Abstract# 2056: Capicua (*CIC*) mutations in gliomas in association with MAPK activation for exposing a potential therapeutic target

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Background:

- *CIC* is a tumor suppressor gene, transcriptional repressor, and a member of the high mobility (HMG)-box protein family
- *CIC* is a negative regulator of MAPK and RTK pathways
- *CIC* Mutations have been reported in 40% of oligodendrogliomas
- The purpose of this study was to explore the key signaling pathways associated with *CIC*

Methods:

- Consecutive glioma tumors were analyzed using Nex-Gen sequencing of the DNA (NextSeq, 592 genes or NovaSeq, whole-exome) and RNA (NovaSeq, whole transcriptome sequencing) and IHC (Caris Life Sciences, Phoenix, AZ).
- Immune cell fraction was calculated by QuantiSeq; MAPK activation score (MPAS) was evaluated using RNAseq data (Wagle 2018).
- Comparative analysis was done using Chi-square or Fisher's-exact test when appropriate. With p values adjusted for multiple corrections (q) by Benjamini-Hochberg.

Selected References:

Wang B, et al. Cell Rep. 2017; 18(6):1534-1557
Lam YC, et al. Cell. 2006; 127(7): 1335-47
Okimoto RA, et al. Nat Genet. 2017; 49(1): 87-96
Lee Y, et al. Dev Cell. 2011; 21(4): 746
Wagle MC, et al. NPJ Precision Oncology. 2018; 2:7

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Results:

- A total of 5266 gliomas were analyzed
- *CIC* mutations occurred in 3.7% of tumors, most frequently in oligodendrogliomas (50%) (Table)
- *CIC* mutations were associated with a higher prevalence of *IDH1/2* mutations
- There exists an overall mutual exclusivity for *CIC* with other MAPK genomic drivers (*NF1, BRAF, KRAS, EGFRamp, EGFRvar)*- Fig 1
- *CIC* mutations were associated with increased MPAS score in oligodendrogliomas (p=0.01), particularly when compared to tumors lacking additional MAPK drivers (p=0.001)- Fig 2

Table- Prevalence of CIC mutations in glioma tumors

Cancer Types	MT	WT	Total	%
Glioblastoma	**24**	**3729**	**3753**	**0.6%**
Astrocytoma	**16**	**813**	**829**	**1.9%**
Astrocytoma-Anaplastic/Grade 3/High Grade	12	498	510	2.4%
Astrocytoma-Diffuse/Grade 2/Low Grade	4	257	261	1.5%
Astrocytoma-Pilocytic/Grade 1	0	58	58	0.0%
Ependymoma	**0**	**13**	**13**	**0.0%**
Ganglioglioma	**0**	**24**	**24**	**0.0%**
Glioneuronal	**0**	**27**	**27**	**0.0%**
Gliosarcoma	**1**	**127**	**128**	**0.8%**
Mixed/unclear	**12**	**173**	**185**	**6.5%**
Oligodendroglioma	**143**	**142**	**285**	**50.2%**
Oligodendroglioma-Anaplastic/Grade 3/High Grade	73	69	142	51.4%
Oligodendroglioma-Diffuse/Grade 2/Low Grade	70	73	143	49.0%
Pleomorphic xanthoastrocytoma	**0**	**22**	**22**	**0.0%**
Total	**196**	**5070**	**5266**	**3.7%**

Figure 1- Molecular comparison of *CIC*-mutant vs. wild type tumors. a. comparison in all tumors. b. canonical MAPK drivers in astrocytoma and glioblastoma. C. canonical MAPK drivers in oligodendrogliomas

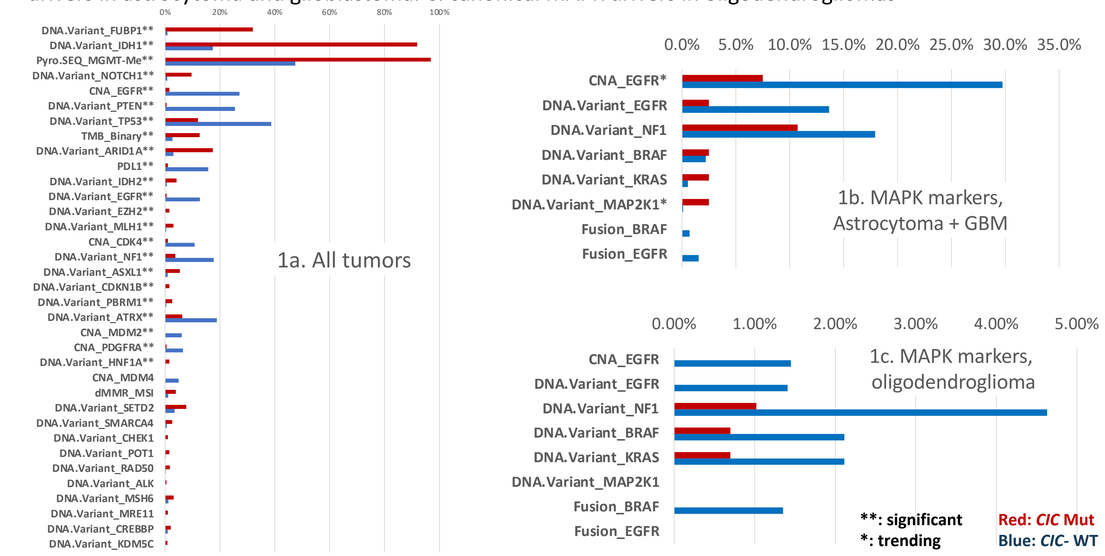
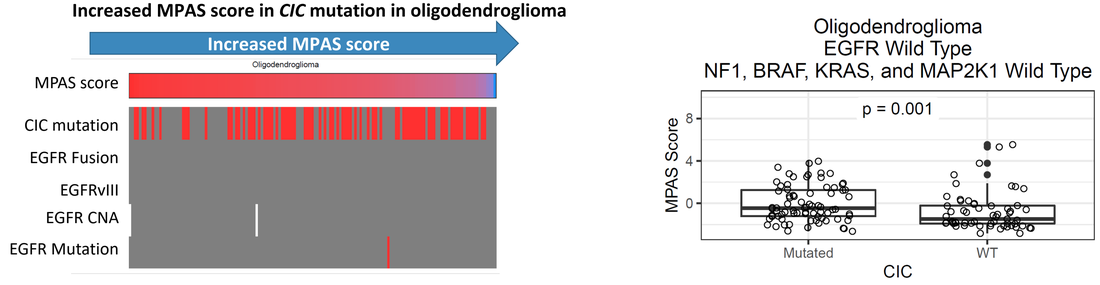


Figure 2- MPAS score in oligodendroglioma tumors and association with canonical MAPK drivers.

CIC mt were associated with increased MPAS score in oligodendrogliomas (p=0.01) and the effect was more obvious when *CIC* mt were compared to tumors lacking additional MAPK drivers (p=0.001).

The effect is not seen in astrocytic tumors, although *EGFR* alterations including CNA, *EGFRvIII, EGFR* fusion, and mt were independently associated with increased MPAS scores (p<0.001).

Increased MPAS score in *CIC* mutation in oligodendroglioma



Conclusions:

CIC mutations are detected frequently in oligodendrogliomas and are associated with a more favorable prognostic markers. Targeted inhibition of MAPK pathway could be explored.