology? Cancer Genet Cytogenet 1994;78:46–52.
10. Lindblom A, Ruttledge M, Collins VP, Nordenskjold M, Dumanski JP. Chromosomal deletions in anaplastic meningiomas suggest multiple regions outside chromosome 22 as important in tumor progression. Int J Cancer 1994;56:354–357.
11. Al Saadi A, Latimer F, Madercic M, Robbins T. Cytogenetic studies of human brain tumors and their clinical significance. Cancer Genet Cytogenet 1987;26:127–141,
12. Maltby EL, Ironside JW, Battersby RD. Cytogenetic studies in 50 meningiomas. Cancer Genet Cytogenet 1988;31:199–210.
13. Menon AG, Rutter JL, von Sattel JP, Synder H, Murdoch C, Blumenfeld A, Martuza RL, von Deimling A, Gusella JF, Houseal TW. Frequent loss of chromosome 14 in atypical and malignant meningioma: identification of a putative “tumor progression” locus. Oncogene 1997;14:611–616.
14. Ozaki S, Nishizaki T, Ito H, Sasaki K. Comparative genomic hybridization analysis of genetic alterations associated with malignant progression of meningioma. J Neurooncol 1999;41:167–174.
15. Lamszus K, Kluwe L, Matschke J, Meissner H, Laas R, Westphal M. Allelic losses at 1p, 9q, 10q, 14q, and 22q in the progression of aggressive meningiomas and undifferentiated meningeal sarcomas. Cancer Genet Cytogenet 1999;110:103–110.
16. Matsuno A, Nagashima T, Matsuura R, Tanaka H, Hirakawa M, Murakami M, Tamura A, Kirino T. Correlation between MIB-1 staining index and the immunoreactivity of p53 protein in recurrent and non recurrent meningiomas. Am J Clin Pathol 1996;106:776–781.
17. Nagashima G, Aoyagi M, Yamamoto S, Wakimoto H, Ohno K, Yamamoto K, Hirakawa K. P53 overexpression and proliferative potential in malignant meningiomas. Acta Neurochir 1999;141:53–61.
18. Wang JL, Zhang ZJ, Hartman M, Smits A, Westermark B, Muhr C, Nister M. Detection of TP53 gene mutation in human meningiomas: a study using immunohistochemistry, polymerase chain reaction single strand confirmation polymorphism and DNA sequencing techniques on paraffin-embedded samples. Int J Cancer 1995;64:223–228.
19. Ellison DW, Lunec J, Gallagher PJ, Steart PV, Jaros E, Gatter KC. Accumulation of wild-type p53 in meningiomas. Neuropathol Appl Neurobiol 1995;21:136–142.
20. Prayson RA. Malignant meningioma: a clinicopathologic study of 23 patients including MIB I and p53 immunohistochemistry. Am J Clin Pathol 1996;105:719–726.
21. Arie P, Kari A, Tom JB, David WK, Chiao HW, Judit R O’Fallon, Burt GF, Bernard WS, Roert BJ. Detection of p16, RB, CDK4, and p53 gene deletion and amplification by Fluorescence In Situ Hybridization in 96 gliomas. Am J Clin Pathol 1999;112:801–809.
22. Xinwei, Tatsuo T, Shumin W, Yuka M, Kohsuke S, Fumihiko S. Detection of numeric abnormalities of chromosome 17 and p53 deletion by Fluorescence In situ Hybridization in pleomorphic adenomas and carcinomas in pleomorphic adenoma correlation with p53 expression. Am Cancer Soc 1997;79:2314–2319.
23. Jutta A, Petra M, Niclas Z, Heinz G, Heinz L, Heinz H, Johannes D. Absence of p53 deletions in bone marrow plasma cells of patients with monoclonal gammopaty of undetermined significance. Br J Haematol 1998;103:1161–1163.
24. Monica H, David S, Bert V, Curtis CH. P53 Mutations in Human Cancers. Science 1991;253:49–53.
25. Karadeniz C, Berberoğlu S. Genetic regulation of apoptosis and cancer. THOD 1996;6:151–155.
26. Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM. The prognostic significance of MIB-

1, p53, and flow cytometry in completely resected primary meningiomas. Cancer 1998;82:2262–2269.
27. Ohkoudo M, Sawa H, Harra M, Satuta K, Aişo T, R, Yamamoto H, Maemura E, Shiina Y, Fuji M, Saito I. Expression of p53, MDM2 protein and Ki-67 antigen in meningiomas. J Neurooncol 1998;38:41–43.
28. Mashiyama S, Murakami Y, Yoshimoto T, Sekiya T, Hayashi K. Detection of gene mutations in human brain tumors by single- strand confirmation polymorphism analysis of polymerase chain reaction products. Oncogene 1991;6:1313–1318.
29. Kwak T, Nishizaki T, Nakayama H, Kakino S, Ito H, Kimura Y. Detection of structural aberrations of chromosome 17 in malignant gliomas by fluorescence in situ hybridization (FISH). Acta Oncol 1995;34:27–30.
30. Stuppia L, Calabrese G, Peila R, Guanciali-Franchi P, Morizio E, Spadano A, Palka G. P53 loss and point mutation are associated with suppression of apoptosis and progression of CML into myeloid blastic crisis. Cancer Genet Cytogenet 1997;98:28–35.
31. Stephen JD, John F, Steven RR, Cheryl AM, Robert BJ. Use of fluorescence in situ hybridization to detect loss of chromosome 10 in astrocytomas. J Neurosurg 1995;83:316–323.
32. Reid T, Baldini A, Rand TC, Ward DC. Simultaneous visualization of seven different DNA probes by in situ hybridization using combinatorial fluorescence and digital imaging microscope. Proc Natl Acad Sci USA 1992;89:1388–1392.
33. Casartelli C, Rogatto SR, Barbieri NJ. Karyotypic evolution of human meningioma. Progression through malignancy. Cancer Genet Cytogenet 1989;40:33–45.
34. Doco-Fenzy M, Cornillet P, Scherpereel B, Depernet B, Bisiau-LeconteS, Ferre D, Pluot M, Graftiaux JP, Teyssier JR. Cytogenetic changes in 67 cranial and spinal meningiomas: relation to histopathological and clinical pattern. Anticancer Res 1993;13:845–850.
35. Rey JA, Pestana A, Bello MJ. Ctytogenetics and molecular genetics of nervous tumors. Oncol Res 1992;4:321–331.
36. Lamszus K, Vahldiek F, Mauther VF, Schichor C, Tonn J, Stavrou D, Fillbrandt R, Westphal M, Kluwe L. Allelic losses in neurofibromatosis 2-associated meningiomas. J Neuropathol Exp Neurol 2000;59:504–512,
37. Dumanski JP, Roleau GA, Nordenskold M, Collins VP. Molecular genetic analysis of chromosome 22 in 81 cases of meningioma. Cancer Res 1990;50:5863–5867.
38. Arai H, Beppu T, Wada T, Yoshida Y, Kuba Y, Suzuki M, Ogawa A. Pathological analyses of early recurrence and malignant transformation in meningiomas. Brain Tumor Pathol 1998;15:37–40.
39. Crossen PE. Genes and chromosomes in chronic B-cell leukemia. Cancer Genet Cytogenet 1997;94:44–51.
40. Cano I, Martinez J, Qevedo E, Pinilla J, Martin-Recio A, Rodriguez A, Castaneda A, Lopez R, Perez Pino T, Hernandez-Navarro F. Trisomy 12 and p53 deletion in chronic lymphocytic leukemia detected by fluorescence in situ hybridization: association with morphology and resistance to conventional chemotherapy. Cancer Genet Cytogenet 1996;90:118–124.
41. Nanashima A, Tagawa Y, Yasutake T, Taniguchi Y, Sawai T, Nakagoe T, Ayabe H. Analysis of p53 gene deletions in colorectal cancers using fluorescence in situ hybridization. Surg Today 1997;27:999–1004.
42. Soenen V, Preudhome C, Roumier C, Daudignon A, Lai JL, Fenaux P. 17p deletion in acute myeloid leukemia an myelodysplastic syndrome. Analysis of breakpoints and deleted segments by fluorescence in situ. Blood 1998;91:1008–1015.
43. Hollstein M, Soussi T, Thomas G, von Brevern MC, Bartsch H. P53 gene alterations in human tumors: perspectives for cancer control recent results. Cancer Res 1997;143:369–389.
44. Wies JS, Franklin WA, Drabkin H, Gemmill R, Sidransky D, Anderson MW. Genetic markers for early detection of cancer and outcome measures for response to chemoprevention. J Cell Biochem Suppl 1997;28–29:64–73.
45. Chozick BS, Benzil DL, Stopa EG, Pezzullo JC, Knuckey NW, Epstein MH, Finkelstein SD, Finch PW. Immunohistochemical evaluation of erB-2 and p53 protein expression in benign and atypical human meningiomas. J Neurooncol 1996;27:117–126.
46. Karamitopoulou E, Perentes E, Tolnay M, Probst A. Prognostic significance of MIB 1, p53, and bcl-2 immunoreactivity in meningiomas. Hum Pathol 1998;29:140–145.