Hereditary Tumor Syndromes Associated with CNS/PNS Tumors

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Case-Based Questions (please see page 3 for answers)

1.	An 8-year-old boy with family history of Li-Fraumeni syndrome was diagnosed with a posterior fossa mass consistent with medulloblastoma. What is the expected histologic and molecular subtype of this patient's medulloblastoma?	
	a.	Non-WNT/non-SHH, group 3, classic subtype
	b.	Non-WNT/non-SHH, group 4, anaplastic/large cell subtype
	c.	SHH-activated and TP53-mutant, anaplastic/large cell subtype
	d.	SHH-activated and TP53-wildtype, classic subtype
	e.	WNT-activated, Desmoplastic and nodular subtype

2.	A 35-year-old patient with new-onset seizures was found to have a rim-enhancing temporal lobe tumor and sections show a diffusely infiltrating glioma with prominent giant cells, microvascular proliferation and necrosis. Which of the staining results below indicate possibility of a hereditary tumor syndrome?	
	a.	ATRX loss in tumor nuclei
	b.	BRAF V600E positivity in tumor cells
	c.	IDH1 R132H positivity in tumor cells
	d.	MLH1 loss in tumor nuclei
	e.	P53 positivity in 5% of tumor cells

3.	A 3-year-old girl presented with in intraventricular mass involving the right lateral ventricle and sections show sheet-like growth of pleomorphic epithelioid cells in the background of papillary regions, with abundant mitotic activity and geographic necrosis. Immunohistochemical stains for keratin and transthyretin were positive and OLIG2 and GFAP were negative. What is the most likely germline gene alteration in this patient?	
	a.	APC truncating mutations
	b.	MSH6 frameshift mutations
	c.	RB1 truncating mutations
	d.	TP53 truncating mutations
	e.	VHL frameshift mutations

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Correct Answers and Rationales

Question 1 Correct Answer and Rationale: **c- SHH-activated and TP53-mutant, anaplastic/large cell subtype**

Rationale: Medulloblastomas seen in the setting of Li-Fraumeni syndrome are essentially always SHH-activated and TP53-mutant subtype, and they frequently show anaplastic large cell morphology.

Question 2 Correct Answer and Rationale: **d – MLH1 loss in tumor nuclei**

Rationale: suggestive of mismatch repair deficiency, which would require further evaluation of the patient for a possible germline alteration to exclude Lynch Syndrome

Question 3 Correct Answer and Rationale: **d- TP53 truncating mutations**

Rationale: The tumor described above is a choroid plexus carcinoma, most frequently harboring TP53 mutations. Significant percentage of the tumors are seen in the setting of Li-Fraumeni syndrome, which is caused by germline TP53 mutations including truncating, frameshift or damaging missense, or focal gene deletions.