

Novel Oncogene Discovery in Meningiomas

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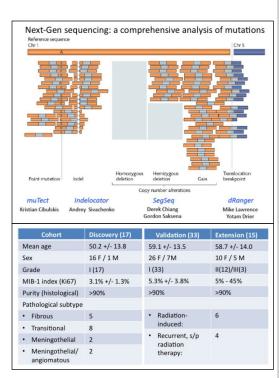
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Introduction

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 nextgeneration 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**).



Results

Meningioma genomes are simple compared to other sequenced tumors

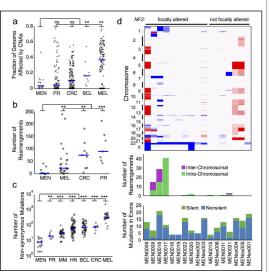


Fig 2. Meningiomas harbor fewer copy-number alterations (a), rearrangements (b), and non-synonymous mutations (c) than other published tumors (refs). (d) The landscape of somatic genetic alterations in the discovery set of meningiomas.

NF2 bi-allelic inactivation

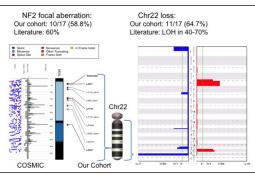
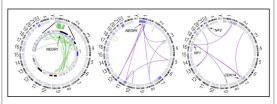


Fig 3. As expected, *NF2* was identified as the top hit, with over half of tumors harboring nonsense mutations, frame-shift indels, or splice site mutations leading to NF2 disruption. One sample had a translocation affecting the *NF2* gene and a nearby region of chr22. All samples with *NF2* mutations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

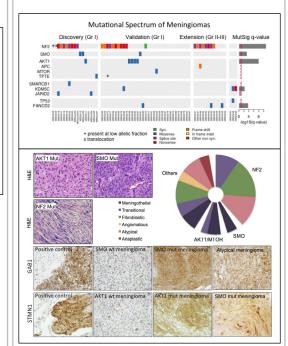


Fig 5. Mutations in SMO and AKT1 are

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)

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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

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