Meningioma gene mutations

- High-resolution detection of copy number alterations in single cells with HiScanner
- Merlin immunoreactivity fails to predict neurofibromatosis type 2 mutations in human meningiomas
- Radiation-Induced Meningiomas Have an Aggressive Clinical Course: Genetic Signature Is Limited to NF2 Alterations, and Epigenetic Signature Is H3K27me3 Loss
- Total whole-arm chromosome losses predict malignancy in human cancer
- Clinicopathologic and Genomic Characteristics of Minute Pulmonary Meningothelial-like Nodules
- Integrated Clinical Genetic Analysis of Meningiomas Causing Bony Hyperostosis Shows More Severe Clinical Course and Overexpression of Secreted Pro-osteogenic Factors
- Short-term efficacy assessment of brigatinib for the treatment of neurofibromatosis type 2: A retrospective study
- High de novo mutation rate in Iranian NF2-related schwannomatosis patients with a report of a novel NF2 mutation

Meningioma pathogenesis is closely linked to specific gene mutations. The most well-characterized mutations in meningiomas include:

1. NF2 (Neurofibromin 2)

1. **Location:** Chromosome 22q12
2. **Frequency:** Found in ~40–60% of all meningiomas
3. **Function:** Tumor suppressor gene encoding **merlin**, which regulates cytoskeletal organization and cell proliferation.
4. **Clinical Association:** More common in **high-grade (WHO II/III)** and **lateral skull base** meningiomas.
5. **Sporadic vs. Syndromic:** Frequently mutated in **sporadic meningiomas** and almost universally affected in **NF2-related meningiomatosis**.

—- The GSTM1 null genotype is a novel biomarker of 1p-22q-NF2- meningioma recurrence that resolves heterogeneity in existing meningioma subtypes and may be used to guide future clinical management decisions on extent of treatment to improve patient outcomes [1)]

2. TRAF7 (TNF Receptor-Associated Factor 7)

1. **Location:** Chromosome 16p13
2. **Frequency:** Found in ~25% of meningiomas
3. **Function:** Regulates apoptosis and NF-κB signaling.
4. **Clinical Association:** More common in **non-NF2 mutant meningiomas**, particularly **meningothelial and secretory histology**.
5. **Prognosis:** Usually associated with **benign (WHO I) meningiomas**.

3. KLF4 (Kruppel-Like Factor 4)

1. **Location:** Chromosome 9q31
2. **Frequency:** Found in ~10–15% of meningiomas, often co-occurring with **TRAF7 mutations**.
3. **Function:** A transcription factor important for maintaining cellular differentiation.
4. **Clinical Association:** Strongly linked to **secretory meningiomas**, often coexisting with **TRAF7 mutations**.
5. **Prognosis:** Typically **benign**.

4. SMO (Smoothened)

1. **Location:** Chromosome 7q32
2. **Frequency:** ~5% of meningiomas.
3. **Function:** Part of the **Hedgehog signaling pathway**, critical in embryogenesis and tumorigenesis.
4. **Clinical Association:** Found in **midline skull base meningiomas (olfactory groove, tuberculum sellae)**.
5. **Therapeutic Target: Hedgehog pathway inhibitors** (e.g., vismodegib) could be a potential treatment.

5. POLR2A (RNA Polymerase II Subunit A)

1. **Location:** Adjacent to **NF2** on chromosome 22q.
2. **Clinical Association:** When deleted along with NF2, meningiomas tend to be **more aggressive**.

6. AKT1 (V-Akt Murine Thymoma Viral Oncogene Homolog 1)

1. **Location:** Chromosome 14q32
2. **Frequency:** Found in ~10–15% of meningiomas.
3. **Function:** A key component of the **PI3K-AKT pathway**, promoting cell survival and proliferation.
4. **Clinical Association:** Common in **skull base meningiomas**, especially **meningothelial** subtype.
5. **Therapeutic Target:** Potentially targetable with **AKT inhibitors**.

7. PIK3CA (Phosphatidylinositol 3-Kinase Catalytic Subunit Alpha)

1. **Location:** Chromosome 3q26
2. **Frequency:** Found in ~7% of meningiomas.
3. **Function:** Activates the **PI3K-AKT-mTOR** pathway.
4. **Clinical Association:** Frequently co-occurs with **AKT1 mutations**.
5. **Therapeutic Target: PI3K inhibitors** may be effective.

8. TERT (Telomerase Reverse Transcriptase) Promoter Mutations

1. **Location:** Chromosome 5p15.33
2. **Frequency:** Found in **high-grade meningiomas** (WHO II/III).
3. **Function:** Promotes **telomerase activity** and **cellular immortality**.
4. **Clinical Association:** Strong predictor of **poor prognosis**, **recurrence**, and **shorter survival**.

9. BAP1 (BRCA1-Associated Protein 1)

1. **Location:** Chromosome 3p21
2. **Frequency:** Rare but linked to **aggressive meningiomas**.
3. **Function:** Tumor suppressor involved in **DNA damage repair**.
4. **Clinical Association:** Loss-of-function mutations are seen in **high-grade (WHO III) meningiomas**.

10. CDKN2A/B (Cyclin-Dependent Kinase Inhibitor 2A/B) Deletions

1. **Location:** Chromosome 9p21
2. **Frequency:** Found in **anaplastic (WHO III) meningiomas**.
3. **Function:** Regulates **cell cycle arrest via p16INK4a and p14ARF**.
4. **Clinical Association:** Strong predictor of **malignancy and poor prognosis**.

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Genetic Classification and Therapeutic Implications Meningiomas can now be classified based on **genetic alterations** rather than just histopathology:

1. **NF2-mutant meningiomas**

1. **Location:** Lateral and convexity meningiomas.
2. **Prognosis:** Higher recurrence rates.
3. **Potential Therapy:** None currently targeted, but merlin-related pathways are under study.

2. **Non-NF2-mutant meningiomas**

1. **More common in skull base and midline locations**.
2. **Better prognosis unless TERT or CDKN2A/B alterations are present**.

3. **Aggressive/malignant meningiomas**

1. **Mutations:** TERT promoter, CDKN2A/B loss, BAP1 mutations.
2. **Therapeutic Targets:** CDK inhibitors, immunotherapy trials.

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Key Takeaways - **NF2 mutation** → Most common, associated with **lateral convexity meningiomas**, higher grade. - **TRAF7, KLF4, AKT1, SMO** → Associated with **skull base meningiomas**, generally benign. - **PIK3CA, AKT1** → Targetable with **PI3K/AKT inhibitors**. - **TERT, CDKN2A/B, BAP1** → Associated with **high-grade meningiomas and poor prognosis**.

Would you like insights on potential targeted therapies or current clinical trials for specific mutations?

Loss of chromosome 22q and the neurofibromatosis-2 (NF2) gene to other non-NF2 driver mutations (KLF4, TRAF7, AKT1, SMO, etc.) discovered using next generation sequencing [2)].

Prior studies have demonstrated a relationship between underlying tumor genetics and lymphocyte infiltration in meningiomas. In this study, the authors aimed to further characterize the relationship between meningioma genomics, CD4+ and CD8+ T-cell infiltration, and oncological outcomes of meningiomas. Understanding specific characteristics of the inflammatory infiltration could have implications for treatment and prognostication.

Immunohistochemically stained meningioma slides were reviewed to assess the CD4+ and CD8+ cell infiltration burden. The relationship between immune cell infiltration and tumor genomics was then assessed using an adjusted ANOVA model. For a specific gene identified by the ANOVA, the relationship between that mutation and tumor recurrence was assessed using Cox regression.

In immunohistochemically stained samples from a subcohort of 25 patients, the mean number of CD4+ cells was 42.2/400× field and the mean number of CD8+ cells was 69.8/400× field. Elevated CD8+ cell infiltration was found to be associated with the presence of a mutation in the gene encoding for DNA polymerase epsilon, POLE (51.6 cells/hpf in wild-type tumors vs 95.9 cells/hpf in mutant tumors; p = 0.0199). In a retrospective cohort of 173 patients, the presence of any mutation in POLE was found to be associated with a 46% reduction in hazard of progression (HR 0.54, 95% CI 0.311-0.952; p = 0.033). The most frequent mutation was a near-C-terminal nonsense mutation.

A potential association was found between mutant POLE and both an increase in CD8+ cell infiltration and progression-free survival. The predominant mutation was found outside of the known exonuclease hot spot; however, it was still associated with a slight increase in mutational burden, CD8+ cell infiltration, and progression-free survival. Alterations in gene expression, resulting from alterations in POLE, may yield an increased presentation of neoantigens, and, thus, greater CD8+ cell-mediated apoptosis of neoplastic cells. These findings have suggested the utility of checkpoint inhibitors in the treatment of POLE-mutant meningiomas [3].

Several Familial Tumor Syndromes of the Central Nervous systems are characterized by increased meningioma risk, and the genetics of these syndromes provides mechanistic insight into sporadic disease. The best defined of these syndromes is neurofibromatosis type 2, which is caused by a mutation in the NF2 gene and has a meningioma incidence of approximately 50%. This finding led to the subsequent discovery that NF2 loss-of-function occurs in up to 60% of sporadic tumors. Other important familial diseases with increased meningioma risk include nevoid basal cell carcinoma syndrome, multiple endocrine neoplasia 1 (MEN1), Cowden syndrome, Werner syndrome, BAP1 tumor predisposition syndrome, Rubinstein Taybi syndrome, and familial meningiomatosis caused by germline mutations in the SMARCB1 and SMARCE1 genes.

Other intrinsic risk factors (gender, ethnic groups, allergic conditions, familial and personal history, genetic polymorphisms)

Meningioma molecular pathogenesis

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molecular targets for therapeutic intervention. Further studies are needed to resolve the functional relevance of specific genes whose significance in sporadic disease remains to be elucidated [4].

Understanding these disrupted pathways will aid in deciphering the relationship between various genetic changes and their downstream effects on meningioma pathogenesis. Torres-Martin et al. identified a subset of genes that were upregulated in meningiomas and schwannomas when compared to their respectively healthy tissues, including PDGFD, CDH1 and SLIT2. Thus, these genes should be thoroughly studied as targets in a possible combined treatment [5].

Classic cytogenetic studies have disclosed a progressive course of chromosomal aberrations, especially in high-grade meningiomas. The application of unbiased next-generation sequencing approaches has implicated several novel genes whose mutations underlie a substantial percentage of meningiomas. These insights may serve to craft a molecular taxonomy for meningiomas and highlight putative therapeutic targets in a new era of rational biology-informed precision medicine [6].

The major known genetic contributor to meningioma formation was NF2, which is disrupted by mutation or loss in about 50% of tumors. Besides NF2, several recurrent driver mutations were recently uncovered through next-generation sequencing.

Tang et al., performed whole-genome sequencing across 7 tumor-normal pairs to identify somatic genetic alterations in meningioma. As a result, Chromatin regulators, including multiple histone members, histone-modifying enzymes and several epigenetic regulators, are the major category among all of the identified copy number variants and single nucleotide variants. Notably, all samples contained copy number variants in histone members. Recurrent chromosomal rearrangements were detected on chromosome 22q, 6p21-p22 and 1q21, and most of the histone copy number variants occurred in these regions. These results will help to define the genetic landscape of meningioma and facilitate more effective genomics-guided personalized therapy [7].

Non-NF2 meningiomas concern AKT1, SMO, KLF4 and TRAF7. The molecular mechanisms underlying tumorigenesis of high histological grades have been progressively deciphered with the recent discovery of TERT promoter mutations in progressing tumors. A better understanding of the genetics and clinical behavior of high-grade meningiomas is mandatory in order to better design future clinical trials. New genetically engineered mouse models of benign and histologically aggressive meningioma represent a substantial resource for the establishment of relevant pre-clinical trials. By studying the mechanisms underlying these new tumorigenesis pathways and the corresponding mouse models, we should be able to offer personalized chemotherapy to patients with surgery- and radiation-refractory meningiomas in the near future [8].

An understanding of the genetic and molecular profile of meningioma would provide a valuable first step towards developing more effective treatments for this intracranial tumor. Chromosomes 1, 10, 14, 22, their associated genes, and other potential targets have been linked to meningioma proliferation and progression. It is presumed that through an understanding of these genetic factors, more educated meningioma treatment techniques can be implemented. Future therapies will include combinations of targeted molecular agents including gene therapy, si-RNA mediation, proton therapy, and other approaches as a result of continued progress in the understanding of genetic and biological changes associated with meningiomas [9].

Some authors believe that even with a long-term follow up, the more aggressively removed

meningiomas will regrow, possibly because of remaining cells or the molecular biology of the tumors.

Cytogenetics aspects involved in the recurrence and progression of World Health Organization (WHO) grade I meningiomas are well known, including losses in 1 p and other chromosomal abnormalities and play an important role in the recurrence of the meningioma [10) 11)].

Classic cytogenetic studies have disclosed a progressive course of chromosomal aberrations, especially in high-grade meningiomas. The application of unbiased next-generation sequencing approaches has implicated several novel genes whose mutations underlie a substantial percentage of meningiomas. These insights may serve to craft a molecular taxonomy for meningiomas and highlight putative therapeutic targets in a new era of rational biology-informed precision medicine [12)].

Kirches et al. report detailed genomic analyses of 37 pediatric meningiomas by sequencing and DNA methylation profiling. Histologically, the series was dominated by meningioma subtypes with aggressive behavior, with 70% of patients suffering from WHO grade II or III meningiomas. The most frequent cytogenetic aberrations were loss of chromosomes 22 (23/37 [62%]), 1 (9/37 [24%]), 18 (7/37 [19%]), and 14 (5/37 [14%]). Tumors with NF2 alterations exhibited overall increased chromosomal instability. Unsupervised clustering of DNA methylation profiles revealed separation into three groups: designated group 1 composed of clear cell and papillary meningiomas, whereas group 2A comprised predominantly atypical meningiomas and group 2B enriched for rare high-grade subtypes (rhabdoid, chordoid). Meningiomas from NF2 patients clustered exclusively within groups 1 and 2A. When compared with a dataset of 105 adult meningiomas, the pediatric meningiomas largely grouped separately. Targeted panel DNA sequencing of 34 tumors revealed frequent NF2 alterations, while other typical alterations found in adult non-NF2 tumors were absent. These data demonstrate that pediatric meningiomas are characterized by molecular features distinct from adult tumors [13)]

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