Molecular Alterations in Skull Base Meningiomas: Implications for Prognosis and Management

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Abstract

Skull base meningiomas represent ~20–25% of all meningiomas, most commonly arising in the anterior (30–40%), middle (40–50%), and posterior fossae (20–30%).

Their clinical behavior often diverges from what is expected based on histopathologic grade, underscoring the need for molecular risk stratification.

This review synthesizes current evidence on molecular drivers in skull base meningiomas. NF2 inactivation (20–40%) is more frequent in posterior fossa tumors and is associated with chromosomal instability and higher recurrence.

Results

Functional studies further highlight that *TRAF7* mutations modulate the tumor immune microenvironment, with upregulated PD-L1, IDO, and TDO2 expression, suggesting suppression of anti-tumor immune responses.

AKT1 mutations are also associated with elevated TDO2. Epigenetic alterations, including DNA methylation subclasses and H3K27me3 loss, further refine risk stratification and often outperform WHO grading in predicting recurrence.

TRAF7 mutations (15–25%) that co-occur with *KLF4*, *AKT1*, or *PIK3CA* alterations, predominate in anterior and middle fossa lesions, particularly in the sphenoid wing and planum sphenoidale.

TRAF7-mutated tumors typically display benign meningothelial histology with low recurrence risk. *TRAF7* and *KLF4* co-mutations define the secretory subtype, which remains benign but may present with more peritumoral edema.

KLF4 mutations are also enriched in petroclival tumors. *SMO* mutations (5–7%) localize to the anterior midline and are associated with calcification and a higher recurrence rate.

AKT1 mutations (10–15%, E17K hotspot) activate PI3K/mTOR signaling and are targetable, typically located in the anterior skull base and foramen magnum.

TERT promoter mutations (5–10%) and CDKN2A/B deletions (5–8%) identify aggressive biology, especially in recurrent posterior fossa disease, predicting early recurrence and poor survival.

Conclusions

Integrating these molecular insights into surgical planning can guide the extent of resection, inform adjuvant therapy selection, and support personalized follow-up strategies.

Tumors with benign molecular profiles, such as *TRAF7* or *TRAF7/KLF4*-mutated secretory meningiomas, may allow less aggressive surgical approaches, whereas high-risk tumors with *TERT* or CDKN2A/B alterations warrant close surveillance and consideration for adjuvant therapy.

Prospective, molecularly guided studies are essential to validate these findings and to develop standardized risk stratification frameworks, advancing precision care in skull base meningioma management.