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ARTICLE

Genomic Alterations in Low-Grade, Anaplastic Astrocytomas and Glioblastomas

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To extend our understanding of potential stepwise genetic alterations that may underlie tumor progression from low-grade astrocytomas to glioblastomas, histopathologic and comparative genomic hybridization analyses were performed on tumor specimens from 68 primary lesions, including 40 glioblastomas, 10 anaplastic and 18 low-grade astrocytomas. The number of aberrations per case increased towards the higher grade tumors (grade II: 1.66±1.49; grade III: 2.80±1.68; grade IV: 3.02±1.07; F=6.955, p=0.002). A gain of 7/7q was common and the most frequently seen aberration in low-grade astrocytomas, whereas loss of 10q was the most frequently seen anomaly in anaplastic astrocytomas and glioblastomas. Chromosome 7p amplification was only detected in glioblastomas. Chromosome 10/10q deletion and combination of 1p, 19q and 17p deletions were specific to high-grade astrocytic tumors. Sequences of chromosome 7 and 10 seem to have pivotal roles in the biology of human gliomas. The genomic copy deletions of chromosomes 1p and 19q might provide an alternative mechanism in the genesis of astrocytomas. (Pathology Oncology Research Vol 13, No 1, 39–46)

Key words: anaplastic astrocytoma, comparative genomic hybridization, genomic imbalances, glioblastoma multiforme, low-grade astrocytoma

Introduction

Astrocytomas comprise the most frequent primary brain neoplasm. They are characterized by wide variations in histology and clinical course. These tumors include grade II astrocytoma (LGA), grade III anaplastic astrocytoma (AA) and grade IV glioblastoma (GBM).

Previous cytogenetic and molecular analyses have revealed several genetic changes typical for human glial neoplasms. However, GBMs have been at the center of these efforts and thus are likely to reflect late events of tumor progression. The molecular events that trigger the development of LGA and AA are not clearly identified.

Previous studies applying cytogenetic, comparative genomic hybridization (CGH) and loss of heterozygosity (LOH) methods demonstrated nonrandom genomic aberrations in astrocytomas. Loss of heterozygosity of the p53 gene, genomic copy alterations on chromosomes 1, 5, 7, 9 and 19 have been reported as the most common detectable changes in grade II astrocytomas, whereas LOH on chromosome 19q and p16, Rb gene mutations, and genomic copy number alterations on chromosome 7, 8, 9, 10, 13 and 20 have been disclosed as being frequently observed aberrations in AA.[12,16,18,21]

The characterization of genomic abnormalities is a useful strategy toward the understanding of tumor initiation and progression, and may help to identity specific genes involved in these processes. Analysis of genetic pathologies may help to advance diagnosis, grading and classification, and to determine appropriate therapeutic approaches for tumors of astrocytic lineages. CGH provides comprehensive information about genomic copy number aberrations across the entire genome in a single hybridization, and is an important technique for evaluating genotypic differences among the same grade tumors as well as to study relationships between genomic alterations.

This study was undertaken to identify genomic imbalances in LGAs, AAs and GBMs, and to further our understanding of any genetic alterations that may underlie the assumed tumor progression from LGA to AA and GBM.

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Materials and Methods

Tumor material

Histopathological and comparative genomic hybridization (CGH) analyses were performed on tumor specimens from 68 primary lesions of astrocytic tumors obtained before radiation therapy. The tumors were classified according to the WHO histologic classification: 40 glioblastomas (WHO grade IV), 10 anaplastic (WHO grade III) and 18 low-grade astrocytomas (WHO grade II). The ratios of males to females were 11:7, 7:3 and 22:18 for grade II, III and IV tumors, respectively. All tumor samples were available as paraffin-embedded materials. For each tumor, four serial sections were obtained. The first and last sections were stained with hematoxylin and eosin for histopathologic analysis to ensure that the principal cellular and anaplastic areas were selected from each tumor for further analysis.

Comparative genomic hybridization

The identification of DNA sequence copy number changes was accomplished by CGH. Tumor DNA isolated from 10-μm-thick sections of paraffin-embedded tumor tissue and reference DNA from the peripheral blood of a karyotypically normal man were amplified and labeled with Spectrum Green and Spectrum Red (Vysis, Inc., Downers Grove, IL, USA) directly conjugated nucleotides, respectively. Slides were viewed on an Axiophot fluorescence microscope (Carl Zeiss, Oberkochen, Germany), and images were captured and stored using a Photometrics CCD camera with MacProbe version 4.11 software (Perceptive Scientific International, Chester, UK). For each hybridization, at least fifteen high quality metaphases were analyzed, and average green-to-red fluorescence intensity ratio profiles were generated for each chromosome. Chromosomes were identified based on their inverted DAPI banding, and fluorescence ratio profiles were calculated for each chromosome, using data from at least eight representative copies of each chromosome (range 8-27). Average ratio profiles with 95% confidence intervals were generated for each tumor. CGH ratio values of 1.20 and 0.80 were used as the upper and lower thresholds, respectively, for the identification of chromosomal imbalances. The procedures in the experiments of this study were in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Results

We studied 18 grade II, 10 grade III and 40 grade IV astrocytomas, and CGH profiles were successfully obtained from all 68 samples.

Low-grade astrocytomas (grade II)

Eleven patients were male and seven were female. Patients' age ranged from 14 to 57 years (mean±SD: 36.3±13.0). Of 18 cases, 14 tumors (77.8%) showed genomic copy number changes. Total changes/case ranged from 0 to 5 (mean±SD: 1.66±1.49). The sex, age, tumor location, and genomic alterations detected by CGH analysis in these tumors are given in *Table 1* and *Fig. 1*. Tumors with oligodendroglial components were excluded from our study. The most frequent aberration was gain on chromosome 7/7q, followed by gains on 8q (4 cases), 20q (3 cases) and loss of 19q. Of three tumors with 19q deletion, two occurred simultaneously with the loss of 1p, and no further genomic copy number changes were noticeable in these three tumors. In all cases examined, gain of 8q never occurred in cases with 7/7q gain. Low-grade astrocytic tumors with 8q gain occurred more frequently in younger patients than those with 7/7q gain (23.7 versus 41.4 years).

Anaplastic astrocytomas (grade III)

The mean (±SD) age of the 7 male and three female patients was 44.7±11.1 years (range 32-65). The sex, age, tumor site, and genomic alterations detected by CGH analysis are given in *Table 2* and *Fig. 2*. Out of 10 cases, 9 tumors (90%) showed genomic alterations. The total genomic copy number changes/case ranged from 0 to 8 (mean±SD: 2.80±1.68). The most frequently seen aberra-

***Table 1*. Features and CGH results of the cases with low-grade astrocytoma**

Case	*Sex*	*Age*	*Tumor site*	*Gains*	*Losses*
1	M	57	parietal	7q	
2	M	23	occipital	8q24, 9p	12q
3	F	39	parietal		5p
4	F	43	parietal	7q, 9q	3p, 22q
5	F	23	temporal	8q24	12q
6	M	40	parietal	7q	
7	M	26	occipital	8q24	
8	F	14	temporal	9q, 20q, 21q	X, 17p
9	F	28	parietal		
10	M	48	temporal		
11	F	23	parietal	8q24	
12	M	32	frontal	7, 20q	16p, 22q
13	M	24	occipital		19q
14	M	35	parietal	7, 20q	
15	F	47	frontal		1p, 19q
16	M	54	frontal		1p,19q
17	M	57	parietal		
18	M	40	parietal		

M: male, F: female

tions in anaplastic astrocytomas were a loss of 10/10q (5 cases), 9p (3 cases), 1p (3 cases) and gain on chromosome 7/7p (3 cases).

Glioblastoma multiforme (GBM) (grade IV)

CGH analysis disclosed that all tumors had genomic copy number aberrations (100%) (*Table 3, Fig. 3*). The mean (±SD) age was 51.8±10.9 years (range 29-72). Total changes/case ranged from 1 to 6 (mean±SD: 3.02±1.07). The number of increased copies/tumor was 1.5, whereas signal reductions indicative of deletions were the most frequently seen. The number of deletions/tumor was 1.90. The most commonly detected chromosomal mutation involved chromosome 10, for which decreased fluorescence signal intensity was observed in 21 tumors. Nine of these 21 tumors had partial 10q deletions. The other frequently seen aberration involved chromosome 7: twelve tumors had chromosome 7 gain, whereas three and six tumors showed partial 7q and 7p alterations, respectively. The six tumors with 7p aberration showed amplification localized to a narrow chromosomal region consistent with band 7p13. The second most common increased signal intensity was restricted to a specific band consistent with 12q13-q15. This aberration was seen in ten tumors. Chromosome 1 gain was seen in seven tumors, but no partial regions of this chromosome could be detected. The increasing genetic material in chromosomal arm 20q was also revealed in five tumors.

Of the deletions, the second most commonly decreased signal intensity was restricted to a specific band consistent with 1p which was noticeable in ten tumors. The other detected losses were 9p, 13q, 22q (6 cases), X/Xq (5 cases), 19q (4 cases), and 3p, 5q, 17p, 19p and 21q (3 cases).

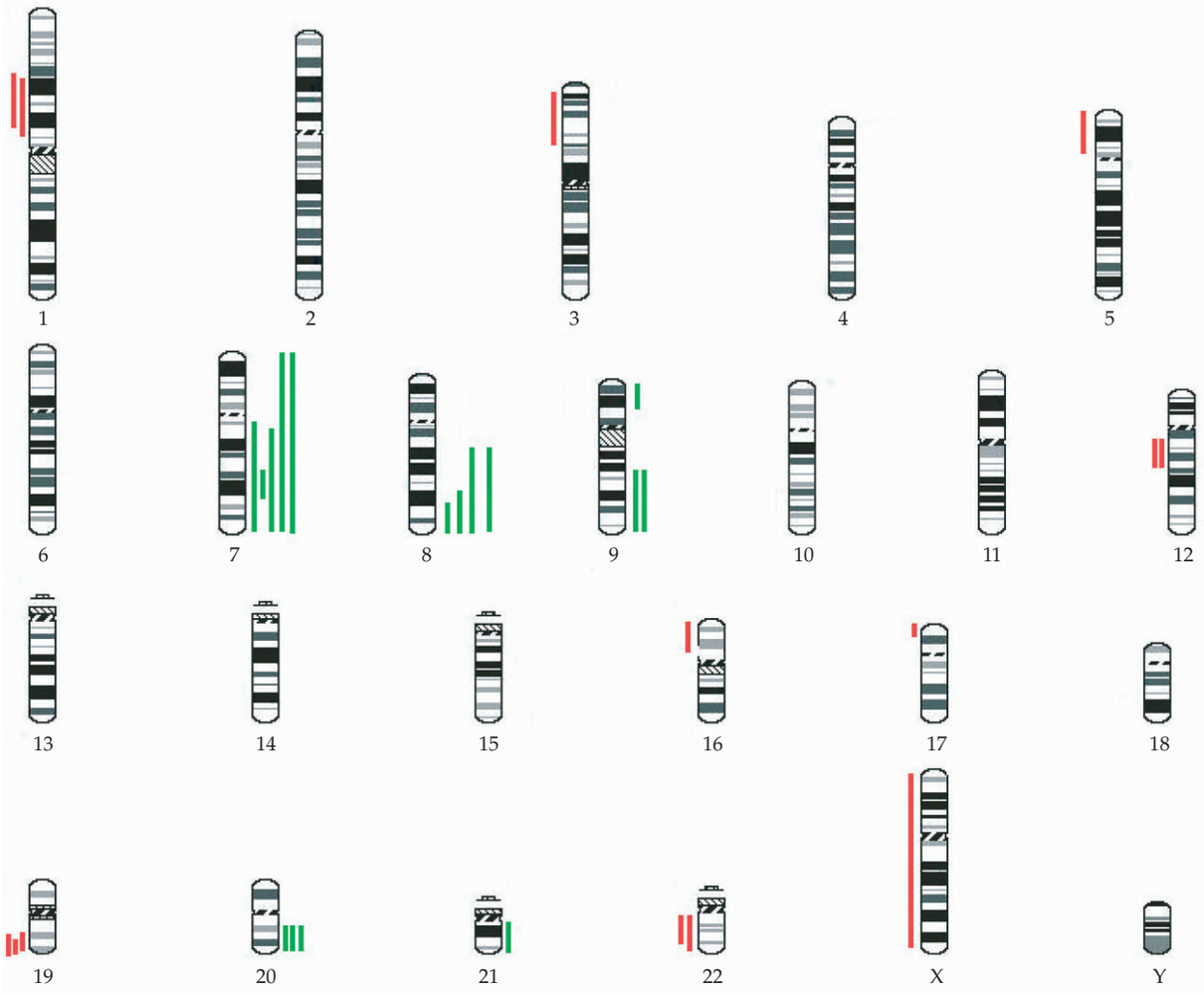

Figure 1. *Summary of genomic copy number imbalances detected by CGH in 18 grade II astrocytomas. Losses are indicated by lines on the left of each chromosome ideogram, whereas lines on the right show gains. Copy number increases were seen in chromosomes 7, 8, 9 and 20, whereas partial deletions were detected especially in chromosome 19.*

Table 2. **Features and CGH results of the cases with anaplastic astrocytoma**

Case	*Sex*	*Age*	*Tumor site*	*Gains*	*Losses*
1	M	38	parietal	7p12-p13, Xq	1p, 10q23-qter
2	M	49	frontal	1q	9p, 10, 11p
3	F	33	occipital	12q13-q15	
4	M	61	frontal	9q, 15q	1p, 13q, 19q
5	M	65	frontal	7, 12q13-q15	9p, 10q23-qter
6	M	48	temporal		9p
7	M	41	frontal	1q	1p, 17p, 19q
8	M	40	parietal	7p12-p13	10q23-qter, 13q
9	F	40	frontal	20q	10q23-qter
10	F	32	occipital		

M: male, F: female

In three tumors, combinations of chromosome 1p, 17p13-p14 and 19q deletions were the only detected aberrations. No relationship between the combination of chromosome aberrations and patient age and/or tumor site could be defined.

Discussion

The detection of DNA variation in cancer is one of the most promising approaches in understanding the basis of tumorigenic processes. In the present study, genomic copy number aberrations were observed in 92.7% of the astrocytic tumors analyzed. The number of aberrations per case increased towards the higher grade tumors (grade II: 1.66±1.49; grade III: 2.80±1.68; grade IV: 3.02±1.07;

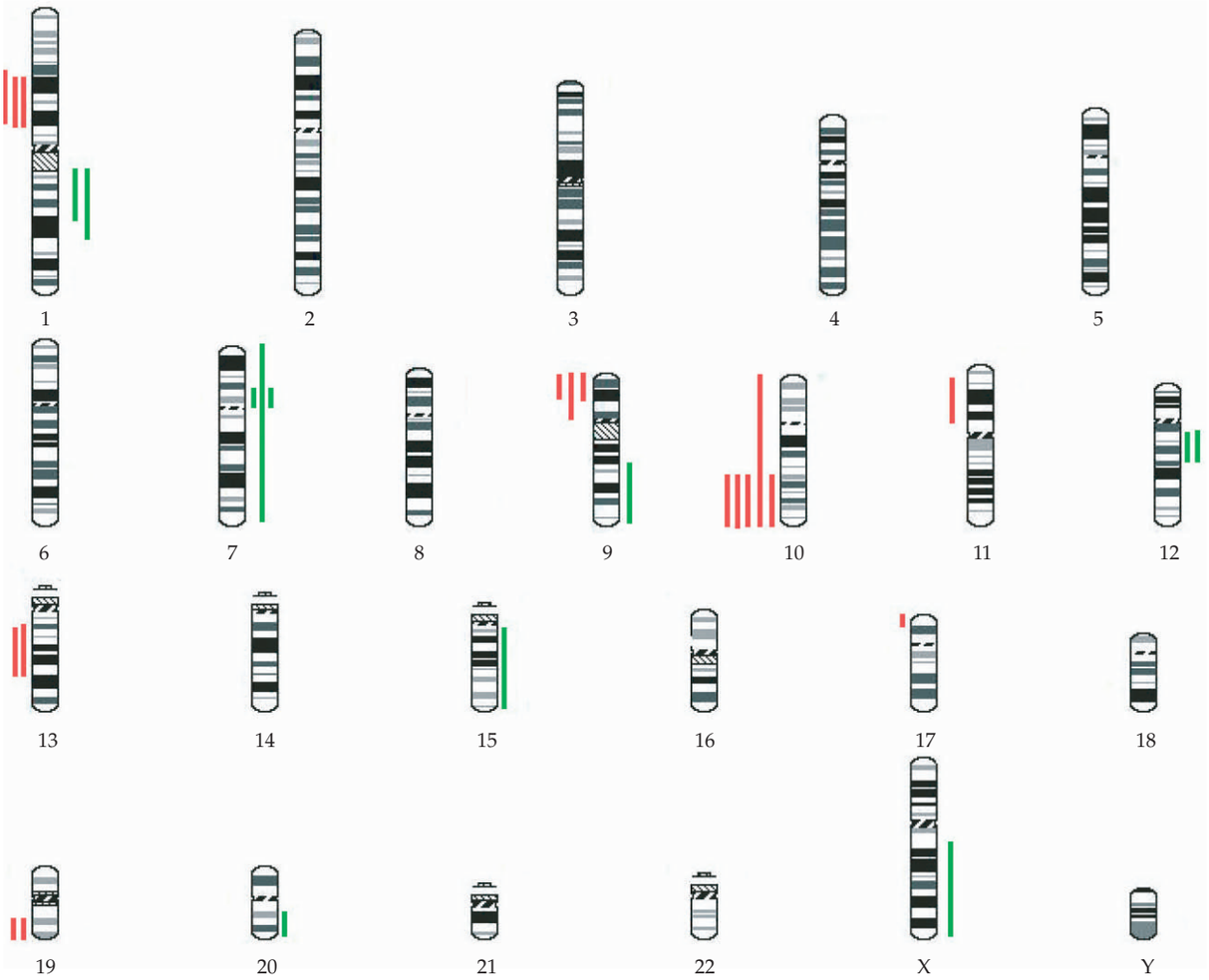

Figure 2. *Summary of genomic copy number imbalances detected by CGH in 10 grade III astrocytomas. Losses are indicated by lines on the left of each chromosome ideogram, whereas lines on the right show gains. The frequency of deletions was higher than that of genomic copy number increases. Partial chromosome 10 deletion was significant.*

F=6.955, p=0.002). This result indicates that the number of aberrations increases with progression of histopathologic malignancy in astrocytic tumors.

Low-grade astrocytomas

According to the genomic copy number aberrations detected, grade II tumors could be classified into five different subgroups: one with normal karyotype, one with 1p and 19q deletions, another group with relative gain on 8q, a different one with gain of 7/7q and lastly one with other chromosomal aberrations. This grouping agrees with results of Hirose et al who have performed similar classifications in their cases. Moreover, they have suggested that copy number aberrations provide a basis for a clinically relevant classification system for these tumors.[10]

The gain on the whole chromosome 7 or 7q was the most frequently seen aberration (5/18 cases) in low-grade tumors, as has also been reported in previous studies.[10,24] Whole or partial gain of chromosome 7 was also frequently seen in our glioblastoma series (15/40 cases). This aberration has been reported as the most striking microscopically detectable aberration in glioblastomas, where the presence of this genomic alteration supports a pivotal role of chromosome 7 sequences in the biology of human gliomas.[1,19] Accordingly, we propose that the gain of chromosome 7q might be a genetic change associated with tumor initiation in the astrocytic tumors. Previous studies showed that the MET oncogene, located in 7q31, which encodes the hepatocyte growth factor/scatter factor receptor, was amplified in about = 20% of astrocytomas and its transcript was abundant in these tumors.[10,27] Other cancer-related genes located in this area might be involved in the initiation of astrocytic tumors. A gain of chromosome 7q31-qter has also been reported as a frequently seen abnormality in oligodendrogliomas by array-CGH, and CDK6 and MET have been suggested as candidate oncogenes in astrocytomas.[14]

Allelic losses of 1p and 19q have been reported as frequently seen aberrations in oligodendroglial tumors and correlated with better survival and more favorable response to chemotherapy.[5,6] Chromosome 1p and/or 19q

Table 3. **Features and CGH results of the cases with glioblastoma**

Case	*Sex*	*Age*	*Tumor site*	*Gains*	*Amplification*	*Losses*
1	F	51	frontal	20q		1p,10, 22q, X
2	M	60	frontal			1p, 17p13-p14, 19q
3	F	58	parietal	20q		10q23-qter
4	F	64	parietal	7	7p12-13	9p, 10
5	M	50	temporal			1p, 17p13-p14, 19q
6	F	68	frontal		7p12-13	5q, 9p, 10, 13q, 22q
7	M	67	temporal	1, 7		10, 19q
8	F	49	temporal		12q13-q15	1p
9	F	31	frontal	12q13-q15		Xq
10	M	44	frontal	1		X, 3p
11	M	39	frontal	12q13-q15		5q, 21q
12	M	40	temporal		12q13-q15	1p
13	M	49	parietal	1, 2p		13q
14	F	32	parietal		12q13-q15	1p, 4q
15	F	59	frontal	7	7p12-13	10q23-qte
16	F	45	frontal	12q13-q15		Xq
17	F	72	frontal	7		10
18	M	35	frontal	4p	12q13-q15	1p, 3p
19	M	50	frontal			13q, 22q
20	F	52	parietal	7		5q, 10
21	M	68	frontal	7q		9p, 10, 13q, 21
22	M	44	parietal	12q13-q15		
23	F	40	parietal	20q		22q
24	M	56	parietal	1, 7		10q23-qter, 19p
25	M	69	parietal	1, 7		9p, 10
26	F	52	parietal	2p, 7, 20q		10
27	M	53	parietal	7		10q23-qter, 19p
28	M	58	temporal		7p12-13	10q23-qter, 13q, 22q
29	M	60	occipital	7		10q23-qter, 21q
30	M	50	temporal			1p, 4q
31	M	42	occipital			1p, 17p13-p14, 19q
32	F	40	temporal			Xq
33	F	50	frontal		12q13-q15	1p
34	M	61	temporal	7		9p, 10, 22q
35	F	53	temporal	7q		3p, 10
36	M	60	parietal	1, 20q		10q23-qter
37	F	55	frontal			10, 13q
38	F	56	parietal	7q	7p12-13	10q23-qter
39	M	29	parietal	1, 12q13-q15		19p
40	M	61	temporal	7	7p12-13	9p, 10q23-qter

M: male, F: female

deletions in low-grade astrocytomas have also been reported in previous studies.[10,16] Allelic loss of chromosome 1p has been associated with several human malignancies such as hepatocellular carcinomas and gastric cancer.[8,17] This aberration has also been reported as a genetic change associated with tumor initiation in meningiomas.[2,3] A loss of 19q has been frequently seen in gliomas.[1,26] In the present study, losses of 1p and 19q were seen in two cases, whereas chromosome 19q was the sole abnormality in one case. These cases were classified into one group since no further aberrations were detected in these tumors. Because tumors with oligodendroglial components were excluded from our study, we speculate that the presence of 1p and/or 19q deletions might also be involved in the initiation of astrocytomas. However, further studies are necessary to determine the effects of these alterations in relation to the prognosis of the disease.

Chromosome 8q gain has been the most frequently seen alteration in the series of Nishizaki et al.[19] They have also detected this alteration in glioblastoma series, although with lower frequency. In the present study, 8q24 gain was detected in 4/18 cases and, interestingly, none of the low-grade tumors showed gains of both 8q and 7p. Therefore, tumors with 8q24 gain were classified into a different group. However, this genomic alteration was not seen in higher grade tumors. A previous study has reported 8q gain/amplification in both low- and high-grade astrocytomas, and suggested that in GBM gene amplification on 8q develops from precursor changes by further increases in copy number.[18] However, this has not been proved in our series.

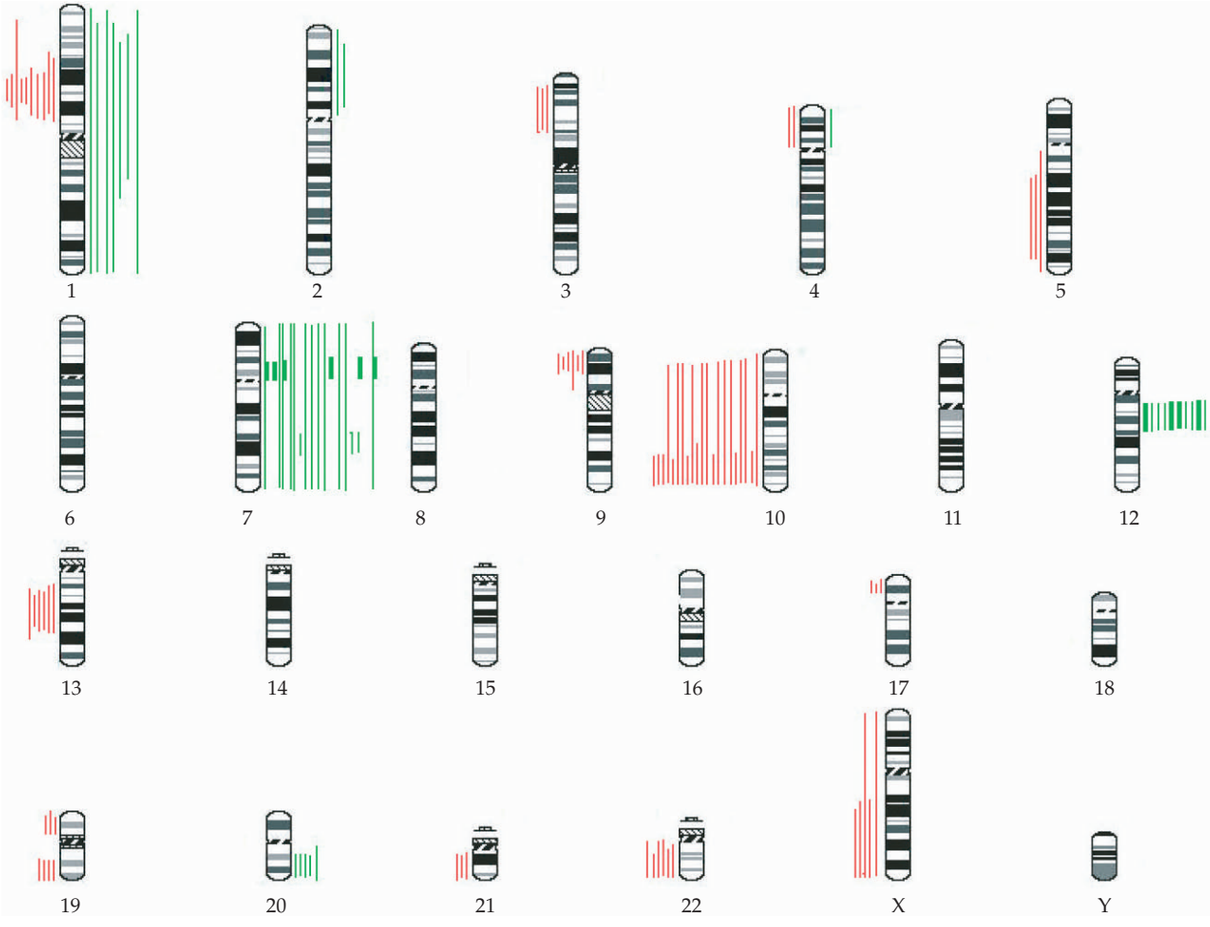

Figure 3. *Summary of genomic copy number imbalances detected by CGH in 40 grade IV astrocytomas. Losses are indicated by lines on the left of each chromosome ideogram, whereas lines on the right show gains. Chromosome regions to which amplification sites could be mapped and amplification of sequences in chromosomal regions are indicated by thick lines. The distribution of genomic copy number aberrations was nonrandom in glioblastomas. Whole and/or partial gains of chromosome 7, partial amplification of chromosome 12 and deletion of chromosome 10 were the most frequently seen alterations.*

Anaplastic astrocytomas

In previous studies, a gain on chromosome 7 has been reported as the most frequently detected aberration in grade IV and anaplastic astrocytomas.[1,15] Kunwar et al suggested that +7q and +7p are associated with shorter survival independently of age, whereas the presence of a normal chromosome 7 is associated with longer survival. These studies have categorized patients on the basis of genotype, particularly the status of chromosome 7: normal chromosome 7, +7q and +7p. They have concluded that a gain on 7p represents a poor prognostic marker regardless of age and that this alteration occurs more frequently in older patients.[15] In our study, however, the patients with 7p gain were younger.

Because of the ability of CGH to detect chromosomal changes across the entire genome, this technique is also useful for elucidating the relationship between alterations, such as the loss of chromosome 10q and the gain of 7p. Gain at 7p12-p13 always occurred concurrently with the loss of 10q, which is consistent with the results of previous studies.[15,18]

Glioblastoma multiforme

Although various clinical and histopathologic parameters involved in good prognosis have been reported,[7,23] genetic markers related to a better prognosis of GBM patients could not currently be determined. Therefore, characterization of genetic abnormalities will improve our understanding of the initiation and progression of the disease and may help to identify specific genes involved in these processes.

Among the changes seen in GBM, deletions occurred more frequently than gains (75 of 121 total aberrations). Whole or partial loss of chromosome 10 and whole or partial gain/amplification of chromosome 7 were the most frequently seen aberrations, which have previously been reported as frequent abnormalities in primary GBMs. In the present study, the frequency of chromosome 7 aberrations was higher in grade IV than in grade II and III tumors. Another characteristic feature detected in our study was that the partial gain of 7q was more frequently seen in low-grade tumors, whereas a gain/amplification of 7p was detected with increasing frequency in grade III and IV tumors. Candidates for oncogenes on 7p include EGRF, which is assigned to 7p12. The EGRF gene is the most frequently amplified oncogene in astrocytic tumors; its overexpression has been shown in about 60% of primary GBMs.[11,25]

The importance of chromosome 10 loss in the prognosis of GBM has been reported previously.[1,22,23] Three separate regions on chromosome 10 have been implicated in GBM: one in the telomeric region of 10p and the others in the telomeric and centromeric regions of 10q.[13] In our series the common region of loss was 10q23-qter which shows the inactivation of tumor suppressor genes in the telomeric region of 10q. Loss of heterozygosity on 10q has been reported as a marker for shorter survival.[20,23,24] The PTEN gene (10q23.31) and the DMBT1 gene (10q25.3-q26.1) have been reported to be mutated in GBMs.[25,28] In the study of Inda et al, differential PCR assays were performed to test for homozygous deletions at the loci PTEN and DMBT1.[11] Their results showed that 10q was a frequent target of deletions in GBM but homozygous deletions of these tumor suppressor genes did not occur. Moreover, it has been shown that inhibition of cell growth occurred through the p13/Akt/p27 pathway. These results suggest that PTEN participates in the genesis of GBM and might be a candidate therapeutic target.[9] Although a loss of 10q is more common than homozygous deletion of these tumor suppressor genes, other genetic events including point mutations or promoter hypermethylation of the genes might be involved in the inactivation of these important tumor suppressor genes; further molecular analysis might show the importance of these genes in the progression of GBMs. In our series, cases (4/6) with 7p amplification had a simultaneous loss of 10q, whereas the remaining 2 cases with 7p amplification had whole chromosome 10 deletions. In our previous study a tendency toward the combination of chromosome 7/7p amplification with chromosome 10 deletions was seen in tumors with poor prognosis. Therefore, we suggested that oncogenes located on chromosome 7 might have some regulatory effects on tumor suppressor genes of chromosome 10.[1]

Gain/amplification of 12q13-15 is another frequently seen aberration in our GBM series. Detection of this aberration only in higher grade tumors might imply that oncogenes located on 12q13-15 have important roles in the progression of astrocytic tumors. Cyclin-dependent kinase (CDK4) is a gene located on 12q14; previous studies showed that the CDK4 gene is one of the Rb1 pathway genes and its amplification disrupts the pathway.[4]

In three cases, losses of 1p, 19q and 17p were the only detected aberrations. The 1p/19q deletion combination was also detected in lower grade tumors of our cases. However, addition of the loss of 17p into this combination was an interesting feature in higher grade tumors. In our previous study the combination of 1p, 17p13-p14 and 19q deletions has also been reported in patients with longer survival time.[1] Although we could not evaluate the present cases in respect to their survival, we suggest that detection of only 1p, 17p13-p14 and 19q deletions in some higher grade tumors might show an alternative mechanism in the progression of astrocytic tumors.

In conclusion, some of the copy number aberrations that map specific locations are nonrandom events and gene(s) located in these areas seem to be involved in tumor progression. Detection of genomic copy number aberrations similar to those found in previous studies indicates that these nonrandom aberrations might be important molecu-

lar mechanisms in astrocytic tumor initiation, progression and behavior. Therefore, further molecular and array analyses in larger series are necessary to identify genetic alterations, and also to understand if there is a correlation between these genetic abnormalities and patients' survival.

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