




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

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Received: 26 January 2021 / Revised: 20 March 2021 / Accepted: 28 March 2021 / Published online: 12 April 2021
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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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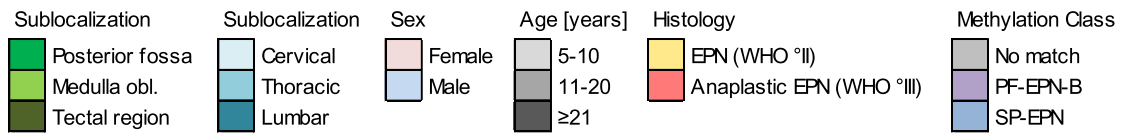
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Table 1 Data overview table over 33 NF2-associated ependymomas

Sample number	Localization	Sublocalization	Sex	Age	Histology	Methylation class	Score	Available details on NF2					
								Bilateral vestib. schwannomas	Meningiomas	Schwannomas	Additional spinal EPNs	1 st degree relative with NF2	Germline variant
1	Intracranial	Posterior fossa	Female	5-10	Anaplastic EPN (WHO °II)	SP-EPN	<0.3						c.673delinsGT, p.Met225Valfs*24
2		Posterior fossa	Female	11-20	Anaplastic EPN (WHO °II)	SP-EPN	<0.3	■	■	■	■	■	c.592C>T, p.Arg198Ter
3		Posterior fossa	Male	5-10	EPN (WHO °II)	SP-EPN	0.99						
4		Medulla obl.	Male	5-10	EPN (WHO °II)	SP-EPN	/				■	■	
5		Medulla obl.	Female	11-20	EPN (WHO °II)	SP-EPN	0.99	■	■	■	■	■	
6		Tectal region	Female	11-20	EPN (WHO °II)	SP-EPN	0.78	■	■	■	■	■	
7	Spinal	Cervical	Male	5-10	EPN (WHO °II)	SP-EPN	0.93						
8		Cervical	Male	11-20	EPN (WHO °II)	SP-EPN	0.99	■	■				
9		Cervical	Male	5-10	EPN (WHO °II)	SP-EPN	/			■	■		
10		Cervical	Female	11-20	EPN (WHO °II)	SP-EPN	/						
11		Cervical	Male	5-10	EPN (WHO °II)	SP-EPN	/	■	■				
12		Cervical	Male	11-20	EPN (WHO °II)	SP-EPN	/	■	■				
13		Cervical	Female	11-20	EPN (WHO °II)	SP-EPN	/			■	■		
14		Cervical	Female	11-20	EPN (WHO °II)	SP-EPN	/	■	■			■	
15		Cervical	Female	11-20	EPN (WHO °II)	SP-EPN	/						
16		Cervical	Female	11-20	EPN (WHO °II)	SP-EPN	0.99	■	■	■	■	■	
17		Cervical	Male	11-20	EPN (WHO °II)	SP-EPN	0.9	■	■	■	■	■	
18		Cervical	Male	11-20	EPN (WHO °II)	SP-EPN	0.99						
19		Cervical	Female	11-20	EPN (WHO °II)	SP-EPN	/			■	■		c.112G>T, p.Glu38*
20		Cervical	Male	11-20	EPN (WHO °II)	SP-EPN	/						c.447+2T>C
21		Cervical	Male	11-20	EPN (WHO °II)	SP-EPN	/			■	■		large deletion in exon 4
22		Cervical	Male	11-20	EPN (WHO °II)	SP-EPN	0.99	■	■				c.357delCTT,p.119 del Phe
23		Cervical	Male	11-20	EPN (WHO °II)	SP-EPN	0.95						
24		Cervical	Female	11-20	EPN (WHO °II)	SP-EPN	0.99	■	■	■	■	■	c.592C>T, p.Arg198Ter
25		Cervical	Female	11-20	Anaplastic EPN (WHO °III)	SP-EPN	/						
26		Cervical	Male	11-20	EPN (WHO °II)	SP-EPN	0.99						
27		Cervical	Male	11-20	EPN (WHO °II)	SP-EPN	/						
28		Cervical	Female	11-20	Anaplastic EPN (WHO °III)	SP-EPN	/	■	■	■	■	■	
29		Cervical	Female	11-20	EPN (WHO °II)	SP-EPN	/						
30		Cervical	Female	11-20	EPN (WHO °II)	SP-EPN	1						
31		/	Male	11-20	EPN (WHO °II)	SP-EPN	0.38						c.97A>G, p.Met33Val and c.94 G>T, p.Glu32*
32		/	Female	11-20	EPN (WHO °II)	SP-EPN	0.98						
33		/	Male	11-20	Anaplastic EPN (WHO °III)	SP-EPN	0.99	■	■	■	■	■	



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.moleculareuropathology.org)

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

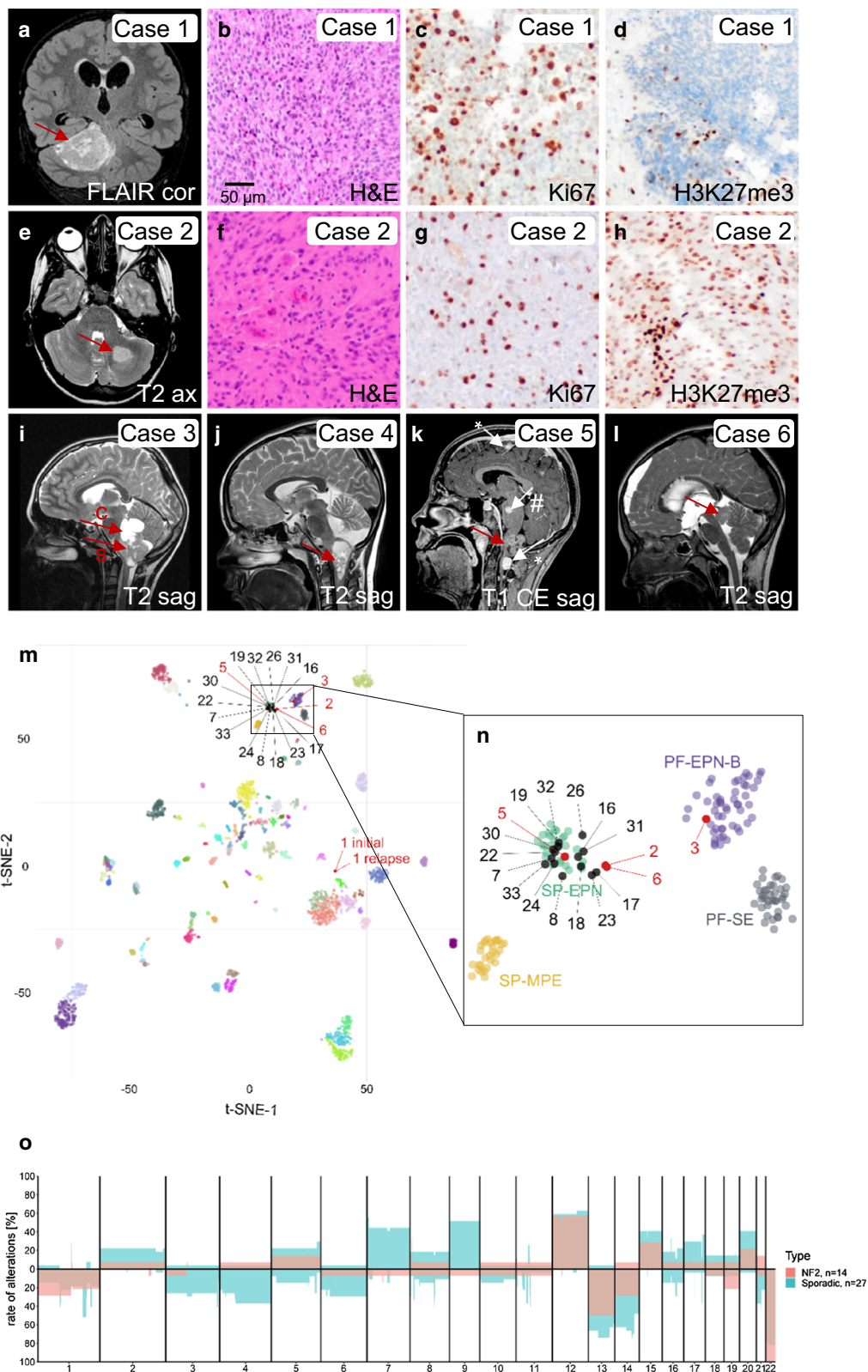


Fig. 1 Ependymomas in NF2 patients. MRIs demonstrate intracranial localization of cases 1–6 (**a**, **e**, **i–l**). Red arrows indicate ependymomas, white arrows meningiomas (*) or schwannomas (#). Representative histology lacks typical pseudorosettes (**b**, **f**), but shows high proliferation in 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

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00401-021-02304-4>.

Acknowledgements We thank Nicole Bernhardt (Hamburg) for technical support. C.K. was sponsored by a fellowship of the University Cancer Center Hamburg (UCCH). U.S. receives funding from the Fördergemeinschaft Kinderkrebszentrum Hamburg.

Funding Open Access funding enabled and organized by Projekt DEAL.

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