Proc. Natl. Acad. Sci. USA
Vol. 84, pp. 9275–9279, December 1987
Medical Sciences

Deletion mapping of a locus on human chromosome 22 involved in the oncogenesis of meningioma

(carcinogenesis/restriction-fragment-length polymorphism/recessive mutations)

JAN P. DUMANSKI*†, ELISABETH CARLBOM†‡, V. PETER COLLINS*, AND MAGNUS NORDENSKJÖLD†

*Ludwig Institute for Cancer Research, Stockholm Branch, Box 60004, S-10401 Stockholm, Sweden; ‡Department of Neurosurgery, Karolinska Hospital, S-10401 Stockholm, Sweden; and †Department of Clinical Genetics, Karolinska Hospital, S-10401 Stockholm, Sweden

Communicated by George Klein, September 8, 1987

ABSTRACT **The genotypes were analyzed at 11 polymorphic DNA loci (restriction fragment length alleles) on chromosome 22 in tumor and normal tissue from 35 unrelated patients with meningiomas. Sixteen tumors retained the constitutional genotype along chromosome 22, while 14 tumors (40%) showed loss of one constitutional allele at all informative loci, consistent with monosomy 22 in the tumor DNA. The remaining 5 tumors (14%) showed loss of heterozygosity in the tumor DNA at one or more chromosome 22 loci and retained heterozygosity at other loci, consistent with variable terminal deletions of one chromosome 22 in the tumor DNA. The results suggest that a meningioma locus is located distal to the myoglobin locus, within 22q12.3–qter. Multiple loci on other chromosomes also were studied, and 12 of the 19 tumors with losses of chromosome 22 alleles showed additional losses of heterozygosity at loci on one to three other chromosomes. All tumors that retained the constitutional genotype on chromosome 22 also retained heterozygosity at all informative loci on other chromosomes analyzed, suggesting that the rearrangement of chromosome 22 is a primary event in the tumorigenesis of meningioma.**

Meningioma, a common intracranial tumor in man, is generally benign and has its highest incidence during the fifth and six decades of life. On average twice as many females are affected as males. The majority of the cases are sporadic and have solitary tumors (1). However, there are indications that a genetic predisposition for developing a meningioma exists—e.g., reports of familiar aggregations of meningiomas (2–5), two monozygotic twins both with multiple tumors (6), and a patient with a constitutional ring chromosome 22 who had multiple meningiomas (7). Extensive cytogenetical analysis of cultured meningioma cells undertaken during the last two decades have frequently revealed monosomy 22 and, in a small number of cases, deletions of the long arm of chromosome 22 (8). Furthermore, patients with hereditary bilateral acoustic neurinomas may develop meningiomas as a second tumor form (9). Recently, loss of chromosome 22q alleles in acoustic neurinomas has been reported (10, 11).

Specific chromosome deletions and monosomy involving chromosomes 13 and 11 are frequent in retinoblastoma and Wilms tumor cells, respectively (12). Such patients may carry constitutional deletions of these chromosomes, predisposing for multiple tumors (13). Furthermore, molecular genetic studies of retinoblastoma and Wilms tumors have revealed rearrangements specifically affecting chromosomes 13q and 11p, respectively (14). These rearrangements serve to unmask recessive mutations predisposing for oncogenesis. Retinoblastoma and Wilms tumors are sometimes associated with primary tumors in other tissues. Such tumors may carry similar genetic rearrangements of the same chromosomal regions (15–17).

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

The information available on meningiomas shows obvious parallels to the observations in retinoblastoma and Wilms tumor and suggests that recessive mutations on chromosome 22 may be involved in the tumorigenesis of meningioma. We have studied primary tumor material from meningiomas in an attempt to regionally localize a meningioma locus by deletion mapping using polymorphic DNA markers.

MATERIALS AND METHODS

Human Tissue Samples. Surgical specimens of meningiomas were obtained from 35 unrelated patients (25 female and 10 male patients). Tumor tissue was frozen at −135°C for between 1 month and 1 year before isolation of the DNA. Constitutional tissue DNA was isolated from peripheral blood or primary skin fibroblast culture (case 24). Clinical details of the cases studied are summarized in Table 1.

Recombinant DNA Probes. The polymorphic DNA markers used are listed in Tables 2 and 3. A 540-base-pair (bp) *Bam*HI fragment of the plasmid phu-C-λ-2 was used as probe for the immunoglobulin light chain constant region locus (*IGLC*). For the myoglobin locus (*MB*), a 0.6-kilobase (kb) *Bam*HI–*Bgl* II fragment of the plasmid HM27.B2.9 was used. This fragment displays the *Taq* I polymorphism (1.6- and 1.3-kb alleles) but not the additional constant bands (19).

Southern Hybridizations and Densitometric Analysis. High molecular weight DNA was isolated from peripheral blood leukocytes and tumor tissue as described (21). Restriction endonuclease digestion, agarose gel electrophoresis, Southern transfer, prehybridization, hybridization of the membranes to the probes radiolabeled with ^{32}P by random priming, and autoradiography were performed as reported (21, 22).

Bound probes were removed from the membranes by treatment with 0.4 M NaOH, and these were repeatedly rehybridized. Several combinations of two or three different recombinant DNA probes were simultanously hybridized to the same Southern blot membrane. When loss of alleles was detected in the tumor tissue DNA on one chromosome, the analysis was repeated with a new membrane and a new combination of probes specific for other chromosomes together with the probe detecting the loss of allele.

Quantitative densitometric scanning of the x-ray films was performed with an LKB Ultroscan XL scanning densitometer. The autoradiographic signals corresponding to heterozygous loci on different chromosomes were densitometrically quantified and electronically integrated to normalize for different amounts of DNA in the normal and tumor tissue lanes.

RESULTS

Monosomy and Deletions of Chromosome 22. Loss of constitutional chromosome 22 alleles were detected in 19 of the 35 tumors studied. These 19 tumors could be divided into

Table 1. Clinical summary of patients

Case no.	Sex	Age at diagnosis, yr	Histopathology*	Localization†	Tumor cells‡, % in sample
1	Male	51	Transitional	Convexity	90
2	Male	23	Meningotheliomatous	Convexity	85
3	Female	53	Fibrous	Convexity	85
4	Female	69	Fibrous	Spinal	95
5	Female	53	Meningotheliomatous	Convexity	95
6	Female	49	Meningotheliomatous	Skull base	90
7	Female	75	Meningotheliomatous	Convexity	90
8	Female	73	Transitional	Skull base	95
9	Male	59§¶	Anaplastic	Convexity	60
10	Female	56	Meningotheliomatous	Convexity	95
11	Female	66§	Fibrous	Convexity	60
12	Female	57	Transitional	Convexity	90
13	Female	49	Fibrous	Convexity	95
14	Female	68§	Fibrous	Spinal	75
15	Female	77§	Fibrous	Convexity	90
17	Male	50	Transitional	Convexity	80
18	Male	61	Transitional	Convexity	85
19	Female	72	Meningotheliomatous	Spinal	90
20	Female	27	Anaplastic	Skull base	95
21	Male	43	Psammomatous	Skull base	95
22	Female	64	Psammomatous	Spinal	85
23	Male	43	Meningotheliomatous	Convexity	85
24	Female	9	Transitional	Intraventricular	95
25	Female	63	Transitional	Convexity	90
26	Female	39	Anaplastic	Skull base	85
27	Male	66§	Transitional	Convexity	90
28	Female	66	Transitional	Skull base	90
29	Male	56	Fibrous	Convexity	80
30	Female	37	Meningotheliomatous	Convexity	80
31	Male	63	Transitional	Convexity	85
32	Female	72	Fibrous	Convexity	75
33	Female	41	Anaplastic‖	Convexity	95
34	Female	44	Meningotheliomatous**	Convexity	85
35	Female	59§	Transitional††	Spinal	85
36	Female	78	Transitional	Convexity	95

All patients with the exception of case no. 24 (no follow up) were known to be alive as of April 1987. Case no. 6 had been previously treated with chemotherapy for acute myelocytic leukemia at the age of 47.

*Histopathological control of each investigated sample of the tumor tissue was obtained. The tumors were classified according to the World Health Organization (18).

†"Convexity" includes the localization of the tumor parasaggitaly, at the pterion and elsewhere on the convexity of the brain. "Skull base" includes localization at the pons angle.

‡The percentage of tumor cell nuclei in each sample investigated was estimated histopathologically.

§Patients studied at recurrence.

¶When first diagnosed at the age of 51, the tumor of case no. 9 had only increased cell density and could not be classified as an anaplastic meningioma.

‖Heterogenous tumor with areas of meningioma (transitional type) and anaplastic meningioma. Three samples of this tumor were studied—meningioma, mixed meningioma-anaplastic meningioma, and anaplastic meningioma. An estimation of the percentage of tumor cell nuclei in each tumor sample gave approximately the same result.

**Difficult to classify; extensive myxomatous changes were noted. The father of this patient had both meningioma and malignant glioma.

††Atypical, high frequency of mitoses and cell polymorphism.

two groups. One group consisted of 14 tumors (40% of all tumors, for details, see Table 2), which showed loss of one constitutional allele at all informative loci on chromosome 22. This finding is consistent with monosomy due to a nondisjunction event and loss of one chromosome 22 in the tumor tissue. The other group consisted of 5 tumors (14%; cases 11, 29, 32, 33, and 34), which showed retention of constitutional heterozygosity in the tumor tissue DNA at one or more chromosome 22 loci and loss of heterozygosity at least at one other locus.

The constitutional and tumor tissue genotypes at the *D22S9* locus defined by *Taq* I genomic blot analysis for restriction-fragment-length polymorphisms, which we call the "*D22S9* (*Taq* I) locus," and at the *MB* locus in case 34 are shown in Fig. 1*A*. Both constitutional alleles are retained at the *D22S9* (*Taq* I) locus, while the longer allele is lost at the *MB* locus in the tumor tissue DNA. Case 34 retained the constitutional heterozygosity in the tumor tissue DNA at the *D22S10* (*Pst* I) locus (Fig. 1*B*) and at three other chromosome 22 loci: *IGLV* (*Taq* I), *IGLV* (*Kpn* I), and *D22S1* (*Bgl* II) (Table 2; autoradiograms not shown).

Similarly, case 33 was constitutionally heterozygous at the *D22S9* (*Taq* I) and *MB* loci. As shown in Fig. 1*C*, three different samples of the tumor tissue all showed a retained

Table 2. Loss of heterozygosity on chromosome 22 in meningiomas

Case no.	Locus* (enzyme)										
	D22S9 (*Taq* I)	*D22S9* (*Msp* I)	*IGLV* (*Kpn* I)	*IGLV* (*Taq* I)	*IGLC* (*Eco*RI)	*D22S1* (*Bgl* II)	*D22S1* (*Taq* I)	D22S10 (*Taq* I)	*D22S10* (*Pst* I)	*MB* (*Taq* I)	*SIS* (*Hin*dIII)
Cases with monosomy 22											
1	*1*	—	—	*2*	—	—	—	*1*	—	*2*	—
3	—	—	*2*	*1*	*1*	—	*1*	—	—	—	*1*
4	*1*	—	*2*	*2*	—	*2*	—	—	*1*	*1*	—
7	*1*		—	—	—	—	—	—		*1*	—
10	*2*	—	*1*	*1*	*1*	—	—	—	*2*	*2*	—
13	*2*	—	*1*	—	*1*	—	—	*1*	*1*	*2*	—
14	—	—	*2*	*3*	*1*	—	—	—	*2*	—	*1*
15	(*2*)	—	*1*	—	—	—	—	—	—	(*2*)	—
18	—	—	*3*	*1*	—	—	—	—	*2*	*1*	*1*
22	—	—	*1*	—	—	*1*	—	—	—	—	—
23	*2*	—	*3*	*2*	—	—	*2*	—	—	*2*	*1*
26	*1*	—	—	—	—	*1*	—	—	*2*	—	*1*
27	*2*	2	—	—	—	—	—	—	—	—	*1*
31	*1*	—	—	1,2	—	*1*	—	—	*2*	—	—
Cases showing 22q deletions											
11	1,2	—	—	—	—	1,2	—	—	1,2	(2,2)†	*1*
29	—	—	—	1,2	(1,1)†	(*1*)	—	*2*	—	*2*	—
32	1,2	—	—	1,2,3	(1,1)†	*1*	—	—	—	(*2*)	*1*
33‡	1,2	—	—	(1,1)†	*3*	*1*	*2*	—	*2*	*2*	—
34	1,2	—	1,2	1,2	—	1,2	—	—	1,2†	*2*	(*1*)

Two or more different numbers (e.g., 1,2 or 1,2,3) indicate the restriction fragment length alleles present in tumor tissue at loci that were constitutionally heterozygous. Italicized numbers indicate loss of one constitutional allele. Constitutional homozygosity is indicated by —. Absence of an entry indicates no data. Numbers in parentheses ( ) indicate retention or loss of alleles at constitutionally homozygous loci as established by densitometric scanning. Decreased intensity of the autoradiographic signal at these loci was interpreted as indicating a loss of one of two constitutionally homozygous alleles.

*The gene probes used were *IGLC*, phu-C-λ-2; *IGLV*, pV3.3; *SIS*, pSM-1; and the anonymous chromosome 22 loci: *D22S1*, pMS3-18; *D22S9*, p22/34; and *D22S10*, p22C1-18. *D22S9* was regionally localized to 22q11 (19). The chromosomal markers *IGLV*, *IGLC*, *D22S1*, *MB*, and *SIS* were ordered on chromosome 22q as described (20). *D22S10* has been assigned to chromosome 22 (19). Note that the results obtained from cases 29 and 34, assuming that the deletions in these cases are not interstitial, indicate the regional localization of this marker between *IGLV* and *MB*, which corresponds to 22q11.1–13.1.

†A breakpoint region.

‡All three specimens of the tumor (meningioma and anaplastic meningioma) gave identical results (see Table 1).

constitutional genotype at the *D22S9* (*Taq* I) locus, while the longer allele at the *MB* locus had been lost. The three tumor tissue samples were derived from different parts of the tumor with distinctly different morphologies (see Table 1). In addition to these loci, all three samples of tumor tissue showed loss of one constitutional allele at four other chromosome 22 loci: *IGLC* (*Eco*RI), *D22S10* (*Pst* I), *D22S1* (*Taq* I), and *D22S1* (*Taq* I) (Table 2; autoradiograms not shown).

In Fig. 2*A* constitutional and tumor tissue genotypes of case 11 are presented. In this experiment three different probes were hybridized simultaneously to the same membrane. Retained constitutional heterozygosity in the tumor tissue DNA was found at the *D22S9* locus on chromosome 22 and the *APOC2* locus on chromosome 19. Case 11 was constitutionally homozygous at the *MB* locus. There was no decreased intensity of the autoradiographic signal at the *MB* locus in the tumor tissue DNA compared with the normal DNA (Fig. 2). Retained constitutional heterozygosity in the tumor DNA of case 11 also was detected at the *D22S1* (*Bgl* II) (Fig. 2*B*) and *D22S10* (*Pst* I) loci (Table 2, autoradiogram not shown), while loss of the shorter allele was found in the tumor tissue DNA at the *SIS* locus (Fig. 2*C*).

In Fig. 3 autoradiograms showing constitutional and tumor tissue genotypes at different chromosome 22 loci of case 32 are presented. Retained heterozygosity in the tumor tissue DNA was demonstrated at the *D22S9* (*Taq* I) (Fig. 3*A*) and *IGLV* (*Taq* I) loci (Table 2; autoradiogram not shown). Loss of constitutional heterozygosity in the tumor DNA of case 32 was found at the *D22S1* (*Bgl* II) locus (Table 2, autoradiogram not shown) and at the *SIS* locus as shown in Fig. 3*B*.

In the tumor tissue DNA from case 29, constitutional heterozygosity was retained at the *IGLV* (*Taq* I) locus (Fig. 4*A*), while one constitutional allele was lost at the *MB* (Fig. 4*B*) and *D22S10* (*Taq* I) loci (Table 2; autoradiogram not shown).

The five meningiomas detailed above (cases 11, 29, 32, 33, and 34) showed retention of the constitutional genotypes on chromosome 22 in the tumor DNA at centromeric loci and loss at telomeric loci. This is consistent with variable terminal deletions of one chromosome 22 in the tumor tissue DNA. The breakpoints were localized within four different regions as detailed in Table 2. The only segment of chromosome 22 consistently lost in the tumor tissue DNA of these five cases is the part distal to the *MB* locus. This corresponds to 22q12.3–qter and suggests that the proposed recessive meningioma locus is located within this part of the chromosome.

No evidence for an interstitial deletion on chromosome 22 could be found in any tumor with 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 19 cases with loss of constitutional alleles. This indicates that the loss of alleles of one chromosome 22 was due to deletion or monosomy of chromosome 22 rather than mitotic recombination or loss and reduplication of the remaining alleles. The remaining hybridization signal, when one constitutional allele was lost in the tumor tissue DNA, varied in different tumors and corresponded well with the presence of normal stromal cellular DNA, lymphocytic infiltrate, etc., in the tumor material as histopathologically verified in Table 1.

Table 3. Loss of heterozygosity in meningiomas

Case no.	Chromosomes remaining heterozygous	Chromosomes losing heterozygosity
1	1, 3, 7, 11, 13, 16, 19	22, 14, 17
2	6, 11, 13, 17, 22	ND
3	1, 7, 11, 13, 14, 17	22
4	6, 7, 11, 13, 14, 17, 19	22
5	1, 6, 11, 13, 16, 19, 22	ND
6	2, 6, 11, 13, 17, 22	ND
7*	14	22, 11, X
8	1, 2, 10, 11, 19, 22	ND
9	2, 3, 6, 7, 11, 13, 14, 15, 17, 19, 20, 22	ND
10	1, 11, 12, 13, 19, X	22, 2
11	2, 6, 11, 12, 13, 14, 15, 17, 19	22q-, 7
12	2, 6, 7, 11, 12, 14, 15, 17, 20, 22, X	ND
13	2, 6, 7, 10, 11, 13, 14, 15, 17, 19, 21, X	22
14	2, 6, 11, 12, 13, 14, 17, 20	22, X
15	6, 12, 13, 14, 15, 17, 19, 20, X	22, 2
17	1, 2, 3, 11, 13, 14, 16, 17, 19, 20, 22	ND
18	1, 2, 3, 7, 11, 12, 13, 17	22
19	1, 3, 6, 8, 13, 15, 22	ND
20	1, 2, 3, 6, 7, 8, 11, 12, 13, 14, 17, 22, X	ND
21	2, 7, 11, 13, 14, 16, 18, 20, 22	ND
22	2, 6, 7, 10, 11, 13, 16, 17, 19	22
23	1, 3, 7, 8, 11, 13, 17, 19	22,6
24	1, 2, 3, 7, 8, 13, 14, 15, 16, 17, 18, 22	ND
25	6, 7, 12, 13, 14, 17, 22, X	ND
26	6, 7, 8, 11, 12, 13, 15, 17, X	22, 1, 10, 18
27	1, 2, 3, 7, 8, 11, 12, 13, 14, 17, 19	22
28	1, 2, 3, 6, 7, 8, 10, 11, 12, 13, 17, 22, X	ND
29	1, 2, 6, 11, 13, 14, 17, 20	22q-, 7, 18
30	6, 11, 12, 13, 14, 15, 17, 20, 22	ND
31	2, 3, 6, 7, 12, 15, 17, 19, 20	22, 11, 14
32	1, 2, 3, 6, 7, 8, 11, 12, 13, 14, 15, 17, X	22q-
33†	6, 7, 11, 12, 13, 14, 15, 17, 19, 20, X	22q-, 1
34	2, 6, 7, 11, 12, 13, 14, 15, 17, 18, X	22q-, 3
35	2, 6, 7, 8, 11, 13, 14, 15, 19, 22, X	ND
36	2, 7, 8, 14, 15, 16, 17, 18, 19, 20, 22	ND

Alleles at loci on each chromosome (except chromosomes 4, 5, 9, 21, and Y) were determined in constitutional and tumor DNA from meningiomas. Chromosomes not delineated above were constitutionally homozygous. The loci examined were *D1S2, AT3, D2S1, CRYG, D3S2, D3S3, D6S10, MetH, CA2, D10S1, D11S12, HRAS1, HBBC, D12S7, D13S1, D13S2, D13S3, D13S4, D13S5, D14S1, D15S1, APRT, D17S1, D17S2, D17S3, D18S1,* APOC2(cDNA), *D19S11, D20S4, D22S1, D22S9, D22S10, IGLC, IGLV, SIS, MB, DXS15, DXS51, DXS52* (the nomenclature is according to ref. 19). ND, not detected.

*Chromosomes 6, 7, 8, 10, 16, 17, and 20 were not analyzed.

†All three specimens of the tumor gave identical results (Table 1).

Sixteen tumors (46%) retained the constitutional genotype in the tumor tissue DNA at all informative loci on chromosome 22 (Table 3). Those that were constitutionally homozygous at the *SIS* locus, the most telomeric chromosome 22 marker used in this study, showed no evidence of loss of any allele as established densitometric scanning (data not shown).

No abnormal bands due to, for instance, translocations close to the investigated loci were detected in any of tumors studied. Furthermore, no correlation between chromosome 22 rearrangements in tumor tissue and parameters such as age and sex of the patient, tumor size, malignancy grade, or clinical course was found.

Loss of Alleles on Other Chromosomes. Multiple loci on other chromosomes were also studied, as shown in Table 3. In addition to chromosome 22 rearrangements, loss of heterozygosity in the tumor tissue DNA was found on chromosomes 1, 2, 3, 6, 7, 10, 11, 14, 17, 18, and X. In one tumor (case 26, an anaplastic meningioma), there was loss of heterozygosity on four chromosomes (including chromosome 22); in four tumors, three chromosomes were affected; six tumors showed losses on two chromosomes; and six showed losses on only chromosome 22. Constitutional heterozygosity in the tumor tissue DNA was retained at all informative loci in 16 tumors (for details see Table 3). All tumors that retained the constitutional genotype on chromosome 22 also retained the constitutional heterozygosity on all other chromosomes studied.

No additional alleles that were not present in the normal tissue DNA were detected in the tumor DNA at any of >50 loci studied, indicating that no mispairing of samples had occurred.

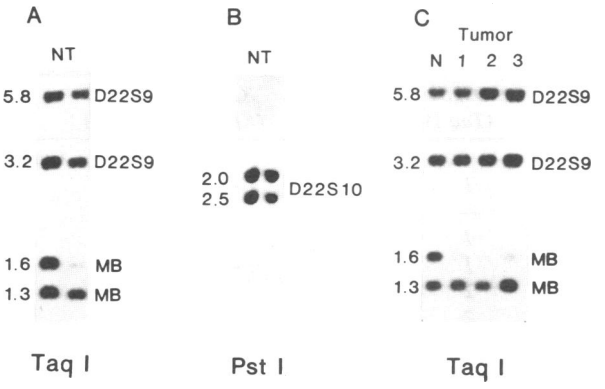

FIG. 1. Loss and retention of constitutional heterozygosity on chromosome 22 in cases 34 (*A* and *B*) and 33 (*C*) in DNA from normal (lanes N) and tumor (lanes T) tissues. The designations of probes used are indicated to the right of each autoradiogram, and the allele length in kb, to the left. (*C*) In case 33, normal tissue (lane N) and three samples of tumor tissue (lanes 1, 2, and 3) were analyzed (see Table 1). *Taq* I and *Pst* I are the enzymes used with the probes to generate the restriction fragment length alleles.

DISCUSSION

In the present study, a tentative locus on chromosome 22 involved in the oncogenesis of meningioma could be region-

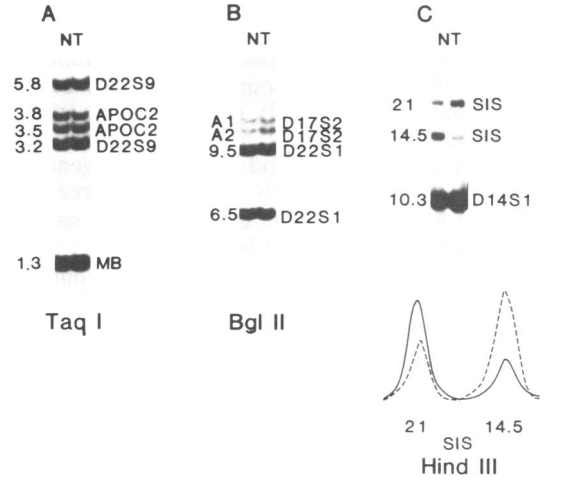

FIG. 2. Alleles present at loci on chromosomes 14, 17, 19, and 22 in the normal (lanes N) and tumor (lanes T) tissue DNA of case 11. The designations of the probes used are indicated to the right of each autoradiogram, and the allele length in kb, to the left. (*A* and *B*) Retention of the constitutional heterozygosity in the tumor DNA at loci on chromosomes 17 (*D17S2*), 19 (*APOC2*), and 22. (*C*) Loss of constitutional heterozygosity at the *SIS* locus shown in an autoradiogram and quantitated by the densitometric tracings of the hybridization signal from the *SIS* alleles (- - -), normal; —, tumor). The 10.3-kb band of the *D14S1* locus on chromosome 14 is not included in the tracings.

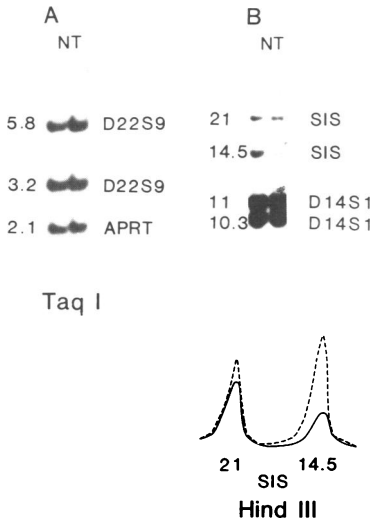

FIG. 3. Retention and loss of constitutional heterozygosity at loci on chromosomes 14 (*D14S1*) and 22 in meningioma of case 32. DNA was obtained from normal (lanes N) and tumor (lanes T) tissue. The designations of the probes used are indicated to the right of each autoradiogram, and allele length in kb, to the left. The homozygous *APRT* locus of chromosome 16 is also shown in *A*. Below the autoradiogram in *B*, densitometric tracings of the autoradiographic signal from *SIS* alleles are shown (- - -, normal; —, tumor).

ally localized, taking advantage of the information provided by tumors with variable terminal deletions of this chromosome. The only segment of chromosome 22 that was consistently lost includes the part between the *MB* locus and the telomere that corresponds to 22q12.3–qter.

The recent isolation of the retinoblastoma locus (17) relied on its detailed localization, based on linkage studies of families in which this disease segregates. It is unlikely that linkage studies will contribute to the precise localization of the meningioma locus because familiar aggregation of meningioma is rare. Therefore, study of deletions on one chromosome 22 in meningioma is an alternative approach.

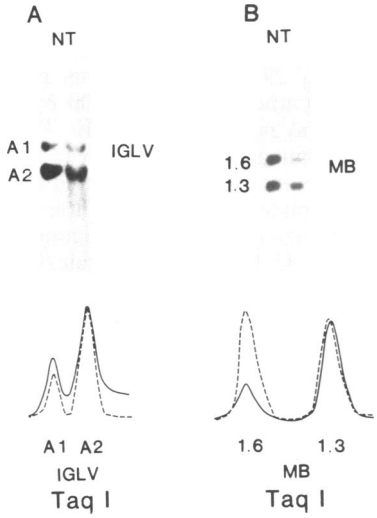

FIG. 4. Retention and loss of constitutional alleles on chromosome 22 in the meningioma of case 29. Normal (lanes N) and tumor (lanes T) tissue DNA are indicated. The designations of the probes used are indicated to the right of each autoradiogram, and allele length in kb, to the left. Densitometric tracings are shown underneath each of the autoradiograms (- - -, normal; —, tumor).

The breakpoints in the tumors with deletions were scattered within four different regions of the long arm of chromosome 22. The localization of the breakpoints between *IGLC* and *D22S1* in cases 29 and 32 and between *IGLV* and *IGLC* in case 33 may correspond to the breakpoint cluster region and the breakpoint region of the 8;22 translocation observed in Burkitt lymphoma, respectively (23).

In addition to chromosome 22 rearrangements, losses of alleles were found on one to three other chromosomes involving 10 different autosomes and on the X chromosome. However, in the tumors that showed such losses, chromosome 22 was always involved. This strongly suggests that the rearrangement on chromosome 22 is a primary and fundamental event in the tumorigenesis of meningioma. This is in agreement with the finding of a patient with a constitutional ring chromosome 22 who had multiple meningiomas (7). Further support for this hypothesis comes from the analysis of the tumor of case 33, which showed different growth patterns in different areas (Table 1). The individual tumor genotypes found in these subfractions were identical with rearrangements involving chromosomes 1 and 22 (Tables 2 and 3). This also would suggest that progression from a benign to an anaplastic meningioma is due to factors that occur subsequently to the rearrangement of chromosome 22.

The authors thank Ulla Aspenblad, Liss Fjelkestam, Maja-Lena Grankvist, Barbro Högrell, and Birgitta Ivarsson for excellent technical assistance; Ann-Mari Olsson for help in manuscript preparation; and Drs. R. White, W. Cavenee, D. Barker, T. Drayna, R. Leach, P. Pearson, E. Bakker, E. Prochownick, G. Vande Woude, R. Tashian, T. Dryja, J. Gusella, M. Wigler, H. Kazezian, L.-C. Tsui, S. Humphries, M. Litt, B. White, P. Leader, J.-C. Kaplan, A. Jeffreys, K. Davies, and S. Mandel and the American Type Culture Collection for providing recombinant DNA probes. This work was supported in part by grants from the Swedish Cancer Society, Inga-Britt och Arne Lundbergs Research Foundation, and the Swedish Work Environmental Fund.

1. Russel, D. S. & Rubinstein, L. J. (1977) *Pathology of Tumors of the Nervous System* (Arnold, London), 4th Ed., pp. 66–67.
2. Gaist, G. & Piazza, G. (1959) *J. Neurosurg.* **16**, 110–113.
3. Joynt, R. J. & Perret, J. E. (1961) *Neurlogy* **11**, 164–165.
4. Joynt, R. J. & Perret, J. E. (1965) *J. Neurol. Neurosurg. Psychiatry* **28**, 163–164.
5. Memon, M. Y. (1980) *Neurosurgery* **7**, 262–264.
6. Sedzimir, C. B., Frazer, A. K. & Roberts, J. R. (1973) *J. Neurol. Neurosurg. Psychiatry* **36**, 368–376.
7. Arinami, T., Kondo, I., Hamaguchi, H. & Nakajima, S. (1986) *J. Med. Genet.* **23**, 178–180.
8. Zang, K. D. (1982) *Cancer Genet. Cytogenet.* **6**, 249–274.
9. Eldridge, R. (1981) *Adv. Neurol.* **29**, 57–65.
10. Seizinger, B. R., Martuza, R. L. & Gusella, J. F. (1986) *Nature (London)* **322**, 644–647.
11. Seizinger, B. R., Rouleau, G., Ozelius, L. J., Lane, A. H., St. George-Hyslop, P., Huson, S., Gusella, J. F. & Martuza, R. L. (1987) *Science* **236**, 317–319.
12. Heim, S. & Mittelman, F. (1987) *Cancer Cytogenetics* (Liss, New York), pp. 227–261.
13. Yunis, J. J. & Ramsay, N. (1978) *Am. J. Dis. Child.* **132**, 161–163.
14. Cavenee, W. K., Koufos, A. & Hansen, M. F. (1986) *Mutat. Res.* **168**, 3–14.
15. Hansen, M. F., Koufos, A., Gallie, B. L., Phillips, R. A., Fogstad, Ø., Brøgger, A., Gedde-Dahl, T. & Cavenee, W. K. (1985) *Proc. Natl. Acad. Sci. USA* **82**, 6216–6220.
16. Koufos, A., Hansen, M F., Copeland, N. G., Jenkins, N. A., Lampkin, B. C. & Cavenee, W. K. (1985) *Nature (London)* **316**, 330–334.
17. Friend, S. H., Bernards, R., Rogelj, S., Weinberg, R. A., Rapaport, J. M., Albert, D. M. & Dryja, T. P. (1986) *Nature (London)* **323**, 643–646.
18. Zülch, K. J. (1979) *International Histological Classification of Tumors* (World Health Organization, Geneva), No. 21.
19. Wiliard, H. F., Skolnick, M. H., Pearson, P. L. & Mandel, J.-L. (1985) *Cytogenet. Cell Genet.* **40**, 360–489.
20. Julier, C., Reghis, A., Szajnert, M. F., Kaplan, J.-C., Lathrop, G. M. & Lalouel, J. M. (1985) *Cytogenet. Cell Genet.* **40**, 665.
21. Lundberg, C., Skoog, L., Cavenee, W. K. & Nordenskjöld, M. (1987) *Proc. Natl. Acad. Sci. USA* **84**, 2372–2376.
22. Feinberg, A. P. & Vogelstein, B. (1983) *Anal. Biochem.* **132**, 6–13.
23. Tippet, P. & Kaplan, J.-C. (1985) *Cytogenet. Cell Genet.* **40**, 268–295.