Investigating Copy Number Alterations and Mutational Signatures in Ultra Rare CNS Tumors

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Background

- Mutational signatures are characteristic patterns of genetic mutations that can point to the origins of specific cancers, uncovering the interplay of intrinsic and extrinsic elements that have impacted the evolution of the disease.[1]
- Copy number changes refer to variations in the number of copies of a specific genomic region in a cell's DNA compared to the normal diploid state.[2]
  - Copy number signatures can be utilized for understanding the processes that cause them, for potentially preventing exposures, and as clinical biomarkers.[2]
- While prior investigations have primarily concentrated on mutational signatures in prevalent cancers like breast and lung cancer, the mutational signatures specific to exceedingly rare brain tumors still pose intriguing questions.
- Studying the mutational signatures in ultra-rare CNS tumors can point to potential clinical treatments to target the type of tumor.

Tumor Type	Location	Incidence Rate
Chordoma	Bones of spine and skull	0.18 and 0.84 per million individuals
Skull Base Chondrosarcoma	Affects cartilage cells of bone	0.2 cases per 100,000 individuals per year
Ganglioglioma	Brain tumor containing mixture of neuronal and glial cells	0.3 to 0.5 cases per 100,000 individuals per year
Metastatic HemangioPericytoma (to spine)	Tumor that arises from pericytes surrounding blood vessels	less than 0.060 per 100,000 individuals per year

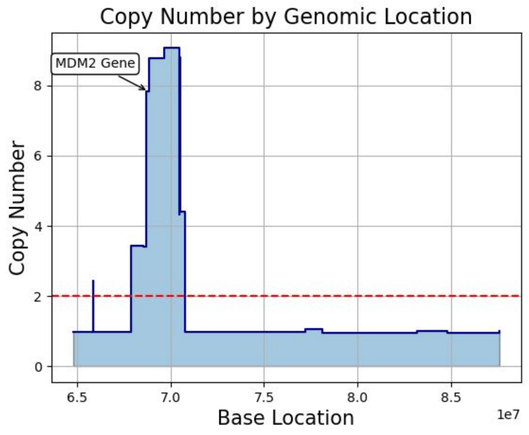
Methods

- Used Mutect2 to identify somatic mutations in each of the samples of chordoma, ganglioglioma, skull base chondrosarcoma, and metastatic hemangiopericytoma.[3]
- Used 2 mutation signature analysis software programs: SigProfilerAssignment[4] and Signal[5] to analyze genomic mutation data and identify any SBS mutational patterns.
- To analyze copy number mutational signatures, PURPLE[6] was used to get the copy number profile for each of the tumor samples and used as input for SigProfilerAssignment
- SigProfilerAssignment was used to analyze not only SBS mutational signatures, as well as copy number, DBS and ID mutational signatures.

Results

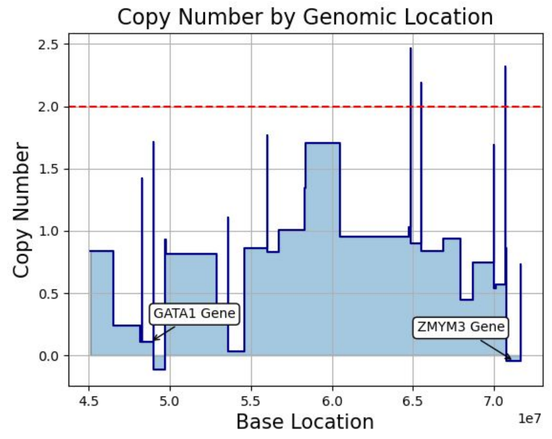
Chordoma

chromosome	gene	driver	category	biallelic
chr10	PTEN	MUTATION	TSG	TRUE
chr12	MDM2	AMP	ONCO	FALSE
chr22	EP300	MUTATION	TSG	FALSE



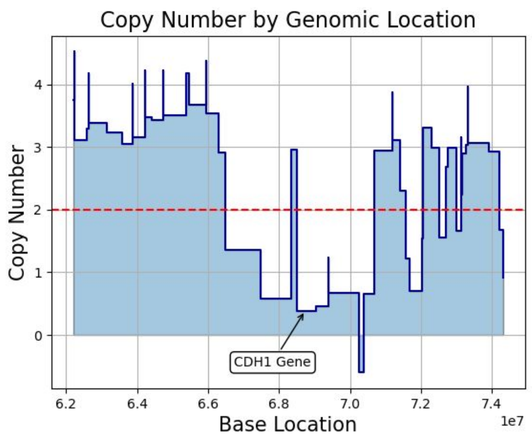
Metastatic HemangioPericytoma

chromosome	gene	driver	category	biallelic
chr5	TERT	MUTATION	ONCO	TRUE
chrX	ZMYM3	MUTATION	TSG	TRUE
chrX	GATA1	DEL	TSG	TRUE



Chondrosarcoma

chromosome	gene	driver	category	biallelic
chr22	EP300	MUTATION	TSG	TRUE
chr16	CDH1	DEL	TSG	TRUE
chr5	NSD1	MUTATION	TSG	TRUE



Ganglioglioma

chromosome	gene	driver	category	biallelic
chr16	CTCF	MUTATION	TSG	TRUE
chr3	BAP1	MUTATION	TSG	FALSE
chr4	PTPN13	MUTATION	TSG	FALSE

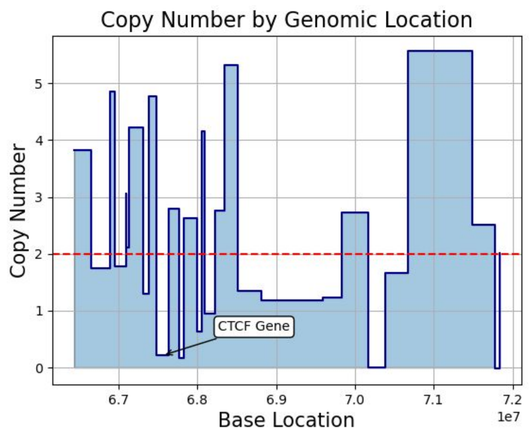


Fig. 1. Using the PURPLE copy number and gene driver files, we were able to analyze copy number alterations found in prominent gene drivers for each tumor type. Each gene driver listed above has a driver likelihood of above 0.99.

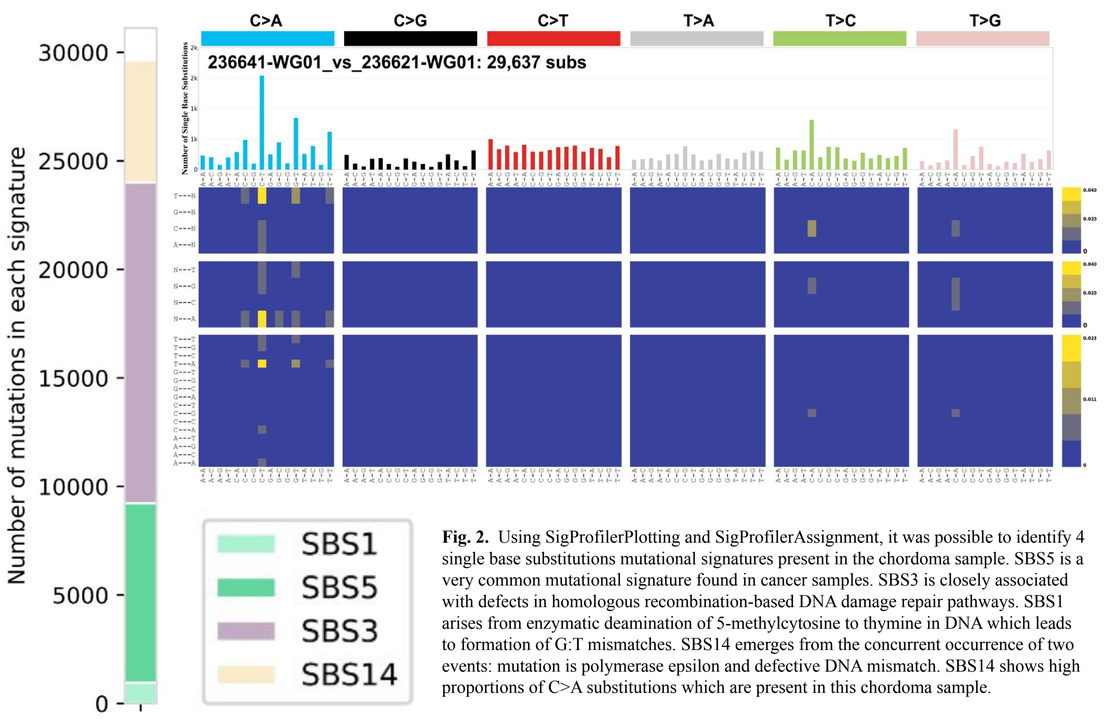


Fig. 2. Using SigProfilerPlotting and SigProfilerAssignment, it was possible to identify 4 single base substitutions mutational signatures present in the chordoma sample. SBS5 is a very common mutational signature found in cancer samples. SBS3 is closely associated with defects in homologous recombination-based DNA damage repair pathways. SBS1 arises from enzymatic deamination of 5-methylcytosine to thymine in DNA which leads to formation of G:T mismatches. SBS14 emerges from the concurrent occurrence of two events: mutation is polymerase epsilon and defective DNA mismatch. SBS14 shows high proportions of C>A substitutions which are present in this chordoma sample.

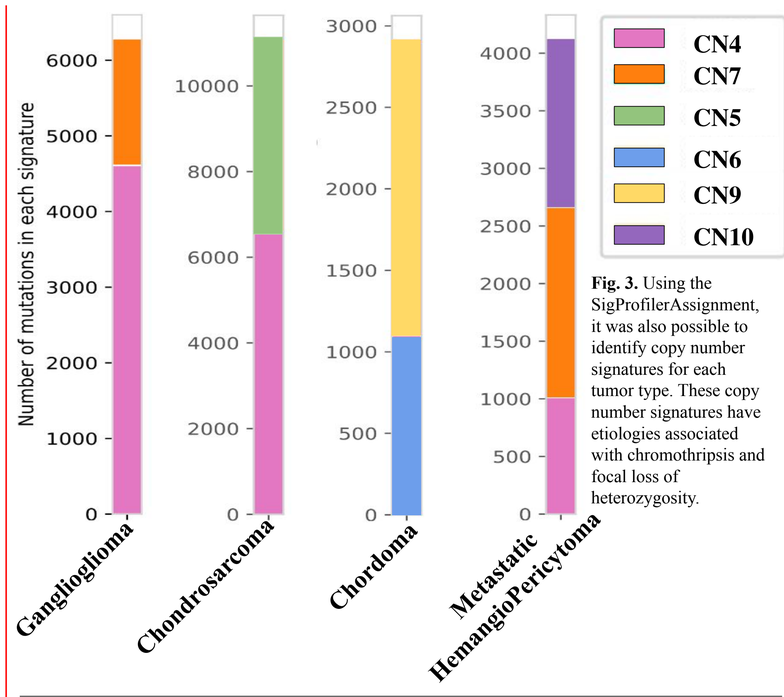


Fig. 3. Using the SigProfilerAssignment, it was also possible to identify copy number signatures for each tumor type. These copy number signatures have etiologies associated with chromothripsis and focal loss of heterozygosity.

Tumor Type	SigProfiler SBS Signatures	Signal SBS Signatures
Chordoma	SBS3 (49.8%) SBS5 (27.9%) SBS14 (19%) SBS1 (3.2%)	SBS8 (45%) SBS20 (28%) SBS3 (22%)
Metastatic HemangioPericytoma	SBS40 (58.6%) SBS5 (21.2%) SBS22 (9%) SBS44 (8%) SBS1 (3.3%)	SBS8 (42%) SBS3 (27%) SBS5 (22%) SBS120(9%)
Chondrosarcoma	SBS40 (59.4%) SBS5 (18%) SBS37 (8.4%) SBS22 (6.9%) SBS6 (5.6%) SBS1 (1.7%)	SBS8 (38%) SBS3 (27%) SBS5 (21%) SBS120(14%)
Ganglioglioma	SBS5 (53.1%) SBS3 (42.8%) SBS1 (4.1%)	SBS8 (32%) SBS3 (29%) SBS5 (21%) SBS120 (18%)

Conclusions

- Gene drivers in each cancer type show prominent copy number alterations and may play a crucial role in shaping the cancer phenotype
- Copy number signatures for these ultra-rare tumors indicate that copy number alterations emerge from chromothripsis and focal loss of heterozygosity
- Discrepancies were observed between SigProfiler and Signal SBS mutational signatures
  - Limited applicability of these algorithms for identifying mutational signatures in rare tumor cases
- Further investigations on multiple samples of the same tumor type would allow for a better understanding of the mutational signatures present in these rare tumors.

References

1) Koh et al. Nat Rev Cancer 2021;21
2) Steele et al. Nature 2022; 606
3) Bejamin et al. bioRxiv 2019; 861054
4) Díaz-Gay et al. bioRxiv 2023 and Tate et al. Nucleic Acids Research 2019
5) Degasperi et al. Nature cancer 2020; 1
6) Cameron et al. bioRxiv 2019; 781013