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High rate of concurrent *BRAF-KIAA1549* gene fusion and 1p deletion in disseminated oligodendroglioma-like leptomeningeal neoplasms (DOLN)

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Disseminated oligodendroglioma-like leptomeningeal neoplasm (DOLN) is a recently described entity that predominantly affects children, is slowly progressive, and exhibits little, if any, parenchymal involvement. Studies to date have demonstrated some similarities between DOLNs and adult oligodendrogliomas with respect to morphology (infiltrative, monotonous cells with round, regular nuclei and perinuclear clearing), immunohistochemistry (synaptophysin, GFAP, Olig-2 expression), and genetics (high rate of chromosome 1p deletions and some 1p19q co-deletions) [5-8]. In contrast however, no DOLNs have been shown to harbor the isocitrate dehydrogenase-1 (IDH1) R132H mutation.

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BRAF abnormalities are common in pediatric low-grade CNS tumors, with the *BRAF-KIAA1549* fusion/tandem duplication at 7q34 identified in approximately, 60 % of cerebellar and optic pathway pilocytic astrocytomas [4]. Others, like pleomorphic xanthoastrocytoma (PXA), ganglioglioma, and dysembryoplastic neuroepithelial tumor (DNET), have shown variable frequencies of activating *BRAF* V600E point mutations [1]. Because DOLNs partially overlap with these neoplasms, we assessed a series of 20 cases for *BRAF* alterations.

We examined 23 archival DOLNs by FISH for the *BRAF-KIAA1549* fusion, and 17 cases for deletions of 1p and 19q (Abbott, North Chicago, IL, USA). One was additionally interrogated by SNP-array. Testing for *BRAF* V600E was also performed on nine cases. Of 15 informative cases for *BRAF-KIAA1549* by FISH, 11 were fusion positive (Fig. 1). Another case was non-informative by FISH, yet harbored a duplication (ch7:138550993-140509923) by SNP-array consistent with gene fusion, for a total of 12 of 16 cases positive for *BRAF-KIAA1549* (75 %). FISH revealed loss of 1p in 10/17 cases (59 %), with 3 of those being co-deleted for 19q (18 %). Of the 12 cases with *BRAF* fusions, 9 had 1p deletion (75 %) and 2 had 19q co-deletion (17 %). None of 9 tested specimens were positive for *BRAF*-V600E mutation.

These findings indicate a high rate of concurrent *BRAF-KIAA1549* gene fusions and 1p deletions in DOLNs. Although *BRAF* fusions are typical of pilocytic astrocytomas, 1p deletions are not, confirming that DOLNs are pathologically and genetically distinct in most cases. These findings also further separate these oligodendroglioma-like tumors from adult oligodendrogliomas, although some overlap remains since 1p19q co-deletion is occasionally found in DOLN and rare *BRAF* fusions have been recently reported in otherwise classic, 1p19q co-deleted oligoden-droglioma [3].

DOLNs have also displayed occasional ganglion cell differentiation and areas of richly myxoid stroma, raising related possible link to gangliogliomas or DNETs, yet none of our 9 tested cases showed evidence of a *BRAF* V600E mutation, suggesting that DOLNs are genetically distinct from those entities as well. First-generation RAF inhibitors have been demonstrated in vitro to paradoxically activate the *BRAF-KIAA1549* fusion protein [9]. Instead, MEK or mTOR inhibitors could be considered in the treatment of DOLNs, as in other fusion-positive tumors [2].

This report examines the role of common BRAF abnormalities in DOLNs and establishes a high frequency of concurrent *BRAF-KIAA1549* fusions and 1p deletions. Although DOLNs are already clinicopathologically distinct, these findings further demonstrate fundamental genetic differences from other entities and implicate a new potential therapeutic target for patients with these otherwise challenging disseminated tumors.

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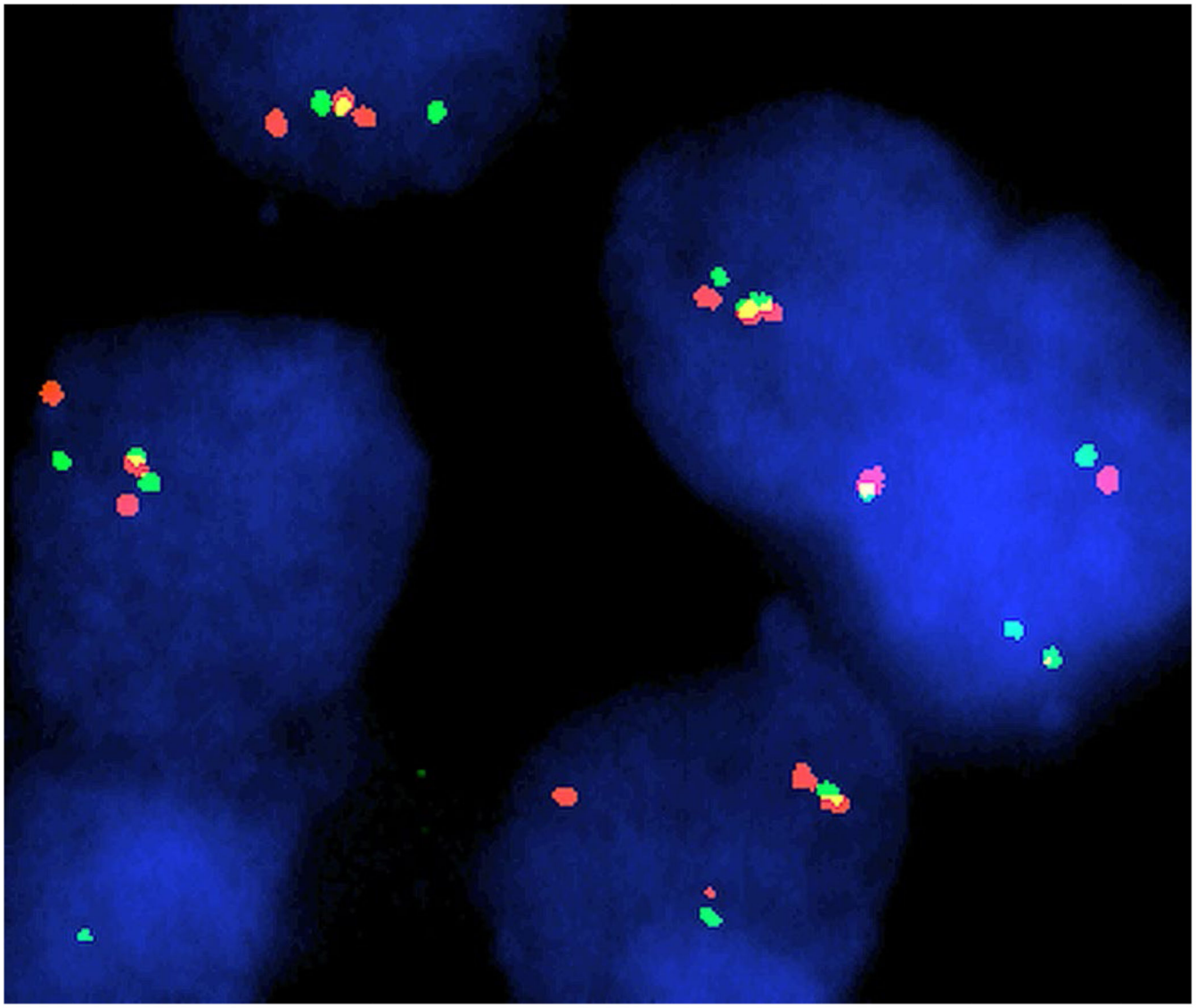

Fig. 1.

DOLN nuclei with FITC-labeled probe RP11-355D18 corresponding to KIAA1549 (*green*) and digoxigenin-labeled probe 726N20 corresponding to BRAF (*red*). *Yellow* signals indicate fusion