# Novel Oncogene Discovery in Meningiomas

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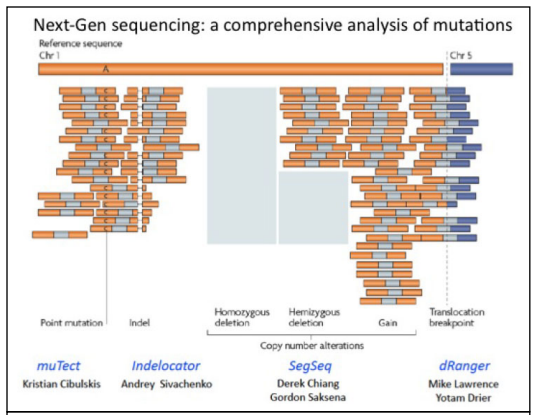
## Introduction

Meningiomas are the most common primary tumor of the central nervous system. Although most are cured by surgery, 20% recur and tend to be minimally responsive to systemic therapy. A major impediment to the treatment is that the somatic genetic events driving meningioma oncogenesis are poorly understood. Although recurrent losses of chromosomes 22q (containing *NF2*), 6q, and 14q have been detected, no genes other than *NF2* have been convincingly linked to meningioma oncogenesis.

## Methods

DNA from seventeen grade I meningiomas and paired blood normals was subjected to next-generation sequencing (11 by 60x whole genome and 6 by exome-capture sequencing). Sequences were analyzed by algorithms for detection of somatic mutations, indels, translocation/rearrangements, and copy number alterations. A mutational significance algorithm (MutSig) was then used to determine significant, recurrent events (**Fig 1, Table 1**).




| Cohort | Discovery (17) | Validation (33) | Extension (15) |
|---|---|---|---|
| Mean age | 50.2 +/- 13.8 | 59.1 +/- 13.5 | 58.7 +/- 14.0 |
| Sex | 16 F / 1 M | 26 F / 7M | 10 F / 5 M |
| Grade | I (17) | I (33) | II(12)/III(3) |
| MIB-1 index (Ki67) | 3.1% +/- 1.3% | 5.3% +/- 3.8% | 5% - 45% |
| Purity (histological) | >90% | >90% | >90% |
| Pathological subtype | | | |
| • Fibrous | 5 | • Radiation-induced: | 6 |
| • Transitional | 8 | | |
| • Meningothelial | 2 | • Recurrent, s/p radiation therapy: | 4 |
| • Meningothelial/ angiomatous | 2 | | |

## Results

### Meningioma genomes are simple compared to other sequenced tumors

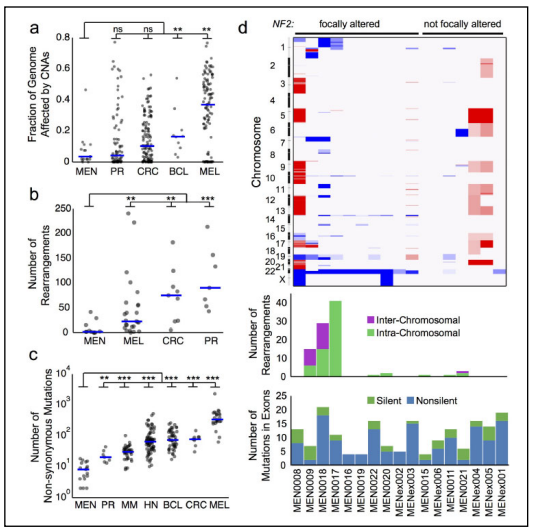



**Fig 2.** Meningiomas harbor fewer copy-number alterations (a), rearrangements (b), and non-synonymous mutations (c) than other published tumors (refs). (d) The landscape of somatic genetic alterations in the discovery set of meningiomas.

### *NF2* bi-allelic inactivation

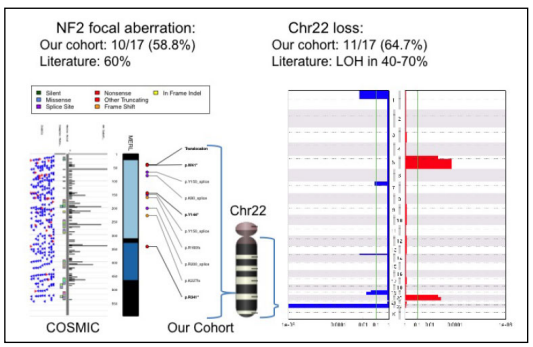
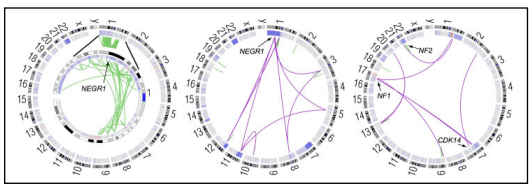



**Fig 3**. As expected, *NF2* was identified as the top hit, with over half of tumors harboring nonsense mutations, frame-shift indels, or splice site mutations leading to NF2 disruption. One sample had a translocation affecting the *NF2* gene and a nearby region of chr22. All samples with *NF2* mutations also showed copy number loss on chr22.

### Novel Rearrangements in Meningiomas

**Fig 3**. Copy number alterations and rearrangements of three meningiomas are depected, including chromothripsis on chr1 (*Left*), which disrupts the putative tumor suppressor *NEGR1*, also disrupted in a second sample (*Center*). Rearrangments in a third sample lead to disruption of multiple tumor suppressors: *NF2, NF1,* and *CDK14*.




### Mutations in oncogenes not previously described in meningiomagenesis

In addition, several known cancer driver mutations were seen co-occurring with *NF2* mutation. Interestingly, we identified a subset of meningiomas that do not harbor *NF2* loss. Some such tumors contain *SMO* and *AKT1* mutations, which may represent novel oncogenes and tumor suppressors driving meningioma tumorigenesis (**Fig 4**).

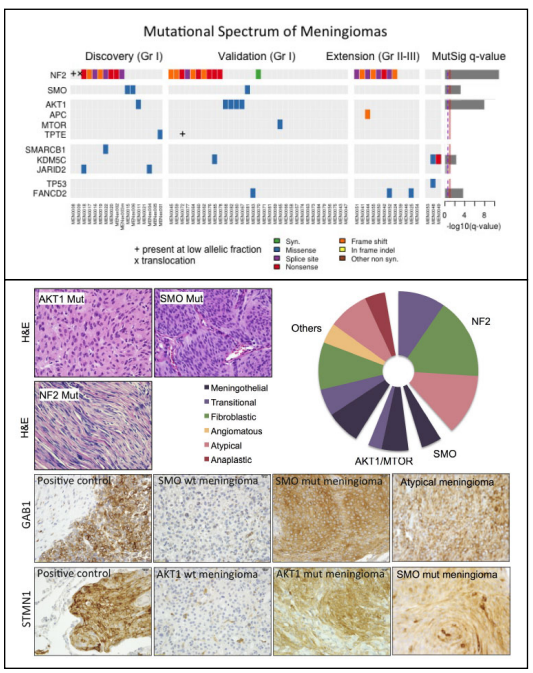
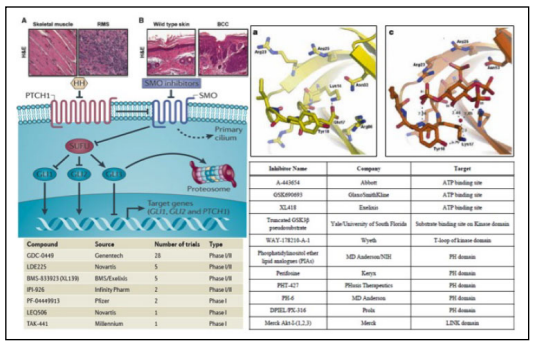



**Fig 5. Mutations in *SMO* and *AKT1*** are associated with particular histologic and immuno-histochemical phenotypes. *SMO* and *AKT1* drive cancer in other tissues and are already the targets of chemotherapy agents. One in six grade I meningiomas harbored a mutation in *SMO* or *AKT1* in our cohort, suggesting immediate potential therapeutic options for such patients.

**Fig 6.** Biology and inhibitors of *SMO* (left) and *AKT1* (right)




## Conclusions

While a majority of the grade I meningiomas we studied showed the classic "two-hit" pattern of somatic mutation and loss of heterozygosity in NF2, we identified a subset of tumors that are NF2-wild-type and discuss the genetic events in these samples that may be affecting novel oncogenes or tumor suppressors.

## References

Bass *Nature Gen* (2011); Berger *Nature* (2011); Berger *Nature* (2012); Beroukhim *Nature* (2010); Carpten *Nature* (2007); Chapman *Nature* (2011); Lohr *PNAS* (2012); Mao *Camcer Res* (2006); Meyerson *Nature Rev Genet* (2010); Ng *Nature Rev* (2011); Stransky *Science* (2011).

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