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Authors

Chen, William C
Vasudevan, Harish N
Choudhury, Abrar
et al.

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William C. Chen, MD[‡]

Harish N. Vasudevan, MD, PhD[‡]

Abrar Choudhury, BS[‡ §]

Melike Pekmezci, MD[¶]

Calixto-Hope G. Lucas, MD[¶]

Joanna Phillips, MD, PhD[¶]

Stephen T. Magill, MD, PhD [ID][§]

Matthew S. Susko, MD, MS[‡]

Steve E. Braunstein, MD, PhD[‡]

Nancy Ann Oberheim Bush, MD, PhD[§]

Lauren Boreta, MD[‡]

Jean L. Nakamura, MD[‡]

Javier E. Villanueva-Meyer, MD[‖]

Penny K. Sneed, MD[‡]

Arie Perry, MD[¶]

Michael W. McDermott, MD[‡]

David A. Solomon, MD, PhD[§]

Philip V. Theodosopoulos, MD[§*]

David R. Raleigh, MD, PhD[‡ § *]

[‡]Department of Radiation Oncology, University of California San Francisco, San Francisco, California; [§]Department of Neurological Surgery, University of California San Francisco, California; [¶]Department of Pathology, University of California San Francisco, San Francisco, California; [‖]Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, California

*Philip V. Theodosopoulos and David R. Raleigh contributed equally to this work.

Correspondence:
David R. Raleigh, MD, PhD,
Helen Diller Family Cancer Research Building,
University of California San Francisco,
1450 3rd St, HD482,
San Francisco, CA 94158, USA.
Email: david.raleigh@ucsf.edu

A Prognostic Gene-Expression Signature and Risk Score for Meningioma Recurrence After Resection

BACKGROUND: Prognostic markers for meningioma are needed to risk-stratify patients and guide postoperative surveillance and adjuvant therapy.

OBJECTIVE: To identify a prognostic gene signature for meningioma recurrence and mortality after resection using targeted gene-expression analysis.

METHODS: Targeted gene-expression analysis was used to interrogate a discovery cohort of 96 meningiomas and an independent validation cohort of 56 meningiomas with comprehensive clinical follow-up data from separate institutions. Bioinformatic analysis was used to identify prognostic genes and generate a gene-signature risk score between 0 and 1 for local recurrence.

RESULTS: We identified a 36-gene signature of meningioma recurrence after resection that achieved an area under the curve of 0.86 in identifying tumors at risk for adverse clinical outcomes. The gene-signature risk score compared favorably to World Health Organization (WHO) grade in stratifying cases by local freedom from recurrence (LFFR, $P < .001$ vs .09, log-rank test), shorter time to failure (TTF, F-test, $P < .0001$), and overall survival (OS, $P < .0001$ vs .07) and was independently associated with worse LFFR (relative risk [RR] 1.56, 95% CI 1.30-1.90) and OS (RR 1.32, 95% CI 1.07-1.64), after adjusting for clinical covariates. When tested on an independent validation cohort, the gene-signature risk score remained associated with shorter TTF (F-test, $P = .002$), compared favorably to WHO grade in stratifying cases by OS ($P = .003$ vs $P = .10$), and was significantly associated with worse OS (RR 1.86, 95% CI 1.19-2.88) on multivariate analysis.

CONCLUSION: The prognostic meningioma gene-expression signature and risk score presented may be useful for identifying patients at risk for recurrence.

KEY WORDS: Meningioma, Biomarker, Gene expression, Prognostic, WHO grade, Recurrence, Survival, Resection, Radiation, Expression, Gene

Meningiomas comprise 38% of all primary intracranial tumors diagnosed in the United States, and are the most common tumor of the central nervous system.[1] Although many meningiomas are slow growing, a significant subset of meningiomas have high World Health Organization (WHO) histopatho-

logic grade, including atypical meningiomas (WHO grade II, 10%-20%) and anaplastic meningiomas (WHO grade III, 3%-5%), and are prone to local recurrence despite optimal local control.[1] Moreover, there are subsets of patients with WHO grade I meningiomas who develop paradoxical recurrences that could not be predicted from histopathologic or clinical features.[2-5]

Recent efforts to characterize the genetic, transcriptional, and epigenetic landscape of meningioma have identified mutually exclusive subgroups of meningiomas harboring recurrent mutations in *TRAF4/KLF4*, *AKT1*, and *SMO*, which almost exclusively occur in clinically indolent tumors.[6-9] WHO grade II and III meningiomas tend to harbor loss of chromosome

22 or inactivating mutations in the tumor suppressor *NF2* and, in some cases, less common alterations in *TERT* and other genes.[10,11] Although high-grade meningiomas are also characterized by chromosomal instability with dramatic copy number variations (CNVs), the clinical and gene-expression significance of most CNVs in meningioma are not fully understood.[12,13] Most recently, methylation-based classification of meningiomas has emerged as a robust prognostic assay, albeit clinically challenging to implement in most centers.[6,13,14] Whole genome transcriptomic profiling has also identified gene-expression-based subgroups of meningiomas that appear to stratify according to location and clinical outcomes,[13,15] but like deoxyribonucleic acid (DNA) methylation-based profiling, these methods remain challenging to implement clinically because of the financial, logistic, and quality assurance burden of these approaches.[16,17]

We and others have shown that high meningioma cell proliferation in resection specimens identifies tumors at risk for adverse clinical outcomes[3,18-21] and that activation of the *FOXM1* target genes drives meningioma cell proliferation across molecular subgroups and WHO grades.[13] These data suggest that convergent gene-expression programs may underlie clinically aggressive meningiomas, which could be leveraged to develop prognostic biomarkers. Similar challenges in other cancer types have led to targeted gene-expression biomarkers now in widespread clinical use, particularly in breast cancer, in which a 21-gene-expression assay has been shown to be predictive of the need for adjuvant chemotherapy in a large randomized trial,[22] and prostate cancer, in which similar assays are available to help risk-stratify patients and guide active surveillance.[23,24]

Objective

The aim of this study was to apply targeted gene-expression analysis to identify a prognostic gene-expression-based signature and risk score for meningioma recurrence after resection.

METHODS

Discovery and Validation Patient Cohorts

Our discovery cohort of patients with meningioma that were treated with resection was comprised of cases between 1990 and 2015 from the University of California San Francisco. Patients were retrospectively identified from an institutional clinical database and biorepository. Clinical data were collected as previously described (**Text**, **Supplemental Digital Content 1**).

In order to identify an independent validation dataset of patients with meningiomas treated with resection, a search was undertaken of the Gene Expression Omnibus (GEO) repository using the term "meningioma," filtered for "expression profiling by array" and human samples (**Table**, **Supplemental Digital Content 2**); datasets were screened for availability of pre-specified clinical data (**Text**, **Supplemental Digital Content 1**). Only one dataset fit these criteria (GSE58037).[25]

Targeted Gene-Expression Analysis and Immunohistochemistry

As previously described,[13] total RNA was extracted from tumor cores from formalin-fixed paraffin-embedded tissue blocks containing 75% or more tumor cells, as determined by hematoxylin and eosin staining. The GX Human Cancer Reference NanoString panel codeset, with 30 additional meningioma related genes (266 total gene probes; **Table**, **Supplemental Digital Content 3**), were synthesized by NanoString technologies (Seattle, Washington). RNA (200 ng per meningioma) was analyzed with the NanoString nCounter Analysis System at NanoString Technologies, according to the manufacturer's protocol.

Bioinformatic and Statistical Analyses

Cases were dichotomized based on time to local recurrence (**Text**, **Supplemental Digital Content 1**). NanoString data were pre-processed according to manufacturer guidelines (**Text**, **Supplemental Digital Content 1**). Prediction analysis for microarrays (PAM), an extension of the nearest centroid classifier,[26] was used to identify a subset of genes from the discovery cohort that were associated with poor outcomes (pamr: Pam: PAM, R package version 1.56.1; R Foundation for Statistical Computing).[27] K-fold cross-validation was performed using the pamr.cv function to determine the optimal shrinkage threshold, resulting in a subset of genes minimizing the classification error (**Text,** **Supplemental Digital Content 1**).

In order to generate a generalizable risk score based on the genes of interest identified by PAM, Z- and log_2-transformed counts of genes of interest were further scaled and constrained using the softmax transformation.[28]

Next, an elastic net regression classifier was trained utilizing K-fold cross-validation, and using the above transformed values as input and the probability of classification as poor-outcome as output. The probability of poor-outcome between 0 and 1 was defined as the meningioma gene-signature risk score. Elastic net regression was performed using the ElasticNetCV function of the Scikit-learn package in Python.[29]

Microarray data from the validation cohort were pre-processed as described previously.[30] An identical set of transformations was applied to the data, and the elastic net classifier from above was applied to the validation cohort to obtain gene-signature risk scores.

CNV data were also obtained from the validation cohort, as previously described.[30] Gene set enrichment analysis was performed using ConsensusPathDB,[31] and protein-protein interaction analysis, clustering, and visualization was performed with the STRING database.[32] All other statistical analyses including Cox proportional hazards regression, Kaplan-Meier survival analysis and log-rank tests, and other standard statistical tests were performed in JMP (JMP®, Version 14.0. SAS Institute Inc, Cary, North Carolina, 1989-2019).

RESULTS

The characteristics of the discovery and validation cohorts are summarized in Table. After dichotomizing the discovery cohort into poor-outcome (N = 25, median local freedom from recurrence [LFFR] 0.70 yr, median overall survival (OS) 2.5 yr) and baseline-outcome cases (N = 71, median LFFR not reached, median OS 11.9 yr), the method of shrunken centroids identified a set of 36 genes that distinguished between outcome subgroups (Figure 1A; **Table**, **Supplemental Digital Content 4**).

TABLE. Meningioma Gene Signature Discovery and Validation Cohort Characteristics

	Discovery cohort	Validation cohort
Clinical characteristic by patient		
Number of unique patients	84	56
Median patient age	60.4y (IQR 52.6-67.6)	64.0 (53.0-76.0)
Number of male patients	33 (39%)	23 (41%)
Number of patients with recurrent meningioma at presentation	22 (26%)	11 (20%)
Number of patients with prior meningioma resections	15 (18%)	Unknown
Number of patients with prior meningioma radiotherapy	18 (21%)	5 (9%)
Number of gross total resections	39 (46%)	47 (84%)
WHO grade of first resection		
I	12 (14%)	35 (63%)
II	64 (76%)	16 (29%)
III	7 (8%)	5 (9%)
Median clinical follow up (yr)	6.4 (IQR 3.6-9.1)	5.4 (2.9-7.0)
Number of patients who died	35 (42%)	10 (18%)
Number of patients who died of meningioma progression	17 (20%)	Unknown
Clinical characteristics by meningioma		
Number of meningiomas	96	56
Number of meningiomas recurrent at presentation	33 (34%)	11 (20%)
Number of meningiomas with prior surgery	19 (20%)	Unknown
Number of meningiomas with prior radiotherapy	29 (30%)	5 (9%)
Number of gross total resections	45 (47%)	47 (84%)
WHO grade		
I	13 (14%)	35 (63%)
II	64 (67%)	16 (29%)
III	19 (20%)	5 (9%)
Number recurred	49 (58%)	11 (20%)

In order to confirm the prognostic significance of these genes, unsupervised hierarchical clustering was performed on the discovery cohort (Figure 1A), which demonstrated robust clustering of cases into 2 subgroups with significant differences in LFFR (median 0.92 vs 7.8 yr, $P < .0001$, log-rank test) and OS (4.0 vs 14.4 yr, $P = .0003$, log-rank test). The subgroup of meningioma cases with the worst outcomes showed increased expression of genes associated with cell-cycle regulation and mitosis (Figure 1B), including *FOXM1*,[33] *BIRC5*,[34] *TOP2A*,[35] *CDC2*,[36] *SFRP4*,[37] and *MYBL2*,[38] as well as concomitant decreased expression of *BMP4*, a signaling molecule involved in embryonic development, differentiation, and bone and cartilage morphogenesis[39]; *CTGF*, which is important for wound healing and fibrosis[40]; *GAS1*, a tumor suppressor[41]; progesterone receptor, which has been implicated in low grade meningiomas[42]; *TMEM30B*, a transmembrane gene product with unknown function.[43,44] Immunohistochemistry (IHC) for representative enriched or suppressed gene products from each cluster confirmed that cases with high SFRP4 staining had worse LFFR (Figure 1C; $P < .0001$), whereas cases with low or absent TMEM30B staining showed a trend towards worse LFFR (Figure 1C; $P = .09$). In further support of the prognostic value of these genes, we have previously shown increased IHC staining of FOXM1 to be strongly associated with worse LFFR and OS.[13] Closer interrogation of the gene signature revealed

that multiple prognostic genes were contained at chromosomal loci frequently affected by CNVs in high-grade meningiomas,[12] including 1p, 1q, 6q, 17q, and 20q (**Figure, Supplemental Digital Content 5A**). Consistently, the expression of 4 genes that were enriched in meningiomas with poor outcomes, *FOXM1*, *TOP2A*, *BIRC5*, and *CDC25C*, was positively associated with the number of CNVs in cases from the validation cohort (**Figure, Supplemental Digital Content 5; Table, Supplemental Digital Content 6**). These data suggest our gene-expression signature may capture genes that are recurrently altered through CNVs associated with clinically aggressive meningiomas.[12,13]

Next, we utilized our 36-gene signature of poor meningioma outcomes to generate a tumor specific gene-signature risk score between 0 and 1 based on an elastic net regression classifier that achieved a cross-validation accuracy of 0.80 and area under the curve (AUC) of 0.86 in distinguishing poor- and baseline-outcome cases in the discovery cohort. The meningioma gene-signature risk score based on this classifier achieved a concordance index (c-index) of 0.75 ± 0.03 ($P < .0001$, Wald test) for LFFR, and 0.72 ± 0.04 for OS ($P < .0001$, Wald test), within the discovery cohort. The risk score was correlated with WHO grade (Figure 1D) and was strongly correlated with faster time to failure (F-test, $P < .0001$; Figure 1D) and compared favorably to WHO grade in stratifying cases by LFFR and OS (Figure 1E). In order to investigate the clinical utility of the meningioma
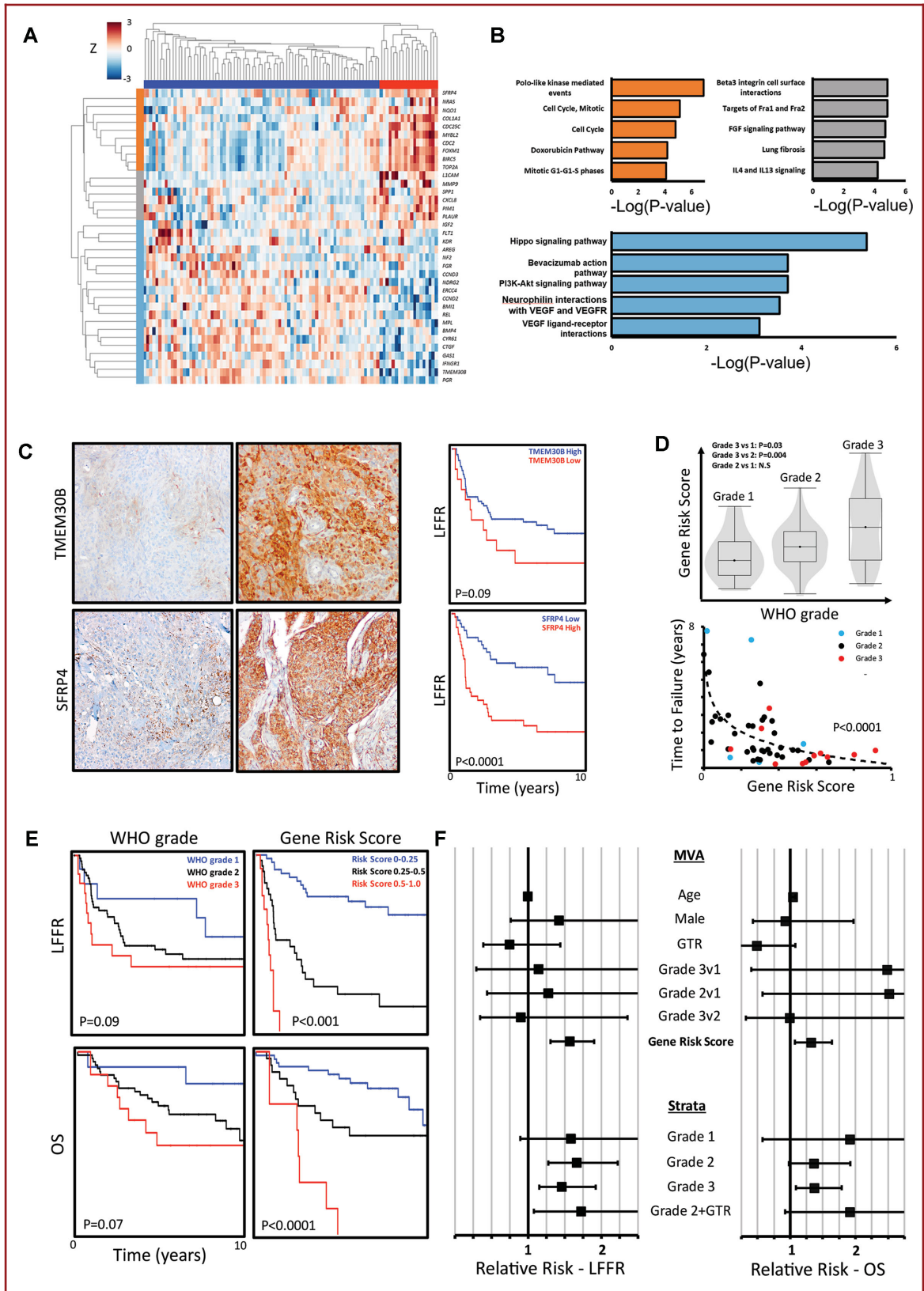
FIGURE 1. *Targeted gene-expression analysis of clinically aggressive meningiomas identifies a prognostic gene signature.* **A**, *Unsupervised hierarchical clustering of prognostic genes identified using PAM confirms the ability of the gene set to stratify meningioma patients into high-risk (red cluster) and lower-risk categories (blue cluster, log-rank test, P < .0001). Gene expression is normalized by row.* **B**, *Gene enrichment analysis of prognostic gene clusters from* **A** *identifies a tightly correlated set of genes involved in cell-cycle processes (orange cluster), and clusters of genes involved in cellular signaling and extracellular matrix interactions (light blue and grey clusters).* **C**, *Representative IHC images demonstrating high TMEM30B staining on the top right (20x magnification) and low/absent TMEM30B staining on the top left. Similarly, representative IHC images demonstrating low SFRP4 staining (20x magnification) on the bottom left and high SFRP4 staining on the bottom right are shown. Low TMEM30B staining (15 of 96 meningiomas, 16%) is associated with a trend towards worse LFFR, and high SFRP4 staining (46 of 94 meningiomas, 49%) is significantly associated with worse LFFR.* **D**, *Elastic net regression was used to generate a gene-signature risk score between 0 and 1 per tumor sample (accuracy 0.80, AUC 0.86). Gene risk score correlates with tumor grade and is correlated with a faster time to failure (TTF) (TTF vs log(gene risk), P < .0001, F-test). Meningiomas with a gene risk score of greater than 0.5 uniformly recur within 2 yr of resection. Meningiomas which did not recur are not plotted.* **E**, *The gene-signature risk score outperforms WHO grade in stratifying LFFR (P < .001 vs P = .09, log-rank test) and OS (P < .0001 vs P = .07, log-rank test).* **F**, *After adjusting for age, sex, extent of resection, and grade using multivariate Cox regression, the gene-signature risk score is independently associated with recurrence (RR 1.56 per 0.1 risk score increase, 95% CI 1.30-1.90) and mortality (RR 1.32 per 0.1 increase, 95% CI 1.07-1.64). After stratifying patients by grade, the gene-signature risk score remains significantly prognostic for meningioma recurrence and mortality on univariate Cox regression. Further, among gross totally resected grade 2 tumors (Grade 2 + GTR), the gene risk score is significantly prognostic of recurrence.*

gene-signature risk score, we constructed a multivariate Cox model of LFFR and OS, incorporating age, sex, extent of resection, WHO grade, and meningioma gene-signature risk score (Figure 1D). After adjusting for these clinical covariates, a higher meningioma gene-signature risk score remained significantly associated with worse LFFR (Figure 1F; relative risk [RR] 1.56 per 0.1 risk score increase, 95% CI 1.30-1.90, P < .0001) and OS (RR 1.32 per 0.1 increase, 95% CI 1.07-1.64, P = .01). Similarly, after stratifying cases in the discovery cohort by WHO grade, the meningioma gene-signature risk score remained significantly associated with worse LFFR among WHO grade II (RR 1.67 per 0.1 increase, 95% CI 1.27-2.22, P = .0003) and III (RR 1.45 per 0.1 increase, 95% CI 1.15-1.92, P = .003) tumors on univariate analysis, and trended towards significance among WHO grade I tumors (P = .10), likely owing to the small sample size of grade I tumors in the discovery cohort. The meningioma gene-signature risk score was similarly associated with worse LFFR among the subgroup of atypical WHO grade II meningiomas status post-gross total resection (GTR) (N = 26, RR 1.72 per 0.1 increase, 95% CI 1.08-2.86, P = .03), and remained significantly associated with worse LFFR among primary meningiomas without prior radiation (N = 60, RR 2.0 per 0.1 increase, 95% CI 1.44-2.81, P < .0001) with a trend towards worse OS (RR 1.50 per 0.1 increase, 95% CI 0.98-2.35, P = .06) in this subgroup (Figure 1F).

Finally, we sought to validate the prognostic utility of our meningioma gene-signature risk score in an independent cohort of meningiomas status post resection at an independent institution. The validation cohort we identified was more representative of a general population of patients with meningiomas, with fewer events of local recurrence (20% vs 58%; Table) or mortality (18 vs 42%). Nevertheless, the meningioma gene-signature risk score was again associated with WHO grade and strongly correlated with faster time to failure (F-test, P = .002; Figure 2A). Moreover, our meningioma gene-signature risk score was able to accurately stratify cases by LFFR (Figure 2B, P = .0004,

log-rank test; **Figure**, **Supplemental Digital Content 7**), and compared favorably to WHO grade in stratifying cases by OS (P = .003 vs P = .10, log-rank test), achieving a c-index of 0.76 ± 0.07 (P = .01, Wald test) for LFFR, and 0.76 ± 0.11 for OS (P = .002, Wald test). Finally, after adjusting for WHO grade, a higher meningioma gene-signature risk score remained significantly associated with worse OS (RR 1.86 per 0.1 increase, 95% CI 1.19-2.88, P = .005) (Figure 2C).
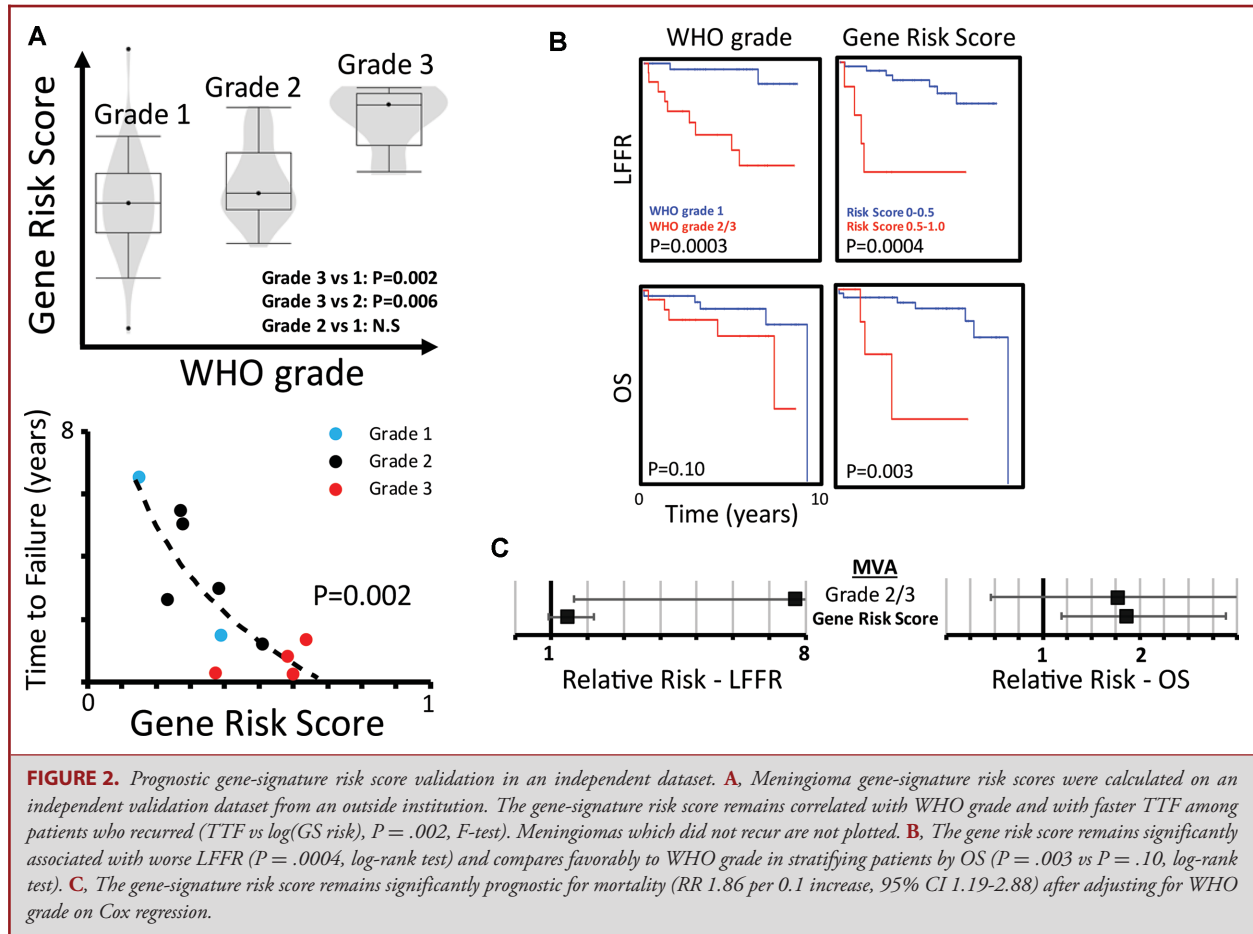
DISCUSSION

Key Findings

More than 15%-20% of meningiomas are high grade, and in clinical practice a subset of patients with meningiomas of all grades experience a clinically aggressive course associated with significant morbidity and mortality.[45-48] Thus, there is an urgent need for better prognostic markers to help delineate clinically aggressive meningiomas. To that end, here, we perform targeted gene-expression analysis on a discovery cohort of meningioma cases that are enriched for clinical endpoints of local recurrence and disease-specific mortality. We identify a 36-gene signature of clinically aggressive meningioma and derive a meningioma gene-signature risk score between 0 and 1 that compares favorably to WHO grade in stratifying cases by risk of recurrence and survival. Moreover, we demonstrate the utility of this gene signature in risk stratifying meningioma patients from an independent validation cohort that is more representative of typical meningioma patients.

Clinical Significance

Longitudinal studies of meningioma patients with long-term follow-up indicate that the 10-yr recurrence rates after primary resection of benign, WHO grade I tumors are upwards of 20%-30%,[45-47] and 40%-50% for WHO grade II tumors.[48-53] These recurrences and subsequent therapies in the form of repeat craniotomy and ionizing radiation are causes of

FIGURE 2. *Prognostic gene-signature risk score validation in an independent dataset. **A**, Meningioma gene-signature risk scores were calculated on an independent validation dataset from an outside institution. The gene-signature risk score remains correlated with WHO grade and with faster TTF among patients who recurred (TTF vs log(GS risk), P = .002, F-test). Meningiomas which did not recur are not plotted. **B**, The gene risk score remains significantly associated with worse LFFR (P = .0004, log-rank test) and compares favorably to WHO grade in stratifying patients by OS (P = .003 vs P = .10, log-rank test). **C**, The gene-signature risk score remains significantly prognostic for mortality (RR 1.86 per 0.1 increase, 95% CI 1.19-2.88) after adjusting for WHO grade on Cox regression.*

significant morbidity and, in many cases, mortality.[46,54,55] Younger patients, in particular, may stand to gain most from appropriate adjuvant management in preventing morbidity and mortality associated with local recurrence, yet may also be more likely to experience long-term toxicities of aggressive therapy, which can include cognitive or neurological effects because of radiation or repeat surgery,[56,57] radiation necrosis, and risk of secondary malignancies or malignant transformation because of radiation.[56,58] The gene signature and risk score identified here could be used to identify high-risk patients who may benefit from aggressive adjuvant management and, conversely, to spare low-risk patients the potential toxicities of more aggressive interventions.

A Gene-Expression Signature of Clinically Aggressive Meningioma

The meningioma gene signature we report consists of enriched genes involved in cell-cycle regulation and proliferation, and suppressed genes involved in stem cell differentiation, wound healing, and tumor suppressor functions.[38-48] As an added marker of external validity, many prognostic genes we identify

have previously been implicated in aggressive meningiomas, including *FOXM1*,[13,59-61] *TOP2A*,[13,62] *BIRC5*,[62] *MYBL2*,[15] and *CDC2*.[62] Prior work from our group demonstrated that elevated expression of *FOXM1* and *FOXM1* target genes, including *TOP2A*, was associated with poorer outcome.[13] *BIRC5*, whose gene product is also known as survivin, is co-expressed with *FOXM1* in breast cancer patients with poor outcomes and drug-resistance.[63] Similarly, *FOXM1* and *MYBL2* are associated with meningiomas identified by gene-expression clustering to have poorer outcomes.[15] Thus, these components of our meningioma gene signature and risk score may be representative of a common or convergent set of genes associated with meningioma cell proliferation and mitosis.

A prior study by Olar et al[64] utilized a similar gene-expression approach to identify an 18-gene marker prognostic for meningioma recurrence; our work builds on this study and goes further by utilizing a novel discovery cohort enriched for clinical events (49 recurrences vs 18), and by also examining mortality as a clinical endpoint. Notably, prognostic genes in both our studies appear to be involved in proliferation, angiogenesis, and invasion.

Strengths and Limitations

The strengths of the present study that distinguish it from previous investigations include (i) the use of a discovery cohort significantly enriched for adverse clinical endpoints, including mortality, the majority of which were documented to be secondary to disease progression; (ii) validation of our meningioma gene-signature risk score using an independent cohort of meningiomas that were representative of the general population of meningioma patients; and (iii) integration of multiple genes whose altered expression have previously been described to be prognostic in meningioma into a unified prognostic model.

Generalizability

This study has several limitations. First, our study is retrospective and thus limited by the inherent biases of retrospective investigations. We attempted to mitigate these by utilizing multiple sources for collection of clinical endpoints and by careful re-review of meningioma pathology and radiology. Second, both our discovery and validation cohorts represent cases from two academic institutions. Although the validation cohort is more representative of a general population of meningioma patients, it nevertheless may not be representative of the larger clinical population encountered outside of academic institutions. Our validation cohort was also limited by a small sample size with relatively few clinical events, precluding the performance of robust multivariate analysis, and tissue was unavailable to us for immunohistochemistry. Ultimately, further validation and calibration of our risk score in a larger cohort will be needed prior to clinical use.

CONCLUSION

A gene signature and prognostic risk score based on targeted gene-expression analysis of meningiomas compared favorably to WHO grade in stratifying cases by LFFR and OS, and may be useful for guiding surveillance or adjuvant therapy after surgery.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content 1. Text. Additional detailed methods.

Supplemental Digital Content 2. Table. List of candidate GEO accession numbers. GEO accession numbers for publicly available meningioma gene-expression datasets.

Supplemental Digital Content 3. Table. List of targeted gene-expression panel genes. List of all 266 genes comprising the NanoString targeted gene-expression panel, with corresponding chromosome locations (between Chrloc and Chrlocend, mapped to Genome Reference Consortium Human Build 38, GRCh38, accessed 3/13/2018). In addition, univariate Cox regression *P*-values, Bonferroni corrected p-values, and beta-coefficients are displayed for each gene.

Supplemental Digital Content 4. Table. List of gene names and descriptions for the 36-gene signature. List of all 36 genes included in the prognostic gene signature, including gene symbol, name, and description taken from Entrez.

Supplemental Digital Content 5. Figure. Correlation of prognostic gene-signature genes with chromosome location and CNV. A, All 266 genes from the discovery dataset are displayed by chromosome location. A moving average of neighboring gene-gene correlation (ρ, window size 4 genes) identified chromosome regions with highly co-expressed genes corresponding to areas of known frequent CNVs in meningioma, including 1p, 1q, 3p, 6q, 7q, 11q, 14q, 17q, 20q, and 22q. Coefficients of univariate Cox regression between gene expression and local recurrence are displayed (β, color-scale -3 to 3), as well as *P*-values (color-scale 0.05-0). Areas of negative β, shown in blue, correspond to areas in which presumed CNV deletions are associated with worse outcome, and areas of positive β, shown in red, correspond to areas in which presumed CNV amplifications are associated with worse outcome. Multiple genes from the prognostic gene signature appear to cluster in the 1p, 1q, 6q, 17q, and 20q regions, although most prognostic genes exist in areas of low neighboring

gene correlation, which may represent conserved areas infrequently affected by CNV. B, Analysis of the total number of CNVs and gene expression in the validation microarray cohort identified 397 genes significantly correlated with CNV number (FDR q-value < .05). 4 gene-signature genes were among these: *FOXM1*, *CDC25C*, *TOP2A*, and *BIRC5*, which form a tightly co-expressed gene network highly correlated with CNV number (*P* < .0001, F-test). STRING protein-protein interaction analysis and clustering of prognostic genes (confidence level threshold 0.7, MCF clustering, inflation parameter = 3) yielded a cluster of proliferative genes (red) containing these CNV-correlated genes: *FOXM1*, *CDC25C*, *TOP2A*, and *CDC25C*, and a cluster of mesenchymal genes involved in osteoblast differentiation and collagen development (yellow).

Supplemental Digital Content 6. Table. Genes correlated with increased CNV in the validation cohort. Univariate linear regression was performed using the Z-score, log-transformed gene-expression values from all probes in the validation dataset as the independent variable, and number of CNVs as the dependent variable. The resulting *P*-value was Bonferroni corrected, and all genes with corrected p-value less than 0.05 are shown, with genes included in the gene signature highlighted in yellow.

Supplemental Digital Content 7. Figure. Grade and gene risk score and expanded validation Kaplan-Meier curves. A, Proportion of WHO grades within gene-signature risk score strata in the discovery and validation cohorts. N = 50, 32, and 14, in the 0-0.25, 0.25-0.50, 0.50-1.0 groups, respectively, in the discovery cohort, and N = 18, 30, and 8 in the same groups, respectively, in the validation cohort. B, Expanded Kaplan-Meier curves for LFFR and OS in the validation cohort, broken down by risk score strata. C, Expanded Kaplan-Meier curves for LFFR and OS in the validation cohort using the gene-signature risk score, linearly re-scaled within the validation cohort between 0 and 1, demonstrating further stratification into low, intermediate, and higher risk groupings. D, Expanded Kaplan-Meier curves for LFFR and OS in the validation cohort, broken down by grade.

COMMENT

This is a well-written paper that adds to the literature on the use of gene expression signatures as a means of better predicting the risk of meningioma recurrence following resection. The authors utilized a discovery cohort enriched for clinical events where the 36-gene signature was constructed from enriched genes involved in cell cycle and proliferation and suppressed genes involved in stem cell differentiation, wound healing and tumor suppressor functions and performed a validation with an independent cohort. This is similar to the work done by Olar et al[1] where a 18-gene expression signature was used. The results of both studies help to identify patients at higher risk for tumor recurrence that may benefit from more aggressive adjuvant management.

Franco DeMonte
Houston, Texas

1. Olar A, Goodman LD, Wani KM, et al. A gene-expression signature predicts recurrence-free survival in meningioma. *Oncotarget*. 2018;9(22):16087-16098.