Molecular biological determinants of meningioma progression and aggressive behavior

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TABLE OF CONTENTS

1. ABSTRACT

Meningiomas are the most commonly reported brain tumor in the United States. Though these tumors are often surgically curable, even World Health Organization (WHO) grade 1 meningiomas can recur. The variability seen in the clinical behavior of meningiomas suggests that these tumors are genetically heterogeneous. The most common genetic aberrations found in meningiomas are deletions of chromosomes 1p, 14q, and 22q. Fluorescent *in situ* hybridization (FISH) analyses have demonstrated the presence of intratumor heterogeneity; however, the loss of a single chromosome region was not indicative of aggressive behavior. In fact, tumors of higher grade are less heterogeneous in that all of the cells tend to demonstrate deletion of these chromosome arms. Tumor suppressor genes that map to these chromosomes have been identified but have not been found to play a significant role in the initiation or progression of the disease. The identification of a marker of aggressive behavior would allow the development of improved clinical protocols based on early intervention for those patients likely to experience a recurrence.

2. INTRODUCTION

Meningiomas are brain tumors that arise from arachnoid cap cells of the dura mater. They are the most commonly reported brain tumor in the United States, accounting for about 27 percent of all primary brain tumors (1). They are typically considered benign tumors that are clinically manageable and surgically curable. However, clinically aggressive behavior in meningiomas is well documented, especially in the case of meningiomas with a high histologic grade (2-4). Most meningiomas are WHO grade I (benign); however, 5 percent to 11 percent are grade II (atypical), and 1 percent to 3 percent are grade III (anaplastic) (5,6).

From diagnosis, the mean survival of patients with a grade III tumor is about 1.5 years, and their 5-year mortality rate is 68 percent (2). Grade II meningiomas are associated with a 5-year recurrence rate of 40 percent, even when gross total resection is achieved. In patients with a grade I meningioma, recurrence rates vary significantly according to the extent of surgical resection—the factor with the greatest impact on prognosis.

Approximately 9.5 percent of Grade I meningiomas recur after gross total resection (Simpson Grade I), 18 percent recur after Simpson Grade II removal, and 20 percent regrow after subtotal resection (Simpson Grades III and IV) (7-9). As described in previous studies, patients whose tumors were not completely removed had a 4.2-fold higher excess risk of death during the second to fifteenth postoperative years compared with patients whose tumors were removed completely (10). However, extensive follow-up after subtotal resection finds that meningiomas have also exhibited no regrowth (11-13). These reports suggest that the molecular and genetic composition of subsets of these tumors has a greater influence on tumor recurrence than extent of surgical resection.

3. GENETIC CHARACTERISTICS OF MENINGIOMAS

Genetic characterization offers a promising possibility for stratifying meningiomas. The technique, which is easy to implement in a histopathology laboratory, can characterize genetic events underlying the formation and progression of meningiomas. Furthermore, genetic aberrations have often pointed to specific genes that have then been studied to evaluate their expression as prognostic markers. Considerable literature details the cytogenetic and molecular genetic findings associated with meningiomas. Unfortunately, the conclusions on the utility of specific chromosomal aberrations for diagnosis, prognostication, or both are often contradictory. These inconsistent findings may reflect that these studies have largely ignored the issue of heterogeneity.

Many investigators have performed cytogenetic analyses (14-18) and molecular genetic analyses, such as fluorescent *in situ* hybridization (FISH) (19-26), spectral karyotyping (17), comparative genomic hybridization (CGH) (27), and loss of heterozygosity (LOH) (28). These data have led investigators to propose a number of multistep models of meningioma progression similar to those proposed for malignant tumors (29-33). Despite some differences in these models, there is consensus that aberrations of chromosome 22 are the most frequently observed genetic abnormalities in meningiomas (22,25) and are likely the first to occur.

The link between a gene on chromosome 22 and meningiomas was first recognized in patients with the inherited disorder neurofibromatosis 2 (NF2) (34). The frequency of meningiomas in these patients led to the discovery of the NF2 tumor-suppressor gene on chromosome 22q12.1 (34), which encodes an intracellular membrane-associated protein named schwannomin or merlin. Even in sporadic meningiomas, which are far more common than NF2-associated meningiomas, the gene appears to play a role in tumor formation, particularly in subtypes with a mesenchymal-like morphology, such as the fibroblast, transitional, and psammomatous variants. A third to a half of sporadic meningiomas has an inactivating mutation in NF2, often with associated loss of the other gene allele. This gene can also be regulated by CpG island methylation and increased proteolysis (33). Other genes on

chromosome 22 may also play a role in the formation of meningiomas.

LOH has been described for as many as 78 percent of sporadic meningiomas, not all of which include the NF2 gene locus (31,35). This finding has led to numerous studies of genes localized to areas of LOH. To date, however, results have been inconsistent, and no conclusive reports of additional genes on chromosome 22 are involved in the formation or progression of meningiomas.

The next most frequently reported genetic abnormalities in meningiomas are deletions of chromosomes 1p and 14q, which are thought to be involved in tumor progression (19-21,26,30,31,36-39). While some investigators cite 14q deletions as being highly correlated with a higher grade and recurrence (19,21), others correlate loss of sequences on chromosome 1p with tumor recurrence (18,38). Specific genes mapped to the regions of deletion on chromosomes 1p and 14q have been investigated, but a consensus on the role of these genes, if any, is lacking. In addition to deletions of chromosomes 1p, 14q, and 22q in meningiomas, there have been reports of LOH on chromosomes 6, 7, 9, 10, 17, 18, 19, and 20 and gains/amplification of sequences on chromosomes 1, 9, 12, 15, 17, 20, and 22 (24,31).

Many other genes have been evaluated for potential roles in the pathogenesis and progression of meningiomas, primarily based on their presence in or near common chromosomal aberrations. Studies have included LOH analysis, epigenetic silencing, changes in gene expression, and mutation analysis. Most of these genes have not been found to play a significant role in meningiomas. Nonetheless, several candidate tumor-suppressor genes have been identified in meningioma pathogenesis and progression, including DAL-1 (40), TSLC-1 (41), CDKN2A (p16^{INK4A}), p14^{ARF}, CDKN2B (p15^{INK4B}) (42,43), and TP73 (37).

4. CLINICAL BEHAVIOR AND GRADE OF MENINGIOMAS

Additional studies have focused on genes implicated in tumorigenesis and progression based on their functions. These include telomerase (hTERT) (44-46), VEGF and its isoforms (47-49), matrix metalloproteinases (50-54), amplification of the putative oncogene PS6K (50), PTEN deletion and/or mutation (55,56), activation of epidermal growth factor receptor (57,58), platelet-derived growth factor (59-61), and insulin-like growth factor II autocrine loops (62-64). Moreover, many clinical, pathological, and molecular techniques have been used in an attempt to identify markers that can predict the aggressiveness of these neoplasms.

Immunohistochemical studies have been used to analyze specific proteins, such as cell proliferation markers (MIB-1) (65,66), p53 (66), the progesterone receptor (PgR) (67-69), VEGF (47,70), and DAL-1 (40). Furthermore, many cellular and molecular biological techniques,

Molecular biological determinants of meningioma

Table 1. Percentages of single and combined chromosomal aberrations in grade I to grade III meningiomas.

Chromosomal Aberrations (homogenous or heterogeneous)[1]	Grade I (n = 59)[2]	Grade II (n = 13)[2]	Grade III (n = 5)[2]
Deletion 1p alone	8.5	0	0
Deletion 14q alone	6.8	0	0
Trisomy 22q alone	8.5	0	0
Deletion 1p + Deletion 14q	6.8	23.1	0
Deletion 1p + Deletion 22q	5.1	0	0
Deletion 1p + Deletion 14q + Deletion 22q	13.6	46.2	20
Deletion 1p + Deletion 14q + Trisomy 22q	1.7	23.1	80

[1] Deletion 22q alone, deletion 1p + trisomy 22q, deletion 14q + deletion 22q, and deletion 14q + Trisomy 22q were found in no cases, [2] Chromosomal aberrations were found in 51% of grade I, 92.4% of grade II, and 100% of grade III meningiomas.
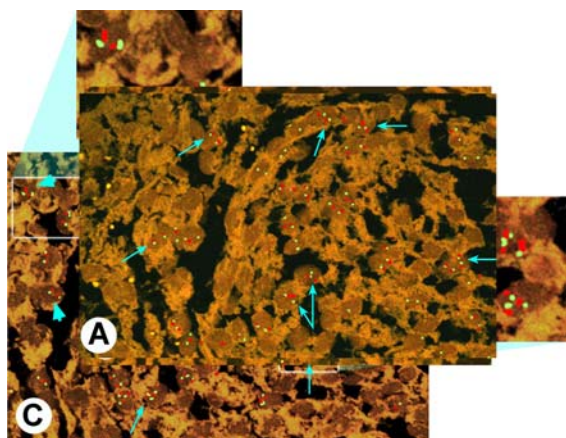

Figure 1. Photomicrographs of FISH analyses of chromosomes 1, 14, and 22 in the same region of a benign meningioma. (A) Chromosome 1: p36 (green), q25 (orange). No deletion of 1p36 (long arrows). (B) Chromosome 14: q13 (green), q32 (orange). No deletion of 14q in both areas (small arrows). (C) Chromosome 22: q11 (orange), q12 (green). No deletion of 22q (arrowheads), trisomy 22q (long arrows) (24). Reproduced with permission from Neuro-Oncology.

including molecular studies such as assessment of nucleolar organizer regions (71), DNA ploidy by flow cytometry (66), and analyses of individual gene expression and protein activity such as telomerase activity (45,46,72,73), have been used in an attempt to differentiate meningiomas. Again, preliminary correlations with tumor grade and survival can sometimes be identified. However, these results have rarely been examined against strictly defined aggressive clinical behavior, such as rapid recurrence within a specific time period.

The definition of aggressive behavior in a typically benign tumor can be debated. Clinically aggressive behavior can include penetration of the arachnoidal border, destruction of bone, rapid regrowth of residual tumor, or recurrence of an apparently completely resected tumor (2,11-13,74). These behaviors are usually considered aggressive because they affect patient survival. However, from a clinical perspective, when the primary tumor is resectable the most important aggressive behavior may be recurrence.

As for most tumors, clinical and pathological findings are the gold standard for diagnosis and prognostication of meningiomas. Though invasion may have clinical ramifications (2,3), the new WHO classification does not use this finding as a criterion for grading these tumors (4). Compared to prior schema (75), this new classification scheme has greatly enhanced the grading of meningiomas and may correlate sufficiently with overall biological behavior. Nonetheless, low-grade meningiomas can demonstrate a clinically aggressive phenotype. Thus, as has been found in other brain tumors, the clinical course of meningiomas can vary within a given histologic grade (2,3), and the behavior of an individual tumor can still be difficult to predict based on histopathological criteria alone. Clinical, pathological, and molecular descriptions of aggressive tumors are needed to allow clinically aggressive subsets of meningiomas to be differentiated from clinically benign meningiomas, even within a given histologic grade, because of discrepancies among the clinical behavior, cellular architecture, and biological makeup of these tumors.

FISH is particularly promising for the development of diagnostic and prognostic tools to enhance current clinical and pathological diagnostic criteria. In clinical laboratories, this technique is often used as a diagnostic and prognostic tool for a number of diseases. In fact, deletion of 1p and 19q, as defined by FISH, is used in the prognostication of patients with oligodendrogliomas (76). FISH may be more sensitive than some other genetic techniques in predicting clinical behavior because it allows direct observation of small chromosomal abnormalities. It is also more sensitive than standard cytogenetic methods because it can be performed directly on tissue and does not require dividing cells.

Furthermore, the ability to analyze tissue allows the presence of heterogeneity in tumors to be observed (24). Heterogeneity has important clinical implications in that removal of the more malignant areas of a heterogeneous tumor can significantly affect patient survival (77). In fact, an understanding of the heterogeneity of these tumors is critical to the interpretation of research data. Inconsistencies across molecular and genetic data from various laboratories (described above) can likely be explained, at least partially, by the heterogeneity of these tumors.

5. DIAGNOSIS, PROGNOSIS, AND REGIONAL HETEROGENEITY

We began our study of meningiomas using FISH to analyze the frequency and distribution (regional
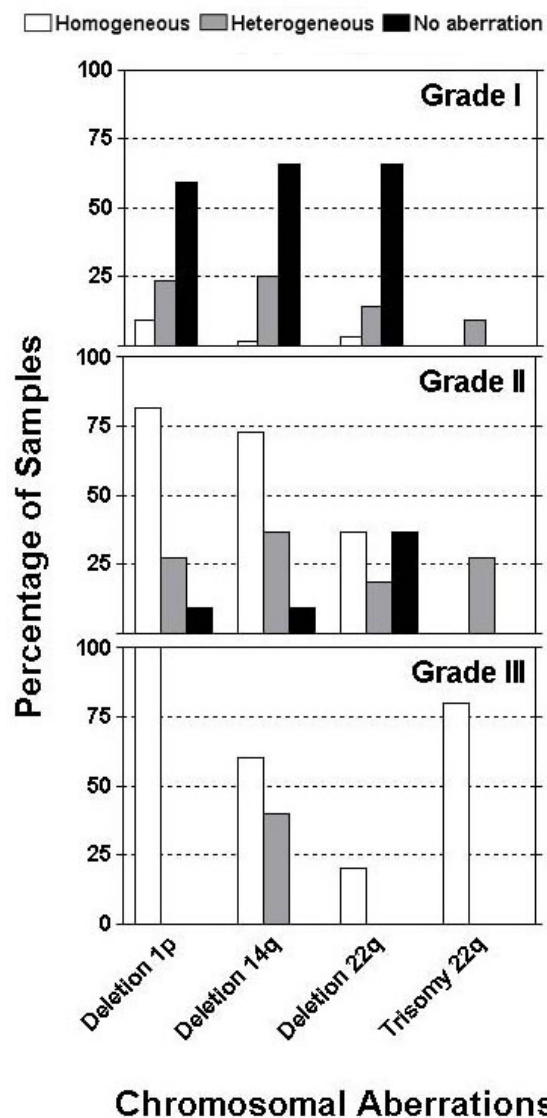
Figure 2. Analysis of individual chromosomal aberrations in grade I, II, and III meningiomas (24). Reproduced with permission from Neuro-Oncology.

heterogeneity) of abnormalities involving chromosomes 1, 14, and 22 (24). As described, abnormalities of these chromosomes are most commonly reported in meningiomas. We then evaluated the correlation of these abnormalities to the clinical outcome of patients. We analyzed eight defined areas of 77 paraffin-embedded meningioma samples (61 grade I, 11 grade II, and 5 grade III tumors) using bacterial artificial chromosomes probes localized to chromosomes 1p36.32, 1q25.3, 14q13.3, 14q32.12, 22q11.2, and 22q12.1-3. Deletions were considered regionally heterogeneous if they were found in fewer than seven regions and homogeneous if they were found in seven or eight regions (Figure 1).

Our data (Figure 2, Figure 3, and Table 1) demonstrated that while chromosomal abnormalities could

be seen in many grade I meningiomas, they were not typically found homogeneously throughout the tumor. Moreover, some grade I tumors showed no abnormalities of these chromosomes, suggesting genetic alterations that were not visible at the level of the chromosome. In contrast, chromosomal abnormalities were always present in grade II and III meningiomas, and the presence of these abnormalities became more uniform throughout higher-grade tumors. Furthermore, the correlations between the presence of chromosomal aberrations and tumor grade were statistically significant.

The data indicate a trend toward earlier recurrence or increased rate of recurrence in the group of meningiomas with chromosomal aberrations compared to the group without aberrations. Of 15 cases of subtotally resected grade I meningiomas without chromosomal aberrations, only three patients showed regrowth of the tumor during a mean clinical follow-up of 6.7 years. However, of the nine patients with subtotally resected grade I meningiomas with chromosomal aberrations, five experienced regrowth in the mean clinical follow-up.

We analyzed the different chromosomal aberrations of these five patients. Three patients, with a regrowth in years 7 and 8, had only heterogeneous chromosomal aberrations of one chromosome. The other two patients, who showed regrowth within 1 and 1.5 years, had heterogeneous aberrations in chromosomes 1p, 14q, and 22q. The mean time to regrowth was shorter in the group with aberrations (4.8 years) than in the group with no chromosomal aberrations (6 years). Furthermore, while specific chromosome deletions did not directly correlate with tumor grade or aggression, chromosomal aberrations were more common in higher grade tumors, and homogeneous changes were seen in high-grade tumors.

Interestingly, the unusual finding of trisomy 22 (as opposed to deletion of 22) was more prevalent in grade III tumors. While most of the tumors have normal copy number or loss of chromosome 22, a small subset of tumors has trisomy. In our work and that of Maillo and colleagues (22-24), trisomy 22 appeared to correlate strongly with rapid recurrence, though the small number of samples precluded statistical analysis. Additional samples are being analyzed to determine if this finding correlates with length of survival.

6. PROLIFERATION INDEX AND PROGRESSION OF MENINGIOMAS

Though the presence of chromosomal abnormalities correlated with early recurrence in our study, this feature alone was insufficient to allow an accurate prediction of clinical behavior. The proliferation index of tumors, as defined by MIB-1 immunohistochemistry, often correlates with tumor aggression. A number of studies have demonstrated the reliability of this index, especially for evaluating the cellular proliferation of meningiomas (78-81). Other studies, however, have failed to find a statistically significant difference in the extent of MIB-1 labeling between nonrecurrent and recurrent meningiomas (82)
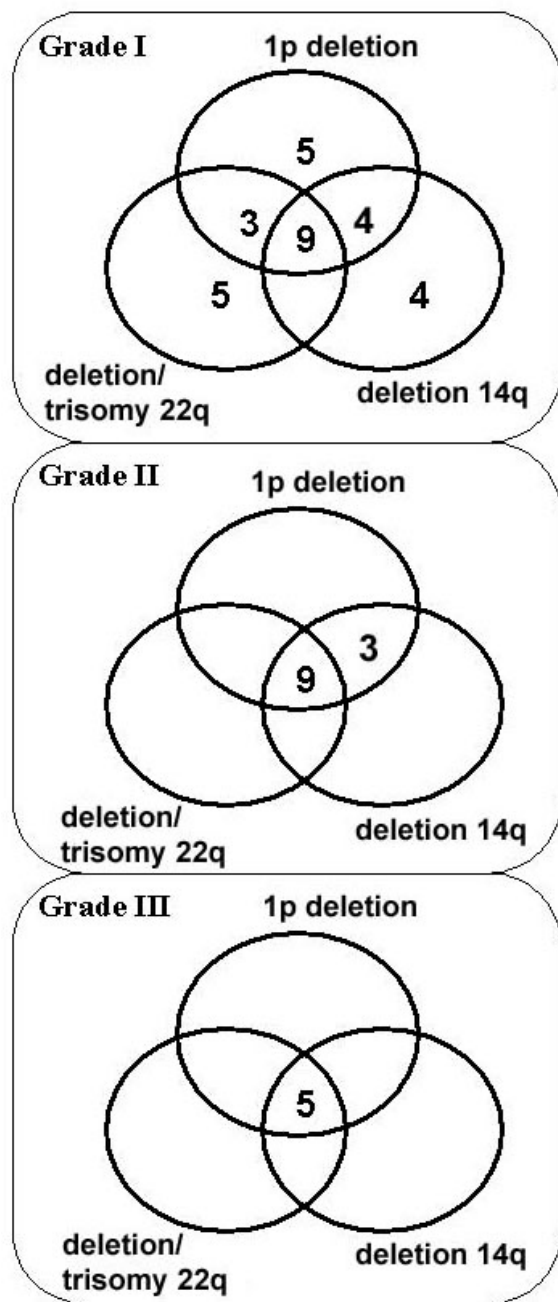
Figure 3. Numbers of patients with single or combined chromosomal aberrations in 59 grade I, 13 grade II, and 5 grade III meningiomas (24). Reproduced with permission from Duke University Press.

In an attempt to determine if the combination of MIB-1 immunohistochemistry and FISH analyses could improve the accuracy of predicting the aggression of meningioma, we correlated clinical, pathological, and immunohistochemical data with molecular findings in a series of 111 WHO grade I and II meningiomas. Aberrations of chromosomes 1, 14, and 22 were analyzed using our novel approach of detecting homogeneous or

heterogeneous regional distribution of abnormalities. This test was critical because many chromosomal lesions would not have been detected if only one region had been examined. Our data confirmed the clinical predictive value of MIB-1 expression in meningiomas. Correlations for histological grade, aggressive tumor signs, and recurrence rate were highly significant.

Sometimes, however, MIB-1 counts of grade I and II tumors differ only slightly and thus cannot facilitate a clinical decision. In such a situation, the verification of certain chromosomal aberrations in tumor specimens may be of major value. The deletion of the short arm of chromosome 1 and the long arm of chromosome 14 (14,16,19,20,83), or the deletion, trisomy, or tetrasomy of chromosome 22 (22,24,26,84) occurred to a considerable extent in atypical meningiomas.

The presence of single chromosomal lesions or diverse combinations of all examined chromosomal lesions (deletion of 1p, 14q, 22q and trisomy of chromosome 22q) significantly correlated to MIB-1 expression in tumors (P < 0.001), to signs of aggressive tumor growth (P < 0.001), and to recurrence rate (P < 0.01). In these patients, almost 50 percent of grade I meningiomas showed no chromosomal aberrations when analyzed by FISH. In contrast, only 7 percent of grade II tumors had no aberrations of the examined chromosomes.

A number of factors associated with using MIB-1 antibodies have implications for the interpretation of the proliferation rate and need to be considered. Due to the heterogeneous nature of neoplasms (24), the extent of surgical sampling and the selection of a block of the tumor become important factors. Our experience in analyzing different regions of tumors for chromosomal aberrations confirmed the importance of examining different regions for MIB-1 and detecting the area with highest proliferation.

The most frequently observed genetic aberrations in meningiomas—deletions of chromosome 22q—have been correlated to inactivation of the NF2 gene (84). However, NF2 mutations have been detected at a similar frequency in grade II and III meningiomas. This finding suggests that these mutations are involved solely in pathogenesis and are not predictive markers for the clinical behavior of these tumors (85-88). Thus, while genetic alterations in these cancers have helped identify some genes involved in meningioma progression, they have not provided conclusive information about markers of tumor aggression.

7. DIFFERENTIATION OF MENINGIOMA SUBTYPES

The advent of newer technologies such as microarray-based gene expression profiling and bioinformatics have helped define previously indistinguishable subsets of common cancers (89-93), including malignant brain tumors (94-99). However, compared to other brain tumors, little work has been done on gene expression profiling of meningiomas. In a small
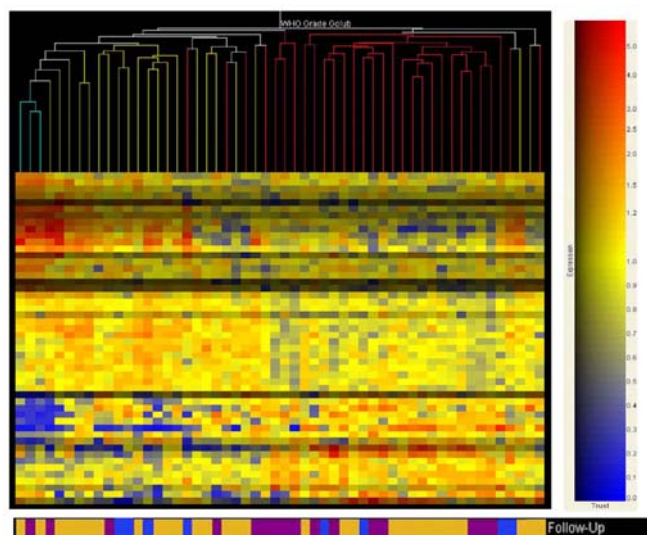
Figure 4. Clustering of grade 1 (n = 30) vs. grade 2 (n = 21) primary meningiomas based on standard correlation of genes and conditions. Gene expression levels are shown according to the color legend. Each row represents a gene expression level. Each column represents a specific tumor sample. Branches are colored according to grade: red = grade 1, yellow = grade 2, and blue = grade 3 (n = 3). Each color in the follow-up key corresponds to the recurrence of each tumor at follow-up. Orange = unknown recurrence status (n = 30), blue = rapid recurrers (n = 8), and purple = no recurrence within 2 years of follow-up (n = 16). (101,102). Reproduced with permission from Neuro-Oncology.

series of meningiomas from a set of 2000 cancer-associated genes, Watson and colleagues (100) discovered a subset of genes that could be used to distinguish WHO grade I from WHO grades II and III tumors. They used the technique of reverse-transcription polymerase chain reaction to confirm their findings in a larger, independent set of 47 meningiomas.

Fathallah-Shaykh and colleagues (100) used a novel algorithm to analyze the expression of 19,200 transcripts across 10 meningiomas in an attempt to predict gene functions underlying biological phenotypes. However, this study compared meningiomas to normal brain tissue and did not delineate meningioma subtypes.

Though these studies suggest the utility of microarray analyses of meningiomas, relatively few data are available on the gene expression profiles of meningiomas, especially in the context of distinguishing molecular subtypes. We have analyzed differential gene expression in 54 meningiomas using Affymetrix U133 Plus 2.0 GeneChip Human Genome oligonucleotide microarrays containing the entire human genome. Extensive clinical parameters were used to group tumors for expression analysis. Genes likely to provide clinically useful diagnostic and prognostic information were mined from gene lists based on analysis of differential expression between groups in the following clinical parameters: WHO grade, primary and recurrent identity, invasion, and whether the tumor recurred within 2 years. Class prediction and clustering analyses were then performed on lists of significant genes to evaluate the ability of these profiles to predict clinical parameters associated with the aggressive phenotype.

Clustering based on analysis of grade I primary versus grade II primary meningiomas differentiated among grades fairly well, though some outliers were still present (Figure 3). These data showed that the molecular classification of meningiomas based on grade is unable to group meningiomas based on rapid-recurrence status. If a molecular basis determines grade, this basis cannot predict recurrence, just as the histopathological basis of grade is unable to predict recurrence consistently.

Not surprisingly, clustering based on analysis of rapid recurrers fairly consistently differentiated tumors that recurred from those that did not within the 2-year follow-up, suggesting a molecular basis for rapid recurrence (Figure 4). Interestingly, some meningiomas that did not recur within 2 years grouped with rapid recurrers to a degree. Those tumors also may be prone to recurrence. Continued follow-up will provide further data on these samples. Interestingly, five of the rapid recurrers were grade I and the remaining three were grade II. The only grade III tumors in this set did not recur within the 2-year follow-up.

These findings further strengthen our hypothesis that WHO grade alone cannot account for molecular subsets of meningiomas that will and will not recur rapidly, and that a molecular subset of these tumors exists. Overall, WHO grade clusters somewhat erratically (Figure 3), though a set of WHO grade I meningiomas that did not recur within the 2 years cleanly grouped together. The list of 167 genes that appears to identify meningiomas prone to rapid recurrence is being studied to develop an immunohistochemical screen that can improve the prediction of patient outcomes and suggest appropriate therapy.
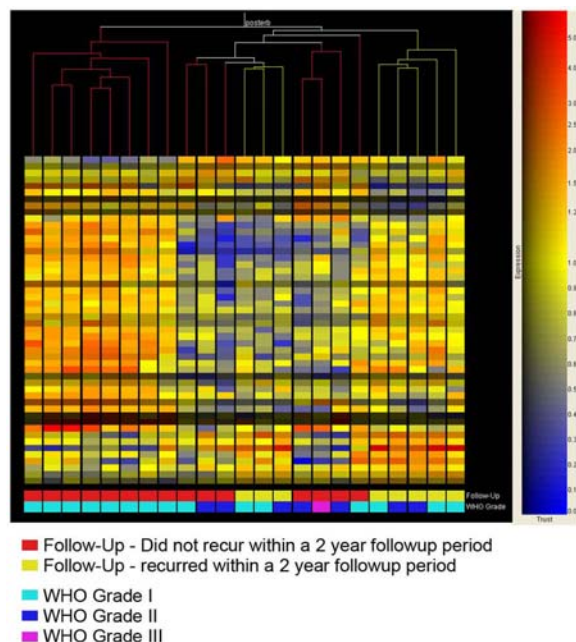
Follow-Up - Did not recur within a 2 year followup period
Follow-Up - recurred within a 2 year followup period

WHO Grade I
WHO Grade II
WHO Grade III

Figure 5. Clustering of recurrence (n = 8) vs. no recurrence at follow-up (n = 16) based on standard correlation of genes and conditions. Gene expression levels are shown according to the color legend in Figure 3. Each row represents a gene expression level. Each column represents a specific tumor sample. Branches are colored according to recurrence at follow-up. Red = no recurrence and yellow = recurrence. Each color in the follow-up key corresponds to this scheme, and each color in the WHO grade key corresponds as follows: light blue = grade 1, dark blue = grade 2, and pink = grade 3. In this example, WHO grade does not significantly correlate with recurrence at follow-up (P = 0.9404) (102).

8. CONCLUSIONS

Considerable progress has been made in defining the biological and molecular aberrations present in all three grades of meningiomas. Nonetheless, the search for markers of clinical aggression leading to accurate diagnosis and prognostication of meningiomas continues to be limited by several factors in pathology and molecular laboratories. The primary limitation in pathology is that diagnosis is based on morphological changes downstream of causative molecular events. At root, patterns of invasion, potential for recurrence, or both may be phenotypic results of distinct molecular subsets of these tumors. In the laboratory, studies such as those described above may be limited by the poor availability of high-grade tumor samples, the presence of tumor heterogeneity, or both. Furthermore, studies rarely consider the genetic instability inherent in tumors that leads to progressive genetic and molecular changes, which are not always directly linked to phenotypic change. Instead, they may be products or artifacts of that instability.

The phenotypic components of an aggressive

meningioma are defined inconsistently across these studies. Sometimes they are defined according to overall survival, sometimes according to recurrence-free survival, and sometimes by WHO grade alone. Though WHO grade is the standard for meningioma diagnosis, the scale fails to account for molecular subsets of these tumors (subsets that guide phenotypic behavior, such as recurrence). Consequently, tumor grade is not always able to predict recurrence. When aggression is based solely on WHO grade, oblique correlations are sought between biological and pathological data rather than direct correlations between biological data and phenotypic data (clinical outcome). Despite these caveats, the results of newer technologies combined with the data available from studies, such as the ones described above and others like them, can lead to improvements in meningioma prognostication.

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Abbreviations: CpG: cytosine phosphate guanine, DAL: differentially expressed in adenocarcinoma of the lung, FISH: fluorescent *in situ* hybridization, LOH: loss of heterozygosity, MIB: mindbomb homolog, NF: neurofibromatosis, VEGF: vascular endothelial growth factor, WHO: World Health Organization

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