Meningioma Genomics: Diagnostic, Prognostic, and Therapeutic Applications

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>doi:10.3389/fsurg.2016.00040</td>
</tr>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:27822290">http://nrs.harvard.edu/urn-3:HUL.InstRepos:27822290</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
Meningioma Genomics: Diagnostic, Prognostic, and Therapeutic Applications

Wenya Linda Bi, Michael Zhang, Winona W. Wu, Yu Mei and Ian F. Dunn*

Department of Neurosurgery, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA

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 NF2, TRAF7, KLF4, AKT1, SMO, and 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

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...
meningothelial 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 nucleoli, 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

---

**PREVALENCE DEMOGRAPHICS**

**GENDER**

- Female > Male
- Female ≥ Male
- Female ≤ Male

**DIAGNOSTIC CRITERIA**

<table>
<thead>
<tr>
<th>GRADE I</th>
<th>GRADE II</th>
<th>GRADE III</th>
</tr>
</thead>
<tbody>
<tr>
<td>~85-95%</td>
<td>~5-10%</td>
<td>~1-5%</td>
</tr>
<tr>
<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>
</tr>
</tbody>
</table>

**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>OVERALL SURVIVAL</th>
<th>PROGRESSION-FREE SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-90%</td>
<td>75-90%</td>
</tr>
<tr>
<td>50-79%</td>
<td>23-78%</td>
</tr>
<tr>
<td>14-34%</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.

---
Despite being the quintessential icon of CNS extra-axial tumors, meningiomas exhibit a similar proclivity for invasiveness. In Simpson's classic analysis of surgical outcomes, high-grade meningiomas, often from a higher grade to lower grade (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 gene 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.

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 gene 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).
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 KLF4<sup>K409Q</sup>, 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). AKT1<sup>E17K</sup> 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

---

**FIGURE 2**  
(A) Recurrent NF2, AKT1, SMO, TRAF7, KLF4, and PIK3CA mutations are collectively present in over 80% of grade I meningiomas. Mutations in AKT1, KLF4, and PIK3CA overlap with TRAF7, but not with each other, and largely occur in a mutually exclusive pattern with NF2 and SMO. Oncogenic driver mutations remain unclear for ~20% of meningiomas [Data aggregated from Ref. (19, 20, 23, 41)].  
(B) Recurrent chromosomal copy number alterations in meningioma. Chromosomal arm-level gains (red) and losses (blue) are observed with increasing frequency in higher-grade meningiomas, compared to grade I meningiomas. §Polysomy 6 is observed in angiomatous subtype of grade I meningiomas [Data adapted from Ref. (6, 32)].
observed in ~7% of non-NF2-mutant meningiomas, and occur mutually exclusive of AKT1 and SMO mutations, although they frequently co-occur with TRAF7 mutations (23). Lastly, ~5.5% of benign meningiomas, or more than 10% of meningiomas without NF2 alteration, express mutations in SMO (19, 20). These SMO alterations result in activation of Hedgehog signaling, another well-characterized pathway in cancer that is notably dysregulated in basal-cell carcinoma and medulloblastoma (28, 29). In basal-cell carcinoma, where over 90% of tumors have mutations in either SMO or PTCH, SMO inhibition has been particularly effective in the setting of locally advanced and metastatic disease (30). Inhibitors of SMO, AKT1, and PIK3CA hold promise as molecularly targeted pharmacotherapy in meningioma.

Collectively, these somatic mutations hold significant promise for advancing the molecular taxonomy of meningioma. However, ~20% of meningiomas remain without an identifiable oncogenic driver mutation to date (31). Beyond mutations, insertions, and deletions at the single nucleotide level, meningiomas harbor a classic constellation of chromosomal copy number alterations (Figure 2B). Monosomy 22 is the most common chromosomal change, observed in 40–70% of meningiomas, across all grades (7). Aside from loss of chromosome 22, the copy number landscape of benign meningiomas is typically neutral. One exception is the angiomatous subtype of grade I meningiomas, which notably express multiple polysomies across the genome, most commonly of chromosome 5 (32). In comparison, higher-grade meningiomas express a markedly higher burden of chromosomal losses and gain. These include frequent loss of chromosomes 1p, 6q, 10, 14q, and 18q, as well as gain of chromosomes 1q, 9q, 12q, 15q, 17q, and 20q (7, 33, 34). Among these, loss of chromosomes 1p and 14q is the most frequent cytogenetic abnormality observed in meningiomas after chromosome 22, affecting half of grade II and nearly all grade III meningiomas (33). Investigations into candidate oncogenes on these chromosomal arms have yet to elucidate clear drivers for meningioma tumorigenesis.

In addition to mutations and copy number alterations, epigenomic changes may provide another complementary biologic mechanism in meningioma development and progression (35). Overall, all existing evidence suggests a progression in genomic complexity in high-grade meningiomas.

**APPLICATIONS OF MOLECULAR TAXONOMY IN MENINGIOMA**

These significant advances in our understanding of meningiomas provide an expanding toolbox to formulate a molecular taxonomy and explore novel therapeutic options for this surprisingly diverse tumor entity. This paradigm shift toward molecular taxonomy is inspired by examples from several tumor types, including glioblastoma, medulloblastoma, and ependymoma, where molecular stratification has transformed their diagnosis and management (36–38). Similarly, associations between molecular signatures with characteristic phenotypes, intracranial locations, tumor subclass, and clinical prognosis have begun to emerge as an increasing number of meningiomas are systematically characterized.

**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 (24), but not NF2 (22), 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/TRA7 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 resistant subclonal growth following targeted therapies, encouraged by molecular cellular and molecular heterogeneity, which may foster clinical responses in several advanced systemic cancers (47). In grade II and III meningiomas that progress after surgery and standard radiation, a phase 2 clinical trial evaluating checkpoint blockade with nivolumab is anticipated to initiate (NCT02648997).

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, known as immune checkpoints, has achieved durable clinical responses in several advanced systemic cancers (47). In grade II and III meningiomas that progress after surgery and standard radiation, a phase 2 clinical trial evaluating checkpoint blockade with nivolumab is anticipated to initiate (NCT02648997).

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


