Diagnosis and management of craniopharyngiomas in the era of genomics and targeted therapy

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Craniohypopharyngiomas are rare intracranial neoplasms that pose clinical challenges due to their location adjacent to vital structures. The authors have previously shown high mutation rates of BRAF V600E in papillary craniopharyngioma and of CTNNB1 in adamantinomatous craniopharyngioma. These activating driver mutations are potential therapeutic targets, and the authors have recently reported a significant response to BRAF/MEK inhibition in a patient with multiply recurrent PCP. As these targetable mutations warrant prospective research, the authors will be conducting a national National Cancer Institute–sponsored multicenter clinical trial to investigate BRAF/MEK inhibition in the treatment of craniopharyngioma. In this new era of genomic discovery, the treatment paradigm of craniopharyngioma is likely to change.

https://thejns.org/doi/abs/10.3171/2016.9.FOCUS16325

KEY WORDS craniopharyngioma; genomics; BRAF V600E; targeted therapy

Craniopharyngiomas are low-grade epithelial neoplasms that arise in the suprasellar region of the brain, adjacent to the optic nerves, brainstem, and pituitary gland."'® Patients with these tumors experience clinical deficits, including vision loss, headaches, panhypopituitarism, and hypothalamic dysfunction, due to damage to vital structures caused by aggressive tumor growth and therapeutic interventions.7,10,24 Surgery can be challenging in craniopharyngioma due to infiltration and compression of such structures as the hypothalamus, ventricular system, and cranial nerves.36 The incidence rate for craniopharyngioma is 0.18/100,000, and craniopharyngiomas constitute 1%–3% of all brain tumors in the US.7,24,24 Craniohypopharyngiomas can be further classified into 2 histological subtypes, adamantinomatous and papillary. Adamantinomatous craniopharyngiomas (ACPs) occur in both children and adults, and have a histological appearance that is distinct from papillary craniopharyngiomas (PCPs), which mainly occur in adults (Table 1). Specifically, ACPs display whorls, cords, and lobules, with stellate reticulum, palisading peripheral columnar epithelium, and “wet” keratin. PCPs, on the other hand, have monomorphic squamous epithelium, fibrovascular cores, thin capillary blood vessels, and scattered immune cells.10,19 However, it is sometimes challenging to make a diagnosis based solely on histology, particularly for small biopsies that can be mistaken for other masses.43

In our recent study on craniopharyngiomas, we found notable mutations that can be used to distinguish between ACP and PCP. Specifically, we found that over 90% of PCPs have BRAF V600E mutations and that over 90% of ACPs have CTNNB1 mutations.6 These findings indicate the importance of genetics in both the diagnosis and clinical management of these tumors. While these 2 tumor types have traditionally been combated with the same treatment options, genomic research has now revealed a potential for targeted therapies for craniopharyngiomas.

Genetic Findings

In line with its benign histological appearance, the genomic landscape of craniopharyngioma is relatively simple, with a nonsynonymous mutation rate of 0.9 per Mb, which is comparable to that of other pediatric and low-grade tumors (Fig. 1A). Moreover, mutations appear to arise from spontaneous deamination, with 58% of tumors
having cytosine to thymidine changes at CpG dinucleotides (Fig. 1A). Interestingly, the vast majority of ACPs and PCPs harbor single exclusive clonal driver mutations in $CTNNB1$ and $BRAF$, respectively. In our recent study, we found $BRAF$ V600E in 94.4% of PCPs and none of the ACPs (Fig. 1B). $CTNNB1$ alterations in the exon 3 degradation-targeting motif were detected in 96% of the ACPs and none of the PCPs (Fig. 1B). Previous studies have reported $CTNNB1$ mutations, but only at 60%–75% frequency in ACPs.\textsuperscript{8,26,41} Interestingly, using immunohistochemistry we were able to detect the expression of these alterations with equal success (Fig. 2). Taken together, our findings, along with others, indicate an underlying genomic basis for histopathological classification and promising clinical detection tools for further study.

The $BRAF$ V600E alteration has been well established as a driver mutation in other neoplasms. This alteration results in constitutive activation of the MAPK (or ERK) signaling pathway conferring growth advantage through modulation of cell proliferation, differentiation, and cell survival. Specifically, the RAS/RAF/MEK/ERK pathway is at the interface of extracellular and intracellular signaling as it translates hormone and growth factor cues into an oncogenic transcriptional program. In a normal state, RAS is GTP activated by these signals and it further activates RAF proteins including ARAF, BRAF, and CRAF. These RAS effectors activate MEKs and then downstream ERKs, master transcriptional regulators of c-Myc, c-Jun, and Ets-1, among others. BRAF V600E mutants are constitutively active, driving proliferation through constant activation of this MAPK network.\textsuperscript{36}

Mutations in $CTNNB1$ have also been seen in other cancers.\textsuperscript{29} This driver mutation leads to accumulation of the protein $\beta$-catenin, which plays a role in cell signaling and cell adhesion. $\beta$-catenin is an important part of the Wnt signaling pathway, which promotes proliferation and differentiation of cells. When the Wnt pathway is inactive, $\beta$-catenin localizes to the cell membrane or the cytoplasm and is marked for degradation. Mutations in $CTNNB1$ activate the Wnt pathway, and $\beta$-catenin shifts into the cytoplasm and nucleus.\textsuperscript{39} Thus, $\beta$-catenin location can be used as an indicator of $CTNNB1$ mutation status, which is readily assessed with standard immunohistochemical stains.

### Targeted Therapy in PCP

Mutations in BRAF V600E have been observed and effectively targeted in other tumor types, including melanoma,\textsuperscript{13,16} ameloblastoma,\textsuperscript{20,27,42} hairy cell leukemia,\textsuperscript{12,13,17,23,33,38} Erdheim-Chester disease,\textsuperscript{21,25} and pleomorphic xanthoastrocytoma.\textsuperscript{12,23,29,32} We recently achieved a clinically significant response in a patient with a recurrent BRAF V600E mutant PCP using targeted BRAF and MEK inhibitors\textsuperscript{5} (Fig. 3). This patient had previously undergone multiple neurosurgical decompressions via craniotomy and suffered from bilateral optic neuropathy and panhypopituitarism due to the rapid growth of this large, cystic tumor. After 17 days of treatment with the BRAF inhibitor dabrafenib, the solid and cystic components of the tumor decreased by 50% and 70%, respectively. For the next 14 days, the MEK inhibitor trametinib was added to the treatment regimen because of research indicating the potential for MEK inhibitors to prevent the development of resistance to BRAF inhibition in melanoma.\textsuperscript{1} This combined BRAF/MEK inhibition led to solid and cystic components of the tumor decreasing in total by 85% and 81%, respectively. Following this targeted therapy, the patient underwent endoscopic transphenoidal resection followed by radiotherapy. The patient is currently symptom free 18 months after radiation. Additionally, of note, we detected circulating BRAF V600E DNA in the patient’s blood at multiple points during the treatment course. This finding indicates that a less-invasive “liquid biopsy” approach may someday be possible in the diagnosis of PCP.

While whole-exome sequencing data for our patient did not reveal any drivers of BRAF inhibitor resistance, possible resistance mechanisms must be kept in mind. A recent study reported an initial remarkable response of a PCP after treatment with the BRAF inhibitor vemurafenib.\textsuperscript{2} However, the patient in that case was not concurrently treated with a MEK inhibitor, and the tumor progressed after 6 weeks of treatment. Although this suggests the importance of MEK inhibition in the targeted treatment of BRAF mutated tumors, the role of BRAF monotherapy versus BRAF and MEK combination therapy needs to be prospectively studied.

Due to the genetic simplicity of craniopharyngiomas, there is great potential for targeted therapy as treatment for these neoplasms. While BRAF inhibitors such as vemurafenib and dabrafenib are currently available, agents that target the Wnt pathway are still in development.\textsuperscript{1} Thus, patients with PCP may immediately benefit from targeted therapy, whereas further studies must be done to develop targeted therapies for patients with ACP.

### Diagnostics

The aforementioned genetic findings have crucial implications in the diagnosis of craniopharyngioma. Most notably, immunohistochemistry can now be used by pathologists to classify suprasellar tumors. One application of this is a recently developed mutation-specific antibody.

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**Table 1. Clinical and histological features of adamantinomatous and papillary craniopharyngiomas**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACP</th>
<th>PCP</th>
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<tbody>
<tr>
<td>Patient population</td>
<td>Mostly children, some adults</td>
<td>Mostly adults</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Loss of vision, headaches, pituitary insufficiency</td>
<td>Loss of vision, headaches, pituitary insufficiency</td>
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<tr>
<td>Histology</td>
<td>Epithelium grows in whorls, cords, lobules; palisading peripheral columnar epithelium, stellate reticulum; “wet” keratin</td>
<td>Well-differentiated monomorphic squamous epithelium; fibrovascular cores, thin capillary blood vessels; scattered immune cells</td>
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<tr>
<td>Genetics</td>
<td>$CTNNB1$ mutation (activation of Wnt pathway)</td>
<td>$BRAF$ V600E mutation (activation of MAPK pathway)</td>
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(VE1) that recognizes BRAF V600E mutant protein, which can be used to differentiate between ACP and PCP. Staining for BRAF V600E can also help to assess lesions such as Rathke’s cleft cysts (RCCs), which can be confused with craniopharyngiomas, particularly when the cyst lining has undergone extensive squamous metaplasia. A recent study examined 33 lesions that were originally diagnosed as RCCs and reclassified 3 of them as PCP based on BRAF status. A caveat to this is that one must take care in examining immunohistochemical specimens for BRAF status, as the VE1 antibody has been shown to react with certain BRAF WT tissues, such as normal cells in the anterior pituitary as well as ciliated epithelial cells. Immunohistochemistry can also be used to diagnose craniopharyngioma based on CTNNB1 status. In PCP, β-catenin is localized to the cell membrane, whereas...
in ACP β-catenin is seen in the cytoplasm and nucleus, which is a marker of activated β-catenin. 

Notably, nuclear localization of β-catenin is not uniform through the neoplastic epithelium of ACPs, and is found rather in both scattered individual cells as well as clusters of cells. Thus, staining for β-catenin could highlight the specific classification of a craniopharyngioma. Although immunohistochemistry is a powerful tool for the diagnosis of these suprasellar tumors, genetic testing alone may be sufficient in making craniopharyngioma diagnoses.

**Clinical Trial**

We will be conducting a Phase II, National Cancer Institute–sponsored multicenter national clinical trial investigating BRAF/MEK inhibitors in patients with PCP,
likely to begin accrual in early 2017. In addition to slowing the development of resistance to BRAF inhibitors, MEK inhibitors have been shown to prevent the formation of squamous-cell carcinoma, which is a complication of BRAF-inhibitor treatment. Thus, we will be exploring the combination of BRAF and MEK inhibitors as a systemic treatment plan. Through this study, pre- and posttreatment tissue will be obtained for whole exome sequencing as well as RNA sequencing to study the genetic drivers of these tumors. Additionally, based on the discovery of circulating BRAF V600E in our patient, we will be testing blood for cell-free DNA throughout the clinical trial.

Conclusions

The research outlined in this review highlights the potential for neoadjuvant approaches in the treatment of craniopharyngioma in patients with specific mutations. It is clear that clonal mutations in the evolution of these genetically simple tumors are crucial for tumor growth and can be targeted by drug therapies. While craniopharyngiomas are traditionally treated with surgery and radiation, it is possible that targeted therapy could reduce the morbidities associated with traditional treatments and lead to better outcomes for patients with these tumors.

References


Disclosures
Dr. Brastianos reports being a consultant for Angiochem and Genentech and has received honoraria from Merck. Dr. Cahill has received honoraria from Merck.

Author Contributions
Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Brastianos. Study supervision: Brastianos, Cahill, Santagata, Barker.

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