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Low rate of R132H *IDH1* mutation in infratentorial and spinal cord grade II and III diffuse gliomas

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Diffuse gliomas not only are more frequent in the cerebral hemispheres but also occur in the brainstem, cerebellum, and spinal cord. In adult populations, 5 % or less localize to the infratentorium [6, 14]. Primary tumors of the spinal cord are uncommon and only 2.5 % are

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diffuse gliomas [6]. In the brainstem, many gliomas are diagnosed solely by radiology and even when a biopsy is obtained it tends to be of minute size, rendering interpretations challenging. Accurate diagnostic ancillary studies on such specimens would therefore be valuable.

Analysis of R132H mutant isocitrate dehydrogenase 1 (*mIDH1*), either by molecular methods or by immunohistochemistry (*mIDH1*-IHC) [4, 5, 13], has been shown to reliably distinguish diffuse astrocytomas from some of their most frequent mimickers, including pilocytic astrocytomas, gangliogliomas, or reactive gliosis [1, 3, 8, 9, 11], or likewise to distinguish oligodendroglioma from other brain tumors with clear cell morphology like neurocytomas or dysembryoplastic neuroepithelial tumors [2]. However, results from *mIDH1*-IHC are only diagnostically useful when positive and although prior reports have shown that about 75 % of supratentorial grade II and III diffuse gliomas are *mIDH1* positive [10], no such data are available in adult infratentorial and spinal cord diffuse gliomas.

We searched our surgical pathology archives (1990–2011) for infratentorial and spinal cord diffuse gliomas, excluding glioblastomas and patients under the age of 16, and selected all cases with paraffin-embedded tissue available. All sections were reexamined and cases were reclassified according to the WHO 2007 criteria. None of the cases had histologic features of ganglioglioma. Small biopsies initially designated “low grade astrocytoma” that showed contrast enhancement, incomplete features of pilocytic astrocytoma, and no recurrence after many years were excluded since they may have represented pilocytic astrocytomas.

A total of 44 cases were selected for *mIDH1*-IHC (clone H09, Dianova, Hamburg, Germany), including 23 brainstem, 12 cerebellar and 9 spinal cord tumors (Table 1). The median age at diagnosis was 36 years (range 16–90) and the male to female ratio was 1.75:1. Two patients had neurofibromatosis type 1 (case B18 and C12). Surprisingly, only 3/44 tumors (7 %) were positive for the mutation, all localizing to the brainstem. None of the cerebellar or spinal cord tumors had the mutation. The median overall survival of this cohort (grade II, 43 months; grade III, 25 months) was similar to that previously reported for same grade supratentorial *IDH* wild-type tumors [12].

The vast majority of these infratentorial and spinal cord specimens were needle or small biopsies with insufficient tissue for DNA extraction and sequencing, as is often the case in routine clinical practice. In the nine cases in which DNA extraction was achieved (six cerebellar and three brainstem tumors), mass spectrometry array mutation profiling (MassARRAY system, Sequenom, San Diego, CA) or fluorescence melting curve PCR analysis [7] confirmed the absence of R132H *IDH1* mutation. Testing for other rarer *IDH1* mutations or mutations in *IDH2* revealed one case with an *IDH1* R132G mutation.

This low rate of R312H *IDH1* mutation is in sharp contrast with the high rate seen in same grade diffuse gliomas in the supratentorial compartment and suggests *mIDH1*-IHC may only rarely be of diagnostic help in the context of small biopsies from infratentorial and spinal cord tumors.

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Table 1

Study cohort listed with patient age at first diagnosis, sex, location, current diagnosis, result of *mIDH1*-IHC, result of *IDH* genotyping, overall survival, and status at last follow-up

Case	Age	Sex	Location	Diagnosis	*mIDH1* IHC	*IDH* genotyping	OS (months)	Alive
B01	27	F	BS (medulla)	DA2	Negative		2	No
B02	21	F	BS (medulla)	DA2	Negative		145	Yes
B03	60	M	BS (medulla)	DA2	Negative		14	No
B04	20	F	BS (pons)	DA2	Negative		17	No
B05	21	M	BS (medulla)	DA2	Negative		90	No
B06	26	F	BS (pons)	DA2	Negative		60	Yes
B07	40	M	BS (medulla)	DA2	Positive		10	Yes
B08	64	M	BS (midbrain)	DA2	Negative		n/a	n/a
B09	16	M	BS	DA2	Negative		n/a	n/a
B10	24	M	BS (medulla)	DA2	Positive		n/a	n/a
B11	56	M	BS (pons)	AA3	Positive		12	No
B12	42	M	BS (pons)	AA3	Negative		171	No
B13	54	M	BS (pons)	AA3	Negative	*IDH*wt (Seq)	13	No
B14	30	F	BS (pons)	AA3	Negative	*IDH*wt (Seq)	66	No
B15	41	M	BS (pons)	AA3	Negative		21	No
B16	40	F	BS (medulla)	AA3	Negative	*IDH*wt (Seq)	114	No
B17	19	M	BS (pons)	AA3	Negative		32	No
B18	24	M	BS (pons)	AA3	Negative		21	No
B19	26	M	BS (pons)	AA3	Negative		6	No
B20	26	M	BS (medulla)	AA3	Negative		4	Yes
B21	30	M	BS	AA3	Negative		n/a	n/a
B22	46	F	BS (pons)	AA3	Negative		n/a	n/a
B23	46	M	BS (medulla)	AA3	Negative		n/a	n/a
C01	49	F	CBL	DA2	Negative		80	No
C02	29	F	CBL	DA2	Negative		48	Yes
C03	63	M	CBL	DA2	Negative		n/a	n/a
C04	42	M	CBL	OA2	Negative		n/a	n/a

Case	Age	Sex	Location	Diagnosis	*mIDH1* IHC	*IDH* genotyping	OS (months)	Alive
C05	90	M	CBL	AA3	Negative	*IDH*wt (Seq)	2	Yes
C06	37	F	CBL	AA3	Negative	*IDH*wt (Seq)	11	No
C07	31	F	CBL	AA3	Negative	*IDH*wt (Seq)	57	No
C08	38	M	CBL	AA3	Negative	*IDH*wt (Seq)	69	No
C09	39	M	CBL	AA3	Negative	*IDH*wt (Seq)	18	No
C10	53	M	CBL	AA3	Negative	*IDH1*-R132G (FMCA)	97	Yes
C11	46	M	CBL	AA3	Negative		12	No
C12	28	M	CBL	AA3	Negative		n/a	n/a
S01	77	F	SC (T12)	DA2	Negative		38	No
S02	28	F	SC (C4–T4)	DA2	Negative		32	Yes
S03	21	F	SC (T6–T8)	DA2	Negative		n/a	n/a
S04	45	M	SC (T6–T11)	O2	Negative		138	Yes
S05	33	M	SC	O2	Negative		43	Yes
S06	39	M	SC (T12–L1)	AA3	Negative		196	Yes
S07	29	F	SC (T11–L2)	AA3	Negative		n/a	Yes
S08	34	F	SC (T12)	AA3	Negative		72	No
S09	31	M	SC (thoracic)	AA3	Negative		29	No

OS overall survival, *F* female, *M* male, *BS* brainstem, *CBL* cerebellum, *SC* spinal cord, *DA2* diffuse astrocytoma WHO grade II, *AA3* anaplastic astrocytoma WHO grade III, *OA2* oligoastrocytoma WHO grade II, *O2* oligodendroglioma WHO grade II, *wt* wild-type, *Seq* Sequenom™, *FMCA* fluorescence melting curve analysis, *n/a* not available