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CLINICAL ARTICLE

Genetic characterization and mutational profiling of foramen magnum meningiomas: a multi-institutional study

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OBJECTIVE Foramen magnum (FM) meningiomas pose significant surgical challenges and have high morbidity and mortality rates. This study aimed to investigate the distribution of clinically actionable mutations in FM meningiomas and identify clinical characteristics associated with specific mutational profiles.

METHODS The authors conducted targeted next-generation sequencing of 62 FM meningiomas from three international institutions, covering all relevant meningioma genes (*AKT1*, *KLF4*, *NF2*, *POLR2A*, *PIK3CA*, *SMO*, *TERT* promoter, and *TRAF7*). Patients with a radiation-induced meningioma or neurofibromatosis type 2 (NF2) were excluded from the study. Additionally, patient and tumor characteristics, including age, sex, radiological features, and tumor location, were retrospectively collected and evaluated.

RESULTS The study cohort consisted of 46 female and 16 male patients. Clinically significant driver mutations were detected in 58 patients (93.5%). The most commonly observed alteration was *TRAF7* mutations (26, 41.9%), followed by *AKT1*^{E17K} mutations (19, 30.6%). Both mutations were significantly associated with an anterolateral tumor location relative to the brainstem ($p = 0.0078$). *NF2* mutations were present in 11 cases (17.7%) and were associated with posterior tumor location, in contrast to tumors with *TRAF7* and *AKT1*^{E17K} mutations. Other common mutations in FM meningiomas included *POLR2A* mutations (8, 12.9%; 6 *POLR2A*^{Q403K} and 2 *POLR2A*$^{(H439\_L443del)}$), *KLF4*^{K409Q} mutations (7, 11.3%), and *PIK3CA* mutations (4, 6.5%; 2 *PIK3CA*^{H1047R} and 2 *PIK3CA*^{E545K}). *POLR2A* and *KLF4* mutations exclusively occurred in female patients and showed no significant association with specific tumor locations. All tumors harboring *AKT1*^{E17K} and *POLR2A* mutations displayed meningothelial histology. Ten tumors exhibited intratumoral calcification, which was significantly more frequent in *NF2*-mutant compared with *AKT1*-mutant FM meningiomas ($p = 0.047$).

CONCLUSIONS These findings provide important insights into the molecular genetics and clinicopathological characteristics of FM meningiomas. The identification of specific genetic alterations associated with tumor location, volume, calcification, histology, and sex at diagnosis may have implications for personalized treatment strategies in the future.

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KEYWORDS foramen magnum; meningioma; skull base; *AKT1*; *NF2*; *POLR2A*; *TRAF7*; oncology

FORAMEN magnum (FM) meningiomas are rare tumors that present formidable surgical challenges and carry the risk of postoperative complications because of their proximity to critical neurovascular structures.[1,2] Consequently, FM meningiomas are associated with a higher incidence of morbidity and mortality compared with meningiomas occurring in other locations.[2,3] Given these factors, it is crucial to delve deeper into the

ABBREVIATIONS FFPE = formalin-fixed paraffin-embedded; FM = foramen magnum; NF2 = neurofibromatosis type 2; NGS = next-generation sequencing.

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