Medulloblastoma: candidate pathways for novel treatment strategies

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Abstract

BACKGROUND: Medulloblastoma, an aggressive but potentially curable CNS disease, remains a treatment challenge due to the biological heterogeneity of the disease. Analysis of actionable targets can provide opportunities in the development of curative therapies. To identify potential candidate genes, we investigated alterations in a cohort of medulloblastoma patients.

METHODS: Tumors from 36 medulloblastoma patients were profiled using immunohistochemistry, next generation sequencing, pyrosequencing, fluorescence in situ hybridization, and fragment analysis at Caris Life Sciences.

RESULTS: Primary tumor location included the posterior fossa (n = 18) and other (n=18). There were 18 adults (9 male, 9 female, median age: 30, range: 18-47 years) and 18 pediatric patients (14 male, 4 female, median age: 7, range: 2-14 years). Medulloblastomas showed the highest expression of MRP1 (88.9%, 8/9 tumors), TUBB3 (85.7%, 18/21 tumors), PTEN (84.8%, 28/33 tumors), TOP2A (83.9%, 26/31 tumors), thymidylate synthase (TS; 80%, 24/30 tumors), RRM1 (71.4%, 15/21 tumors), and TOPO1 (63.3%, 19/30 tumors). Among them, TS expression was higher in males (94.1%, 16/17 tumors) than females (61.5%, 8/13 tumors, p=0.0397). TOP2A overexpression was much higher in non-posterior fossa tumors than in posterior fossa tumors (9/14 and 17/17, respectively, p=0.012). There was low PD-1+ T-cell infiltration (4%, 1/25 tumors) and low expression of PD-L1 on tumor cells (3.7%, 1/27 tumors) in these tumors. Among 19 tumors sequenced, 2 had mutations in TP53 (H178fs, Q167fs), PDE4DIP (E243fs) and FOXO3 (L382fs, G381fs), and one mutation occurred in each of the following: BRCA2 (V220fs/D2242fs), CTNNB1 (G34V), PIK3CA (E545G), ARID1A (I1664fs), SMO (L412F), and PTCH1 (Q694fs).

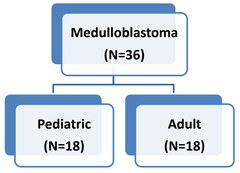
CONCLUSION: Distinct molecular features in adult and pediatric medulloblastomas identified candidate pathways for further interrogation. BRCA2, PIK3CA, ARID1A, SMO, PTCH1 as well as TOP2A, TS, RRM1, and TOPO1 are among potential therapeutic targets for medulloblastoma patients.

Background

Medulloblastoma is the most common malignant CNS pediatric tumor and is less frequent in adults. Current treatment paradigms are based on standard or high-risk criterion, as multimodal therapeutic approaches include surgical resection, cranio-spinal radiation followed by a boost to the tumor bed with concurrent and adjuvant chemotherapy. However, patients < 3 years of age are usually treated postsurgically with high-dose chemotherapy, instead of irradiation, due to the risk of neurocognitive and neuroendocrine dysfunction[1]. Current treatment strategies have shown an improvement in 5-year overall survival to 85% for children with standard-risk disease and ~60% for those with high-risk disease[2,3]. However, identifying novel targeted therapies may help improve disease outcome. Profiling medulloblastoma for potential candidate genes and molecular biomarkers may provide insights into optimal, targeted therapeutic strategies.

Results

Figure 1: patient characteristics



				Total
Tumor location	Posterior Fossa:	N=12	N=6	N=18
	Others:	N=6	N=12	N=18
Gender	Female:	N=4	N=9	N=13
	Male:	N=14	N=9	N=23

Results, continued

Figure 2: Protein expression frequencies in the medulloblastoma cohorts. A: all cases studied (numbers in parentheses indicate the N of positive staining/ total N)**; B: comparison of protein expression in tumors taken from adult patients with pediatric patients; C: comparison of tumors taken from male patients with female patients; D: comparison of tumors taken from posterior fossa with other tumor locations.** (An asterisk indicates statistical significance by Fisher-Exact test)

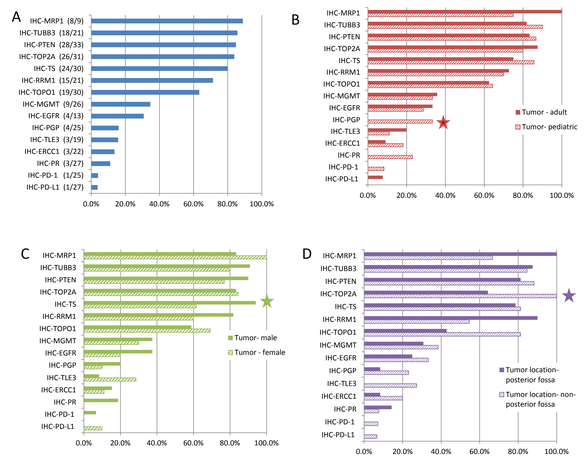
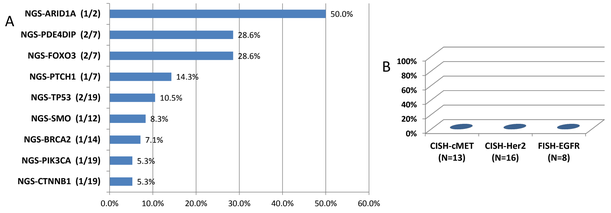


Figure 3: A: Mutation frequencies seen in the cohort (numbers in parentheses indicate the N of mutated cases/ total N)**; B: No gene amplification tested by CISH or FISH were seen in the cohort studied**



Results, continued

Figure 4: Oncoprint of 19 tumors that went through NextGen sequencing. Pathogenic/presumed pathogenic mutations are marked red with protein changes shown; wild type/benign variants are shown in blue. Blank indicates data not available.

	Gender	Age	Tumor location	TP53	PIK3CA	CTNNB1	BRCA2	SMO	FOXO3	PDE4DIP	PTCH 1	ARID1A
case 1	f	31	Other	H178fs								
case 2	m	6	Posterior Fossa	Q167fs			V220fs; D2242fs					
case 3	m	27	Other					L412F				
case 4	m	22	Posterior Fossa						G381fs			
case 5	f	34	Other							E243fs; H1787Y		I1664fs
case 6	m	34	Other		E545G				L382fs		Q694fs	
case 7	f	2	Posterior Fossa							E243fs		
case 8	f	6	Posterior Fossa									
case 9	m	14	Posterior Fossa									
case 10	f	27	Posterior Fossa			G34V						
case 11	m	9	Other									
case 12	f	26	Other									
case 13	f	11	Other									
case 14	f	21	Other									
case 15	f	45	Other									
case 16	m	14	Posterior Fossa									
case 17	m	6	Other									
case 18	m	21	Other									
case 19	f	8	Other									

Conclusions

1. Using a combination of different test technologies on 36 medulloblastoma tumor samples, we found biomarkers expressed at various frequencies, which could be linked to responsiveness to chemotherapies used in medulloblastoma treatments.
2. Distinct molecular features in adult and pediatric medulloblastomas identified candidate pathways for further interrogation. A significantly higher expression of drug efflux pump Pgp in pediatric tumors indicate potential increased chance of drug resistance to its substrate, including etoposide.
3. Higher expression of TOP2A seen in non-posterior fossa medulloblastomas may indicate an aggressive clinical behavior and may suggest the use of TOP2A inhibitors.
4. Targetable gene mutations including BRCA2, PIK3CA, ARID1A, SMO, PTCH1 were seen in our cohort, suggesting potential opportunities for targeted therapies.

References

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