Retrospective evaluation of 404 glioma tumor specimens tested by fusion analysis

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In Bender et al. 2016, “Recurrent MET fusion genes represent a drug target in pediatric glioblastoma

HNSCC Alvarez (33 of 300) 40.0%

Therapies in oligodendrogliomas previously described in gliomas (e.g., EGFR, FGFR3, BRAF and PDGFRA including novel fusions that haven’t been

Conclusions:

- 2 of 3 grade III ependymomas but not in the 2 grade II ependymomas.

- 11 fusions involving targetable fusions.

- Other metastatic astrocytoma (PA) harbored targetable fusions.

- MET kinase domain preserved in predicted fusion breakpoints indicates that the fusion is not in

- Frame fusions were analyzed

- In-frame fusions were analyzed

Methods

- Retrospective evaluation of 404 glioma tumor specimens tested by fusion analysis at a CLIA certified lab (Caris Life Sciences, Phoenix, AZ)

- RNA-sequencing by Archer Fusion assay based on anchored multiple PCR

- Fusion assay based on anchored multiplex PCR

- Potentially Therapeutic: NTRK1

- Potential Therapeutic: Entrectinib, Lorlatinib.

Results

- Table 1: Patient characteristics

- GBM, low grade astrocytoma (PA) harbored targetable fusions.

- Among 404 gliomas N=4, GBM), 5/42 BRAP (GBM). 11 fusions were profiled using the S

- Table 2: Landscape of targetable fusions found. Green squares indicate that the gene sequence at the breakpoint was investigated and the preservation of the kinase domain was confirmed and the fusion event was confirmed to be in-frame. Gray: ZSCAN23: BRAF

- Results, continued

- 2A: MET fusions found

- 2B: NTRK fusions found

- 2C: FGFR fusions found

- 2D: Additional fusions found

Conclusions

- 1. Targetable fusions are frequent events in various glioma subtypes

- 11 of astrocytic tumors harbor targetable fusions identified by RNA sequencing

- Functional studies are needed to fully characterize the novel fusions found

- Identification of kinase-associated transcripts may allow us to exploit therapeutic opportunities with targeted therapies in gliomas.

References

1. Shen D et al. 2019. Recurrent FGFR2/3 fusions replicate a subpopulation targeted by a precision glioblastoma “Precision Medicine, 2019-12-03-10-00”

2. Marini-Raimondi M et al. 2017. “Stable and epigenetic inactivation following targeting of FGFR2 fusions in glioblastoma and gliosarcoma” PNAS (2017-07-16-17-00)

3. Shen D et al. 2019. “Phenotype and Molecular Analysis of GBM Derived from Brain Glioblastoma Precision Medicine, 2019-12-03-10-00”


Abstract

Background: Fusions involving oncogenes have been reported in gliomas and may serve as novel therapeutic targets. We aim to use RNA sequencing to interrogate a large cohort of gliomas for targetable genetic fusions.

Methods: Gliomas were profiled using the ArcherDX FusionAssay assay at a CLIA certified lab. 42 gliomas were analyzed. Fusions with preserved kinase domains were investigated.

Results: Among 404 glioma specimens tested, 24/226 (11%) of glioblastomas (GBM), 5/42 (12%) of anaplastic astrocytoma (AA), 2/25 (8%) of grade II astrocytoma and 3 of 7 (43%) of pilocytic astrocytoma (PA) harbored targetable fusions. In GBMs, 1 of 15 (6.7%) IDH-mutated tumors had a fusion with 22 of 175 (12.6%) IDH wild type tumors had fusions. 46 oligodendrogliomas were profiled and no fusions were identified, which was lower than frequency of fusions in astrocytic tumors (34/300, p = 0.0236). The most frequent fusions seen involved FGFR3 (N = 12), including 3 FGFR3-TACC3 (1A, 6 GBM and 3 gliomas), 1 FGFR3-NR1I3 (AA) and 3 FGFR3-ABAP (GBM). 11 fusions involving MET were seen, 10 in GBM and 1 in AA. The most common MET fusion was PTPRZ1-MET (1 in AA and 4 in GBM), followed by S7-MET (N = 3, GBM), CAP2A-Met (N = 2, GBM) and TPR-MET (N = 1, GBM). 8 NTRK fusions were seen; 1 involving NTRK1 (BCAN-NTRK1, PA), 6 NTRK2 (3 NOS1AP-NTRK2 in AA, GKP1-NTRK2, KCTD8-NTRK2, TRC5222- NTRK2 and SST17-NTRK2, 1 each in GBM and 1 VCAN-NTRK2 in astrocytosis (astrocytosis and glioblastoma); 1 and 1 NTRK3 (EM4A-NTRK3 in GBM, EGFR fusions (2 EGFR-SEPT14 and 3 EGFR-WC2) were seen in 3 GBMs, BRAF in 2 [1 LOC100093631-BRAF in PA and 1 ZSCAN3-BRAF in glioma NOS) and PDGFRB (RAB3IP-PDGFRB, in GBM) in 1. C11orf95-RFA fusions were seen in 2 of 3 grade III ependymomas but not in the 2 grade II ependymomas.

Conclusions: We report targetable fusion genes involving NTRK, MET, EGFR, FGFR3, BRAF and PDGFRB including novel fusions that haven’t been previously described in gliomas (e.g., EGFR-WC2, FGFR3-NR1I3). Fusions were seen in over 10% of astrocytic tumors, while none were oligodendroglialomas. Identification of such kinase associated fusion transcripts may allow us to exploit therapeutic opportunities with targeted therapies in gliomas.