Chromosome Abnormalities in Low-Grade Central Nervous System Tumors

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ABSTRACT: *Ependymomas, oligodendrogliomas, and low-grade astrocytomas are slow-growing central nervous system (CNS) tumors that occur in both adults and children, whereas craniopharyngiomas and choroid plexus papillomas occur predominantly in children. We examined karyotypes of 32 of these low-grade tumors, including ten oligodendrogliomas, six ependymomas, 11 low-grade astrocytomas, four craniopharyngiomas, and one choroid plexus papilloma. Only normal karyotypes were obtained from 6 oligodendrogliomas. The rest had normal stemlines; three tumors had 45,X,−Y sidelines and one tumor had a sideline of monosomy 22. The most frequent abnormalities in the ependymomas were +7 (three tumors), −21 (two tumors), −22 (two tumors), and del(9)(p22) (two tumors). Gains of chromosome 7 and deletions of 9p were found more often in high-grade gliomas. Seven low-grade astrocytomas had normal stemlines, two had chromosome 7 abnormalities, a pilocystic astrocytoma had +der(15), and one tumor had a −Y sideline. The four craniopharyngiomas and one choroid plexus tumor were all apparently normal. The cytogenetics of low-grade CNS tumors differ from higher grade gliomas in that most low-grade tumors show little deviation from the normal karyotype.*

INTRODUCTION

Ependymomas, oligodendrogliomas, and low-grade astrocytomas are slow-growing central nervous system (CNS) tumors that occur in both adults and children, whereas craniopharyngiomas and choroid plexus papillomas occur predominantly in children [1]. Although high-grade brain tumors have been studied cytogenetically in several laboratories [2–5], and recurrent chromosome abnormalities, including deletions of 9p, trisomy 7, and double minute (dmin) chromosomes, have been noted [6], relatively few cytogenetic studies of low-grade brain tumors have been performed. We report the results of chromosome analysis of 32 such low-grade tumors.

MATERIALS AND METHODS

Tumors were studied between January 1987 and June 1990. All tumors for which adequate material existed after routine pathology studies were analyzed. Tumor specimens were obtained as soon as possible postoperatively at the Johns Hopkins Hospital. The tissue was minced to 1- to 2-mm pieces in a laminar flow hood and then further disaggregated by incubation in Dulbecco's modified Eagle's medium (DMEM)/F12 medium (Sigma) containing 200–400 U/ml collagenase type II (Worthington) for two hours to overnight. After centrifugation, the cells were resuspended in DMEM/F12 with 20% fetal calf serum, 33 U/ml penicillin, 33 μg/ml streptomycin, and 2 mM glutamine and were distributed equally on 35- to 60-mm standard plastic tissue culture dishes (Falcon). Occasional specimens were also plated on extracellular matrix-coated plates (ECM; Accurate Chemical and Scientific, Westbury, NY). The dishes were then randomly assigned to an Espec incubator (5% CO_2, 5% O_2, 90% N_2) or Bellco or Napco incubator (95% air, 5% CO_2) and cultured at 36°–37°C. The cells were monitored daily for growth by a phase-contrast microscope.

Timing of harvests was determined solely by cell growth. Cells were exposed to Colcemid (GIBCO) at 0.01–0.1 μg/ml for 4–18 hours depending on the number of mitotic cells observed, treated with prewarmed cancer hypotonic solution [7] for 20–30 minutes at 37°C, and fixed in three changes of 3 : 1 methanol : acetic acid. Slides were made and dried on a 60°C slide warmer, aged at least 1 week before G banding with 0.5% Enzar-t (Armour Pharmaceuticals), and stained with Leishman stain. One to two slides per harvest were examined. A minimum of 20 metaphases and four karyotypes were prepared from each tumor whenever sufficient material was available. Chromosome abnormalities were described according to the standard International System for Human Cytogenetic Nomenclature [8].

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Received September 4, 1991; accepted November 11, 1991.

Cancer Genet Cytogenet 60:67–73 (1992)
0165-4608/92/$05.00

Table 1 Ependymomas

Specimen no.	Pathologic diagnosis and tumor location	Age (yr)/sex	New/ recurrent	No. of days in culture	No. of metaphases	Modal chromosome no.	Stemline karyotype
87-336	Atypical myxopapillary; occipital lobe	F/26	N	6	55	72–80	76,XX,−X,−2,−3,−6,−6,−7,−10,−11,−12,−17,−18,−19,−20,−21,−22,−22[a]
88-182	Anaplastic ependymoma; frontal lobe	F/71	N	2–4	33	42–46	44,XX,+7,del(9)(p22),−16,−21,−22
88-252	Ependymoma, NOS; posterior fossa	F/3	R	4–6	18	42–46	42–46,XX, random losses
88-261	Ependymoma, NOS; thoracic spinal cord	F/48	R	7–10	24	44–47	46,XX
89-278	Malignant ependymoma; cerebellum	F/16	N	4–5	58	50–56	55,XX,+2,+3,+5,+7,+8,+9,+11,+19,+21
90-045	Ependymoma, NOS; frontal lobe	F/50	N	1–8	34	44–47	43–45,X,der(X)t(X;?)(q?;?),+7,del(9)(p22),−13,−13,−16,der(16)t(16;?)(q23;?),−20,der(20)t(20;9?)(q13.2;p22?),+1–2mar

Abbreviations: NOS, not otherwise specified; N/R, newly diagnosed/recurrent tumor.

[a] Based on a tetraploid karyotype.

RESULTS

Six ependymomas were analyzed. Results are summarized in Table 1. Only two tumors were karyotypically normal. Tumor 87-336 was hypotetraploid with numerical losses, and tumor 89-278 was hyperdiploid with numerical gains. Structural abnormalities were observed in tumor 88-182, an anaplastic ependymoma, in which trisomy 7 and del (9)(p22) were present (Fig. 1). Trisomy 7 was observed in tumor 89-278, along with gains of other chromosomes. This tumor was also classified as a malignant ependymoma. Trisomy 7 and del(9)(p22), along with other abnormalities, were also observed in tumor 90-045, (Fig. 2), which was not classified as an anaplastic tumor.

Ten oligodendrogliomas were studied. Results are summarized in Table 2. Six had only normal karyotypes and four had normal stemlines with clonal sidelines. The abnormalities in these subpopulations included loss of Y (3 tumors) and loss of chromosome 22 (1 tumor). Only normal karyotypes were observed in a tumor studied at diagnosis (87-083) and again at recurrence 2 years later (89-115).

The modal number of 11 low-grade astrocytomas was near-diploid. Results are summarized in Table 3. Three were abnormal; all three had structural abnormalities, including a derivative chromosome 7 in 2 tumors (88-160 and 87-290) in addition to other structural abnormalities. Tumor 90-149, a pilocytic astrocytoma, had only an additional der(15)t(15;?)(q24;?) (Fig. 3). All four craniopharyngiomas and the choroid plexus papilloma were near-diploid and had a normal stemline karyotype (Table 4).

DISCUSSION

The low-grade brain tumors that have been reported to date have tended to have fewer chromosome abnormalities than have been found in high-grade brain tumors. This report of 32 tumors extends the cases of low-grade tumors in which chromosomes have been analyzed.

As a group, ependymomas had the largest number of chromosome abnormalities; the most frequent abnormalities observed in our study were trisomy 7 (three tumors), monosomy of 21 and 22 (2 tumors), and del(9)(p22) (two tumors). In the cases in the literature, reported abnormalities have included loss of chromosome 22, derivative (9), derivative (22), and structural changes of chromosomes 10, 12, 17, and X [6, 9–14]. Yang-Feng et al. [15] reported a study of an ovarian ependymoma (glial fibrillary acidic protein-positive tumor) with a modal number of 56. Trisomic chromosomes included 8, 19, and 21, which were among the trisomic chromosomes observed in a malignant ependymoma in this report (tumor 89-278). A metastatic myxopapillary sacrococcygeal ependymoma was chromosomally normal [16], in contrast to our atypical myxopapillary tumor (87-336), which had a hypotetraploid chromosome complement.

In contrast, all oligodendrogliomas had normal stemline karyotypes; four had clonal sidelines involving losses of the Y or chromosome 22. This finding is similar to those in the reports of other investigators [3, 10] and suggests that this group of tumors in particular tend to have normal-appearing karyotypes.

Seven of 10 low-grade astrocytomas in our study were normal. Exceptions included translocations involving chromosomes 7 in two tumors, a translocation of chromosome 5 with unidentified material, a deletion of 1p22, and a derivative chromosome 15. All but one of the tumors reported previously have had normal stemlines with sidelines of −22, −10, +7, XO, and a 9p abnormality [3, 6, 9–11].

All four craniopharyngiomas and the choroid plexus tumor in our series were normal. Reports of cytogenetic

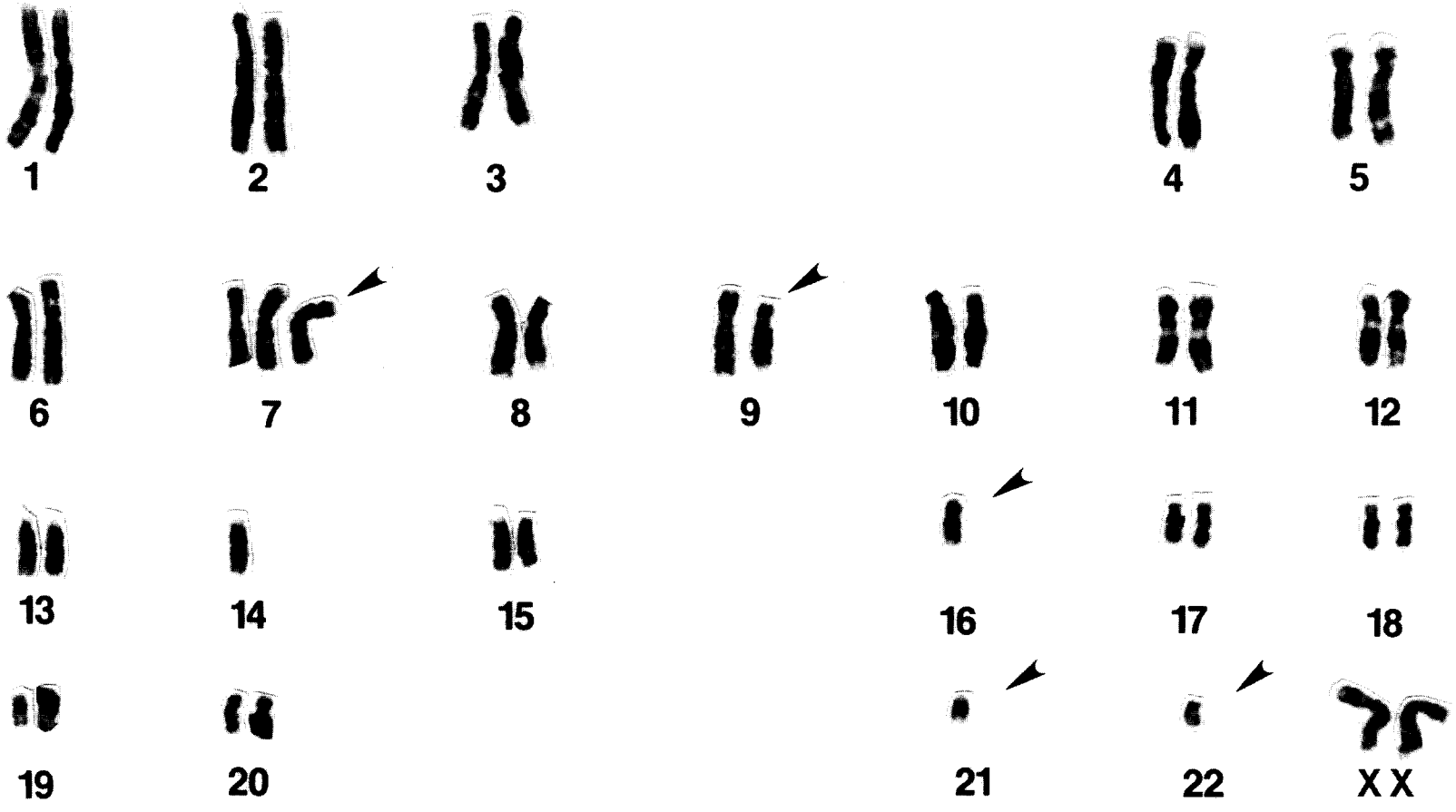

Figure 1 Ependymoma (specimen 88-182). 43,XX,+7,del(9)(p22),−14,−16,−21,−22. Clonal abnormalities (arrowheads); loss of chromosome 14 was incidental to this cell.

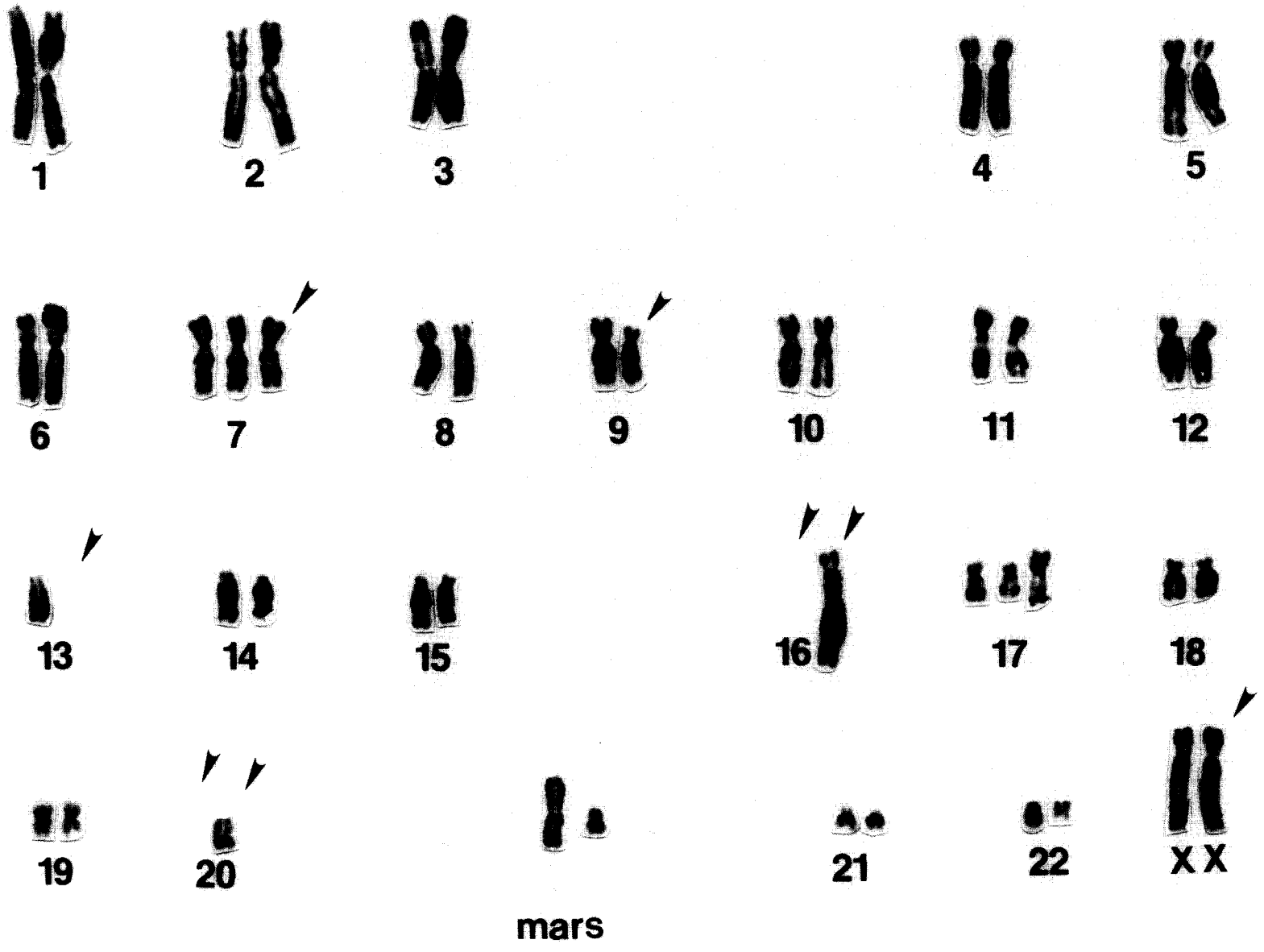

Figure 2 Ependymoma (specimen 90-045): 47,der(X)t(X;?)(?q;?),der(X)t(X;?)(?q;?),+7,del(9)(p22),−13,−16, der(16)t(16;?)(q23;?),+der(17),−20,der(20)t(?9;20)(?p22;q13.2),der(22),+2mar. Clonal abnormalities are designated by arrowheads. The additional, abnormal chromosome 17 and the derivative chromosome 22 observed in this cell could not be shown to be clonal.

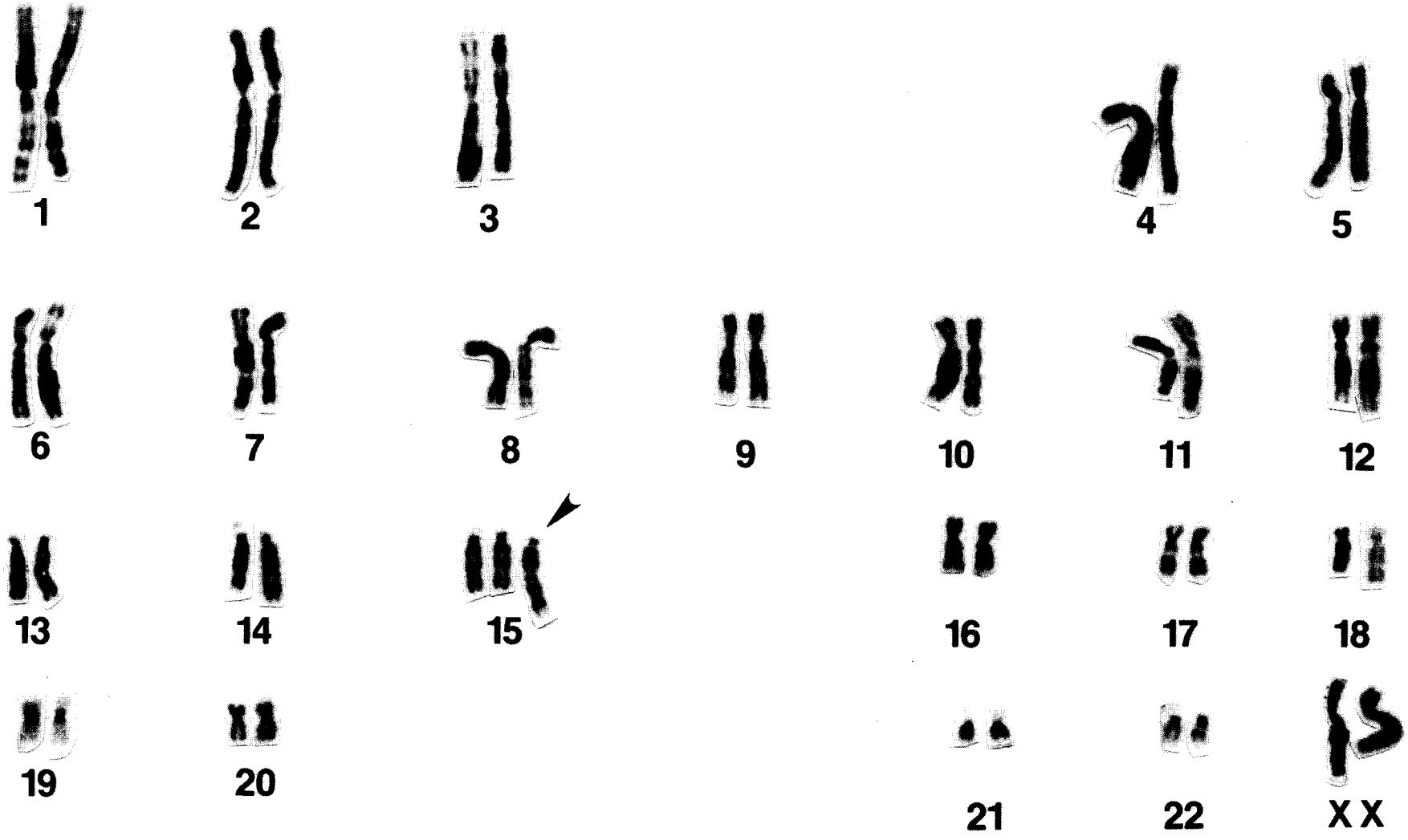

Figure 3 Low-grade astrocytoma (specimen 90-149): 46,XX,+der(15)t(15;?)(q24;?).

Table 2 Oligodendrogliomas

Specimen no.	Pathologic diagnosis and tumor location	Age (yr)/sex	New/ recurrent	No. of days in culture	No. of metaphases	Modal chromosome no.	Stemline karyotype	Sideline
87-054	Atypical oligodendroglioma R parietal lobe	M/56	N	6–16	29	45–46	46,XY	45,X,−Y
87-083[a]	Oligodendroglioma, NOS R frontal lobe	M/46	N	23	13	45–46	46,XY	None
88-062	Mixed oligodendroglioma—astrocytoma grade II L frontal lobe	M/43	N	6–9	69	41–47	46,XY	45,XY,−22
88-074	Oligodendroglioma, NOS R temporal lobe	F/11	N	9	15	43–46	46,XX	None
88-254	Oligodendroglioma, NOS R temporal lobe	M/24	R	6–7	10	46	46,XY	None
89-021	Oligodendroglioma, NOS L parietal region	M/33	N	11–13	61	45–46	46,XY	45,X,−Y
89-115[a]	Anaplastic oligodendroglioma R frontal lobe	M/48	R	2	3	46	46,XY	None
89-205	Oligodendroglioma with extensive microcalcification LNS	F/46	N	6	33	45–46	46,XX	None
89-230	Oligodendroglioma, NOS L temporal lobe	M/3	N	3–8	30	45–46	46,XY	None
90-126	Anaplastic oligodendroglioma with necrosis L frontal lobe	M/43	N	5–6	44	44–47	46,XY	45,X,−Y

LNS, location not specified other abbreviations as in Table 1.

[a] Same patient.

Table 3 Low-grade astrocytomas

Specimen no.	Pathologic diagnosis and tumor location	Age (yr)/sex	New/ recurrent	No. of days in culture	No. of metaphases	Modal chromosome no.	Stemline karyotype
87-214	Astrocytoma NOS L frontal lobe	F/36	N	7–8	54	44–47	46,XX
87-290	Astrocytoma, grade II, with some oligodendroglioma features L temperoparietal area	F/47	N	6–8	46	40–46	45,XX,der(5)t(5;?)(p14;?),t(7;22)(q21;q13.2),+1–3 mars, random losses
87-323	Astrocytoma NOS parietal lobe	M/20	N	2–4	26	43–46	46,XY
88-160	Cellular astrocytoma with minor component of oligodendroglioma L frontal lobe	F/44	N	1–8	15	40–47	40–46,XX,del(1)(p22), der(7)t(7;?)(p11;?), random losses
88-200	Astrocytoma NOS cerebellum	F/2	N	1–3	59	42–47	46,XX
88-238	Astrocytoma NOS brainstem	M/12	N	5–14	18	42–46	46,XY
88-297	Ganglioma temporal parietal area	M/10	N	1–8	34	44–46	46,XY
89-081	Glioma with features of astrocytoma and oligodendroglioma R temporal lobe	F/7	N	4–5	34	45–47	46,XX
90-017	Astrocytoma NOS R temporal lobe	M/47	N	8	33	45–46	46,XY/45,X,−Y
90-129	Astrocytoma NOS R frontal lobe	F/12	N	7	36	43–46	46,XX
90-149	Pilocytic astrocytoma L occipital lobe	F/9	N	5–6	37	45–47	47,XX,+der(15)t(15;?)(q24;?)

Abbreviations as in Table 1.

Table 4 Craniopharyngiomas and other

Specimen no.	Pathologic diagnosis and tumor location	Age/sex	New/ recurrent	No. of days in culture	No. of metaphases	Modal chromosome no.	Stemline karyotype
87-014	Craniopharyngioma suprasellar region	M/6 yr	N	5	23	41–46	46,XY
87-034	Craniopharyngioma R frontal lobe	F/5 yr	N	8	45	44–46	46,XX
89-293	Craniopharyngioma pituitary	F/2 yr	N	3–6	31	45–47	46,XX
90-041	Choroid plexus papilloma ventricle	F/4 mo	N	9	20	46	46,XX
90-128	Craniopharyngioma pituitary	M/5 yr	N	4–6	24	45–46	46,XY

Abbreviations as in Table 1.

studies of choroid plexus papillomas or craniopharyngiomas for comparison are few [3, 11]. Six recurrent laryngeal papillomas were all cytogenetically normal [17], but a basosquamous papilloma of the skin was reported to be near-diploid with four different clones with numerous translocations [18].

Clearly, not all tumors that are generally considered low-grade brain tumors are cytogenetically normal. Perhaps the presence of detectable chromosome abnormalities in some tumors within this group will correlate most closely with the histologic classification of "malignant" with concordant clinical behavior. Additional studies of the tumors generally considered low-grade brain tumors are required to determine whether consistent chromosome abnormalities exist in any subgroup.

Supported by an American Cancer Society Clinical Oncology Career Development Award to (C. G.), a grant from the American Cancer Society Maryland Division, funds from the Andrew W. Mellon Foundation, and Grants No. CA 46289-03 and U01 CA52857 from NIH.

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