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Molecular Genetic Analysis of Chromosome 22 in 81 Cases of Meningioma[1]

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ABSTRACT

Constitutional and tumor tissue genotypes from 81 unrelated patients with meningioma were compared at 25 polymorphic loci (restriction fragments length alleles) on chromosome 22. Thirty tumors (37%) retained the constitutional genotype along chromosome 22, a finding consistent with no detectable aberrations on chromosome 22 as studied. Forty-two tumors (52%) showed loss of one allele at all informative loci consistent with monosomy 22 in the tumor DNA. The remaining 9 tumors (11%) showed retained constitutional heterozygosity in the tumor DNA at one or more centromeric loci and loss of the heterozygosity at other telomeric loci, which is consistent with variable terminal deletions of one chromosome 22q in the tumor DNA. The localization of breakpoints in these 9 cases with deletions suggests that a meningioma locus is localized distal to myoglobin locus, within 22q12.3-qter. The male cases showed a higher percentage of tumors with no detectable aberrations on chromosome 22, a finding which may suggest that tumors of males have preferentially smaller rearrangements on chromosome 22q than those of females or that the male and female cases with no detected aberrations have another mechanism of oncogenesis. In view of the recent findings on the localization of the neurofibromatosis-2 gene on chromosome 22, the data from case 11 of our series suggests that the meningioma and the neurofibromatosis-2 loci are separate entities.

INTRODUCTION

Meningiomas are primary tumors of the meninges and may originate from any of their constituents such as arachnoid cells, fibroblasts, or blood vessels. The common localization of these neoplasms shows parallels with the sites where arachnoid villi are most numerous. It is thus widely accepted that arachnoid cells are most often the cells of origin (1). Histopathologically and clinically, meningiomas represent a heterogeneous group of tumors classified into 9 subtypes with 1-3 malignancy grades (2). These tumors constitute 13-19% of all primary brain tumors (3). They can occur at any age but have their highest incidence during the fifth and sixth decades of life. On average, twice as many females are affected as males (4).

Generally, meningiomas are slowly growing benign neoplasms which may remain silent. Autopsy findings of small asymptomatic meningiomas in patients older than 70 years are not uncommon. In most cases meningiomas are sporadic, solitary tumors, but there are indications of a genetic predisposition. These include familiar aggregations (5-9), sporadic cases with multiple tumors (10), two monozygotic twins both with multiple tumors (11), and a patient with a constitutional ring chromosome 22 who also had multiple meningiomas (12).

Extensive cytogenetic studies of *in vitro* cultured meningioma cells undertaken during the last two decades have shown that monosomy of chromosome 22 is the most consistent chromosomal aberration in these cells. Deletions of the long arm of one chromosome 22 have also been reported in a small number of cases (4, 13). One of the conclusions which could be drawn from these studies is that loss of genetic material from chromosome 22 may represent a fundamental event in the tumorigenesis of meningioma. This conclusion has been confirmed by molecular studies of allele losses in the primary tumor material from meningiomas (14, 15).

Studies of tumors with variable deletions of the long arm of one chromosome 22 provide a way of localizing a tentative meningioma locus on this chromosome. This approach was used to tentatively map meningioma gene(s) to the region telomeric to the MB[3] locus, which corresponds to 22q12.3-qter. This finding was based on deletion mapping of tumor tissue DNA from 35 cases of meningiomas examined for allele losses with 7 markers detecting RFLPs specific for the long arm of chromosome 22. The most telomeric of the markers available at that time was the c-*sis* protooncogene (PDGF-B)(15). We have now significantly increased the number of polymorphic markers on the telomeric part of chromosome 22 in order to study this region in more detail (16, 17).

In this paper we present an extensive analysis of deletions of genetic material in 81 meningiomas from unrelated patients which have been analyzed with 20 polymorphic markers along the entire long arm of chromosome 22. We have focused on the distal part of chromosome 22q between the MB locus and the telomere, in order to establish whether smaller terminal deletions could he identified, which would further sublocalize the tentative meningioma locus within this region.

MATERIALS AND METHODS

Surgical specimens of meningiomas were obtained from 81 unrelated patients (63 females and 18 males). Tumor tissue was frozen at −135° C for 1 month to 2 years prior to the isolation of the DNA. Constitutional tissue was obtained from peripheral blood leukocytes or primary skin fibroblast culture (case 24). The clinical details of the cases studied are summarized in Table 1. The isolation of high molecular weight DNA from tumor and constitutional tissues, restriction endonuclease digestion, agarose gel electrophoresis, Southern transfer, labeling of probes with ^{32}P, hybridization, autoradiography, densitometric analysis, and removal of the bound probes from Southern filters were performed as previously described (15, 18). The polymorphic DNA markers used are listed in Table 2. The DNA fragments of IGLC and MB plasmids which were used as probes in the hybridization experiments were as previously described (15). The probes D22S94 (KI-1105), D22S95 (KI-839), D22S97 (KI-260), and D22S157 (KI-536) were hybridized to the Southern filters under competitive hybridization conditions (17) because they contain repetitive DNA elements.

RESULTS

We compared the constitutional and the tumor tissue genotypes for 20 markers at 25 loci along the long arm of chromosome 22. Based on this comparison, the cases studied could be divided into three groups (Fig 1.).

1. No Detected Aberrations. In 30 cases (37%) the tumor tissue DNA retained the constitutional genotype at all informative loci on chromosome 22, a finding consistent with no

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[3] The abbreviations used are: MB, myoglobin; RFLP, restriction fragment length polymorphism; PDGF-B, platelet-derived growth factor, β-chain; IGLC, immunoglobulin lambda polypeptide, constant region; cM, centimorgan.

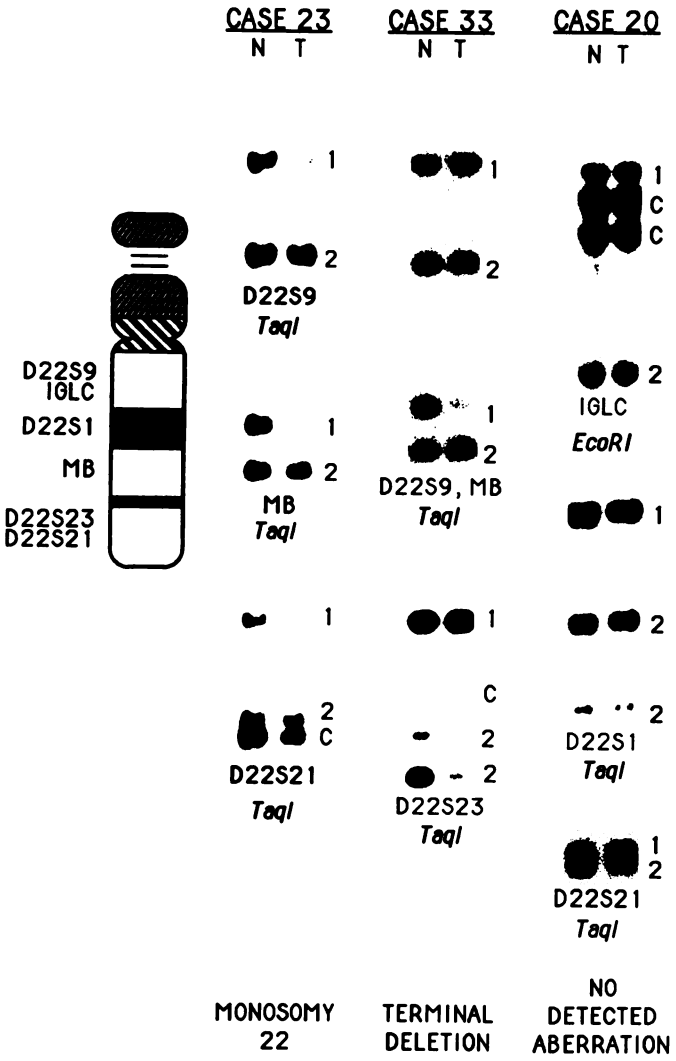

Fig. 1. Three cases of tumors analyzed with some of the polymorphic DNA markers used, along the long arm of chromosome 22. Case 23 (monosomy 22) showed loss of one constitutional allele in the tumor tissue at all three markers (D22S9, MB, D22521), while case 33 (22q deletion) showed retention of the constitutional alleles at the centromeric locus (D22S9) and loss of loci at two more distal loci (MB, D22S23). Case 20 (no detected aberration) showed retention of the constitutional allele in the tumor tissue at all three loci (IGLC, D22S1, D22S21). *N*, constitutional; *T*, tumor tissue; *C*, invariable bands; *1* and *2*, different alleles recognized by the polymorphic markers used.

detectable aberration of chromosome 22 as studied. Special emphasis was put on the search for information on the distal part of chromosome 22 with several markers, to exclude the possibility that tumors with a distal deletion 22q− would be missed. Nine polymorphic markers which map distally to the PDGF-B (c-*sis*) locus were used. All cases in this group showed constitutional heterozygozity at at least two loci localized distally to the PDGF-B locus and retained this heterozygozity in their tumor DNA (Tables 1 and 2).

2. Chromosome 22q Deletions. This group consists of 9 cases (11%) which retained constitutional heterozygosity in the tumor tissue DNA at at least one chromosome 22q locus and lost one constitutional allele at one or more other loci. All of these cases retained the constitutional genotype in the tumor tissue DNA at centromeric loci and lost alleles at telomeric loci, which is consistent with terminal deletions of one chromosome 22q in the tumor tissue DNA (Table 2). The breakpoints in these 9 cases of deletions were scattered within a part of the chromosome equivalent to approximately 52 cM of its genetic length (16, 19) and could be localized to at least five regions. In cases 29, 33, 39, 58, and 64, the breakpoints on chromosome 22 occurred close to the centromere between the markers D22S9 and D22S10 separated by 18 cM, while the breakpoints in cases 11, 24, and 34 occurred more distally on the chromosome between the markers D22S10 and PDGF-B (approximately 35 cM apart). The tumor in case 32 had a breakpoint located between the markers IGLV and D22S1. The most telomeric breakpoint occurred in the tumor of case 11 and was distal to the MB locus as reported previously (15). Thus, the smallest deleted region identified common to all tumors was within that part of the chromosome which corresponds to 22q12.3-qter.

The importance of the use of a large number of markers on the distal part of the chromosome in the search for 22q deletions is illustrated by case 24, previously reported (15) to have no detectable allele loss on chromosome 22 after examination with 7 markers on chromosome 22. When a number of distal markers were applied, loss of one constitutional allele in the tumor tissue DNA was detected at the D22S21 (WI3E), D22S84 (KI-216), D22594 (KI-1105), and D22S97 (KI-260) loci. Subsequent densitometric analysis revealed a decrease in the autoradiographic signal intensity in the tumor tissue DNA at the homozygous MB locus, which is consistent with the loss of one allele (Table 2).

Table 1 *Summary of patients studied and chromosome 22 findings*

Case	Sex	Age at diagnosis (yr)[a]	Histopathology[b]	Localization[c]	Tumor cells (%) in sample[d]	Chromosome 22 aberration[e]
1	M	51	Transitional	Convexity	90	Monosomy
2	M	23	Meningotheliomatous	Convexity	85	ND (1, 3, 6, 8, 13, 17, 18)
3	F	53	Fibrous	Convexity	85	Monosomy
4	F	69[f]	Fibrous[g]	Spinal	95	Monosomy
5	F	53	Meningotheliomatous	Skull base	95	ND (1–6, 14, 20, 23)
6	F	49	Meningotheliomatous	Skull base	90	ND (1–4, 8, 13, 19, 20)
7	F	75	Meningotheliomatous	Convexity	90	Monosomy
8	F	73[f]	Transitional	Skull base	95	ND (1, 2, 4, 6, 16, 18, 23)
9	M	59 (51)[f]	Anaplastic[h]	Convexity	60	ND (5, 6, 13, 15, 21)
10	F	56	Meningotheliomatous	Convexity	95	Monosomy
11	F	66 (53)	Fibrous[i]	Convexity	90	Deletion 22q−
12	F	57	Transitional	Convexity	90	ND (1, 5, 8, 13, 14, 16, 23)
13	F	49	Fibrous	Convexity	95	Monosomy
14	F	68 (63, 58)	Fibrous	Spinal	75	Monosomy
15	F	77 (67, 61)	Fibrous	Convexity	90	Monosomy
16	F	80	Transitional	Convexity	90	Monosomy
17	M	50	Transitional	Convexity	80	ND (2, 3, 14, 15, 18, 23)
18	M	61	Transitional	Convexity	85	Monosomy
19	F	72[f]	Meningotheliomatous	Spinal	90	ND (6, 8, 13, 15, 18)
20	F	27[f]	Anaplastic	Skull base	95	ND (2–4, 6, 9, 13, 14, 18, 21)

Table 1—Continued

Case	Sex	Age at diagnosis (yr)[a]	Histopathology[b]	Localization[c]	Tumor cells (%) in sample[d]	Chromosome 22 aberration[e]
21	M	43	Psammomatous	Convexity	95	ND (2-4, 9, 18, 23)
22	F	64	Psammomatous	Spinal	85	Monosomy
23	M	43	Meningotheliomatous	Convexity	85	Monosomy
24	F	9	Transitional	Intraventricular	95	Deletion 22q−
25	F	63	Transitional	Convexity	90	ND (6, 18, 19, 23)
26	F	39	Anaplastic	Convexity	85	Monosomy
27	M	66 (65)	Transitional	Convexity	90	Monosomy
28	F	66	Transitional	Skull base	90	ND (1, 2, 4, 8, 14, 18, 24)
29	M	56	Fibrous	Convexity	80	Deletion 22q−
30	F	37	Meningotheliomatous	Convexity	80	ND (1-4, 6, 13, 15, 20)
31	M	63	Transitional	Convexity	85	Monosomy
32	F	72[f]	Fibrous	Convexity	75	Deletion 22q−
33	F	41 (42)[f]	Anaplastic	Convexity	95	Deletion 22q−
34	F	44	Meningotheliomatous	Convexity	85	Deletion 22q−
35	F	59 (57)	Transitional[g]	Spinal	85	ND (1, 4-8, 14, 16, 18, 19)
36	F	78[f]	Transitional	Convexity	95	ND (2-7, 13, 14, 17, 18, 23)
37	F	59[f]	Transitional	Convexity	90	Monosomy
38	F	76[f]	Anaplastic	Convexity	90	Monosomy
39	F	62	Fibrous	Convexity	95	Deletion 22q−
41	F	75	Fibrous	Skull base	95	Monosomy
42	F	59	Fibrous	Convexity	90	Monosomy
43	M	76 (73, 71)[f]	Anaplastic	Convexity	90	Monosomy
44	F	73[f]	Meningotheliomatous	Convexity	90	Monosomy
45	F	38[f]	Transitional	Skull base	90	ND (1, 13, 21, 24)
46	F	66 (61, 60, 54, 30)[f]	Anaplastic[h]	Skull base	80	Monosomy
47	F	65	Transitional	Convexity	85	Monosomy
48	F	73 (72, 68)	Transitional[g]	Convexity	90	Monosomy
49	M	66 (63)	Transitional[g]	Convexity	90	ND (4, 8, 20, 22)
50	F	72[f]	Fibrous	Skull base	95	Monosomy
51	F	74	Meningotheliomatous	Convexity	90	ND (1, 2, 13, 14, 20)
52	F	18	Transitional	Convexity	90	Monosomy
53	F	63 (51)	Meningotheliomatous	Skull base	80	Monosomy
54	F	68 (58)	Meningotheliomatous	Skull base	95	ND (1, 5, 6, 14, 15, 20, 23)
55	F	53	Transitional	Skull base	70	ND (2, 4-7, 22-25)
56	F	61	Transitional	Convexity	85	Monosomy
57	F	75	Meningotheliomatous	Convexity	95	Monosomy
58	M	51 (46)	Transitional[g]	Convexity	95	Deletion 22q−
59	F	74	Transitional	Convexity	90	Monosomy
60	F	65 (63, 61)	Transitional[g]	Convexity	90	Monosomy
61	F	69	Meningotheliomatous	Convexity	95	ND (1, 2, 4, 6, 13, 18, 24)
62	F	60 (59)	Psammomatous	Intraventricular[i]	80	Monosomy
63	F	45	Meningotheliomatous	Convexity	90	ND (2, 6, 18, 21, 24)
64	F	45	Fibrous	Convexity	95	Deletion 22q−
65	F	40	Meningotheliomatous	Convexity	95	ND (1, 2, 15, 25)
66	F	66	Fibrous	Convexity	90	Monosomy
67	F	73	Meningotheliomatous[g]	Convexity	90	Monosomy
68	F	42	Transitional	Skull base	65	Monosomy
69	F	64	Meningotheliomatous	Skull base	95	ND (1, 4, 18, 20, 22)
70	F	42	Fibrous	Convexity	90	Monosomy
71	F	67 (66, 64)	Anaplastic	Skull base[i]	90	Monosomy
72	F	76	Meningotheliomatous[g]	Skull base	85	Monosomy
73	F	59	Meningotheliomatous	Convexity	70	ND (8, 18, 21)
74	M	44 (42, 41, 40, 35)[f]	Anaplastic[h]	Convexity	90	ND (13, 17, 18, 21)
75	F	75	Transitional	Spinal	90	Monosomy
76	F	84	Meningotheliomatous	Convexity	95	Monosomy
80	M	46 (44, 35)	Haemangiopericytic	Convexity	95	ND (1, 5, 18, 21, 24)
81	M	66[f]	Anaplastic	Skull base	95	ND (2, 14, 18, 21, 23)
82	F	49 (43, 36)	Meningotheliomatous	Intraorbital	85	Monosomy
84	F	47	Fibrous	Convexity	90	ND (2, 5, 15, 18, 21, 24)
85	M	47	Transitional	Skull base	90	Monosomy
86	M	67	Meningotheliomatous	Skull base	90	ND (1, 2, 13, 15, 18)

[a] If recurrent and surgically treated more than once, the age at earlier or later diagnosis is given in parentheses.

[b] Histopathological control of each investigated sample of tumor tissue was obtained. The tumors were classified according to the World Health Organization (2).

[c] "Convexity" includes the localization of the tumor parasaggitally, at the pterion and elsewhere on the convexity of the brain. "Skull base" includes localization at the pons angle.

[d] The percentage of tumor cell nuclei in each investigated sample was estimated histopathologically.

[e] ND, no aberration detected; numbers in parentheses, loci which were constitutionally heterozygous and retained heterozygosity in the tumor tissue DNA (Table 2).

[f] Deceased patients. Cases 9, 33, 38, 43, 44, 46, and 74 died of aggressive meningiomas. In cases 24 and 71, no follow-up.

[g] Atypical, borderline cases. High cellularity and increased frequency of mitoses as well as cell/nuclei polymorphism. These cases, however, could not be classified as anaplastic meningiomas.

[h] Tumor malignification of cases 9, 46, and 74. When diagnosed earlier, the tumors of these patients could not be classified as anaplastic meningiomas. Case 74 was diagnosed as hemangiopericytic meningioma at the age of 35, 40, and 41 years.

[i] Multiple foci of tumor at localization other than the tumor sample studied. Case 6 had been previously treated with chemotherapy for acute myelocytic leukemia. The father of case 34 had both meningioma and malignant glioma. Case 50 had been previously operated for hyperparathyroidism and colon cancer. Case 74 was treated with postoperative radiotherapy at the age of 44 years. Case 81 was treated with surgery for colon cancer at the age of 53 years. At the age of 56 years he was treated with surgery as well as with postoperative radiotherapy for a pituitary adenoma. At the age of 66 years he was operated for anaplastic meningioma at the parasellar localization. Cases 40, 77, 78, 79, and 83 had to be excluded for technical reasons.

Table 2 *Cases of tumors showing deletions 22q–*

Two numbers (*e.g.*, 1, 2) RFLP alleles present in tumor tissue at loci that were constitutionally heterozygous; italicized numbers, loss of one constitutional allele in the tumor tissue; –, constitutional homozygosity; absence of an entry, no data; numbers in parentheses, retention or loss of alleles at constitutionally homozygous loci as established by densitometric scanning. Decreased intensity of the autoradiographic signal (minimum 30%) at these loci was interpreted as indicating a loss of one of two constitutionally homozygous alleles.

No. of loci studied	Locus/ enzyme[a]	Cases								
		11	24	29	32	33	34	39	58	64
	D22S9									
1	*Taq*I	1, 2	1, 2	–	1, 2	1, 2	1, 2	1, 2	1, 2	1, 2
	IGLV									
2	*Taq*I	–	–	1, 2	1, 2	–	1, 2	*1*	–	*1*
3	*Kpn*I	–	–	–	1, 2	–	1, 2			
	ICLC									
4	*Eco*RI	–	–	–	–	*1*	–	–	*2*	–
	D22S10									
5	*Taq*I	–	–	*2*	–		–	–	–	
6	*Pst*I	1, 2	1, 2	–	–	*2*	1, 2	–	*2*	*1*
	bcr									
7	*Taq*I		1, 2		–	*1*	1, 2	–	–	
	D22S1									
8	*Bgl*II	1, 2	–	–	*1*	*2*	1, 2	–	–	*1*
9	*Taq*I	–	–	–	–	*2*	–			
	D22S28									
10	*Bgl*I	1, 2	–				*1*			
	D22S29									
11	*Taq*I	–	–							
12	*Bcl*I	–	–				*1*			
	MB									
13	*Taq*I	(2, 2)	(*2*)	*2*	–	*2*	*2*	*1*	–	–
	PDGF-B									
14	*Hind*III	*1*	–	–	*1*	–	–	–		–
	CYP2D									
15	*Eco*RI	–	–	*2*	–	–	–	–	–	*1*
	D22S22									
16	*Taq*I	–	–	–		*2*	–		–	
	D22S23									
17	*Taq*I	–	–	–	–	*1*	–	–	–	–
	D22S21									
18	*Taq*I	–	*2*	–	–	*1*	–	*2*	–	–
	D22S82									
19	*Taq*I	*1*				*1*	*2*			
	D22S84									
20	*Pvu*II	–	*1*				*2*		–	
	D22S94									
21	*Taq*I	–	*2*	*1*	*2*	–	*1*	–	–	
	D22S95									
22	*Eco*RV		–				*2*		–	
	D22S97									
23	*Taq*I	*2*	*1*	*2*	–	–	*1*	–	–	*2*
24	*Bgl*II			*2*				–	–	*2*
	D22S157									
25	*Eco*RV	–	–				–		–	

[a] Markers are presented according to the gene order on chromosome 22 (top, centromere; bottom, telomere) (19, 16) and the designations of probes are according to Ref. 20. The markers for anonymous chromosome 22 loci (D22S82, KI-63; D22S84, KI-216; D22S94, KI-1105; D22S95, KI-839; D22S97, KI-260; D22S157, KI-536) were assigned to the region distal to PDGF-B locus on the panel of somatic cell hybrids (15). The other gene probes used were: IGLC, phuC-λ-2; immunoglobulin λ polypeptide, variable region, p V3.3; PDGF-B, (c-*sis*), pSM-1; breakpoint cluster region (bcr), 5′-region of the bcr gene (1.95-kilobase *Hind*III/*Bgl*II fragment); cytochrome P450, subfamily IID, hIID1 (dbl); MB, pHM27.B2.9, and the anonymous chromosome 22 loci: D22S1, pMS3-18; D22S9, p22/34; D22S10, p22C1-18; D22S21, W13E; D22S22, W110D; D22S23, W24F; D22S28, W23C; D22S29, W22D.

No evidence for an interstitial deletion in the tumor tissue DNA could be found in any of the cases studied with any of the probes used. The ratio of copy number of chromosome 22 between the tumor and normal tissue DNA was approximately 1:2 as estimated by densitometric scanning in all 52 cases showing loss of constitutional alleles. This indicates that the loss of alleles of one chromosome 22 was due to a deletion or monosomy of chromosome 22 rather than to mitotic recombination or loss and reduplication of the remaining alleles.

3. **Monosomy 22.** Loss of one constitutional allele in the tumor tissue DNA at all informative loci was detected in 42 cases (52%) (data not shown, Table 1). This is consistent with monosomy 22 in the tumor tissue DNA due to a loss of one chromosome 22 complement.

Sex Distribution, Type of Tumor, and Chromosome 22 Rearrangement. Of the 63 female patients with meningiomas, only 6 (9.5%) had an anaplastic type of tumor, while of the 18 male patients, 4 tumors (22%) were anaplastic meningiomas. The male cases showed a higher percentage of tumors with no aberration on chromosome 22 (50 *versus* 34% in females). This difference is more evident when the anaplastic tumors are compared. Thus, of the 6 female anaplastic meningiomas, 5 showed allele losses on chromosome 22. In contrast, no such aberrations were found in 3 of the 4 anaplastic meningiomas in the males. None of the two tumors classified as hemangiopericytic meningiomas (Table 1) showed any abnormality of chromosome 22.

DISCUSSION

In the present study we confirm the earlier localization of the tentative meningioma gene(s) to the region distal to the MB locus which corresponds to 22q12.3-qter (15) in extensive material. The 30 tumors with no detectable aberrations were examined with numerous distal 22q markers in order to eliminate the possibility that these tumors might include a distal 22q deletion with the breakpoint localized more telomeric than the breakpoint in case 11 and thus better define the position of the tentative meningioma locus. Our analysis did not reveal any such case.

Interstitial deletions which could localize the meningioma locus to a small part of the long arm of chromosome 22 could not be detected with the markers used. It is likely that such deletions exist. In this respect, further studies of the group of tumors with no detectable aberrations on chromosome 22 with a larger number of probes specific for the distal part of chromosome 22 may reveal such cases.

The breakpoints in 9 tumors with 22q deletions were scattered in an region of the chromosome equivalent to a genetic distance of approximately 52 cM and could be localized to at least five subregions on the long arm of chromosome 22. Thus, there did not appear to be any hotspots for the breakpoints. The part of chromosome 22q between the MB locus and the telomere, where no breakpoints could be detected, corresponds to at least 35 cM. The fact that no small, distal deletions of chromosome 22q were found suggests that a deletion of shorter distal fragments than PDGF-B-qter will not result in the neoplastic clonal expansion required for the development of the tumor and that the tentative meningioma gene(s) is likely to be localized distal but close to the MB locus rather than near the telomere of chromosome 22q.

The difference in the distribution of chromosome 22q aberrations detected in females and males is striking. If we assume that cases with no detectable aberrations on chromosome 22 do have mutations of the tentative meningioma locus, the tumors of male patients would appear to have preferentially smaller rearrangements on chromosome 22q than those of females. On the other hand, the mechanism of oncogenesis in the male and female cases with no detected aberrations may be another than that involving the chromosome 22q located meningioma locus.

Earlier it was proposed that the pathogenesis of meningioma and neurofibromatosis-2 involves a gene located on chromosome 22 (21). Recently, the localization of the neurofibromatosis-2 gene has been limited to the region centromeric to the marker D22S28 on the long arm of chromosome 22 (16, 22).

Our data from the tumor of case 11, which retains both copies of chromosome 22 at markers D22528 and MB, suggest that two separate genes are involved in the pathogenesis of these two disorders.

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