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 *MNI* 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.⁶ Specialized meningotheial 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%).^{28,51} 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.¹⁵ 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.^{25,26,53,65} Meningiomas occurring in the setting of NF2 always exhibit chromosome 22q abnormalities. Although familial meningiomas are uncommon, they are also usually associated with NF2.^{13,29} 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).^{7,46} 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).^{4,5,46,63} In addition to 1q loss, chromosome aberrations associated with higher-grade meningiomas include those found in 6q, 10p, 10q, 14q, and 18q (Fig. 3B).^{14,16,77,80} 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.⁷⁰

Abbreviations used in this paper: FISH = fluorescence in situ hybridization; LOH = loss of heterozygosity; NF2 = neurofibromatosis Type 2.

Fig. 1. Photomicrograph of arachnoid villi showing arachnoid cap cells (arrow). H & E, original magnification $\times 40$. (Modified with permission from Ragel and Jensen).

CHROMOSOME 22

Overview of the Chromosome

The link between abnormalities in the long arm of chromosome 22 (that is, 22q) and meningiomas was first suspected in patients with NF2. The hallmark of this disease is bilateral acoustic schwannomas as well as meningiomas (occurring in $\sim 50\%$ of patients).²⁷ Cytogenetic and molecular studies have culminated in the discovery of the *NF2* tumor suppressor gene, located on chromosome 22q12.1, and its protein product (that is, schwannomin or merlin).^{11,26,42,47,79,89,91} An NF2-associated meningioma is relatively rare, however, because the majority of these lesions occur as isolated, sporadic tumors. Nevertheless, deletions of chromosome 22 are found in all NF2-associated meningiomas, and in 54 to 78% of sporadic meningiomas.^{8,19,20,25,46,53,54,56,59,79,89,92-94}

Further analysis of the *NF2* gene in sporadic meningiomas reveals that approximately one third to one half of these tumors have an inactivating mutation, often accompanied by loss of the other allele.^{42,46,73} Thus, the frequency of LOH of chromosome 22 exceeds that of *NF2* gene abnormalities, with deletion mapping showing interstitial deletions not including the *NF2* locus in some meningiomas.⁷³ This discrepancy between the higher incidence of chromosome 22 LOH and the lower frequency of *NF2* gene mutations has led to the search for a second tumor suppressor gene on 22q, in proximity to but distinct from the *NF2* gene.^{2,20,26,43,44,68,72,73,78} These studies have resulted in other possible candidates, including the *BAM22*, *LARGE*, *MN1*, and *IN11* genes (Table 2 and Fig. 4).^{45,65,66,76}

Chromosome 22q

The *NF2* Gene. The *NF2* gene codes for the schwannomin/merlin protein (also known as moesin-, ezrin-, radixin-like protein), which is a part of the band 4.1 families of

cytoskeleton-associated proteins (Table 2). Small insertions or deletions of this gene produce nonsense mutations resulting in a nonfunctional merlin protein.⁵⁰ Loss of the merlin protein results in decreased cell adhesion and tumorigenesis.^{24,32} A reduced expression of schwannomin/merlin has been demonstrated in sporadic meningiomas.⁴¹ 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.⁸⁹ 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 β -adaplin 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 β -adaplin 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*-acetylglucosaminyl-transferase 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, meningioma

TABLE 1
Pathological classification of meningiomas*

Grade	Meningioma Types
I, typical	meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, metaplastic
II, atypical	chordoid, clear cell
III, anaplastic	papillary, rhabdoid

* Based on World Health Organization classification updates by Louis, et al.

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).

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 me-

ningiomas revealed a missing region on chromosome 22 that encodes for the *MN1* gene.⁴⁵ 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. 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).

TABLE 2

Meningioma chromosomal abnormalities and their corresponding genes, proteins, and protein function

Chromosome	Gene(s)	Protein(s)	Function(s)	Notes
22q12.1	<i>NF2</i>	merlin/ schwannomin	regulation of cell growth & motility	merlin protein structurally similar to protein 4.1 (DAL-1) superfamily
22q12	<i>β-adaptin (BAM22)</i>	BAM22	intracellular transport of receptor–ligand complexes	Beta-Adaptin-Meningioma-chromosome 22
22q12.3-q13.1	<i>LARGE</i>	LARGE	synthesis of glycoprotein & glycosphingolipid sugar chains	humanlike acetylglucosaminyltransferase
22q11	<i>MNI</i>	MN1	transcription regulation	
22q	<i>INI1 (SMARCB1/ hSNF5)</i>	INI1	transcription regulation	
1p	der(1)(1qter→ 1p11–22q12→22pter)	unknown	unknown	1p13 implicated in radiation-induced meningiomas
9p21	<i>CDKN2A (p16^{INK4a})</i> , <i>CDKN2B (p15^{INK4b})</i> , <i>p14^{ARF}</i>		cell-cycle checkpoint proteins	
18p11.3	<i>DAL-1</i>		cytoskeletal protein	member of 4.1 protein superfamily

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.^{31,55,84,92} 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.³⁷ 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^{37,92} whose location on chromosome 1p (1p34→1p36.1) and loss of function is correlated with higher-grade meningiomas.

OTHER CHROMOSOMAL ABNORMALITIES IDENTIFIED IN MENINGIOMAS

Many cytogenetic alterations are associated with meningioma progression and typical or anaplastic histology, including the presence of dicentric or ring chromosomes; losses of chromosome arms 1p, 6q, 7, 9p, 10, 14q, 18q, 19, or 20; as well as gains/amplifications of 1q, 9q, 12q, 15q, 17q, or 20q (Figs. 2 and 3A).^{3,14,16,17,35,39,42,58,67,77,80,85,88} The mechanisms by which these losses and gains aid tumor progression are unknown, although several chromosomes and genes appear to have specific associations with benign, atypical, and anaplastic meningioma grades. Benign meningiomas are more liable to have 14q deletions.¹⁶

Approximately two thirds of anaplastic meningiomas exhibit altered cell-cycle checkpoint tumor suppressor genes located on chromosome 9p, including *CDKN2A (p16^{INK4a})*, *p14^{ARF}*, and *CDKN2B (p15^{INK4b})*.^{14,57} Further evidence impli-

cating *CDKN2A* deletions in meningioma pathogenesis comes from the significantly shorter survival times of patients with this deletion, compared with those of patients without it.⁶⁰ The membrane-associated 4.1 protein family *DAL-1* (differently expressed in adenocarcinoma of the lung), located on chromosome 18p11.3, has been suggested as a tumor suppressor.^{30,61}

Other rare molecular abnormalities include *PTEN* gene deletion (10q23), *CDKN2C* gene deletion (1p32), and *RPS 6KB1* 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.^{48,49} 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.^{13,36,82} 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.²² 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,⁸⁷ and the *bcl-2* protooncogene is also correlated with higher-grade

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meningiomas.¹ Furthermore, expression of the *ROS1* oncogene for tyrosine receptor kinase is common in meningiomas, which indicates that it may play a role in the origin of these tumors.⁹⁶ Although no single oncogene has been directly implicated in meningioma development, it is possible that either one or multiple oncogenes mentioned earlier will contribute to this process.

MENINGIOMA CLONALITY

Evidence to support the idea that meningiomas are monoclonal in origin is based on X-chromosome inactivation studies and the observation that most meningiomas have only a single *NF2* gene mutation.³³ Polymerase chain reaction evidence suggests, however, that a small number of meningiomas may be polyclonal in origin.⁹⁷ In regard to multiple meningiomas, X-chromosomal analysis and mutational *NF2* gene analysis suggest that multiple tumors are monoclonal in origin,^{40,83} supporting dural dissemination through the subarachnoid space.⁸⁶ Nevertheless, approximately 50% of multiple meningiomas exhibit different *NF2* gene mutations, indicating independent tumorigenesis origins.⁸³

SPECIAL SITUATION MENINGIOMAS

The NF2-Associated Meningiomas

The NF2-associated meningiomas comprise 1% of all these lesions,⁶² but within the population of patients with NF2, meningiomas are the second most frequent tumor, after vestibular schwannomas. The incidence of meningiomas within this population of patients is between 53 and 83%.²⁷ 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.⁶³ 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 meningiomas and less than 3% of childhood brain tumors, and occur most commonly in the second decade of life.⁶² Unique features of pediatric meningiomas include a higher incidence of intraventricular locations, cystic changes on imaging, lack of dural attachment, and lack of female predilection.^{38,62} Genetically, when compared with adult sporadic meningiomas, pediatric meningiomas have a higher frequency of *NF2* gene mutations as well as 1p and 14q deletions.^{10,62,81} In one study structural abnormalities of chromosome 6 were identified in four of eight cases.¹⁰ Finally, pediatric meningiomas are reported to display more aggressive characteristics.^{10,62}

Radiation-Induced Meningiomas

A radiation-induced meningioma is one that occurs within a previously irradiated field, is histologically different from the original tumor, appears after a period of time has

Fig. 4. Ideogram of the short (p) and long (q) arms of chromosome 22. Arrows indicate locations of proposed meningioma tumor suppressor genes: *MN1*, *INI1*, *BAM22*, *NF2*, and *LARGE*.

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.⁹⁵ Compared 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 malignancy rate, and a higher recurrence rate after treatment with either surgery or radiation.⁴ 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.⁵ Most patients with postradiation meningiomas were exposed during childhood (for example, cranial radiation therapy for the treatment of leukemia, lymphoma, or craniopharyngioma).^{5,74,75,83} For example, in Israel during the 1950s, it was common practice to expose children to low-dose radiation to treat scalp tinea capitis, resulting in a significantly increased incidence of meningiomas once these patients became adults.^{71,74} The estimated relative risk for development of a meningioma is 10-fold greater after exposure to low-dose radiation therapy in childhood.⁷⁴ The mean latency period for radiation-induced meningiomas is between 11 and 43 years after exposure.^{5,95}

Radiation-induced meningiomas usually exhibit a com-

plex karyotype at presentation (that is, the presence of multiple chromosomal arrangements).^{5,95} 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%).^{5,95} 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.⁹⁵

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.

Acknowledgment

We thank Kristin Kraus for her editorial assistance in preparing this paper.

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Manuscript received September 15, 2005.

Accepted in final form October 12, 2005.

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