Comprehensive Molecular Characterization of Spinal Cord Gliomas

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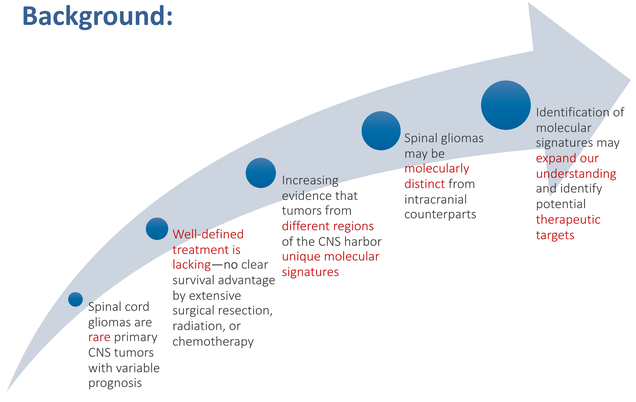
Background:



- In a retrospective study, we comprehensively characterized molecular alterations to identify potential therapeutic strategies in the largest cohort of SCG reported to date.
- Objectives:
  - Comprehensively characterize molecular alterations of spinal gliomas
  - Compare spinal gliomas to intracranial gliomas

Methods

- We performed centralized pathology review and analyzed SCG with next-generation sequencing of DNA (592 gene NextSeq or WES, NovaSeq), RNA (WTS, NovaSeq) and pyrosequencing (MGMT promoter methylation, MGMTme).
- We estimated tumor microenvironment cell infiltration by quanTIseq & Epithelial-Mesenchymal Transition (EMT) by RNAseq.
- We used X2/Fisher's-exact/Mann-Whitney U tests for comparison & determined significance ($p < 0.05$), adjusting for multiple comparison by the Benjamini-Hochberg method ($q < 0.05$).

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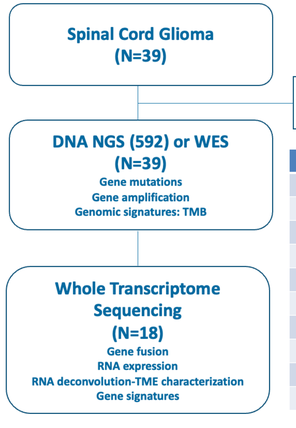
Results:

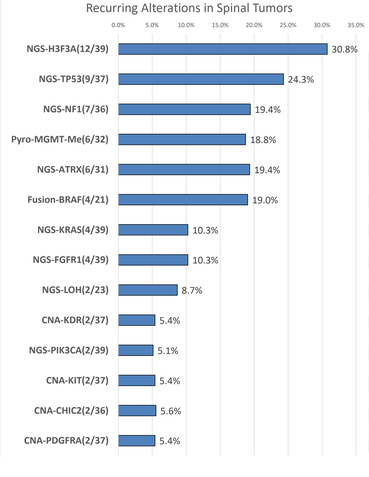
1. Study cohort and patient characteristics

Centralized pathology review categorized 36/39 tumors into high grade vs. low grade tumors



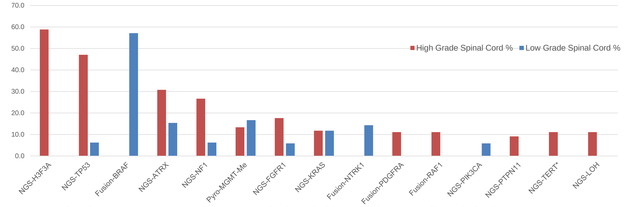
Characteristics	n=39
Gender (%)	
Male	21 (54%)
Female	18 (46%)
Age (years)	28 (1-77)
Male	28 (1-77)
Female	28.5 (4-62)
Grade	
High grade	19
Low grade	17
Unclear/NOS	3

2. Recurring (left) and single (right) alterations seen in the spinal cord tumor cohort

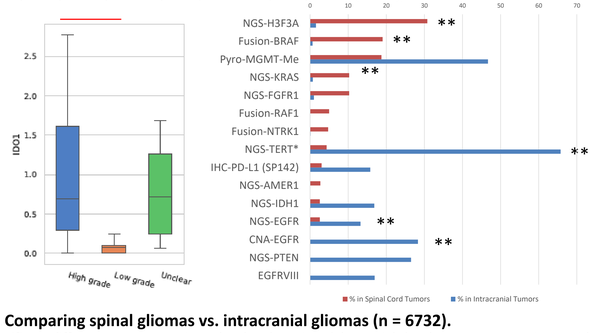


Features	Positive N	Total N	Percent Spinal
NGS-TERT*	1	23	4.3%
NGS-IDH1	1	39	2.6%
Fusion-RAF1	1	20	5.0%
NGS-AMER1	1	37	2.7%
Fusion-NTRK1	1	21	4.8%
IHC-PD-L1 (SP142)	1	33	3.0%
NGS-EGFR	1	39	2.6%
NGS-WT1	1	39	2.6%
Fusion-PDGFRA	1	20	5.0%
CNA-CDK4	1	37	2.7%
NGS-NF2	1	39	2.6%
NGS-BLM	1	39	2.6%
NGS-FUBP1	1	38	2.6%
NGS-ASXL1	1	32	3.1%
CNA-FGF23	1	37	2.7%
NGS-APC	1	39	2.6%
NGS-CHEK2	1	39	2.6%
CNA-CCND2	1	37	2.7%
NGS-BCOR	1	38	2.6%
NGS-ARID1A	1	39	2.6%
NGS-MUTYH	1	39	2.6%
NGS-PIK3R1	1	39	2.6%
NGS-BRAF	1	39	2.6%
NGS-PTPN11	1	19	5.3%

3. Comparing alterations in high grade vs. low spinal tumors



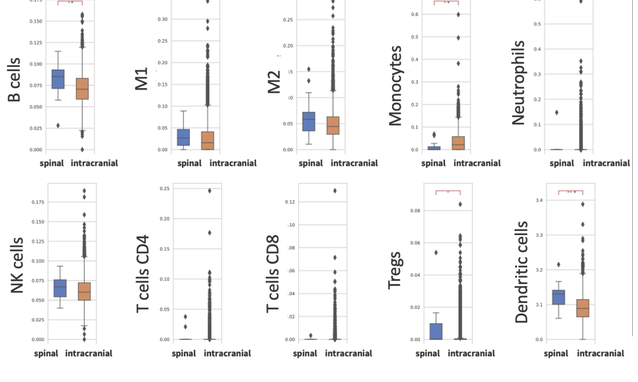
Immune checkpoint genes in spinal tumors (below, left). IDO1 has significantly higher expression in high grade spinal tumors. Other immune checkpoint genes did not show difference (CD80, PDCD1, CTLA4, CD86, CD274, HAVCR2, LAG3, PDCD1LG2, IFNG, CD276 (B7-H3)).



4. Comparing spinal gliomas vs. intracranial gliomas (n = 6732).

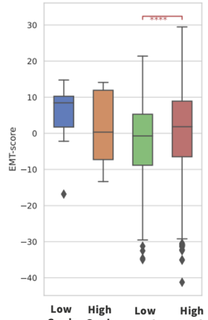
Significant differences were seen in molecular alterations (above, right) – shown are comparisons with $p<0.05$; ** indicate significance after correction for multiple comparison ($q<0.05$)

Comparison in Tumor Microenvironment (bottom); red brackets indicate significance after correction for multiple comparison ($q<0.05$)



5. Molecular alterations in spine vs. intracranial tumors differentiated by grade

	Features	Spinal Cord: Percentage (High grade)	Spinal Cord: Percentage (Low grade)	Intracranial: Percentage (High grade)	Intracranial: Percentage (Low Grade)
	Pyro-MGMT-Me			*	*
	IHC-PD-L1 (SP142)			**	**
Fusion	Fusion-BRAF	*	*	**	**
Fusion	Fusion-NTRK1			**	**
Fusion	Fusion-PDGFRA				
Fusion	Fusion-RAF1				
NGS	NGS-H3F3A	**	**		
NGS	NGS-TP53	*	*	**	**
NGS	NGS-NF1			*	*
NGS	NGS-ATRX			**	**
NGS	NGS-FGFR1			*	*
NGS	NGS-KRAS			*	*
NGS	NGS-LOH			*	*
NGS	NGS-PIK3CA			**	**
NGS	NGS-AMER1				
NGS	NGS-APC				
NGS	NGS-ARID1A				
NGS	NGS-ASXL1				
NGS	NGS-BCOR				
NGS	NGS-BLM				
NGS	NGS-BRAF			**	**
NGS	NGS-CHEK2				
NGS	NGS-EGFR			**	**
NGS	NGS-FUBP1				
NGS	NGS-IDH1			**	**
NGS	NGS-MUTYH			*	
NGS	NGS-NF2				
NGS	NGS-PIK3R1			*	
NGS	NGS-PTPN11			*	
NGS	NGS-TERT*			**	**
NGS	NGS-WT1				
CNA	CNA-CHIC2			**	**
CNA	CNA-KDR			*	*
CNA	CNA-KIT			**	**
CNA	CNA-PDGFRA			**	**



Intracranial higher alterations in:
- MGMT methylation
- IDH1/2 mutations
- pTERT mutation

Spinal cord higher alterations in:
- H3F3A mutations
- BRAF fusions

Similar trends in spine & intracranial
- Higher BRAF fusions in low grade
- Higher 4q12 (CKIT, PDGFRA) amplification in high grade

High EMT associated with high grade in intracranial tumors but not in spinal cord tumors

Conclusions

- Clinical management of SCG is currently drawn from experience with intracranial gliomas. **Our results identify unique molecular features of SCG suggesting an underlying biology distinct from intracranial gliomas.**
- In SCG, H3F3A mutations are exclusive to high grade while BRAF fusions are exclusive to low grade; SCG rarely harbor canonical intracranial alterations such as IDH1, EGFR or MGMTme; and SCG have greater penetration of DCs with less penetration of monocytes.
- We provide a biological explanation for limited effectiveness of current therapies in SCG with **potential implications for chemotherapy, targeted and immunotherapy.** Our work underscores the need for investigations dedicated uniquely to SCG.