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LETTER TO THE EDITOR

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Genetic analysis of foramen magnum meningiomas reveals *AKT1* mutations uncomplicated by *TRAF7* mutations

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Foramen magnum meningiomas (FMMs) are rare, accounting for approximately 1% of intracranial meningiomas [2]. Genetic profiling of intracranial meningiomas in recent years suggests an association between tumor location and driver mutation [1, 3, 4, 6]. What remains to be fully elucidated are the genetic profiles of meningiomas at localized anatomic sites such as the foramen magnum.

The foramen magnum is at the boundary of two anatomic sites, cranial and cervical, and meningiomas at these sites have different genetic profiles. Owing to the extensive adherence of meningiomas to the dura mater, identifying their site of origin, and thus categorizing them by anatomical site, is extremely challenging. For example, if a large meningioma in the cerebellar pontine angle is attached to both the cerebellar tentorium and the petrous bone, either of these may be the true origin site. Even if a meningioma appears to be located in the foramen magnum, it may have originated in the jugular foramen and extended inferiorly or in the cervical spinal cord and extended superiorly.

Meningiomas can be classified based on their feeder artery (as has been proposed for posterior fossa meningiomas) [9] or on their site of attachment to the dura mater (as is conventionally done for large meningiomas). In the present study, we accurately identified the main feeder of meningiomas via preoperative three-dimensional rotational angiography (3DRA) or digital subtraction angiography and defined FMMs according to where the main feeder entered the tumor. Representative images are shown in Fig. 1a. This method enabled us to perform a genetic analysis that is truly limited to meningiomas arising from the foramen magnum.

Twelve patients surgically treated for FMM at our institution from 2003 to 2022 were included in our study. FMMs were defined as those with dural attachment sites below the jugular foramen and above the atlas vertebrae. Also defined as FMMs were large meningiomas with extensive attachment to the dura and a main feeder from the hypoglossal branch of the ascending pharyngeal artery to the dura of the hypoglossal canal or from the segmental branch of the vertebral artery to the dura of the foramen magnum. Patients with meningiomas in the jugular foramen, clivus, or upper cervical spine are excluded from the study. Posterior fossa meningiomas excluding FMMs (i.e., those categorized as clivus, petrous, infratentorial, and cerebellar convexity) were examined for comparison and their feeding center was identified via 3DRA.

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On exome sequencing, *AKT1* p.Glu17Lys was the most predominant driver mutation in FMMs (n = 7, 58%) and was not accompanied by *TRAF7* mutation (Fig. 1b). NF2/22q(−) FMMs were observed in two cases and *POLR2A* mutations in three cases. Two FMMs with *AKT1* mutations also harbored *NF2* and *POLR2A* mutations, respectively (Supplementary Table 1; Cases 6, 7). Most FMMs had a low number of somatic copy number alterations (Fig. 1b). All tumors with *AKT1* mutations were located in the anterior or lateral foramen magnum and not in the posterior foramen magnum. Clinically, *AKT1*-mutant tumors were benign and associated with older age ($p = 0.034$) (Supplementary Table 2). Both *AKT1* and *TRAF7* mutations were present in 3.7% (2/54) of posterior fossa meningiomas excluding FMMs. The distribution of driver mutations in meningiomas originating from the foramen magnum, tentorium, petrous, and clivus is shown in Supplementary Fig. 1.

The most important finding of this study was that *AKT1* p.Glu17Lys was the most frequent driver gene mutation in FMM, whereas *TRAF7* mutations were absent. There were also cases in which *AKT1* and *NF2* mutations and *AKT1* and *POLR2A* mutations occurred simultaneously.

In 74% of common intracranial meningioma cases, *AKT1* mutations are accompanied by *TRAF7* mutations [4]. In our study, all posterior fossa meningiomas, excepting FMMs, exhibited *TRAF7* mutations. In contrast, in a large cohort of spinal meningiomas, *AKT1* mutations coexisted with *TRAF7* mutations in only 9% of cervical cases and were anatomically characteristic of tumors in the ventral and ventrolateral regions of the cervical spinal cord [8]. The foramen magnum is anatomically located at the border between the skull and the cervical spine, and the results of this study indicate that the genetic profile of FMMs may be more similar to that of spinal meningiomas of the cervical spinal cord than to that of common intracranial meningiomas (Fig. 1c).

In meningiomas with *AKT1* and *TRAF7* co-mutations, single-cell DNA sequencing of tumor samples revealed that the *TRAF7* mutation preceded the *AKT1* mutation [5]. Thus, the *TRAF7* mutation is considered to be the more ancestral driver mutation in *AKT1*/*TRAF7*-co-mutated meningiomas. In a recently published multicenter study of FMMs, *TRAF7* was the most commonly observed mutation, followed by *AKT1* mutation [7]. Close review of the results revealed 12 cases of *TRAF7* mutations without *KLF4* mutations, seven cases with both *TRAF7* and *AKT1* mutations, and 12 cases with *AKT1* mutations alone. The proportion of *AKT1*/*TRAF7* co-mutations was lower in FMMs than in other posterior fossa meningiomas. Despite the large number of cases in the cohort, the exact site of origin was not identified; doing so may require including tumors that originate around the jugular foramen or extend downward to the foramen magnum from the clivus. Our findings support the use of the main feeding artery for accurate identification of tumor origin and will aid efforts investigating the association between anatomical location and genetic profile.

In summary, the *AKT1* p.Glu17Lys mutation and the absence of *TRAF7* mutation are genetic features of anterior/lateral FMMs. Our study indicates that FMMs better resemble spinal meningiomas than common intracranial meningiomas in terms of driver mutations.

(See figure on next page.)

Fig. 1 **a** Representative magnetic resonance imaging and three-dimensional rotational angiography of foramen magnum meningiomas and their feeding arteries. Data for case 5 and case 11 (posterior) are shown. The feeding arteries are indicated by yellow arrowheads. **b** Driver mutations and copy number alterations in foramen magnum meningiomas (n = 12). World Health Organization grade, histological subtype, age, and sex, as well as representative driver mutations, are shown. **c** Schematic diagram of the genetic features of the posterior fossa, foramen magnum, and cervical spinal meningiomas

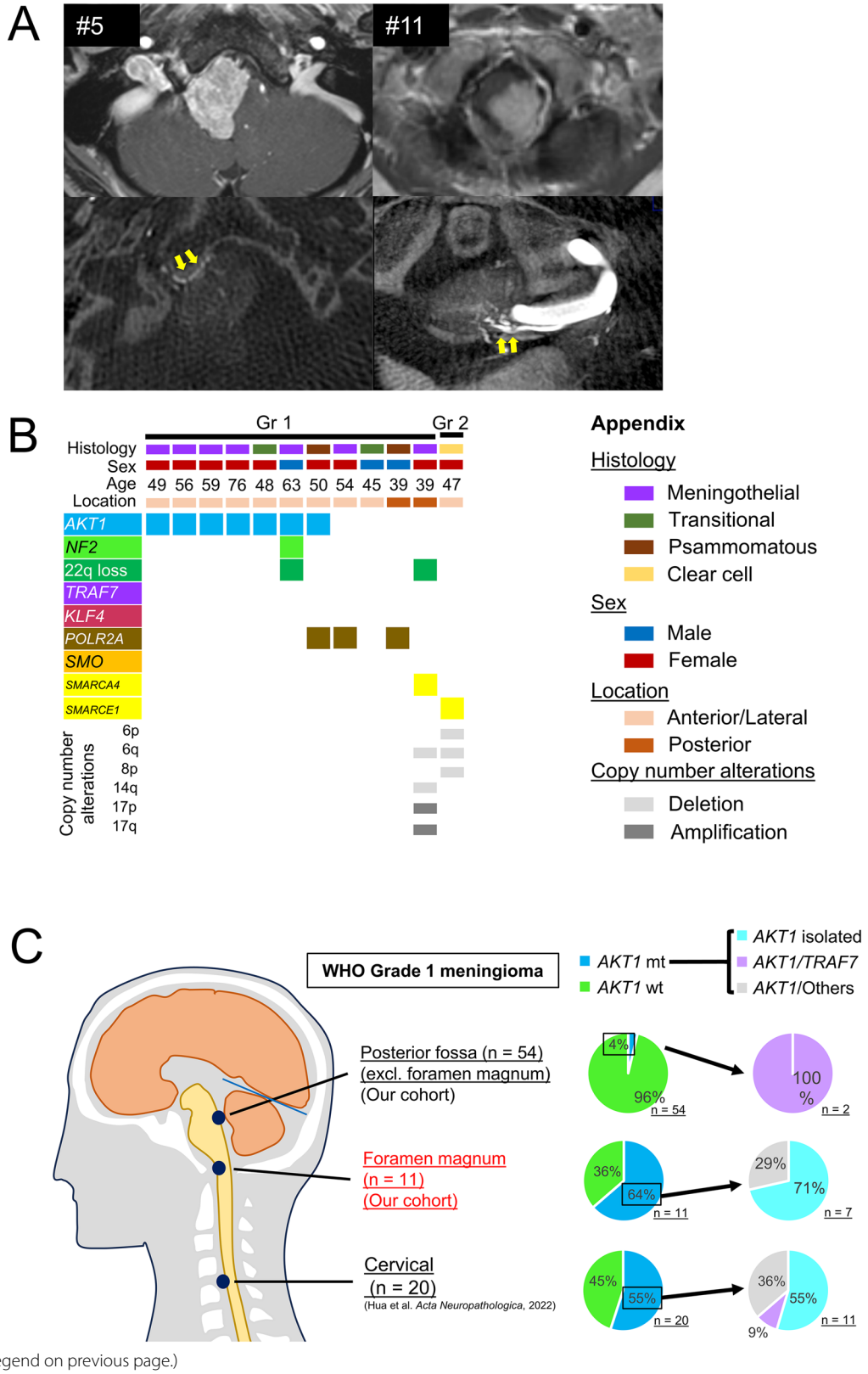

Fig. 1 (See legend on previous page.)

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40478-024-01835-7.

Additional file 1.

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None.

Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yudai Hirano, Satoru Miyawaki, Yu Sakai, Yu Teranishi, Atsushi Okano, Hiroki Hongo, Seiei Torazawa, and Motoyuki Umekawa. Data analysis was performed by Daisuke Komura, Hiroto Katoh, and Shumpei Ishikawa. The first draft of the manuscript was written by Yudai Hirano and all authors commented on previous versions of the manuscript. Nobuhito Saito supervised this project. All authors read and approved the final manuscript.

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Data availability
Data is available upon reasonable request. The authors confirm that the data supporting the findings of this study will be shared upon request from any qualified investigator.

Declarations

Ethics approval and consent to participate
The Institutional Review Board approved the study protocol at The University of Tokyo Hospital (G10028).

Inform consent
All study participants provided informed consent for publication of their information.

Competing interests
The authors have no relevant financial or non-financial interests to disclose.

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