Molecular genetics of meningiomas

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In this article the authors provide a brief description of the current understanding of meningioma genetics. Chromosome 22 abnormalities, especially in the Neurofibromatosis Type 2 (NF2) gene, have been associated with meningioma development. Loss of heterozygosity of chromosome 22 occurs in approximately 60% of meningiomas; however, loss of NF2 gene function occurs in only one third of these lesions. This discrepancy supports the theory that a second tumor suppressor gene exists on chromosome 22, and the authors introduce several possible gene candidates, including BAM22, LARGE, INI1, and MN1 genes. Deletions of 1p have also been shown to correlate with meningioma progression. The genetic similarities and differences among sporadic, NF2-associated, pediatric, and radiation-induced meningiomas are discussed, with the observation that the nonsporadic meningiomas have a higher incidence of multiple chromosomal abnormalities at presentation. Ultimately, a better understanding of the molecular pathways of meningioma tumorigenesis will lead to new, successful treatments.

KEY WORDS • meningioma • neurofibromatosis Type 2 gene • merlin • genetics

The study of chromosomal alterations in tumors is an important tool in identifying genes involved in tumorigenesis and tumor progression. Researchers studying the chromosomal abnormalities in meningiomas have identified chromosome 22q, focusing on the NF2 gene, as responsible for the tumorigenesis in roughly one third to one half of meningiomas.

MENINGIOMAS

Normally slow-growing and benign tumors, meningiomas arise from the central nervous system meninges. Specialized meningothelial cells called arachnoid cap cells are the source of meningiomas (Fig. 1). These cells are most common within the arachnoid villi but may be present throughout the craniospinal arachnoid space.

Prevalence of the Lesions

Meningiomas account for approximately 20% of all primary adult intracranial tumors. They are more common in women (2:1) and generally occur in patients who are between 50 and 60 years old. As shown in Table 1, meningiomas are graded as benign (~ 91% of lesions), atypical (5%), and anaplastic/malignant (4%). The grading of meningiomas takes into account both the tumor subtypes known to have a higher rate of recurrence and the specific histological features that implicate a more aggressive biology. Although most meningiomas can now be removed safely, their intrinsic biology is still the main determinant of overall outcome.

Genetic Alterations

Meningiomas were among the first solid tumors analyzed for genetic abnormalities. Giemsa staining, FISH, comparative genomic hybridization, and spectral karyotyping have been used to elucidate the most common chromosomal abnormalities associated with meningiomas. Abnormalities in the 22q locus have been identified as the most frequent, and approximately 50% of sporadic meningiomas exhibit a chromosome 22q abnormality. Meningiomas occurring in the setting of NF2 always exhibit chromosome 22q abnormalities. Although familial meningiomas are uncommon, they are also usually associated with NF2. Pediatric or radiation-induced meningiomas, on the other hand, tend to have a complex karyotype (that is, multiple chromosomal abnormalities). Chromosome 22 abnormalities (that is, LOH or partial deletion of 22q) are the most frequent ones in benign, atypical, and anaplastic meningiomas (Figs. 2 and 3A). Chromosome 1 abnormalities have been implicated in tumor progression and higher-grade meningiomas. In general, karyotypic abnormalities are more extensive in atypical and anaplastic meningiomas (Fig. 2). In addition to 1q loss, chromosome aberrations associated with higher-grade meningiomas include those found in 6q, 10p, 10q, 14q, and 18q (Fig. 3B). Immunohistochemically, staining for progesterone receptors and the MIB-1 antibody (Ki-67) can aid in differentiating between aggressive tumors (Fig. 2). Progesterone receptor loss correlates with higher meningioma tumor grades, and a higher MIB-1 labeling index has consistently correlated with meningioma recurrence.
Cytogenetic and molecular abnormalities, with deletion mapping showing interstitial deletions not including the NF2 gene on chromosome 22. Interestingly, meningioma subtypes show differences in their frequency of NF2 gene mutation. The most common meningioma subtypes are fibrous, transitional, and meningothelial (Table 1). Although these World Health Organization Grade I subtypes show no difference in their recurrence rates, there are differences in their rates of NF2 mutations. Fibroblastic and transitional meningiomas exhibit NF2 gene mutations in 70 to 80% of tumors, whereas the meningothelial subtype shows NF2 mutations only 25% of the time, suggesting that cytogenetic differences in the tumorigenesis of meningioma subtypes may exist.\(^{39}\) In both atypical and anaplastic meningiomas the frequency of NF2 gene mutations is approximately 70%, a frequency closely matching the mutation rate in fibroblastic and transitional meningiomas.\(^{41}\) Therefore, NF2 gene mutations are probably involved with tumorigenesis but not tumor progression. Recent in vivo experiments in mice support this theory. Biallelic NF2 inactivation of mouse leptomeningeal cells by using Cre-mediated molecular techniques resulted in the development of meningiomas in approximately one third of mice studied.\(^{34}\) This supports the proposition that merlin loss alone is not sufficient for meningioma development.

**The \(BAM22\) Gene.** The \(BAM22\) gene on chromosome 22q12 is a member of the human \(\beta\)-adaptin gene family. The \(BAM22\) gene was cloned from a homozygous deletion on one meningioma.\(^{65}\) Further analysis revealed that inactivation of the \(BAM22\) gene occurred in nine (12.7%) of 71 sporadic meningiomas, with both the \(BAM22\) and NF2 genes affected in two lesions. Although the function of the \(BAM22\) protein is unknown, its similarity to members of the \(\beta\)-adaptin family indicates that it may have a role in intracellular transport of proteins in the trans-Golgi network.

**The \(LARGE\) Gene.** The \(LARGE\) gene was identified in the 22q12.3-q13.1 region as a possible meningioma tumor suppressor gene candidate by applying LOH studies. Gene cloning of this segment characterized a protein that is structurally similar to members of the N-acetylglucosaminyltransferase family. Glycosyltransferase enzymes synthesize glycoprotein and glycosphingolipid sugar chains within different compartments of the Golgi network. Evidence of a role for glycosyltransferase enzymes in tumorigenesis exists (for example, various growth factor receptors appear to be regulated by gangliosides).\(^{66}\) Specifically, meningiomas

### Table 1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Meningioma Types</th>
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<tr>
<td>I, typical</td>
<td>meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, metaplastic</td>
</tr>
<tr>
<td>II, atypical</td>
<td>chordoid, clear cell</td>
</tr>
<tr>
<td>III, anaplastic</td>
<td>papillary, rhabdoid</td>
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* Based on World Health Organization classification updates by Louis, et al.
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tumor samples can be divided into ganglioside GD3-normal and GD3-rich groups. Furthermore, monosomy 22 correlates with GD3 content, and meningiomas with monosomy 22 show a greater likelihood of recurrence. Therefore, the LARGE gene is implicated in meningioma tumorigenesis because of its location on chromosome 22, but no evidence exists to implicate this gene directly.

The MN1 Gene. Analysis of a patient with multiple meningiomas revealed a missing region on chromosome 22 that encodes for the MN1 gene. Further analysis of this tumor showed an absence of the MN1 protein with an intact NF2 gene, suggesting a possible role for the MN1 protein in tumor suppression. The function of the MN1 protein is unknown, although based on its amino acid structure, it most likely plays a role in transcription.

The INI1 Gene. The INI1 gene is located on chromosome

Fig. 2. Proposed schematic of meningioma tumor progression. Production of vascular endothelial growth factor (VEGF) is associated with peritumoral edema. Loss of chromosome 1p is a decisive step in meningioma progression to higher WHO grade. Immunohistochemically, higher-grade tumors are associated with a decrease in progesterone receptor staining and an increase in MIB-1 nuclear staining. (Reprinted with permission from Ragel and Jensen).

Fig. 3. A: Representative Giemsa-band karyotype of a benign meningioma exhibiting the classic finding of monosomy 22 (that is, LOH of chromosome 22) (arrow). B: Representative Giemsa-band karyotype of a malignant meningioma exhibiting multiple chromosomal abnormalities (that is, a complex karyotype), including LOH of chromosomes 1 and 17; multiple copies of 7, 9, and 20; and extra chromosomal material of 2 and 6 (arrows).
22q and was analyzed for mutations in 126 meningiomas. The analysis showed that four (3%) of 126 exhibited an identical mutation in exon 9. The function of the INI1 protein is unknown, but its structure suggests that it functions in transcriptional regulation by remodeling chromatin in an adenosine 5’-triphosphate–dependent fashion. 76

**CHROMOSOME 1**

Deletions of the short arm of chromosome 1 are the second most frequent alteration detected on cytogenetic analysis of meningiomas (after chromosome 22 anomalies). 9 According to FISH studies showing monosomy 1p in 70% of atypical and almost 100% of anaplastic meningiomas, this indicates a correlation between loss of chromosome 1p and meningioma progression. 31, 55, 84, 106 Loss of 1p also correlates with tumor recurrence; the rate of recurrence is 30% with loss of 1p but only 4.3% when 1p is retained. 31 It is unknown which gene on the 1p arm results in the clinical effects on tumor, but research has identified alkaline phosphatase as a possible tumor suppressor 27, 32 whose location on chromosome 1p (1p34–1p36.1) and loss of function is implicated in radiation-induced meningiomas. 60 Other rare molecular abnormalities include PTEN gene deletion (10q23), CDKN2C gene deletion (1p32), and RPS6KB1 gene amplification (17q23). 14, 16, 17, 64 No specific tumor suppressor genes associated with meningiomas have been elucidated on chromosome 7. Nevertheless, two growth factors often implicated in meningioma growth and development, epidermal growth factor receptor and insulin-like growth factor–II are located on chromosome 7. 12, 90 Cytogenetic alterations can also include changes in chromosome number. Sixty percent of meningiomas have been found to be hypodiploid, 33% diploid, 4.5% hyperdiploid, and 2.5% hypotriploid. 52 Complex karyotypes with hypodiploidy, structural rearrangements such as ring chromosomes, dicentrics, double minutes, and association between satellites seem to be associated with aggressive tumor characteristics. 46, 49 Identification of a microsatellite instability phenotype in meningiomas has also been described. 69

**ONCOGENE EXPRESSION IN MENINGIOMAS**

Several studies have shown increased expression of oncogenes in meningioma tumorigenesis. Human meningiomas are marked by enhanced expression of the c-sis and c-myc oncogenes. 13, 36, 62 Similarly, the rare Ha-ras and c-mos oncogenes have a higher activation in individuals with intracranial tumors, including meningiomas, than in healthy patients. 18, 23 It has been proposed that the nuclear transcription-regulating genes c-myc and c-fos are normally under the control of tumor suppressor genes, which are lost in meningiomas. 23 This is supported by the greater than 70% occurrence of protooncogene messenger RNA expression for c-myc and c-fos in meningiomas. Mutation in the tumor suppressor gene TP53 has been considered a reliable marker for malignant transformation of meningioma, 57 and the bcl-2 protooncogene is also correlated with higher-grade...
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Meningiomas. Furthermore, expression of the RO51 onco-
gene for tyrosine receptor kinase is common in meningi-
omas, which indicates that it may play a role in the origin
of these tumors. Although no single oncogene has been
directly implicated in meningioma development, it is pos-
sible that either one or multiple oncogenes mentioned ear-
lier will contribute to this process.

MENINGIOMA CLONALITY

Evidence to support the idea that meningiomas are mon-
oclonal in origin is based on X-chromosome inactivation
studies and the observation that most meningiomas have
only a single NF2 gene mutation. Polymerase chain reac-
tion evidence suggests, however, that a small number of
meningiomas may be polyclonal in origin. In regard to
multiple meningiomas, X-chromosomal analysis and muta-
tional NF2 gene analysis suggest that multiple tumors are
monoclonal in origin, supporting dural dissemination
through the subarachnoid space. Nevertheless, approxi-
mately 50% of multiple meningiomas exhibit different NF2
gene mutations, indicating independent tumorigenesis ori-
gins.

SPECIAL SITUATION MENINGIOMAS

The NF2-Associated Meningiomas

The NF2-associated meningiomas comprise 1% of all
these lesions, but within the population of patients with
NF2, meningiomas are the second most frequent tumor, af-
after vestibular schwannomas. The incidence of meningiomas
within this population of patients is between 53 and 83%. Higher proliferative indices and histological grades have
been reported by some, whereas others have stated that
NF2-associated meningiomas are no more aggressive than
sporadic tumors. In general, childhood meningiomas are
more likely to be associated with NF2, warranting careful
examination for NF2 stigmata. Loss of function of the NF2
gene is generally thought to be the major contributing factor
to meningioma development in these patients, as described
earlier.

Pediatric Meningiomas

Pediatric meningiomas represent less than 2% of all me-
ningiomas and less than 3% of childhood brain tumors, and
occur most commonly in the second decade of life. Unique
features of pediatric meningiomas include a higher inci-
dence of infraventricular locations, cystic changes on imag-
ing, lack of dural attachment, and lack of female predi-
lection. Genetically, when compared with adult sporadic
meningiomas, pediatric meningiomas have a higher fre-
cuency of NF2 gene mutations as well as 1p and 14q dele-
tions. In one study structural abnormalities of chro-
mosome 6 were identified in four of eight cases. Finally,
pediatric meningiomas are reported to display more aggres-
sive characteristics.

Radiation-Induced Meningiomas

A radiation-induced meningioma is one that occurs with-
in a previously irradiated field, is histologically different
from the original tumor, appears after a period of time has
elapsed since irradiation (usually ≥ 5 years), does not occur in
a patient with a family history of phakomatosis, and was
not present before radiation therapy was administered. Com-
pared with sporadic meningiomas, radiation-induced
lesions occur in patients of a young age at presentation and
have a higher incidence of multiple tumors, a higher malig-
nancy rate, and a higher recurrence rate after treatment with
either surgery or radiation. Although approximately two
thirds of sporadic meningiomas occur in women, radiation-
induced meningiomas appear to have an equal male/female
ratio or even a male predominance. Most patients with
postradiation meningiomas were exposed during childhood
(for example, cranial radiation therapy for the treatment of
leukemia, lymphoma, or craniopharyngioma). For ex-
ample, in Israel during the 1950s, it was common practice
to expose children to low-dose radiation to treat scalp linea
capitis, resulting in a significantly increased incidence of
meningiomas once these patients became adults. The es-
timated relative risk for development of a meningioma is
10-fold greater after exposure to low-dose radiation therapy
in childhood. The mean latency period for radiation-in-
duced meningiomas is between 11 and 43 years after expo-
sure. Radiation-induced meningiomas usually exhibit a com-
plex karyotype at presentation (that is, the presence of multiple chromosomal arrangements).5,6 Unlike sporadic meningiomas, in radiation-induced lesions NF2 gene inactivation and loss of chromosome 22 are less frequent, with LOH in chromosome 22 occurring in 29 to 56% of cases, compared with 43 to 80% of tumors displaying a loss or translocation of 22q.5,21 The most frequent cytogenetic abnormalities are found on chromosomes 1p (57-89%), 6q (67%), and 22 (29-58%).5,6 A study of six radiation-induced meningiomas discovered the same chromosomal abnormality on the region of 1p13, implicating an unknown gene in this region in the pathogenesis of radiation-induced meningiomas.6

CONCLUSIONS
Chromosomal abnormalities have been detected along with meningioma development in numerous studies using Giemsa staining, FISH, comparative genomic hybridization, and spectral karyotyping techniques. The LOH of chromosome 22 occurs in approximately 60% of meningiomas and loss of NF2 gene function is found in approximately 33%, but abnormalities in other chromosomes and genes have also been implicated. Sporadic, NF2-associated, pediatric, and radiation-induced meningiomas are recognized as potentially having various genetic differences. Further research into how meningioma tumorigenesis and development are affected by the numerous reported irregularities will be necessary to exploit successful new treatments.

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References

B. T. Ragel and R. L. Jensen

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76. Schmitz U, Mueller W, Weber M, et al: INI1 mutations in me-

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