Genomic landscape of intracranial meningiomas

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Meningiomas are the most common primary intracranial neoplasms in adults. Current histopathological grading schemes do not consistently predict their natural history. Classic cytogenetic studies have disclosed a progressive course of chromosomal aberrations, especially in high-grade meningiomas. Furthermore, the recent application of unbiased next-generation sequencing approaches has implicated several novel genes whose mutations underlie a substantial percentage of meningiomas. These insights may serve to craft a molecular taxonomy for meningiomas and highlight putative therapeutic targets in a new era of rational biology-informed precision medicine.

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MENINGIOMAS are the most common primary intracranial neoplasms in adults, accounting for 35.8% of all primary CNS tumors and more than 53% of all benign CNS tumors diagnosed in the US.⁶⁵ Autopsy and imaging studies suggest an even higher prevalence, affecting almost 3% of women.⁹⁸ These lesions are believed to arise from progenitor cells that give rise to both the arachnoid cap cells of the arachnoid layer and fibroblasts that reside in the inner dura mater.^{18,45}

The vast majority of meningiomas are indolent.³⁶ A small percentage, however, display malignant behavior characterized by invasive growth patterns and/or markedly higher recurrence rates. Notably, even meningiomas that lack histological features of malignancy recur at significant rates. Multimodality therapy including surgery and radiation is often used in the management of these subsets of meningioma, but other therapeutic modalities

have failed to improve control rates. Aggressive meningiomas and the meningiomatosis that occur in hereditary syndromes remain difficult clinical problems. Although most meningiomas are “benign,” there is substantial morbidity associated with recurrence, and clinical management remains challenging for clinicians worldwide.

Unbiased genome- and exome-wide sequencing approaches have implicated a central core of gene mutations that are associated with a substantial percentage of these tumors. This information may highlight therapeutic targets and enhance biological classification of meningioma.^{12,22} Just as an improved understanding of genomic alterations has changed the way we classify and treat cancers including chronic myelogenous leukemia, melanoma, and lung cancer, similar interrogation of the meningioma genome has revealed potential novel treatment pathways for patients harboring these tumors.⁵⁹

ABBREVIATIONS hpf = high-power field; MAPK = mitogen-activated protein kinase; mTOR = mammalian target of rapamycin; NF2 = neurofibromatosis Type 2; PI3K = phosphoinositide-3-kinase.

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Histopathological Classification

The current diagnostic criteria for meningiomas are largely predicated on histological features. The WHO defines 3 grades of meningiomas, with Grade II and III meningiomas associated with significantly greater rates of recurrence, morbidity, and mortality (Fig. 1).⁵⁵ Grade I tumors display a broad range of morphological features and are divided into numerous histological subtypes: meningothelial, fibrous or fibroblastic, transitional (containing both meningothelial and fibroblastic components), psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic (Fig. 2). Patients with Grade I meningiomas have a 10-year overall survival of 80%–90% and progression-free survival of approximately

75%–90%, with outcome influenced by extent of resection, location of tumor, and patient age.^{77,95,96}

Grade II (also known as atypical) meningiomas are defined by a specific set of morphological criteria and 2 distinct histological variants (clear cell and chordoid). Atypical meningiomas are defined by the presence of 4–19 mitoses per 10 microscopic hpf (40×), or the presence of 3 of 5 of the following criteria: sheetlike growth, spontaneous necrosis, high nuclear-to-cytoplasmic ratio, prominent nucleoli, and increased cellularity. Brain invasion is not included in the diagnostic paradigm of meningioma grading, but its presence implies a similar recurrence rate and risk of mortality to those found in atypical meningiomas.⁶⁹ Grade II meningiomas are associated with up to 8-fold

FIG. 1. Chart showing the genomic landscape of Grade I, II, and III meningiomas. Demographic data, current WHO diagnostic criteria, histological subtypes, recurrent copy number alterations, and mutations across meningiomas are shown. *Brain invasion is not formally a criterion of Grade II meningiomas, but observation of brain invasion connotes a similar risk for recurrence as in atypical meningioma.

FIG. 2. Photomicrographs showing meningioma histological subtypes. Grade I tumors encompass (A) meningothelial, (B) fibrous or fibroblastic, (C) transitional, (D) psammomatous, (E) secretory, (F) angiomatous, (G) microcystic, (H) lymphoplasmacyte-rich, and (I) metaplastic subtypes. Grade II tumors include (J) atypical, (K) clear cell, and (L) chordoid meningiomas. Grade III meningiomas include (M) anaplastic, (N) papillary, and (O) rhabdoid subtypes. H & E, original magnification $\times 20$ (A–H, J–N), and $\times 40$ (I and O). Images for lymphoplasmacyte-rich, metaplastic, and papillary subtypes courtesy of Dr. Arie Perry.

higher recurrence rates than Grade I meningiomas, with a 10-year overall survival of 53%–79% and progression-free survival of 23%–78%, dependent on the extent of resection and adjuvant therapies.^{28,67,92,93}

The most aggressive types are Grade III, or anaplastic/malignant meningiomas, and these are defined by a mitotic index of 20 or greater per 10 hpf. It can sometimes be difficult to recognize these tumors as meningiomas because they can morphologically resemble sarcoma or carcinoma. Papillary and rhabdoid histological variants are also designated as WHO Grade III. Grade III menin-

giomas are associated with a 10-year overall survival of 14%–34% and progression-free survival of 0%.^{28,66}

Management Challenges in the Era of Precision Medicine

Of the manifold challenges in the clinical management of these tumors, we highlight 2 particular areas that could be influenced by improved understanding of meningioma genomics: 1) the difficulty in accurately predicting the natural history of meningiomas based solely on histopathological grade, and 2) the lack of effective systemic medical therapies for meningiomas.

Predicting Natural History Based on Tumor Grade

Even though histological grade is helpful in prognostication of the natural history, meningiomas with low-grade histological features may recur despite adequate resection, whereas meningiomas with high-grade features may not. In these circumstances, the histological appearance of a meningioma inconsistently predicts biological behavior. Traditional histopathological definitions based on cytoarchitecture, cellularity, density of mitoses, nuclear pleomorphism, tumor necrosis, and presence of brain invasion have proved invaluable for guiding the management of patients with meningioma. However, a certain amount of subjectivity in applying standard WHO criteria and interobserver variability can confound grading. Retrospective review of meningioma grade when applying the WHO 1993, 2000, or 2007 criteria led to reclassification of up to 30% of tumors, both from lower grade to higher grade and from higher grade to lower grade.^{6,103} WHO Grade I meningiomas with borderline atypical features, as defined by an elevated MIB-1 proliferation index, or the presence of only 1 or 2 of the features required for a WHO Grade II designation, can also complicate counseling of patients and determining the optimal treatment strategy. Some diagnosticians may apply different thresholds when deciding on the presence of certain histological features. Tissue sampling can also lead to variability, because only representative portions of very large meningiomas are analyzed.

Histological descriptions likely do not capture all of the information necessary to understand tumor behavior. Therefore, additional molecular tools could potentially yield more reliable prognostic information as well as provide powerful additional information to better direct the optimized use of specific targeted therapeutic strategies. Molecular taxonomy has transformed the clinical management of several tumors in recent decades. Within the CNS, medulloblastomas, glioblastomas, and ependymomas provide benchmarks for integrating molecular diagnoses with subsequent decisions for adjuvant treatment and prognostication.^{13,64,101} Histological entities that are classically clustered together are partitioned into distinct disease subgroups, with characteristic patient demographics, genomic signatures, and clinical course. Molecular classification of meningiomas has also been proposed;¹⁷ further refinements of this concept based on a continuous variable of molecular aberrations with strong correlation to outcome are in progress, and may improve our ability to understand a patient's clinical course prospectively.

Paucity of Medical Treatments for Meningiomas

For most meningiomas, surgery and radiation remain the mainstays of treatment. Complete resection of a Grade I meningioma including all dural attachments in the setting of observed growth, symptoms, or impending neurological deficit is frequently curative.⁸⁶ However, this is not always achievable, especially with meningiomas located at the skull base and with high-grade (Grade II or III) meningiomas. Chemotherapeutic options are limited to recurrent cases that have exhausted surgical and radiation options, and these approaches have shown only limited to poor efficacy.¹⁰⁰

Clinical trials of targeted therapeutics for meningioma to date have used agents that target classic oncogenic pathways such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and mammalian target of rapamycin (mTOR).^{46,100} However, in these trials, patients are enrolled based on recurrence status but not on the presence of a definitive molecular marker that can predict response to the trial intervention. Notably, besides the long-established role for *NF2* in the development of meningioma, other oncogenic drivers of meningioma development and progression have remained elusive until recently. Unlike in a number of other cancers in which targeted therapeutics can be leveraged to disable genetic aberrations that serve as the main oncogenic drivers (e.g., BRAF inhibitors for melanoma⁸⁹ or cKIT inhibitors in gastrointestinal stromal tumors and chronic myelogenous leukemia²⁶)—the so-called “mutation-to-drug” paradigm—such approaches have not been possible in meningioma. These limitations call for better understanding of the molecular underpinnings of meningiomas and a shift toward an objective stratification for these tumors.

Germline Genomic Alterations in Hereditary Meningioma Syndromes

In patients with multiple meningiomas as a consequence of hereditary syndromes, the tumors are particularly challenging to manage. Because these syndromes often involve loss of function in key tumor suppressors, there may be reluctance to use modalities such as radiation therapy in the eventuality that this treatment leads to disease progression of targeted areas and the transformation of otherwise nontransformed normal tissue.⁷ Thus, detailed understanding of the biology of these conditions is critical to improving medical options for these patients.

Neurofibromatosis Type 2

Initial insight into the genetic alterations that lead to meningiomas was derived from associated familial syndromes (Table 1). The first and most thoroughly described of these syndromes is neurofibromatosis Type 2 (NF2), in which 50%–75% of patients develop one or more meningiomas. The underlying gene, *NF2*, is a well-defined tumor suppressor that encodes the protein Merlin. Mutation, allelic inactivation, or loss of the tumor suppressor *NF2* gene and its parent chromosome 22 have been implicated in approximately 40%–60% of sporadic meningiomas in addition to those afflicted with neurofibromatosis.^{12,22,30,79} *NF2* probably plays an early driver role in meningioma

TABLE 1. Hereditary syndromes with meningiomas

Syndrome	Gene Affected	Chromosome Locus
Cowden disease	<i>PTEN</i>	10q23.31
Gardner syndrome	<i>APC</i>	5q21-22
Gorlin (nevoid basal cell carcinoma) syndrome	<i>PTCH</i>	9q22.3
Li-Fraumeni syndrome	<i>TP53</i> <i>CHEK2</i>	17q11.2 22q12.1
Multiple endocrine neoplasia Type 1	<i>MEN</i>	11q13
Multiple meningiomas & schwannomas	<i>SMARCB1</i>	22q11.23
Multiple spinal meningiomas	<i>SMARCE1</i>	17q21.2
Neurofibromatosis Type 1	<i>NF1</i>	17q11.2
Neurofibromatosis Type 2	<i>NF2</i>	22q
Rubinstein-Taybi syndrome	<i>CREBBP</i> <i>EP300</i>	16p13.3 22q13
von Hippel-Lindau syndrome	<i>VHL</i> <i>CCND1</i>	3p26-25 11q13
Werner syndrome	<i>LMNA</i> <i>RECQL2</i>	1q21.1 8p12-p11.2
Turner syndrome	—	XO

— = none (purely a chromosomal abnormality).

formation, given its alteration in both low-grade and high-grade tumors,⁷⁰ as well as the development of meningiomas in *NF2*-knockout mice.^{44,45}

Multiple hypotheses exist for the mechanism by which alterations in *NF2* result in tumor formation. Merlin belongs to the protein 4.1 family, which serve to link membrane proteins to the cytoskeleton, and facilitates contact-dependent inhibition of cellular proliferation.²⁴ Loss of Merlin activates downstream oncogenic and mitogenic pathways such as Ras/mitogen-activated protein kinase (MAPK), Notch, phosphoinositide-3-kinase (PI3K), Hippo, and mTOR, leading to uncontrolled neoplastic growth.^{34,38,39,62,78} In addition to dysregulation of specific signaling pathways, *NF2*-mutated meningiomas may also exhibit greater chromosomal instability than *NF2*-wild type counterparts.³² However, no targetable dependency in the NF2 pathway currently exists.

Other Germline Syndromes

Germline mutations in the Switch/Sucrose nonfermentable (SWI-SNF) chromatin-remodeling complex gene *SMARCB1/INI1/SNF5/hSNF5*, located on chromosome 22q11, have been identified in several families with multiple meningiomas and schwannomas^{5,21,97} but appear to be only one of many contributors in the full spectrum of patients with multiple meningiomas.³³ Interestingly, mutation or loss of the SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin subfamily B member 1 (*SMARCB1*) is a signature of tumors with rhabdoid morphology, including malignant rhabdoid tumors (MRT) and atypical teratoid/rhabdoid tumors (ATRT),^{37,50} and results in persistent activation of the AKT oncogenic signaling pathway.²⁵ This raises the question of whether

alterations in *SMARCB1* might also contribute to tumorigenesis in sporadic rhabdoid meningiomas.

Mutations in another member of the SWI-SNF family, *SMARCE1*, have been noted in families with multiple spinal meningiomas as well as several cases of cranial meningiomas.^{87,88} This familial syndrome occurs in the absence of schwannomas and is transmitted with autosomal dominant inheritance. In patients with germline *SMARCE1* aberrations, chromosome 22 and *NF2* appear to be normal.

Other familial syndromes involving meningiomas include neurofibromatosis Type 1 (*NF1*, 17q11.2); Cowden disease (*PTEN*, 10q23.31); Gorlin or nevoid basal cell carcinoma syndrome (*PTCH*, 9q22.3); Li-Fraumeni syndrome (*TP53*, 17q11.2; *CHEK2*, 22q12.1); Gardner syndrome (*APC*, 5q21-22); Rubinstein-Taybi syndrome (*CREBBP*, 16p13.3; *EP300*, 22q13); von Hippel-Lindau syndrome (*VHL*, 3p26-25; *CCND1/cyclin D1*, 11q13); Werner syndrome (*LMNA*, 1q21.1; *RECQL2*, 8p12-p11.2); and multiple endocrine neoplasia Type 1 (*MEN*, 11q13).⁸⁴ Multiple meningiomas have been observed in patients with mutations in *CCM3/PDCD10*, a gene associated with cerebral cavernous malformations that contributes to proliferation and resistance to apoptosis via activation of AKT signaling,^{20,48,56,75} and the *SUFU* gene, which regulates hedgehog signaling.¹ Taken together, the multitude of familial syndromes associated with meningiomas suggests that many diverse mechanisms may lead to the proliferation and growth of meningioma. Further study into how each of these genetic lesions predisposes patients to tumor formation will be critical to optimization of medical strategies as well as enhancement of our biological insight into these syndromes.

Somatic Genomic Alterations in Meningiomas

Although meningiomas that arise in hereditary syndromes may offer mechanistic insights, the majority of meningiomas arise sporadically. Over the last several years, the application of genomic approaches has given us a high-resolution picture of the types of somatic alterations—at both the level of copy number and of single-nucleotide changes—that underlie these tumor types and set the stage for novel clinical trials.

Chromosomal Copy Number Alterations

Cytogenetic studies shed early insight into chromosomal-level alterations in meningiomas. The most common alteration observed in Grade I meningiomas is monosomy of chromosome 22, which is observed in 40%–70% of cases.⁶⁹ Aside from this recurrent copy number alteration, the copy number landscape of Grade I tumors is typically balanced. One exception is the angiomatous subtype of benign meningiomas, which harbors multiple polysomies across the genome, most commonly of chromosome 5.² Atypical and anaplastic meningiomas express frequent loss of chromosomes 1p, 6q, 10, 14q, and 18q, as well as gain of chromosomes 1q, 9q, 12q, 15q, 17q, and 20q (Fig. 1), with a propensity for increased genomic aberrations with higher grade.^{15,16,69}

Recurrent chromosomal gains and losses have prompted investigation into candidate driver genes within these regions. The losses of chromosomes 1p and 14q are the next 2 most frequent cytogenetic abnormalities observed in meningiomas (after chromosome 22 loss), affecting half of Grade II and nearly all Grade III meningiomas.¹⁶ Investigations of an array of candidate driver genes on chromosome 1p, including *TP73*,⁵⁴ *CDKN2C*,¹¹ *RAD54*,⁶⁰ *EPB41*,⁷² *GADD45A*,⁷² and *ALPL*,⁶³ have yet to provide concrete evidence for a consistent role in meningioma tumorigenesis. Similarly, malignant meningiomas have decreased expression of several tumor suppressor genes on chromosome 14q, such as *NDRG2*⁵⁷ and the noncoding RNA *MEG3*,¹⁰⁴ but rarely have direct mutations in these candidates. One possible mechanism leading to reduced gene expression, in the absence of inactivating mutations, is silencing through methylation.^{8,52,53,57} The identification of somatic mutations in *SMARCB1* and in the histone demethylases *KDM5C* and *KDM6A* in Grade I meningiomas suggests a role for epigenetic modification driving tumor inception.¹²

Aberrations in chromosome 9p may disrupt cell cycle regulation due to the location of several important cell cycle genes on 9p21, including *CDKN2A*, *CDKN2B*, and *ARF*.¹¹ *INK4a/p16* (encoded by *CDKN2A*) and *INK4b/p18* (encoded by *CDKN2B*) inhibit the cyclin-dependent kinases CDK4 and CDK6, respectively, whereas *ARF/p14* promotes p53 activity through repression of its inhibitor, the murine double minute 2 (*MDM2*) protein.⁹¹ Frequent deletions or inactivating mutations in these cell cycle regulators are found in anaplastic meningiomas, and correlate with shorter survival.⁶⁸

Loss of chromosome 10 is frequently observed in multiple cancers, including high-grade meningiomas. However, alterations in the influential tumor suppressor *PTEN* are not regularly observed in meningiomas.^{10,71} Credible driver genes underlying chromosome 17q amplifications and 18p losses in malignant meningiomas have yet to be identified.^{14,15}

Chromosome 22 Mutation Candidates

NF2 remains the most commonly altered genetic locus across all meningiomas.^{12,22,35,61} In some tumors, one allele harbors an *NF2* mutation while the other harbors *NF2* copy loss, resulting in a double hit. Meningiomas with broad-range loss in chromosome 22 and preserved expression of wild-type *NF2* suggested the presence of adjacent genes on chromosome 22q that may also play a role in tumorigenesis. Potential candidate genes on chromosome 22 that could contribute to the pathogenesis of meningioma include *SMARCB1*,⁸² checkpoint kinase 2 (*CHEK2*),¹⁰² and clathrin heavy chain polypeptide gene (*CLH-22/CTCLI*).

Somatic mutations and loss of *SMARCB1*, in addition to the germline mutations previously discussed, have been reported in sporadic meningiomas, highlighting a growing recognition of epigenetic modifiers in a number of diverse and molecularly distinct cancer types.¹² Similarly, isolated mutations of *CHEK2* have been noted in meningiomas,¹² in addition to frequent codeletion with *NF2* given their proximity on 22q12.2.¹⁰² *CHEK2* contributes to homologous and nonhomologous mechanisms of DNA repair and

is postulated to serve as a tumor suppressor during cell cycle progression. Frequent loss of expression and rare rearrangement is also seen across meningiomas with the *CLH-22* gene, located on 22q11, but its functional role remains to be elucidated.

Somatic Mutations Revealed by Next-Generation Sequencing Approaches

In the last 3 years, the use of next-generation DNA sequencing has yielded new insights into recurrent mutations that occur in meningiomas. Specifically, recurrent somatic mutations in 4 genes were identified.^{12,22} These mutated genes include the classic proto-oncogene v-Akt murine thymoma viral oncogene homolog 1 (*AKT1*), the Hedgehog pathway signaling member smoothened (*SMO*), the proapoptotic E3 ubiquitin ligase TNF receptor-associated factor 7 (*TRAF7*), and the pluripotency transcription factor Kruppel-like factor 4 (*KLF4*). Collectively, these mutations are present in up to 40% of sporadic meningiomas, appear preferentially in tumors at the skull base, and almost always occur without associated *NF2* mutation or chromosome 22 loss (Fig. 3).

Mutations in *TRAF7*, located on chromosome 16p13, are observed in 12%–25% of meningiomas.²² A majority of meningiomas with *TRAF7* mutations also harbor mutations in *AKT1* or *KLF4* mutations, but not both.^{22,74} However, *TRAF7* mutations occur in a mostly mutually exclusive fashion with *SMO* mutations, *NF2* mutations, and chromosome 22 loss.²² The mechanism and downstream effectors of this mutation remain to be discovered.

A subset of *TRAF7*-mutated tumors harbor the *AKT1*^{E17K} mutation, which is observed in 6.8% of meningiomas.^{22,80} *AKT1*, located on chromosome 14q32, is mutated at low frequency in a range of cancers including carcinoma of the breast, lung, and colon.⁹ In meningioma, recurrent *AKT1* mutations produce a known oncogenic alteration of glutamic acid to lysine at codon 17 (E17K), and appear exclusive of *NF2*, *KLF4*, and *SMO* mutations.²² The *AKT1*^{E17K} mutation results in activation of downstream effectors of the PI3K/AKT/mTOR oncogenic pathway, rendering it a potential target by selective AKT inhibitors, several of which are currently in Phase I and II clinical testing for the treatment of a broad range of cancers.

Similarly, *SMO* mutations result in downstream activation of Hedgehog signaling, another well-characterized pathway in cancer that is notably dysregulated in basal cell carcinoma and medulloblastoma.^{43,73} In basal cell carcinoma, where more than 90% of tumors have mutations in either *SMO* or *PTCH*, inhibition of SMO has been particularly effective in the setting of locally advanced or metastatic disease, with vismodegib receiving FDA approval in early 2012.⁸³ *SMO* mutations are observed in approximately 5.5% of Grade I meningiomas, or in greater than 10% of non-*NF2*-altered tumors.^{12,22}

Last, *KLF4*, located on chromosome 9q31, is a transcription factor that promotes reprogramming of differentiated somatic cells back to a pluripotent state.⁹⁴ A recurrent mutation in *KLF4*^{K409Q} results in a lysine-to-glutamine substitution at codon 409 (K409Q), and is observed in 15.7% of Grade I meningiomas. *KLF* mutations co-oc-

FIG. 3. Charts showing distribution of *NF2*, *AKT1*, *SMO*, *TRAF7*, and *KLF4* mutations in Grade I meningiomas. **A:** Recurrent oncogenic driver mutations in Grade I meningiomas include *TRAF7*, *AKT1*, *KLF4*, and *SMO*, which largely occur in a mutually exclusive pattern with *NF2*. Mutations in *KLF4* and *AKT1* overlap with *TRAF7*, in proportion to the areas represented in the Venn diagram. **B:** Distribution of *TRAF7*, *AKT1*, *KLF4*, *SMO*, and *NF2* mutations across Grade I meningiomas. Recurrent oncogenic changes remain unclear for approximately 20% of meningiomas (designated by the question mark). *NF2* mutation or loss is designated by the section symbol. Data aggregated from Brastianos and Horowitz et al. and from Clark et al.

cur with *TRAF7* mutations and are exclusive of *NF2* and *AKT1* mutations.²² Alteration of this pluripotent transcription factor may represent a recapitulation of embryological mechanisms to drive tumor formation.

Genotype-Phenotype Associations in Meningioma

The genetic makeup of meningiomas is increasingly recognized to produce characteristic phenotypes. In the case of *NF2*, inactivation of this gene is observed in 70%–80% of fibroblastic and transitional meningiomas, but less than 1% of secretory meningiomas. This profound difference in mutation frequency suggests that some morphological subtypes of meningioma harbor subtype-specific oncogenic mutations other than *NF2*, which was corroborated by the discovery of mutations in *AKT1*, *SMO*, *TRAF7*, and *KLF4* (Table 2).

Genetic Hallmarks of Meningioma Subtypes

Nearly all cases of secretory meningioma harbor mutations in both *KLF4*^{K409Q} and *TRAF7* but lack mutations in *NF2*.⁷⁴ The *KLF4* mutation has not been observed in any other nonsecretory meningiomas, CNS tumors, or systemic malignancies. *TRAF7* mutations overlap with *KLF4* mutations but are found in a larger spectrum of meningioma subtypes,²² including 97% of secretory meningiomas and 8% of nonsecretory meningiomas.⁷⁴ *AKT1* mutations, in contrast, are common in Grade I meningothelial meningiomas and increasingly rare with progressively higher grades of malignancy.⁸⁰

Clear cell meningiomas, in the hereditary multiple spinal meningioma syndrome and some cranial locations, are associated with loss-of-function mutations in *SMARCE1*.^{87,88} The role of this mutation in sporadic clear cell meningiomas merits further validation.

In addition to mutation signatures of meningioma subtypes, angiomatous meningiomas have been reported to harbor a unique profile of multiple chromosomal polysomies, most frequently of chromosome 5.² An unbalanced translocation between chromosomes 1 and 3 has also been proposed as a marker of chordoid meningiomas.⁹⁰ The concept of subtype-specific genomic alterations points to a potential molecular taxonomy for meningiomas in the future.

Location-Specific Genetic Signatures

Specific genetic alterations not only associate with histopathological subtypes, they also correlate with the dis-

tribution of tumors. Convexity meningiomas more often harbor mutations in *NF2* and chromosome 22 loss of heterozygosity, and belong to the fibroblastic and transitional subtypes. In contrast, meningiomas along the anterior cranial base typically retain chromosome 22q heterozygosity and are more likely to express mutations in *SMO* or *AKT1/TRAF7*.^{12,22} This concurs with observations that cranial base meningiomas are predominantly of the meningothelial subtype, because *AKT1* mutations are largely found in meningothelial meningiomas.^{12,47}

Genetic Basis of High-Grade Meningiomas

One fundamental question that remains unanswered is whether high-grade meningiomas result from transformation of a low-grade precursor through acquisition of additional oncogenic drivers, or as de novo malignant tumors. Clinical experience and cytogenetic studies suggest that distinct primary de novo and secondary transformation pathways exist that result in high-grade meningiomas, each with a molecular signature, akin to the pattern observed in glioblastoma multiforme.^{3,99}

In one series of recurrent meningiomas with documented histopathological progression, a similar pattern of chromosome 22, 1p, and 14q loss existed in both Grade I and Grade II–III recurrences.³ Other studies have identified progressive loss of chromosomes 1p, 6q, 9p, 10, 14q, 18q, and 19q in atypical and anaplastic meningiomas as compared with benign Grade I meningiomas (Fig. 1).⁹⁹ In addition, high-grade meningiomas are associated with gains of 1q, 9q, 12q, 15q, 17q, and 20q. Anaplastic meningiomas in particular have frequent loss of chromosome 9p and amplification of 17q23.⁷⁶ The acquisition of these changes over time suggests underlying chromosomal instability with progressive meningioma grade. Such instability could be innate to an oncogenic driver within the incipient tumor or induced by external factors.^{3,4,29}

Despite the recognition of recurrent chromosomal changes in malignant progression of meningiomas, underlying gene targets that may be driving such changes largely remain elusive. It may be that gains and losses of specific chromosomal arms reflect a more pervasive underlying genomic instability, resulting from the convergence of several aberrant signaling pathways. Another innate source of genomic instability relates to progressive lengthening of telomeres.^{19,49,51,81,85} Telomerase activation has been demonstrated in 10% of Grade I, 50% of Grade II, and 95% of Grade III meningiomas. Interestingly, mutations of the telomerase reverse transcriptase (*TERT*) gene promoter that result in increased expression of *TERT* mRNA are associated with meningiomas that relapse, with the highest frequency of *TERT* promoter mutations (28%) present in relapsing meningioma that have undergone histological progression.³¹

In summary, the genetic mutations and chromosomal aneuploidy found in meningiomas implicate a critical role for cell cycle disruption, the hedgehog (Hh) pathway, and the PI3K/Akt pathway in tumorigenesis. Gene expression studies and cell line models further suggest activation of MAPK, Notch, and growth factor autocrine loops in meningiomas.^{23,40–42,58} Aside from mechanisms that promote

TABLE 2. Meningioma subtype-specific genetic alterations

Subtype	Associated Genetic Alteration	Inheritance
Meningothelial	<i>AKT1</i> (E17K)	Sporadic
Fibroblastic, transitional	<i>NF2</i>	Sporadic, familial
Secretory	<i>KLF4</i> (K409Q), <i>TRAF7</i>	Sporadic
Angiomatous	Polysomy 5	Sporadic
Clear cell	<i>SMARCE1</i>	Familial
Chordoid	der(1)t(1;3)(p12-13;q11) translocation	Sporadic

uncontrolled proliferation, malignant meningioma may also usurp the telomerase clock to escape senescence and possibly immunomodulate the meningioma's microenvironment.²⁷ Greater insight into recurrent drivers underlying malignant transformation may be acquired through future genomic studies.

Conclusions

The study of meningioma is undergoing a renaissance due to the application of multiplatform molecular, genomic, and epigenetic profiling. These large-scale, systematic approaches inform a molecular taxonomy that promises to influence diagnosis, disease classification, and, ultimately, clinical management; indeed, the mutational and copy number profiles of meningiomas are increasingly appreciated to predict anatomical location, histological phenotype, and clinical outcome, offering profound implications for adjuvant therapy options and patient counseling.

Further understanding of the factors that drive meningioma development and progression will lead to the classification of every patient's tumor according to its signature alterations, ushering in an era in which meningiomas will be considered in the same light as other tumors whose molecular underpinnings have fueled the nascent precision-medicine age.

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Disclosures

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Author Contributions

Conception and design: IF Dunn, Bi. Acquisition of data: Bi. Analysis and interpretation of data: Bi, Brewster. Drafting the article: IF Dunn, Bi. Critically revising the article: IF Dunn, Bi, Abedalthagafi, Horowitz, Agarwalla, Mei, Aizer, GP Dunn, Al-Mefty, Alexander, Santagata, Beroukhi. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: IF Dunn, Bi. Study supervision: IF Dunn.

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