Integrative Genomic Characterization of Lower Grade Gliomas

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On behalf of the TCGA Lower Grade Gliomas Analysis Working Group
Diffuse Gliomas: 2007 WHO Classification

**Astrocytomas**
- Infiltrating Astrocytoma (WHO grade II)
- Anaplastic Astrocytoma (WHO grade III)
- Glioblastoma (WHO grade IV)

**Oligodendrogliomas**
- Oligodendroglioma (WHO grade II)
- Anaplastic Oligodendroglioma (WHO grade III)

**Mixed Oligoastrocytomas**
- Oligoastrocytoma (WHO grade II)
- Anaplastic Oligoastrocytoma (WHO grade III)
Astrocytoma (WHO grade II and III)

IDH, TP53, ATRX mutations

Median Survival:
Grade II: 60 mo
Grade III: 36 mo

Progress to GBM (Secondary GBM)
Oligodendroglioma (WHO grade II and III)

1p/19q co-deletion
IDH, CIC, FUBP1, TERT promoter

Median Survival:
Grade II: 120 mo
Grade III: 60 mo

Chemosensitive
Oligoastrocytoma (WHO grade II and III)

Ambiguous Morphology
Brain Tumor Histogenesis

Harvey Cushing
Percival Bailey
1926
Distinguishing Among the Gliomas

“There are also many cells which appear to be transitions between gigantic oligodendroglia and astrocytes. It is impossible to classify them as belonging in either group”


60-70% concordance among neuropathologists in the diagnosis of diffuse gliomas

Coons SW et al. *Cancer*. 1997;79:1381
Interobserver variation of the histopathological diagnosis in clinical trials on glioma: a clinician’s perspective

Martin J. van den Bent


<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Standard of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma multiforme</td>
<td>Combined chemo-irradiation (60 Gy) with temozolomide</td>
</tr>
<tr>
<td>Grade III tumors</td>
<td>Radiotherapy 60 Gy, value of adjuvant chemotherapy and of combined chemo-irradiation unproven</td>
</tr>
<tr>
<td>Low grade glioma</td>
<td>Radiotherapy 45–55 Gy, higher dosages of RT correlated with more toxicity, unproven role for upfront chemotherapy alone</td>
</tr>
<tr>
<td>Oligodendroglial tumors</td>
<td>Initial management with upfront chemotherapy widely accepted, regardless of tumor grade</td>
</tr>
</tbody>
</table>

Table 1  Standard of care in gliomas
## Comprehensive Analysis of 500 Lower Grade Gliomas

<table>
<thead>
<tr>
<th>Data type</th>
<th>Platform</th>
<th>Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic mutations</td>
<td>Whole exome</td>
<td>Broad Institute</td>
</tr>
<tr>
<td></td>
<td>Whole genome</td>
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</tr>
<tr>
<td>DNA copy-number</td>
<td>Affymetrix SNP6</td>
<td>Broad Institute</td>
</tr>
<tr>
<td>mRNA expression (incl. fusions)</td>
<td>RNA-Seq (Illumina HiSeq)</td>
<td>UNC</td>
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<tr>
<td>DNA methylation</td>
<td>Infinium 450</td>
<td>USC</td>
</tr>
<tr>
<td>microRNA expression</td>
<td>miRNA-Seq</td>
<td>BCGCS</td>
</tr>
<tr>
<td>Protein levels &amp; phosphorylation</td>
<td>RPPA</td>
<td>MD Anderson</td>
</tr>
<tr>
<td>DNA copy-number / rearrangements</td>
<td>Low-pass whole genome sequencing</td>
<td>Harvard</td>
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</table>
TCGA Lower Grade Gliomas: Data Freeze for Biomarker Manuscript

<table>
<thead>
<tr>
<th>Data type</th>
<th>Platform</th>
<th># samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exome sequencing</td>
<td>Illumina</td>
<td>290</td>
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<tr>
<td>Whole genome sequencing</td>
<td>Illumina</td>
<td>23</td>
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<tr>
<td>DNA copy number</td>
<td>Affymetrix SNP6</td>
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<tr>
<td>DNA copy number</td>
<td>Low pass whole genome</td>
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<tr>
<td>mRNA</td>
<td>RNA-Seq</td>
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<tr>
<td>DNA methylation</td>
<td>Infinium 450</td>
<td>268</td>
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<tr>
<td>microRNA expression</td>
<td>miRNA-Seq</td>
<td>295</td>
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<tr>
<td>Protein levels</td>
<td>RPPA</td>
<td>241</td>
</tr>
</tbody>
</table>

293 cases, with overlapping data on 254 for major platforms
MutSigCV Identifies Significantly Mutated Genes and Reveals Mutation Classes

IDH mutations occur in ~80% of LGGs
1) CIC, FUBP1, Notch1, PIK3CA mutations (mostly oligo)
2) TP53 and ATRX mutations (mostly astro and oligoastro)

IDH wt LGG have mutations similar to GBM
LGG: Copy Number Alterations

By Histology

NMF Clustering

Hailei Zhang
Andrew Cherniack
OncoSign
(Oncogenic Signatures)

Giovanni Ciriello et al., Nat Gen, 2013
OncoSign Identifies 3 Molecular Classes Largely Based on IDH and 1p/19q status

Giovanni Ciriello
Jason Huse
DNA Methylation Status

Houtan Noushmehr
Peter Laird
mRNA Expression Clustering

1500 most variable genes selected by MAD.

Consensus Hierarchical Clustering (Pearson).

At k=6, 4 large clusters.

Mark Vitucci
Ryan Miller
Clustering of molecular data (Copy Number, mRNA, miRNA, methylation) identifies 3-5 subtypes

Mark Vitucci
Houtan Noushmehr
Andy Cherniak
Gordon Robertson
Mark Vitucci
Clustering of Clusters identifies 3 molecular classes largely based on IDH and 1p/19q status.
# Three Robust, Non-overlapping LGG Classes

<table>
<thead>
<tr>
<th>IDHmut-code1</th>
<th>IDHmut-non-code1</th>
<th>IDHwt</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH mutant</td>
<td>IDH mutant</td>
<td>IDH wt</td>
</tr>
<tr>
<td>1p/19q del</td>
<td>1p/19q intact</td>
<td>+7, -10</td>
</tr>
<tr>
<td>CIC mut</td>
<td>TP53 mut</td>
<td>EGFR amp</td>
</tr>
<tr>
<td>FUBP1 mut</td>
<td>ATRX mut</td>
<td>PTEN mut</td>
</tr>
<tr>
<td>TERT mut</td>
<td>8q24 amp</td>
<td>NF1 mut</td>
</tr>
<tr>
<td>Notch1 mut</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Outcomes

Event Free Survival

Overall Survival

Laila Poisson
IDHwt LGGs have Mutation Frequencies Similar to Glioblastoma

Fraction of samples with specific alteration in gene

- TP53
- RB1
- PTEN
- PIK3R
- PIK3C
- PIK3C2
- PDGFRA
- NF1
- MET
- MDM4
- MDM2
- MDM1
- IDH1
- FGFR3
- FGFR2
- FGFR1
- EGFR
- CDKN2C
- CDKN2A
- CDK6
- CDK4
- BRAF
- ATRX

Mia Gifford
Olena Morozova
Sofie Salama
IDHwt LGGs have Oncogenic Gene Fusions Similar to Glioblastoma

Olena Morozova
Sofie Salama
Roel Verhaak
IDHwt LGGs have Clinical Outcomes Similar to Glioblastoma

Laila Poisson
RPPA: Supervised clustering
189 Antibodies

Rehan Akbani and Gordon B. Mills
RPPA: Supervised clustering
14 Tyrosine Kinase Antibodies
Summary

6 histopathologic diagnoses can be distilled into 3 robust, clinically relevant molecular classes

IDH mutant, 1p/19q co-deleted gliomas: CIC, FUBP1, TERT promoter, Notch1 and PIK3CA mutations

IDH mutant, non-codel gliomas: TP53, ATRX, 8q24

IDH wild type LGG have molecular alterations and clinical behavior similar to GBM
Thank You!

TCGA LGG
Analysis Working Group

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Manuscript Coordinator: Ken Aldape
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