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# A Review of the Histologic, Genetic and Molecular Characteristics of Meningioma Pathogenesis and Progression

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**ABSTRACT:**

Meningiomas are the most common intracranial tumor in humans. The heterogeneity of these tumors lends difficulty to the genetic, epigenetic, and molecular changes that occur in meningioma pathogenesis, progression, and recurrence. Current de facto classification schemes are based on histologic evaluation of tumor specimens and do not consider molecular markers or other newer modalities. In this paper, we review the major genetic, epigenetic, and molecular changes that have been associated with the oncogenesis and progression of meningiomas. We pay special attention to those changes associated with recurrence and higher grade tumors. Finally, we comment on the challenges and potential for future therapies of these tumors.

**Running Title:** Review of meningioma genetics

**Keywords:** meningioma, review, genetics, pathogenesis, progression, molecular

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Meningiomas are the most common primary intracranial neoplasm, comprising 35.8% of CNS tumors. The annual incidence of these tumors is 7.44 cases per 100,000 persons; the incidence increases with age, increasing dramatically after age 65[1]. Females are more than twice as likely to develop a meningioma than males[2]. Though they are typically slow-growing and non-invasive, meningiomas commonly compress adjacent structures, causing neurologic signs and symptoms which often lead to patients seeking treatment. Risk of recurrence is increased with younger age at diagnosis, subtotal resection, increasing histologic grade, specific histologic subtypes, high proliferative index, and brain infiltration[2-4].

The neoplastic origin is thought to be of arachnoid cap cells from the outermost layer of the arachnoid. This is based on observation of functional and cytologic similarities between these and meningioma cells, especially considering the changes arachnoid cap cells undergo with age: i.e., increased clusters forming whorls and psammoma bodies, identical to histologic findings in meningioma specimens[5,6]. The current WHO grading scheme classifies the tumors as Grade I (benign, approx. 80%), Grade II (atypical, 15-20%), or Grade III (malignant/anaplastic, 1-3%)[7-12]. Grade II and III meningiomas are significantly more aggressive locally; dissemination is rare, although some studies have found evidence of tumor cells in areas of normal dura away from the tumor mass, as well as cases of multiple meningiomas in which all resected tumors from the same patient displayed identical NF2 mutations[13-15].

There have been several models proposed to understand the pathogenesis of meningiomas. The WHO grading scheme utilizes histologic subclassification[16]. Meningiomas have also been classified on an anatomic basis, correlated by location with prognosis and histologic grade (i.e., non-skull-base meningiomas are at increased risk of higher WHO grade versus skull-base meningiomas)[17,18]. However, this may be an epiphenomenon, as the location of the tumor significantly influences the extent of resection, which in turn influences the risk of recurrence[19].

## HISTOLOGIC CLASSIFICATION OF MENINGIOMAS

There are nine Grade I subtypes, three Grade II subtypes, and three Grade III subtypes in the WHO grading scale, most recently revised in 2007 (Table 1)[16]. Although genetic and immunohistochemical (IHC) markers have been increasingly employed in the evaluation of meningiomas, grading of meningiomas is based entirely on conventional histologic criteria as defined by the WHO[12,20,21].

### *WHO Grade I meningiomas*

As many as 80% of all meningiomas are slow-growing benign tumors of WHO grade I[22]. The nine WHO Grade I meningioma subtypes are considered benign; for these lesions there is a greater than 2:1 female predilection[23]. Although these tumors may be managed in a variety of ways depending on location, symptoms, and patient's age and wishes, gross total resection (GTR) of Grade I tumors is usually curative. One series demonstrated a 9.8% 10-year retreatment rate (repeat surgery, of benign meningiomas for all resection grades. Additionally, although traditionally the extent of resection of meningiomas has been considered the primary predictor of recurrence[4], some authors have demonstrated that the risk of recurrence does not differ between Simpson Grade I-III grades[24,25].

### *WHO Grade II meningiomas*

Since the WHO revised the diagnostic criteria of Grade II meningiomas in 2000 and 2007, there has been a significant increase in atypical meningioma diagnosis[26]. Tumors classified as Grade II now comprise 10-30% of all meningiomas[11]. Grade II meningiomas behave more aggressively than Grade I tumors, and have a high rate of recurrence (41% at 5 years)[3,27]. For instance, in chordoid meningiomas, subtotal resection has been shown to be an invariable predictor of recurrence, even up to 16 years postoperatively[28].

### *WHO Grade III Meningiomas*

*(Continued on page 27)*

TABLE 1 – WHO GRADE SUBTYPES

| TABLE 1 – WHO GRADE SUBTYPES | |
|---|---|
| **SUBTYPE** | HISTOLOGIC FEATURES |
| | |
| **GRADE I** | |
| **Meningothelial** | Arachnoid-like cells in lobules surrounded by collagenous septae; intralobular pseudosyncytial arrangement; intranuclear clear spaces with eosinophilic pseudoinclusions |
| **Fibrous/fibroblastic** | Fibroblast-like cells with elongated nuclei forming intersecting fascicles; collagen- and reticulin-rich matrix |
| **Transitional/mixed** | Combination of meningothelial and fibrous features; extensive concentric whorls and psammoma bodies |
| **Psammomatous** | Predominant psammoma bodies; extensive calcification or possible ossification |
| **Angiomatous** | Greater than 50% of the tumor volume occupied by blood vessels of diverse appearance; vasculature greatly hyalinized; tumor cells demonstrate degenerative nuclear changes |
| **Microcystic** | Thin elongated cell processes and mucinous matrix; resemble arachnoidal trabecular cells; pleomorphic cells common |
| **Secretory** | Gland-like intracellular spaces filled with PAS-positive inclusions (pseudopsammoma bodies); inclusions also demonstrate CEA, epithelial, and secretory marker immunoreactivity; mast and histiocytic cells relatively common |
| **Lymphoplasmacyte-rich** | Prominent inflammatory infiltrate; rare |
| **Metaplastic** | Variable mesenchymal differentiation (bony, cartilaginous, fat, and xanthomatous tissue elements); rare |
| | |
| **GRADE II** | |
| **Chordoid** | Regions of eosinophilic cellular trabeculae with vacuolated cytoplasm in myxoid background, interspersed with tissue with meningothelial appearance |
| **Clear cell** | Glycogen-rich cytoplasm; typically lack whorl pattern |
| **Atypical** | Tumors which do not fall into another category but have 4 mitotic figures per HPF OR 3 of the following:<br>- Patternless growth<br>- Hypercellularity<br>- Small cell foci with high N:C ratio<br>- Prominent nucleoli<br>- Necrotic foci<br>Additionally, tumor histology consistent with a Grade I subtype are considered Grade II if brain invasion is evident (WHO 2007) |
| | |
| **GRADE III** | |
| **Papillary** | Perivascular psudopapillary pattern (clearly visualized with CD34 immunohistochemical staining); commonly demonstrate brain invasion |
| **Rhabdoid** | Cytoplasmic eosinophilic inclusions consisting of intermediate filaments; frequently have high proliferative index. |
| **Anaplastic** | Tumors which do not clearly fall into another category, but demonstrate cytologic features of frank malignancy, or ≥20 mitotic figures/HPF. |

Abbreviations: PAS = periodic acid-Schiff; CEA = carcinoembryonic antigen; HPF = high-powered field;

N:C ratio = nucleus:cytoplasmic ratio; WHO = World Health Organization

Meningiomas classified as WHO Grade III are considered anaplastic/malignant and are further differentiated into three subtypes (Table 1). Papillary meningiomas are more common in younger patients and frequently recur; they can metastasize within the subarachnoid space or even outside of the CNS[29-31].

*The prognostic importance of WHO grading – is it becoming less relevant?*

Although molecular and genetic studies of meningiomas are being increasingly used to characterize these tumors, the standard classification scheme remains the WHO grading scale. As tumor grade increases, the recurrence rate increases and prognosis of the patient markedly decreases; the ten-year survival rate for Grade III tumors is 14.2%[32,33]. However, even benign meningiomas may still recur following Simpson Grade I resection[4,24,25,33,34]. Therefore, timely definitive diagnosis of the tumor and determination of its specific characteristics is paramount to the patient's well-being. Some have suggested the use of MIB-1 labeling indices as a key to predict recurrence[35]. Although the WHO grading scale has recently been revised (in 2000 and 2007) to standardize the diagnostic criteria for each grade, like any subjective scale it is susceptible to sampling error and inter-user variability[36,37]. Additionally, some tumors vary in aggressiveness from the norm, within the spectrum of each grade[35,38]. Multiple studies have also shown that tumor location (i.e., non-skull base vs. skull base) is a significant factor in tumor grade and malignant potential at both diagnosis and recurrence[17,19,35,39]. Adjuvant radiation modalities, including stereotactic radiosurgery, have been shown to be effective in arresting the growth of intracranial meningiomas, including those tumors arising from difficult-to-access skull base locations, with minimal morbidity[40-48]. At any rate, the WHO classification scheme does not always accurately predict the behavior of these lesions, and some authors have called for new schemes based in part on molecular markers and/or cytogenetic evaluation of the tumor[38,49,50]. Indeed, a great deal of recent investigation in the genetic and epigenetic changes of these tumors has begun to clarify the complex heterogeneity of meningioma pathogenesis and progression[6,20,51].

## GENETIC CHANGES IN MENINGIOMA PATHOGENESIS AND PROGRESSION

Although many genes have been implicated in the pathogenesis of meningiomas, a clear understanding of the specific, stepwise genetic changes required for meningiomas to develop and progress has not been elucidated. In benign tumors, loss of heterozygosity of chromosome 22 is a common finding, but other mutations are rarely found[52,53]. Meningiomas with higher grade have more complex karyotypes, but there is a great deal of heterogeneity among tumors of the same grade. Chromosomal losses on 1p, 6q, 9p, 10q, 14q, and 18q, as well as gains on 1q, 9q, 12q, 15q, 17q, and 20q, have been identified in this subset of meningiomas[53-56]. Here we review the major known genetic aberrations in meningiomas, in light of the associations with the WHO grading scale.

*Loss of heterozygosity of chromosome 22 and the merlin protein*

Loss of heterozygosity (LOH) of chromosome 22 is the most frequent abnormality in all meningioma types; it is always found in meningiomas occurring in patients with neurofibromatosis 2 (NF2) gene mutations[16,20,57-60]. Loss of NF2 expression is variable within the most common WHO Grade I subtypes, with mutations occurring in fibroblastic (70%) and transitional (83%) types far more frequently than in meningothelial (25%) types[61]. Inactivation of NF2 in grade II and III meningiomas is present in about 70% of cases, suggesting that the loss of the gene is a common event of tumorigenesis rather than malignant progression[62-64].

The NF2 gene is located on 22q12.2, encoding a tumor suppressor protein called schwannomin or merlin (moesin, ezrin, radixin-like protein)[65,66]. This 70-kDa protein is part of the 4.1 superfamily of cystoskeletal proteins, linking actin cytoskeleton to plasma membrane proteins. Merlin contains three domains, including the N-terminal FERM domain, which interacts with other cytoskeletal regulators, including other ERM proteins[67,68].

Proposed functions of the merlin product includes contact-mediated growth inhibition and secondary signaling pathways[64,66,67,69-72]. Various NF2 gene mutations have been found in up to 60% of meningiomas, including small insertions, nonsense mutations, deletions affecting splicing sites, or terminal deletions of the NF2 sequence[73,74]; these mutations result in an inactive form of merlin which has been shown to aid tumorigenesis through decreased cell adhesion and dysregulation of several pathways, including the Ras and Hippo pathways[75-77].

Merlin has also been demonstrated to regulate contact inhibition of growth through a complex with other 4.1 superfamily proteins and CD44[72]. It has been suggested that the merlin-ERM-CD44 interaction forms a molecular "switch": in a phosphorylated state the merlin protein interacts with ezrin, moesin, radixin, and CD44 to promote growth in the absence of cell/matrix contact. Once contact is achieved, the complex reconfigures without the ERM proteins and results in cellular arrest[71].

Recently, merlin has been proposed to interact with as-yet unspecified membrane proteins, resulting in signal transduction that phosphorylates LATS1/2. LATS1/2 inhibits a downstream effector of the Hippo pathway called Yes-associated peptide (YAP). When the expression of merlin is reduced, YAP is upregulated which results in cellular hyperplasia, delayed cell-cycle exit, apoptosis inhibition, and enhanced cell survival[77].

*DAL-1 (4.1B) and 4.1R*

The DAL-1 gene on the 18p11.3 locus encodes another member of the 4.1 superfamily (namely, protein 4.1B); the loss of expression of this gene has been demonstrated in up to 76% of Grade II and 87% of Grade III lesions and has also been associated with familial meningiomas. Although originally thought to be part of early tumorigenesis, the loss of the DAL-1 gene product has more recently been implicated in meningioma progression[78-80]. The gene for a third 4.1 superfamily protein, 4.1R, is located at 1p36; it is also lost in up to 40% of meningiomas Overexpression of this protein in vitro has been shown to reduce cellular proliferation[81-83].

Collectively, this data suggests a critical role of the protein 4.1 superfamily of cytoskeletal in the formation and progression of meningiomas, although the exact mechanisms have yet to be defined.

*1p and 14q aberrations and elusive tumor suppressor candidates*

Losses on 1p and 14q are the next most common mutations after LOH of 22q, and these aberrations have been independently correlated with increased tumor grade and increased recurrence rate[54,55,84-91]. Several candidates genes on 1p (including *CDKN2C, p18, ALPL, RAD54 L, p73,* and *EPB41*) have been identified, but further analysis has failed to find mutations or polymorphisms of these genes[92-96].

*Loss of expression of NDRG3 and MEG3 is associated with aggressive tumor phenotype*

Potential tumor suppressor genes on 14q include *NDRG3* at 14q11.2 and *MEG3* at 14q32[88]. Inactivation of the *NDRG2* gene has been shown to be a frequent feature in Grade III meningiomas as well as in a subset of Grade II tumors with clinically aggressive behavior[88]. However, the precise role of *NDRG2* in the progression of meningiomas remains unknown. Recently, a study evaluating the role of the *MEG3* gene has suggested an important role in the progression of these tumors[97]. *The MEG3* transcript is a non-coding RNA with anti-proliferative functionality; it is readily expressed in normal arachnoidal cells, but loss of expression was common in both human meningioma specimens and two established human meningioma cell lines. The degree of expressional loss/prevalence of allelic loss in human specimens was also correlated with increasing tumor grade.

*The 9p21 locus contains three cell-cycle regulatory genes*

Losses of 9p have been proportionately associated with increasing tumor grade; tumor suppressor genes implicated include *CDK2NA/P16$^{INKa}$*, *p14$^{ARF}$*, *and CDK2NB/p15$^{ARF}$*, all found at the 9p21 locus[6,20,56,92,98]. The products of these genes are associated with regulation of the $G_1$/S-phase cell cycle checkpoint.

*CDK2NA/CDK2NB*

The CDK2NA gene alternate reading frame product p14ARF interacts with the p53 pathway via the inhibition of mouse double homolog 2 (MDM2), which allows promotion of p53 to regulate the G1-S-phase checkpoint. Several studies have suggested that inactivation of the CDK2NA gene through various mechanisms (homozygous deletions, hypermethylation) is an important factor in the tumorigenesis and progression of higher-grade meningiomas[98-101].

Epigenetic mechanisms such as hypermethylation of genes and gene promoters have been correlated with atypical and anaplastic tumors[102], but a clonal evolution model based on the loss of expression of these genes has not yet been made clear[84,92,103,104].

*TIMP3*

The tissue inhibitor of metalloproteinase 3 (TIMP3) gene is located close to the NF2 gene, at 22q12.3. Its protein product is an inhibitor of matrix metalloproteinases (MMPs), a family of extracellular matrix proteases whose dysregulation has been implicated in the progression and invasive and metastatic potential of many human tumors, including meningiomas[105-107]. An additional tumor suppression function of the TIMP3 gene unrelated to MMPs has also been elucidated[108]. Gene silencing of TIMP3 through hypermethylation has been shown to correlate with higher-grade, aggressive meningiomas[109]. Upregulation of another protein known as urokinase plasminogen activator (uPA) (part of an additional extracellular matrix protease pathway that interacts with TIMP3), has also been correlated with increased tumor grade, invasive behavior, and recurrence[106,110].

## THE ROLE OF SEX HORMONE RECEPTORS

Sex hormone receptors have long been suspected to play a role in the pathogenesis of meningiomas due to the higher overall predominance in females[111]. It has been well studied that a majority of benign meningiomas express progesterone receptors[111-119]. Despite the female predominance, meningiomas tend to be more aggressive in males, which further clouds the involvement of sex hormones in pathogenesis.

*Progesterone Receptor*

Early studies have shown that a high percentage of meningiomas express PR[112,120-122]. Others have demonstrated that meningiomas with PR-positive cells, even if few in number, have a better prognosis than tumors with complete absence of the receptor[116]. However, reports of higher incidences of PR-positive cells in recurrent disease suggests that PR may play a role in recurrent meningiomas[123].

*Estrogen and androgen receptors*

The role of estrogen and androgen signaling has also been controversial. Estrogen receptor (ER) positivity ranges from 7.1%-40.3% in Grade I tumors, and ER-positive cells have been shown to have a higher MIB-1 proliferation index than ER-negative tumors[116,123]. Androgen receptor and artomatase have also been implicated in tumorigenesis and recurrence[115,119,120,123]. Although there is a strong case for the role of estrogen and androgens signaling in tumorigenesis, studies reporting no difference in receptor levels between men and women invalidate the conclusion that PR and ER is responsible for the predominance of meningiomas in females[123].

## THE CURRENT CHALLENGES AND FUTURE THERAPIES OF MENINGIOMA TREATMENT

As meningioma treatment moves towards therapies targeted at the specific genetics and biology of the patient's tumor, a formidable challenge remains due to the limited understanding of the complex heterogeneity of this disease. Studies have identified karyotypically frequent areas of aberrations and some specific gene candidates for tumorigenesis and progression, but the associations of these mutations with specific oncogenic

events remains unknown. Epigenetic analytical data has also produced promising correlations of gene expression regulation and tumor properties, but the data is difficult to synergize with an incomplete picture of the cytogenetic progression of disease. Also frustrating is the lack of effective chemotherapeutics for these tumors as well as the difficulty in creating stable cell lines and animal models for experimentation. As such, the mainstay treatments for meningiomas remain: surgical resection, stereotactic radiosurgery, and radiotherapy. Although these modalities may never disappear, in the future a combination of these coupled with molecular therapies tailored to the individual genetics and molecular biology of the patient's tumor holds great promise in the treatment of this disease.

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