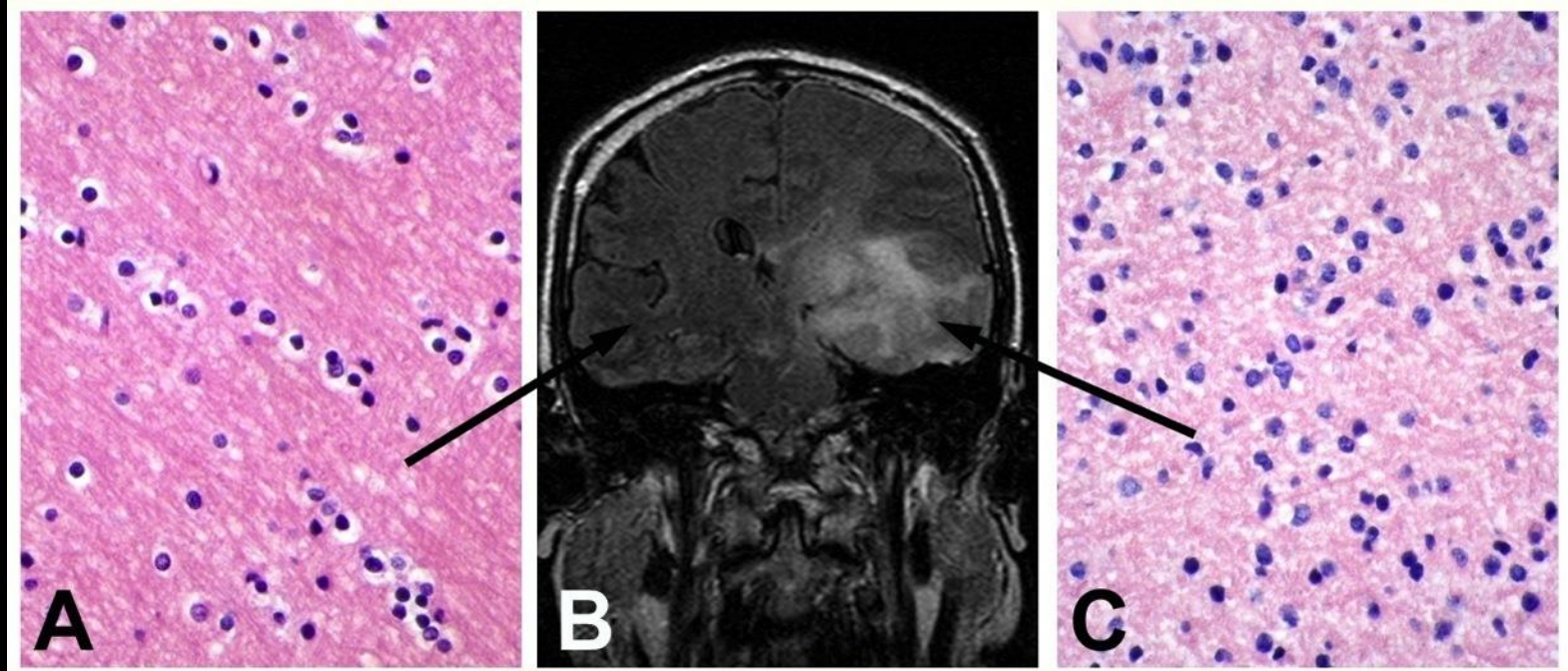


Integrative Genomic Characterization of Lower Grade Gliomas

Daniel J. Brat MD, PhD
Emory University School of Medicine

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)

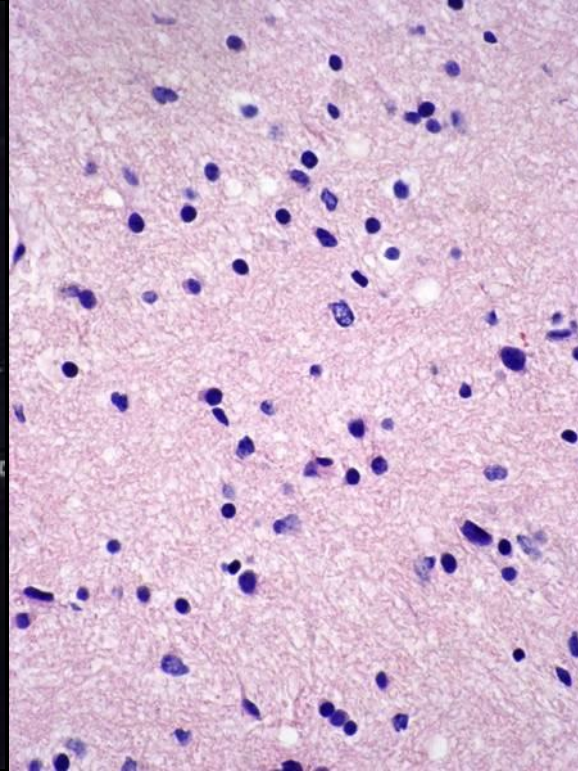
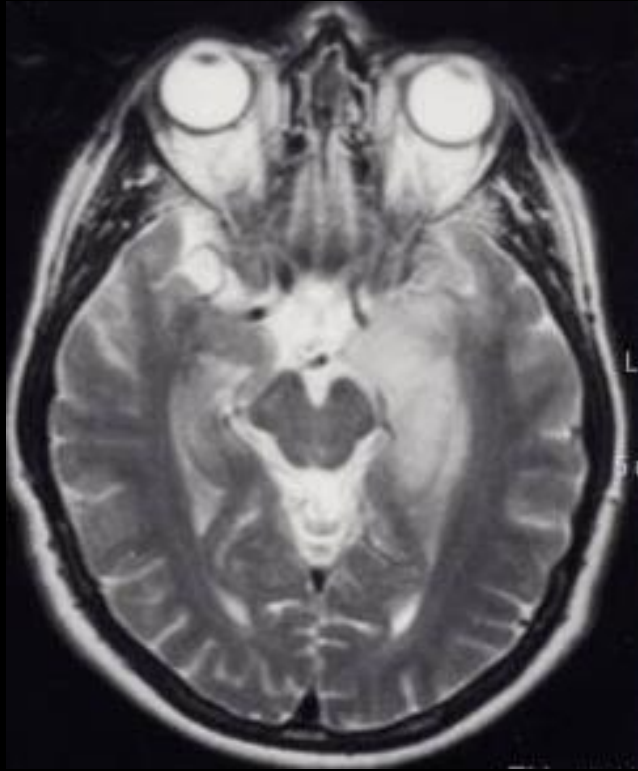
Anaplastic Oligodendroglioma (WHO grade III)

Mixed Oligoastrocytomas

Oligoastrocytoma (WHO grade II)

Anaplastic Oligoastrocytoma (WHO grade III)

Astrocytoma (WHO grade II and III)

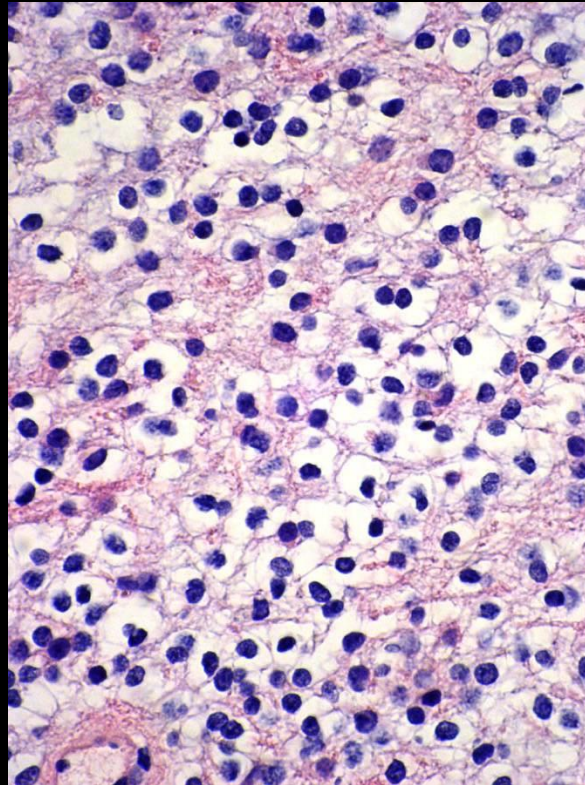
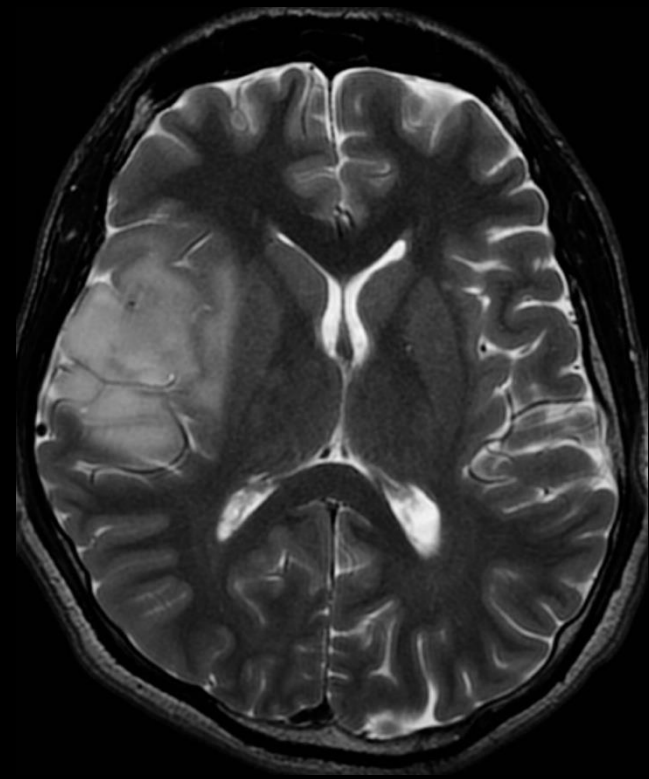


IDH, TP53, ATRX
mutations

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

Progress to GBM
(Secondary GBM)

Oligodendroglioma (WHO grade II and III)

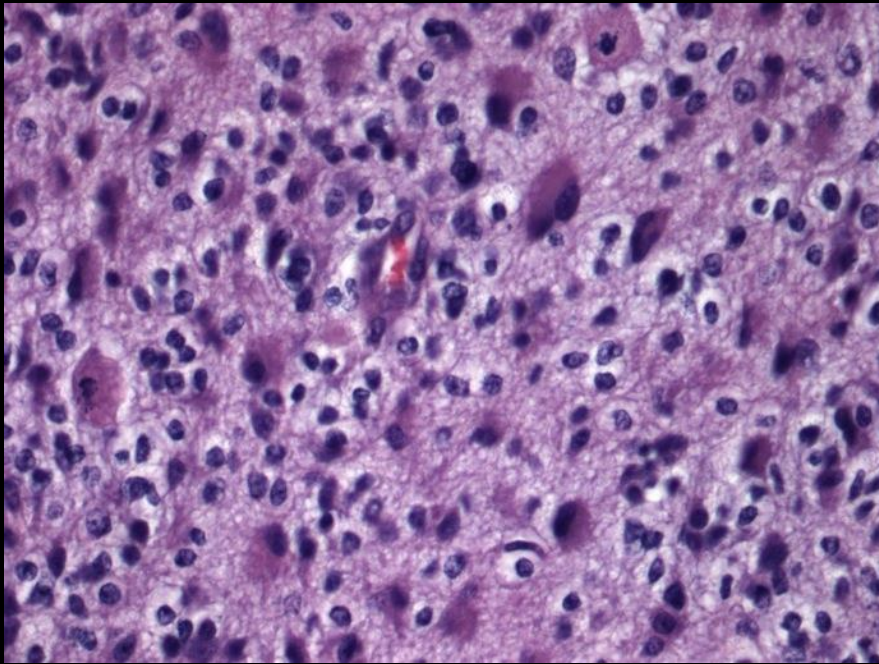


1p/19q co-deletion
IDH, *CIC*, *FUBP1*,
TERT promoter

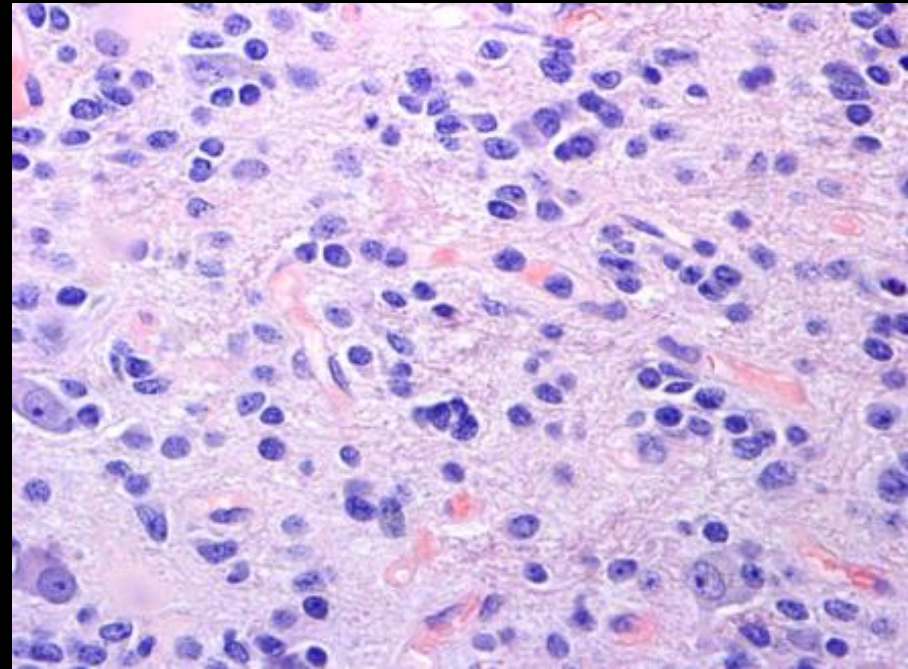
Median Survival:
Grade II: 120 mo
Grade III: 60 mo

Chemosensitive

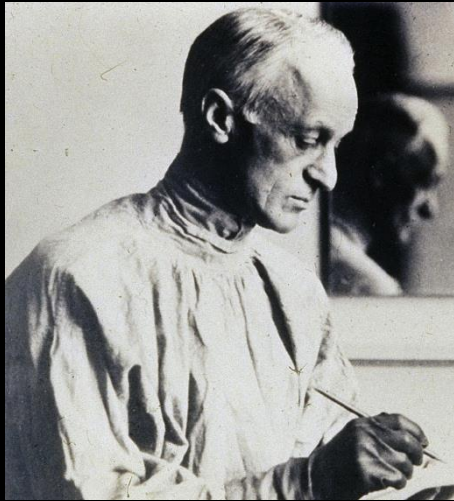
Oligoastrocytoma (WHO grade II and III)



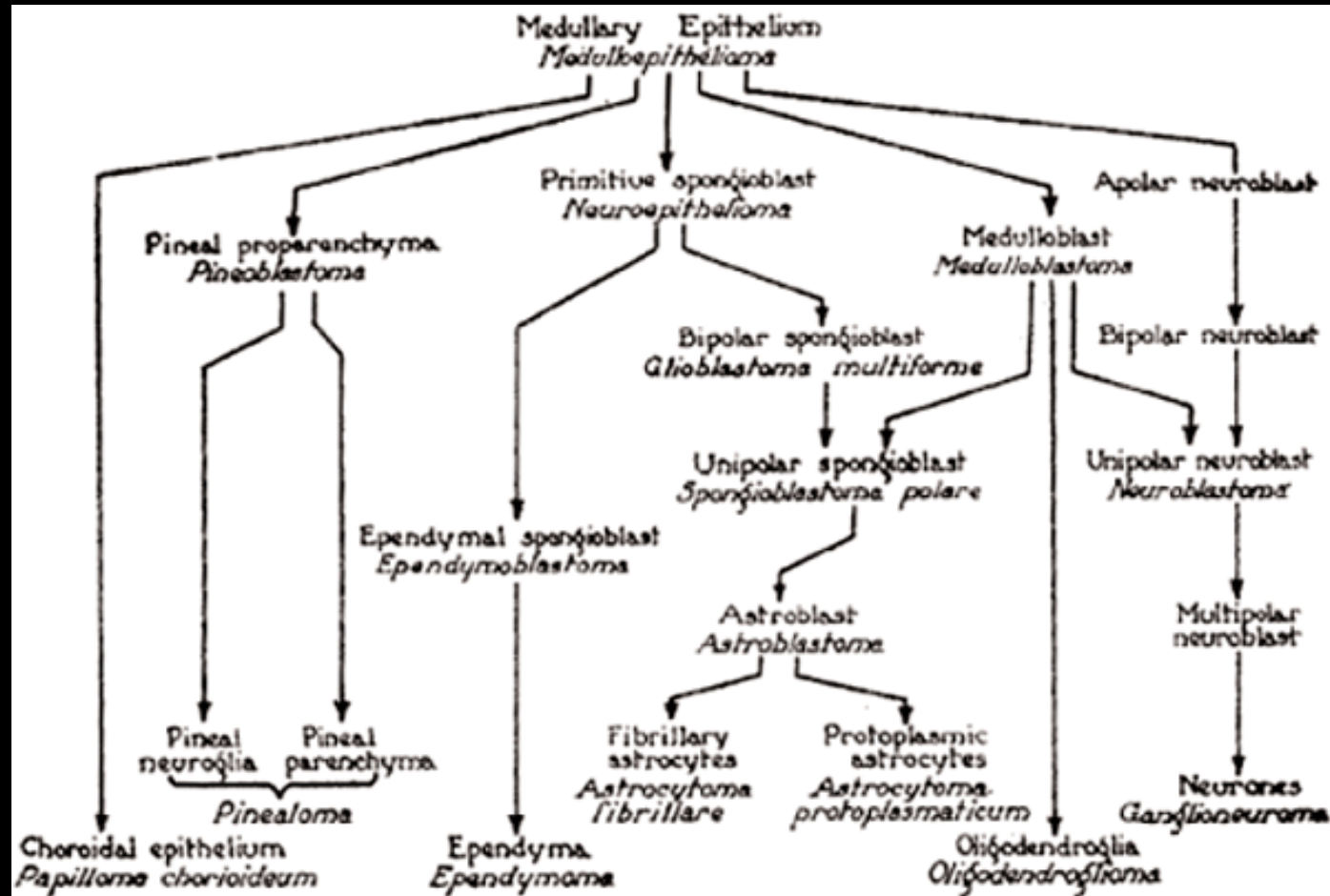
Ambiguous Morphology



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”

Bailey P, Bucy PC. *Oligodendrogliomas of the brain.*
J Pathol Bacteriol 1929: 32:735

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

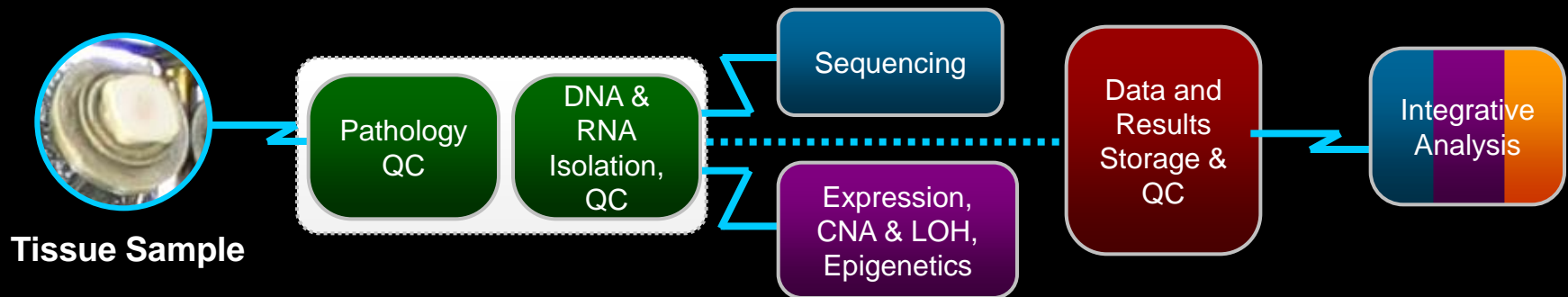
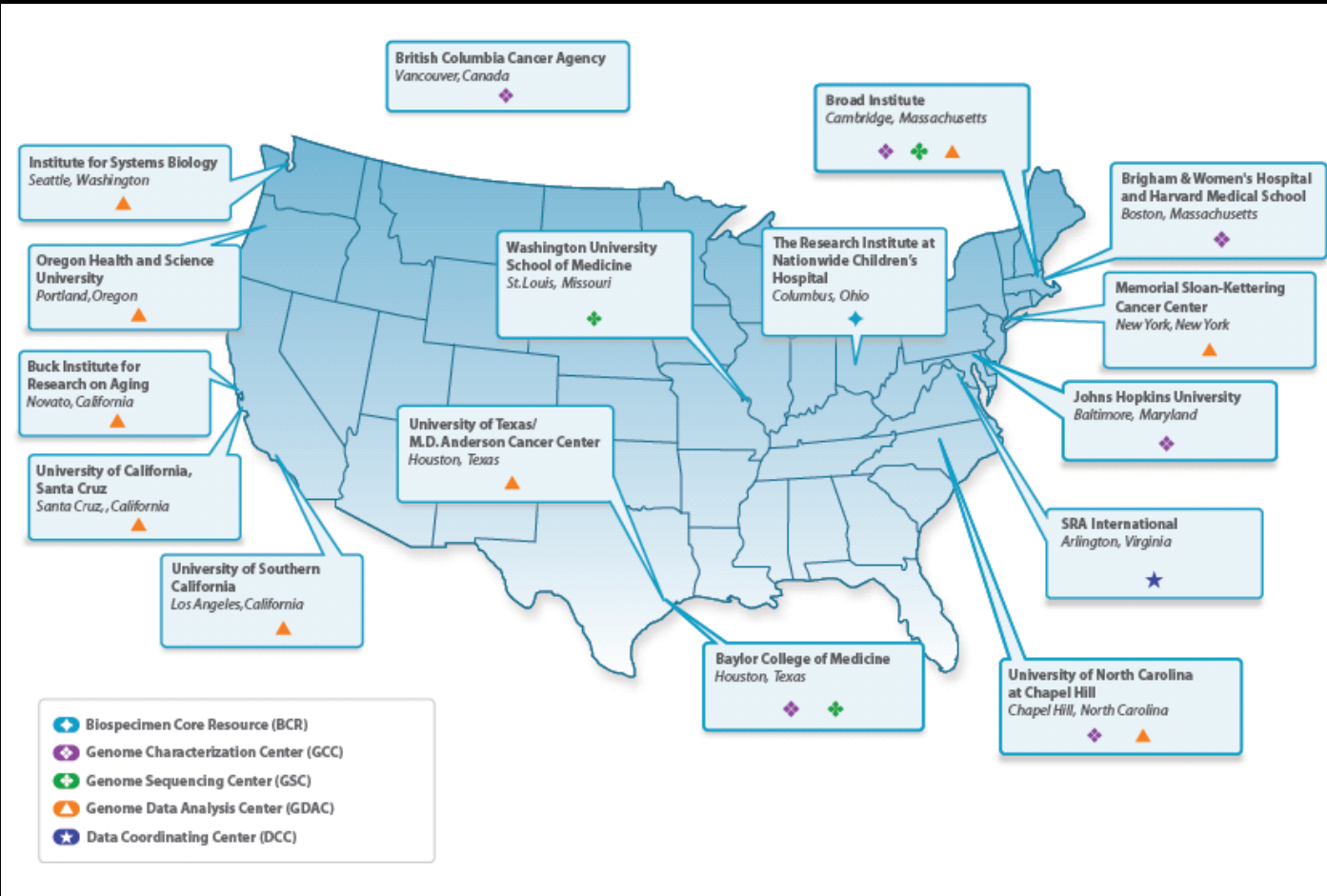
Martin J. van den Bent

Acta Neuropathol (2010) 120:297–304

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

Table 1 Standard of care in gliomas

TCGA Research Network



Comprehensive Analysis of 500 Lower Grade Gliomas

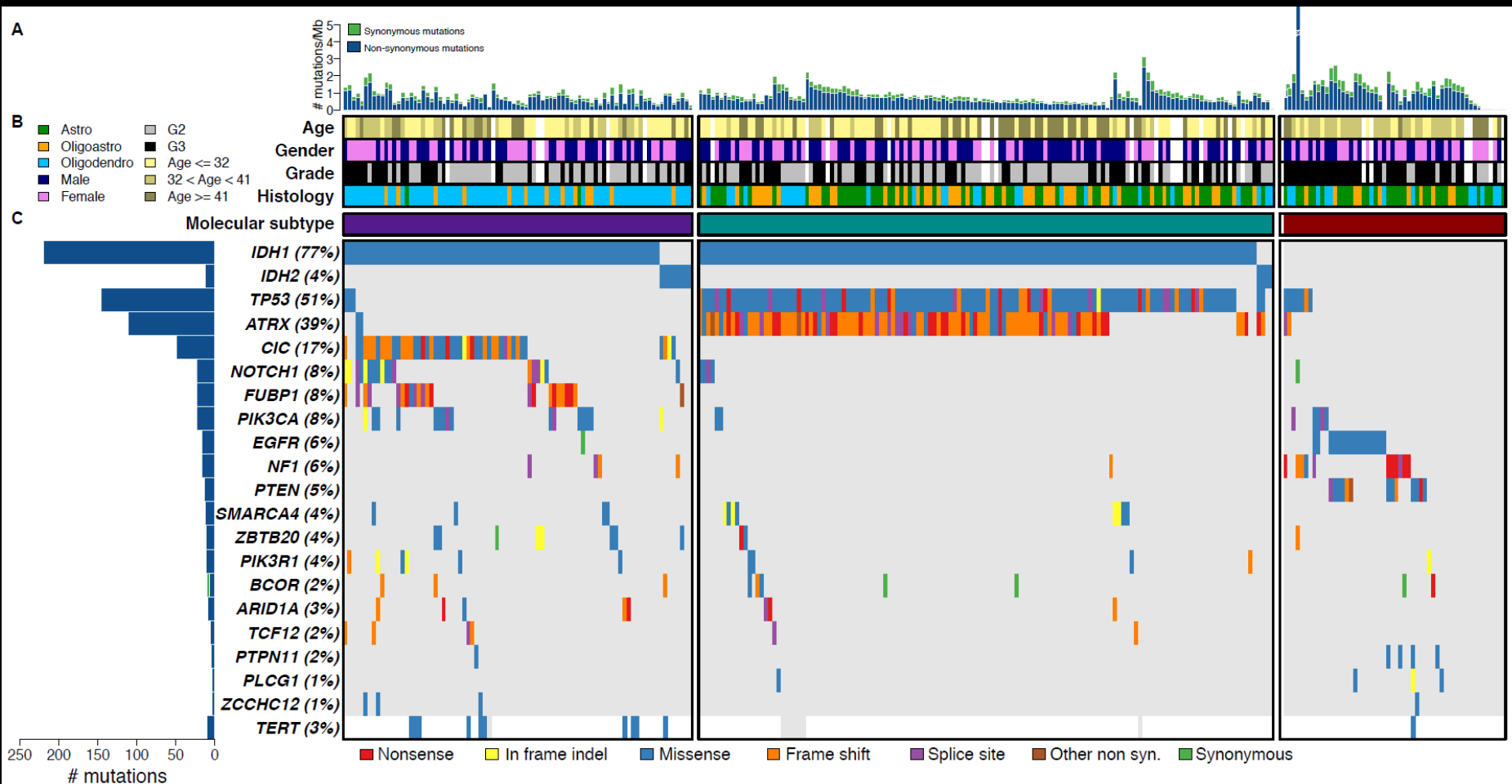
Data type	Platform	Center
Somatic mutations	Whole exome Whole genome	Broad Institute
DNA copy-number	Affymetrix SNP6	Broad Institute
mRNA expression (incl. fusions)	RNA-Seq (Illumina HiSeq)	UNC
DNA methylation	Infinium 450	USC
microRNA expression	miRNA-Seq	BCGCS
Protein levels & phosphorylation	RPPA	MD Anderson
DNA copy-number / rearrangements	Low-pass whole genome sequencing	Harvard

TCGA Lower Grade Gliomas: Data Freeze for Biomarker Manuscript

Data type	Platform	# samples
Exome sequencing	Illumina	290
Whole genome sequencing	Illumina	23
DNA copy number	Affymetrix SNP6	271
DNA copy number	Low pass whole genome	43
mRNA	RNA-Seq	269
DNA methylation	Infinium 450	268
microRNA expression	miRNA-Seq	295
Protein levels	RPPA	241

293 cases, including 100 astrocytomas, 76 oligoastrocytomas and 117 oligodendrogliomas, with overlapping data on 254 for major platforms

MutSigCV Identifies Significantly Mutated Genes and Reveals Mutation Classes



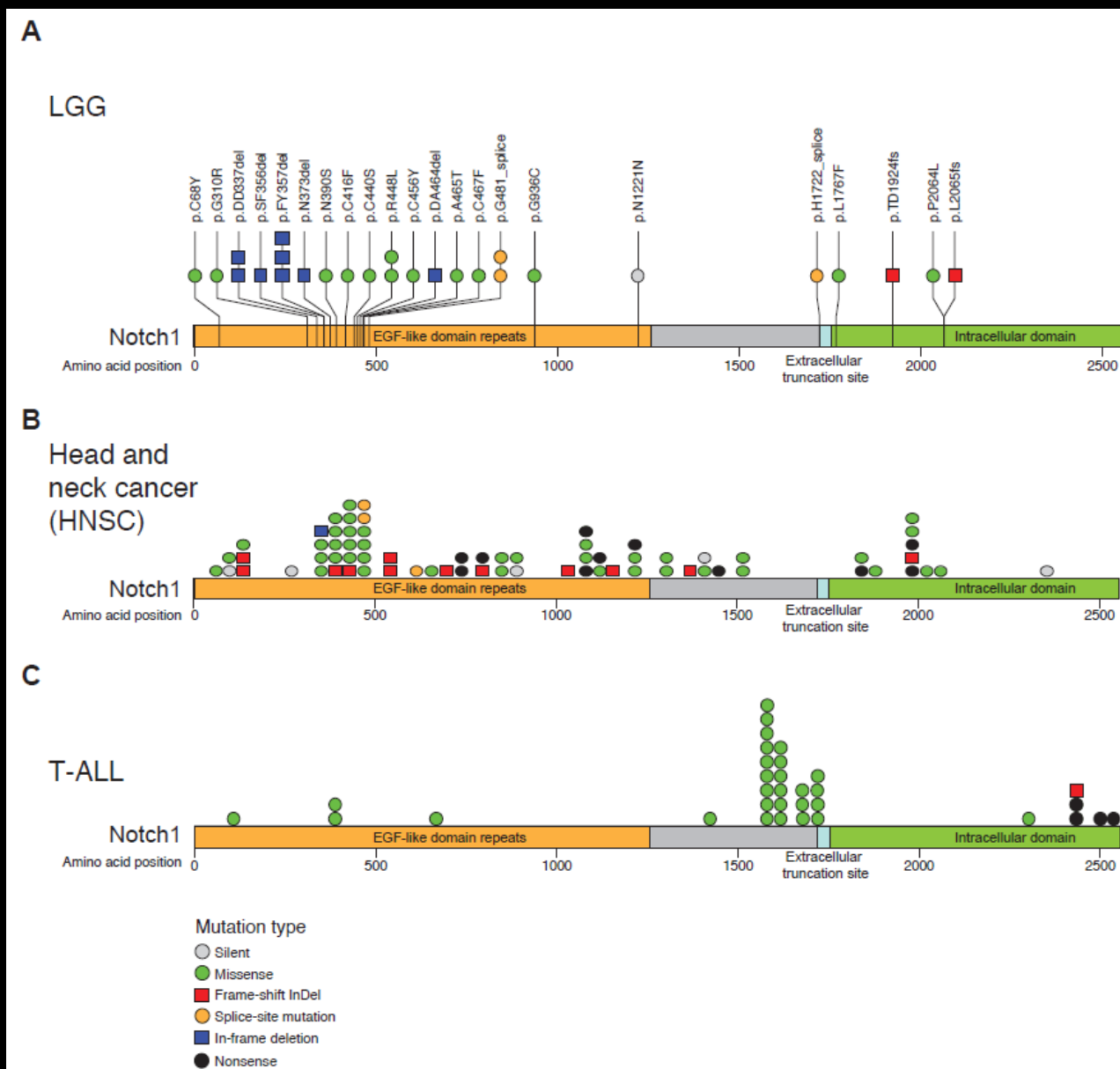
IDH mutations occur in ~80% of LGGs

- 1) CIC, FUBP1, Notch1, PIK3CA mutations (mostly oligo)
- 2) TP53 and ATRX mutations (mostly astro and oligoastro)

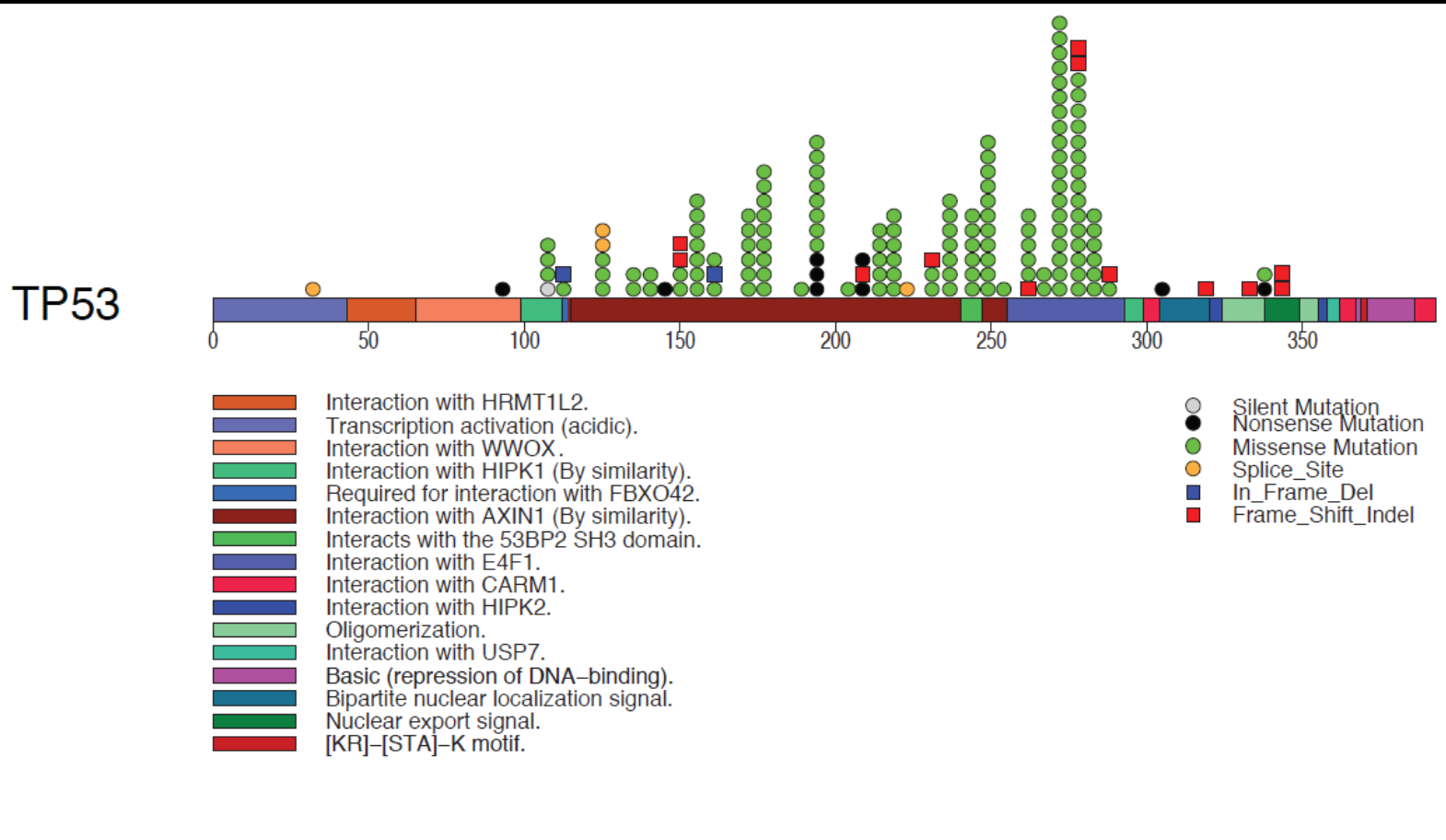
IDH wt LGG have mutations similar to GBM

Esther Rheinbay
Hailei Zhang
Jaegil Kim

Notch1 Mutations in *IDH*mut-codeL LGGs

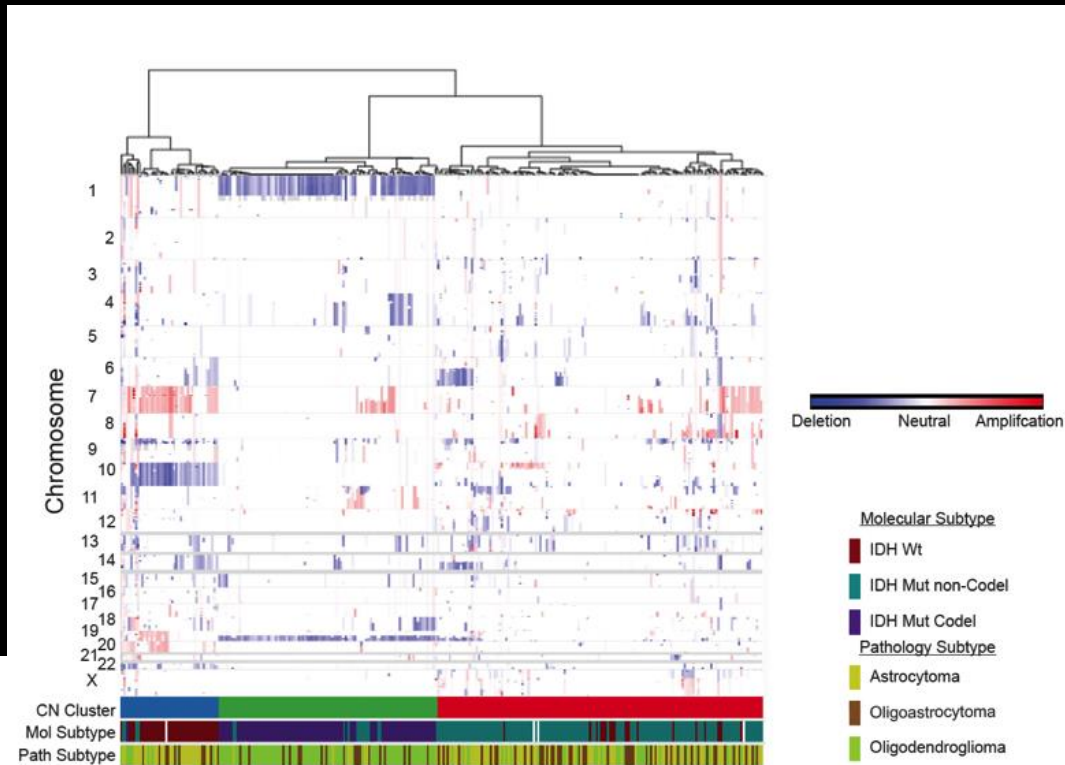
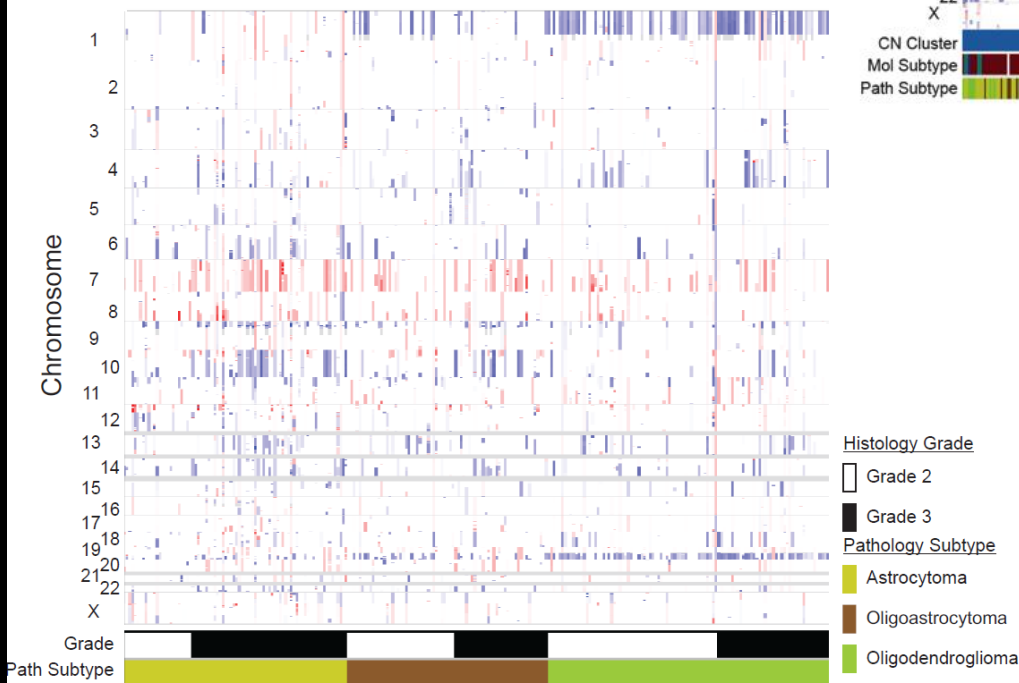


TP53 Mutations in *IDH*mut-non-codeL LGGs: 95%



LGG: Copy Number Alterations

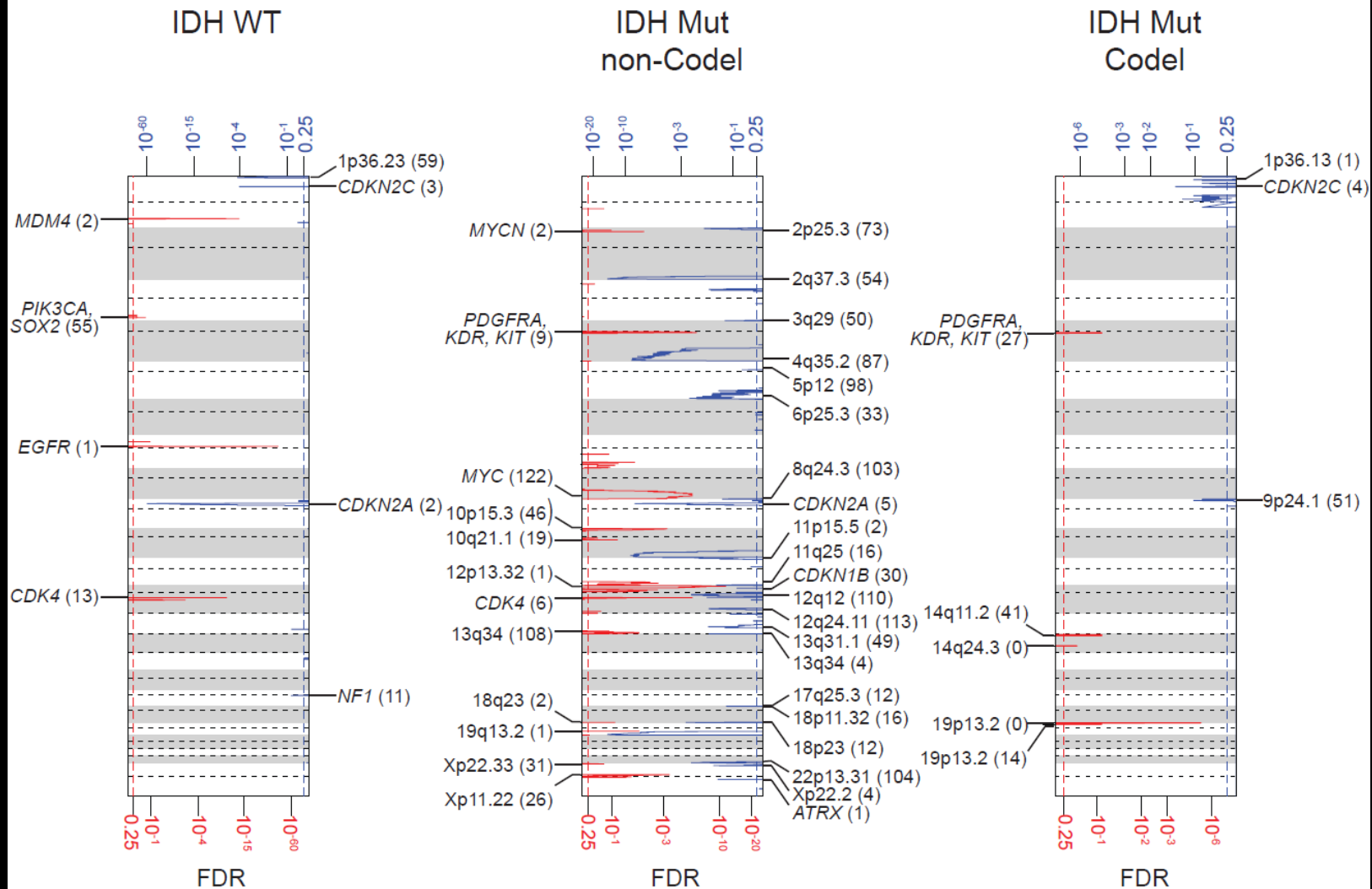
By Histology



Hierarchical Clustering

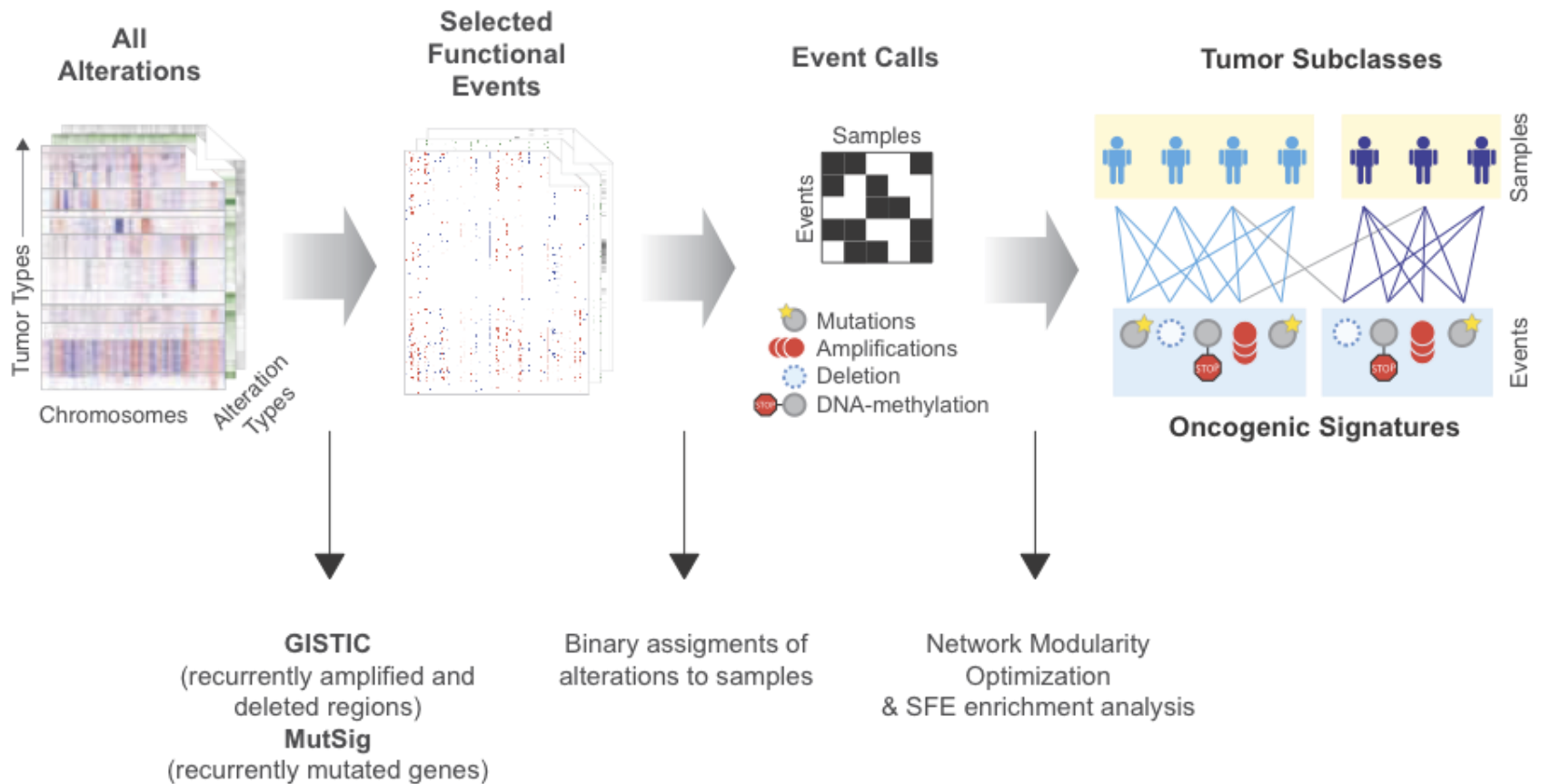
Hailei Zhang
Andrew Cherniack

Focal Amplifications and Deletions



OncoSign

(Oncogenic Signatures)



Giovanni Ciriello et al.,
Nat Gen, 2013

OncoSign Identifies 3 Molecular Classes Largely Based on IDH and 1p/19q status

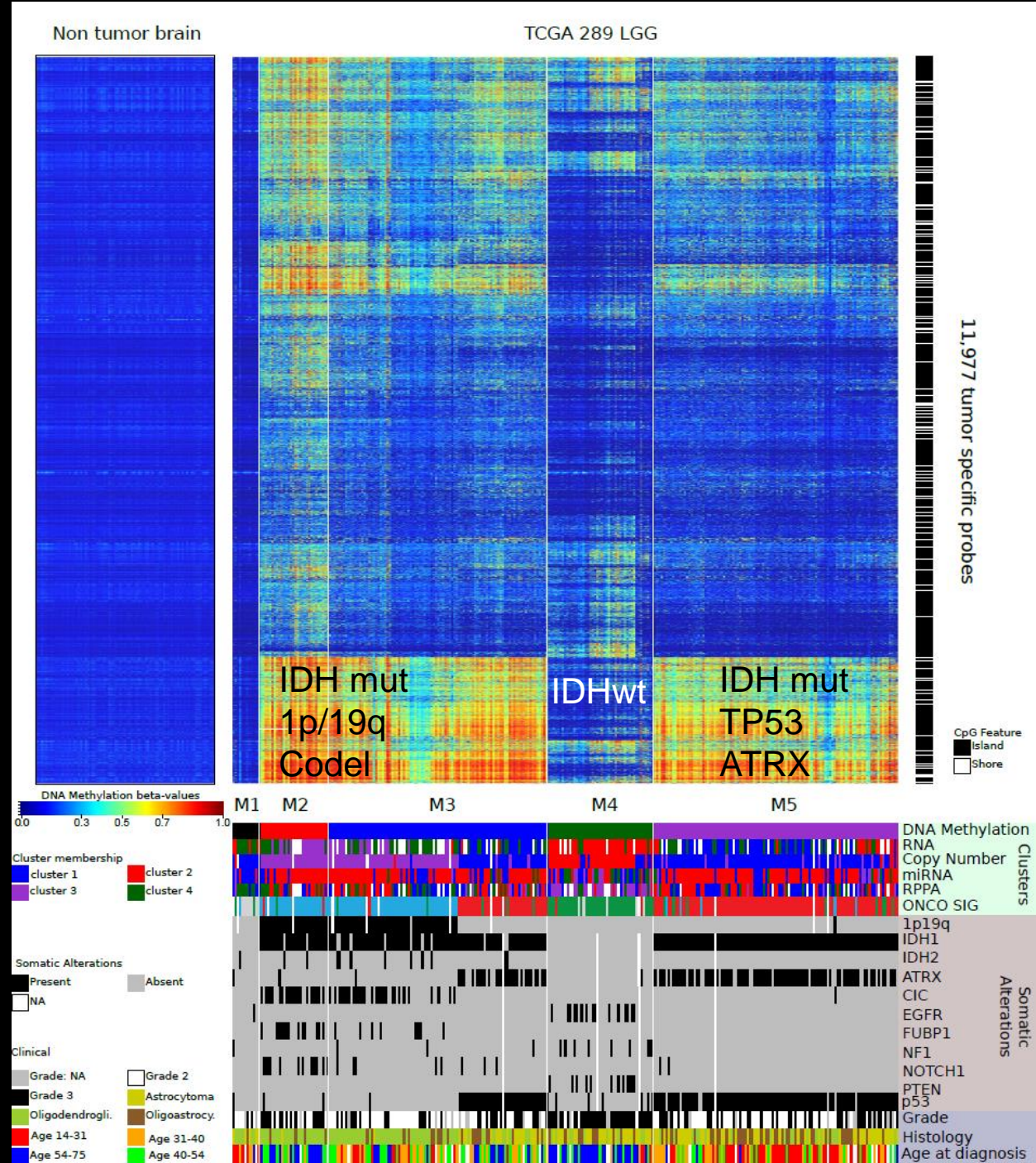


Giovanni Ciriello
Jason Huse

Conclusion 1:

Genomic alterations in LGG correlate better with IDH-codel status than histology

DNA Methylation Status



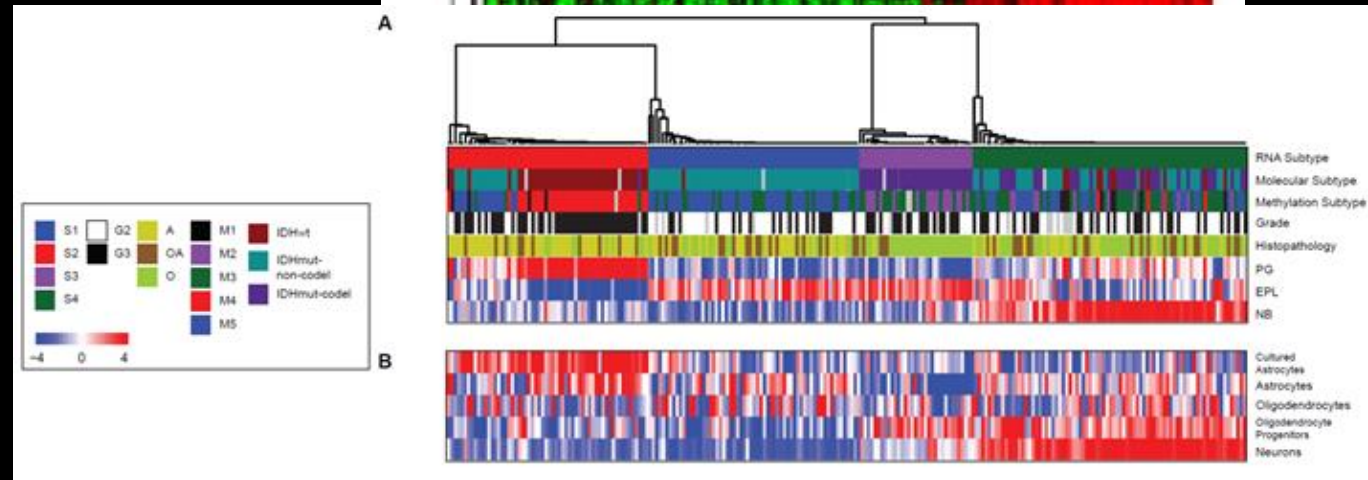
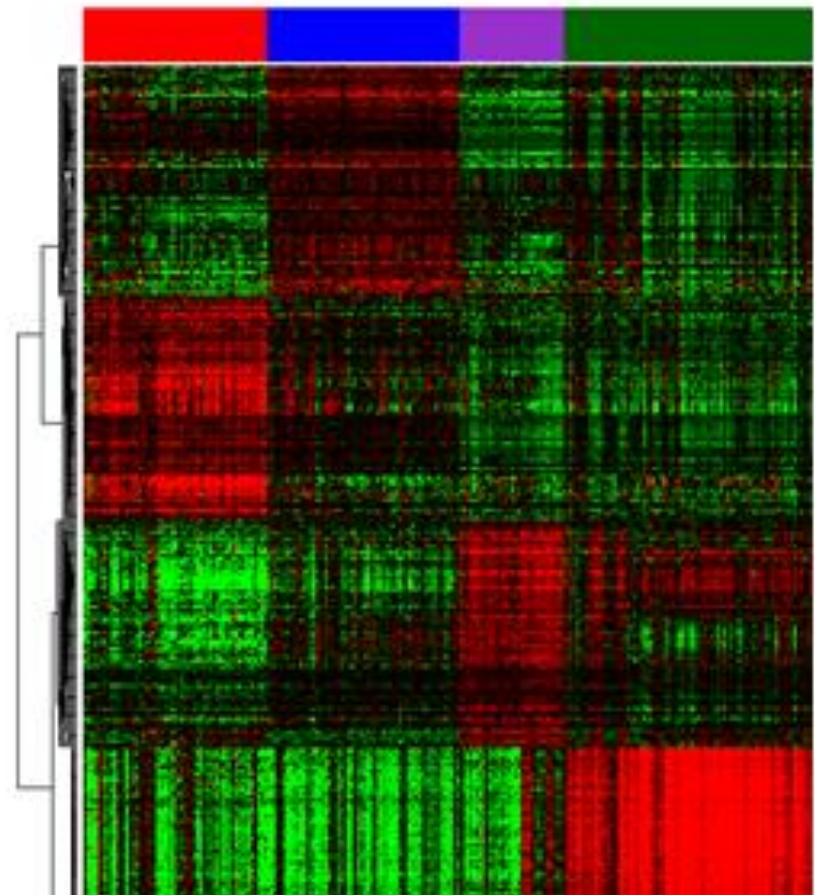
Houtan Noushmehr
Peter Laird

mRNA Expression Clustering

1500 most variable genes selected by MAD.

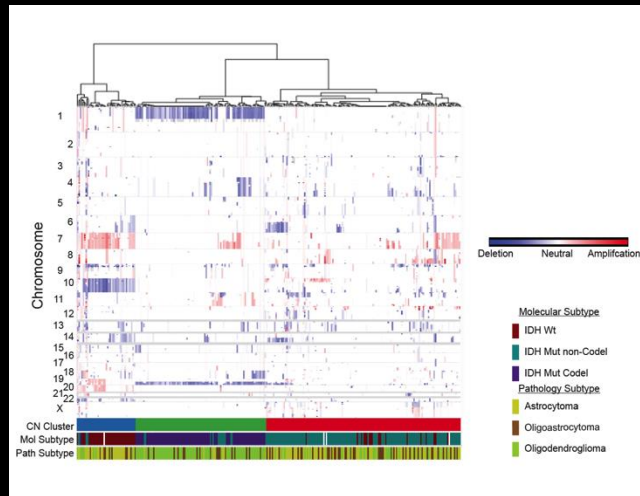
Consensus Hierarchical Clustering (Pearson).

At $k=6$, 4 large clusters.



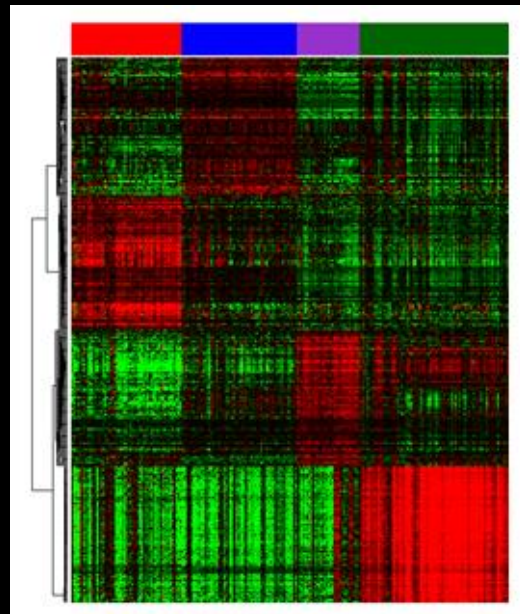
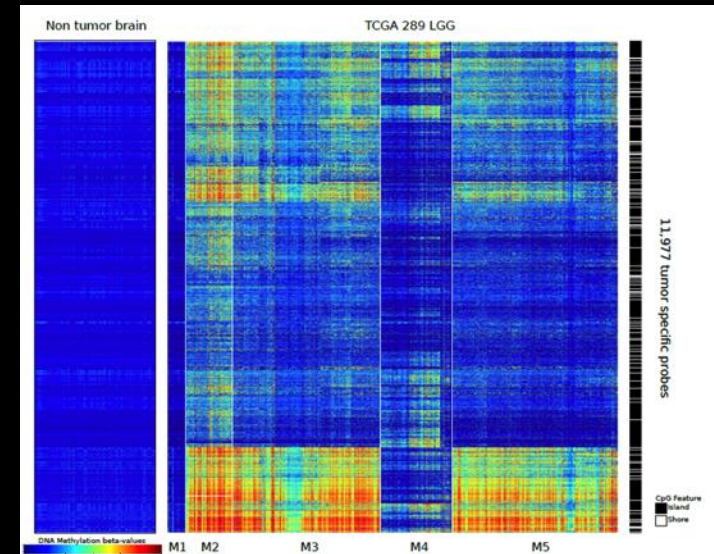
Mark Vitucci
Ryan Miller

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



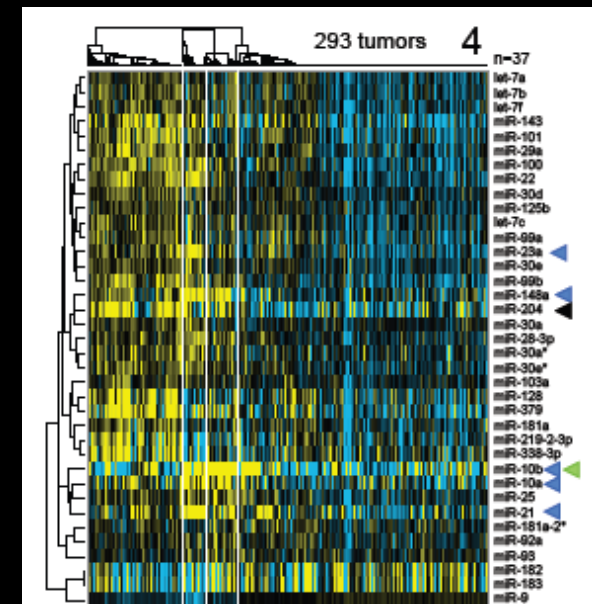
Andy Cherniak

Houtan
Noushmehr



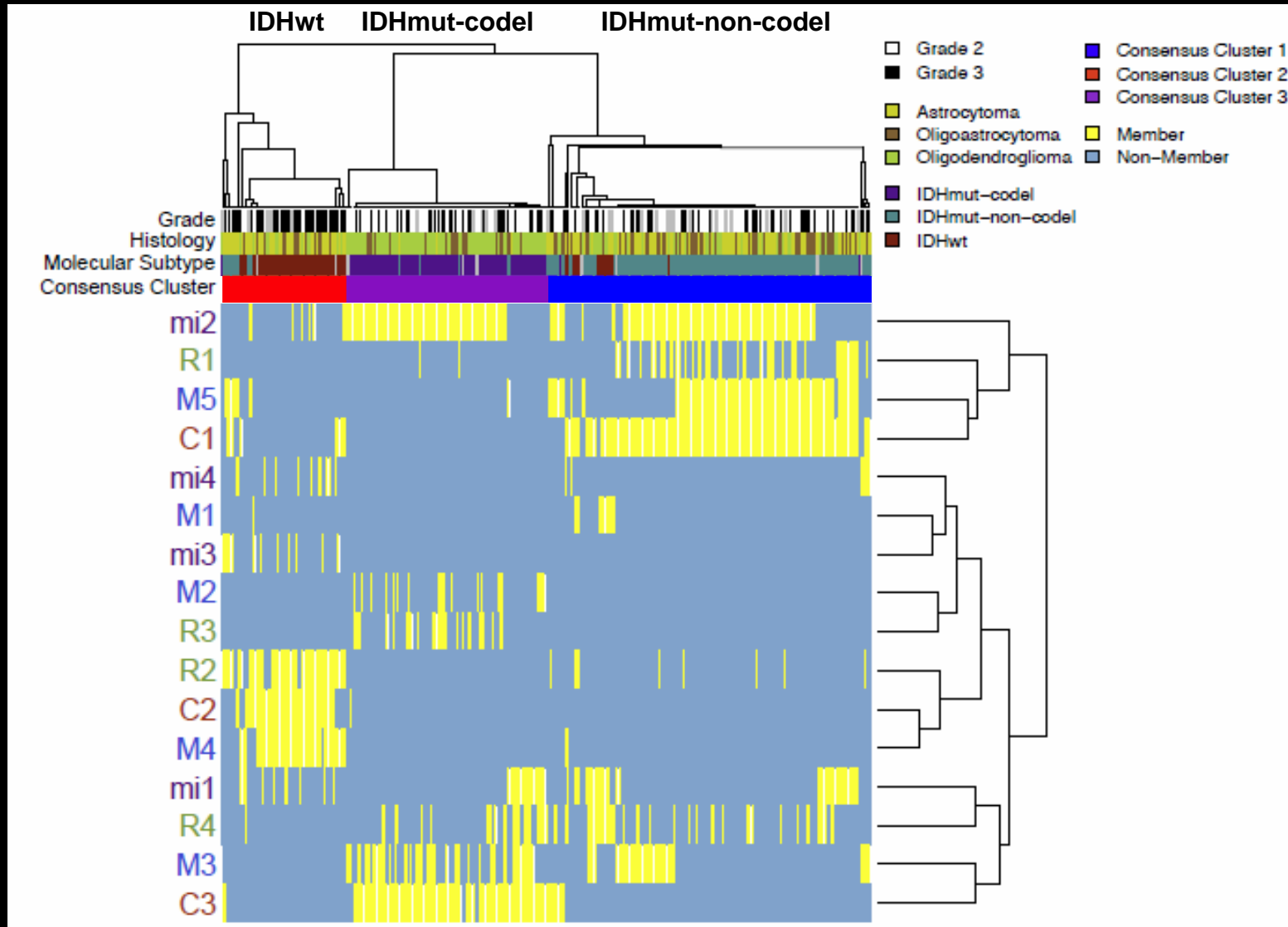
Mark Vitucci

Gordon
Robertson



Clustering of Clusters Identifies 3 Molecular Classes

Largely Based on IDH and 1p/19q status



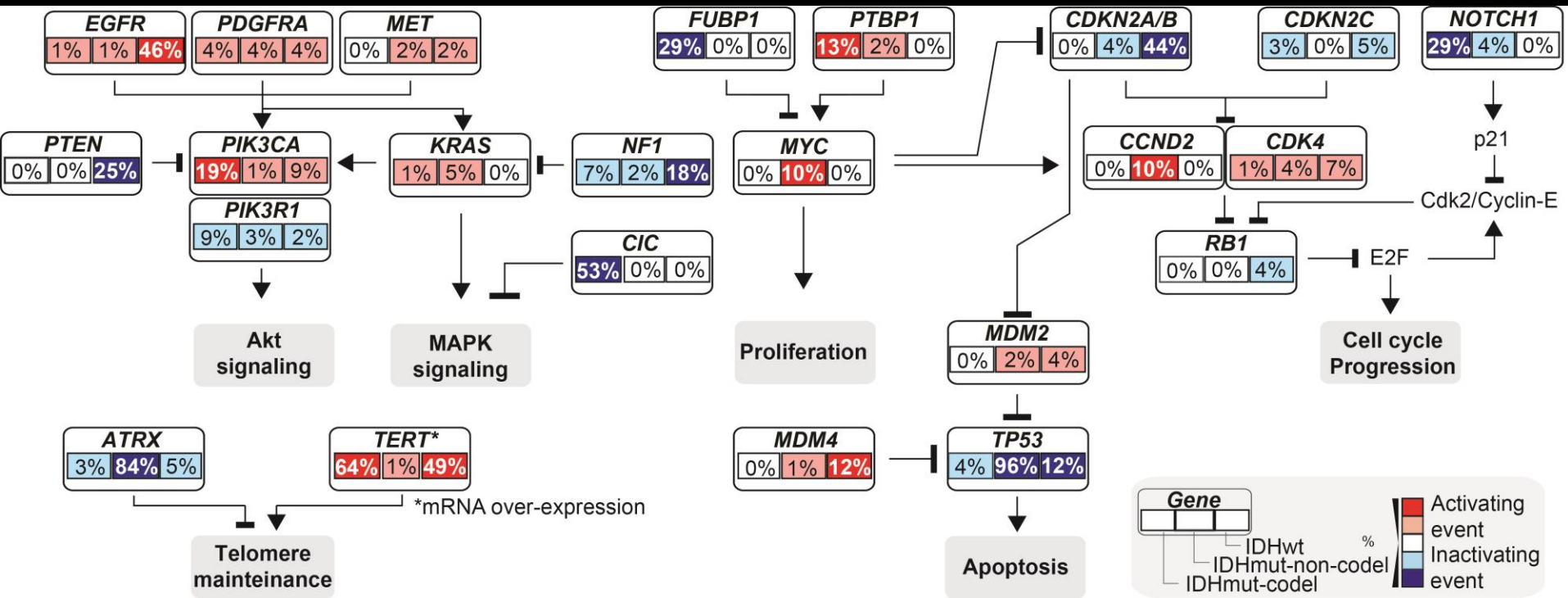
Mia
Gifford

Sofie
Salama

Conclusion 2:

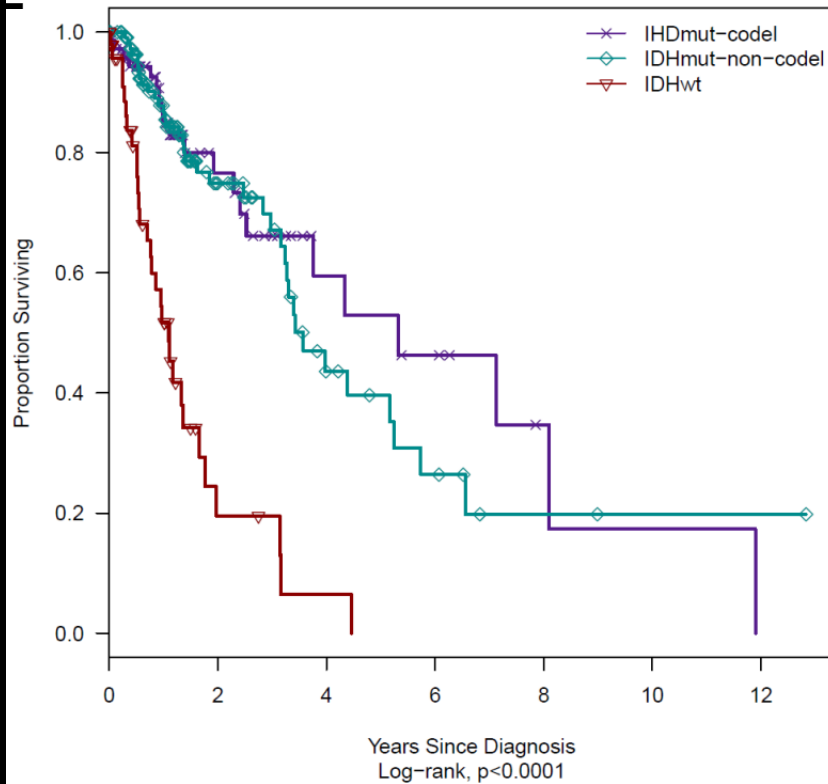
Multiplatform biologic classes of LGG correlate better with IDH-codel status than histology

Pathway Activation in LGG Subtypes

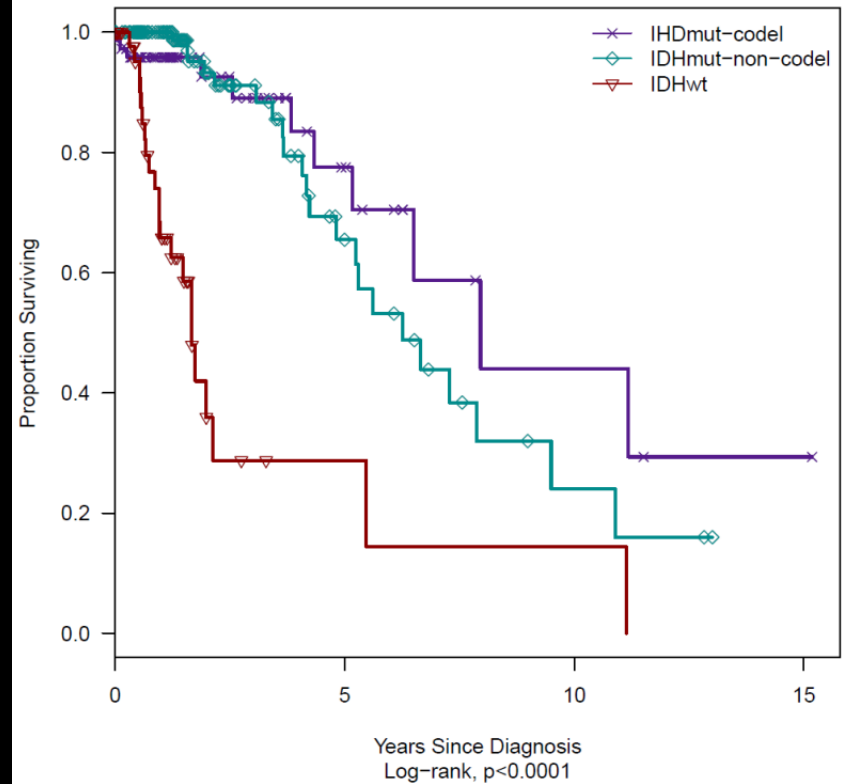


Clinical Outcomes

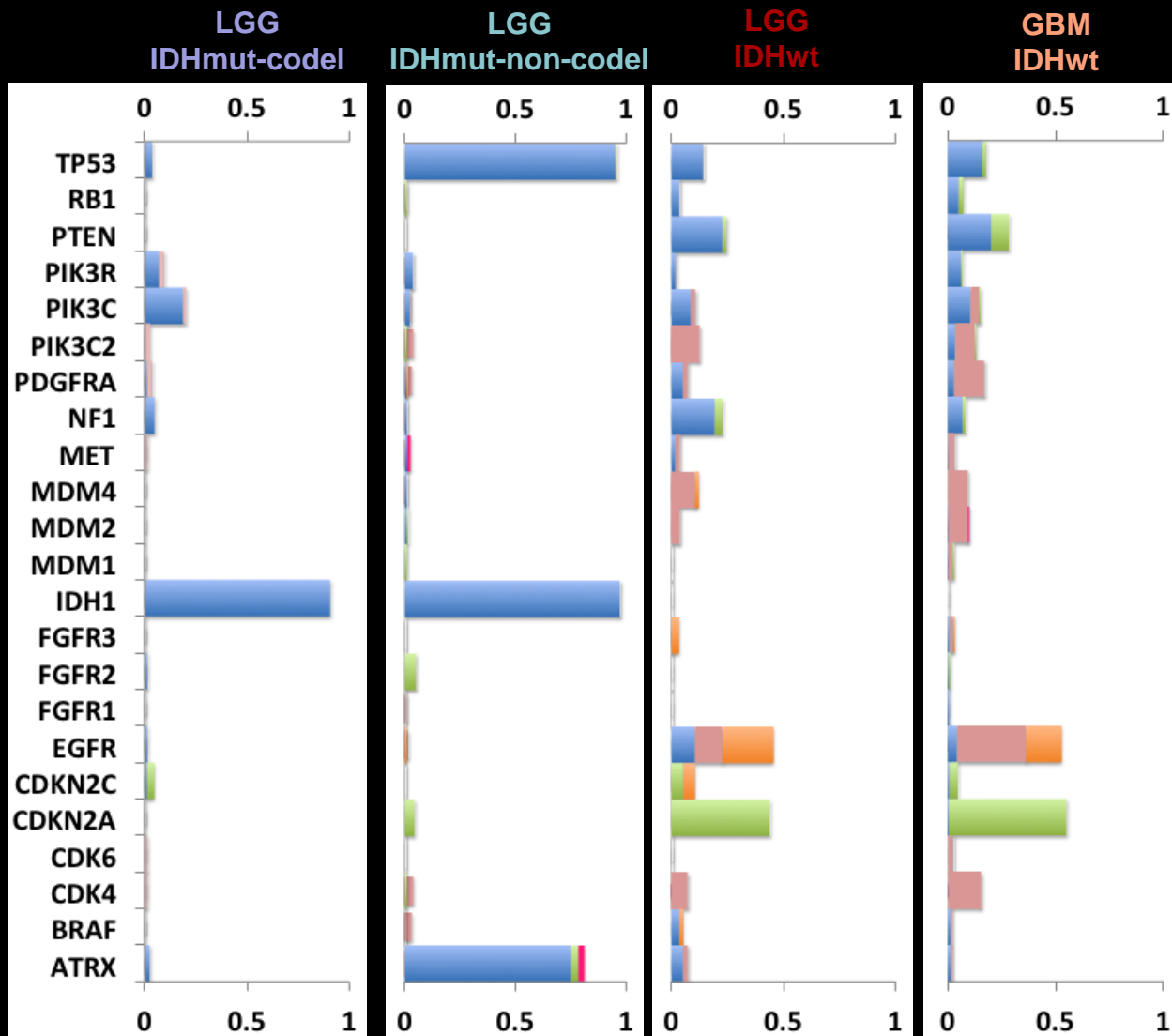
Event Free Survival



Overall Survival



IDHwt LGGs have Mutation Frequencies Similar to IDHwt Glioblastoma



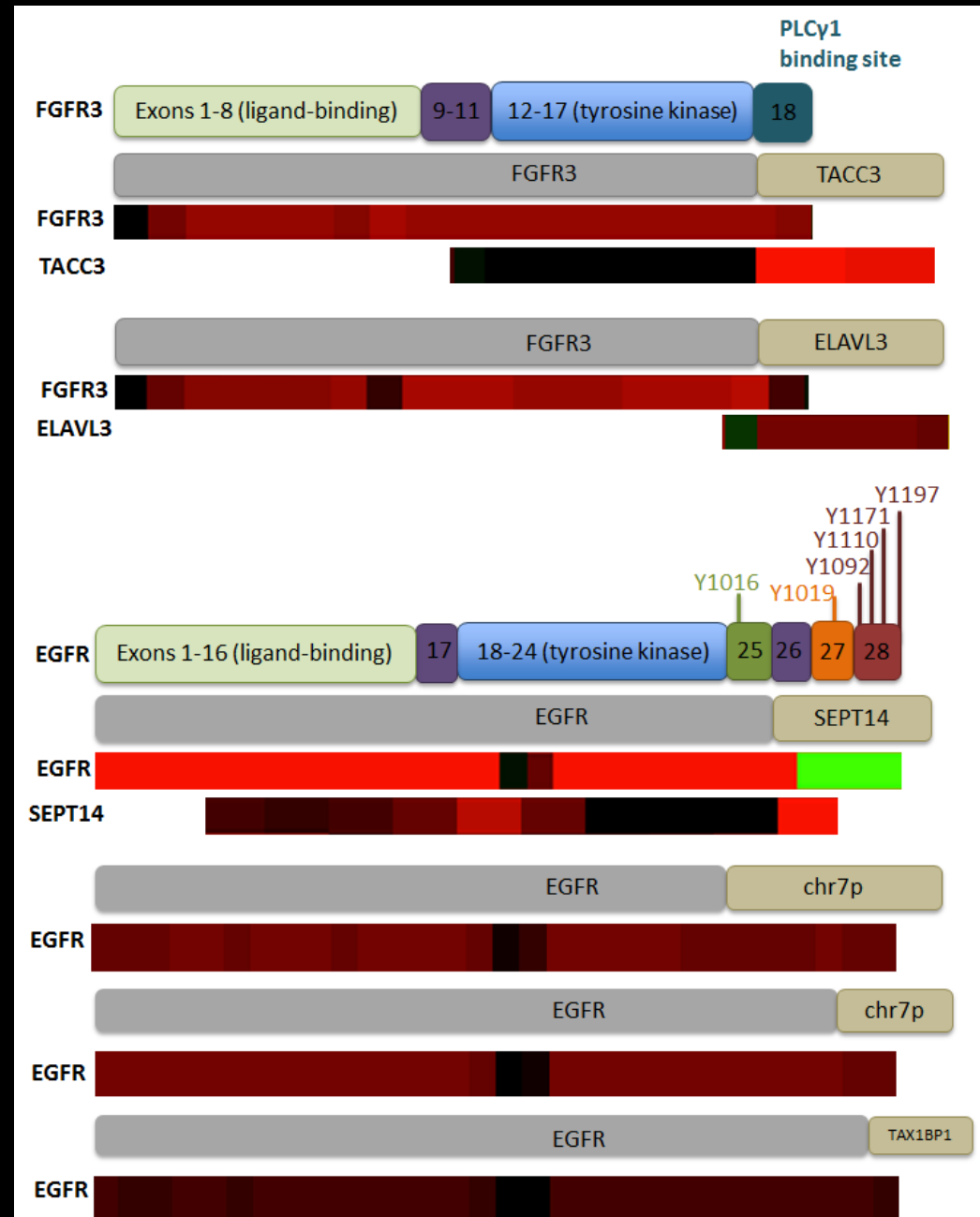
Fraction of samples with specific alteration in gene

SNV/indel Amplification Deletion SV Fusion Two or more aberrations

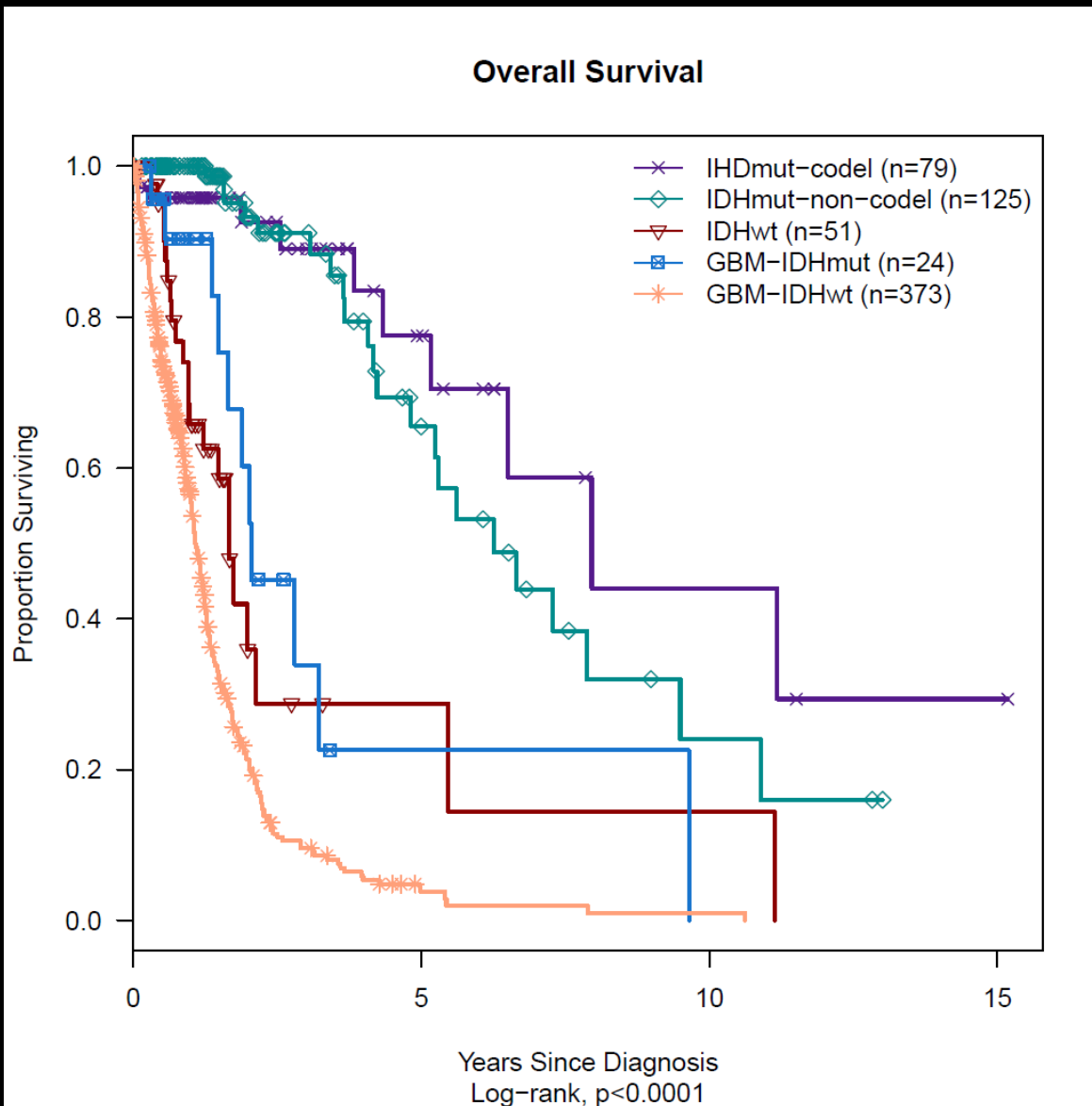
Mia Gifford
Olena Morozova
Sofie Salama

IDHwt LGGs have Oncogenic Gene Fusions Similar to Glioblastoma

Olena Morozova
Sofie Salama
Roel Verhaak



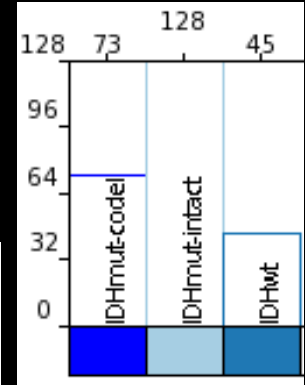
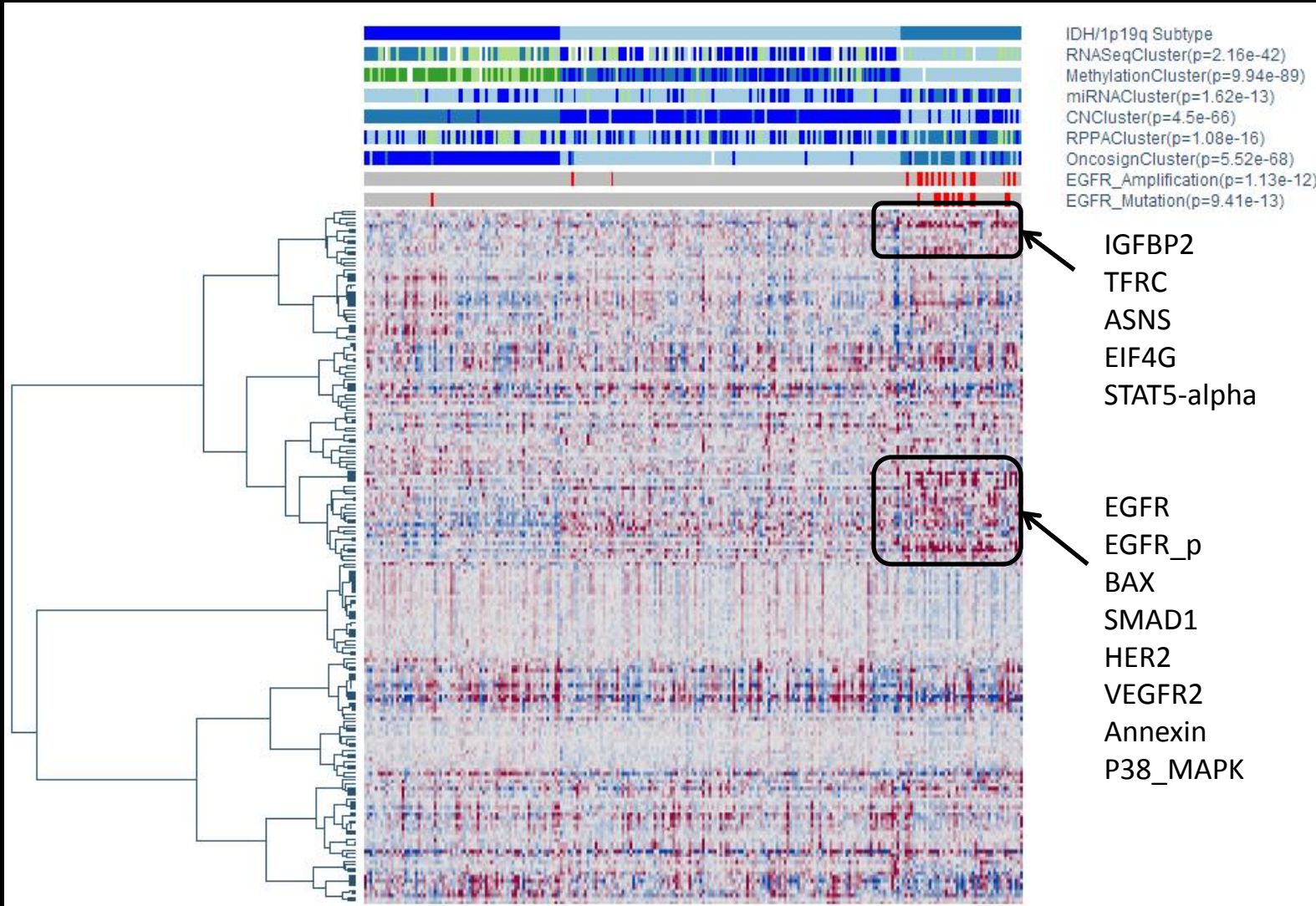
IDHwt LGGs have Clinical Outcomes Similar to Glioblastoma



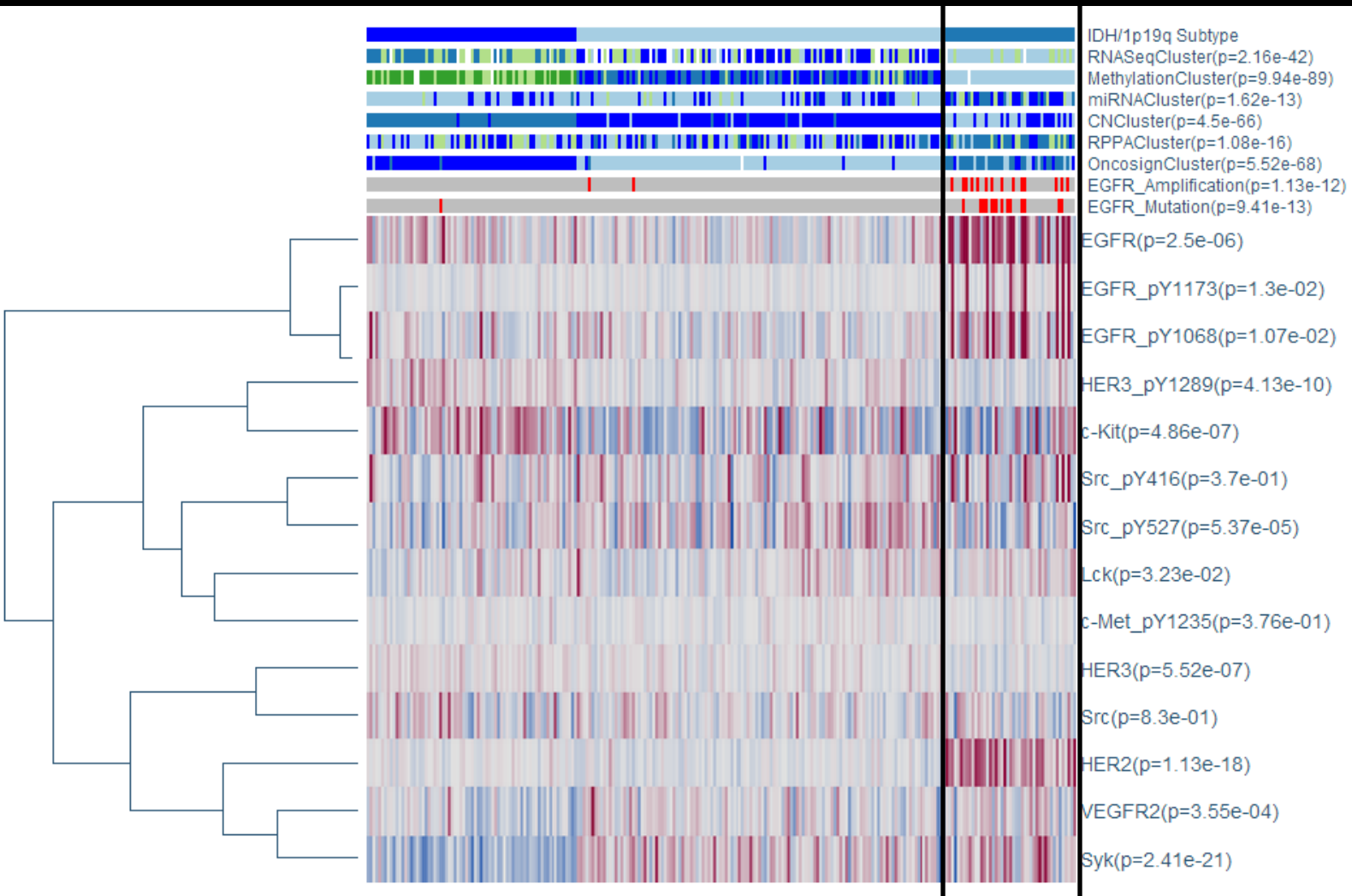
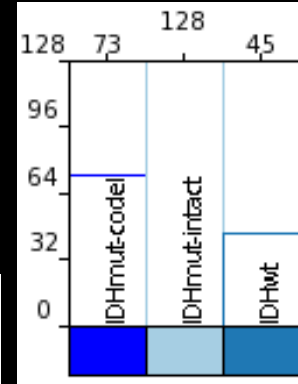
Conclusion 3:

IDHwt LGG are genetically and clinically similar to IDHwt GBM.

RPPA: Supervised clustering 189 Antibodies



RPPA: Supervised clustering 14 Tyrosine Kinase Antibodies



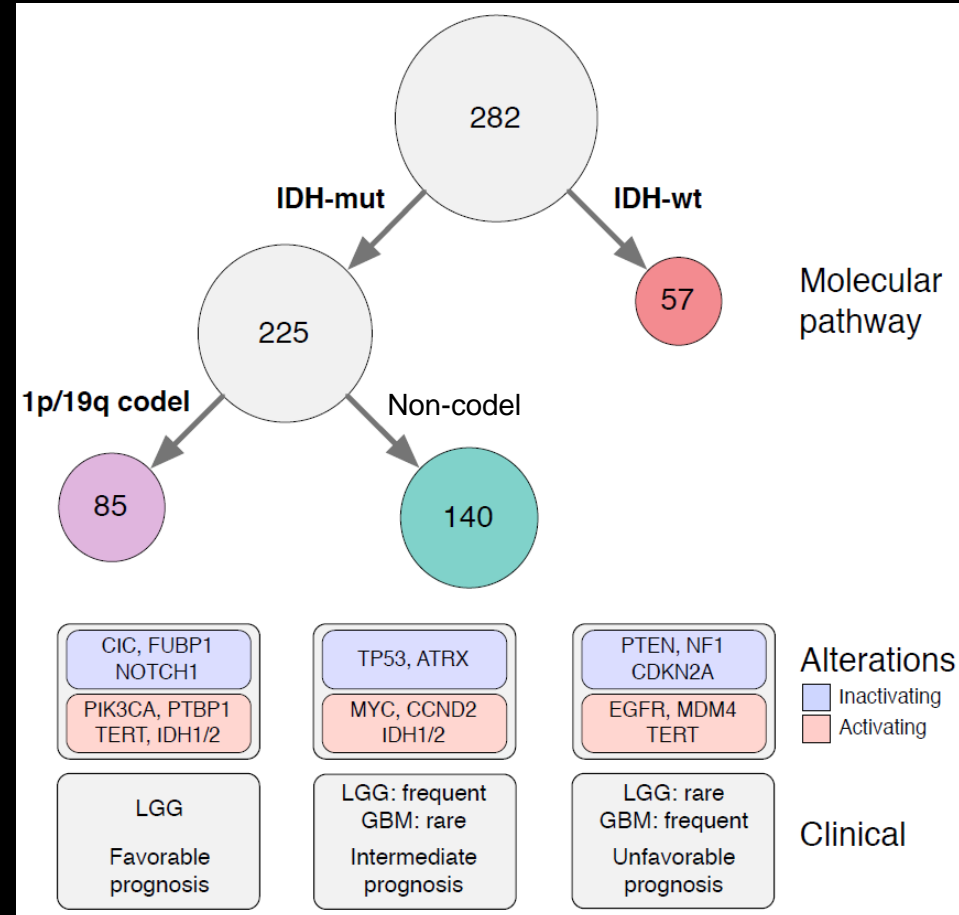
Summary

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

Co-Chairs:	Dan Brat, Al Yung
Data Coordinator:	Lee Cooper
Manuscript Coordinator:	Ken Aldape
Analysis Coordinators:	Roel Verhaak, Sofie Salama
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