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CORRESPONDENCE

Neurofibromatosis type 2 predisposes to ependymomas of various localization, histology, and molecular subtype

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Neurofibromatosis Type 2 (NF2) is a tumor predisposition syndrome resulting from inactivating alterations in the *NF2* gene. Patients typically develop multiple neoplastic and dysplastic lesions, predominantly in the nervous system. Apart from schwannoma and meningioma, ependymoma belongs to the typical tumor spectrum of these patients. Sporadic ependymomas encompass multiple clinically relevant subgroups based on localization, genetic alterations as well as epigenetic and transcriptomic tumor profiles [3]. However, the spectrum of ependymomas in patients with NF2 is less clear. Open questions are, whether NF2-associated ependymomas are strictly limited to the spinal cord, which molecular subgroups they encompass, and how they may be distinguished from sporadic cases. Here, we present data from 33 NF2-associated ependymomas (Table 1). In-line with previous studies [2, 4], most tumors were located in the spinal cord, but often lacked typical pseudorosettes (Suppl. Fig. 1, online resource). However, we also identified 6 intracranial cases (cases 1–6), 3 of them arising distant from the medulla oblongata as suggested by MRI (cases 1, 2, and 6, Fig. 1, Suppl. Fig. 2, online resource). NF2 patients with intracranial tumors were 10.9 years old on average, as compared to 19.4 years in NF2 patients with spinal ependymoma (SP-EPN) and 41 years in patients with SP-EPN without reported NF2 [3]. In part, intracranial tumors displayed signs of anaplasia and loss of H3K27 trimethylation (Fig. 1, Suppl. Fig. 3, online resource), had to be treated aggressively, and resulted in the patient's death (Suppl. Table 1, online resource). DNA methylation profiling and application of the brain tumor classifier [1] identified a significant match for posterior fossa ependymoma, group B (PF-EPN-B) for case 3. Case 5 that was attached to the medulla oblongata matched the methylation class of spinal ependymoma (SP-EPN). Three other intracranial cases remained without significant match (Table 1, for *t*-SNE analysis, see Fig. 1m). All 14 SP-EPN with available molecular data clearly fell into the methylation class of SP-EPN. However, copy number variation profiles of NF2-associated SP-EPN showed a rather flat genome compared to sporadic SP-EPN (Fig. 1n). Together, our data indicate that the spectrum of CNS tumors in NF2 patients includes ependymomas of different types and localizations.

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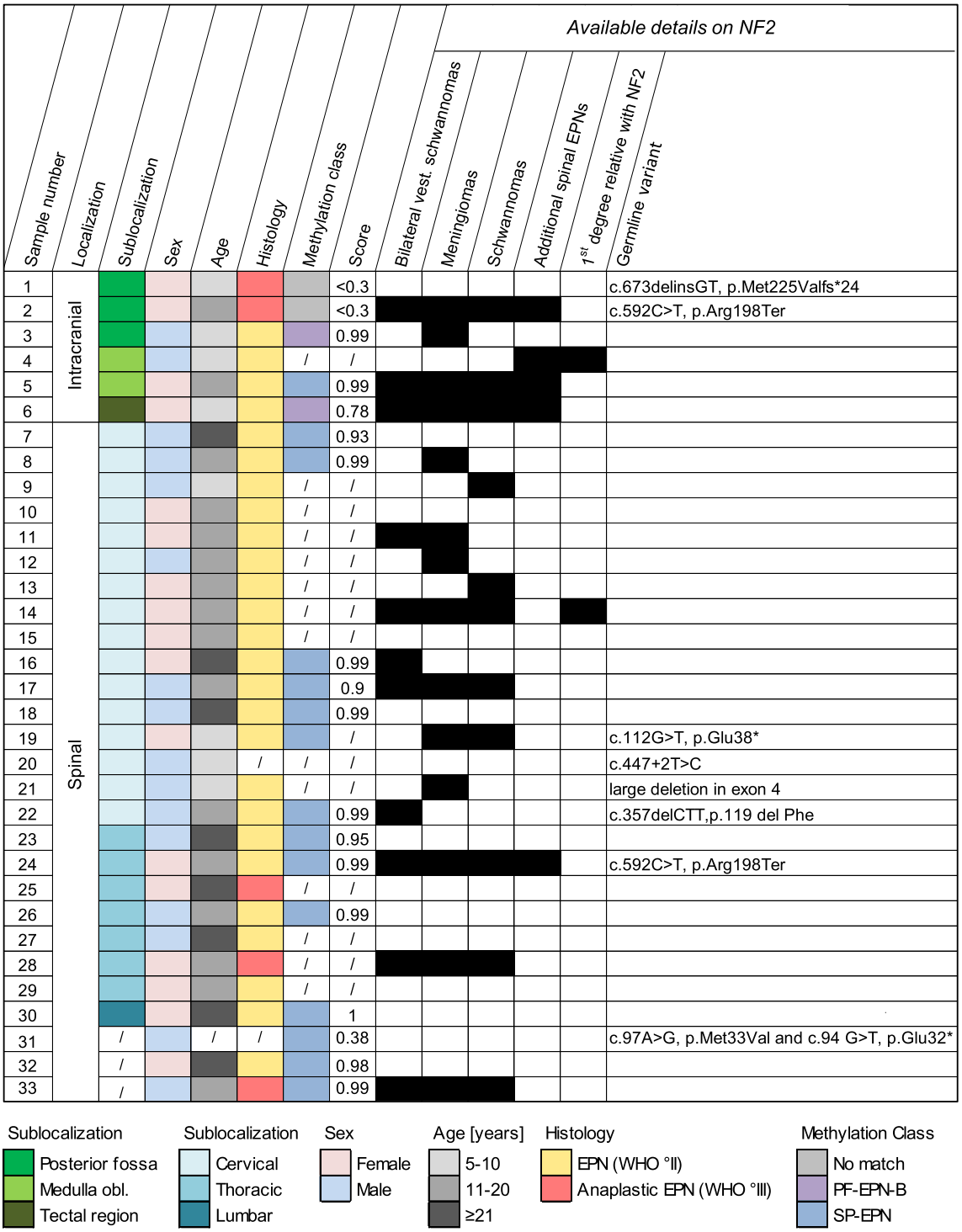
Table 1 Data overview table over 33 NF2-associated ependymomas



All patients were diagnosed with NF2. One patient was diagnosed with a SP-EPN at the age of 11 and an intracranial EPN in the fossa posterior at the age of 15 (samples 24 and 2, respectively). Additional patient data relevant to the NF2 diagnosis were collected whenever available: reported occurrence of other NF2-associated tumors is depicted as a black square. For 8 cases, genetic profiling was accessible. Germline variants were detected after alignment with the RefSeq transcript NM_000268.3 (cases 19, 22, 31), NM_000268.4 (cases 2, 20, 24) or NM_181831.2 (case 1). Score = calibrated score from version 11bv4 of the DKFZ brain tumor classifier (www.molecularneuropathology.org)

EPN ependymoma, *i. ventr.* intraventricular, *NF2* neurofibromatosis type 2, *PF-EPN-B* posterior fossa ependymoma group B, *SP-EPN* spinal ependymoma, *vest.* vestibular

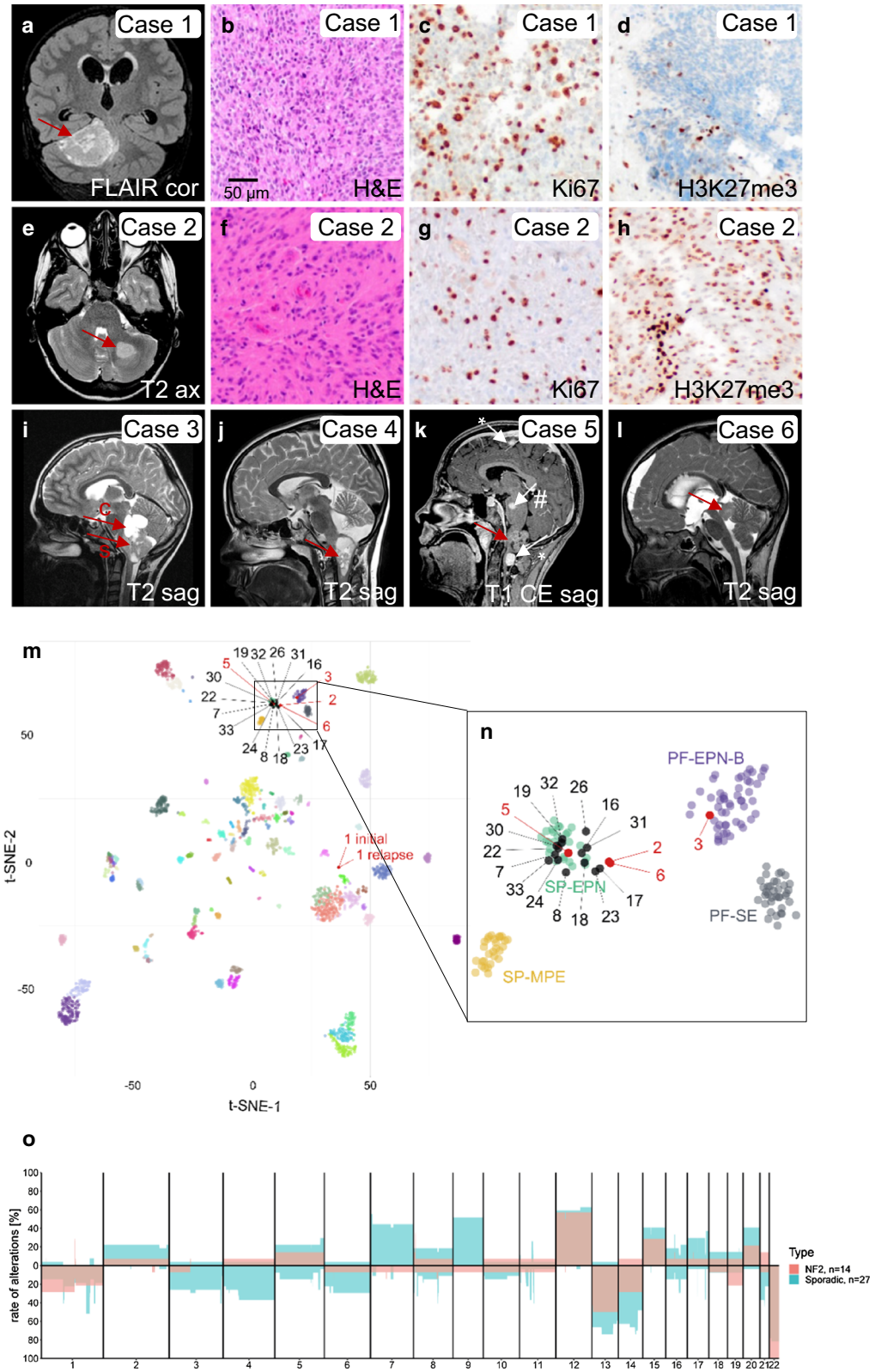


Fig. 1 Ependymomas in NF2 patients. MRIs demonstrate intracranial localization of cases 1–6 (**a**, **e**, **i**–**l**). Red arrows indicate ependymomas, white arrows meningiomas (*) or schwannomas (#). Representative histology lacks typical pseudorosettes (**b**, **f**), but shows high proliferation in cases 1 and 2 (**c**, **g**). H3K27 trimethylation was lost in case 1 (**d**), but retained in case 2 (**h**). *T*-SNE plot (**m**) including all DNA methylation classes published by Capper et al. 2018 [1] shows that case 1 is unrelated to any of the reference classes. Sample 3 clearly falls into the class of PF-EPN-B (**n**). Intracranial cases 2, 5, and 6 as well as all 14 spinal tumors fell into the class of SP-EPN. Cumulative copy number variation profiles from reference SP-EPN ($n=27$) [1] and NF2-associated SP-EPN ($n=14$) suggest less chromosomal aberrations in NF2-associated cases (**o**). *ax* axial, *c* cystic, *cor* coronal, *s* solid, *sag* sagittal, *FLAIR* fluid-attenuated inversion recovery sequence, *CE* contrast enhancement

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