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AN INTEGRATED PERSPECTIVE ON POTENTIAL RISK FACTORS FOR MENINGIOMA DEVELOPMENT: A REVIEW

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ABSTRACT

Introduction: Contemporary neuro-oncology considers meningioma development to result from a complex interplay between genetic predisposition, endocrine status, and metabolic background. Such an integrated approach is essential for the development of early diagnostic strategies, identification of high-risk populations, and implementation of personalized therapeutic principles in neurosurgical practice. The aim of this review was to systematize the most recent literature data concerning the integrated analysis of factors contributing to meningioma development.
Methods: A comprehensive literature search was conducted using the PubMed and Google Scholar databases, focusing on peer-reviewed studies published between 2016 and 2025.The following keywords were used: meningioma, NF2, TERT, genetic studies, chromosomal abnormalities.
Conclusions: A review of the current scientific literature indicates that meningioma development is driven by the complex interaction of genetic, hormonal, metabolic, and exogenous factors. Key molecular drivers include mutations in NF2, TRAF7, KLF4, SMO, and TERT, as well as epigenetic alterations. Hormonal status and metabolic disturbances, particularly obesity, insulin resistance, and dyslipidemia, appear to modulate tumor growth dynamics and recurrence risk. Ionizing radiation represents a major exogenous trigger of tumorigenesis. Further interdisciplinary research is required to improve understanding of meningioma pathogenesis and to facilitate the implementation of advanced diagnostic and therapeutic strategies.

KEYWORDS

Meningioma, NF2, TERT, Genetic Studies, Chromosomal Abnormalities

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Introduction

Meningioma is a typically benign tumor of the central nervous system that arises from arachnoid cap cells of the arachnoid mater and pluripotent mesenchymal cells of the vascular layer of the pia mater. The majority of these tumors are classified as WHO grade I, indicating a benign biological behavior. However, approximately 20% of cases may exhibit atypical or malignant features, with a recurrent or progressive clinical course (Bance et al., 2025).

Meningiomas represent the most common primary neoplasms of the central nervous system. According to data from the Central Brain Tumor Registry of the United States (CBTRUS), between 2018 and 2022, meningioma was the most frequently reported non-malignant histopathological subtype. It accounted for 42.6% of all CNS tumors, including malignant meningiomas, and 57.4% of all non-malignant tumors, with a higher incidence observed in women compared to men. Histologically, the majority of meningiomas are benign (80.1%), while others are classified as atypical (18.3%) or malignant (1.6%). The 10-year survival rate averages 60.1% for patients with malignant meningiomas and 83.4% for those with benign tumors (Ostrom et al., 2023).

The etiology of meningiomas is complex and remains incompletely understood. Multiple factors are believed to contribute to their development, including genetic, immunological, and environmental influences. Among genetic factors, inactivation of the NF2 gene (Paramasivam et al., 2019), mutations in the TRAF7 gene (Zotti et al., 2017), and mutations in the KLF4 gene (Preusser et al., 2018) have been identified as key contributors. Environmental risk factors include exposure to ionizing radiation (Brenner et al., 2020; Rajaraman et al., 2021) and hormonal influences (Roland et al., 2024). Genetic predisposition has also been reported (Pawloski et al., 2021, Claus et al., 2022; Hielscher et al., 2023). In contrast, no significant associations have been identified between meningioma development and factors such as head trauma, allergic conditions, occupational exposure, or dietary patterns. Therefore, many potential risk factors require further investigation.

Methodology

The present study was conducted as a comprehensive synthesis of scientific literature regarding key risk factors contributing to the development of meningioma. A systematic search was performed across the PubMed and Google Scholar databases, focusing on peer-reviewed studies published between 2016 and 2025. The search strategy employed keywords such as "meningioma," "NF2," "TERT," "genetic studies," and "chromosomal abnormalities," with a primary focus on the etiology and pathogenesis of the disease.

Priority was given to studies detailing biological mechanisms, including NF2 mutations, TRAF7 and AKT1 alterations, H3K27me3 loss, the role of hormonal receptors (progesterone and estrogen), and the impact of ionizing radiation and metabolic processes. Special attention was paid to the integrated molecular classification systems of meningiomas (Nassiri et al., 2021) and their correlation with clinical manifestations and prognosis.

This integrated approach ensures a comprehensive understanding of both the clinical epidemiology of meningiomas and the fundamental biological pathways of their development, providing a robust evidence base for clinical and research perspectives.

Results

Genetic factors

The vast majority of meningiomas are sporadic, meaning they arise in the absence of inherited genetic predisposition, in contrast to meningiomas associated with hereditary syndromes such as neurofibromatosis type 2. The oncogenesis of sporadic meningiomas involves a range of primary chromosomal alterations, including chromosomal aberrations, driver mutations, and epigenetic modifications (Driver et al., 2022). More than twenty gene alterations have been identified in somatic meningiomas (Smith et al., 2020; 2021). Recurrent somatic mutations have been reported in AKT1, TRAF7, TERT, SMO, KLF4, POLR2A, TP53, and PTEN, indicating that dysregulation of multiple signaling pathways contributes to meningioma development (Nassiri et al. 2021).

Advances in molecular genetic techniques for assessing gene mutational status, together with accumulating research data, demonstrate that alterations in the neurofibromatosis type 2 gene (NF2; NM_000268) represent the most common molecular cause of meningiomas, while germline pathogenic variants of NF2 are associated with the development of multiple meningiomas. Loss of neurofibromin 2 protein (merlin, also known as schwannomin) has been observed in approximately 50-60% of meningioma patients.

Additionally, loss of chromosome 22, which harbors the NF2 gene locus, is detected in 40–80% of meningioma cases (Rajaraman et al., 2021).

The NF2 gene is a tumor suppressor gene located on chromosome 22 that encodes the protein merlin (schwannomin), which plays a critical role in regulating cell proliferation and preventing tumor formation. Mutations in this gene lead to neurofibromatosis type 2, a hereditary or sporadic disorder characterized by the development of benign tumors of the nervous system. In addition, NF2 regulates several cytoskeleton-associated proteins, including paxillin, actin, and syntenin, which are involved in cytoskeletal remodeling, cell adhesion, and migration. Loss of NF2 function may activate oncogenic signaling pathways, including the Ras/mitogen-activated protein kinase (MAPK), Notch, phosphoinositide 3-kinase (PI3K)/AKT, Hippo, and mTOR pathways (Mei et al., 2017).

Proteomic analysis, DNA methylation profiling, and targeted sequencing have identified specific molecular signatures in lower-grade meningiomas, including alterations in NF2, AKT1, and KLF4, as well as co-occurring mutations such as ATM–BIVM–ERCC5, PIK3C2B–SDHD, and ERCC4–MET. Proteomic studies of NF2-deficient tumors have also demonstrated upregulation of Annexin A3 (ANXA3), which is associated with increased cellular proliferation. These findings suggest that:

- The co-occurrence of multiple mutations may reflect synergistic effects that promote tumor growth;
- Genetically defined subgroups exhibit distinct gene expression patterns and proteomic clustering, particularly in NF2-deficient (NF2−/−) low-grade meningiomas with additional mutations;
- Annexin A3 (ANXA3) represents a key regulator of proliferation in NF2-deficient meningiomas (Clark et al., 2016).

A study identified several mutations in NF2-wildtype meningiomas, including mutations in TRAF7 (TNF receptor–associated factor 7), KLF4 (Kruppel-like factor 4), AKT1, and SMO. These findings also demonstrated that genetic alterations influence tumor location. Specifically, meningiomas harboring mutations in TRAF7, KLF4, and AKT1 exhibit distinct anatomical distributions compared to tumors with NF2 or SMO mutations. Mutations in TRAF7, KLF4, and AKT1 are more frequently observed in skull base meningiomas. Preusser et al. reported that AKT1 mutations occur in approximately 30% of skull base meningiomas (Preusser et al., 2018).

In 2021, Nassiri et al. proposed an integrated molecular classification of meningiomas based on comprehensive molecular genetic profiling (Table 1).

This classification incorporates DNA methylation patterns, mRNA expression profiles, somatic mutations, and copy number variations to define four consensus molecular groups with distinct biological and clinical characteristics, designated Molecular Groups 1-4 (MG1-MG4). This approach enables the generation of a comprehensive molecular tumor profile based on methylation patterns, chromosomal aberrations, microRNA expression, protein biomarkers, somatic mutations, and single-cell sequencing data.

Importantly, this classification considers not only the presence of specific mutations (e.g., NF2 mutations), but also the mutation type and its functional impact on protein structure. Higher-grade meningiomas (WHO Grade II–III) are frequently characterized by nonsense and frameshift mutations, which result in premature protein truncation.

Table 1. Integrative Molecular Classification of Meningiomas

Mole-cular Group	Group Name	Key Molecular Features	Common Genetic Alterations	Biological Characteristics	Clinical Behavior / Prognosis
MG1	Immunogenic	Immune-enriched transcriptomic profile	NF2 mutations, chromosome 22q loss	High immune cell infiltration, inflammatory signaling	Relatively favorable prognosis, longer progression-free survival
MG2	Benign NF2-wildtype	Genomically stable, low aneuploidy	TRAF7, AKT1, KLF4, SMO	Low proliferative index, benign biology	Best prognosis, often WHO grade 1
MG3	Hypermetabolic	Metabolic pathway activation	Mixed mutations, increased chromosomal instability	Elevated metabolic activity, moderate proliferation	Intermediate prognosis, higher recurrence risk
MG4	Proliferative	Cell cycle and proliferation signatures	NF2 mutations, CDKN2A/B loss, widespread copy-number alterations	High mitotic index, aggressive tumor biology	Worst prognosis, frequent recurrence, often high-grade

Note. Adapted from "A clinically applicable integrative molecular classification of meningiomas," by F. Nassiri et al., 2021, *Nature, 597*(7874), p. 120. https://doi.org/10.1038/s41586-021-03850-3

The four molecular groups are defined as follows:

- MG1 – Immunogenic: characterized by prominent immune cell infiltration and NF2-mutant meningiomas, with relatively favorable recurrence-free survival.
- MG2 – Benign NF2-wildtype: includes NF2-wildtype tumors with mutations in TRAF7, AKT1, or KLF4, or chromosomal polysomies; generally associated with favorable prognosis.
- MG3 – Hypermetabolic: characterized by increased metabolic activity, higher levels of aneuploidy, and poorer clinical outcomes.
- MG4 – Proliferative: characterized by high proliferative activity, frequent chromosomal losses, and the worst clinical prognosis among all molecular groups.

This molecular classification provides prognostic value beyond the conventional WHO histopathological grading system, with MG4 (proliferative) tumors demonstrating the poorest clinical outcomes, whereas MG2 (benign NF2-wildtype) tumors are associated with the most favorable prognosis.

Comprehensive genomic studies (Evans et al., 2020) have identified several hereditary tumor predisposition syndromes associated with a significantly increased risk of meningioma development. These include Cowden syndrome, schwannomatosis (associated with NF2, SMARCB1, and LZTR1 mutations), BAP1 tumor predisposition syndrome, and meningiomatosis (multiple meningioma syndrome).

Cowden syndrome is a rare hereditary disorder with an estimated prevalence of 1 in 200,000 to 1 in 250,000 individuals. Its primary pathogenic mechanism involves mutations in the PTEN gene located on chromosome 10, which are detected in approximately 80% of patients (Evans et al., 2020). Meningiomas are not a primary diagnostic feature of Cowden syndrome but occur in approximately 8% of affected individuals and are considered an associated manifestation. The syndrome is characterized by multiple hamartomatous and neoplastic lesions involving the skin, mucous membranes, and internal organs, including oral papillomas, trichilemmomas, acral keratoses, macrocephaly, gastrointestinal hamartomas, breast cancer (affecting up to 85% of patients), thyroid cancer (approximately 35%), and confirmed pathogenic PTEN mutations.

Schwannomatosis represents a group of rare genetic disorders that were previously classified under neurofibromatosis type 2. These disorders are characterized by the development of multiple tumors of the nervous system. One of the key manifestations of certain schwannomatosis subtypes is the development of meningiomas, occurring in approximately 50–70% of affected individuals. Meningiomas are most commonly observed in patients with NF2-associated schwannomatosis (Evans et al., 2020). BAP1 tumor predisposition syndrome is a rare hereditary cancer syndrome caused by germline mutations in the BAP1 gene, resulting in increased susceptibility to multiple malignancies, including cutaneous melanoma, uveal melanoma, renal cell carcinoma, and meningiomas (Carbone et al., 2020). The pathogenic mechanism involves loss of tumor suppressor function of the BAP1 protein, leading to impaired regulation of cell proliferation and tumor suppression.

Meningiomatosis (multiple meningioma syndrome) is defined by the presence of two or more spatially distinct meningiomas occurring either simultaneously (synchronously) or sequentially (metachronously). This condition is diagnosed in approximately 1–10% of patients with meningiomas. Its development is frequently associated with neurofibromatosis type 2 (NF2). Evidence also suggests an association with mutations in the SMARCB1, SUFU, and SMARCE1 genes; however, the inheritance pattern and penetrance remain incompletely characterized (Weller et al., 2017).

In addition, meningiomas may occur as part of other hereditary syndromes, including Gorlin syndrome, Cowden syndrome, Werner syndrome, and Gardner syndrome (Weller et al., 2017).

Hormonal factors

A substantial body of evidence indicates that certain forms of hormonal therapy, including oral contraceptives and hormone replacement therapy (HRT), are associated with an increased risk of meningioma development. The expression of hormone receptors in meningioma tissue is well documented, with progesterone receptors detected in up to 90% of cases, androgen receptors in up to 88%, and estrogen receptors in approximately 30% of tumors (Shu et al., 2019; Portet et al., 2020; Malueka et al., 2022; Roland et al., 2024).

A large national case-control study conducted by Roland et al. (2024) demonstrated a significant increase in the risk of intracranial meningioma associated with prolonged use of certain progestogens. The risk

was higher with long-term exposure to high doses. According to the authors, these findings suggest that exogenous hormonal stimulation plays a role in the development of meningioma.

The use of progestins has been particularly associated with an elevated risk of meningioma (Weill et al., 2021; Voormolen et al., 2021). Cyproterone acetate, a synthetic progestin, has been shown to induce meningioma development in a dose-dependent manner. Consequently, its use is contraindicated in patients with current or prior meningioma (Weill et al., 2021). Furthermore, evidence indicates an increased risk associated with the use of medrogestone, medroxyprogesterone acetate, and promegestone (Roland et al., 2024).

Roland et al. (2024) conducted a large-scale study evaluating the risk of intracranial meningioma associated with prolonged exposure to specific progestogens, including progesterone, hydroxyprogesterone, dydrogesterone, medrogestone, medroxyprogesterone acetate, promegestone, dienogest, and levonorgestrel-releasing intrauterine systems, administered via various routes such as oral, transdermal, vaginal, intramuscular, and intrauterine delivery. The study demonstrated a significant association between prolonged exposure to medrogestone (5 mg orally), medroxyprogesterone acetate (150 mg intramuscularly), and promegestone (0.125–0.5 mg orally) and an increased risk of intracranial meningiomas requiring surgical intervention.

It has also been proposed that mutations in the PIK3CA oncogene may represent a key molecular mechanism underlying hormone-associated meningioma development (Clark et al., 2016). Specifically, mutations affecting the catalytic subunit p110α of phosphatidylinositol 3-kinase (PI3K), encoded by the PIK3CA gene, have been identified in meningioma tissue samples, suggesting activation of the PI3K/AKT signaling pathway as a potential mediator of hormonally driven tumor growth.

Ionizing radiation

The association between ionizing radiation exposure and the development of meningiomas has been extensively investigated. Evidence indicates that even low doses of ionizing radiation can induce cellular mutations and increase the risk of tumorigenesis. One of the primary mechanisms underlying radiation-induced cellular damage involves the generation of reactive oxygen species (ROS), which disrupt essential biological macromolecules, including proteins, nucleic acids, and lipids, through oxidative stress pathways involving glutathione and superoxide dismutase (Hall et al., 2018).

DNA damage represents a central mechanism mediating the carcinogenic effects of ionizing radiation. Radiation-induced DNA damage can lead to impaired DNA replication and transcription, genomic instability, and malignant cellular transformation (Jeggo et al., 2016).

Ionizing radiation has been shown to increase the risk of meningioma development by approximately 6–10-fold (Brenner et al., 2020; Rajaraman et al., 2021). One of the most well-established clinical contexts associated with secondary meningioma formation is prior cranial radiotherapy administered for primary brain tumors, resulting in radiation-induced meningiomas (RIMs) (Yamanaka et al., 2017; Raheja et al., 2017).

Comparative analyses of radiation-induced meningiomas and sporadic meningiomas indicate that RIMs tend to exhibit more aggressive biological behavior, including higher growth rates (approximately 3.83 cm^3/year) and a greater likelihood of classification as WHO Grade II tumors. Molecular studies have demonstrated that approximately 90% of radiation-induced meningiomas harbor alterations in the NF2 gene, while approximately 26% exhibit loss of H3K27me3, an epigenetic marker associated with aggressive tumor behavior. Case reports have also documented the development of meningiomas following exposure to relatively low-dose radiation during medical procedures. For example, Kim et al. (2025) reported a case of a giant meningioma that developed 2.5 years after a minimally invasive endovascular procedure performed under fluoroscopic guidance. This finding highlights the potential role of cumulative low-dose radiation exposure (approximately 1.3 Gy) in meningioma pathogenesis (Goldbrunner et al., 2021).

Paradoxically, stereotactic radiosurgery (SRS) remains an important therapeutic modality for the treatment of meningiomas, including those induced by prior radiation exposure. High-dose focused radiation (>52 Gy) has been shown to effectively control tumor growth and induce tumor regression. However, patients previously exposed to cranial irradiation remain at elevated risk for the development of additional secondary tumors, necessitating lifelong MRI surveillance (Goldbrunner et al., 2021).

Furthermore, the risk of secondary brain tumor development following cranial irradiation in pediatric populations remains significant. Kim et al., 2025, reported that the risk of secondary brain tumor formation may reach up to 8.9% within 10 years after radiation therapy for primary brain tumors in children. Radiation-induced meningiomas in this population also demonstrate a tendency toward multifocal growth within the irradiated field.

Metabolic disorders

Increasing attention in contemporary scientific literature has been directed toward systemic metabolic dysfunction as a potential contributor to meningioma development. Obesity, insulin resistance, and chronic systemic inflammation are recognized as modifiable risk factors that may create a tumor-promoting microenvironment. However, the molecular mechanisms by which metabolic imbalance modulates gene expression in arachnoid cap cells remain incompletely understood.

In the study by Takahashi et al. (2019), the association between body mass index (BMI) and the risk of meningioma development was analyzed. The findings indicate that obesity, rather than merely being overweight, may play a significant role in the pathogenesis of meningioma. The study also highlights the need for further investigation into the biological mechanisms linking metabolic disturbances to tumor growth.

One of the key biological mechanisms linking obesity to meningioma development involves hormone dysregulation resulting from excess adipose tissue. Adipose tissue functions as an active endocrine organ capable of peripheral aromatization of androgens into estrogens, resulting in chronically elevated circulating estrogen levels in obese individuals. Given the high expression of progesterone receptors and, to a lesser extent, estrogen receptors in meningioma cells, hormonal imbalance may promote tumor cell proliferation and contribute to the growth of previously latent neoplastic lesions (Lauby-Secretan et al., 2016).

Another critical pathogenic mechanism associated with obesity is chronic low-grade systemic inflammation (Iyengar et al., 2016). Increased production of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), as well as adipokines such as leptin and resistin, creates a systemic pro-tumorigenic environment that can promote cellular proliferation, angiogenesis, and inhibition of apoptosis (Lauby-Secretan et al., 2016). Leptin, in particular, has been proposed as a potential mediator of meningioma growth through activation of oncogenic signaling pathways, including JAK/STAT and PI3K/AKT (Candelaria et al., 2016).

Obesity is also associated with metabolic abnormalities such as insulin resistance and hyperinsulinemia, which may contribute to tumorigenesis (Lauby-Secretan et al., 2016). Increased activity of insulin-like growth factor-1 (IGF-1) promotes cellular proliferation and inhibits apoptosis, representing an additional mechanism through which metabolic dysfunction may facilitate the development and progression of meningiomas (Sánchez-Jiménez et al., 2019).

Overall, obesity represents an important modifiable risk factor for meningioma development, acting through complex interactions involving hormonal dysregulation, inflammatory signaling, and metabolic pathway alterations (Takahashi et al., 2019).

Conclusions

Meningioma is a multifactorial neoplasm whose development is driven by a complex interplay of genetic, hormonal, metabolic, and environmental factors. Current evidence indicates that tumorigenesis is influenced not only by classical genetic alterations, including mutations in NF2, TRAF7, KLF4, SMO, and TERT, but also by epigenetic mechanisms that play a critical role in determining tumor biological behavior and clinical course.

Endocrine status represents a significant contributing factor, as evidenced by the marked sex-related differences in incidence, the frequent expression of progesterone and estrogen receptors in meningioma tissue, and the observed associations with hormonal therapy and reproductive factors. Hormonal regulation likely influences not only tumor initiation but also modulates tumor progression dynamics and recurrence risk.

Among exogenous risk factors, ionizing radiation remains the most well-established environmental contributor to meningioma development. Radiation-induced DNA damage, including double-strand breaks, chromosomal aberrations, and genomic instability, represents a key mechanism of tumorigenesis. These processes may act synergistically with underlying genetic susceptibility and hormonal–metabolic influences to promote tumor formation and progression.

Metabolic disturbances, including obesity, insulin resistance, dyslipidemia, and chronic inflammation, should also be considered important modifying factors that contribute to meningioma development. These conditions may promote tumor growth through hormonal dysregulation, activation of oncogenic signaling pathways, and the creation of a pro-tumorigenic systemic environment.

Further interdisciplinary research integrating molecular genetic, epidemiological, and clinical data is essential to advance understanding of meningioma pathogenesis and to facilitate the translation of these findings into improved diagnostic, prognostic, and therapeutic strategies in neuro-oncology.

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