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Molecular Genetic Evidence for Subtypes of Oligoastrocytomas

DAVID MAINTZ, KLAUS FIEDLER, JENS KOOPMANN, BRITTA ROLLBROCKER, STEFAN NECHEV, DORIS LENARTZ, ARMIN P. STANGL, DAVID N. LOUIS, JOHANNES SCHRAMM, OTMAR D. WIESTLER, AND ANDREAS VON DEIMLING

Abstract. The histogenesis of oligoastrocytomas remains controversial, with some data arguing similarity of oligoastrocytomas to astrocytic tumors, and other data suggesting closer relationships with oligodendroglial neoplasms. Since the molecular genetic changes in astrocytomas differ from those of oligodendrogliomas, we characterized 120 astrocytic and oligodendroglial tumors, including 38 oligoastrocytomas, for genetic alterations that occur disproportionately between astrocytomas and oligodendrogliomas, i.e. *TP53* gene mutations and allelic loss of chromosomes 1p, 17p and 19q. As previously reported, *TP53* mutations were common in astrocytic gliomas, occurring in approximately half of WHO grade II and III astrocytomas, but in only 5% of WHO grades II and III oligodendrogliomas. Allelic losses of chromosomes 1p and 19q, however, were common in oligodendrogliomas (41% and 63%), but less frequent in astrocytomas (9% and 35%). Oligoastrocytomas showed *TP53* mutations in 12/38 (32%) cases and allelic losses of chromosomes 1p and 19q in 52% and 70%, respectively. Most importantly, *TP53* mutations and allelic losses on chromosomes 1p and 19q were inversely correlated in oligoastrocytomas ($p < 0.011$ and $p < 0.019$). These data suggest the existence of two genetic subsets of oligoastrocytomas, one genetically related to astrocytomas and the other genetically related to oligodendrogliomas. Histologically, those oligoastrocytomas with *TP53* mutations were more often astrocytoma-predominant, while those with chromosome 19q loss were more often oligodendroglioma-predominant.

Key Words: Allelic Loss; Astrocytoma; LOH; Mutation; Oligoastrocytoma; Oligodendroglioma; *TP53*.

INTRODUCTION

Oligoastrocytomas are defined as tumors "with a conspicuous mixture of neoplastic oligodendrocytes and astrocytes, either diffusely intermingled or separated into distinct areas" (see Fig. 1) (1). This relaxed definition allows substantial latitude in the diagnosis of this entity and, as a consequence, results in high interobserver variability in oligoastrocytoma diagnosis. The recent observations that oligoastrocytomas are chemosensitive tumors have made such variability a clinically relevant problem and have necessitated the identification of independent and objective means of diagnosing oligoastrocytomas (2).

The molecular genetic changes that characterize human gliomas have been studied extensively over the last few years (3, 4). Interestingly, some molecular genetic alterations are far more common in astrocytomas than in oligodendrogliomas, while others predominate in oligodendrogliomas but are rare in astrocytomas. For instance, *TP53* gene mutations occur in 30–50% of astrocytomas but in only 5% of oligodendrogliomas (5–8); on the other hand, chromosome 1p and 19q losses occur in 40–70% of oligodendrogliomas but in only 10–40% of astrocytomas (9–12). Only a few studies, however, have specifically addressed the problems unique to oligoastrocytomas. Chromosome 1p and 19q losses occur frequently in oligoastrocytomas and are found in both the oligodendroglial and astrocytic components (11). In addition, chromosome LOH17p occurs in oligoastrocytomas, although the *TP53* gene may not be the target of these allelic losses (12).

More detailed knowledge of the molecular genetic alterations that characterize oligoastrocytomas may contribute to the development of an objective means of diagnosing oligoastrocytomas. In the present study, we examined 120 gliomas, with specific attention to 38 oligoastrocytomas, for *TP53* gene mutations and allelic losses of chromosomes 1p, 17p and 19q—the molecular genetic changes characteristic of astrocytomas or oligodendrogliomas.

MATERIALS AND METHODS

Tumor Specimens, Histopathology and Control DNA

Tumor and corresponding blood samples were obtained from patients treated at the University Hospital Bonn, the Massachusetts General Hospital, Boston, the University Hospital Zurich and the Hospital Köln Merheim, Cologne, between 1992 and 1995. All tumors were classified by two neuropathologists (AvD, DNL) according to WHO guidelines (1). All tumor specimens were examined microscopically prior to phenolic DNA extraction (13). In order to analyze representative samples of oligoastrocytomas, multiple tumor fragments approximating a total weight of 1 gram were pooled for DNA extraction. The series included 25 astrocytomas WHO grade II (A II; mean age 34.6 years), 32 anaplastic astrocytomas WHO grade III (A III;

From the Department of Neuropathology, University of Bonn Medical Center, Bonn, Germany (DM, KF, JK, BR, SN, ODW, AvD), the Department for Neurosurgery, Hospital Cologne-Merheim, Cologne, Germany (DL), the Department of Neurosurgery, University Hospital Bonn, Bonn, Germany (APS, JS), and the C.S. Kubik Laboratory for Neuropathology and Molecular Neuro-Oncology Laboratory, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (DNL).

Correspondence to: Andreas von Deimling, MD, Institut für Neuropathologie, Universitätskliniken Bonn, Sigmund-Freud-Straße 25, D-53105 Bonn, Germany.

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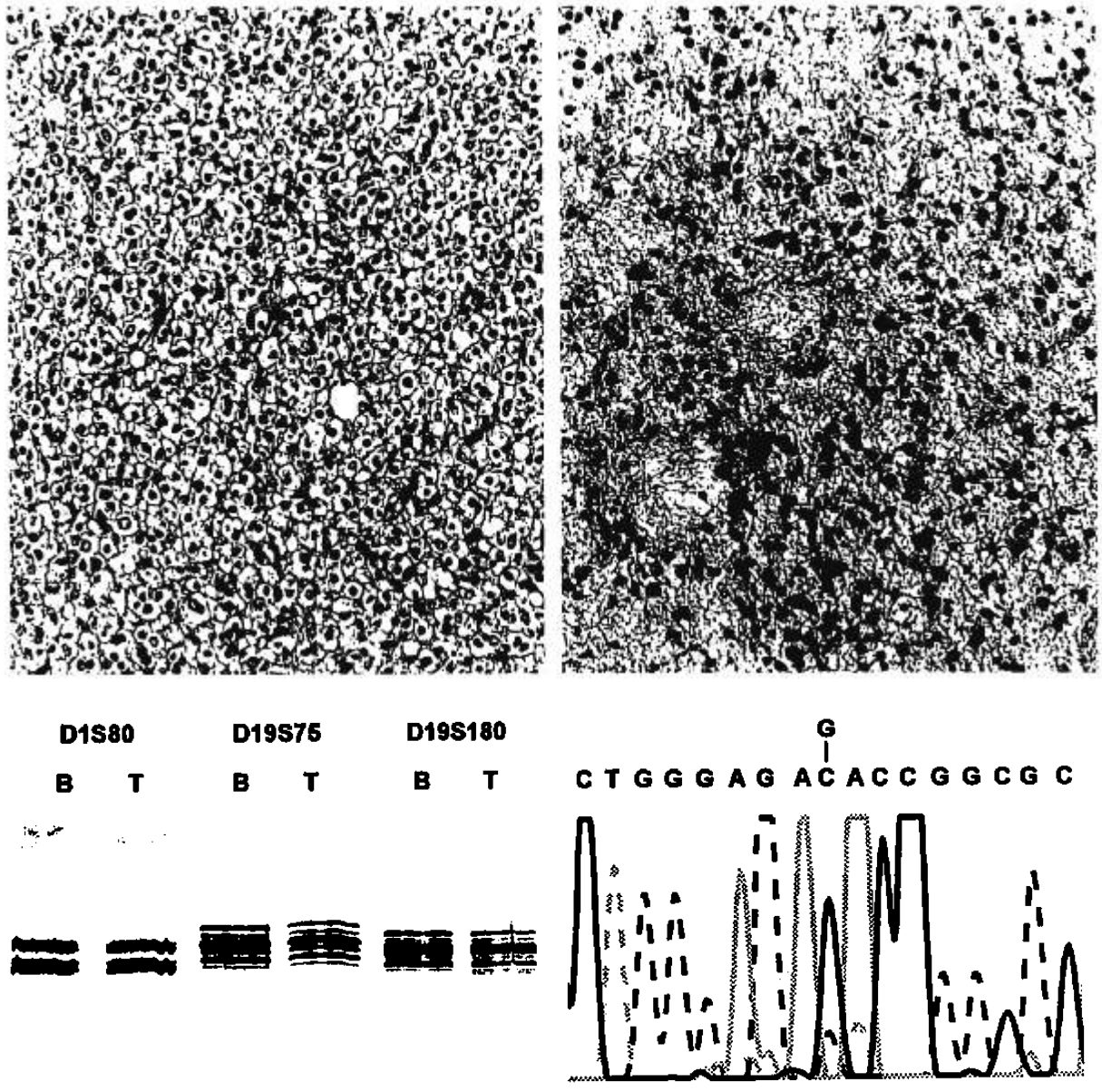

Fig. 1. Oligoastrocytoma with a mutation in the *TP53* gene and maintenance of heterozygosity at the chromosomal arms 1p and 19q. Oligodendroglial differentiated areas (left upper panel) and astrocytic differentiated areas (right upper panel) were photographed from the same section. HE ×80. The tumor tissue revealed maintenance of heterozygosity on chromosome 1p with the marker D1S80 and on chromosome 19q with markers D19S75 and D19S180. Sequence analysis revealed a G→C transition in exon 8, codon 281 of the *TP53* gene resulting in an Asp → His exchange. B = lymphocyte DNA; T = tumor DNA.

mean age 40.9 years), 19 oligodendrogliomas WHO grade II (O II; mean age 38.7 years), 6 anaplastic oligodendrogliomas WHO grade III (O III; mean age 46.2 years), 21 oligoastrocytomas WHO grade II (OA II; mean age 36.7 years) and 17 anaplastic oligoastrocytomas WHO grade III (OA III; mean age 43.2 years). OA were subdivided into a compact type characterized by distinct areas of each histologic component and into a diffuse type with predominant intermingling of astrocytic and oligodendroglial cells (14). In addition, the extent of astrocytic and oligodendroglial portions in the compact type of OA was semiquantitatively assessed. The following scores were applied: O > A when the oligodendroglial portion exceeded 60%; O = A when the oligodendroglial portion ranged between 60% and 40%, and O<A when the oligodendroglial portion amounted to less than 40% of the sections examined.

Microsatellite Analysis for Loss of Heterozygosity

In order to identify allelic losses the following primer pairs were used for nonradioactive microsatellite analysis: D1S80 (1p36–p35), FGR (1p36.2–p36.1), D17S520 (17p12), TP53 (17p13.1), D17S5 (17p13.3), D19S178 (19q13), APOC2 (19q13.2), D19S180 (19q13), and D19S601 (19q13). PCR products were separated on 8% denaturing acrylamide gels and

visualized by silver staining. Loss of heterozygosity (LOH) was scored as previously described (15).

SSCP Analysis and Direct Sequencing

For analysis of the *TP53* gene a set of previously published primers was employed. PCR was performed in a volume of 10 μl containing 10 ng of DNA, 50 mM KCl, 10 mM Tris-HCl, 200 μM of each dNTP, 0.1% gelatin, 20 pmol of each primer, 1.0 to 2.0 mM MgCl, and 0.025 U Taq polymerase. Initial denaturation at 94°C for 3 minutes (min) was followed by 30 cycles on an automated thermal cycler (Hybaid, Omnigene, USA). These included denaturation at 94°C for 30 seconds (sec), annealing at 57°C for 40 sec and extension at 72°C for 40 sec. A final extension step at 72°C for 10 min was added. Single strand conformation polymorphism (SSCP) analysis was performed on a sequencing apparatus (Pokerface II, Hoefer, San Francisco, USA) using 8% and 12% acrylamide gels and electrophoresis at 3 W to 20 W and variable temperatures for 14 hours (h). Silver staining of the gels was performed as previously described (16, 17). Aberrantly migrating SSCP bands were excised and the DNA was extracted as described (18). After reamplification with the same set of primers, the PCR products were sequenced on a semiautomated sequencer (Applied Biosystems, model 373A) using a Taq cycle sequencing kit (Applied Biosystems). Each amplicon was sequenced bidirectionally.

Statistical Analysis

For statistical analysis of the correlation for 2 independent variables, Fisher's Exact test was applied.

RESULTS

TP53 Mutations and Allelic Losses in Astrocytomas, Oligodendrogliomas and Oligoastrocytomas: SSCP analysis and consecutive bidirectional sequence analysis of the *TP53* gene revealed a total of 45 mutations in 43 of 120 gliomas included in this study. All mutations resulted in alterations at the protein level. *TP53* mutations were detected in 15/25 A II (60%), in 15/32 A III (47%), in 1/19 O II (5%) in 0/6 O III, in 6/21 OA II (29%), and in 6/17 OA III (35%). One A II and one OA III carried two mutations (see Table 1). In addition, a common polymorphism affecting codon 213 was seen in one A II, one A III and three OA II. The mutational spectrum did not differ significantly between the different tumor types. In the astrocytoma group, 25 transitions, 2 transversions and 4 deletions were observed. The single mutation in the oligodendroglioma group was a transition. Within the oligoastrocytoma group 10 transitions and 3 transversions were seen. The common hot spot mutations in codons 273, 248 and 175 were detected in both astrocytomas and oligoastrocytomas (see Table 1). Representative data are shown in Figure 1.

The entire set of astrocytomas, oligoastrocytomas and oligodendrogliomas was examined for allelic losses in 2 loci on chromosomal arm 1p, in 3 loci on chromosomal arm 17p, and in 3 loci on chromosomal arm 19q. LOH1p was observed in 0/19 informative A II, in 5/24 informative A III (21%), in 4/12 informative O II (33%), in 3/5 informative O III (60%), in 9/16 informative OA II (56%), and in 8/17 informative OA III (47%). LOH 17p was observed in 11/21 informative A II (52%), in 17/30 informative A III (57%), in 2/17 informative O II (12%), in 0/6 informative O III, in 5/20 informative OA II (25%), and in 6/17 informative OA III (35%). LOH 19q was observed in 4/20 informative A II (20%), in 13/29 informative A III (45%), in 10/18 informative O II (56%), in 5/6 informative O III (83%), in 14/21 informative OA II (67%), and in 12/16 informative OA III (75%). The LOH data are compiled in Table 2.

Association of TP53 Mutations with LOH1p, LOH17p and LOH19q

Ninety-three patients were informative for at least one marker on chromosome 1p. Of these, 4 patients exhibited LOH1p and carried a *TP53* gene mutation, 25 patients with LOH1p appeared wildtype in the *TP53* gene, 32 were heterozygous for all informative markers on chromosome 1p and carried a *TP53* gene mutation, and 32 were heterozygous for all informative markers on chromosome 1p and appeared wildtype in the *TP53* gene. There was a significant inverse correlation of LOH1p and *TP53* gene mutations ($p = 0.0011$, Table 3-A1). This inverse association of LOH1p and *TP53* mutations was also observed in the group of 33 OA II and OA III ($p < 0.011$; Table 3-A2), but not in O II and O III and A II and A III.

One hundred eleven patients were informative for at least one marker on chromosome 17p. Of these, 26 patients showed both LOH17p and *TP53* gene mutations, 15 patients exhibited LOH17p and appeared wildtype in the *TP53* gene, 14 were heterozygous for all informative markers on chromosome 17p and carried a *TP53* gene mutation, and 56 were heterozygous for all informative markers on chromosome 17p and appeared wildtype in the *TP53* gene. LOH17p was significantly associated with *TP53* gene mutations ($p < 0.0001$, Table 3B).

One hundred ten patients were informative for at least one marker on chromosome 19q. Of these, 11 patients showed both LOH19q and *TP53* gene mutations, 47 patients exhibited LOH19q and appeared wildtype in the *TP53* gene, 28 were heterozygous for all informative markers on chromosome 19q and carried a *TP53* gene mutation, and 24 were heterozygous for all informative markers on chromosome 19q and appeared wildtype in the *TP53* gene. There was a significant inverse correlation of LOH19q and *TP53* gene mutations ($p = 0.0002$; Table 3-C1). This inverse association of LOH19q and *TP53* mutations was also observed in the group of 37 OA II and OA III ($p < 0.019$; Table 3-C2). In A II and A III a tendency for an inverse association of LOH19 and *TP53* mutations was observed ($p < 0.082$). Due to

TABLE 1
TP53 Mutations in Astrocytomas, Oligoastrocytomas and Oligodendrogliomas

ID	Tissue	Exon	Codon	Mutation	Amino acid substitution
88	A II	ex 7	256	ACA → #CA	Frameshift
256	A II	ex 5	162/178	ATC → AGC/CAC → #AC	Ile → Ser/frameshift
516	A II	ex 8	273	CGT → TGT	Arg → Cys
578	A II	ex 6	205	TAT → CAT	Tyr → His
2032	A II	ex 8	273	CGT → TGT	Arg → Cys
2154	A II	ex 6	195	ATC → ACC	Ile → Thr
2198	A II	ex 5	135	TGC → TAC	Cys → Tyr
2232	A II	ex 7	239	AAC → GAC	Asn → Asp
2278	A II	ex 8	273	CGT → TGT	Arg → Cys
2284	A II	ex 8	273	CGT → TGT	Arg → Cys
2308	A II	ex 8	273	CGT → TGT	Arg → Cys
2434	A II	ex 8	273	CGT → TGT	Arg → Cys
3022	A II	ex 7	258	GAA → AAA	Glu → Lys
3294	A II	ex 7	245	GGC → GTC	Gly → Val
3642	A II	ex 5	131	AAC → ###	del Asn
24	A III	ex 6	205	TAT → TGT	Tyr → Cys
50	A III	ex 8	262	GGT → G#T	Frameshift
62	A III	ex 5	175	CGC → CAC	Arg → His
348	A III	ex 5	132	AAG → AGG	Lys → Arg
356	A III	ex 7	242	TGC → TAC	Cys → Tyr
580	A III	ex 5	132	AAG → AGG	Lys → Arg
984	A III	ex 8	273	CGT → TGT	Arg → Cys
2150	A III	ex 5	175	CGC → CAC	Arg → His
2224	A III	ex 7	246	ATG → ATA	Met → Ile
2362	A III	ex 5	176	TGC → TGT	Cys → Trp
2386	A III	ex 8	273	CGT → TGT	Arg → Cys
2392	A III	ex 8	273	CGT → TGT	Arg → Cys
2540	A III	ex 6	220	TAT → TGT	Tyr → Cys
2754	A III	ex 8	273	CGT → CAT	Arg → His
2784	A III	ex 8	273	CGT → TGT	Arg → Cys
360	O II	ex 7	246	ATG → ATA	Met → Ile
252	OA II	ex 5	156	CGC → GGC	Arg → Gly
296	OA II	ex 8	285	GAG → AAG	Glu → Lys
318	OA II	ex 7	248	CGG → TGG	Arg → Trp
500	OA II	ex 5	145	CTG → CCG	Leu → Pro
2018	OA II	ex 5	175	CGC → CAC	Arg → His
3744	OA III	ex 8	273	CGT → TGT	Arg → Cys
346	OA III	ex 5	175	CGC → CAC	Arg → His
520	OA III	ex 8	273	CGT → TGT	Arg → Cys
552	OA III	ex 7/ex 8	249/281	AGG → GGG/GAC → CAC	Arg → Gly/Asp → His
562	OA III	ex 5	in 5	Ggt → Ggg	Splice acceptor
3778	OA III	ex 7	248	CGG → TGG	Arg → Trp
3878	OA III	ex 8	273	CGT → TGT	Arg → Cys

= deleted base; small letters = intronic bases.

the incidence of only one *TP53* mutation in this group, the corresponding analysis for O II and O III was not performed.

Association of LOH1p/LOH19q, LOH 1p/LOH 17p and LOH 17p/LOH19q

Ninety-one patients were informative for at least one marker on both chromosomal arms 1p and 19q. Of these 91 patients, 26 exhibited both LOH 1p and LOH 19q, three had LOH 1p and maintained heterozygosity at 19q, 20 had LOH 19q and maintained heterozygosity at 1p, and 42 were heterozygous for both 1p and 19q. LOH 1p was therefore closely associated with LOH 19q ($p < 0.0001$; Table 4-A1). Among the different tumor types and WHO grades, the positive association of LOH1p with LOH19q was significant for O II/O III ($p < 0.01$; Table 4-A2) and OA II/OA III ($p < 0.002$; Table 4-A3). Among 18 A II, LOH1p was not observed and LOH19 occurred in only 4 tumors. In 26 A III, LOH19q was observed in 12 and LOH1p in 6 cases; however, there was no association between these lesions.

One hundred eight patients were informative for at least one marker on both chromosomal arms 17p and 19q. Of these 108 patients, 15 exhibited both LOH 17p

TABLE 2
Allelic Losses on Chromosomal Arms 1p, 17p and 19q and *TP53* Mutations in 120 Gliomas

Tumors	LOH 1p/inf	LOH 17p/inf	LOH 19q/inf	*TP53*mut in patients (*TP53*mut)/ all patients
A II	0/19	11/21	4/20	15(16)/25
A III	5/24	17/30	13/29	15/32
O II	4/12	2/17	10/18	1/19
O III	3/5	0/6	5/6	0/6
OA II	9/16	5/20	14/21	6/21
OA III	8/17	6/17	12/16	6(7)/17
Total	29/93	41/111	58/110	43(45)/120

LOH = loss of heterozygosity; inf = informative patients; *TP53*mut = mutations of the *TP53* gene.

and LOH 19q, 25 had LOH 17p and maintained heterozygosity at 19q, 42 showed LOH 19q and maintained heterozygosity at 17p, and 26 were heterozygous for both 1p and 19q. LOH 17p was inversely associated with LOH 19q ($p < 0.018$; Table 4B).

Ninety patients were informative for at least one marker on both chromosomal arms 1p and 17p. Of these 90 patients, 5 exhibited LOH on both chromosomal arms 17p and 19q, 27 had LOH 17p and maintained heterozygosity at 19q, 22 had LOH 1p and maintained heterozygosity at 17p, and 36 were heterozygous for both 1p and 19q. LOH 1p was inversely associated with LOH 17p ($p < 0.032$; Table 4C).

Histopathological Analysis of Oligoastrocytomas and Association with Genetic Findings

Thirty-three of the 38 OA were subclassified as compact and 5 OA were subclassified as diffuse. In 16 OA, an approximately equal extent of oligodendroglial and astrocytic areas was observed (O = A). In 7 OA, astrocytic portions exceeded oligodendroglial portions (O < A) and in 15 OA, the oligodendroglial areas predominated (O > A). There was no association of the compact/diffuse types with the molecular genetic parameters examined. In contrast, the predominance of astrocytic differentiation in OA was associated with *TP53* mutations ($p < 0.023$) and inversely associated with LOH1p ($p < 0.04$). However, such associations should be interpreted with caution given the possibility of sampling errors.

DISCUSSION

The histogenesis of oligoastrocytoma remains controversial. Microdissection studies have demonstrated that these lesions are clonal neoplasms with varying phenotypes rather than "collision" tumors (11). Furthermore, the available molecular genetic and chemotherapeutic response data suggest that oligoastrocytomas are biologically more similar to oligodendrogliomas than to astrocytomas. For instance, oligoastrocytomas display frequent allelic loss of chromosomes 1p and 19q and respond to PCV chemotherapy (2). On the contrary, in patients not treated with PCV, the prognosis of patients with oligoastrocytomas approaches that of astrocytoma rather than that of oligodendroglioma, with survival worsening as the astrocytic component increases (19). Such data argue that the astrocytic component plays a key role for survival in patients not treated with PCV chemotherapy.

Our analysis of 57 astrocytomas and 25 oligodendrogliomas confirms previous reports that chromosome 1p and 19q loss occur most commonly in oligodendrogliomas, whereas *TP53* mutations and chromosome 17p loss occur primarily in astrocytomas (5, 6, 9, 11, 12, 20, 21). We therefore sought to use these molecular genetic markers for a detailed analysis of oligoastrocytomas. The 38

TABLE 3
Contingency Tables for Allelic Losses on Chromosomal Arms 1p, 17p, 19q and *TP53* Mutations

A1: *TP53* and Chr1p in all tumors (n = 93)

	*TP53*mut	*TP53*wt
MOH1p	32	32
LOH1p	4	25

$p = 0.0011$

A2: *TP53* and Chr1p in OA (n = 33)

	*TP53*mut	*TP53*wt
MOH1p	9	7
LOH1p	2	15

$p = 0.0104$

B: *TP53* and Chr17p in all tumors (n = 111)

	*TP53*mut	*TP53*wt
MOH17p	14	56
LOH17p	26	15

$p < 0.0001$

C1: *TP53* and Chr19q in all tumors (n = 110)

	*TP53*mut	*TP53*wt
MOH19q	28	24
LOH19q	11	47

$p = 0.0002$

C2: *TP53* and Chr19q in OA (n = 37)

	*TP53*mut	*TP53*wt
MOH19q	7	4
LOH19q	5	21

$p = 0.0183$

mut = mutation; wt = wild type; MOH = maintenance of heterozygosity; LOH = loss of heterozygosity; OA = oligoastrocytoma. All analyses were performed with Fisher's Exact test.

TABLE 4
Contingency Tables for Allelic Losses on Chromosomal Arms 1p, 17p and 19q

A1: Chr1p and Chr19q in all tumors (n = 91)

	MOH1p	LOH1p
MOH19q	42	20
LOH19q	3	26

$p < 0.0001$

A2: Chr1p and Chr19q in O (n = 17)

	MOH1p	LOH1p
MOH19q	7	3
LOH19q	0	7

$p = 0.0098$

A3: Chr1p and Chr19q in OA (n = 32)

	MOH1p	LOH1p
MOH19q	9	6
LOH19q	1	16

$p = 0.0017$

B: Chr17p and Chr19q in all tumors (n = 108)

	MOH19q	LOH19q
MOH17p	26	42
LOH17p	25	15

$p = 0.0175$

C: Chr1p and Chr17p in all tumors (n = 90)

	MOH17p	LOH17p
MOH1p	36	27
LOH1p	22	5

$p = 0.0319$

mut = mutation; wt = wild type; MOH = maintenance of heterozygosity; LOH = loss of heterozygosity; OA = oligoastrocytoma. All analyses were performed with Fisher's Exact test.

oligoastrocytomas showed genetic alterations characteristic of both astrocytoma and oligodendroglioma. Notably, however, the genetic changes were not random. While close associations were noted between allelic loss of 17p and *TP53* mutations as well as between chromosome 1p and 19q losses, most significantly, *TP53* mutations and chromosome 1p/19q losses were inversely related. This provided strong evidence for genetic subsets of oligoastrocytoma, some with "astrocytic" genetic changes, others with "oligodendroglial" genetic changes (see Fig. 2). The more common subtype shows chromosome 1p/19q losses but rarely harbors *TP53* mutations; these tumors are genetically related to oligodendroglioma. The less common subtype carries *TP53* mutations but rarely has chromosome 1p/19q loss; these tumors are genetically similar to astrocytoma. In a series of 16 oligoastrocytomas, Reifenberger et al noted a mutually exclusive relationship between LOH 17p and LOH 19q (12). Our larger series shows that these changes are not necessarily mutually exclusive, but are inversely related to one another.

In our series, *TP53* mutations were detectable in a fraction of oligoastrocytomas, and there was a good correlation between *TP53* mutations and chromosome LOH 17p. This finding differs from that reported by Reifenberger et al, in which chromosome 17p loss was not accompanied by *TP53* gene mutations in oligoastrocytomas. These authors speculated that a second chromosome 17p tumor suppressor gene may be involved in the genesis of oligoastrocytomas. Our data, however, indicate that *TP53* is the target of allelic chromosome 17p loss in

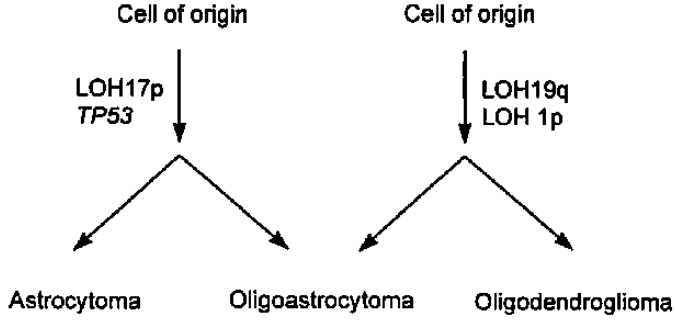

Fig. 2. A model for molecular genetic subsets of oligoastrocytomas.

at least a subset of oligoastrocytomas. Differences in mutation detection methodologies may account for the differences between the two studies. Alternatively, differences in the definition of oligoastrocytomas could account for the varying results; for instance, inclusion of cases that we would have classified as pure oligodendroglioma would have resulted in a low incidence of *TP53* mutations in their series. In the 3 tumors that we had previously microdissected and that were shown to carry allelic loss of chromosomes 1p and 19q, *TP53* mutations were not present (11). Although none of the other tumors was amenable to an analysis of separate components following microdissection, the detection of *TP53* mutations in the oligodendroglial and astrocytic components provided useful information on whether *TP53* alterations are early events or specific to the astrocytic component. Finally, it is interesting to note that the mutational spectra

of *TP53* mutations were similar in astrocytomas and oligoastrocytomas.

To determine whether these putative genetic subsets reflected other biological differences in oligoastrocytomas, we evaluated the tumors histologically. All OA were classified as diffuse or compact (14) and the approximate proportions of oligodendroglial and astrocytic components were determined. Thirty-three of the 38 oligoastrocytomas were compact and five were diffuse. Due to the vast majority of the compact over the diffuse type, there was no association with molecular genetic parameters. However, five of 12 oligoastrocytomas with *TP53* mutations were predominantly astrocytic, while astrocytoma-predominance was noted in only 2 of 24 oligoastrocytomas without *TP53* mutations. Only one of the 17 OA with LOH1p was predominantly astrocytic, while astrocytoma-predominance was observed in 6 of 16 OA without LOH1p. Thus, the predominance of astrocytic differentiation appeared to be associated with "astrocytic" genetic changes, i.e. *TP53* mutations and a low rate of LOH1p. While such analysis is clearly susceptible to sampling error, it hints that the molecular genetic differences may reflect clinicopathologically relevant parameters. Comparison of molecular genetic data with clinical variables, such as survival and response to chemotherapy, will be necessary to clarify whether such putative subsets are clinically important.

In conclusion, we present evidence for 2 molecular genetic variants of oligoastrocytomas. One genetic variant is characterized by TP53 mutations and the absence of LOH1p/LOH19q. The other genetic variant is characterized by LOH1p/LOH19q and the absence of TP53 mutations (see Fig. 2). These 2 variants accounted for approximately 75% of all OA in our study, and it is therefore possible that further molecular variants of OA exist. These observations provide an additional basis for further neuropathological and clinical studies.

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