Chromosome Abnormalities in Meningeal Neoplasms: Do They Correlate with Histology?

Constance A. Griffin, Ralph H. Hruban, Patricia P. Long, Nava Miller, Peggy Volz, Benjamin Carson, and Henry Brem

ABSTRACT: *Thirty-three meningeal neoplasms were karyotyped, and the results were compared with histologic features. Thirteen neoplasms had no discernible abnormality or sex chromosome loss only; nine had monosomy or structural abnormality involving only chromosome 22; and 11 had other chromosome abnormalities with or without chromosome 22 involvement. Histologic evidence of invasion was not associated with an abnormal karyotype in the three angioblastic tumors examined. All seven fibroblastic meningiomas had abnormal karyotypes, with monosomy 22 the most common change. Abnormal karyotypes were detected in 76% of syncytial and 55% of transitional meningiomas. When these results were combined with those from 259 meningeal tumors reported since 1987, abnormal karyotypes were detected in at least half of all histologic types. Chromosome changes secondary to those involving chromosome 22 may indicate additional areas of the genome that play a role in tumor progression. In the combined series, chromosome losses were most frequently observed in meningiomatous and transitional histologies; chromosomes 1, 6, 14, 18, and Y each were lost in 10 or more meningiomas, whereas only chromosome 20 was gained at the same frequency. Structural abnormalities most frequently involved chromosome 1. These changes are distinctly different from those observed in other common intracranial neoplasms, specifically astrocytic neoplasms.*

INTRODUCTION

Meningiomas are usually benign and frequently can be cured by surgical removal. A few meningiomas, however, are more aggressive. Some meningiomas recur, and some are even frankly malignant. The histologic features that correlate with this aggressive behavior include brain invasion, mitotic activity, and necrosis [1]. Monosomy of chromosome 22 is frequently observed in meningiomas, although other aneusomies and structural rearrangements have also been reported [2–14]. We sought to determine whether the karyotype of meningeal neoplasms correlates with histology and histologic parameters of invasion and to identify chromosomes other than chromosome 22 that are involved in numerical or structural changes.

MATERIALS AND METHODS

Between January 1987 and March 1990, 38 surgically resected meningeal neoplasms were cytogenetically analyzed. Cytogenetic analysis was performed by previously published techniques [15]. Chromosome abnormalities were described according to International System for Human Cytogenetic Nomenclature guidelines [16, 17]. The histologic features of all 38 meningiomas were also reviewed by one of us (R.H.H). The neoplasms were evaluated for indexes of aggressive behavior, including the existence or lack of deep or superficial brain invasion, bone invasion, other invasion, necrosis, cellularity, increased mitotic activity (defined as more than five mitoses per 10 high-powered fields), and prominent nucleoli [1]. These histologic studies were performed without previous knowledge of cytogenetic results.

RESULTS

Thirty-three of the 38 meningeal neoplasms were successfully analyzed. The remaining five neoplasms did not grow sufficiently in short-term culture for analysis. The patients were aged 22–76 years; 28 were women and 10 were men. Of the 33 karyotypable tumors, 27 were newly diagnosed and six had recurred after surgical resection and/or radiotherapy. Histologic tumor subtypes included angioblastic (three tumors), secretory (one), syncytial (nine), transitional (13), and fibroblastic (seven).

The modal chromosome number was near-diploid in all but one of 33 cases. No discernible clonal chromosome abnormality could be identified in 12 tumors, and only loss

From The Johns Hopkins Oncology Center and Departments of Pathology and Neurosurgery, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

Address reprint requests to Constance A. Griffin, M.D., The Johns Hopkins Oncology Center, 600 N. Wolfe St., Room 1-109, Baltimore, MD 21287-8934.

Received January 8, 1994; accepted March 24, 1994.

Cancer Genet Cytogenet 78:46–52 (1994)
0165-4608/94/$07.00

Table 1 No discernible chromosome abnormality or sex chromosome loss only

Spec. no.	Case no./age (yr)/sex	N/R	Histology	Aggression	Location	Days in culture	No. of metaphases	Modal No.	Karyotype
89-022	1/63/F	N	Angioblastic	B,E,F,G	Posterior fossa	4–6	81	46	46,XX
89-056	2/22/F	R[a]	Angioblastic	C,E,F,G	Parietal	6–9	52	46	46,XX
89-160	3/64/F	N	Angioblastic	F,G	Retroorbital	3	31	46	46,XX
89-092	4/46/F	N	Secretory	None	Sphenoid	3–4	32	46	46,XX
87-055	5/40/F	R[b]	Syncytial	C,D,	Ethmoid	9	42	46	46,XX
89-328	6/59/M	N	Syncytial	None	Parasellar	6	26	45–46	46,XY
90-019	7/67/M	N	Syncytial	A	Sphenoid	4	41	45–46	45,X, - Y
87-013	8/57/M	R[c]	Transitional	C,D	Sphenoid	5–6	18	45–46	45–46,XY
87-015	9/34/F	N	Transitional	None	Parasellar	5–6	29	46	46,XX
88-004	10/57/F	N	Transitional	None	Cerebrum	23	49	46	46,XX
88-263	11/71/F	N	Transitional	B	Frontoparietal	2–9	22	46	46,XX
89-034	12/65/F	R[d]	Transitional	None	Frontal	5–13	111	46	46,XX
89-254	13/60/F	N	Transitional	None	Cranial nerve	3–6	23	45–47	46,XX

Abbreviation: N/R, new/recurrent.

Aggression indexes: A, deep brain invasion; B, superficial brain invasion; C, bone invasion; D, other invasion; E, necrosis; F, cellularity; G, > five mitoses in 10 high-power fields; H, nucleoli.

[a] Originally diagnosed in 1988; no previous radiation therapy.

[b] Year of original diagnosis not available; no record of previous radiation therapy.

[c] Originally diagnosed in 1984; no previous radiation therapy.

[d] Originally diagnosed in 1988; no record of previous radiation therapy.

of the Y chromosome was observed in one tumor (Table 1). Monosomy of chromosome 22 as the sole abnormality was observed in eight neoplasms, and a partial chromosome 22 monosomy, del(22)(q12.1) was the sole abnormality identified in one neoplasm (Table 2). Complex karyotypes in addition to monosomy 22 were observed in six tumors, whereas complex karyotypes but with apparently two normal copies of chromosome 22 were noted in four tumors, and one tumor had an inv(22) in conjunction with additional abnormalities (Table 3). An example of one such tumor (case 30) is shown in Figure 1.

In all, 15 of the 33 neoplasms (45%) expressed one or more histologic indexes of aggressive behavior. We correlated the presence of these indexes in the neoplasms with the results of cytogenetic analysis. Seven (54%) of the 13 neoplasms with no discernible chromosome abnormality (Table 1) or loss of only a sex chromosome had at least one index of aggression, including three of the four recurrent tumors in this group. Eight (73%) of the 11 neoplasms with abnormalities involving chromosomes other than chromosome 22 (Table 3) had at least one parameter including three of the four recurrent tumors in this group. In contrast, none (0%) of the nine neoplasms exhibiting only a chromosome 22 abnormality (Table 2) expressed any indexes of aggressive behavior and none of these were recurrent tumors.

We correlated the chromosome abnormalities with other histologic features. All three angioblastic tumors had normal karyotypes; all expressed at least one parameter of aggression. The single secretory meningioma had a normal karyotype and no indexes of aggression. Of the nine syncytial meningiomas, one had monosomy 22 and five had a complex karyotype either with (three tumors) or without (two tumors) abnormalities of chromosome 22. Only two of these five tumors expressed indexes of aggression. The remaining three syncytial meningiomas were normal. Of the 13 transitional meningiomas, three had abnormalities involving only chromosome 22 and four had additional chromosome abnormalities; the remaining six were normal. All four of these meningiomas expressed indexes of aggression. Five of the seven fibroblastic meningiomas were monosomic for chromosome 22, and two had abnormalities of 22 along with other abnormalities. Aggressive parameters were observed in both these meningiomas. The results are summarized in Table 4.

DISCUSSION

We explored the relation between histology and karyotype in classifying meningiomas. The karyotypes observed in this series of 33 meningeal neoplasms can be divided into three groups: those with no discernible chromosome abnormality or sex chromosome loss only (13 neoplasms), those with chromosome 22 abnormality only (nine neoplasms), and those with other chromosome abnormalities with or without chromosome 22 involvement (11 neoplasms). All but one were diploid or near-diploid. Our data therefore confirm the frequently reported observation of loss of chromosome 22 as a primary genetic change in meningiomas. Loss of heterozygosity studies support this observation at the molecular level, and a tumor suppressor gene is hypothesized to reside in the distal region of chromosome 22 [18, 19].

Genetic changes could be expected to result in phenotypic changes, including expression of parameters of aggression, but we noted no clear correlation between abnormal karyotypes and invasion (Table 4).

Invasiveness was not associated with an abnormal karyotype in the three angioblastic tumors we examined. All three were invasive and had only normal karyotypes. These neo-

Table 2 Chromosome 22 abnormality only

Spec. no.	Case no./age (yr)/sex	N/R	Histology	Aggression	Location	Days in culture	No. of metas	Modal no.	Karyotype
88-258	14/53/F	N	Syncytial	None	Parasagittal	5	27	45	45,XX, - 22
88-250	15/75/F	N	Transitional	None	Posterior fossa	5-6	29	45-46	45,XX, - 22/46,XX, del(22)(q12.1)
89-013	16/63/F	N	Transitional	None	Cerebrum	5	18	44-45	44,XX, - 22,inc
89-200	17/68/F	N	Transitional	None	Parietal	5	11	45	45,XX, - 22
87-090	18/62/F	N	Fibroblastic	None	Frontoparietal	5-7	51	43-45	45,XX, - 22
88-048	19/45/F	N	Fibroblastic	None	Suboccipital	3	25	45	45,XX, - 22
89-232	20/76/F	N	Fibroblastic	None	Cerebellopontine angle	8	23	45-46	46,XX/45,XX - 22
89-245	21/58/F	N	Fibroblastic	None	Not specified	5	22	44-45	44-45,XX, - 22
89-327	22/67/F	N	Fibroblastic	None	Not specified	2-7	83	45	45,XX, - 22

Abbreviations as in Table 1.

plasms, also known as intracranial hemangiopericytomas, are believed to be of mesenchymal origin, arising from a precursor cell different from the meningioma precursor [1]. Cytogenetic analysis of eight other cases has been reported, including four cases described as "angiomatous meningioma" [13], three as "hemangioblastic meningioma" [9, 13], and one as a "hemangiopericytic meningioma" [11]. Monosomy 22 has been reported in five of these cases, with additional chromosome abnormalities in two of the five.

All seven fibroblastic meningiomas had abnormal karyo-

Table 3 Chromosome abnormalities involving more than chromosome 22

Spec. no.	Case no./ age (yr)/sex	N/R	Histology	Aggression	Location	Days in culture	No. of metas	Modal No.	Karyotype
88-089	23/53/F	N	Syncytial	C,G	Cerebrum	3	54	40-42	40,X, - X, - 2,der(1)t(1;2)(p11;p11),der(6)t(1;6)(p11;p11),der(10)t(2;10)(q21;q21), + der(17)t(17;19)(p11;p11), - 19, - 22,inc
89-028	24/69/M	R[a]	Syncytial	None	Cerebrum	6-11	12	46	46,XY,add(11)(p15)
89-131	25/61/F	N	Syncytial	None	Cerebrum	8	32	60-63	60-63,XXX, - 1, - 2, + 5, - 6, - 7,inv(9), - 11, - 15, + 21, - 22,inc
89-298	26/75/F	N	Syncytial	B	Cerebello-pontine angle	7	49	45-46	46,XX,ins(5)(?q11),r(21)
89-308	27/65/F	N	Syncytial	None	Sphenoid	6-12	36	45-47	45,XX,del(2)(p16),add(11)(q24), - 22
89-046	28/75/M	N	Transitional	A,E,F,G	Posterior fossa	6-8	41	38-39	39,X, - Y,add(1)(p32), - 10, - 14, - 16, - 18
89-273	29/72/F	N	Transitional	E,F,G,H	Frontal	4	39	46	46,XX, + 7, - 22
89-311	30/52/F	N	Transitional	E,F,G	Frontal	4	27	39-43	39-43,XX,del(1)(p31), + del(1)(q22), - 6, der(11)t(6;11)(q11;p14), - 18,add(19)(q13.4), - 21, - 22
89-320	31/42/F	N	Transitional	E,F	Cerebrum	1-3	48	45-46	45,XX, - 1, - 6, - 7, der(10)t(1;10)(q25;q26), der(11)t(11;22)(p15;p11), t(15;22)(q10;q10)
90-097	32/48/M	N	Fibroblastic	F	Cerebrum	2	20	43-44	43-44,X, - Y,del(1)(p12), der(7)t(7;12)(q11;p13), inv(22)(q11q13),inc
88-217	33/20/F	R[b]	Fibroblastic	D	Posterior fossa	7	34	41-42	41-42,XX,del(11)(q13q21), - 22, + mar,inc

Abbreviations as in Table 1.

[a] Original diagnosis in 1980; no history of radiation therapy.

[b] Originally diagnosed with brainstem glioma in 1972, for which radiation therapy was given.

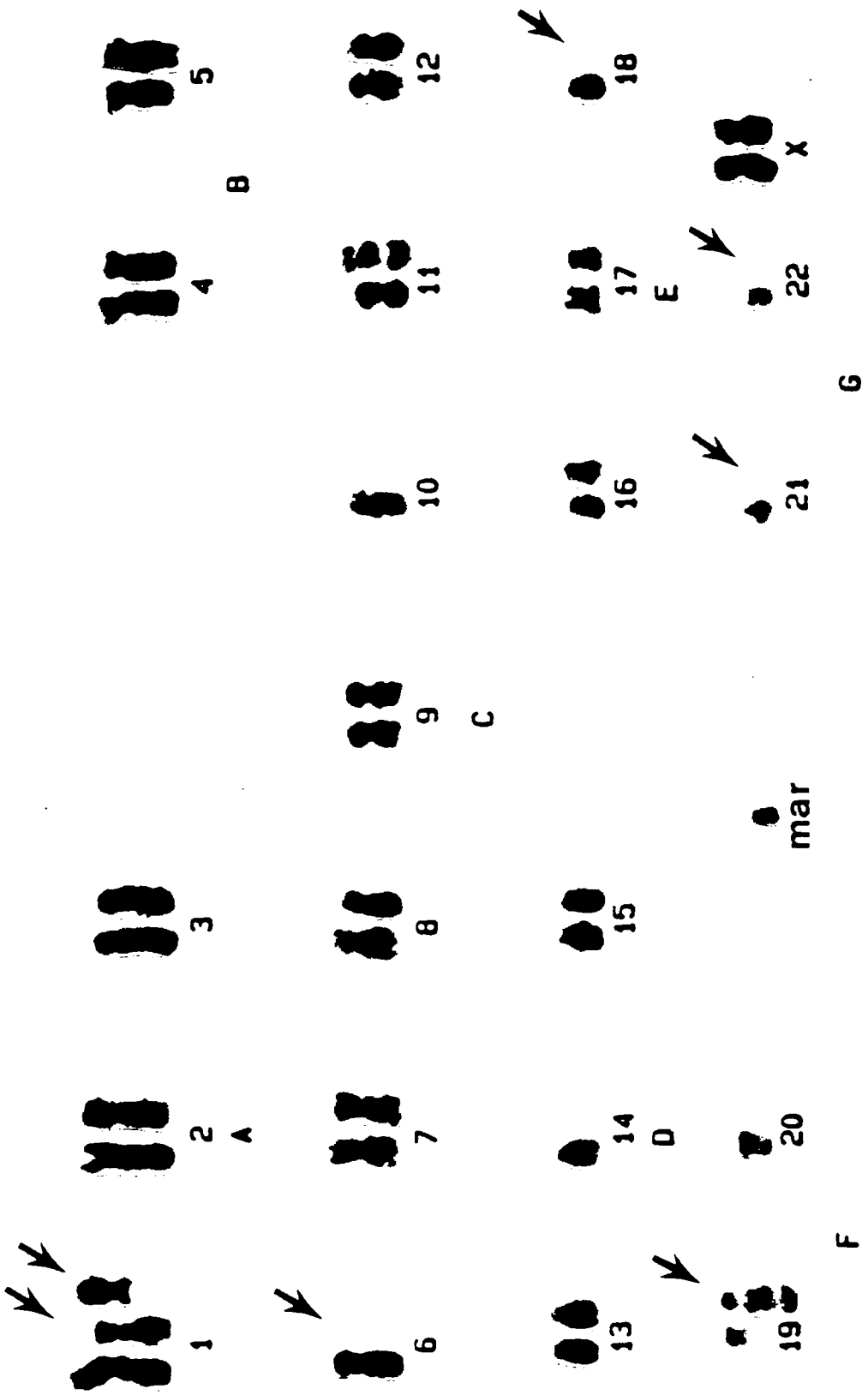

Figure 1 Representative karyotype from case 30: 41,XX,del(1)(p31), + del(1)(q22), - 6, - 10,der(11)t(6;11)(q11;p14), - 14, - 18,add(19)(q13.4), - 20, - 21, - 22, + mar. Clonal abnormalities are indicated by arrows.

Table 4 Chromosome abnormalities correlated with histology and parameters of invasion

Histology	No. of tumors	No. with one or more parameter (P) (%)[a]	No. with complex karyotype (%)[a]	Total with abnormal karyotype (K) (%)[a]	No. with both P and K (%)[a]
Angioblastic	3	3 (100)	0 (0)	0 (0)	0 (0)
Secretory	1	0 (0)	0 (0)	0 (0)	0 (0)
Syncytial	9	4 (44)	5 (56)	6 (67)	2 (22)
Transitional	13	6 (46)	4 (31)	7 (54)	4 (38)
Fibroblastic	7	2 (29)	2 (29)	7 (100)	2 (29)

[a] Percentage of all tumors with this histology.

types in this series, with chromosome 22 monosomy the most common change. Although this histologic category infrequently expressed parameters of invasion, both tumors that did so also had additional chromosome abnormalities.

We did not observe as strong a correlation between karyotype and histologic subtype in the other categories of meningiomas we examined. We observed abnormal karyotypes in 76% of the syncytial and 55% of the transitional meningiomas. Casalone et al. [4] reported that the proportions of chromosome abnormalities differed between the histologic types in their series, as did Maltby et al. [8]. To place our results in context with those from a larger number of tumors, we combined ours with those from 259 meningeal tumors reported since 1987 [3–14]. As summarized in Table 5, 161 (55%) of meningiomas had an abnormal karyotype. Abnormal karyotypes were detected in at least half of all histologic types. Fibrocytic meningioma had the largest percentage (73%) of abnormal karyotypes, but the heterogeneity in histologic diagnoses used to describe meningeal tumors make comparisons between different series very difficult. This issue is not likely to be resolved without use of a uniform nomenclature system for describing histologic subtypes of meningiomas.

Genetic instability is believed to accompany tumor progression; therefore, the secondary chromosome changes observed in meningiomas (those in addition to changes involving chromosome 22) are of interest and may indicate additional areas of the genome containing genes that play a role in tumor progression. We observed numerical and structural abnormalities involving various chromosomes. Figure 2 sums the gains and losses of whole normal copies of chromosomes (excluding chromosome 22) from this series and in the 259 tumors already described [3–14]. Losses were most frequently observed in meningiomatous and transitional histologies, and chromosomes 1, 6, 14, 18, and Y each were lost in 10 or more meningiomas. In contrast, the only chromosome in which gain was observed in 10 or more meningiomas was chromosome 20. These changes are distinctly different from the primary chromosome loss of chromosome 7 and gain of chromosome 10 that characterize other common intracranial neoplasms, specifically astrocytic neoplasms [20–22]. Structural abnormalities involving chromosomes other than chromosome 22 are shown in Figure 3; obviously, chromosome 1 contains the most frequently identified chromosomal breakpoints, apparently randomly distributed along the chromosome. Because involvement of chromosome 1 has been observed frequently in many solid neoplasms [23] it probably is not specific for meningiomas.

This work was supported in part by an American Cancer Society Clinical Oncology Career Development Award (C.G.), a grant from the American Cancer Society Maryland Division, funds from the Andrew W. Mellon Foundation, and Grant No. CA 46289-03 from NIH. The author appreciates the assistance of Michelle Carroll in manuscript preparation.

REFERENCES

1. Burger PC, Scheithauer BW, Vogel FS (1991): Surgical pathology of the nervous system and its coverings. Churchill Livingstone, New York, pp. 67–111.
2. Zang KD (1982): Cytological and cytogenetical studies on human meningioma. Cancer Genet Cytogenet 6:249–274.
3. Lopez-Gines C, Piquer J, Cerda-Nicolas M, Barcia-Solorio J, Barcia-Marino C (1989): Meningiomas: Karyotypes and histological patterns. Clin Neuropathol 3:130–133.
4. Casalone R, Granata P, Simi P, Tarantino E, Butti G, Buonaguidi

Table 5 Correlation of histology and karyotype in 292 meningeal tumors

Parameter	Meningotheliomatous[a]	Fibrocytic[b]	Transitional	Angioblastic[c]	Psammomatous	Other[d]	Total
No. of tumors	106	49	86	11	18	21	292
No. with abnormal karyotype (%)	48(45)	36(73)	47(55)	5(45)	12(67)	13(62)	161(55)

[a] Includes syncytial and endotheliomatous categories used by Casalone et al. [4], Katsuyama et al. [6], Lopez-Gines et al. [3], and this study.

[b] Includes fibroblastic and fibrous categories used by Maltby et al. [8] and Poulsgard et al. [9, 12].

[c] Includes angiomatous, hemangioblastic, and hemangiopericytic categories used by Casalone et al. [4], Rey et al. [11], Poulsgard et al. [9, 12], and Westphal et al. [14].

[d] Includes sarcomatous category used by Casartelli et al. [7], secretory category (this study) and histology not specified by Poulsgard et al. [9, 12], Casalone et al. [4], Wesphal et al. [14], and Lopez-Gines et al. [3].

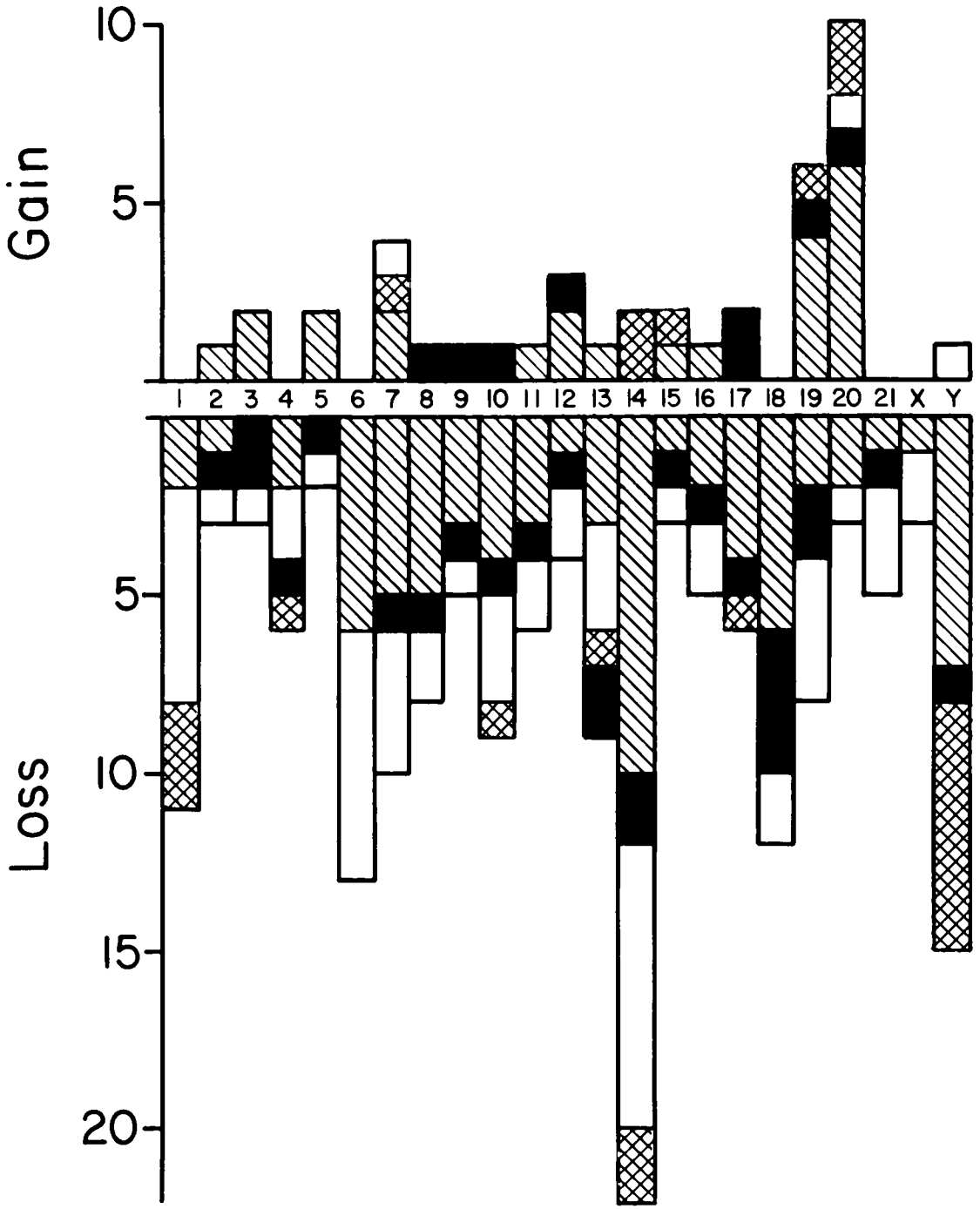

Figure 2 Clonal numerical chromosome changes (excluding chromosome 22) in 292 meningeal tumors [this study; 3, 6–9, 11–14]. Only loss and gain of copies of whole normal chromosomes are shown. Striped bars indicate meningiomatous histology (including syncytial and endotheliomatous categories used by Casalone et al. [4], Katsuyama et al. [6], Lopez-Gines et al. [3], and us; open bars indicate transitional histology; solid bars indicate fibrocytic histology (including the fibroblastic and fibrous categories used by Maltby et al. [8] and Poulsgard et al. [9, 12]); cross-hatched bars indicate other histologic categories. Meningiomatous and transitional histologies were most frequently involved in chromosome losses. Losses of chromosomes 1, 6, 14, 18, and Y were observed in 10 or more tumors each; the only chromosome which gain was observed in 10 or more tumors was #20.

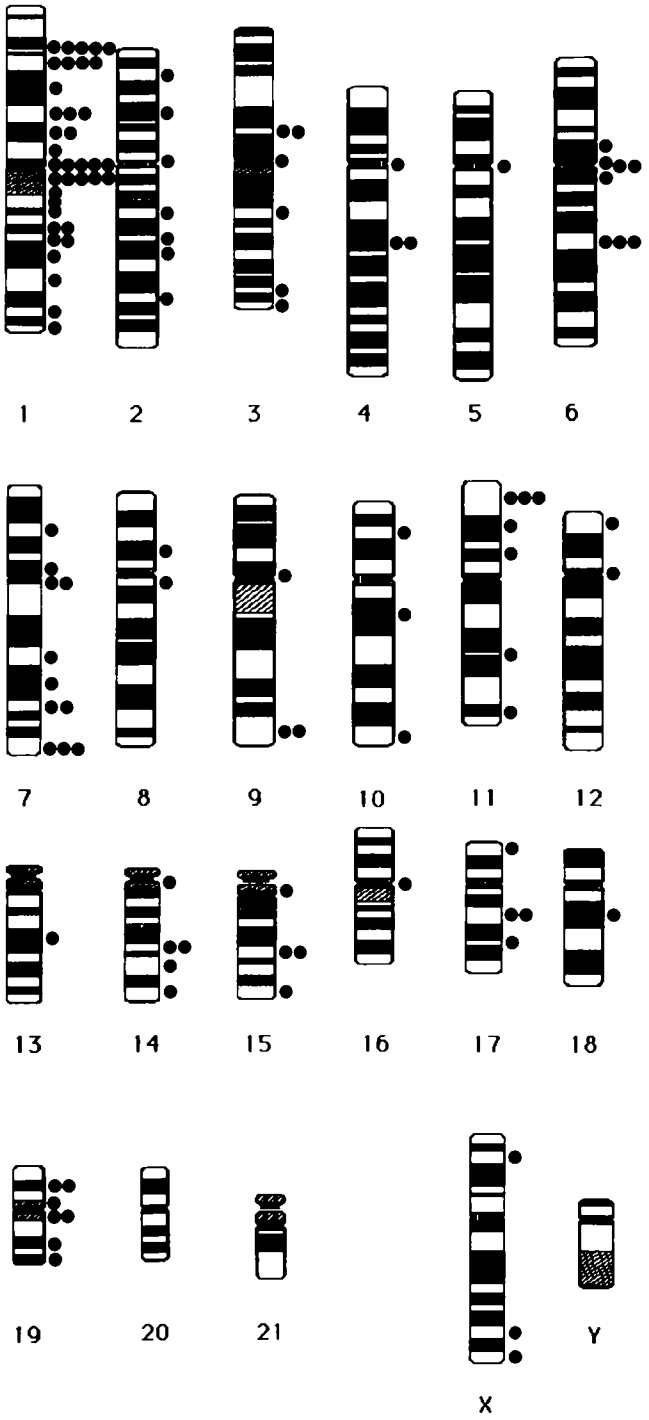

Figure 3 Identified clonal chromosome breakpoints involved in structural rearrangements in 292 meningeal tumors (excluding chromosome 22). Chromosome 1 was most frequently involved, with a random distribution along the chromosome.

R, Faggionato F, Knerich R, Solero L (1987): Recessive cancer genes in meningiomas? An analysis of 31 cases. Cancer Genet Cytogenet 27:145–149.

5. Saadi AA, Latimer F, Madercic M, Robbins T (1987): Cytogenetic studies of human brain tumors and their clinical significance. II. Meningioma. Cancer Genet Cytogenet 26:127–141.
6. Katsuyama J, Papenhauses PR, Herz F, Gazivoda P, Hiraon A, Koss LG (1986): Chromosome abnormalities in meningiomas. Cancer Genet Cytogenet 22:63–68.
7. Casartelli C, Rogatto SR, Neto JB (1989): Karyotypic evolution of human meningioma. Cancer Genet Cytogenet 40:33–45.
8. Maltby EL, Ironside JW, Battersby RDE (1988): Cytogenetic studies in 50 meningiomas. Cancer Genet Cytogenet 31:199–210.
9. Poulsgard L, Ronne M, Schroder HD (1989): Cytogenetic studies of 18 meningiomas and their clinical significance. I. Anticancer Res 9:109–112.
10. Seizinger BR, DeLeMonte S, Atkins L, Gusella JF, Martuza RL (1987): Molecular genetic approach to human meningioma: Loss of genes on chromosome 22. Proc Natl Acad Sci USA 84:5419–5423.
11. Rey JA, Bello MJ, deCampos JM, Kusak E, Moreno S (1988): Chromosomal involvement secondary to -22 in human meningiomas. Cancer Genet Cytogenet 33:275–290.
12. Poulsgard L, Schroder HD, Ronne M (1990): Cytogenetics studies of 11 meningiomas and their clinical significance. II. Anticancer Res 10:535–538.
13. Casalone R, Simi P, Granata P, Minelli E, Giudici A, Butti G, Solero CL (1990): Correlation between cytogenetic and histopathological finds in 65 human meningiomas. Cancer Genet Cytogenet 45:237–243.
14. Westphal M, Hänsel R, Kunzmann F, Hölzel F, Herrmann HD (1989): Spectrum of karyotypic aberrations in cultured human meningiomas. Cytogenet Cell Genet 52:45–49.
15. Griffin CA, Long PP, Carson BS, Brem H (1992): Chromosome abnormalities in low-grade central nervous system tumors. Cancer Genet Cytogenet 60:67–73.
16. ISCN (1985): An International System for Human Cytogenetic Nomenclature Harnden, DG, Klinger HP (eds.); published in collaboration with Cytogenet Cell Genet (Karger, Basel, 1985); also in Birth Defects: Original Article Series, Vol. 21, No. 1 (March of Dimes Birth Defects Foundation, New York, 1985).
17. Mitelman F (ed.) ISCN 1991 Guidelines for Cancer Cytogenetics, S. Karger, Basel.
18. Dumanski JP, Rouleau GA, Nordenskjold M, Colline VP (1990): Molecular genetic analysis of chromosome 22 in 81 cases of meningioma. Cancer Res 50:5863–5867.
19. Deprez RH, Groen NA, van Biezen NA, Hagemeijer A, van Drunen E, Koper JW, Avezaat CJ, Bootsma D, Zwarthoff EC (1991): A t(4:22) in a meningioma points to the localization of a putative tumor-suppressor gene. Am J Hum Genet 48:783–790.
20. Bigner SH, Mark J, Burger PC, Mahaley MS, Bullard DE, Muhlbaier LH, Bigner DD (1988): Specific chromosomal abnormalities in malignant human gliomas. Cancer Res 48:405–411.
21. Jenkins RB, Kimmel DW, Moertel CA, Schultz CG, Scheithauer BW, Kelly PJ, Dewald GW (1989): A cytogenetic study of 53 human gliomas. Cancer Genet Cytogenet 39:253–279.
22. Griffin CA, Long PP, Brem H, Carson BS (1992): Chromosome analysis of 50 high grade astrocytomas [Abstract 22]. Cancer Genet Cytogenet 59:106.
23. Mitelman F (1991): Solid tumors. In: Catalogs of Chromosome Aberrations in Cancer F Mitelman, ed. Lund, Sweden: A. J. Wiley-Liss, pp.1479–1498.