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Myxoid glioneuronal tumor of the septum pellucidum and lateral ventricle is defined by a recurrent *PDGFRA* p.K385 mutation and DNT-like methylation profile

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Data availability

Scanned image files of the H&E stained slides from which representative images are presented are available for downloading and viewing at the following link: https://figshare.com/projects/Myxoid_glioneuronal_tumor_of_the_septum_pellucidum_and_lateral_ventricle/35651. Sequencing and methylation 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.

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The septum pellucidum ("translucent wall") is a thin, triangular membranous structure that runs sagittally from the corpus callosum down to the fornix and separates the left and right lateral ventricles of the brain. The septum pellucidum consists of two laminae of both white and gray matter. During fetal development there is a space between the two laminae called the cavum septum pellucidum, which disappears during infancy in most individuals. The septum pellucidum is the anatomic site of origin of a spectrum of uncommon neuroepithelial tumors that include central neurocytoma, subependymoma, and low-grade glioneuronal tumors morphologically resembling either dysembryoplastic neuroepithelial tumor (DNT) or rosette-forming glioneuronal tumor (RGNT). Multiple case series or individual case reports have described DNT-like or RGNT-like low-grade glioneuronal tumors of the septum pellucidum and lateral ventricle, which are distinct from the typical cortical and fourth ventricular locations of DNT and RGNT, respectively [1, 5, 16]. Molecular analysis of these tumors has revealed absence of *IDH1/2* mutation and co-deletion of chromosomes 1p/19q that genetically define oligodendroglioma [5, 16]. Additionally, they have been found to lack alterations in *FGFR1*, *BRAF*, *MYB*, and *MYBL1* that characterize the majority of DNT, RGNT, and other low-grade neuroepithelial tumors [5].

To investigate the molecular pathogenesis of these enigmatic low-grade glioneuronal neoplasms of the septum pellucidum and lateral ventricle with DNT-like or RGNT-like histologic features, we assembled a cohort of tissue specimens from four patients (Fig. 1a and Supplementary Table 1 [Online Resource 1]). The three male and one female patients ranged in age at time of initial surgery from 8–31 years. One patient had presented with cognitive disturbance, one with headaches, and two were asymptomatic with brain imaging that had been performed for unrelated indication. Pre-operative imaging demonstrated non-enhancing, T2-hyperintense, lobulated masses centered in the septum pellucidum (n=3) or genu of the corpus callosum (n=1) (Fig. 1b, Supplementary Table 2, and Supplementary Figure 1 [Online Resources 1 and 2]). Multi-nodularity typical of cortically-based DNT was absent in all cases. Two patients had localized disease, one patient had an additional small focus of dissemination in the posterior horn of the lateral ventricle (#3), and one patient had extensive dissemination throughout the ventricular system (#2).

All four cases were histologically characterized by a low-grade proliferation of neoplastic glial cells with oligodendroglial cytology (i.e. uniform round nuclei with delicate chromatin) in a mucin-rich stroma (Fig. 1c, Supplementary Table 3, and Supplementary Figure 2 [Online Resources 1 and 2]). A prominent or at least focal feature in all cases was columnar arrangement of the oligodendroglioma-like cells along with ganglion cells "floating" in mucin-filled lacunae. All cases lacked the multi-nodularity that is typical of cortically-based DNT. Two of the cases (#2 and #3) additionally demonstrated well-formed neurocytic rosettes, composed of tumor cells surrounding central areas of neuropil. No Rosenthal fibers, eosinophilic granular bodies, or calcifications were observed in any of the cases. Mitotic activity, significant nuclear pleomorphism, necrosis, and microvascular proliferation were uniformly absent. The neoplastic glial cells demonstrated GFAP and OLIG2 positivity by immunostaining, while the floating neurons and neurocytic rosettes showed synaptophysin positivity. CD34-positive ramified cells were not seen in the two evaluated cases. The Ki-67 labeling index was uniformly low (less than 5%).

Genomic DNA was extracted from formalin-fixed, paraffin-embedded tumor tissue, and targeted capture-based next-generation DNA sequencing was performed as previously described using the UCSF500 Cancer Panel [7–9, 12, 13], which assesses approximately 500 cancer-associated genes for mutations, copy number alterations, and structural variants including gene fusions (Supplementary Table 4 [Online Resource 1]). All four cases demonstrated dinucleotide substitutions at codon p.K385 in the *PDGFRA* gene, three resulting in a lysine to leucine change (p.K385L) and one resulting in a lysine to isoleucine change (p.K385I) (Fig. 1d and Supplementary Table 5 [Online Resource 1]). The 20–44% allele frequencies of these *PDGFRA* mutations were consistent with being heterozygous somatic variants in each case. *PDGFRA* encodes the platelet-derived growth factor receptor alpha, a transmembrane receptor tyrosine kinase known to signal through the Ras-Raf-MAP kinase and PI3-kinase-Akt-mTOR pathways. While *PDGFRA* alterations including gene amplification, intragenic deletions/rearrangements, and missense mutations are known to be common in high-grade diffuse gliomas in both children and adults, these *PDGFRA* alterations invariably co-occur with other pathogenic alterations such as p.K27M mutation of *H3F3A* or *HIST1H3B* genes in diffuse midline gliomas or *TERT* promoter mutation and *CDKN2A* deletion in IDH-wildtype glioblastomas [10, 11]. *PDGFRA* mutation has not been identified as the solitary genetic driver in any CNS tumor entity to date. Of note is a recent study of 91 low-grade neuroepithelial tumors in children and young adults that identified two cases with solitary *PDGFRA* alterations, one of which was morphologically classified as "DNT" and the other as "oligoastrocytoma" [14]. Both tumors were located in the temporal lobe with precise location not further specified, and both tumors harbored similar dinucleotide substitutions at codon p.K385 as seen in the four tumors in this series, one resulting in p.K385L and the other p.K385I. These mutations all result in substitution from a basic amino acid (lysine) to a hydrophobic amino acid (leucine or isoleucine) at a codon that is located in the extracellular ligand binding domain. While the precise functional consequence of this recurrent p.K385 mutation in *PDGFRA* is uncertain at present, it is very likely to be an oncogenic, gain-of-function mutation that causes constitutive activation of the kinase domain in the absence of ligand. Interestingly, mutations at codon p.K385 of *PDGFRA* appear to be specific to glial and glioneuronal tumors, as other human tumor types

with frequent *PDGFRA* mutations, such as gastrointestinal stromal tumors, have not been found to harbor variants at this codon (Catalog of Somatic Mutations In Cancer database, version 85 release).

Besides *PDGFRA* mutation, no additional pathogenic mutations, amplifications, deletions, or structural variants were identified involving any of other assayed genes that included *IDH1*, *IDH2*, *H3F3A*, *HIST1H3B*, *HIST1H3C*, *MYB*, *MYBL1*, *ATRX*, *TERT* (including promoter region), *CIC*, *FUBP1*, *TP53*, *MDM2*, *MDM4*, *PPM1D*, *ACVR1*, *BRAF*, *RAF1*, *PTPN11*, *KRAS*, *NF1*, *MAP2K1*, *PRKCA*, *FGFR1–3*, *NTRK1–3*, *EGFR*, *MET*, *ALK*, *PTEN*, *PIK3CA*, *PIK3R1*, *AKT1*, *TSC1*, *TSC2*, *MTOR*, *CDKN2A*, *CDKN2C*, *RB1*, *CDK4*, *CDK6*, *CCND1–3*, *BCOR*, *BCORL1*, *NF2*, *RELA*, and *YAP1*. No chromosomal copy number gains, losses, or focal amplifications or deletions were identified in any of the tumors (Supplementary Table 6 and Supplementary Figure 3 [Online Resources 1 and 2]).

Genome-wide DNA methylation profiling was performed as previously described [3] using the Illumina MethylationEPIC BeadChip (850k array) to further characterize these four myxoid glioneuronal tumors of the septum pellucidum and lateral ventricle with *PDGFRA* p.K385 mutation. Unsupervised clustering of DNA methylation patterns alongside 300 previously characterized CNS neoplasms encompassing a spectrum of low grade glial and glioneuronal tumor entities revealed that each of the four tumors closely clustered with cortically-based dysembryoplastic neuroepithelial tumors and did not cluster with rosette-forming glioneuronal tumors, central neurocytomas, or other neuroepithelial tumor entities (Fig. 2).

Together, these findings suggest that such DNT-like or RGNT-like low-grade glioneuronal neoplasms of the septum pellucidum and lateral ventricles may be a distinct entity, for which we propose the terminology “myxoid glioneuronal tumor of the septum pellucidum and lateral ventricle, *PDGFRA*-mutant” (MGNT of SP/LV). While these four tumors all shared morphologic overlap and clustered by genome-wide methylation analysis with DNT, they lacked the cortical location, the multinodular architecture, and *FGFR1* or *BRAF* mutation, gene fusion, or kinase domain tandem duplication that characterize the vast majority of DNT [14, 15, 17]. While two of these four tumors shared morphologic overlap with RGNT, they did not cluster by genome-wide methylation analysis with RGNT and also lacked the location in the fourth ventricle and combination of *FGFR1* plus *PIK3CA* or *PIK3R1* alterations that characterize the majority of RGNT [4, 6]. In addition, they lacked the *KIAA1549-BRAF* fusion that is typical of pilocytic astrocytoma and diffuse leptomeningeal glioneuronal tumor, the *BRAF* mutation or fusion that is typical of ganglioglioma, and the *MAP2K1* mutation that is typical of multinodular and vacuolating neuronal tumor of the cerebrum (MVNT) [12–14, 17]. No *PRKCA* fusions or kinase domain mutations were identified in any of the cases, providing genetic distinction from papillary glioneuronal tumor and chordoid glioma of the third ventricle [2, 7].

In summary, we have identified a recurrent *PDGFRA* p.K385 hotspot mutation as the solitary pathogenic alteration in DNT-like and RGNT-like low-grade glioneuronal tumors of the septum pellucidum, which together with their stereotypic anatomic location, should help facilitate accurate diagnosis of this distinct neuroepithelial tumor entity for which we

propose the name “myxoid glioneuronal tumor of the septum pellucidum and lateral ventricle, *PDGFRA*-mutant”.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Patient ID	Age (yrs)	Sex	Tumor location	Presenting symptoms	Genetic alteration
MGNT of SP/LV #1	22	M	septum pellucidum and lateral ventricle	cognitive disturbance	PDGFRA p.K385L
MGNT of SP/LV #2	31	M	septum pellucidum with ventricular dissemination	none (incidental)	PDGFRA p.K385I
MGNT of SP/LV #3	10	M	septum pellucidum and lateral ventricle	none (incidental)	PDGFRA p.K385L
MGNT of SP/LV #4	8	F	corpus callosum and periventricular white matter	headaches	PDGFRA p.K385L

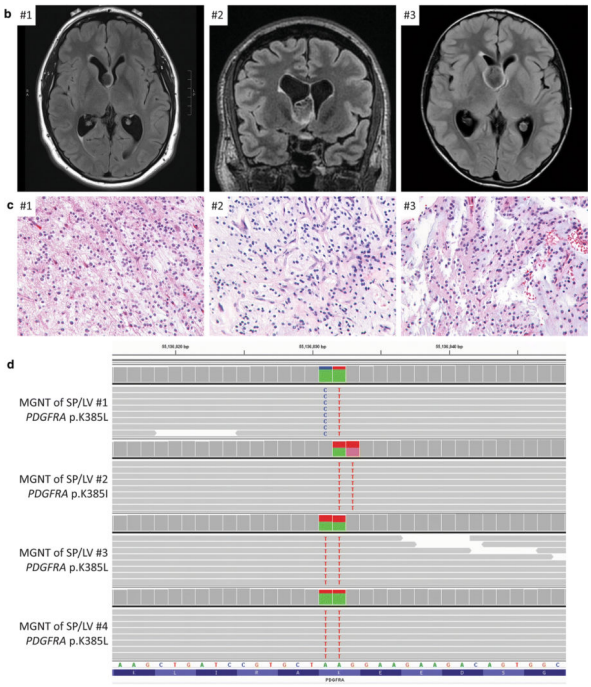

Figure 1.

Myxoid glioneuronal tumor of the septum pellucidum and lateral ventricle is defined by a recurrent *PDGFRA* p.K385 hotspot mutation. **a**, Table of the clinicopathologic features of the four patients with MGNT of SP/LV and the identified *PDGFRA* mutations. **b**, Pre-operative magnetic resonance imaging for patients #1–3. **c**, Tumor histology of cases #1–3. Hematoxylin and eosin staining, 40x magnification. **d**, Snapshot from the Integrated Genome Viewer showing sequencing reads containing a dinucleotide substitution at codon p.K385 of the *PDGFRA* gene in all four cases. Reference transcript NM_006206.

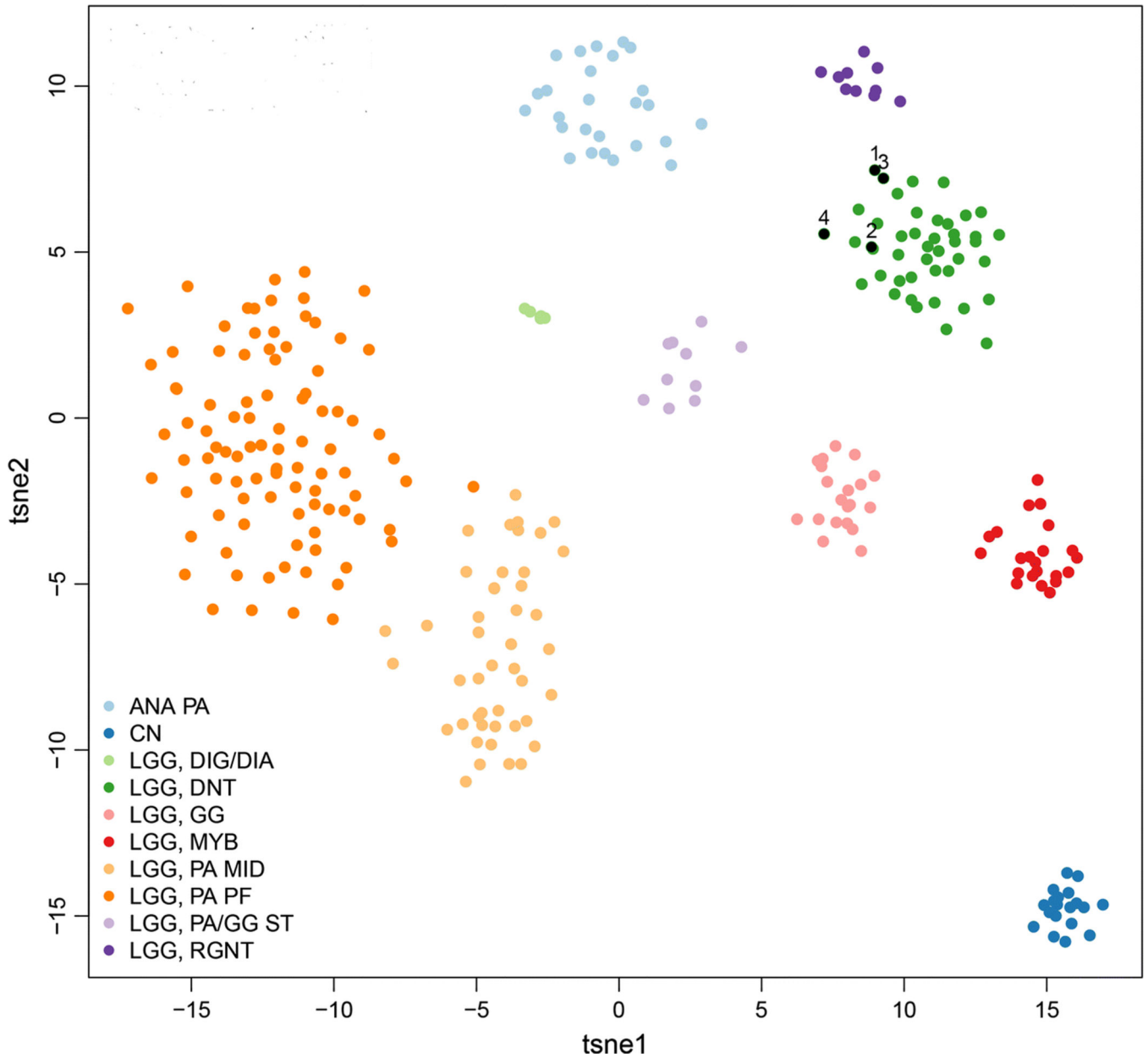

Figure 2.

Myxoid glioneuronal tumor of the septum pellucidum and lateral ventricle is defined by a DNT-like methylation profile. Unsupervised clustering of DNA methylation patterns for the four MGNT of SP/LV (black circles numbered 1 through 4), alongside 300 previously characterized glial and neuronal neoplasms. Shown is a two-dimensional representation of pairwise sample correlations using the 10,000 most variably methylated probes by t-distributed stochastic neighbor embedding (tSNE) dimensionality reduction. Reference methylation classes are: ANA PA, anaplastic pilocytic astrocytoma. CN, central neurocytoma. LGG DIG/DIA, desmoplastic infantile ganglioglioma/astrocytoma. LGG DNT, dysembryoplastic neuroepithelial tumor. LGG GG, ganglioglioma. LGG MYB, low grade glioma with *MYB* or *MYBL1* rearrangement. LGG PA MID, midline pilocytic

astrocytoma. LGG PA PF, posterior fossa pilocytic astrocytoma. LGG PA/GG ST, supratentorial/hemispheric pilocytic astrocytoma and ganglioglioma. LGG RGNT, rosette-forming glioneuronal tumor.