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Genetic Signature of Oligoastrocytomas Correlates with Tumor Location and Denotes Distinct Molecular Subsets

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Oligoastrocytomas are heterogeneous tumors that have molecular features that overlap with either oligodendrogliomas or astrocytomas. Differences in the frequency of chromosomal losses of 1p and 19q in oligodendrogliomas are related to tumor location, with a low rate of allelic loss in tumors of the temporal and a high rate in tumors of the frontal, parietal, and occipital lobes. To test the possibility of regional molecular heterogeneity in oligoastrocytoma, we examined a series of 203 gliomas including 68 oligoastrocytomas and two control groups of 73 oligodendrogliomas and 62 astrocytomas for allelic losses of chromosomal arms 1p and 19q, and *TP53* mutations, and compared these data with tumor localization. Common molecular alterations were found in oligodendrogliomas and oligoastrocytomas arising in extratemporal sites. In respect to the molecular parameters analyzed, temporal oligoastrocytomas were either indistinguishable from astrocytoma or similar to temporal oligodendrogliomas. Oligodendroglial neoplasms can thus be separated into three molecular subsets, two of which include lesions with the morphological features of oligodendrogliomas and oligoastrocytomas and one resembling temporal oligoastrocytoma. Molecular subclassification thus unifies previous findings about prognosis, behavior, response to therapy, genotype, and location in oligodendroglial tumors. ***(Am J Pathol 2002, 161:313–319)***

Oligodendroglial tumors, including oligodendrogliomas and oligoastrocytomas, constitute between 5% and 18% of all primary human brain tumors.[1–4] Advances in diagnostic recognition and clinical management have succeeded in a dramatic improvement of the clinical outcome of patients with anaplastic oligodendroglioma. Distinct molecular subsets of oligodendroglial tumors also have highly differential responses to therapy.[5,6] Therefore, the further identification and evaluation of diagnostic parameters with high prognostic power is of great interest in oligodendroglial neoplasms.

Somatic deletions on the short arm of chromosome 1 [loss of heterozygosity (LOH) 1p] and the long arm of chromosome 19 (LOH 19q) are typical of oligodendroglioma and oligoastrocytoma.[7–12] To date, however, neither the 1p nor 19q gene has been identified. Although LOH 19p is also frequently seen in anaplastic astrocytomas and may be associated with tumor progression, LOH 1p is more closely associated with oligodendroglial gliomas.[13] The combination of LOH 1p and LOH 19q is observed only rarely in gliomas other than oligodendroglioma and oligoastrocytoma.[11]

Oligoastrocytomas exhibit both astrocytic and oligodendroglial morphologies.[14] Because of the rather vague criteria for defining oligoastrocytoma, the incidence of oligoastrocytoma varies considerably between different studies. Based on molecular findings, oligoastrocytomas occupy an intermediate position between oligodendrogliomas and astrocytomas. From 30 to 70% of oligoastrocytomas show LOH 1p and LOH 19q[8–12,15] thus genetically resembling oligodendrogliomas, whereas ~30% show mutations in the *TP53* gene or LOH 17p[10,16] suggesting a relation to astrocytomas. Significantly, LOH 1p and LOH 19q are inversely associated with *TP53* muta-

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tions.[16] On microdissection, identical genetic alterations have been identified in astrocytic and oligodendroglial portions, indicating a clonal origin of oligoastrocytomas.[11] Although one might assume that in oligoastrocytomas the astrocytic component implies a less favorable prognosis, most studies could not confirm differences in outcome between oligodendroglioma and oligoastrocytoma.[17–19]

LOH 1p and LOH 19q have been associated with chemosensitivity and durable responses to chemotherapy in patients with anaplastic oligodendrogliomas.[5,6] In addition, patients with oligodendrogliomas and anaplastic oligodendrogliomas exhibiting these molecular lesions have longer overall survival from the time of diagnosis.[5,6,20–22] Further, LOH 1p may indicate a better response to chemosensitivity and prolonged survival in a small group of astrocytomas and oligoastrocytomas. In oligoastrocytomas, a subset has been shown to respond favorably to procarbacine lomustine (CCNU)/vincristine-based chemotherapy.[23,24]

Recently, an association was identified between the incidence of genetic lesions in oligodendroglioma and tumor location.[25] Anaplastic oligodendrogliomas located in the frontal, parietal, and occipital lobes were significantly more likely to harbor LOH 1p and LOH 19q, than those arising in the temporal lobe, insula, and diencephalon. In addition, LOH1p and LOH 19q were significantly correlated with a bilateral growth pattern. Because of the strong predictive value of LOH 1p and LOH 19q, these findings may argue for differential therapy approaches in patients with oligodendrogliomas depending on gross tumor localization. The morphological and genetic similarities between oligodendrogliomas and oligoastrocytomas naturally raise the question of whether molecular subsets of oligoastrocytomas correlate with tumor location. The present study was thus conducted to clarify and extend molecular subclassification of oligoastrocytomas. To this end, we analyzed a series of 203 gliomas, including 68 oligoastrocytomas and two control groups of 73 oligodendrogliomas and 62 astrocytomas, for LOH 1p, LOH 19q, and *TP53* mutations, with respect to tumor location.

Materials and Methods

Tissue Samples

Two hundred three gliomas, consisting of 37 oligodendrogliomas World Health Organization (WHO) grade II (O II), 36 anaplastic oligodendrogliomas WHO grade III (O III), 38 oligoastrocytomas WHO grade II (OA II), 30 anaplastic oligoastrocytomas WHO grade III (OA III), 28 astrocytomas WHO grade II (A II), and 34 anaplastic astrocytomas WHO grade III (A III), and corresponding blood samples were obtained from patients treated at the Charité Hospital in Berlin, the Helios Klinikum in Buch, the University Hospital in Würzburg, the Neukölln Hospital in Berlin, the University Hospital in Bonn, the University Hospital in Tübingen and the Massachusetts General Hospital in Boston between 1992 and 2001. Because no clearly defined parameters for the diagnosis of oligoastrocytoma have been established, we required for this diagnosis the lesser represented component to amount to at least 20% of the material examined. Among the 203 tumors, 103 were located in the frontal, 53 in the temporal, 17 in the frontotemporal, 11 in the parietal, 6 in the parietotemporal, 7 in the ventricular, 3 in the occipitotemporal, and 1 in the occipital region; 2 were from the spinal cord. All tumors were classified graded by neuropathologists according to the 2000 WHO criteria and all cases were reviewed by one neuropathologist (AvD).[26] Thirty-one patients with oligoastrocytomas reported on in an earlier study were included.[16] Before extraction of DNA from tumor tissues and leukocytes by standard methods, all tumor samples were examined by frozen sections to exclude contaminating nontumorous portions.[11]

Microsatellite Analysis for LOH

The microsatellite markers D1S1608 (1p36.31), D1S548 (1p36.23), D1S1597 (1p36.21), D1S1592 (1p36.13), and D1S1161 (1p35.1) were used to identify LOH 1p. For determining LOH 19q, the markers D19S431 (19q12), D19S433 (19q12), D19S559 (D19q13.2), and D19S601 (19q13.33) were used. Amplification conditions and primer sequences are based on corresponding Genome Database entries (*www.gdb.org*). Polymerase chain reaction products were separated on 8% denaturing acrylamide gels and visualized by silver staining. LOH was scored as previously described.[27]

Single-Strand Conformation Polymorphism Analysis and Direct Sequencing

For analysis of the *TP53* gene, a set of previously published primers for exons 5 to 8 were used. Polymerase chain reaction was performed in a volume of 10 μl containing 10 ng of DNA, 50 mmol/L KCl, 10 mmol/L Tris-HCl, 200 mmol/L of each dNTP, 0.1% gelatin, 20 pmol of each primer, 1.0 to 2.0 mmol/L $MgCl_2$, and 0.025 U *Taq* polymerase. Initial denaturation at 94°C for 3 minutes was followed by 30 cycles on an automated thermal cycler (Biometra, Göttingen, Germany). These included denaturation at 94°C for 30 seconds, annealing at 57°C for 40 seconds, and extension at 72°C for 40 seconds. A final extension step at 72°C for 10 minutes was added. Single-strand conformation polymorphism analysis was performed on a sequencing apparatus (BlueSeq 400; Serva, Marburg, Germany) using 8% and 14% acrylamide gels and electrophoresis at 3 to 6 W and variable temperatures for 15 hours. Silver staining of the gels was performed as previously described.[28,29] Aberrantly migrating single-strand conformation polymorphism bands were excised and the DNA was extracted as described.[30] After reamplification with the same set of primers the polymerase chain reaction products were sequenced on a semiautomated sequencer (model 373A; Applied Biosystems, Foster City, CA) using a *Taq* cycle sequencing kit (Applied Biosystems). Each amplicon was sequenced bidirectionally.

Table 1. Molecular Alterations in Oligodendrogliomas, Oligoastrocytomas, and Astrocytomas

			Frequency for distinct tumor sites						
Histology	Molecular alteration	Frequency	Frontal	Parietal	Occipital	Ventricular	Temporal + other lobe	Temporal	Spinal
O	LOH 1p	49/70	36/44	2/2	0/1	2/2	6/8	3/13	–
	LOH 19q	55/73	38/46	2/2	1/1	2/2	8/9	4/13	–
	LOH1p/19q	49/70	36/44	2/2	0/1	2/2	6/8	3/13	–
	TP53 mut	4/56	3/33	0/2	–	0/2	0/6	1/13	–
OA	LOH1p	40/64	26/33	3/5	–	–	4/5	7/21	–
	LOH 19q	48/67	27/32	3/5	–	–	5/6	13/24	–
	LOH1p/19q	37/63	24/32	3/5	–	–	3/5	7/21	–
	TP53 mut	17/61	5/29	2/5	–	–	0/5	10/22	–
A	LOH1p	8/53	5/21	0/3	–	0/5	2/10	1/12	0/2
	LOH 19q	18/58	8/21	0/4	–	3/5	4/11	2/15	1/2
	LOH1p/19q	5/49	4/18	0/3	–	0/5	1/10	0/11	0/2
	TP53 mut	25/53	11/20	3/4	–	1/4	6/11	4/12	0/2

O, Oligodendrogliomas; OA, oligoastrocytoma; A, astrocytoma; LOH, loss of heterozygosity; *TP53* mut, detection mutation in exons 5 to 8 of *TP53*; –, no data available. Numbers of cases with alterations are given in respect to informative cases (for LOH data) and in respect to cases examined (for *TP53* mutation data)

Statistical Analysis

For statistical analysis Statview 4.0 (SAS, Cary, NC) was used. For the analysis of nominal and independent variables, chi-square and Fisher's exact tests, were applied. The distribution of age and nominal variables was analyzed by *t*-test.

Results

Two hundred three gliomas and corresponding blood samples were analyzed for LOH 1p and LOH 19q and for mutations in exons 5 to 8 of the *TP53* tumor suppressor gene. The informative cases had the following alterations: 97 tumors showed LOH 1p (24 O II, 25 O III, 21 OA II, 19 OA III, 2 A II, 6 A III) and 121 cases had LOH 19q (28 O II, 27 O III, 27 OA II, 21 OA III, 4 A II, 14 A III). Combined LOH 1p and LOH 19q was detected in 91 cases (24 O II, 25 O III, 20 OA II, 17 OA III, 2 A II, 3 A III). In 46 tumors a *TP53* mutation was detected (1 O II, 3 O III, 10 OA II, 7 OA III, 13 A II, 12 A III). Data are summarized in Table 1.

Oligodendrogliomas from nontemporal sites had significantly more LOH 1p and LOH 19q than those situated in the temporal lobes. Within the respective regions, LOH frequencies in O II did not differ from those in O III. LOH 1p occurred in 36 of 44 frontal, 2 of 2 ventricular, 0 of 1 occipital, 2 of 2 parietal, and only 3 of 13 temporal oligodendrogliomas ($P = 0.0001$, chi-square test). LOH 19q occurred in 38 of 46 frontal, 2 of 2 ventricular, 1 of 1 occipital, 2 of 2 parietal, and only 4 of 13 temporal oligodendrogliomas ($P = 0.0004$, chi-square test).

Because those tumors involving both the temporal and another lobe seemed to reflect the alterations seen in nontemporal tumors, we divided the oligodendrogliomas into the three categories: temporal, nontemporal, and temporal with another lobe. Indeed, 40 of 49 nontemporal O, 6 of 8 O involving the temporal and another lobe, and 3 of 13 temporal O exhibited LOH 1p ($P = 0.0002$, chi-square test). The data for LOH 19q were: 43 of 51 nontemporal O, 8 of 9 O involving the temporal with another lobe, and 4 of 13 nontemporal O exhibited LOH 19q ($P = 0.0006$, chi-square test). *TP53* mutations were rare and not associated with specific brain regions.

Oligoastrocytomas of nontemporal origin had significantly more LOH 1p than those situated in the temporal lobes. Within the respective regions, LOH frequencies in OA II did not differ from those in OA III. LOH 1p occurred in 26 of 33 frontal, 3 of 4 frontotemporal, 3 of 5 parietal, 1 of 1 parietotemporal, and only 7 of 21 temporal oligoastrocytomas ($P < 0.0001$, chi-square test). LOH 19q occurred in 27 of 32 frontal, 3 of 4 frontotemporal, 1 of 1 occipitotemporal, 3 of 5 parietal, 1 of 1 parietotemporal, and 13 of 24 temporal oligoastrocytomas. We also divided oligoastrocytomas into the three categories: temporal, nontemporal, and temporal with another lobe. Twenty-nine of 38 nontemporal OA, 4 of 5 OA involving the temporal with another lobe, and 7 of 21 temporal OA exhibited LOH 1p ($P < 0.004$, chi-square test). The data for LOH 19q were: 30 of 37 nontemporal OA, 5 of 6 OA involving the temporal with another lobe, and 13 of 24 nontemporal OA exhibited LOH 19q ($P = 0.06$, chi-square test). *TP53* mutations were seen in 7 of 34 nontemporal OA, in 0 of 5 OA affecting the temporal with another lobe, but in 10 of 22 temporal OA ($P < 0.05$, chi-square test). Figure 1 depicts a representative case of temporal oligoastrocytoma with *TP53* mutation. In 57 oligoastrocytomas with both LOH 1p and *TP53* data, a significant inverse association was detected between LOH 1p and *TP53* mutation ($P < 0.0001$, Fisher's exact test). This inverse association was also seen for LOH 19q and *TP53* mutation ($P = 0.0004$, Fisher's exact test). Because 31 cases from an earlier study had been included that showed a similar distribution, the analyses were repeated excluding those cases: the remaining 26 oligoastrocytomas again demonstrated that LOH 1p ($P < 0.005$, Fisher's exact test) and LOH 19q ($P < 0.005$, Fisher's exact test) tend not to occur with *TP53* mutations. Interestingly, patients with tumors of the temporal lobe (mean, 36 years) were younger ($P < 0.05$, *t*-test) than patients with nontemporal tumors (mean, 41 years). Within the temporal tumor group, patients with *TP53* mu-

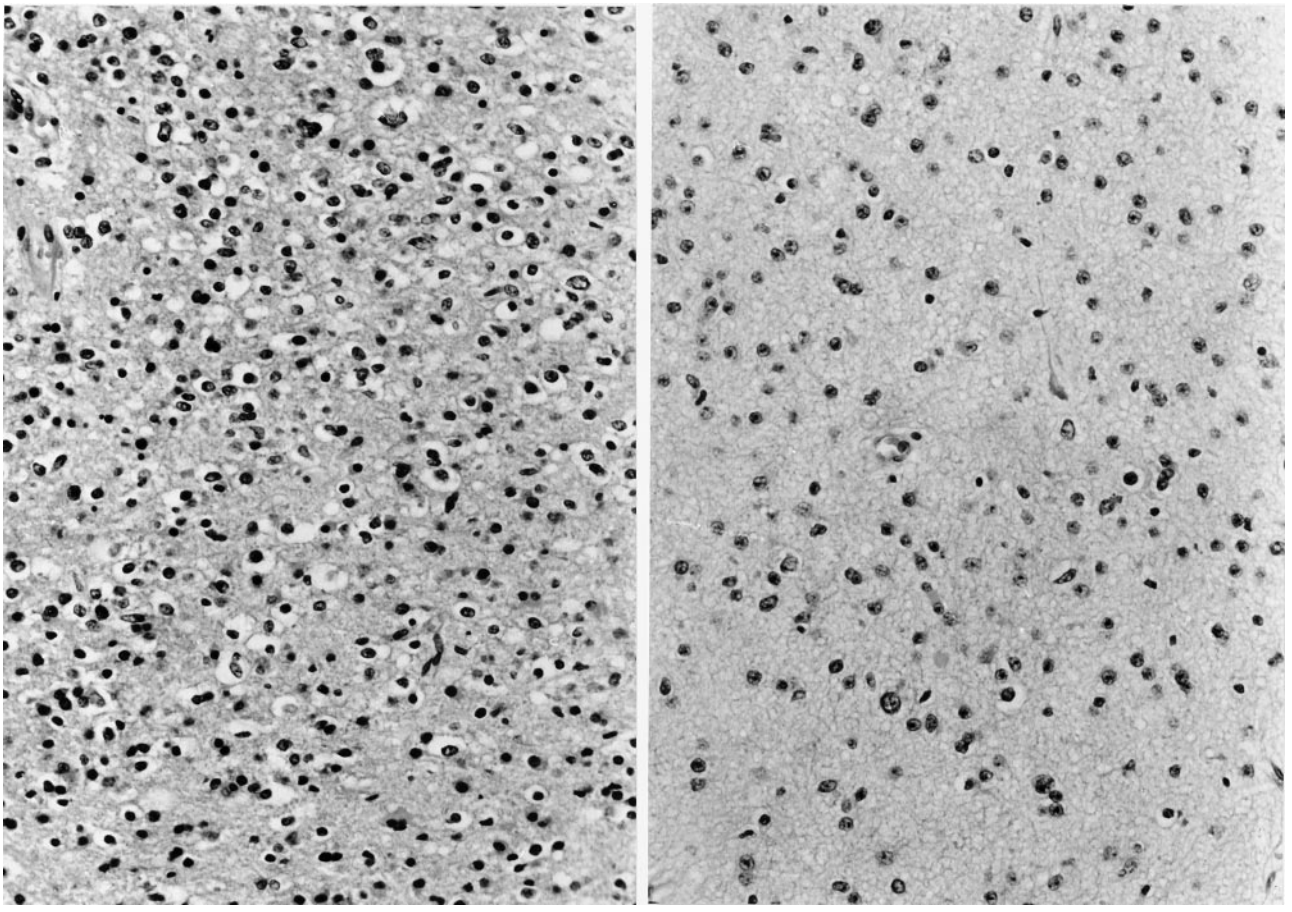

Figure 1. Temporal oligoastrocytoma WHO grade II (case 3744) with *TP53* mutation. **Left**: Oligodendroglial differentiation (H&E; original magnification, ×200). **Right**: Astrocytic differentiation. The tumor DNA carries a somatic C → T transition resulting in an Arg → Cys change in codon 273 in exon 8 of *TP53*.

tations (mean, 33 years) were younger than those without this alteration (mean, 38 years).

Astrocytomas did not exhibit different frequencies of either LOH 1p and LOH 19q or *TP53* mutations with respect to tumor localization. LOH 19q occurred more frequently in A III than in A II. Only 4 of 26 A II but 14 of 32 A III exhibited LOH 19q ($P < 0.025$, Fisher's exact test). The LOH 1p frequencies did not differ for A II (2 of 25) and A III (6 of 28). *TP53* mutations occurred in 13 of 26 A II and 12 of 27 A III.

Discussion

To clarify the nosological position of oligoastrocytoma among the diffuse gliomas, we analyzed a series of 203 gliomas, including 68 oligoastrocytomas, and two control groups of 73 oligodendrogliomas and 62 astrocytomas, for LOH 1p, LOH 19q, and *TP53* mutations, with particular emphasis on correlations with tumor location. Both control groups—the pure astrocytomas and oligodendrogliomas—displayed molecular genetic features similar to those reported in the literature. Oligodendrogliomas and oligoastrocytoma had LOH 1p and LOH 19q in the majority of the cases.[7–12]The overall low frequency of *TP53* mutations in oligodendrogliomas also confirmed previous studies.[10,16,31] Although LOH 1p was a rare event in astrocytomas, evenly distributed among WHO II and III grades, LOH 19q was significantly associated with higher grade, thereby further supporting the suggestion that a progression-associated tumor suppressor gene resides on this chromosomal arm.[13]

We next correlated these molecular findings with tumor location. Astrocytomas did not exhibit any associations between molecular genetic features and location. Furthermore, in oligodendrogliomas, *TP53* mutations did not correlate with tumor site. Nonetheless, as previously reported, temporal lobe oligodendrogliomas have significantly less frequent LOH 1p and LOH 19q than their morphologically indistinguishable nontemporal counterparts.[25] Although such differences can be assessed easily for tumors occupying a single site, such as the temporal lobe, a considerable percentage of lesions involve both the temporal lobe and portions of either the frontal, parietal, or occipital lobes. We therefore placed those oligodendrogliomas involving more than one lobe into a separate category; these tumors had genetic features similar to the group of nontemporal oligodendrogliomas. The findings indicate that those oligodendrogliomas without LOH 1p and LOH 19q predominantly arise in the temporal lobes.

Oligoastrocytomas showed a similar distribution of LOH 1p and LOH 19q with respect to tumor location as

that noted for oligodendrogliomas. Allelic losses of 1p and 19q were significantly less frequent in temporal oligoastrocytomas, whereas those oligoastrocytomas affecting temporal and additional lobes were similar to nontemporal oligoastrocytomas. However, oligoastrocytomas within the temporal lobe had significantly more frequent *TP53* mutations than the oligoastrocytomas affecting other sites. This may reflect the general problem of separating mixed oligoastrocytomas from astrocytomas and may indicate that temporal oligoastrocytomas not only differ with respect to LOH 1p and LOH 19q, but are also enriched by a fraction of tumors possibly resembling astrocytoma. This line of argument is supported by the observation of an inverse association of LOH 1p and *TP53* mutations in oligoastrocytomas. Although 32 of 57 oligoastrocytomas had LOH 1p without *TP53* mutation and 13 of 57 had *TP53* mutations without LOH 1p, only 2 of 57 exhibited both LOH 1p and *TP53* mutations ($P < 0.0001$, Fisher's exact test). This clearly demonstrates the existence of different pathogenetic pathways in the genesis of oligoastrocytomas and also confirms our previous study.[16] Analysis excluding 31 cases already studied in the previous series[16] further demonstrated the same two molecular subsets in the remaining 21 samples ($P < 0.005$, Fisher's exact test), thereby confirming the initial study[16] using an independent series of tumors. In fact, only one of those 10 temporal oligoastrocytomas with *TP53* mutation had LOH 1p. Taken together, these data indicate extensive genetic overlap between oligodendrogliomas and oligoastrocytomas in nontemporal sites, raising the question of whether these tumors represent variants of the same entity. In the temporal lobe, approximately half of the oligoastrocytomas share genetic features with astrocytomas, ie, presence of *TP53* mutation and absence of LOH 1p and 19q, suggesting that these tumors may indeed be astrocytomas with some histological features resembling oligodendroglioma. It is thus possible that there are three molecular subsets of oligodendroglial tumors, differing not by morphology but on molecular grounds. Such a model would include a set of predominately extratemporal oligodendroglial tumors with LOH 1p and LOH 19q, and a set of predominately temporal lesions without these alterations—with both sets including morphologically defined oligodendrogliomas as well as oligoastrocytomas. In addition, there appears to be a third set of oligoastrocytomas with *TP53* mutations in the temporal lobe that are genetically similar to astrocytomas. However, it should be pointed out that oligoastrocytomas and astrocytomas may well differ for other genetic alterations frequently described in astrocytomas such as CDKN2A deletions or LOH 22q. A model for oligodendroglial tumors is shown in Figure 2. Such a model may imply that these tumors arise from different progenitor cell populations.[32]

Developmental studies on oligodendrocyte differentiation in the chick embryo suggests the existence of two distinct oligodendrocyte precursors emerging from the alar anterior entopeduncular area and from basal rhombomeric foci; however, this study also concluded that all telencephalic oligodendrocyte progenitors are derived from the alar anterior entopeduncular area.[33] Further evidence is provided by the identification of oligodendrocyte precursors with differential expression of *PDGFR-α* and *plp/dm-20*, respectively.[34] These observations point toward the possibility of human oligodendrogliomas arising from different progenitor cell populations. On the other hand, mouse models using controlled ectopic expression in either precursor or maturing astrocytic cells have modeled human glioblastomas, astrocytomas, oligodendrogliomas, or oligoastrocytomas, depending on the oncogenic stimuli.[35–37] Although these findings allow one to speculate that different tumors could arise from the same progenitor cell population, they also allow tumors of a similar origin to exhibit morphologically distinct appearances.[32] Another hypothesis may be to postulate stepwise occurrence of genetic alterations and different detection times for temporal and nontemporal tumors. However, earlier recognition of temporal tumors because of early onset of epilepsy seems not to be the cause. Although temporal tumor patients indeed are significantly younger, this is mainly because of the patient group of oligoastrocytomas with *TP53* mutations. This rather supports the notion of initial genetic heterogeneity among these lesions.

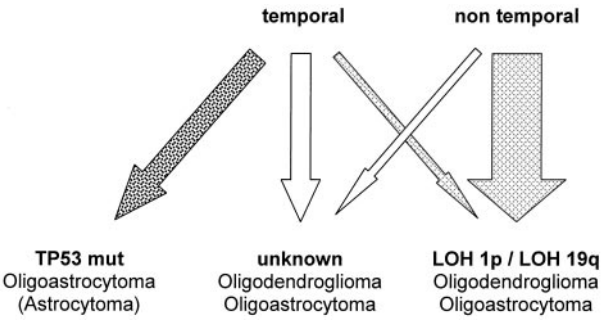

Figure 2. Model for molecular subdivision of oligodendroglial tumors. Oligodendrogliomas and oligoastrocytomas with LOH 1p/LOH 19q (**light-gray arrows**) are located predominantly in nontemporal regions of the brain. Oligodendrogliomas and oligoastrocytomas without LOH 1p/LOH 19q (**white arrows**) are located predominantly in temporal regions of the brain. Oligoastrocytomas with *TP53* mutations (**dark-gray arrow**) mostly arise in the temporal lobes and may resemble astrocytomas. The width of the **arrows** approximates the frequency of the three subsets in the present study.

On a practical level, the pathologist is left with the problem of how to classify oligodendroglial tumors. The classic distinction between oligodendrogliomas and oligoastrocytomas is problematic because of lack of clearly discriminating parameters.[26] Quantifying areas of astrocytic and oligodendroglial differentiation and applying threshold values is complicated by the insuperable problem of sampling bias, and is potentially aggravated by the tendency of reactive changes at tumor margins to mimic astrocytic proliferation. At a molecular level, the differences between morphologically defined oligodendrogliomas and oligoastrocytomas seem to disappear. Instead, a regional molecular heterogeneity emerges that may be used for molecular classification. Such an approach results in pooling oligodendroglial tumors based on the presence or absence of LOH 1p and LOH 19q, and, raise the radical possibility of dismissing temporal oligoastrocytomas with *TP53* mutations as astrocytomas. Clinical reports are supportive for a molecular classifica-

tion of oligodendroglial tumors. LOH 1p and LOH 19 q have been demonstrated as powerful tools to predict survival.[5,21,22] One study on anaplastic oligodendrogliomas demonstrated these molecular parameters to be the most powerful predictors of response to chemotherapy.[5] The regional heterogeneity of molecular parameters in oligodendroglial tumors also finds clinical support in the observation that patients with frontal oligodendrogliomas have better outcomes.[38] Taken together, a subclassification on molecular grounds provides a cogent approach to unifying previous findings about prognosis, behavior, response to therapy, genotype, and location in oligodendroglial tumors. The emerging clinicogenetic associations suggest that oligodendroglial tumors will require molecular subdivision in the near future.

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