Molecular genetics of meningiomas: a systematic review of the current literature and potential basis for future treatment paradigms

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Although a majority of meningiomas are benign neoplasms, those occurring at the cranial base may be challenging tumors to treat because of extensive tissue invasion, an inability to achieve gross-total microscopic resection, and local tumor recurrence and/or progression. A more comprehensive understanding of the genetic abnormalities associated with meningioma tumorigenesis, growth, and invasion may provide novel targets for grading assessments and individualizing molecular therapies for skull base meningiomas. The authors performed a review of the current literature to identify genes that have been associated with the formation and/or progression of meningiomas. Mutations in the NF2 gene have been most commonly implicated in the formation of the majority of meningiomas. Inactivation of other tumor suppressor genes, including DAL-1 and various tissue inhibitors of matrix metalloproteinases, upregulation of several oncogenes including c-sis and STAT3, and signaling dysregulation of pathways such as the Wnt pathway, have each been found to play important, and perhaps, complementary roles in meningioma development, progression, and recurrence. Identification of these genetic factors using genome-wide association studies and high-throughput genomics may provide data for future individualized treatment strategies.

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**Key Words** • meningioma • genetics • skull base • DNA sequencing • genomics

MENINGIOMAS are among the most common primary intracranial tumors, with a reported incidence of 4.4 per 100,000 person-years.89 The true prevalence is likely even greater, as incidental meningiomas have been reported in 2.3% of autopsy examinations.61 Most commonly diagnosed in middle-aged and elderly patients, cranial meningiomas are roughly 10-fold more common than spinal meningiomas.84 Meningiomas located at the base of the skull may present a unique therapeutic challenge, based on local invasion of critical neurovascular structures that often limit the ability to eradicate the burden of disease. Gross-total resection can be difficult to achieve without significant operative morbidity, and although radiosurgery is frequently implemented as an adjunctive strategy for residual tumor, it is often contraindicated due to extensive tumor burden or proximity to eloquent, radiosensitive tissue.14,15,71,100

The majority of meningiomas are benign, but a subset display histologically or clinically more aggressive behavior. The WHO classification distinguishes these tumors as Grade I (benign), Grade II (atypical), or Grade III (anaplastic/malignant).69 Although 90% of meningiomas are slow-growing Grade I tumors, these can cause significant morbidity via mass effect on neighboring structures. Atypical meningiomas account for 6%–8% of cases, whereas 2%–3% are frankly malignant tumors associated with brain invasion, early recurrence, and decreased progression-free and overall survival.52 A diagnosis of anaplastic meningiomas, for instance, is characterized by a median survival time of less than 2 years.70

Grade I meningiomas are typically classified as one of the following histopathological subtypes: meningothelial, fibroblastic, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, or metaplastic. Grade II meningiomas, on the other hand, are typically more aggressive clear cell and chordoid tumors, and Grade III meningiomas are usually rhabdoid or papillary subtypes.46,84 The genetic and molecular bases for the wide variety of biological behavior and histopathological subtypes that are encountered clinically remains

**Abbreviations used in this paper:** GWAS = genome-wide association studies; Hh = hedgehog; LOH = loss of heterozygosity; MMP = matrix metalloproteinase; SNP = single nucleotide polymorphism; TCGA = The Cancer Genome Atlas; TIMP = tissue inhibitor of metalloproteinase; Wnt = wingless.
to be determined. In comparison with primary intraaxial brain tumors such as gliomas, the genetics of meningiomas are poorly understood and relatively understudied.

A further understanding of the genes and signaling pathways associated with meningioma formation, growth, and transformation is likely to provide a foundation for future assessment of histological and clinical behavior and response to potential gene therapies and individualized treatment regimens. This information would be particularly constructive in evaluating potential treatment plans for cranial base meningiomas, the management of which is already challenging with currently available surgical and radiation treatment paradigms. The authors present a systematic review of the genes currently associated with the development, progression, and recurrence of meningiomas. The article then provides a brief discussion of potential future avenues of research and targeted therapeutic paradigms employing novel genetic techniques such as next-generation sequencing data analysis and high throughput genomics.

Genetics

Tumor Suppressor Genes

Tumor suppressor genes are those that encode proteins whose function is to inhibit the development of neoplastic processes. These genes generally follow the 2-hit hypothesis originally proposed by Knudson in 1971, in which both alleles for a particular tumor suppressor gene must be rendered ineffective for the cell to escape its normal regulatory processes. The most common tumor suppressor genes that have been associated with the development of meningiomas are NF2, DAL-1, and various tissue inhibitors of matrix metalloproteinases (TIMPs). In addition, the short arm of chromosome 9 has been shown to harbor several genes related to tumor suppression, including CDKN2A, CDKN2B, and p14ARF.

The NF2 gene is a tumor suppressor gene that is commonly involved in the development of meningiomas and other neoplasms of the central and peripheral nervous system (Table 1). Using linkage analysis, the NF2 gene has been localized to chromosome 22q; biallelic inactivation of the NF2 gene results in loss of the merlin protein and may be associated with the development of multiple meningiomas and schwannomas (Type II neurofibromatosis). Recent analysis of the merlin protein has demonstrated that its function in the protein 4.1 family as part of the actin cytoskeleton is intimately involved in the regulation of cell proliferation and cell growth in human tumor cells. Alterations in the merlin protein could therefore substantially affect cell shape and favor the appearance of more mesenchymal-like phenotypes rather than epitheloid-like ones. With respect to this histopathology, only 28.5% of meningothelial meningiomas show reduced NF2 expression in comparison with 86% of other meningioma subtypes. Based on the frequency with which meningothelial subtypes typically occur at the anterior skull base, Kros et al. used LOH analysis, karyotyping, and fluorescence in situ hybridization in 42 cases of sporadic meningiomas, demonstrating a significant correlation between tumor localization at the anterior skull base and an intact chromosome 22q.

DAL-1 (differentially expressed in adenocarcinoma of the lung) is another gene that is part of the protein 4.1 superfamily, and encodes the 4.1B protein. Loss of heterozygosity of DAL-1 at chromosome 18p11.3 was originally reported in 60% of sporadic meningiomas. While loss of DAL-1 was initially believed to be an early event in the tumorigenesis pathway of meningiomas, Nunes et al. reported that only 12 (19%) of 62 meningiomas analyzed as part of their study had LOH of DAL-1. Eleven of those 12 also had LOH of the NF2 gene, which suggested that DAL-1 may be involved in the progression rather than initiation of meningioma formation. They also found that 3 of 4 WHO Grade II meningiomas had monosomy of chromosome 18, while large deletions of 18p were found in only 2 of 13 WHO Grade I meningiomas.

Tissue inhibitors of metalloproteinases are proteins that regulate MMP activity and help to regulate cell proliferation, apoptosis, and angiogenesis. Both the TIMP1 and TIMP3 genes have been implicated in the aggressive behavior and invasion of meningiomas. Halaka et al. reported that invasive meningiomas produce significantly lower levels of TIMP-1 compared with noninvasive meningiomas. Because TIMP-1 functions to inhibit MMP-9

### TABLE 1: Meningioma tumor suppressor genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Product</th>
<th>Function</th>
<th>Meningioma Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF2</td>
<td>22q12.2</td>
<td>merlin protein</td>
<td>links cell membrane proteins to cytoskeleton</td>
<td>early event tumorigenesis</td>
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<tr>
<td>DAL-1</td>
<td>18p11.32</td>
<td>4.1B protein</td>
<td>links cell membrane proteins to cytoskeleton</td>
<td>early event tumorigenesis, progression</td>
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<td>TIMP1</td>
<td>Xp11.3-p11.23</td>
<td>metalloproteinase inhibitor 1</td>
<td>inhibits MMP-9 activity</td>
<td>meningioma invasion</td>
</tr>
<tr>
<td>TIMP3</td>
<td>22q12.1</td>
<td>metalloproteinase inhibitor 3</td>
<td>inhibits MMP-2 and MMP-9 activity</td>
<td>higher meningioma grade</td>
</tr>
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<td>9p21.3</td>
<td>p16 protein</td>
<td>cell cycle control</td>
<td>higher meningioma grade</td>
</tr>
<tr>
<td>CDKN2B</td>
<td>9p21.3</td>
<td>p15 protein</td>
<td>cell cycle control</td>
<td>higher meningioma grade</td>
</tr>
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<td>p14ARF</td>
<td>9p21.3</td>
<td>p14arf protein</td>
<td>cell cycle control</td>
<td>higher meningioma grade</td>
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<td>NDRG2</td>
<td>14q11.2</td>
<td>NDRG2 protein</td>
<td>possible cell growth &amp; apoptosis; N-myc target</td>
<td>higher meningioma grade, recurrence</td>
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<td>BAM22</td>
<td>22q12.2</td>
<td>beta adaptin</td>
<td>endocytosis</td>
<td>possible early event tumorigenesis</td>
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<td>DLC1</td>
<td>8p22-p21.3</td>
<td>DCL1 protein</td>
<td>rho GTPase activator</td>
<td>meningioma replication rate</td>
</tr>
</tbody>
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A review of the molecular genetics of meningiomas

activity, Mizoue et al.\textsuperscript{8} examined the role of the TIMP-1/MMP-9 balance using a cell immunoblot assay in 20 meningiomas. They found that reduced secretion of TIMP-1 was associated with an increase in the infiltrative capacity of meningiomas. Paek et al.\textsuperscript{65} compared 10 patients with confirmed microcystic meningiomas to a control group of 6 patients with meningothelial, atypical, or transition- al subtypes using immunohistochemistry and real-time reverse transcriptase polymerase chain reaction. They found that patients harboring microcystic meningiomas had relative mean values of TIMP-1 that were lower than their control group, suggesting that a TIMP-1/MM-9 imbalance was associated with the formation of microcysts. The role of TIMP-3 in the behavior of meningiomas was recently demonstrated by sequencing 50 meningiomas, of which 27 were WHO Grade I, 11 were WHO Grade II, and 12 were WHO Grade III.\textsuperscript{4} In this study, the authors demonstrated that TIMP3 inactivation via methylation was associated with a more aggressive and higher-grade meningioma phenotype; TIMP3 promoter hypermethylation was observed in 67\% of anaplastic meningiomas, compared with 22\% of atypical and 17\% of benign meningiomas.

Chromosome 9 is of particular importance in the development of malignant meningiomas because of 3 notable tumor suppressor genes located on its short arm. \textit{CDKN2A} and \textit{CDKN2B} are genes located at 9p21 that regulate cell cycle progression at the G1/S-phase checkpoint by inhibiting cyclin-cdk complexes. The \textit{p14ARF} gene is also located on 9p21 and produces a protein that blocks Mdm2-mediated degradation of p53.\textsuperscript{37} Boström et al.\textsuperscript{7} used comparative genomic hybridization and microsatellite analysis to show that a complete loss of 9p was found in 38\% of anaplastic meningiomas, 18\% of atypical meningiomas, and only 5\% of benign meningiomas. Furthermore, intact 9p chromosomes containing homozygous deletions of \textit{CDKN2A}, \textit{CDKN2B}, and \textit{p14ARF} were identified in 46\% of anaplastic meningiomas and 3\% of atypical meningiomas. The authors concluded that inactivation of these particular tumor suppressor genes with subsequent dysregulation of the G1/S-phase checkpoint was an important feature in the rapid growth and malignant behavior of anaplastic meningiomas. A recent analysis by Goutagny et al.\textsuperscript{31} using SNP arrays and gene sequencing showed that although no recurrent chromosomal alterations were identified as meningiomas progressed from Grade I to Grade II, the most frequent genomic alteration upon progression to Grade III was a loss of \textit{CDKN2A/CDKN2B} from 9p.

The N-Myc downstream-regulated gene 2 (\textit{NDRG2}) has also been shown to play an important role in the pathogenesis of meningiomas. Using expression profiling with quantitative PCR and immunohistochemistry, Lusis et al.\textsuperscript{45} demonstrated that \textit{NDRG2} was consistently downregulated in both anaplastic meningiomas, as well as a subset of atypical meningiomas exhibiting clinically aggressive behavior. Skiriute et al.\textsuperscript{83} also showed that \textit{NDRG2} was downregulated in recurrent meningiomas compared with those of primary benign origin in a group of 35 meningiomas. In addition, several other tumor suppressor candidate genes have been implicated in the development or progression of meningiomas. According to 1 study, \textit{BAM22}, a member of the beta-adaptin gene family, was found to be inactivated in 9 of 71 meningiomas.\textsuperscript{32} Although its exact function remains unknown, its role as a potential tumor suppressor may involve intracellular transport of proteins in the trans-Golgi network.\textsuperscript{78} By profiling RNA from 6 meningiomas and 4 dural specimens, the deleted in liver cancer 1 gene (\textit{DLC1}) was confirmed to be downregulated as well.\textsuperscript{94} Subsequent transfection of \textit{DLC1} complementary DNA into primary cultures of 5 meningiomas resulted in decreased replication in those specimens.

\textbf{Oncogenes}

Oncogenes are genes that are normally responsible for the growth and differentiation of cells. When oncogenes become mutated, however, they lose their ability to be inactivated and become tumor-inducing agents via autonomous stimulation. Mechanisms by which they gain this function include an absolute increase in the oncogene product or the acquisition of new tumorigenic properties. Although they are less likely to result in meningioma tumorigenesis than biallelic tumor suppressor loss, various oncogenes have been demonstrated to play a critical role in the formation of select meningiomas.

The overexpression of \textit{c-sis} has been detected in some meningiomas (Table 2).\textsuperscript{41,51,88} Although its exact function in the development of meningiomas has yet to be fully determined, its role in encoding the B-chain of platelet-derived growth factor-B suggests that it may stimulate cell growth and sustain maintenance of those tumors.\textsuperscript{29} \textit{C-myc} and \textit{c-fos} are nuclear transcription-regulating genes that are normally under the control of tumor suppressor genes; overexpression of these transcripts may contribute to growth factor autocrine loop signaling.\textsuperscript{15,37} The occurrence of the rare \textit{Ha-ras} and \textit{c-mos} alleles was found at a higher incidence in intracranial tumors including meningiomas compared with normal healthy individuals.\textsuperscript{9,97,98} Expression of both \textit{TP73} and \textit{bcl-2} has been correlated with higher meningioma grades as well.\textsuperscript{1,62}

Recently, the role of \textit{STAT3} was implicated in the pathogenesis of meningiomas.\textsuperscript{101} By using reverse transcriptase polymerase chain reaction, Western blot analysis, and immunohistochemistry, Zhang et al.\textsuperscript{101} showed that the frequency and expression of \textit{STAT3} was enhanced with increasing tumor grade compared with no expression in normal dural tissue. Constitutively active \textit{STAT3} was significantly associated with expression of vascular endothelial growth factor, a major inducer of tumor angiogenesis.\textsuperscript{26}

\textbf{Signaling Pathways}

Cell signaling pathways are networks of signal cascades that control various intracellular processes such as embryogenesis, cell differentiation, and cell proliferation. The mutation of any one gene product within the cascade can affect the signal transduction of the entire pathway, leading to the development of cancers and cancer stem cells.\textsuperscript{29} Two signaling pathways that have been heavily implicated in the progression of meningiomas are the Hh
and Wnt signaling pathways (Table 3). Furthermore, the notch, transforming growth factor beta, and insulin receptor signaling pathways have also been associated with meningioma progression.13,38,68,79,97

The Hh signaling pathway is intimately involved in cell proliferation and differentiation, angiogenesis, cellular matrix remodeling, and stem cell homeostasis.44,92 Laurendeau et al.44 investigated the role of Hh pathway deregulation in 36 meningiomas of varying grades. In comparison with normal tissue, Hh pathway activators including the SMO, GLI1, GLI2, GLIS2, and FOXM1 mRNA were found to be overexpressed in both aggressive and benign meningiomas. The SPP1 and IGF2 genes, known to be involved in cell proliferation and migration, were found to be overexpressed in the more aggressive WHO Grade II and III tumors. PTCH1, an Hh pathway ligand receptor, had previously been described as a tumor suppressor in sporadic meningiomas in patients with basal cell nevus syndrome.98 Laurendeau et al.44 found PTCH1 mRNA levels were lower in Grade I meningiomas compared with their Grade II or III counterparts, suggesting that this gene may be involved in the initial tumorigenesis of meningiomas, but is not likely to play a significant role in the progression to more aggressive lesions.

The Wnt signaling pathway has also been implicated in meningioma progression. The tumor suppressor gene CDH1 is an important modulator of the Wnt signaling pathway,52 and has been shown to be downregulated in clinically aggressive meningiomas, including those invading the pia mater and skull.67,82,102 Intact CDH1 expression has also been significantly associated with lower rates of postoperative meningioma recurrence.102 The breakpoint cluster region (BCR) gene has been shown to be a negative regulator of the Wnt pathway.39,78 Recent LOH analysis of the BCR gene demonstrated significantly lower expression in 149 meningiomas, suggesting it is likely to be a tumor suppressor candidate involved in meningioma pathogenesis.96 SFRP1 is part of the gene family of secreted frizzled-related proteins (SFRPs) that are able to downregulate Wnt signaling. Pérez-Magán et al.68 used gene expression profiling in 112 original and recurrent meningioma samples to demonstrate evidence of SFRP1 downregulation in patients with meningioma recurrence compared with primary tumors.

**Discussion**

Meningiomas are among the most common of all primary intracranial tumors, with approximately 25% arising at the skull base.7 The management of meningiomas in this location is challenging due to the proximity of critical vasculature and neuronal structures including the circle of Willis, arterial perforators, the brainstem,
A review of the molecular genetics of meningiomas

cranial nerves, and optic pathways. Although gross-total microscopic resection (Simpson Grade I) of meningiomas may predict improved clinical outcomes, aggressive operative resection of locally invasive tumors can lead to significant morbidity and death.\textsuperscript{3,12,51,64} A more common treatment paradigm currently relies on aggressive surgical tumor debulking followed by stereotactic radiosurgery to regions of residual tumor. Stereotactic radiosurgery, with or without subtotal resection, has been reported to be an extremely viable primary or secondary option, with long-term tumor control rates ranging from 82% to 98%.\textsuperscript{2,36,59,100} On the other hand, adjunctive radiation or radiosurgery has also been associated with a variety of potential complications, including radiation necrosis, peritumoral edema, visual loss, hypopituitarism, and death.\textsuperscript{19,28} With the advent of new radiosurgical techniques, the treatment of meningiomas becomes more precise and the identification and characterization of selected genes and their respective roles in meningioma formation and progression.

Little information exists as to why a subset of meningiomas become aggressive and/or invasive. To date, only 2 gene expression studies have been performed to address this question. These investigations used old microarray platforms that interrogate few genes, with inconsistent results.\textsuperscript{21,97} The following sections address high throughput technologies that can more quickly and accurately analyze whole-genome samples, and therefore potentially identify new genetic associations with meningioma development, progression, and invasiveness.

Genome-Wide Association Studies

The genome-wide association methodology has been made possible with the advent of high-density SNP genotyping arrays and the knowledge acquired from the international HapMap project.\textsuperscript{35} The HapMap was designed to create a genome-wide database of patterns of human genetic variation, with the expectation that these patterns would be useful for genetic association studies of common diseases.\textsuperscript{48} High-throughput SNP arrays allow the interrogation of hundreds of thousands of SNPs in the human genome, chosen to capture most of the human genetic variation based on the HapMap project, and then identify specific genomic regions or loci where there is a difference of patterns of genetic variation between cases and control subjects.\textsuperscript{34} Compared with traditional genetic linkage or candidate gene association studies, GWAS provide a powerful approach to identify common, low-penetrance disease loci by assaying the genome in an unbiased and hypothesis-free manner. As a result, many detected associations provide new insights into pathophysiology, suggesting previously unsuspected etiologic pathways for common diseases that can be used in identifying new therapeutic targets and developing targeted interventions.

Large-scale GWAS have already been used in a diverse array of common and complex diseases, including various cancers such as breast, prostate, colorectal, and lung, as well as melanoma, leukemia, and neuroblastoma.\textsuperscript{22,91} These studies identified more than a few dozen susceptibility loci, confirming that susceptibility to these cancers is polygenic. Additionally, many of these loci were detected at low power, indicating that many additional disease loci are likely to be detected with larger studies. Furthermore, the loci were not previously suspected to be related to carcinogenesis, and some of them point to altogether new disease mechanisms. As of January 2011, meningiomas have not been investigated by GWAS, suggesting that future genomic studies on meningiomas may benefit from this approach. Meningiomas are an interesting candidate for this type of analysis, as most are benign. However, the small subset that display malignant phenotypes and aggressive clinical behavior may help elucidate a mechanism of malignant transformation in CNS tumors.

High-Throughput Sequencing

A new generation of sequencing platforms that pro-
duce high-throughput genome or transcriptome sequence data has now made it possible for individual laboratories to generate enormous amounts of sequence data. High-throughput sequencing allows simultaneous examination of complete genomes of the same species, revealing more and more details about how individual genomes as well as individual aspects of their regulation differ from each other. The inclusion of transcriptome sequencing, chromatin-immunoprecipitation sequencing, and epigenetic analysis (DNA methylation or histone modification chromatin immunoprecipitation) adds unprecedented resolution, enabling the detection of even subtle differences such as alternative splicing of individual exons, or base-level binding preferences. There is no doubt that the upcoming mountains of sequencing data will advance functional genomics studies, human disease studies, upcoming mountains of sequencing data will advance functional genomics studies, and population genetic studies, metagenomics, clinical diagnosis, as well as other areas of biomedical importance. Furthermore, high-throughput sequencing data may also provides the foundation for new strategies in systems biology and personalized medicine.

Several cancers have been investigated by high-throughput, whole-genome sequencing approaches, and results from these studies provide important insights into the genetics of cancer susceptibility, formation, and progression. For example, by sequencing the genomes of a cancer (primary tumor or cell lines) and a paired lymphoblastoid cell line from the same person, it is possible to infer the comprehensive catalog of somatic mutations from an individual cancer. To date, several cancer types have been subjected to large-scale whole-genome sequencing. These initial findings illustrate the potential for next-generation sequencing to provide unprecedented insights into mutational processes, cellular repair pathways, and gene networks associated with cancer.

The Cancer Genome Atlas is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, especially large-scale genome sequencing. TCGA is a joint effort of the National Cancer Institute and the National Human Genome Research Institute, 2 of the 27 Institutes and Centers of the NIH, US Department of Health and Human Services. The first successfully completed pilot project from TCGA involved glioblastoma, which provided new insights into the roles of ERBB2, NF1, and TP53, uncovered frequent mutations of the PI3 kinase regulatory subunit gene PIK3R1, and facilitated a network view of the pathways altered in the disease development. Currently, TCGA is expanding its efforts to aggressively study 20 or more additional cancers and yield a comprehensive, rigorous, and publicly accessible data set that will improve our ability to diagnose, treat, and prevent cancer. Among the CNS cancers, however, only glioblastoma was selected to be studied by TCGA. Therefore, although we may glean some general knowledge from TCGA on the genetics of brain tumor development, the results from TCGA will not directly and specifically advance our understanding of meningioma genetics. Additional efforts will be necessary to identify genetic risk factors and oncogenes or tumor suppressors that are specifically activated or inactivated in meningio-

mas, especially in more clinically aggressive (Grade II/III) subtypes.

Technologies that can quickly and accurately analyze whole-genome samples for genetic variations can be applied to meningioma samples or the serum of patients harboring these tumors. The identification of new genetic associations may help develop diagnostic or prognostic tools that can determine susceptibility to invasive or malignant meningiomas at an early stage, potentially laying the groundwork for customized treatment strategies.

Conclusions

Meningiomas of the cranial base are typically histologically benign tumors but may cause significant treatment challenges due to invasion of critical neurovascular structures, morbidity associated with aggressive resection, local tumor recurrence and/or progression, and toxicity from adjunctive radiation-based treatments. Advances in our understanding of the genetic abnormalities in meningioma pathogenesis have provided substantial insights into the molecular biology of these tumors, and may pave the way for highly selective future therapies with an unprecedented safety profile. Continued work in this area would provide genetic assessment tools to complement current systems for histological and immunochemical grading. Identification of dysregulated genetic targets would also offer data that would serve as a foundation for the development of individualized molecular therapies. The use of genome-wide association studies and high-throughput genomics may be able to rapidly detect additional genetic associations with meningioma growth and development.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Pham, Zada, Mack. Acquisition of data: Pham, Zada, Mosich, Mack. Analysis and interpretation of data: Pham, Zada, Mosich, Wang, Mack. Drafting the article: Pham, Zada, Mosich, Wang, Mack. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors.

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A review of the molecular genetics of meningiomas

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A review of the molecular genetics of meningiomas


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