CNS 2018 ANNUAL MEETING
HOUSTON, TEXAS
OCTOBER 6-10, 2018

# Meningioma with Multiple Drivers: Genomic Landscape and Clinical Correlations

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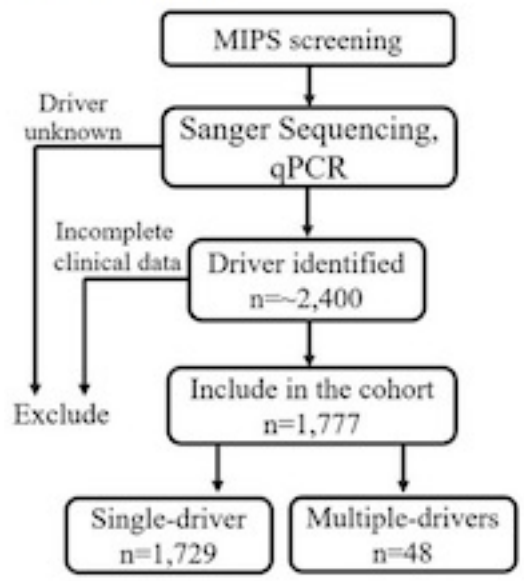
## Introduction

- Most meningiomas cluster into mutually exclusive groups with distinctive clinical correlations based on a mutation in one of the well-established drivers (NF2, TRAF7, KLF4 +/- TRAF7, PI3K +/-TRAF7, Sonic Hedgehog signaling pathway mutations SMO, SUFU, PRKAR1A, SMARCB1/SMARCE1, POLR2A) [1-5].
- However, some tumors concomitantly harbor two or more of these typically mutually exclusive driver mutations. The characteristics of meningiomas with multiple drivers have not been previously investigated.
- Our objective was to characterize the genomic landscape and clinical features of meningiomas with multiple drivers.

## Materials and Methods

- In our lab, we identified and characterized a cohort of meningioma with multiple drivers

**Figure 1. Meningiomas with multiple drivers cohort identification**




- For the analysis of clinical features, we utilized two-tailed Fisher's exact tests for nominal data and Kruskal-Wallis tests for ordinal data.

**Table 1. Clinical features of meningiomas with multiple drivers**

| N=48 | | |
|---|---|---|
| **Gender** | | |
| | Female | 33 (69%) |
| | Male | 9 (19%) |
| | Unknown | 6 (12%) |
| **Age at Surgery** | | |
| | Median | 61.5 |
| | Range | 29-84 |
| **Primary vs. Recurrent** | | |
| | Primary | 38 (80%) |
| | Recurrent | 5 (10%) |
| | Unknown | 5 (10%) |
| **Anatomic Location** | | |
| Intracranial | | 39 (81%) |
| | Skull base | 19 (54%) |
| | Non-skull base | 16 (46%) |
| Extracranial | | 2 (4%) |
| Unknown | | 7 (15%) |
| **Histology** | | |
| | Atypical | 10 (21%) |
| | Chordoid | 2 (4%) |
| | Meningothelial | 16 (34%) |
| | Microcystic | 1 (2%) |
| | Mixed | 1 (2%) |
| | Psammomatous | 4 (8%) |
| | Transitional | 3 (6%) |
| | Unknown | 11 (23%) |
| **WHO Grade** | | |
| | I | 32 (67%) |
| | II | 15 (31%) |
| | III | 0 |
| | Unknown | 1 (2%) |

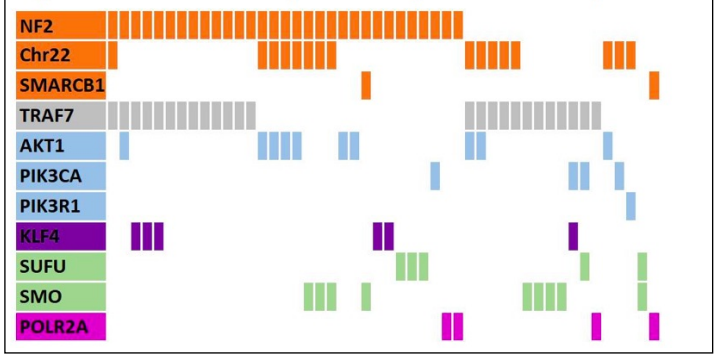
**Table 2. Clinical features of multiple vs. single driver meningioma groups, *significant findings only***

| | Multiple Driver | Single driver | P |
|---|---|---|---|
| N | 48 | 1,729 | |
| Recurrence | 5 (10.5%) | 41 (4.5%) | 0.047 |
| WHO Grade | | | 0.015 |
| I | 32 (68%) | 1403 (82%) | |
| II | 15 (32%) | 283 (17%) | |
| III | 0 | 18 (11%) | |
| Histology | | | 0.001 |

**Table 3. Clinical features of multiple driver meningiomas harboring NF2/Chr 22 loss vs. single driver meningiomas with NF2/Chr 22 loss , *significant findings only***

| | Multiple Driver NF2/Chr22 loss | SingleDriver NF2/Chr22 loss | P |
|---|---|---|---|
| N | 39 | 941 | |
| Histology | | | 0.002 |
| Fibrous | 0 | 119 (20%) | 0.03 |
| Location | | | |
| Skull base | 13 (46%) | 158 (23%) | 0.011 |

**Figure 2. Genomic landscape of meningiomas with multiple drivers**




## RESULTS

- A cohort of 48 meningiomas with multiple drivers was identified (~2% of all meningiomas)
- Compared with the single driver meningioma group, tumors with multiple drivers were significantly more recurrent, had higher grade, and demonstrated distinct histological distribution
- Meningioma with multiple drivers harbored significantly more NF2 mutation/Chr22 loss (81%) than single driver tumors (54%).
- Compared to single driver tumors with NF2 mutation/Chr22 loss, multiple driver meningiomas that harbored NF2 mutation/Chr22 loss demonstrated skull base predilection (in particular, tumors with additional KLF4 and PIK3 mutations) and relative absence of fibrous histological type.

## CONCLUSIONS

Meningioma with multiple drivers demonstrate distinct genomic and clinical features with potential prognostic and therapeutic significance. The mechanism of occurrence of multiple drivers in a tumor remains unknown and requires further investigation.

## REFERENCES

1. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic Analysis of Non-NF2 Meningiomas Reveals