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Oncogenic PI3K mutations are as common as *AKT1* and *SMO* mutations in meningioma

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See the editorial by Zadeh et al., on pages 603–604.

Background. Meningiomas are the most common primary intracranial tumor in adults. Identification of *SMO* and *AKT1* mutations in meningiomas has raised the possibility of targeted therapies for some patients. The frequency of such mutations in clinical cohorts and the presence of other actionable mutations in meningiomas are important to define.

Methods. We used high-resolution array-comparative genomic hybridization to prospectively characterize copy-number changes in 150 meningiomas and then characterized these samples for mutations in *AKT1*, *KLF4*, *NF2*, *PIK3CA*, *SMO*, and *TRAF7*.

Results. Similar to prior reports, we identified *AKT1* and *SMO* mutations in a subset of non-*NF2*-mutant meningiomas (ie, ∼9% and ∼6%, respectively). Notably, we detected oncogenic mutations in *PIK3CA* in ∼7% of non-*NF2*-mutant meningiomas. *AKT1*, *SMO*, and *PIK3CA* mutations were mutually exclusive. *AKT1*, *KLF4*, and *PIK3CA* mutations often co-occurred with mutations in *TRAF7*. *PIK3CA*-mutant meningiomas showed limited chromosomal instability and were enriched in the skull base.

Conclusion. This work identifies PI3K signaling as an important target for precision medicine trials in meningioma patients.

Keywords: aCGH, *AKT1*, meningioma, molecular pathology, *NF2*, *PIK3CA*, *SMO*.

Meningiomas are the most common primary brain tumors in adults.[1] Inactivation of *NF2* by mutations and by monosomy 22 is a well-established driver of a substantial number of meningiomas.[2–5] Recent genomic analyses have shown that *AKT1*, *KLF4*, *SMARCE1*, *SMO*, and *TRAF7* are commonly mutated in non-*NF2*-mutant meningiomas.[6–10]

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These genomic studies have shown that the patterns of mutations and chromosomal aberrations found in meningiomas are associated with distinct histological subtypes and anatomic distribution of the tumors within the central nervous system.[11] For example, *KLF4(K409Q)* and *TRAF7* mutations co-occur in secretory meningiomas,[7,8] while mutations in *SMARCE1* occur in clear-cell meningiomas.[9,10] Fibroblastic meningiomas harbor *NF2* mutations,[6,7] while angiomatous meningiomas lack *NF2* mutations but have multiple chromosomal polysomies.[12] Meningiomas arising in the convexities and posterior skull base often have inactivating mutations in *NF2* and monosomy 22, while meningiomas arising in the anterior and lateral skull base tend to have mutations in *SMO (L412F, W535L) or AKT1 (E17K)*.[6,7]

Based on this genomic data, a multicenter National Cancer Institute-sponsored phase 2 study (NCT02523014) of vismodegib and afuresertib is underway for patients with progressive or recurrent *SMO* and *AKT1*-mutant meningiomas, respectively. To date, medical therapies for meningiomas refractory to surgery and radiation have been largely ineffective,[13–15] and this clinical trial of vismodegib and afuresertib is the first study in meningiomas that directly targets the oncogenic drivers of this disease.

The frequent occurrence in meningiomas of monosomy 10, which leads to PTEN loss[11,16] and the presence of *AKT1* mutations,[6,7] suggests that activation of the PI3K pathway is important in the pathogenesis of some meningiomas.[11,17,18] We investigated if *PIK3CA* mutations also occur frequently in meningiomas and characterized both mutations and chromosomal copy number changes that might co-occur with *PIK3CA* mutations in a clinical cohort of 150 meningiomas.

Materials and Methods

Specimens, Clinical Characteristics, and Genomic Characterization

We conducted a genetic analysis of meningioma specimens following approval by the Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) Institutional Review Board. Array-comparative genomic hybridization (aCGH) was performed prospectively as part of routine clinical care on 181 meningioma samples that were either reviewed in consultation, investigated because of clinical request from the treating physician, or were resected at Dana Farber/Brigham and Women's Cancer Center between May 2012 and July 2014. The meningioma cohort used in this study is representative of the general patient population at our institution and includes all meningioma specimens received during the indicated time frame from which ample material was available for genomic analysis. All tumors came from different patients. All aCGH testing was performed within a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory in the Clinical Cytogenetics Laboratory/Center for Advanced Molecular Diagnostics at Brigham and Women's Hospital (see below for details).[19,20] Review of the available clinical history did not reveal definitive information to support any of these cases being syndromic. Sequencing of matched normal germline DNA was not performed for this study, precluding definitive determination of the syndromic status. One hundred and fifty samples (Supplementary material, Table S1) had sufficient DNA available for sequencing (see below for details). All meningioma samples were first reviewed during the clinical evaluation after resection and then again by 2 neuropathologists (M.A.A., S.S.). Genomic characterization of a small subset of cases (5 having somatic mutation testing, 16 aCGH) was previously reported.[12] The samples were classified and graded according to World Health Organization (WHO) criteria.[1] Tumor recurrence was defined by a qualitative assessment based on clinical judgement whether the measurable lesion on MR imaging had increased by ≥25% (bidirectional area). Information about treatment and extent of resection were provided for *AKT1* mutant cases.

Array-comparative Genomic Hybridization Using Formalin-fixed Paraffin-embedded Samples

To identify tumor-specific genomic copy number alterations, we performed OncoCopy, an aCGH test using a stock 1 × 1 M Agilent SurePrint G3 Human CGH Microarray chip. Two micrograms of DNA, corresponding to ∼10 × 5 μm standard formalin-fixed paraffin-embedded (FFPE) sections or 6 × 1 mm punches containing at least 50% tumor, were obtained from each specimen. Genomic DNA isolated from FFPE blocks was hybridized with genomic DNA isolated from a commercial reference DNA sample (Promega). The array platform contained 963 029 probes spaced with a 2.1 kb overall median probe spacing and a 1.8 kb probe spacing in RefSeq genes across the human genome. Data analysis was performed according to standard settings of the CLIA laboratory as previously described.[12,20] Copy number alterations (CNAs), which we routinely assess in clinical aCGH reports for meningiomas, are presented here for each sample (Supplementary material, Table S1), with events scored individually for single copy loss of 11 loci.[21] The number of CNAs was summed to generate a cytogenetic abnormality score (CAS).[21] For example, if a patient had a loss of chromsomes 1p, 4p, and 10q, the CAS would be 3.

DNA Isolation and Exon Sequencing of Meningioma Formalin-fixed Paraffin-embedded Samples

We obtained tumor DNA from ∼5–10 mm × 0.6 mm punches (diameter 1 mm, Miltex) from FFPE tissue blocks containing at least 50% tumor using a QIAamp DNA FFPE Tissue Kit (Qiagen). The concentration of double-stranded DNA from the tumors was quantified using a Quant-iT PicoGreen dsDNA Assay Kit (Life Technologies). For consult cases, the tumor DNA remaining from the aCGH analysis was used for sequencing.

All exons of *AKT1*, *KLF4*, *NF2*, *PIK3CA*, *SMO*, and *TRAF7* were sequenced from the tumor samples using a custom, next-generation sequencing assay developed at the Center for Cancer Genome Discovery at the Dana-Farber Cancer Institute according to methods previously described.[12] In brief, prior to preparation of the library, 200 ng of double-stranded DNA were fragmented into ∼250 bp segments using Covaris sonication (LE220 Focused-ultrasonicator, Covaris). Fragmented DNA was purified using Agencourt AMPure XP beads (Beckman Coulter), ligated to sequencing adaptors with sample-specific barcodes during library preparation (SPRIworks HT, Beckman Coulter) and quantified and normalized based on Miseq Nano sequencing (Illumina Inc.). For exon enrichment, libraries

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were pooled in equal mass to a total of 500 ng, and exonic regions were captured with the SureSelect Target Enrichment system (Agilent Technologies). The capture pool was sequenced in one lane of the HiSeq 2500 system (Illumina Inc.) in rapid-run mode.

Mutation analysis for single nucleotide variants was performed using MuTect v1.1.4 and annotated by Oncotator (http://www.broadinstitute.org/oncotator/). Matched normal DNA was not used in this analysis. We used the SomaticIndelDetector tool, which is part of the Genome Analysis ToolKit (GATK), for indel calling. MuTect and SomaticIndelDetector were run in paired mode using internal control CEPH DNA as the normal control DNA for tumor samples that did not have a matched normal. The CEPH DNA (Coriell Institute for Medical Research, # NA10831) was purified from a B-lymphocyte-derived cell line from a Caucasian female in Utah. Furthermore, a germline variant filter was applied; nonsynonymous variants were filtered against the Exome Sequencing Project (ESP) database ESP6500SI-V2 (http://evs.gs.washington.edu/EVS/). Variants that were present in >1% of African-American or European-American individuals and that were not reported in the COSMIC database (Catalogue Of Somatic Mutations In Cancer, http://cancer.sanger.ac.uk/cosmic) more than two times were considered to be germline. A minimum allelic fraction of 0.05 (ie, >5% of the sequencing reads contained the mutation) was used as a threshold of mutation calling. Mutation frequency is reported as allelic fractions (eg, 0.25 allelic fraction equals 25% of allele reads containing the specified change).

Association of genetic features within our cohort was assessed using the odds ratio (OR), the quantification of association between two given properties in a given population. OR values >2 were considered to be associated. Since the OR is a function of cell probability, association significance was recovered from ORs and marginal probabilities ($P < .05$). Mutual exclusivity was assessed using the Fisher exact test where indicated in the text ($P < .05$).

Table 1. Demographic and pathologic data of cohort

Meningioma Clinical Cohort Data	
Total cases	150
Age, mean (range), y	58 (22–90)
Sex (F:M)	95:55
WHO grade	
I	104
II	41
III	5
Location	
Skull base	73
Convexity	70
Intraventricular	2
Spinal	4
Unknown	1
Primary tumor	118
Recurrent tumor	32
Radiation-induced tumor	12

Results

Our cohort of 150 meningiomas included 73 tumors from the skull base, 70 from the convexities, four from the spinal cord, and two from the ventricles (Table 1). The cohort included 104 WHO grade I, 41 grade II, and 5 grade III meningiomas. The mean age of the participants was 57 years. Ninety-five participants were female, and 55 were male (Table 1). Twelve of the tumors were radiation-induced.

Fifty-five of the 150 meningiomas had mutations in *NF2*, and 85 had monosomy 22 (Fig. 1 and Supplementary material, Table S1–S3). Of the 95 meningiomas that lacked *NF2* mutations, 7 tumors (7.4%; 4.7% of all cases in this cohort) harbored 5 different well-established oncogenic mutations in *PIK3CA*, which encodes the phosphoinositide-3-kinase (PI3K) catalytic subunit p110α. Individual cases had E110del, N345K, E453K, and E545K mutations, and 3 cases had H1047R mutations (Fig. 2A and Supplementary material, Table S1). Allelic fractions ranged from 0.25 to 0.54 (ie, 25%–54% of the allele reads contained the specified genetic alteration). One additional case harbored a mutation (HC419del) of unclear significance, which we therefore excluded from further analysis.

Of the non-*NF2*-mutant meningiomas, 23 had mutations in *TRAF7*, with all of the mutations located within the C-terminal 7 WD40-repeat regions. Ten cases had *KLF4(K409Q)* mutations, 9 had *AKT1*(E17K) mutations, and 6 had *SMO* mutations (including 5 cases with the L412F mutation and one with a W535L mutation; Fig. 1 and Supplementary material, Table S1). In all, 16 tumors harbored mutations in a component of the PI3K signaling pathway (16.8% of non-*NF2*-mutant meningiomas; 10.7% of all cases in this cohort).

All nine *AKT1*(E17K)-mutant meningiomas had a CAS[21] of zero, indicating no significant arm level CNAs (Fig. 1). Two of the 9 *AKT1*(E17K) mutations were detected in recurrent tumors, and one was detected in a meningioma that subsequently recurred (Fig. 1, see Supplementary material, Table S1 for clinical details). Six of the 9 *AKT1*(E17K)-mutant meningiomas arose in the skull base (Fig. 2B and Supplementary material, Table S1), two arose over the frontal lobes, and one was a spinal metastasis (MG-79) from a primary meningioma in the clivus region (Supplementary material, Table S1).

Four of the six *SMO*-mutant tumors (five L412F and one W535L) arose in the skull base (Fig. 2B and Supplementary material, Table S1). Two *SMO*(L412F)-mutant meningiomas arose over the convexities (parietal and parietal-occipital areas). The other three *SMO*(L412F)-mutant meningiomas arose in the midline of the skull base (olfactory groove, tuberculum/planum sphenoidale), and the *SMO*(W535L)-mutant meningioma arose in the clinoid-to-sphenoid wing area. All *SMO*-mutant tumors lacked chromosomal instability and had a CAS of zero (Supplementary material, Table S1).

As previously described,[7,8] *TRAF7* and *KLF4(K409Q)* mutations frequently co-occurred in secretory meningiomas (OR = 33, $P = .003$) (Fig. 1 and 2C). All eight of the meningiomas with both *TRAF7* and *KLF4* mutations occurred in the skull base (Fig. 1 and 2B). *AKT1*(E17K) mutations tended to co-occur with *TRAF7* mutations (OR = 27, $P = .006$) (Fig. 1 and 2C). However, mutations in *SMO* were mutually exclusive with mutations in *TRAF7*, *KLF4*, *AKT1*, *PIK3CA*, and *NF2* (Fisher exact test $P = .005$) (Fig. 1 and 2C).

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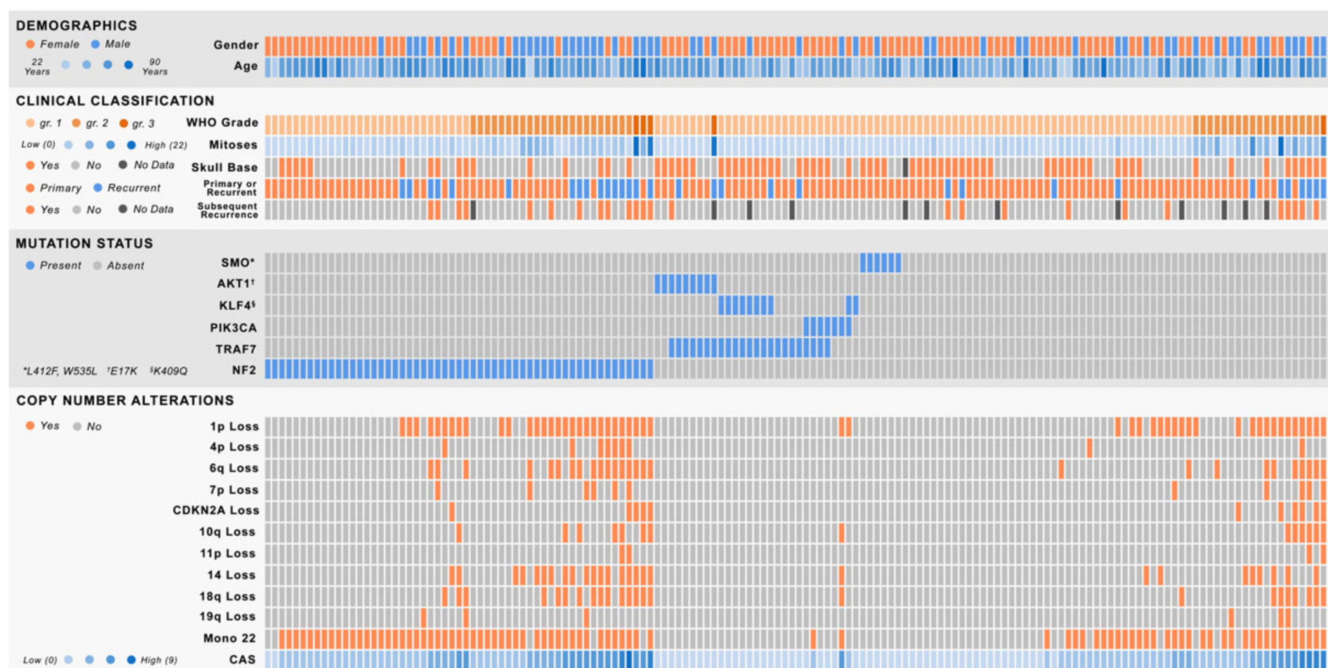

Fig. 1. Mutation and copy number profiling of a clinical cohort of meningiomas. Data are shown for all 150 patient samples for which both copy number alterations and exome sequencing of target genes were available. The top panel displays patient demographics. The second panel displays clinical and pathologic information. The third panel shows mutation status, and the bottom panel shows copy number alterations. The cytogenetic abnormality score (CAS)[21] is plotted in the bottom row. Dark grey symbols denote samples with unavailable data. The data used to generate these plots and an additional, sortable table are available in Supplementary material, Tables S1 and S2, respectively. Supplementary material, Table S2 contains numerical values for age (y), mitoses (per 10 high-power fields), and cytogenetic abnormality score (CAS).[21]

All *PIK3CA* mutations occurred in primary tumors (Fig. 1 and Supplementary material, Table S1). Six of the seven meningiomas with oncogenic mutations in *PIK3CA* all had WHO grade I histology and CAS of zero, and all occurred in females. Five of these six grade I *PIK3CA*-mutant meningiomas occurred in association with the skull base (Fig. 1 and 2B). The remaining grade I meningioma (MG-12) with a *PIK3CA* mutation (N345K) arose in the falx just above—but not in direct contact with—the tuberculum sella and the planum sphenoidale (Supplementary material, Table S1 and S2). Interestingly the patient had a synchronous meningioma in close proximity to the falx tumor, which was located in the left clinoidal region and was not characterized genetically. This raises the possibility of intracranial seeding of the falx from the skull-based meningioma. Of note, two tumors in the cohort harbored whole arm copy-number gains of chromosome 3q (MG-13 and MG-33) where *PIK3CA* is located (Supplementary material, Table S1). Both of these tumors arose in the petroclival region of the skull base, lacked mutations in the genes tested, and had few other copy number changes, which raised the possibility that 3q gain could also stimulate tumor growth by possibly activating PI3K signaling.

The only *PIK3CA*-mutant meningioma (MG-248, E453K) that showed higher grade features (WHO grade I with atypical features) did not arise in the skull base. This tumor arose in the right temporal convexity as a sole lesion pushing into the Sylvian fissure. While this tumor displayed some atypical histologic features (prominent nucleoli and hypercellularity with 2 mitoses per 10 high-power fields), the features did not satisfy criteria for WHO grade II. Unlike the other *PIK3CA*-mutant tumors that lacked atypical features and were clearly WHO grade I, this meningioma harbored numerous copy number losses, many of which are commonly found in WHO grade II meningiomas including single copy loss of 1p and monosomies of 10, 14, 18, and 22 (CAS = 5) (Supplementary material, Table S1 and S2). These findings suggest a different pathobiology underlying the formation of this tumor, unlike the other chromosomally stable *PIK3CA*-mutant tumors that were located in the skull base. A gross total resection was achieved for all seven *PIK3CA*-mutant meningiomas. To date, none of these tumors have recurred; albeit, the median follow up is short (15.4 months, Supplementary material, Table S1).

Similar to the *AKT1*(E17K)-mutant meningiomas, *PIK3CA*-mutant meningiomas tended to co-occur with *TRAF7* mutations (OR = 8.7) (Fig. 1 and 2C). All 4 tumors with both *PIK3CA* and *TRAF7* mutations arose in the skull base (Fig. 1). *AKT1* and *PIK3CA* mutations were mutually exclusive, as were *SMO* and *PIK3CA* mutations (Fig. 1 and 2C). None of the 12 radiation-induced meningiomas harbored mutations in *AKT1*, *PIK3CA*, or *SMO*. Interestingly, one of the *PIK3CA*-mutant meningiomas (MG-121, H1047R) that lacked a *TRAF7* mutation had a co-occurring *KLF4(K409Q)* mutation, which suggested overlapping and redundant mechanisms for activating proliferative programs (Fig. 2C). This tumor also arose in the skull base and, similar to *TRAF7*/*KLF4*-mutant meningiomas, also displayed focal CEA-immunoreactive secretory deposits. The WHO

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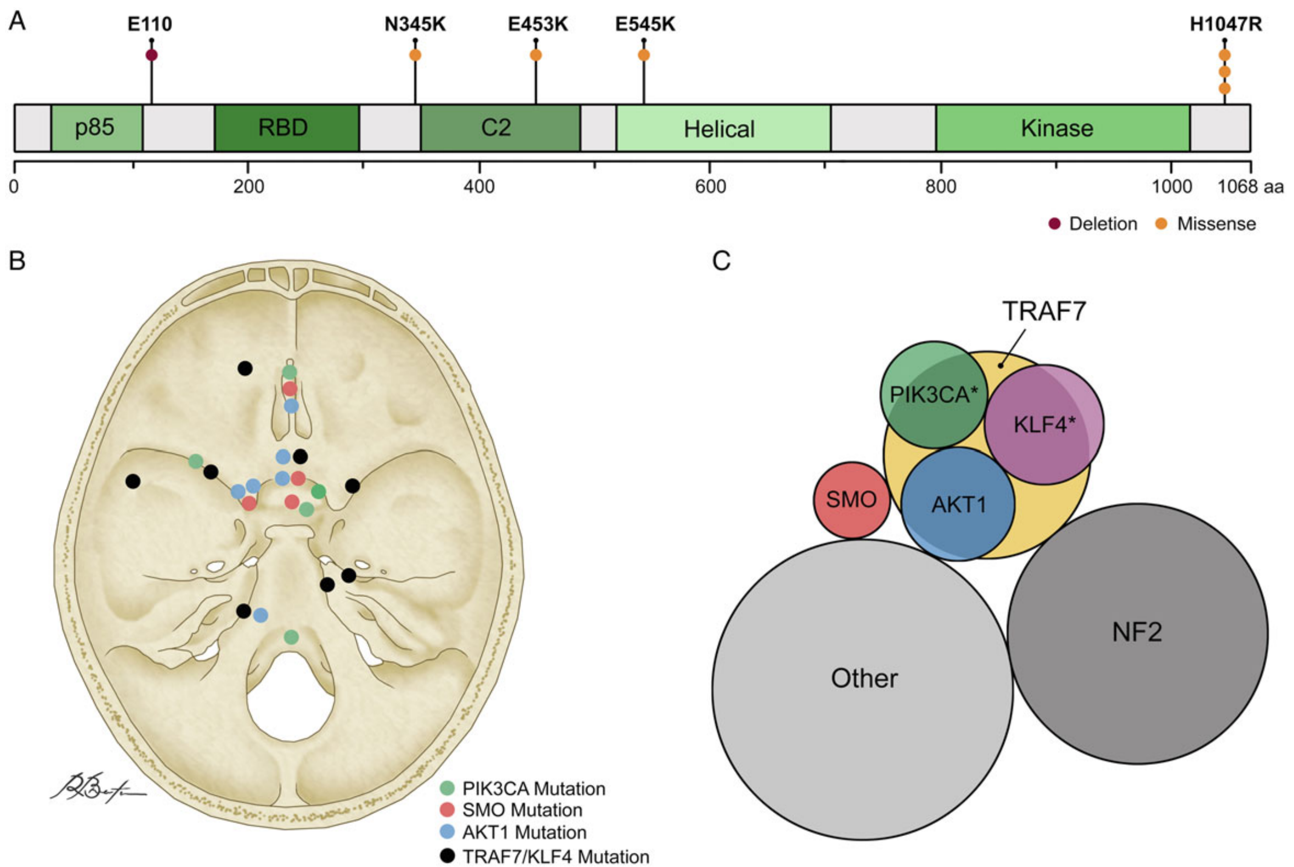

Fig. 2. Diagrams summarizing mutation analysis. (A) Schematic diagram of PI3K protein encoded by the *PIK3CA* gene and indicating the location of missense mutations and deletions relative to defined functional domains. (p85, PI3K p85 regulatory subunit binding domain; RBD, Ras-binding domain; C2, calcium-dependent phospholipid-binding domain; Helical, PI3K helical domain; Kinase, PI3/PI4 kinase domain). (B) Schematic diagram depicting the approximate location of *PIK3CA*, *SMO*, *AKT1*, and *TRAF7/KLF4*-mutant meningiomas in the skull base. (C) Venn diagram showing the relationship of mutations in *NF2*, *TRAF7*, *SMO* (L412F and W535L), *AKT1* (E17K), *KLF4 (K409Q)*, and *PIK3CA*. The circle labeled "other" represents meningiomas in which we did not detect a mutation in the 6 genes evaluated in this study. The asterisks indicate that one *PIK3CA* mutant-meningioma harbored a *KLF4* mutation, which is not illustrated in figure 2C.

grade I *PIK3CA*-mutant meningioma with atypical features (MG-248), while harboring numerous arm level changes, lacked both *TRAF7* and *KLF4(K409Q)* mutations, again supporting a different pathobiology for this higher-grade meningioma.

Discussion

While only a subset of meningiomas harbors mutations in *PIK3CA*, the prevalence of meningiomas in the USA is high, affecting ∼170 000 people.[22] Our study demonstrates that ∼4% to ∼5% of meningiomas harbor mutations in *PIK3CA*. Thus, the number of people with *PIK3CA*-mutant meningiomas may be substantial.

Prior studies have reported *PIK3CA* mutations in meningiomas in individual cases. Two reports found the H1047R mutation in PI3K, each in higher-grade meningiomas (one was a WHO grade II meningioma and the other a WHO grade III).[23,24] This context differs significantly from the context in which we found *PIK3CA* mutations in our cohort—predominantly in WHO grade I meningiomas arising in the skull base. Both of these prior studies did not use sample cohorts that were representative of naturally occurring patient populations. While our cohort has more than twice as many WHO grade I meningiomas as higher grade (II and III) meningiomas, both of the prior cohorts included roughly twice as many higher-grade meningiomas as WHO grade I meningiomas.[23,24]

In Clark et al, whole-exome sequencing was performed on 50 meningiomas with matched normal DNA.[7] In that cohort, one case (MN-289) harboring an oncogenic mutation in *PIK3CA* (R108H) was detected.[7] Similar to the cases in our report, that *PIK3CA*-mutant meningioma was a WHO grade I tumor that arose in the skull base, in the middle cranial fossa along the sphenoid wing. However, the frequency of *PIK3CA* mutations in the larger cohort used in that study is unknown as the targeted sequencing performed on 250 additional meningioma cases interrogated the mutation status of only *TRAF7*, *KLF4*, *AKT1*, *SMO*, and *NF2*. *PIK3CA* was not included in that targeted resequencing effort.

One strength of our current study is that we assessed both the copy number status of a relatively large cohort of

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meningiomas in addition to the mutation status of a panel of meningioma-relevant genes. With this approach, we have demonstrated a propensity for *PIK3CA*-mutant meningiomas to arise in the skull base and have shown that such meningiomas tend to have meningothelial/transitional histology. Moreover, we showed that *PIK3CA*-mutant meningiomas lacked *NF2*, *AKT1*, and *SMO* mutations while tending to harbor *TRAF7* mutations. In addition, these tumors tended to display a low level of chromosomal instability. The limitations of this study included not analyzing matched normal DNA; this analysis may have improved the ability to detect mutations. In addition, our patient cohort comprised meningiomas that had been resected within the past several years; therefore, the long-term follow-up needed to assess clinical outcomes is not yet available.

Clinical management of patients with skull-based meningiomas can be very challenging because of the proximity and involvement of critical neurological and vascular structures. Significant morbidity can result from tumor growth and the requisite surgery including loss of vision due to optic nerve damage, diplopia resulting from damage to one or more oculomotor muscles and neuronal ischemia. In some clinical series, vision loss has been reported in 20% –35% of cases.[25–27]

Therapeutics targeting the PI3K pathway are currently in clinical development for multiple cancer types,[28–30] including the brain tumor, glioblastoma.[31] Factors limiting the effectiveness of PI3K inhibitors for the treatment of other brain tumors (such as glioblastoma[31–33]) may not be impediments for treating meningioma. Blood-brain barrier penetrance is not required, and presumably the relative genomic simplicity of *PIK3CA*-mutant meningiomas reduces the likelihood of multiple escape pathways emerging during targeted PI3K inhibition. Thus, targeting PI3K and its signaling pathway could have an important role in the treatment of recurrent meningiomas.

Efforts to detect *PIK3CA*-mutations from cell-free DNA in people with suspected meningiomas arising in the skull base could also lead to neoadjuvant approaches that might improve the safety and efficacy of subsequent surgery and radiation, ultimately resulting in reduced morbidity. Such approaches might also allow control of tumor growth in patients for whom surgery is contraindicated. We have raised the possibility of similarly managing other low-grade tumors with targetable genetic drivers that arise in critical areas of the brain.[34–37] Now, it is important to critically assess the effect of inhibiting PI3K signaling on tumor progression and response rate in patients with *PIK3CA*-mutant meningioma in a prospective phase 2 study.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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Conflict of interest statement. The authors declare no competing financial interests.

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