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.

Methods

- Used Mutect2 to identify somatic mutations in each of the samples of chordoma, ganglioglioma, skull base chordosarcoma, and metastatic hemangiopericytoma.³
- Used 2 mutation signature analysis software programs: SigProfilerAssignment⁴ and Signal⁵ to analyze genomic mutation data and identify any SBS mutational patterns.
- To analyze copy number mutational signatures, PURPLE⁶ 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

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

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) Diaz-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