

## Letter to the editor

### **BRAF-V600E mutation in pediatric and adult glioblastoma**

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With the recent identification of the *BRAF* rearrangement/duplication in pediatric pilocytic astrocytomas (PA),<sup>1–3</sup> there has been renewed interest in the contribution of the *BRAF* gene to brain tumorigenesis. While the signature *KIAA1549:BRAF* fusion represents a common alteration in PA, activating mutations in the *BRAF* kinase gene (V600E) are more commonly observed in other glioma histological subtypes and malignancy grades. In this regard, we and others have previously found relatively few *BRAF*-V600E mutations in PA (<10% cases),<sup>1–4</sup> whereas *BRAF*-V600E mutations are frequently identified in pleomorphic xanthoastrocytomas (WHO grades II and III; 50%–65% cases),<sup>5–8</sup> gangliogliomas (20%–75% cases),<sup>6–10</sup> and to a lesser frequency in diffuse gliomas,<sup>6,11</sup> dysembryoplastic neuroepithelial tumors,<sup>10</sup> desmoplastic infantile astrocytoma/ganglioglioma,<sup>10</sup> and atypical teratoid/rhabdoid tumors arising in a background of either ganglioglioma or pleomorphic xanthoastrocytoma.<sup>7</sup> In contrast, approximately 5% of adult high-grade gliomas, as well as a distinctive subset of adult diffuse low-grade gliomas, harbor *BRAF*-V600E mutations.<sup>6,11,12</sup> Since most *BRAF*-V600E-positive glial neoplasms are encountered in young persons, we investigated the frequency of this mutation in pediatric high-grade gliomas.

Immunohistochemical analyses were conducted using a *BRAF*-V600E-specific antibody on tissue microarrays containing pediatric gliomas from 2 different institutions (Washington University and University of California, San Francisco) (clone VE1; Spring Bioscience; dilution 1:100). Using this method, none of the low-grade pediatric gliomas ( $n = 75$ ; 67 WHO grade I PAs, 6 WHO grade II astrocytomas, 1 WHO grade II oligodendroglioma, and 1 WHO grade II mixed oligoastrocytoma) harbored a *BRAF*-V600E mutation. Of note, 23 of the PA tumors (34%) arose outside of the cerebellum. In contrast, 3 of 11 WHO grade III anaplastic astrocytomas (27%) and 3 of 25 (12%) WHO grade IV glioblastomas (GBMs) were *BRAF*-V600E immunoreactive. All of the *BRAF*-V600E-immunopositive glioblastomas were primary GBM.

To determine whether the low frequency of *BRAF*-V600E mutation observed in pediatric GBM was comparable to that observed in their adult counterparts, we examined 39 adult GBMs

by immunohistochemistry. Three of these adult GBM tumors (7.7%) were *BRAF*-V600E immunoreactive: Two of these were giant-cell variants, and the expression appeared to be limited to the “monstrous cells”. Similar to their pediatric counterparts, all of these *BRAF*-V600E-immunopositive tumors were primary glioblastoma. Of note, these *BRAF* mutant tumors were generally found in younger patients (35–43 years with a mean age of 39 years compared to 27–79 years with a median age of 55.4 years for *BRAF*-V600E-immunonegative tumors;  $P = .0495$ ). None of the *BRAF*-V600E-immunopositive tumors harbored the isocitrate dehydrogenase-1 (IDH1) R132H mutation. In addition, 2 of these tumors arose in women, despite a slight overall male preponderance in our series (25 males:14 females). The results of our series are comparable to the documented frequencies reported in the literature for adults (9/152 cases; 5.9%).<sup>4,6,12–14</sup>

While there were few *BRAF*-V600E-positive adult GBMs in our series, one of these patients is currently alive at 4.5 years. This finding is intriguing because at least 2 of the previously reported adult GBMs also exhibited prolonged survival (3 years).<sup>11,12</sup> It is possible that *BRAF*-V600E mutations are either encountered in rarer, more favorable subtypes of GBM or that they confer different biological properties to these glial neoplasms, translating to improved clinical outcomes. In this regard, *BRAF*-V600E mutations have been reported to occur in over 50% of epithelioid GBM.<sup>12</sup> This uncommon histologic variant appears to be more common in young adults,<sup>12</sup> and is equally represented in males and females in one series as opposed to the male predominance typically seen in rhabdoid GBM.<sup>15</sup> However, whether or not adult patients carrying *BRAF*-V600E mutations have a survival advantage remains to be established using additional patient cohorts.

Coupled with encouraging therapeutic studies demonstrating that *BRAF* and *MEK* inhibitors exhibit therapeutic efficacy in *BRAF*-V600E; *Ink4a*-deficient murine malignant glioma preclinical studies,<sup>16</sup> the potential preselection of patients with GBM by *BRAF*-V600E mutation for *BRAF*/*MEK* inhibitor treatment may prove beneficial in combination with other therapies.

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