Pathology and Molecular Genetics of Meningioma: Recent Advances

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Abstract

Meningiomas are the most common intracranial primary neoplasm in adults. Although the spectrum of clinical and molecular genetic issues regarding meningiomas remains undefined, novel genetic alterations that are associated with tumor morphology, malignancy, or location have recently been discovered. This review focuses on recent advances in understanding of the heterogeneous pathology of meningiomas, particularly on associations between the clinical, histological, etiological, epidemiological, and molecular genetical aspects of the neoplasm.

Key words: meningioma, pathology, diagnosis, immunohistochemistry, molecular genetics

Introduction

Meningiomas, which arise from arachnoid cap (meningothelial) cells, are one of the most frequently encountered intracranial tumors accounting for 20–36% of all primary tumors with an annual incidence rate of up to 1.8–13 per 100,000 population.¹⁻⁴ The incidence of meningiomas appears to be increasing owing to further exposure to environmental risk factors or sensitive diagnostic modalities.²⁻⁴

Meningiomas are categorized into three World Health Organization (WHO) grades with 15 histological subtypes, indicating heterogeneous clinical and molecular genetic characteristics.² Although most meningiomas are benign and categorized as WHO Grade I with a slow-growing behavior, some subtypes corresponding to WHO Grades II and III are associated with a higher risk of recurrence and shorter survival times. Moreover, some tumors relapse frequently and occasionally undergo malignant transformation or metastasis.

This article reviews the recent advances in the understanding of and the associations between the histological, etiological, epidemiological, and molecular genetical aspects of meningiomas.

Histology

Nine histological subtypes, namely, meningothelial, fibrous (fibroblastic), transitional (mixed), psamomatous, angiomatous,⁶ microcystic (Fig. 1), secretory⁷,⁸ (Fig. 2), lymphoplasmacyte-rich,⁹ and metaplastic meningiomas are listed as Grade I in the WHO 2007 classification.² Three subtypes, that is, chordoid¹⁰,¹¹ (Fig. 3), clear cell¹²⁻¹⁴ (Fig. 4), and atypical meningiomas¹⁵ are classified as Grade II, and three subtypes, namely, papillary¹⁶ (Fig. 5), rhabdoid¹⁷,¹⁸ (Fig. 6), and anaplastic (malignant) meningiomas¹⁹ are categorized as Grade III.

Tumor invasion is histologically recognized as a finger-like, a tongue-like, or a knobby protrusion into the underlying brain tissue (Fig. 7). Brain-invasive histologically benign meningiomas have recurrence or mortality rates similar to those of atypical meningioma (Grade II).¹⁵

Atypical meningioma (WHO Grade II) can be diagnosed on the basis of increased mitotic activity, that is, 4 or more mitoses per 10 high-power fields, or 3 or more of the following 5 histological features: (1) increased cellularity, (2) small cells with a high nuclear:cytoplasmic ratio, (3) prominent nucleoli, (4) uninterrupted patternless or sheet-like growth, and (5) foci of spontaneous or geographic necrosis²,¹⁵,¹⁹,²⁰ (Fig. 8) (Table 1).

The frequency of Grade II meningiomas has shown an increasing trend to 18%, 26%, and 30% when the WHO 1993, 2000, and 2007 criteria were applied, respectively.²¹,²² Grade III meningiomas have accounted for 1–3%.²,²² Grades II and III meningiomas occur far less frequently in the skull base and spine, and the occurrence of tumors in
Fig. 1  Microcystic meningioma (HE: original magnification, ×20). HE: hematoxylin and eosin.

Fig. 2  Secretory meningioma (a: HE, b: cytokeratin, AE1/AE3, c: CEA, original magnification, ×20). CEA: carcinoembryonic antigen, HE: hematoxylin and eosin.

Fig. 3  Chordoid meningioma (HE: original magnification, ×20). HE: hematoxylin and eosin.

Fig. 4  Clear cell meningioma (HE: original magnification, ×20). HE: hematoxylin and eosin.

Fig. 5  Papillary meningioma (HE: original magnification, ×20). HE: hematoxylin and eosin.
the “non-skull base” is an independent risk factor for Grades II and III meningiomas. Currently, histologic grade is the best predictive factor for local recurrence. The reported recurrence rates of Grades I, II, and III meningiomas are 7–25%, 29–52%, and 50–94%, respectively. Anaplastic meningiomas are associated with 19% risk of metastatic disease and inferior survival.

Other rare histological variants include oncocytic, xanthomatous, mucinous, lipoblastic/vacuolated, sclerosing, glial fibrillary acidic protein (GFAP)-expressing whorling-sclerosing, inflammation-rich meningiomas, and meningiomas with GFAP expression, with a glandular or pseudoglandular pattern, with granulofila-

mentous inclusions, with pericytes associated with peritumoral brain edema, resembling that of schwannoma, with intracytoplasmic inclusions, with muscle actin-positive cells, and with rheumatoid nodules. Petaloid tyrosine-rich crystals are also a rare finding. Melanocytic colonization occurs in rare cases. Cases with total ossification or calcification have also been reported.

As for the clinicopathologic assessment and grading of embolized meningiomas, microscopic foci of necrosis have been identified in 40–89% of embolized meningiomas compared to 16% of nonembolized meningiomas. An intravascular embolization material was visible in 67%, and was
encountered most frequently in large to medium dural arteries and less commonly in smaller vessels within the meningioma substance.\textsuperscript{56} Necrosis and macronucleoli represented common findings in embolized meningiomas.

Necrosis in nonembolized meningiomas (e.g., atypical meningiomas) usually occurs in small foci, occasionally surrounded by pseudopalisading tumor cells. On the other hand, necrosis in embolized tumors occurs in large geographic areas with an abrupt line of demarcation from the viable tumor tissue, with prominent macronucleoli in perinecrotic areas. To avoid overgrading, necrosis showing an abrupt line of demarcation and focal perinecrotic macronucleoli are not included in grading assessment.\textsuperscript{57}

**Association between Peritumoral Brain Edema and Meningioma**

Peritumoral brain edema (PTBE) is frequently observed in cases of microcystic, secretory, or angiomatous meningiomas.\textsuperscript{58} PTBE in meningioma patients has been found to be caused at least partly by the activities of vascular endothelial growth factor (VEGF). The involvement of other factors, such as mast cells, hypoxia induced factor 1 (HI-F-1), aquaporin 4 (AQP4), aquaporin 5 (AQP5), matrix metalloproteinase-9 (MMP-9), and interleukin 6 (IL-6) have also been identified. These factors may play a role in PTBE either individually or in combination, particularly by affecting microcirculatory environments.

Mast cells are numerous in some secretory meningiomas,\textsuperscript{59} and are occasionally abundant in some tumors with PTBE,\textsuperscript{60} suggesting their important role in edema formation.\textsuperscript{61,62}

Regarding the correlation of mast cells and HI-F-1 expression in meningiomas of various grades with PTBE formation, PTBE has also been shown to be correlated with tryptase (mast cells) and HI-F-1 expression. Immunohistochemical tryptase expression was observed in 40% of low grade and in 90% of high grade meningiomas; HI-F-1 in 56% of low grade and in 84% of high grade meningiomas. Mast cells and hypoxia are thus involved in meningioma progression and may be associated with PTBE formation.\textsuperscript{61}

As for the expression of AQP4 in human supratentorial meningiomas with PTBE and the correlation of VEGF with edema formation, higher immunohistochemical expression of AQP4 was found in the PTBE group, in which the AQP4 protein level correlated with the extent of edema, compared to the nonedema group. Higher VEGF expression was also observed in the PTBE group. Thus, AQP4 may be involved in the formation of PTBE, and is closely related to the expression of VEGF.\textsuperscript{63}

In addition, AQP5 expression was found to be positively correlated with PTBE in association with the AQP5-1364 AA genotype. It is considered to be an interesting new candidate involved in brain edema formation in meningioma patients.\textsuperscript{64}

The VEGF-A pathway and tumor capillary length may be essential for the formation of PTBE in meningioma cases.\textsuperscript{65} VEGF and MMP-9 play a central role in the development of PTBE. MMP-9 expression was immunohistochemically shown to be positively related to VEGF expression and pial blood supply, and such expression promoted the occurrence of brain edema by inducing disruption of the arachnoid membrane and formation of pial blood supply.\textsuperscript{66}

Regarding the influence of interleukin-6 on the development of PTBE in meningiomas, the IL-6 mRNA level was found to be 7.72 times greater in the PTBE group than in the nonedema group. IL-6 protein was immunohistochemically localized in the cytoplasm of the tumor cells, and was detected at a higher rate in edematous meningiomas than in noneedematous meningiomas (75% vs 30%, respectively). The severity of PTBE was significantly correlated with IL-6 expression. Thus, IL-6 expression may contribute to PTBE development in meningioma patients.\textsuperscript{67}

**Immunohistochemistry**

Since extra-axial tumors histologically mimicking meningiomas are frequently encountered, immunohistochemical differentiation is essential.\textsuperscript{68} Meningioma cells are immunohistochemically positive for epithelial membrane antigen (EMA) in 50–100% of tumors.\textsuperscript{69} Cytokeratin (CK) 18, but not CK20, is also commonly positive in meningiomas.\textsuperscript{70}

In secretory meningiomas, pseudopsammoma bodies (periodic acid Schiff-positive eosinophilic secretory materials) and their surrounding tumor cells are positive for carcinoembryonic antigen (CEA), and the surrounding cells are positive for CK, but tend to be negative for vimentin\textsuperscript{71} (Fig. 2). In “true secretory meningiomas”, an elevated serum CEA level is present.\textsuperscript{72}

Most meningiomas are generally negative for GFAP, but they may be positive for a filament-rich rhabdoid lesion.\textsuperscript{17,73} A rare variant of meningioma with whorling-sclerosing features has been shown to have GFAP-positive cells.\textsuperscript{33,34} For invasive meningiomas, GFAP-positive astrocytes have been found deep in the tumor, usually in contact with blood vessels.\textsuperscript{74}

For the differential diagnosis of meningiomas, claudin-1 appears to be a useful marker showing positive staining only in 50% of meningiomas, but
negative staining in solitary fibrous tumors, hemangiopericytomas, and vestibular schwannomas.\(^7\)\(^5\)

S-100 protein may be useful for distinguishing meningiomas from schwannomas, but 90% of fibrous meningiomas are also positive for S-100 protein.\(^7\)\(^5\)\(^7\)\(^6\) Immunostaining for Wilms tumor-1 (positive in schwannomas), and claudin-1 and ezrin (positive in meningiomas) is helpful for distinguishing schwannomas from fibroblastic meningiomas.\(^7\)\(^3\)

Almost all solitary fibrous tumors are positive for CD34, but 40% of fibrous meningiomas and 60% of atypical meningiomas are also positive for CD34.\(^7\)\(^5\)\(^7\)\(^8\) Meningeal hemangiopericytoma and solitary fibrous tumors have been shown to carry the NAB2-STAT6 fusion and can be diagnosed by immunohistochemical nuclear expression of STAT6 protein. Specifically, the presence of NAB2-STAT6 fusion protein was shown in 17/17 hemangiopericytomas and can be diagnosed by immunohistochemical nuclear expression of STAT6 protein.\(^7\)\(^3\)\(^8\) The presence of the NAB2-STAT6 fusion protein immunohistochemically resulted in a strong nuclear signal for STAT6.

Positive immunostaining of brachyury in chordoma can exclude chordoid meningioma.\(^6\)\(^8\)\(^8\)\(^0\)

Besides histological differential diagnosis, numerous immunohistochemical studies have been performed to elucidate the biological behavior of meningiomas or patient prognosis, on routinely processed formalin-fixed paraffin-embedded sections, using markers for proliferative potential, growth factors, fatty acid synthesis, or genetic molecules.

Phosphohistone-H3 (PHH3) has been reported as a mitosis-specific marker of meningiomas.\(^8\)\(^1\)\(^\)\(^2\)\(^9\)\(^2\) Immunohistochemical detection of mitotic figures with anti-PHH3 antibody facilitates counting of the mitotic index to evaluate Grades II and III meningiomas in accordance with the WHO 2007 classification.\(^2\)\(^3\)

Furthermore, immunohistochemical evaluation of the proliferative potential of meningiomas with bromodeoxyuridine (B UdR) or the MIB-1 antibody (Ki-67) is useful to predict patient prognosis. The recurrence rate was 100% for tumors with a B UdR labeling index (LI; S-phase fraction) of ≥ 5%, 56% for tumors with LIs of 3–5%, and 31% for tumors with LIs of 1–3%. The time to reoperation in months can be predicted from the B UdR LI as: 70.0 × B UdR LI (%)\(^{-1}\).\(^2\)\(^1\)\(^2\) The formula can be used to estimate the doubling time of individual tumors and to predict the period of greatest risk of recurrence of meningiomas.\(^8\)\(^3\)

The MIB-1 (Ki-67) positivities were estimated as 1.2–3.8%, 3.3–7.2%, and 9.5–14.7% in benign, atypical, and anaplastic meningiomas, respectively.\(^8\)\(^4\)\(^8\)\(^5\) An MIB-1 LI of > 4.2% was strongly associated with decreased recurrence-free survival in primary meningiomas.\(^8\)\(^6\)

Male sex is an independent risk factor for high MIB-1 positivity.\(^7\)\(^7\)\(^8\)\(^8\) For skull base meningiomas, they usually grow slowly and exhibit significantly lower MIB-1 positivity than non-skull base tumors.\(^7\)\(^7\)\(^9\)\(^9\) The mean MIB-1 index of embolized meningiomas is not significantly different from that of control meningiomas without embolization.\(^9\)\(^0\) Regarding the effect of embolization of meningiomas, an increased MIB-1 index is noted around embolization necrosis.\(^9\)\(^1\)

It has been shown that 88% of primary meningiomas expressed the progesterone receptor (PR), 40% expressed the estrogen receptor (ER), and 39% expressed the androgen receptor (AR).\(^9\)\(^2\) PRs are commonly positive in Grade I meningiomas, but are less prominent in Grades II and III meningiomas as a risk predictive marker.\(^9\)\(^3\)\(^9\)\(^4\) Ki-67 index and PR positivity are inversely correlated.\(^9\)\(^5\) No clear gender predominancy was noted in AR positivity. Compared to benign meningiomas, atypical and anaplastic meningiomas are less likely to express AR.\(^9\)\(^2\)

Somatostatin antiproliferative and antiangiogenic activities, together with the expression of somatostatin receptors (SSTRs), account for the use of somatostatin analogues in the treatment of meningiomas. An immunohistochemical study of SSTR2A demonstrated its high expression in high grade meningiomas, in correlation with the high Ki-67 positivity. A significant correlation was also found between SSTR2A expression and a high microvessel density of meningiomas. These findings provide the basis for the use of somatostatin analogue-based therapies in the treatment of meningiomas.\(^9\)\(^6\)

Importantly, immunohistochemical detection of fatty acid metabolism-associated proteins is a useful tool for assessing meningioma grade, invasiveness, aggressiveness, and recurrent status.\(^9\)\(^7\)\(^9\)\(^8\) The expression of fatty acid synthase (F aS), the enzyme responsible for the de novo synthesis of fatty acids, was immunohistochemically detected in 62.9% of Grades II and III meningiomas compared to 29.8% of Grade I meningiomas, and was prominent in Grade I meningiomas with a high MIB-1 index.\(^9\)\(^8\) The expression levels of F aS or brain fatty acid binding protein (BFABP) were significantly higher in brain-invasive or recurrent meningiomas.\(^9\)\(^7\)\(^9\)\(^8\) Radiation-induced meningiomas expressed FAS, which positively correlated with the MIB-1 index.\(^9\)\(^8\)

Cyclooxygenase 2 (COX-2) immunohistochemical expression was significantly associated with BFABP status, and both COX-2 and BFABP expressions were stronger in Grade II meningiomas than in meningiomas without BFABP expression.\(^9\)\(^8\)

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Grade I meningiomas. Age and COX-2 status were
prognostic in progression-free survival. Patients
with moderate or strong COX-2 expression had
worse outcome than patients with negative or weak
COX-2 expression.\(^{100}\)

Osteopontin protein, an integrin-binding protein
involved in proliferation, adhesion, migration, and
angiogenesis, is a valuable marker for predicting
the risk of early recurrence within WHO Grade I
meningiomas.\(^{101,102}\) The immunohistochemical
osteopontin staining score was shown to be 6 times
higher in meningiomas with early recurrences
than in nonrecurring meningiomas.\(^{101}\) Another
study revealed that the osteopontin staining score
correlated with the WHO meningioma grade and
Ki-67 index, as well as with the recurrence of
WHO Grade I meningiomas.

Cancer/testis (CT) genes represent a unique
class of genes, which are expressed by germ cells,
normally silenced in somatic cells, but activated in
various cancers. NY-ESO-1 protein, one of the CT
gene products, was shown to be expressed immu-
nohistochemically in 108 of 110 meningiomas.
Higher levels of NY-ESO-1 expression positively
correlated with higher tumor grade, and with worse
disease-free and overall survival. NY-ESO-1 expres-

sion may lead to a humoral immune response in
patients with meningioma. Considering the limited
treatment options for patients with meningioma,
the potential of NY-ESO-1-based immunotherapy
should be explored.\(^{103}\)

AKT2 (protein kinase B), an important protein
in the phosphoinositide 3-kinase (PI3K) signaling
pathway, is overexpressed in various malignant tumors.
The immunohistochemical expression of AKT2 in
meningiomas was associated with pathological grade
and recurrence, and with Ki-67 immunoreactivity.\(^{104}\)
Thus, AKT2 may be a useful molecular marker for
predicting the biology of meningiomas.

The aberrant expression of CD163, a 130-kDa trans-
membrane protein expressed in human monocytes
and macrophages, is known to be associated with the
poor prognosis of patients with breast or colorectal
cancers. Fifty-two percent of meningiomas were
immunohistochemically positive for CD163, including
Grade I (48.5%) and Grade II (71.4%) tumors, and
its expression correlated with histological atypical
parameters that directly predict the prognosis of
meningioma.\(^{105}\) In nude mice, CD163-overexpressing
meningioma cells showed significant suppression of
apoptosis and accelerated tumor growth.\(^{105}\)

**Etiology/Epidemiology**

Meningiomas are considered to be derived from
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meningothelial (arachnoidal) cells.\(^{2}\) Most meningi-
omas arise from unknown causes, although some
occur after ionizing radiation exposure or in the
background of neurofibromatosis 2 (NF2).\(^{71}\)

Data from atomic bomb survivors demonstrated
a significantly elevated incidence of meningiomas
compared to a nonexposed population with a rela-
tive risk of 6.48.\(^{106,107}\)

Radiation-induced meningiomas were reported in
the 1960s after low-dose irradiation therapy of the
scalp for tinea capitis.\(^{108}\) These meningiomas are
categorized into three groups based on the amount
of radiation administered: low (< 10 Gy), moderate
(10–20 Gy), and high (< 20 Gy) doses with average
latencies of 35, 26, and 19–24 years, respectively.\(^{109,110}\)
Radiation-induced meningiomas are more commonly
of high grade, and are occasionally multifocal, highly
proliferative, and occur in younger age groups.\(^{2,111}\)
Because the frequency of NF2 mutations or the loss
of chromosome 22 is lower in radiation-induced
meningiomas, and structural abnormalities in 1p,
18q, or 10q are more common than in sporadic
meningiomas, a different pathogenesis is speculated
for radiation-induced meningiomas.\(^{2,69,112}\)

Meningiomas are more commonly diagnosed in
women at a ratio of 1.7–2.1:1,\(^{2,4}\) but atypical and
anaplastic meningiomas occur more predominantly in
men.\(^{2,15,19}\) The reason for this gender distribution is
still unclear. Several studies have reported a positive
association between the use of hormone replacement
therapy and meningioma development.\(^{113}\) However,
other studies have found little evidence to support
a link between meningioma development and oral
contraceptives or hormone replacement therapy.\(^{4,92,114}\)
The number of men who undergo procedures such as
orchectomy and vasectomy is very low.\(^{115}\)

The association between pregnancy and rapid
growth of meningioma has long been appreciated.
The rapid tumor growth is more often due to
potentially reversible hemodynamic changes rather
than hormone-induced cellular proliferation during
pregnancy.\(^{116}\)

The association between obesity and the risk of
meningioma development appears to be controversial.
A meta-analysis suggested that obesity is associated
with an increased risk of meningioma in women,
but not in men.\(^{117}\) On the other hand, a different
study revealed that an increased body mass index
(BMI) is associated with a two-fold increased risk
of developing meningioma in men. Exogenous expo-
sure to estrogen-like products, such as the use or
ingestion of soy products, may be associated with
a reduced risk of meningioma in men; however,
endogenous estrogen-associated factors such as a
high BMI may increase the risk.\(^{115}\)
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Case-control studies have found no conclusive evidence of an association between the use of mobile and cordless phones and the development of meningioma.\textsuperscript{118–120}

Molecular Genetics

The most consistent cytogenetic change in meningiomas is loss of chromosome 22.\textsuperscript{121} In addition, atypical meningiomas show allelic loss of chromosomes 1p, 6q, 9q, 10q, 14q, 17p, and 18q, suggesting progression-associated genes at these loci. More frequent loci are lost in anaplastic meningiomas for 6p, 9p21, 10, and 14q.\textsuperscript{2}

Among many genetic alterations in meningiomas, the loss of the short arm of chromosome 1 is the second most frequent chromosomal abnormality. Loss of heterozygosity analysis revealed gender-specific discrepancies in the frequency of 1p aberrations, and a correlation between the gene expression level and gender was found to be significant for the ELAVL4 gene, being lower in men than in women. Meningiomas may present different features depending on patient gender, and ELAVL4 may be involved in the pathogenesis of meningiomas in male patients.\textsuperscript{122} This observation supports previous reports suggesting that meningiomas may be gender-related tumors.\textsuperscript{123}

Meningiomas are closely associated with the tumor suppressor syndrome NF2, with 50–75% of individuals with NF2 developing a meningioma during their lifetime.\textsuperscript{124} Allelic loss of 22q12 resulted in a loss of the NF2 gene product merlin or neurofibromin 2. Loss of the NF2 gene is detected in the majority of NF2-associated, and 40–60% of sporadic meningiomas, and is assumed as an early tumorigenic event.\textsuperscript{69,125} Fibrous, transitional, and psammomatous meningiomas frequently carry NF2 mutations, but meningothelial, secretory, and microcystic subtypes rarely harbor NF2 mutations. Particularly, mutations are less frequent in meningiomas of the anterior skull base region.\textsuperscript{2,69} Atypical and anaplastic meningiomas also possess a high frequency of NF2 mutations, matching those in fibrous, transitional, and psammomatous subtypes.

NF2 gene products are members of a cell membrane/cytoskeleton-associated protein 4.1 superfamily, and a loss of 4.1B protein expression or gene deletion is found in 60–70% of meningiomas regardless of tumor grade, also suggesting early tumorigenic events.\textsuperscript{2,69,126} Loss of expression of TSLC-1, a 4.1B binding partner, is correlated with increased malignant grade and reduced patient survival.\textsuperscript{127}

Abnormalities of chromosome 14 have also been reported in higher grade meningiomas as well as in recurrent meningiomas, and it has long been supposed that chromosome 14q contains a tumor suppressor gene. Maternally expressed gene 3 (MEG3) is an imprinted gene located at 14q32 that encodes a non-coding RNA. Loss of MEG3 expression, its genomic DNA deletion, and the degree of promoter methylation have been found to be associated with aggressive tumor growth. MEG3 may have a significant role as a novel long noncoding RNA tumor suppressor in meningiomas.\textsuperscript{128}

N-Myc downstream-regulated gene 2 (NDRG2) located at 14q11.2 is another specific gene candidate for malignant progression on chromosome 14, which is consistently down-regulated in Grade III meningiomas. The loss of NDRG2 expression was significantly associated with hypermethylation of the NDRG2 promoter. NDRG2 expression will be a useful and functionally relevant biomarker for predicting aggressive behavior in patients with meningioma.\textsuperscript{129,130}

Novel mutations have been recently discovered in non-NF2 meningiomas in two large-scale genome-wide genotyping and exome sequencing studies.\textsuperscript{131,132} Although the most common mutated gene is NF2, newly discovered mutations in TRAF7 (24%), encoding a proapoptotic E3 ubiquitin ligase, AKT1 (10–15%), encoding a key effector of PI3K signaling, KLF4 (10%), encoding 3 C2h2 zinc finger motifs, and SMO (3–5%), encoding a negative regulator of the Hedgehog pathway, were mutually exclusive of NF2 mutations. AKT1 mutation at 66% concomitantly occurred with TRAF7 mutation. KLF4 mutation (K409Q) almost always concomitantly occurred with TRAF7 mutation. SMO mutations are mutually exclusive from the other mutations. Immunohistochemical detection of the AKT1 and SMO activation pathways can be made, and the pathways may respond to PI3K or Hedgehog inhibitor therapy.\textsuperscript{131} In addition, such mutation types are correlated with anatomical tumor location and histological subtypes.\textsuperscript{132} NF2 mutations are significantly associated with higher grades of meningiomas located in the cerebral and cerebellar hemispheres with increased number of large-scale chromosomal abnormalities. NF2 mutation or loss of chromosome 22 is predominantly found in the hemispheres with nearly all posterior cerebral (parieto-occipital), cerebellar, or spinal meningiomas. Non-NF2 meningiomas are nearly always benign with chromosomal stability. Among the skull base tumors, the vast majority of non-NF2 meningiomas were located in the medial skull base, whereas the lateral and posterior skull base

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had NF2 mutations or loss of chromosome 22. All meningiomas with SMO mutation are located in the near midline anterior skull base (Table 2). The data supported that skull base meningiomas grow slowly with lower Ki-67 positivity than non-skull base tumors, and that non-skull base meningioma is one of the independent risk factors for WHO Grades II and III meningiomas.

Interestingly, nearly 100% of secretory meningiomas are defined by combined KLF4 (K409Q) and TRAF7 mutations. None of the secretory meningiomas have NF2 mutations.

The activating E17K mutation in the AKT1 gene has been detected in several tumor entities. In a series of 1,437 tumors including 391 primary intracranial brain tumors and 1,046 tumors of the coverings of the central and peripheral nervous system, AKT1E17K mutations were exclusively found in meningiomas and occurred in 65 of 958 of these tumors. A strong preponderance was seen in the variant of meningothelial meningioma WHO Grade I of basal and spinal localization. In contrast, AKT1E17K mutations were rare in WHO Grade II and absent in WHO Grade III meningiomas. Since a strong up-regulation of secreted frizzled-related protein 1 (SFRP1) expression was suggested in all meningiomas with AKT1E17K mutation, SFRP1 immunohistochemistry may be a reliable surrogate marker for the detection of AKT1E17K mutations.

Heterozygous loss-of-function mutations in SMARCE1 (SWi/SNF chromatin-remodeling complex subunit gene), are identified in individuals with familial multiple spinal meningiomas without NF2 mutations. Tumors from individuals with SMARCE1 mutations were of the clear-cell histological subtype, which were negative for SMARCE1 immunostaining. These studies define new roles for SMARCE1 in the pathogenesis of multiple spinal meningiomas and reinforce the importance of the SWI/SNF complex in tumors with clear-cell histology.

The chromatin remodeling gene SMARCB1, also known as INI1, hSNF5, and BAF47, may also be involved in the development of multiple meningiomas. The SMARCB1 exon 2 missense mutation predisposes individuals to the development of meningiomas and multiple schwannomas, occurring via the same genetic pathways, and this mutation preferentially induces cranial meningiomas located at the falx cerebri.

Maintenance of telomere length is a key process in malignant progression, and mutations in the telomerase reverse transcriptase (TERT) promoter have recently been identified in various types of tumors. A high incidence of TERT promoter mutations is found in patients with meningiomas undergoing malignant histological progression. Tumors showing relapse without histological progression exhibited no TERT promoter mutation. TERT promoter mutations are pivotal genetic alterations involved in the malignant progression of meningiomas and could be used as a biomarker to identify meningiomas at risk of malignant transformation.

**Conclusion**

In recent years, there has been a rapid increase in the number of studies aiming to clarify the clinical and molecular genetic issues regarding meningiomas, particularly those involving comprehensive genomic analyses. More novel investigations to further elucidate the heterogenous pathology and genetic alterations associated with the morphology and malignancy of meningiomas may pave the way to the discovery of new therapeutic agents for the common and diverse entities of the neoplasm. Update findings are summarized in Table 3.

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Table 3  Summary of updated findings

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Conflicts of Interest Disclosure

The author declares no conflicts of interest. The author, who is a member of the Japan Neurosurgical Society, has registered the online Self-reported COI Disclosure Statement Forms.

References


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Meningioma Pathology and Genetics


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