# Meningioma Genomics: Diagnostic, Prognostic, and Therapeutic Applications

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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 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

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 of meningioma, as stratified by grade. Clinical outcomes are influenced by age, comorbidities, extent of resection, adjuvant therapy, and tumor location.

#### Clinical Outcomes at 10 Years

<table>
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<tr>
<th>Grade</th>
<th>Overall Survival</th>
<th>Progression-Free Survival</th>
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<tbody>
<tr>
<td>I</td>
<td>80-90%</td>
<td>75-90%</td>
</tr>
<tr>
<td>II</td>
<td>50-79%</td>
<td>23-78%</td>
</tr>
<tr>
<td>III</td>
<td>14-34%</td>
<td>0%</td>
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**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 challenges and therapeutic approaches.

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.

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 challenges and therapeutic approaches.
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 KLF4\(^{K409Q}\), 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 \(\sim\)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\(^{E17K}\) 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

![Diagram of somatic mutations in meningiomas](https://example.com/diagram.png)

**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 \(\sim\)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 5 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, epigenetic 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.

### 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<sup>E409Q</sup> 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/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 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).

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**REFERENCES**


**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


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