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Multinodular and vacuolating neuronal tumor of the cerebrum is a clonal neoplasm defined by genetic alterations that activate the MAP kinase signaling pathway

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Initially described in 2013, multinodular and vacuolating neuronal tumor of the cerebrum (MVNT) is a low-grade neuronal neoplasm of the cerebral hemispheres composed of small to medium sized neuronal cells arranged in nodules involving the deep cortex and subcortical white matter, showing prominent intracytoplasmic and stromal vacuolation [8]. The tumor cells are typically immunopositive with some glial and neuronal markers (OLIG2 and synaptophysin) but negative for others (GFAP and NeuN), and are associated with ramified CD34-positive processes in adjacent parenchyma. The radiologic features of MVNT are distinct and include predominantly solid, T2-hyperintense lesions in the deep cortical ribbon and superficial white matter with variable internal nodularity and typically absent contrast enhancement [1, 8, 11]. Patients may be asymptomatic or can present with seizures or headaches, and all pathologically proven cases have reportedly followed a benign

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Data availability

Scanned image files of the H&E and phospho-ERK stained slides from which representative images are presented are available for downloading and viewing at the following link: https://figshare.com/projects/Multinodular_and_vacuolating_neuronal_tumor_of_the_cerebrum_MVNT_/28260. Sequencing data files are available from the authors upon request.

Compliance with ethical standards

This study was approved by the Committee on Human Research of the University of California, San Francisco, with a waiver of patient consent.

Conflict of interest

The authors declare that they have no competing interests related to this study.

clinical course to date [1, 8, 11]. The molecular basis of MVNT is unknown, and some authors have suggested that MVNT is a malformative lesion rather than a true clonal neoplasm [4, 13].

To investigate the molecular pathogenesis of MVNT, we assembled a cohort of archival tissue specimens from eight patients diagnosed with MVNT (Fig. 1a), four of which have been previously described [8, 11]. The four male and four female patients ranged in age at time of resection from 11–63 years (median 39 years). Four patients had presented with seizures, two with headaches, one with episodes of confusion, and one with numbness and tingling of the hand. Pre-operative imaging for all cases demonstrated non-enhancing, T2-hyperintense multinodular lesions localized in the deep cortex and superficial white matter of the frontal or temporal lobes (Fig. 1b–e). Six cases demonstrated histologic features of pure MVNT (Fig. 1f), while two cases (#2 and #8) demonstrated vacuolated areas resembling MVNT mixed with other non-vacuolated areas resembling ganglioglioma. Genomic DNA was extracted from lesional tissue that had been macrodissected from formalin-fixed, paraffin-embedded blocks or unstained sections. Targeted capture-based next-generation DNA sequencing was performed as previously described using the UCSF500 Cancer Panel [10], which assesses approximately 500 cancer-associated genes for mutations, copy number alterations, and structural variants including gene fusions (Supplementary Table 1 [Online Resource 1]). Immunohistochemistry was performed on whole formalin-fixed, paraffin-embedded tissue sections using phospho-ERK Thr202/Tyr204 antibodies (Cell Signaling, cat #4370, clone D13.14.4E, 1:10,000 dilution).

Two cases demonstrated missense mutations in the *BRAF* gene (p.L597R and p.G469S, Supplementary Figure 1 and Supplementary Table 2 [Online Resources 1 and 2]), neither of which are the more common p.V600E hotspot mutation, but both of which are known to be activating mutations that have been recurrently identified in Langerhans cell histiocytosis, Erdheim-Chester disease, and melanomas lacking *BRAF*p.V600E mutation or other genetic alterations in the Ras-Raf-MAP kinase signaling pathway [5, 7, 12]. Five cases demonstrated alterations in exon 2 of the *MAP2K1* gene, two of which were hotspot missense mutations (p.Q56P, Supplementary Figure 2 [Online Resource 2]) and three of which were small in-frame deletions (Supplementary Figure 3 [Online Resource 2]). Identical mutations in exon 2 of *MAP2K1* have been recurrently found in Langerhans cell histiocytosis, Erdheim-Chester disease, and melanomas in a mutually exclusive manner with alterations in *BRAF* or other genes in the MAP kinase pathway and have been shown to cause activation of the MAP kinase signaling pathway [3, 6, 12]. The last case demonstrated an *FGFR2-INA* in-frame gene fusion (Supplementary Figure 4 and Supplementary Table 3 [Online Resources 1 and 2]), harboring a similar breakpoint to the recurrent *FGFR2* fusions in intrahepatic cholangiocarcinomas that result in a fusion protein including the entirety of the intracellular tyrosine kinase domain [2]. The two cases with mixed MVNT-like and ganglioglioma-like components that were separately extracted and sequenced demonstrated the same *BRAF* mutation (MVNT #2) and *FGFR2* fusion breakpoints (MVNT #8) in their two respective components, indicating that both components arose from the same ancestral clone. The allele frequencies of the *BRAF* and *MAP2K1* mutations that ranged from 1–21% are consistent with heterozygous somatic variants in each case (Supplementary Table 2 [Online Resource 1]). No additional pathogenic mutations, amplifications, deletions, or structural

variants were identified in any of the tumors. No chromosomal copy number alterations were identified in any of the tumors (Supplementary Figure 5 [Online Resource 2]). In each of the six MVNT that were assessed by immunohistochemistry using antibodies against phospho-ERK (MVNT #3 – #8), robust staining was observed in the neoplastic neurons as well as some of the small admixed glial cells (Fig. 1f–g and Supplementary Figure 6 [Online Resource 2]). This phospho-ERK staining was equivalent to the levels seen in other glioma types harboring known genetic alterations within the MAP kinase signaling pathway (e.g. pilocytic astrocytoma with *KIAA1549-BRAF* fusion, Supplementary Figure 6 [Online Resource 2]).

Together, these findings suggest that MVNT is a clonal neoplasm characterized by solitary pathogenic alterations that cause activation of the Ras-Raf-MAP kinase signaling pathway. As such, MVNT are genetically similar to gangliogliomas, pilocytic astrocytomas, and dysembryoplastic neuroepithelial tumors; however, MVNT do not appear to commonly harbor the *BRAF* p.V600E mutation that is typical of ganglioglioma, *KIAA1549-BRAF* fusion that is typical of pilocytic astrocytoma, or *FGFR1* kinase domain duplication or mutation that is typical of dysembryoplastic neuroepithelial tumor. The genetic profile of MVNT is also similar to another recently described epilepsy associated neoplasm that has been termed “polymorphous low-grade neuroepithelial tumor of the young” [9]. However, the genetic profile of MVNT appears to be distinct from several other glial and glioneuronal neoplasms. No concurrent *CDKN2A* deletions were identified in any of the cases, suggesting that MVNT are genetically distinct from the majority of pleomorphic xanthoastrocytomas. No *PRKCA* fusions or kinase domain mutations were identified in any of the cases, suggesting that MVNT are genetically distinct from the majority of papillary glioneuronal tumors and chordoid gliomas. No *IDH1*, *IDH2*, *TP53*, *ATRX*, *TERT* promoter, *CIC*, or *FUBP1* mutations were identified in any of the cases, suggesting that MVNT are genetically distinct from the majority of diffuse lower-grade gliomas in adults. No *TSC1*, *TSC2*, *AKT*, *MTOR*, or *PTEN* mutations were identified in any of the cases, suggesting that MVNT are also genetically distinct from the majority of subependymal giant cell astrocytomas, cortical malformations of tuberous sclerosis, sporadic focal cortical dysplasias, and dysplastic cerebellar gangliocytoma.

In conclusion, the identification of a molecular signature for MVNT, together with the characteristic radiographic and histologic features, should help facilitate accurate diagnosis of this distinct neuroepithelial tumor associated with favorable prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Multinodular and vacuolating neuronal tumor of the cerebrum (MVNT) is defined by genetic alterations that activate the MAP kinase signaling pathway. **a**, Table of the clinicopathologic features of the eight patients with MVNT and the pathogenic genetic alterations identified in this study. **b-e**, Pre-operative axial (b-c) and coronal (d-e) T2-weighted magnetic resonance imaging for patient MVNT #1. **f,g**, H&E staining (f) and phospho-ERK immunostaining (g) on MVNT #7. **h**, Snapshot from the Integrated Genome Viewer for MVNT #7 showing sequencing reads containing a small in-frame deletion in exon 2 of the *MAP2K1* gene.