Meningioma Genomics: Diagnostic, Prognostic, and Therapeutic Applications

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There has been a recent revolution in our understanding of the genetic factors that drive meningioma, punctuating an equilibrium that has existed since Cushing's germinal studies nearly a century ago. A growing appreciation that meningiomas share similar biologic features with other malignancies has allowed extrapolation of management strategies and lessons from intra-axial central nervous system neoplasms and systemic cancers to meningiomas. These features include a natural proclivity for invasion, frequent intratumoral heterogeneity, and correlation between biologic profile and clinical behavior. Next-generation sequencing has characterized recurrent somatic mutations in \(\text{NF2} \), \(\text{TRAF7} \), \(\text{KLF4} \), \(\text{AKT1} \), \(\text{SMO} \), and \(\text{PIK3CA} \), which are collectively present in ~80% of sporadic meningiomas. Genomic features of meningioma further associate with tumor location, histologic subtype, and possibly clinical behavior. Such genomic decryption, along with advances in targeted pharmacotherapy, provides a maturing integrated view of meningiomas. We review recent advances in meningioma genomics and probe their potential applications in diagnostic, therapeutic, and prognostic frontiers.

Keywords: meningioma, genomics, molecular taxonomy, targeted therapy, precision medicine

Meningioma genetics are undergoing a revolution in taxonomy and molecular stratification, punctuating an equilibrium that has existed since Cushing's germinal studies nearly a century ago (1). The understanding of meningiomas rests on a growing appreciation that these tumors share similar features with other intra-axial central nervous system (CNS) neoplasms as well as systemic cancers. Moreover, maturing technologies in genomics and immunotherapy are increasingly intersecting to provide an integrated view on meningioma biology. We review recent advances in meningioma genomics and probe their potential applications in diagnostic, therapeutic, and prognostic frontiers.

MENINGIOMA HISTOPATHOLOGIC CLASSIFICATION

Meningiomas account for over a third of all primary CNS tumors diagnosed in the United States, with ~18,000 new cases diagnosed annually and a prevalence of 97.5/100,000 individuals, making them the most common primary intracranial neoplasms in adults (2, 3). Most meningiomas are considered benign. A small, but growing, proportion display aggressive behavior characterized by invasive growth patterns and higher rates of recurrence (4).

Meningiomas are classified by the World Health Organization (WHO) system as grades I, II, and III, with higher grades associated with greater rates of morbidity and mortality (Figure 1) (5). Grade I meningiomas display a broad range of morphologic features and are considered histologically benign, with fewer than 4 mitoses/10 microscopic high-power fields (HPF). Nine subtypes of benign meningiomas are recognized by the WHO: meningothelial, fibroblastic, transitional (containing both...
**Prevalence Demographics**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female &gt; Male</td>
<td>Mitoses &lt; 4/10 hpf</td>
<td>Mitoses 4 - 19/10 hpf OR 3/5 of the following: Necrosis High nuclear/cytoplasmic ratio Prominent nucleoli Architectural sheeting Hypercellularity OR Clear cell/chordoid histology Brain Invasion</td>
<td>Mitoses ≥ 20/10 hpf OR Frank anaplasia OR Papillary/rhabdoid histology</td>
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<td>Female ≥ Male</td>
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**Histologic Subtypes**

- Meningothelial
- Fibrous (Fibroblastic)
- Transitional (Mixed)
- Psammomatous
- Angiomatous
- Microcystic
- Secretory
- Lymphoplasmacyte-rich
- Metaplastic
- Atypical
- Chordoid
- Clear Cell
- Anaplastic
- Papillary
- Rhabdoid

**Clinical Outcomes at 10 Years**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
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<tbody>
<tr>
<td>Overall Survival</td>
<td>80-90%</td>
<td>50-79%</td>
<td>14-34%</td>
</tr>
<tr>
<td>Progression-Free Survival</td>
<td>75-90%</td>
<td>23-78%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Figure 1** | Demographics, WHO diagnostic criteria, histologic subtypes, and clinical outcomes at 10 years follow-up for meningioma, as stratified by grade. *Clinical outcomes are influenced by age, comorbidities, extent of resection, adjuvant therapy, and tumor location.

Meningeal and fibroblastic components), psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic.

Grade II, also known as atypical, meningiomas are defined by the presence of 4–19 mitoses/10 HPF or 3 of 5 criteria: sheet-like growth, spontaneous necrosis, high nuclear to cytoplasmic ratio, prominent nuclei, and increased cellularity. Meningiomas with two or less of the five atypical features are classified as grade I meningiomas with atypical features, and incur a higher risk of recurrence than benign meningiomas without atypical features (6). Two distinct histologic variants, clear cell and chordoid, are considered grade II meningiomas as well. In addition, the presence of brain invasion implies a similar recurrence rate and risk of mortality as atypical meningiomas (7).

Grade III meningioma is synonymous with anaplastic or malignant meningioma. Morphologically, they can resemble sarcoma or carcinoma, challenging pathologic diagnosis, and also include the papillary and rhabdoid histologic variants. Grade III meningiomas harbor a mitotic index of 20 or greater per 10 HPF, and classically lose markers of differentiation, such as epithelial membrane antigen. Patients with anaplastic meningiomas observe an aggressive clinical course of tumor recurrence and premature mortality.

**Challenges in Meningioma Management**

The histopathologic classification of meningioma provides a powerful harbinger for its natural history. However, clinical outcome in a subset of patients belies the designated pathologic grade for the tumor. Improved understanding of the genomic underpinnings of meningioma offers new strategies for molecular
Limitations of Diagnostic Criteria
On initial detection of an extra-axial mass lesion consistent with meningioma on imaging, no reliable parameters exist to date for predicting tumor grade, and ultimately, biologic course. A number of radiographic metrics are under investigation, including nature of the tumor–brain interface, intratumor heterogeneity, lesion irregularity, intrinsic tumor diffusion and perfusion characteristics, and peritumoral edema, but all merit further validation. Furthermore, tumor location, such as parasagittal and falx, may portend a more aggressive nature to the meningioma. Ultimately, mass effect leading to existing or impending symptoms, steadfast radiographic growth over a period of observation, and patient preference dictate the decision to intervene on a suspected meningioma.

Variations in operative philosophy, operative technique, and choice and timing of radiation permeate clinical practice. In general, maximal surgical resection without compromise of neurologic function imparts the most optimal prognosis for the patient. Standard of care typically invokes adjuvant radiation therapy for malignant meningiomas, with greater variability in the administration and timing of radiation for atypical meningiomas. This variability in management strategy for intermediate grade meningiomas is further complicated by shifts in diagnostic criteria over time (5, 8–10).

For example, application of the 2000 instead of the 1993 WHO guidelines results in a change in classification in up to 30% of high-grade meningiomas, often from a higher grade to lower grade (11). The 2007 WHO guidelines introduced less of a paradigm shift, but brain invasion remained ambiguous as a marker for atypical meningioma (12). The evolution of WHO grading scales associates with an improved correlation between grade and survival (13). However, inter-observer differences and representative sampling of select sections from large tumors may bias the final grading and, therefore, prediction of natural history. As with other CNS tumors, unbiased criteria for diagnostic stratification, such as molecular signatures, can abet definitive stratification of tumor class. Furthermore, an association between such molecular signatures, tumor phenotype, and, ultimately, prognosis would improve initial planning for treatment interventions.

Meningioma as an Invasive Tumor
Independent of tumor classification, the clinical course of meningiomas following surgical resection highlights its biologic proclivity for invasiveness. In Simpson's classic analysis of symptomatic recurrence following resection of meningiomas, residual dural attachment and juxtaposition to venous sinuses – which serve as a potential haven for neoplastic cells in the absence of bulk tumor – were associated with significantly higher rates of recurrence (14). Furthermore, meningiomas with benign histopathologic features that invade the brain exhibit a similar likelihood of recurrence as higher grade, atypical, meningiomas. Thus, despite being the quintessential icon of CNS extra-axial tumors, the invasive potential of meningioma cells highlights an inherent limitation to debulking strategies and should be accounted for in therapeutic strategies.

Intratumoral Heterogeneity
Surgical resection aside, radiation serves as a common adjuvant treatment for meningioma, especially in high-grade and recurrent tumors. A few biological agents, such as hydroxyurea and somatostatin inhibitors, have been trialed with limited success in meningiomas refractory to standard treatment modalities (15). These treatments rely upon the biologic response of non-senescent tumor cells. Additionally, the development of targeted pharmacologic inhibitors, as widely studied for systemic cancers and discussed below for meningioma, presumes a global distribution of the oncogenic driver or modulator target. The presence of intratumoral heterogeneity poses a fundamental impediment to the efficacy of these therapeutic strategies.

The observation of meningioma heterogeneity stems from a number of potential etiologies, including intratumoral necrosis, cystic degeneration, heterogeneous tumor cell expansion, imbalances in cell density, and hemorrhage. In particular, subclonal expansion within an admixture of functionally distinct cancer cells has been posited to account for incomplete treatment response, acquired and innate treatment resistance, and disease relapse for malignancies, such as glioblastoma and systemic cancers. Similarly, molecular and cellular heterogeneity is increasingly appreciated in meningioma (16), and may present a similar challenge to the development of therapeutic strategies.

These characteristics of meningiomas echo challenges posed by other tumors, some of which serve as exemplars in decrypting the molecular code toward a more unified front in diagnosis and treatment, as discussed below.

Genomics of Meningioma
Meningioma represents one of the first tumors associated with a genomic driver, with the initial identification of neurofibromin (NF2), the causative gene for neurofibromatosis 2 (NF2), in which 50–75% of patients develop one or more meningiomas. Sporadic low- and high-grade meningiomas are also observed to harbor mutations, allelic inactivation, and loss of the NF2 in ~40–60% of tumors, resulting in alteration of its protein derivative, Merlin (17–20). The development of meningiomas in NF2-knockout mice corroborates its role as an early oncogenic driver in meningioma tumorigenesis (21, 22).

More recently, several additional recurrent somatic mutations have been identified through next-generation sequencing approaches, which are collectively present in ~40% of sporadic meningiomas (Figure 2A) (19, 20, 23). These genes are the pro-apoptotic E3 ubiquitin ligase TNF receptor-associated factor 7 (TRAF7), the pluripotency transcription factor Kruppel-like factor 4 (KLF4), the proto-oncogene v-Akt murine thymoma viral oncogene homolog 1 (AKT1), the Hedgehog pathway signaling member smoothened (SMO), and the oncogene PIK3CA. Notably, mutations of these genes in meningiomas occur to large degree without concurrent alteration of NF2 or loss of chromosome 22.
The most common of these is TRAF7, located on chromosome 16p13, which harbors a mutation in 12–25% of meningiomas (20). TRAF7 mutations frequently co-occur with mutations in KLF4, AKT1, or PIK3CA, and are mutually exclusive with SMO and NF2 mutations (20, 23, 24). A recurrent mutation in KLF4K409Q, located on chromosome 9q31 and resulting in a lysine to glutamine substitution at codon 409 (K409Q), represents the next most frequent somatic alteration observed to date – affecting ~15% of benign meningiomas. This may recapitulate embryologic mechanisms to spur tumor formation, given the role of KLF4 as a transcription factor that promotes reprogramming of differentiated somatic cells back to a pluripotent state in normal development (25). Another recurrent mutation in AKT1, located on chromosome 14q32, is observed in 6.8% of meningiomas and produces a glutamic acid to lysine substitution at codon 17 (E17K) (20, 26). AKT1E17K mutation results in downstream activation of the PI3K/AKT/mTOR oncogenic pathway, rendering it targetable by selective AKT inhibitors, several of which are currently under investigation for the treatment of cancers of the breast, lung, and colon, among others (27). Oncogenic mutations in PIK3CA are
Genetic Hallmarks of Meningioma Subtypes

The histologic subtype and location of meningioma associates with its molecular profile (Table S1 in Supplementary Material). Grade II and III meningiomas harbor an incremental complement of chromosomal alterations, as discussed above. Copy number gains, especially polysomy 5, are also characteristic of angiomatous meningiomas, a grade I subtype (32).

Focally, inactivation of NF2, through copy loss or mutation, occurs in 70–80% of fibroblastic and transitional meningiomas. By contrast, secretory meningiomas almost uniformly harbor mutations in both TRAF7 and KLF4 but not NF2 (24), while meningothelial meningiomas are associated with AKT1 mutations (26). Additionally, clear cell meningiomas are associated with loss-of-function mutations of SMARCE1 in the hereditary multiple spinal meningioma syndrome and some cranial locations (39, 40).

Interestingly, genetic alterations also correlate with anatomic location in some meningiomas. Mutations in SMO or AKT1/TRAF7 are most frequently observed in meningiomas of the anterior cranial base (19, 20). In comparison, convexity meningiomas are more likely to express NF2 mutations and loss of heterozygosity of chromosome 22. The association between tumor location and genotype may aid candidate selection in future clinical trials that target specific oncogenic mutations.

Predicting Clinical Outcome

Aside from the role of molecular biomarkers in abetting the diagnosis of meningioma, one fundamental question in the clinical management of meningioma patients is the risk of recurrence following surgical resection. There is particular ambiguity among grade II meningiomas, for which no consensus exists regarding appropriate adjuvant treatment modality and timing. Recently, analysis of a cohort of atypical meningiomas following gross total resection revealed an association between increased chromosomal copy number alterations and risk of recurrence (41). By summing the incidence of broad copy number events across an aggregate pool of common chromosomal aberrations in meningiomas, this strategy bypasses the limitations of assessing isolated molecular candidates in meningioma oncogenesis and offers a rapid molecular appraisal of potential outcome through routine clinical cytogenetic testing. In other words, patients harboring grade II meningiomas with high chromosomal disruption, which may have a higher risk of recurrence, may benefit from closer surveillance or adjuvant therapies.

The validity of such molecular prognostication strategies remains to be proven in future studies. If corroborated, they may serve a powerful tool in counseling patients, guiding management decisions, and stratifying clinical trials.

Designing Rational Strategies in Meningioma Treatment

Elucidation of critical oncogenic drivers in a number of cancers (e.g., BRAF in melanoma or KIT in gastrointestinal stromal tumors) has enabled targeted therapies in the so-called “mutation-to-drug” paradigm (42, 43). Such an approach is now feasible in...
meningioma with the recent identification of AKT1, SMO, and PIK3CA mutations, which opens the door for targeted pharmacotherapeutics in ~20% of grade I meningiomas. A clinical trial targeting AKT1 and SMO is currently underway for progressive meningiomas (NCT02523014).

While this genomically stratified trial augurs an exciting direction for refractory meningiomas that progress after standard therapy, other meningiomas that do not express these mutations, including most high-grade tumors, remain devoid of effective pharmacologic options. Furthermore, recognition of intratumoral cellular and molecular heterogeneity, which may foster resistant subclonal growth following targeted therapies, encourages investigation of alternative treatment strategies – such as immunotherapy (44).

Deployment of the innate and adaptive immune response offers an attractive option for genomically complex tumors, where presumably a higher neoantigen load is available for immune targeting (45, 46). Suppression of inhibitors of T-cell activation offers an attractive option for genomically complex tumors, where immunotherapy (44).

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CONCLUSION
Contemporary advances in molecular, genomic, epigenetic, and immune profiling has ushered a renaissance in the study of meningiomas. These systematic approaches suggest a molecular taxonomy that promises to influence diagnosis, disease classification, and, ultimately, clinical management. Furthermore, appreciation of shared biological characteristics between meningiomas and other CNS cancers – including invasiveness and intratumoral heterogeneity – may lead to an expansion of the therapeutic arsenal in the treatment of this increasingly disparate tumor.

AUTHOR CONTRIBUTIONS
WLB and IFD drafted the manuscript and supervised the study. MZ, WW, and YM contributed to data collection. All authors critically revised the manuscript and approved the final submission.

SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fsurg.2016.00040

REFERENCES

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