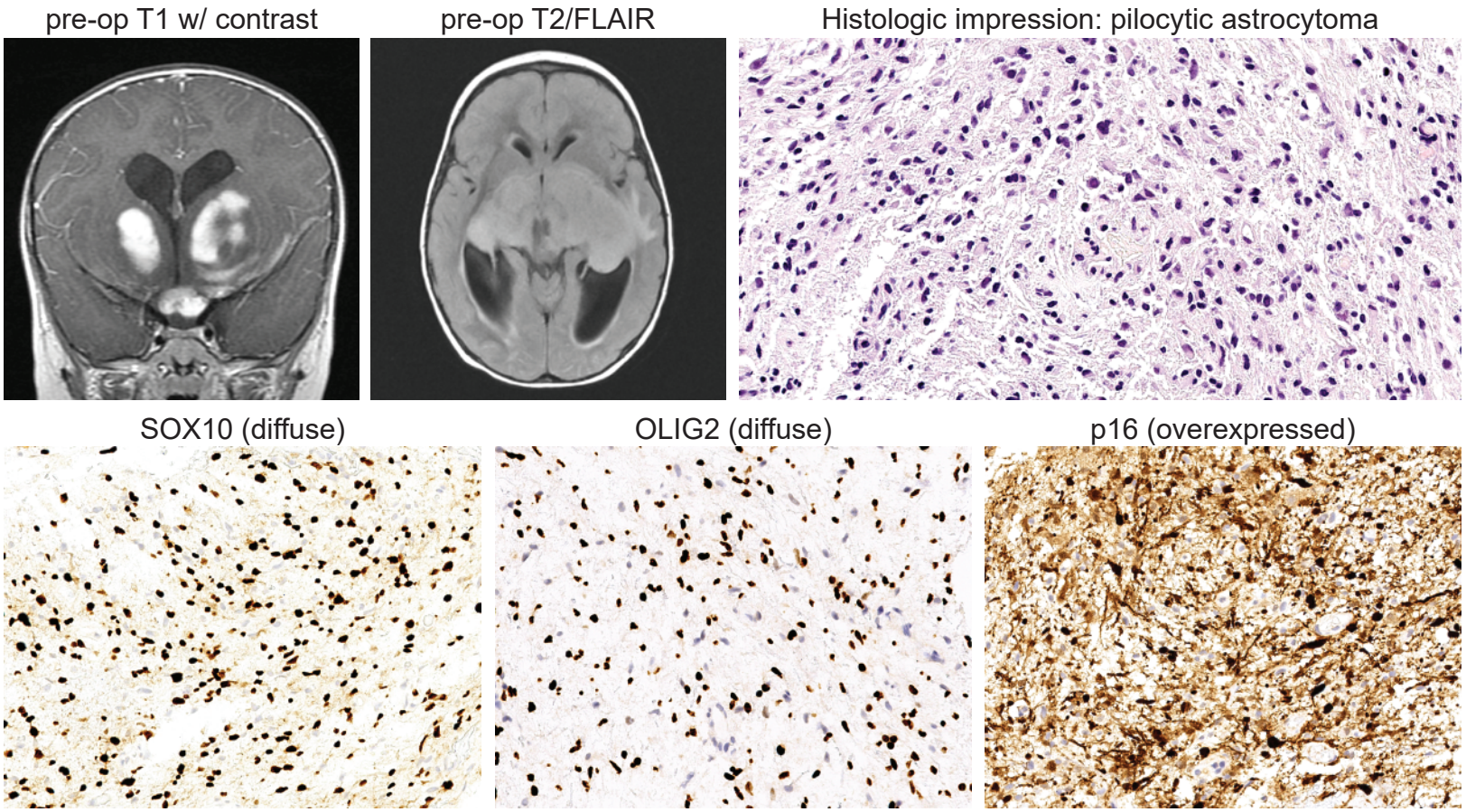
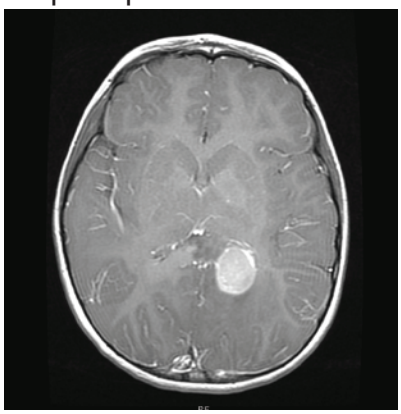


Supplementary Figure 1. Imaging and histologic features of gliomas arising in patients with NF1. Pilocytic astrocytoma, NF1-associated, occurring in the optic pathway (patient #5, top). Pilocytic astrocytoma, NF1-associated, occurring in the cerebellum (patient #29, bottom).

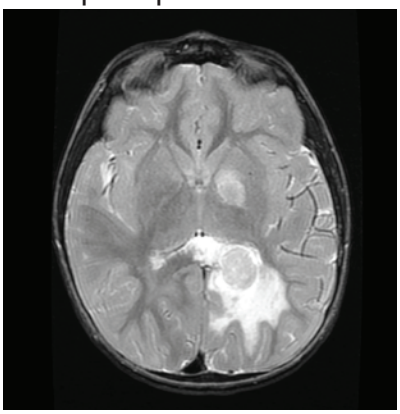
Glioma arising in the setting of NF1, low-grade molecular group

Pt #9; 5 y/o F; cerebral tumor; *NF1* bialleleic inactivation only; DNA me3 = PA, NF1-associated

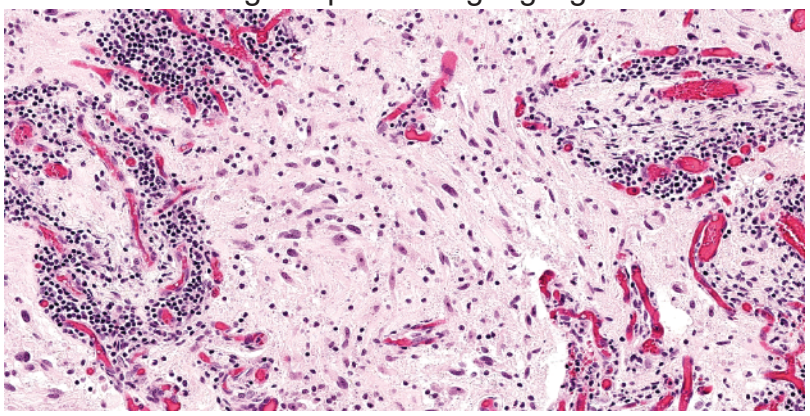
pre-op T1 w/ contrast



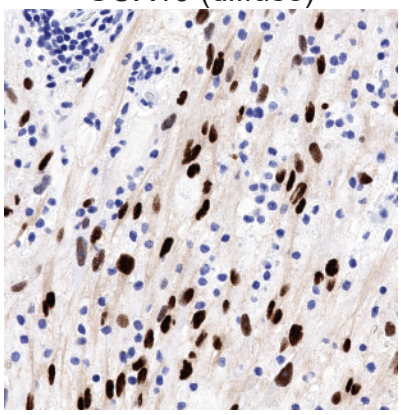
pre-op T2/FLAIR



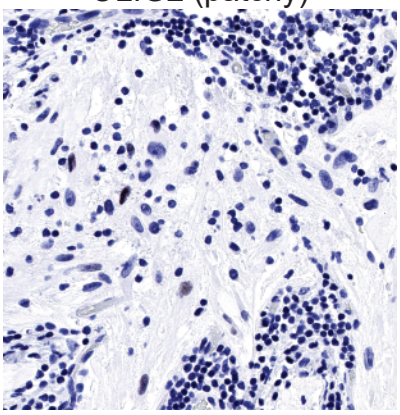
Histologic impression: ganglioglioma



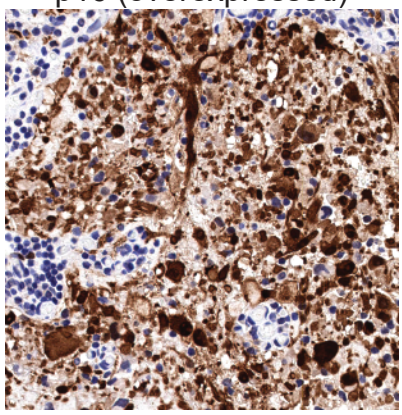
SOX10 (diffuse)



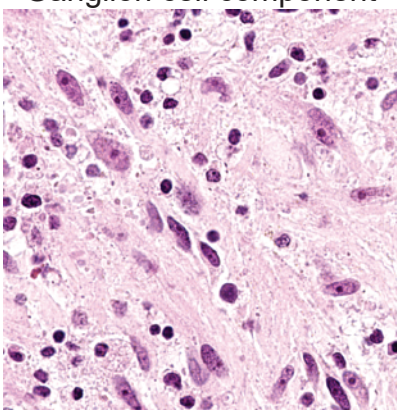
OLIG2 (patchy)



p16 (overexpressed)



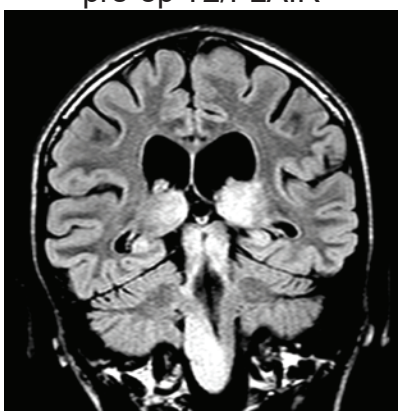
Ganglion cell component



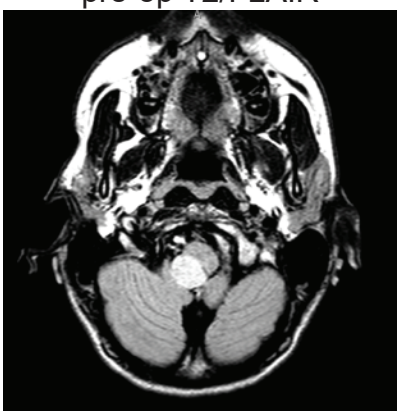
Glioma arising in the setting of NF1, low-grade molecular group

Pt #19; 15 y/o M; brainstem tumor; *NF1* biallelic inactivation only; DNA me3 = PA, NF1-associated

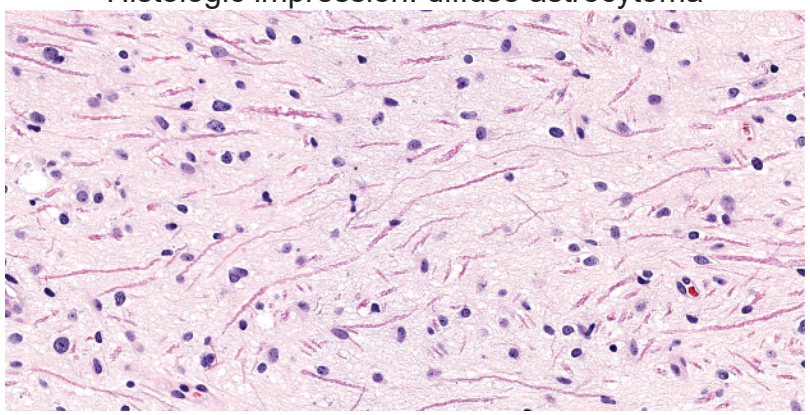
pre-op T2/FLAIR



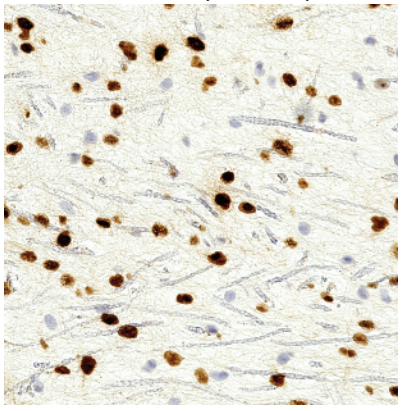
pre-op T2/FLAIR



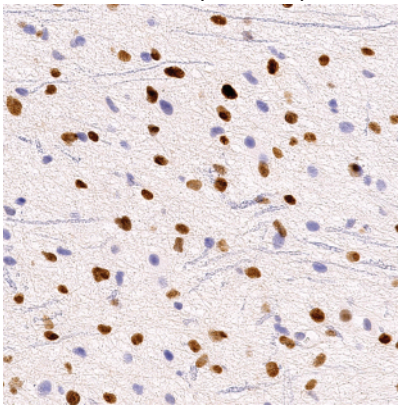
Histologic impression: diffuse astrocytoma



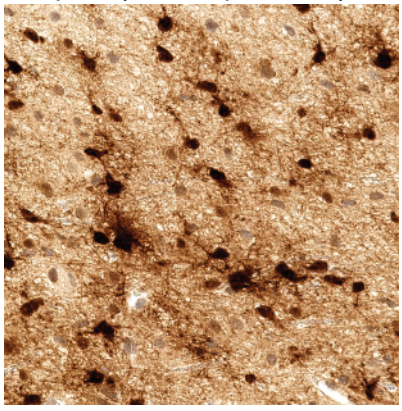
SOX10 (diffuse)



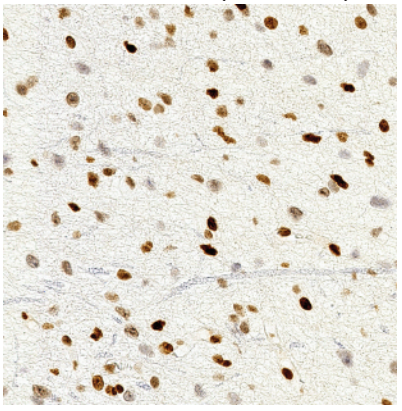
OLIG2 (diffuse)



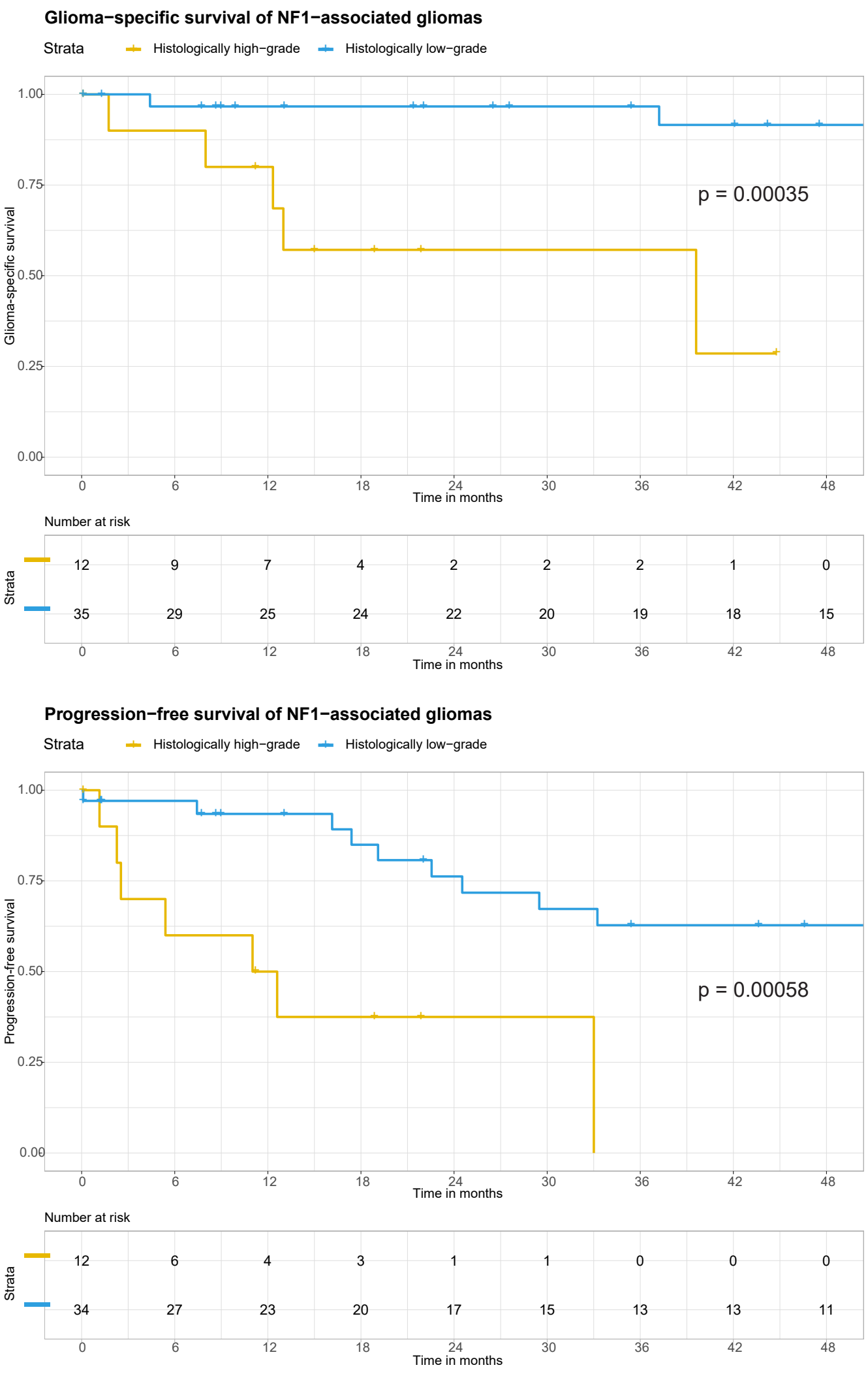
p16 (overexpressed)



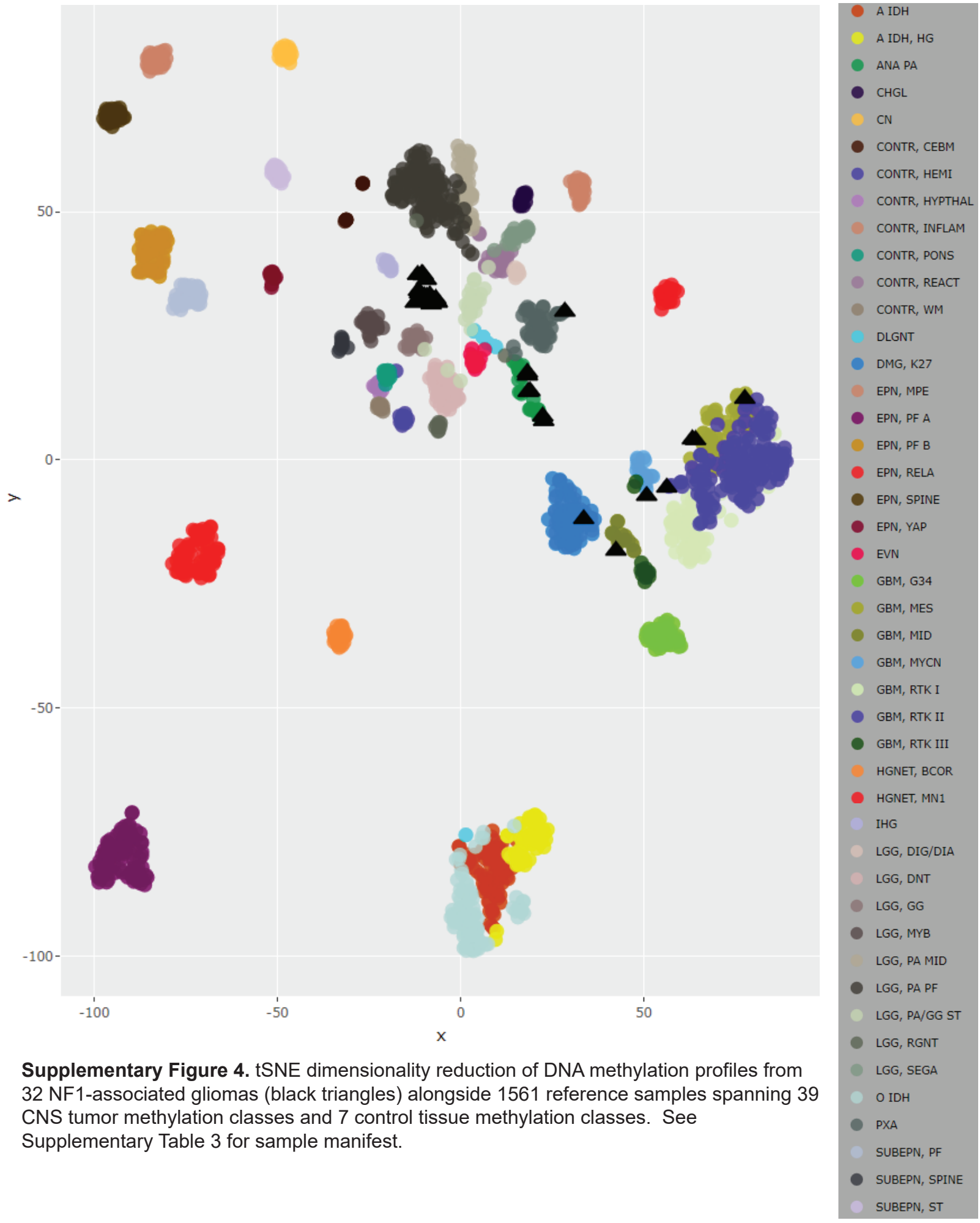
H3K27me3 (retained)



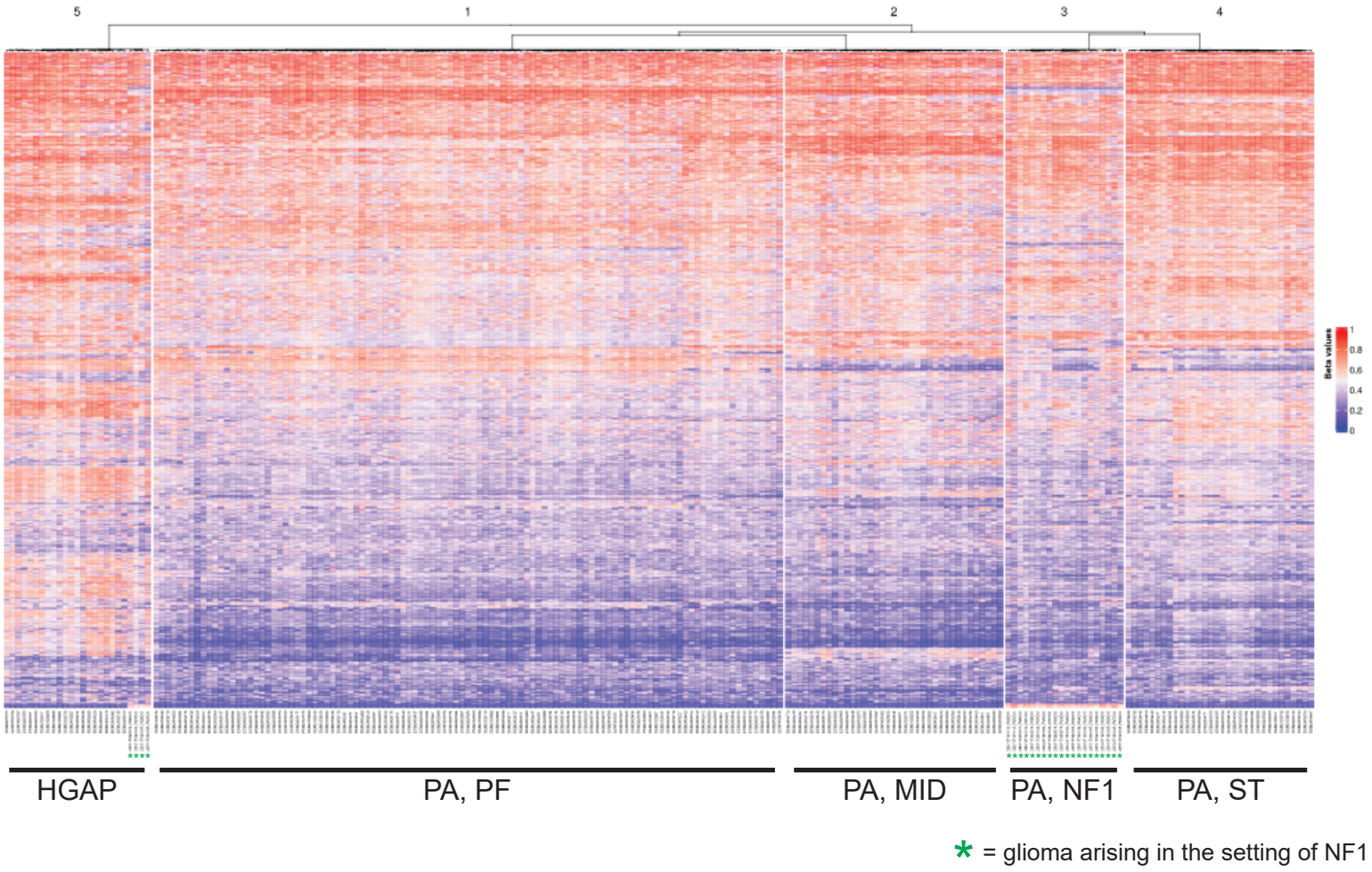
Supplementary Figure 2. NF1-associated gliomas belonging to the new epigenetic class of “Pilocytic astrocytoma, NF1-associated” include occasional tumors with histologic features resembling ganglioglioma and diffuse astrocytoma.



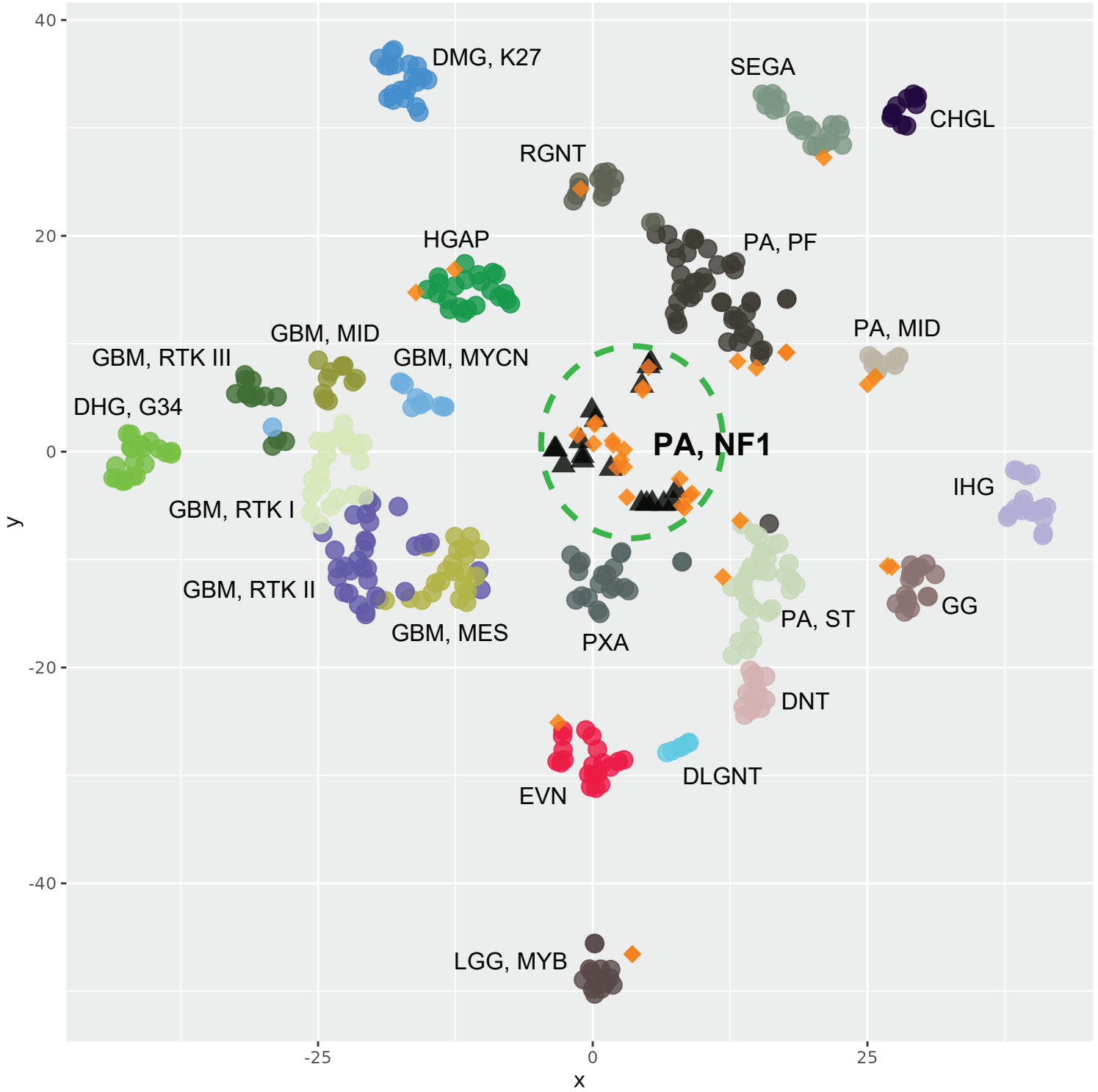
Supplementary Figure 3. Kaplan-Meier curves comparing glioma-specific survival (above) and progression-free survival (below) for the 47 NF1 patients stratified by tumor histologic features.



Supplementary Figure 4. tSNE dimensionality reduction of DNA methylation profiles from 32 NF1-associated gliomas (black triangles) alongside 1561 reference samples spanning 39 CNS tumor methylation classes and 7 control tissue methylation classes. See Supplementary Table 3 for sample manifest.



Supplementary Figure 5. Unsupervised hierarchical clustering of DNA methylation profiles from 24 NF1-associated gliomas alongside reference cohorts of high-grade astrocytoma with piloid features (HGAP), posterior fossa subclass of pilocytic astrocytoma (PA, PF), midline subclass of pilocytic astrocytoma (PA, MID), and supratentorial subclass of pilocytic astrocytoma (PA, ST). See Supplementary Table 4 for sample manifest.

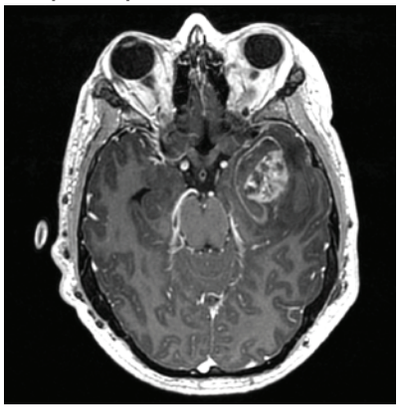


Supplementary Figure 6. DNA methylation clustering analysis of 18 NF1-associated pilocytic astrocytomas from this study (black triangles) and 43 histologically low-grade gliomas arising in children with NF1 (orange diamonds) from the Synodos NF1 LGG study (Fisher et al. *Acta Neuropath* 2021, 141(4):605-617, Synapse ID: syn5698493), alongside a reference set of CNS tumor samples (circles). Shown is a two-dimensional tSNE plot generated from the 25,000 most variably methylated probes with the following parameters: perplexity = 10, theta = 0.5, max_iter = 1000. Reference methylation classes depicted include: CHGL, chordoid glioma; DHG, G34, diffuse hemispheric glioma, H3 G34-mutant; DLGNT, diffuse leptomeningeal glioneuronal tumor; DMG, K27, diffuse midline glioma, H3 K27-altered; DNT, dysembryoplastic neuroepithelial tumor; EVN, extraventricular neurocytoma; GBM, MES, glioblastoma, mesenchymal subtype; GBM, MID, glioblastoma, midline subclass; GBM, MYCN, glioblastoma, MYCN subclass; GBM, RTK I glioblastoma, RTK I subclass; GBM, RTK II, glioblastoma, RTK II subclass; GBM, RTK III, glioblastoma, RTK III subclass; GG, ganglioglioma; HGAP, high-grade astrocytoma with piloid features; IHG, infant-type hemispheric glioma; LGG, MYB, low-grade glioma with *MYB*/*MYBL1* rearrangement; PA, MID, midline pilocytic astrocytoma; PA, PF, posterior fossa pilocytic astrocytoma; PA, ST, supratentorial/hemispheric pilocytic astrocytoma; PXA, pleomorphic xanthoastrocytoma; RGNT, rosette-forming glioneuronal tumor; SEGA, subependymal giant cell astrocytoma.

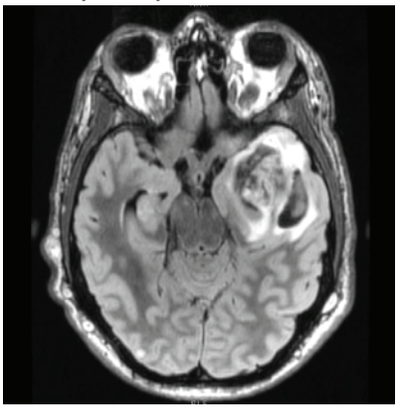
Glioma arising in the setting of NF1, high-grade molecular group

Pt #39; 20 y/o M; *NF1* & *SUZ12* bialleleic deletion + *BRAF* p.V600E + *CDKN2A/B* homo del; DNA me3 = PXA

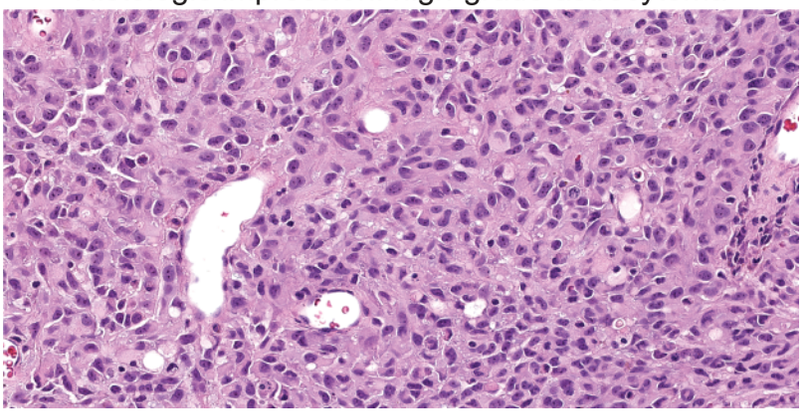
pre-op T1 w/ contrast



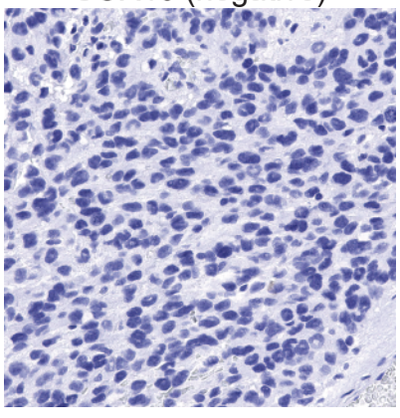
pre-op T2/FLAIR



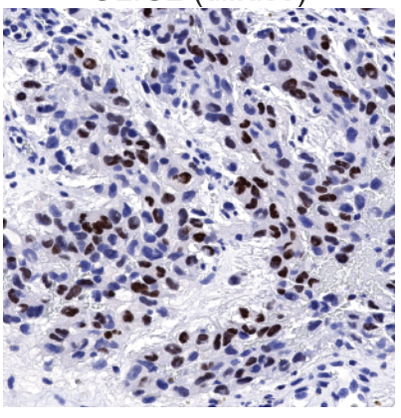
Histologic impression: high-grade astrocytoma



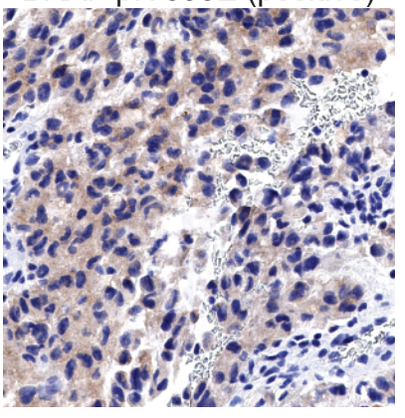
SOX10 (negative)



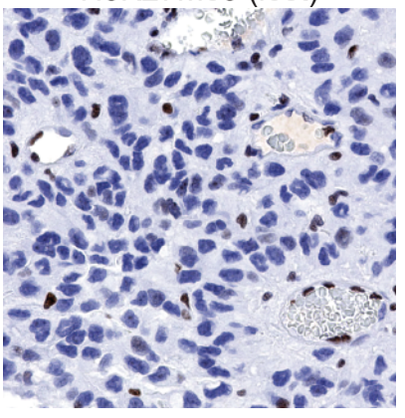
OLIG2 (diffuse)



BRAF p.V600E (positive)



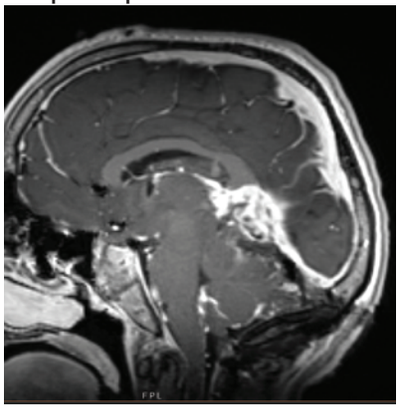
H3K27me3 (lost)



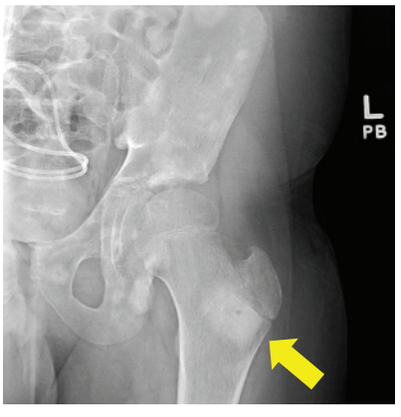
Glioma arising in the setting of NF1, high-grade molecular group

Pt #45; 12 y/o M; *NF1* bialleleic inactivation + *SUZ12* deletion + *ATRX* & *TP53* mutations; DNA me3 = DMG, K27

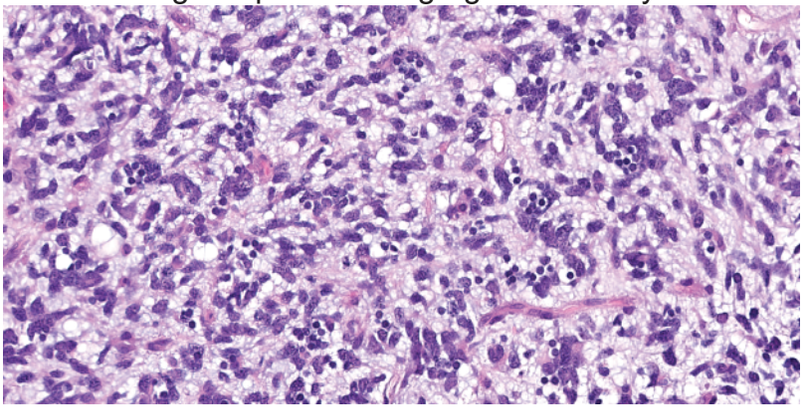
pre-op T1 w/ contrast



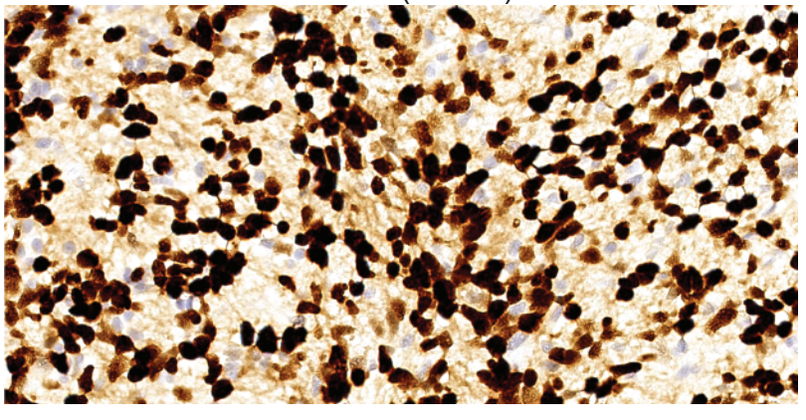
femur metastasis



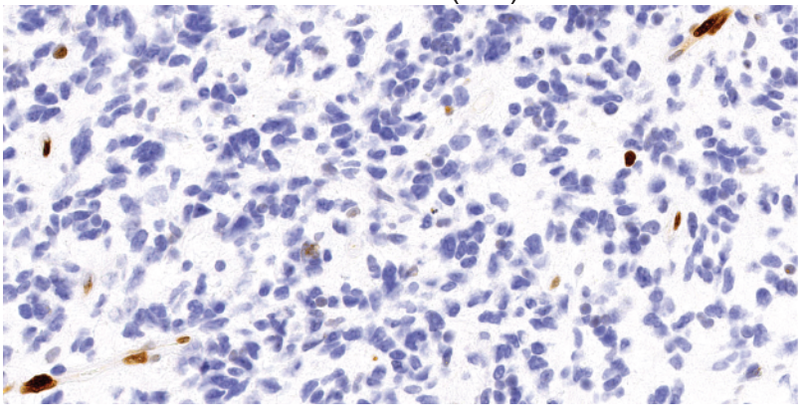
Histologic impression: high-grade astrocytoma



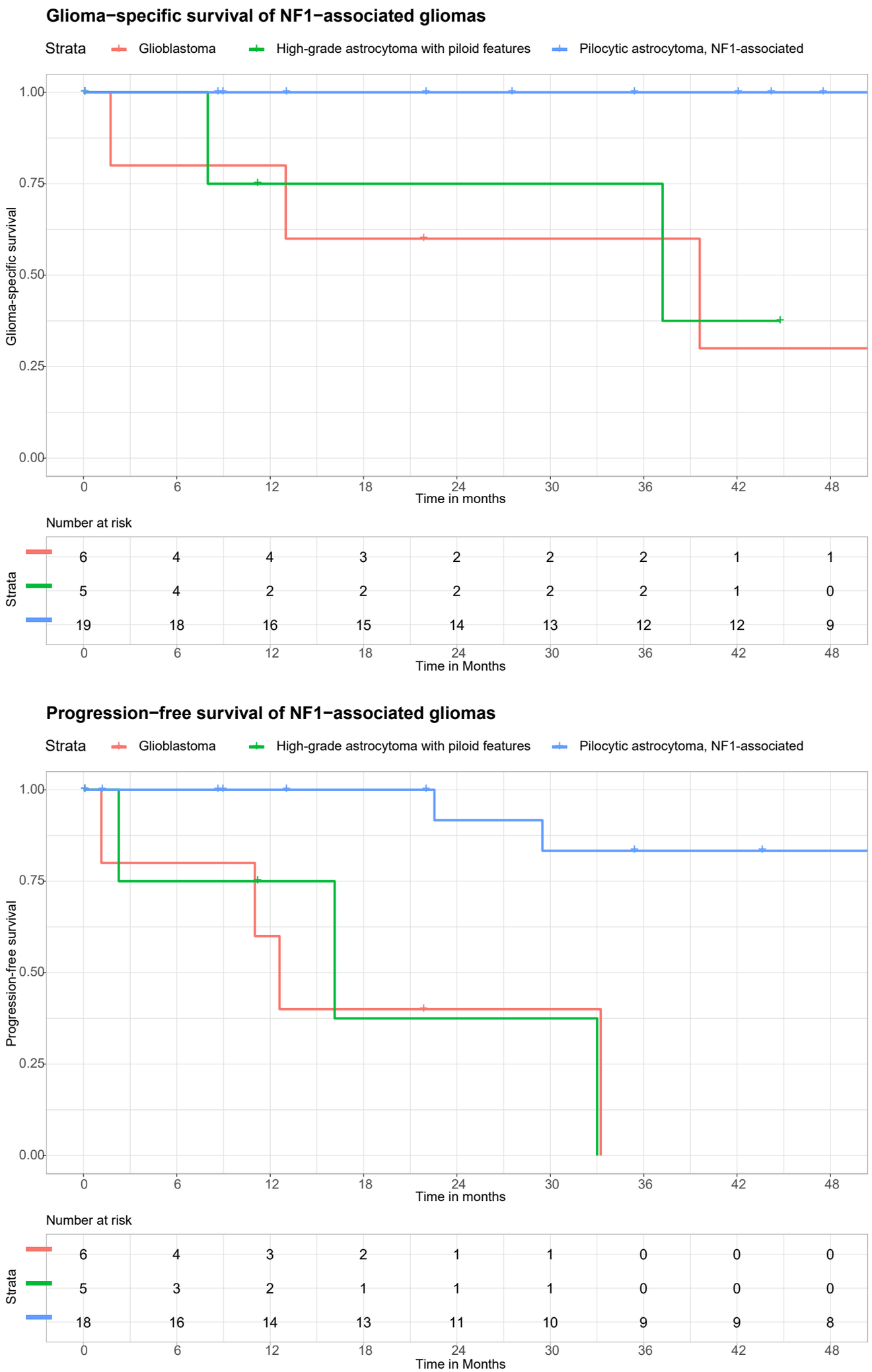
SOX10 (diffuse)



H3K27me3 (lost)



Supplementary Figure 7. NF1-associated gliomas belonging to the high-grade molecular group with additional oncogenic alterations beyond *NF1* inactivation include rare tumors epigenetically aligning with either pleomorphic xanthoastrocytoma (PXA) or H3 K27-altered diffuse midline glioma (DMG, K27).



Supplementary Figure 8. Kaplan-Meier curves comparing glioma-specific survival (above) and progression-free survival (below) for 30 NF1 patients stratified by epigenomic tumor classification.