

Pan - Glioma Integrative Analysis

A TCGA Project Since 2006

Houtan Noushmehr, PhD
(co-chair)

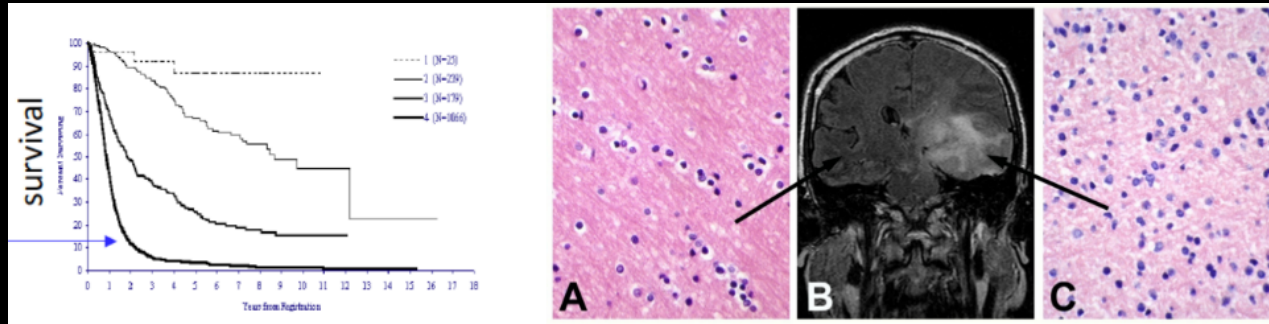
University of São Paulo, Brazil
Department of Genetics

May 12, 2015

On Behalf of the TCGA {LGG+GBM} AWG

Brain Cancer

- Glioblastoma multiforme (GBM)
 - Most common brain cancer
 - grade IV - astrocytoma
 - poor survival (median survival 14 months)
- Lower grade glioma (LGG)
 - grade II/III - diffuse.
 - mix histology: astrocytoma; oligodendroglioma; oligoastrocytoma
 - better survival.



Images by Daniel Brat

Histological grading inversely correlates with outcome

Tumor Type	Median survival (months)
Grade II oligodendroglioma	120
Grade II astrocytoma	60
Anaplastic oligodendroglioma (grade III)	60
Anaplastic astrocytoma (grade III)	36
Glioblastoma (grade IV)	15

Diagnostic concordance of histological grading between multiple observers: 50-75%

TCGA Glioma Updates {EST. 2006}

2 Marker Paper

Version 1.0 (2008)

Vol 455 | 23 October 2008 | doi:10.1038/nature07385 nature

ARTICLES

Comprehensive genomic characterization defines human glioblastoma genes and core pathways

The Cancer Genome Atlas Research Network*

~200 TCGA GBM

Version 2.0 (2013)

Cell Resource

The Somatic Genomic Landscape of Glioblastoma

Cameron W. Brennan,^{1,2,46,*} Roel G.W. Verhaak,^{3,11,49} Aaron McKenna,^{4,49} Benito Campos,^{5,4} Houtan Noushmehr,^{7,8} Sofie R. Salama,⁹ Siyuan Zheng,³ Debyani Chakravarty,¹ J. Zachary Sanborn,⁹ Samuel H. Berman,¹ Rameen Beroukhi,^{4,10} Brady Bernard,¹⁰ Chang-Jun Wu,¹¹ Giannicola Genovese,¹¹ Ilya Shmulevich,¹⁰ Jill Barnholtz-Sloan,¹¹ Lihua Zou,⁴ Rajulasham Vegesna,³ Sachet A. Shukla,⁴ Giovanni Giniello,¹⁴ W.K. Yung,¹⁴ Wei Zhang,¹⁵ Carrie Sougnez,⁴ Tom Mikkelsen,¹⁶ Kenneth Aldape,¹⁵ Doreen D. Bigner,¹⁷ Erwin G. Van Meir,¹⁸ Michael Prados,¹⁹ Andrew Sloan,²⁰ Keith L. Black,²¹ Jennifer Echbacher,²² Gaetano Finocchiaro,²³ William Friedman,²⁴ David W. Andrews,²⁵ Abhijit Guha,²⁶ Mary Iacocca,²⁷ Brian P. O'Neill,²⁸ Greg Foltz,²⁹ Jerome Myers,²⁶ Daniel J. Weisenberger,³ Robert Penny,³¹ Raju Kucherlapati,³² Charles M. Perou,³³ D. Neil Hayes,³³ Richard Gibbs,³⁴ Marco Marra,³⁵ Gordon B. Mills,³⁶ Eric Lander,⁴ Paul Spellman,³⁷ Richard Wilson,³⁸ Chris Sander,¹² John Weinstein,³ Matthew Meyerson,^{4,12} Stacey Gabriel,⁴ Peter W. Laird,⁴ David Haussler,^{3,39} Gad Getz,⁴ Lynda Chin,^{4,13,1} and TCGA Research Network

462 Cell 155, 462–477, October 10, 2013

~540 TCGA GBM

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462 Cell 155, 462–477, October 10, 2013

2 Companion Paper

Verhaak et al. 2010

Cell PRESS Cancer Cell Article

Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in *PDGFRA*, *IDH1*, *EGFR*, and *NF1*

Roel G.W. Verhaak,^{1,2,17} Katherine A. Hoadley,^{3,4,17} Elizabeth Purdom,⁷ Victoria Wang,⁸ Yuan Qi,^{4,8} Matthew D. Wilkerson,^{4,5} C. Ryan Miller,^{4,8} Li Ding,⁹ Todd Golub,^{1,10} Jill P. Mesirov,¹ Gabriele Alexe,¹ Michael Lawrence,^{1,2} Michael O'Kelly,^{1,2} Pablo Tamayo,¹ Barbara A. Weir,^{1,2} Stacey Gabriel,¹ Wendy Winckler,^{1,2} Supriya Gupta,¹ Lakshmi Jakkula,^{1,2} Heidi S. Feller,¹ J. Graeme Hodgson,¹³ C. David James,¹² Jann N. Sarkaria,¹³ Cameron Brennan,^{1,4} Ari Khatib,¹⁵ Paul T. Spellman,¹⁶ Richard K. Wilson,⁷ Terence F. Spoor,¹² Joe W. Gray,¹ Matthew Meyerson,⁷ Gad Getz,¹ Charles M. Perou,^{3,4,8} D. Neil Hayes,^{4,8,*} and The Cancer Genome Atlas Research Network

Cancer Cell 17, 98–110, January 19, 2010

Noushmehr et al. 2010

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Identification of a CpG Island Methylator Phenotype that Defines a Distinct Subgroup of Glioma

Houtan Noushmehr,^{1,13} Daniel J. Weisenberger,^{1,13} Kristin Diefelso,^{2,13} Heidi S. Phillips,^{2,13} Kanan Pujara,² Benjamin P. Berman,¹ Fel Pan,¹ Christopher E. Pelloski,¹ Erik P. Sulman,⁴ Krishna P. Bhat,² Roel G.W. Verhaak,^{5,8} Katherine A. Hoadley,^{7,8} D. Neil Hayes,^{7,8} Charles M. Perou,^{7,8} Heather K. Schmidt,⁹ Li Ding,⁹ Richard K. Wilson,⁹ David Van Den Berg,¹ Hui Shen,¹ Henrik Bengtsson,¹⁰ Pierre Neuvial,¹⁰ Leslie M. Cope,¹¹ Jonathan Buckley,^{1,12} James G. Herman,¹¹ Stephen B. Baylin,¹¹ Peter W. Laird,^{1,14*} Kenneth Aldape,^{2,14} and The Cancer Genome Atlas Research Network

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Cancer Cell 17, 510–522, May 18, 2010

TCGA
GBM
(n=4)

GBM Marker Paper, v2

Cell, 2013

(presented by Roel Verhaak - 2nd TCGA Symp.)

Youtube Video:
<https://goo.gl/tjgLmB>



Table 1. Characterization Platforms and Data Availability

Data Type	Platforms	Cases in 2008	Cases in 2013
DNA sequence of exome	Illumina on native DNA	0	291
	Sanger on native DNA	91	148
	Illumina on whole genome amplified DNA	0	163
DNA sequence of whole genome	Illumina on native DNA	0	42
DNA copy number/genotype	Affymetrix SNP6	206	578
	Agilent 224K/415K	206	413
mRNA expression profiling	Affymetrix U133A	206	544
	Affymetrix Exon	201	417
mRNA sequencing	Illumina on native cDNA	0	164
CpG DNA methylation	Illumina GoldenGate	242	242
	Illumina 27K	0	285
	Illumina 450K	0	113
miRNA expression profiling	Agilent	205	491
Protein expression profiling	Reverse phase protein arrays	0	214
Clinical characteristics	Tier 1/Tier 2	206	543

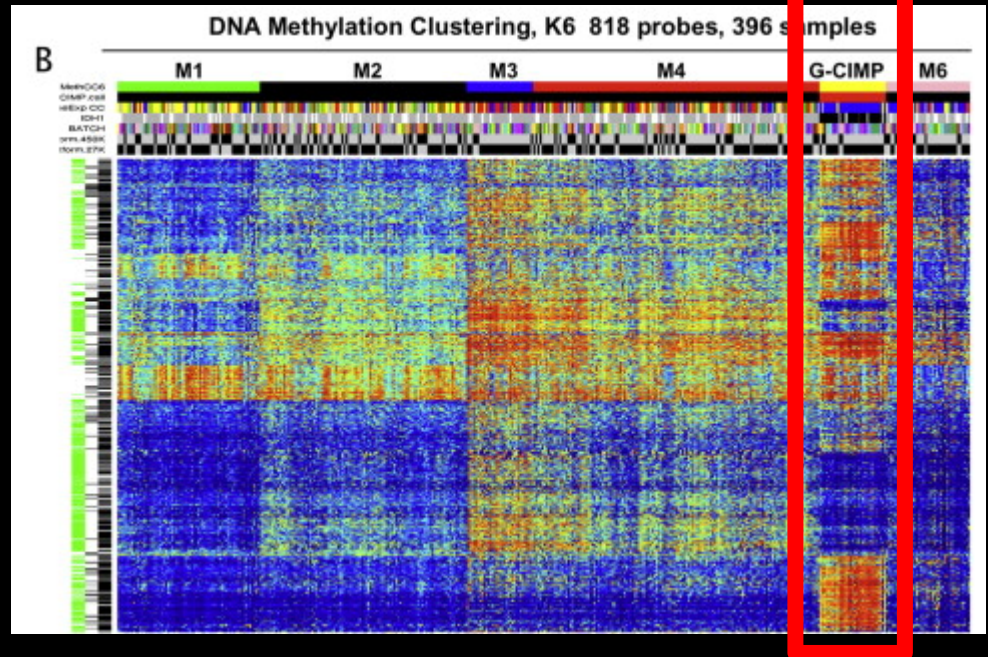
- Identified novel mutations and rearrangements in EGFR.
- TERT promoter mutation correlates with expression (role in telomerase reactivation).
- G-CIMP confirmed with best survival

IDH1 & IDH2 mutations in glioma

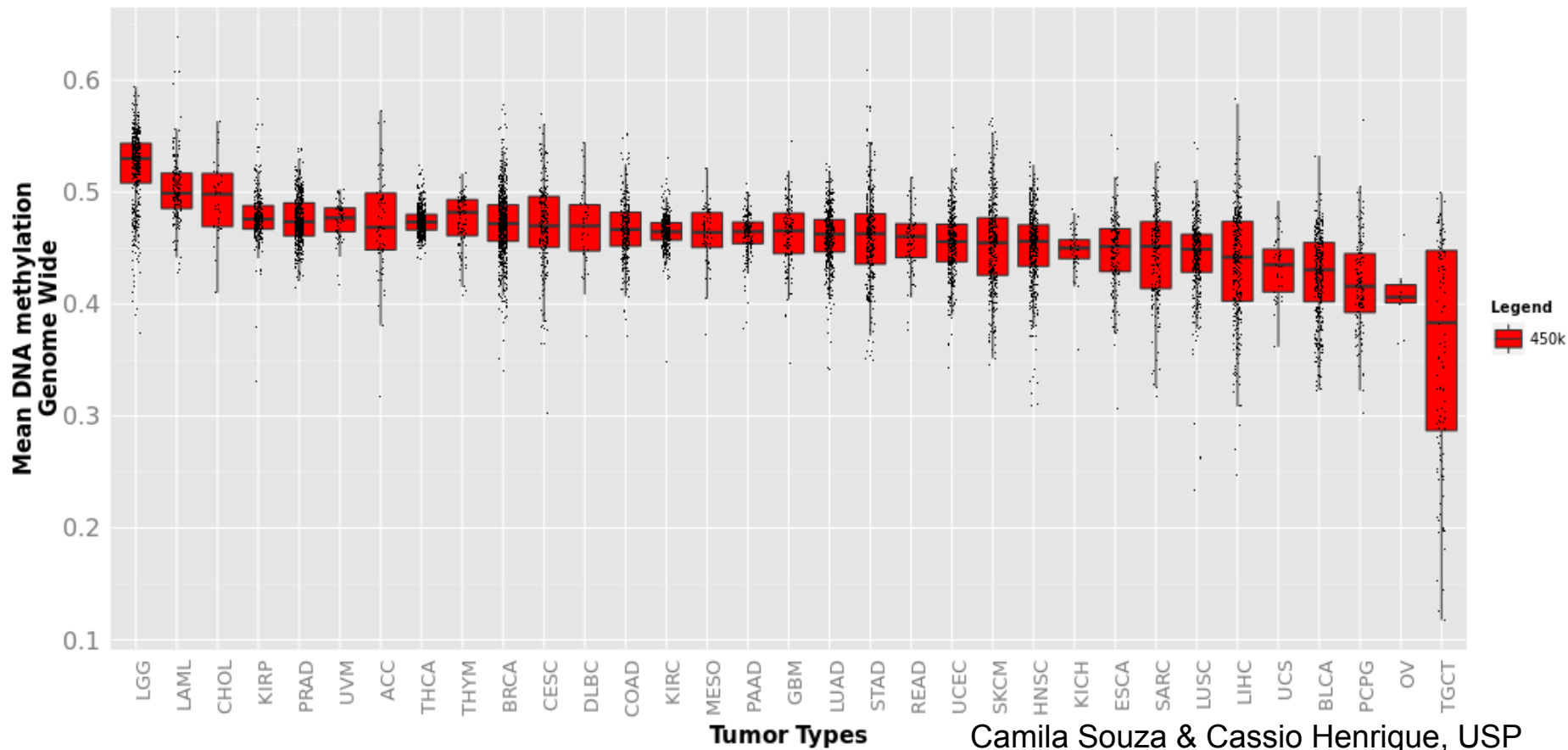
9% of GBM; Proneural G-CIMPs:

- Younger
 - Better Survival
 - IDH1mutants
- 70-95% of LGGs

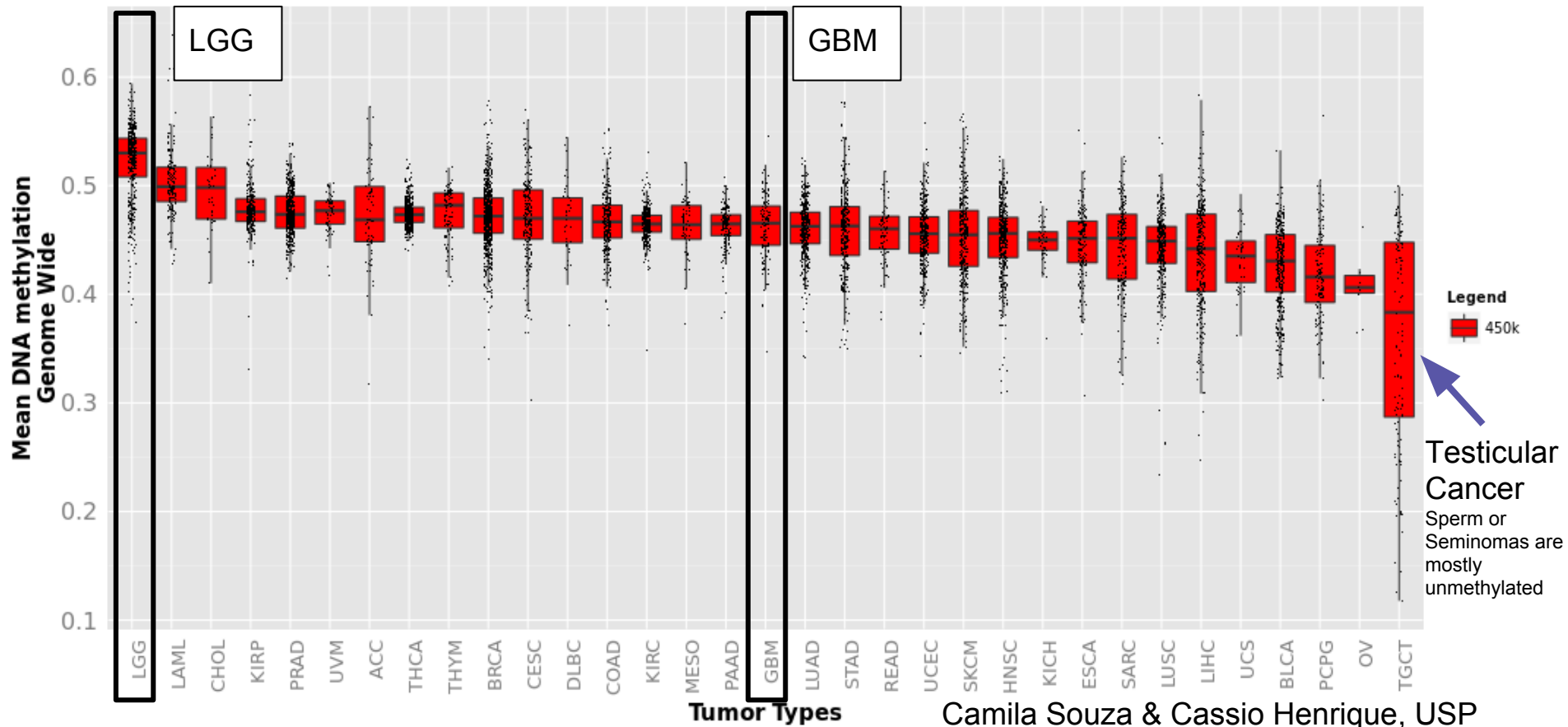
Yan et al. *NEJM* 2009, Noushmehr et al. *Cancer cell* 2010, Brennan et al. *Cell* 2013, TCGA Research Network, *NEJM*, 2015 (in press)



Epigenomic Landscape across 10,000+ TCGA Tumors

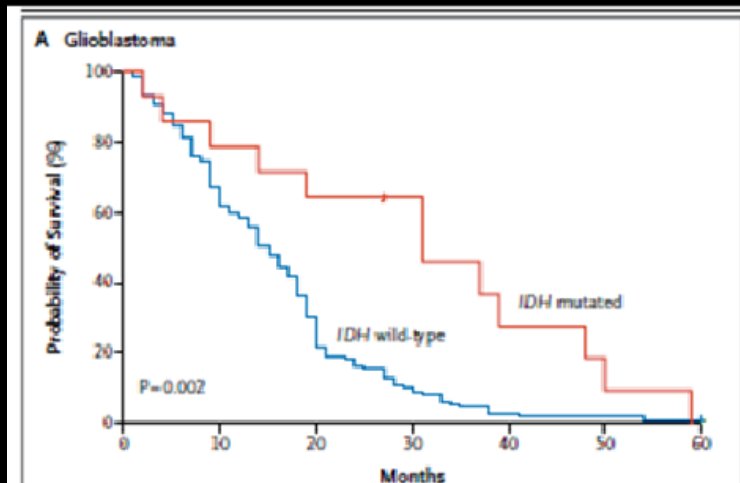


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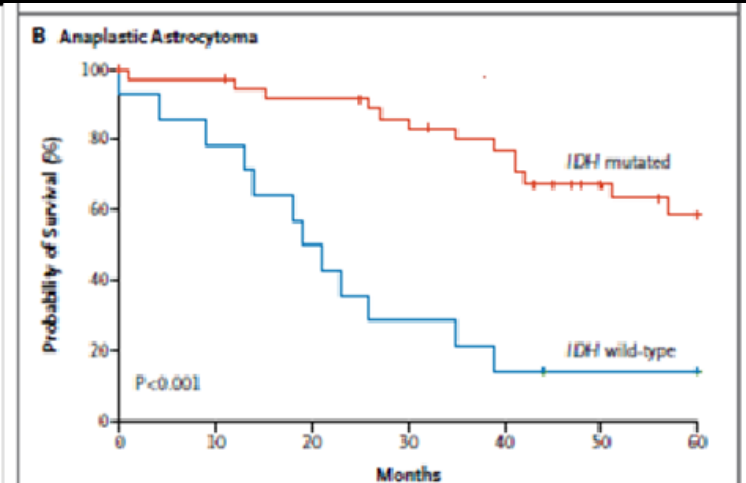


IDH mutations correlate with favorable outcome in GBM and Astrocytoma (e.g. LGGs)

GBM



Anaplastic Astrocytoma



Yan et al. *NEJM* 2009, Noushmehr et al. *Cancer cell* 2010, Brennan et al. *Cell* 2013, TCGA Research Network, *NEJM*, 2015 (in press)



Youtube Video:
<https://goo.gl/qqG38>

LGG Marker Paper

NEJM, 2015 - in press

(presented by Daniel Brat - 3rd TCGA Symp.)

- 1) IDHmut-codel;
- 2) IDHmut-non-codel;
- 3) IDHwt (GBM-like)
 - *IDH* wild-type LGGs, regardless of histology, had genomic aberrations and clinical behavior similar to primary glioblastoma.
 - Nearly all *IDH*-mutant LGGs without 1p/19q co-deletion had mutations in *TP53* (95%) and *ATRX* was frequently inactivated (84%).
 - LGGs that were *IDH*-mutant and 1p/19q co-deleted had the most favorable clinical outcomes and were associated with mutations in *CIC*, *FUBP1*, *NOTCH1* and the *TERT* promoter.

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

GBM Marker Paper, v2

Cell, 2013

(presented by Roel Verhaak - 2nd TCGA Symp.)

LGG Marker Paper

NEJM, 2015 - in press

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Pan-Glioma (LGG+GBM)

- AWG - formed 1.5 year ago;

Analysis is currently in the writing stage (submission soon).

- Characterize the molecular differences between LGG and GBM
- Understand the LGG-GBM-like (IDHwt) and the G-CIMP-LGG-like (IDHmut)

Clinical & Molecular characteristics of 1,122 Gliomas

Feature	All (n=1122)
<i>Clinical</i>	
<i>Histology (n)</i>	
<u>Astrocytoma</u>	169 (15.06%)
<u>Glioblastoma</u>	590 (52.58%)
<u>Oligoastrocytoma</u>	114 (10.16%)
<u>Oligodendroglioma</u>	174 (15.51%)
Unknown	75 (6.68%)
<i>Grade (n)</i>	
G2	216 (19.25%)
G3	241 (21.48%)
G4	590 (52.58%)
Unknown	75 (6.68%)
<i>Age</i>	
Median (LQ-UQ)	51 (39-63)
Unknown (n)	75
<i>Survival</i>	
Median (CI)	20.7 (19.3-23.2)
Unknown (n)	76
<i>KPS</i>	
<70	119 (10.61%)
70-80	315 (28.07%)
90	123 (10.96%)
100	140 (12.48%)
Unknown	425 (37.88%)

<i>Molecular</i>	
<i>IDH1/2 status</i>	
Mutant	454 (40.46%)
WT	524 (46.7%)
Unknown	144 (12.83%)
<i>1p/19q codeletion</i>	
Yes	171 (15.24%)
No	913 (81.37%)
Unknown	38 (3.39%)
<i>MGMT promoter</i>	
Methylated	613 (54.63%)
Unmethylated	319 (28.43%)
Unknown	190 (16.93%)

- GBMs (606) vs LGGs (516)*.
- Addition of 290 LGG since NEJM 2015
- *IDH* status known for 87% of the samples.

*updated recently

Floris Barthel, LGG-GBM AWG

Molecular profiling of the largest glioma dataset to date

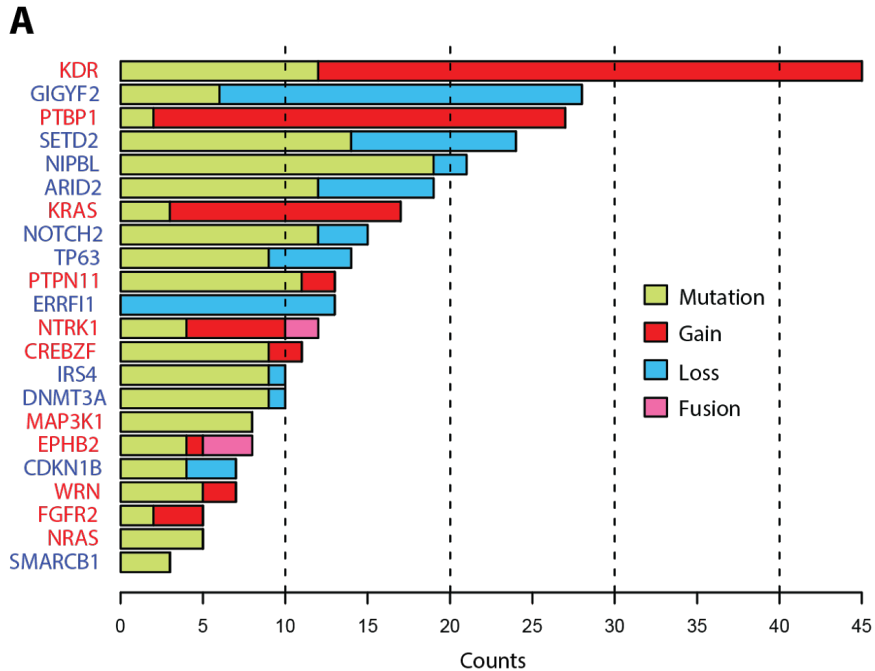
Data Type/Platform	Total (n=1122)
Array-based	
<i>Gene expression array</i>	
Affymetrix U133A	378
<i>DNA methylation array</i>	
Illumina HM 450K	645
Illumina HM 27K	287
<i>DNA copy number array</i>	
Affymetrix SNP6	1087
Sequencing-based	
<i>mRNA sequencing</i>	
Illumina HiSeq cDNA	667
<i>Exome sequencing</i>	
Illumina HiSeq native DNA	804
Illumina HiSeq amplified DNA	163
<i>Sanger sequencing</i>	
Solid ABI	158
<i>Whole genome sequencing</i>	
Illumina HiSeq	71
<i>Low-Pass sequencing</i>	
Illumina HiSeq	52
<i>Targeted sequencing</i>	
Illumina HiSeq	287

- Gene expression
n=1,045
- DNA copy number
n=1,084
- DNA methylation
n=932
- Somatic mutation
n=804

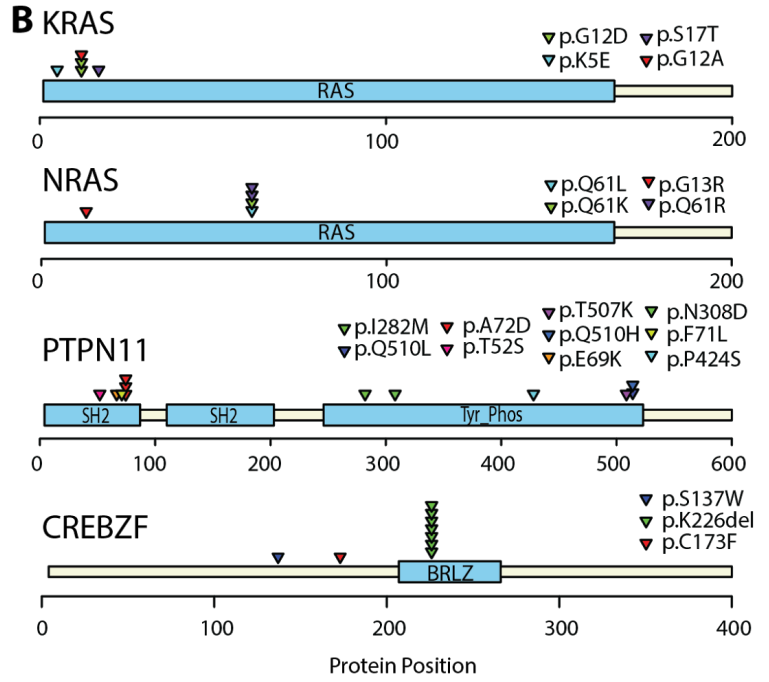
Genomic Landscape

- ★ GISTIC found 57 disjoint amplification and 105 deletion regions (N=1084)
- ★ MutSig found 100 genes; 30 of which were previously reported (Brennan et al. Cell 2013; LGG Marker paper, NEJM 2015).
- ★ Usual Suspects: IDH1, TP53, ATRX, EGFR, PTEN, PIK3CA, PIK3R1, NF1

Novel glioma driving oncogenes



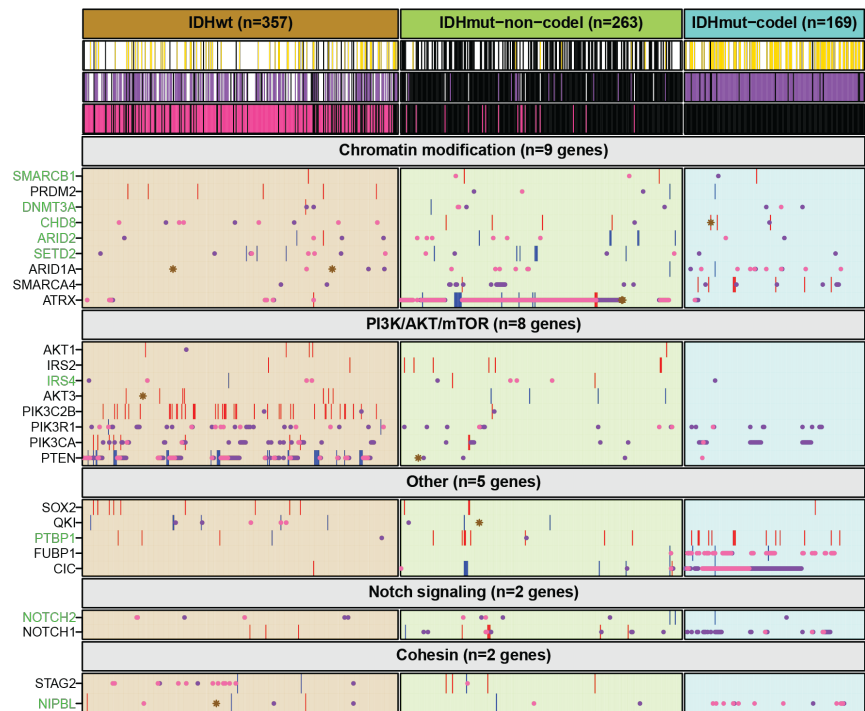
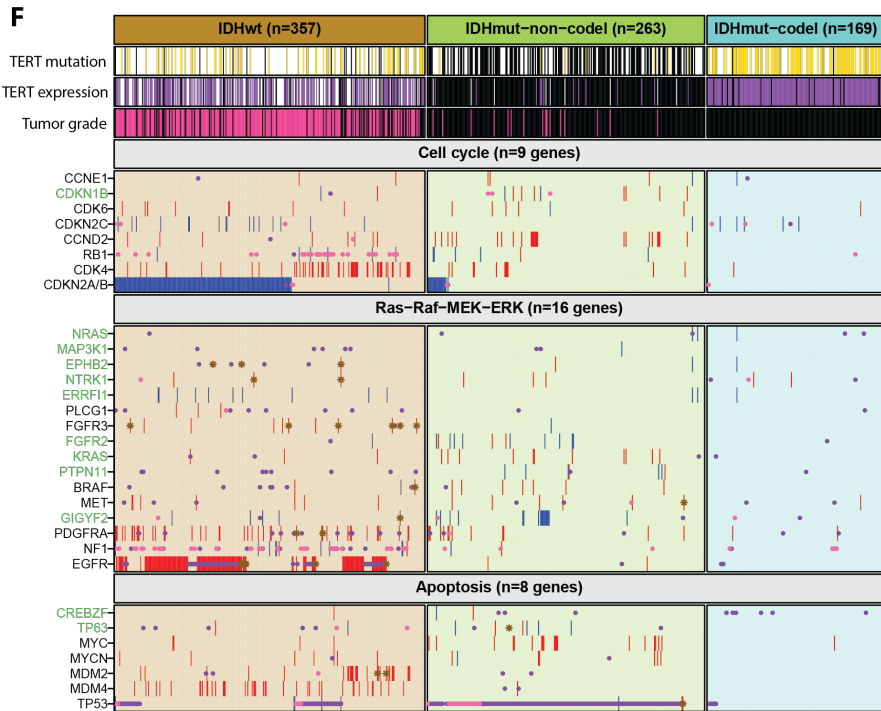
Possible oncogene
Possible tumor suppressor gene



F. Barthel, MD. Anderson

This distinction is based on evidence in literature and patterns of mutation.

Genomic Landscape of Gliomas by Pathways



Alterations

- Gain
- Loss
- SNV/In-frame indel
- Truncating mutation
- * Fusion

Alteration frequency

- Mutation
- Gain
- Loss
- Fusion

TERT mutation

- Mutant
- Wild-type

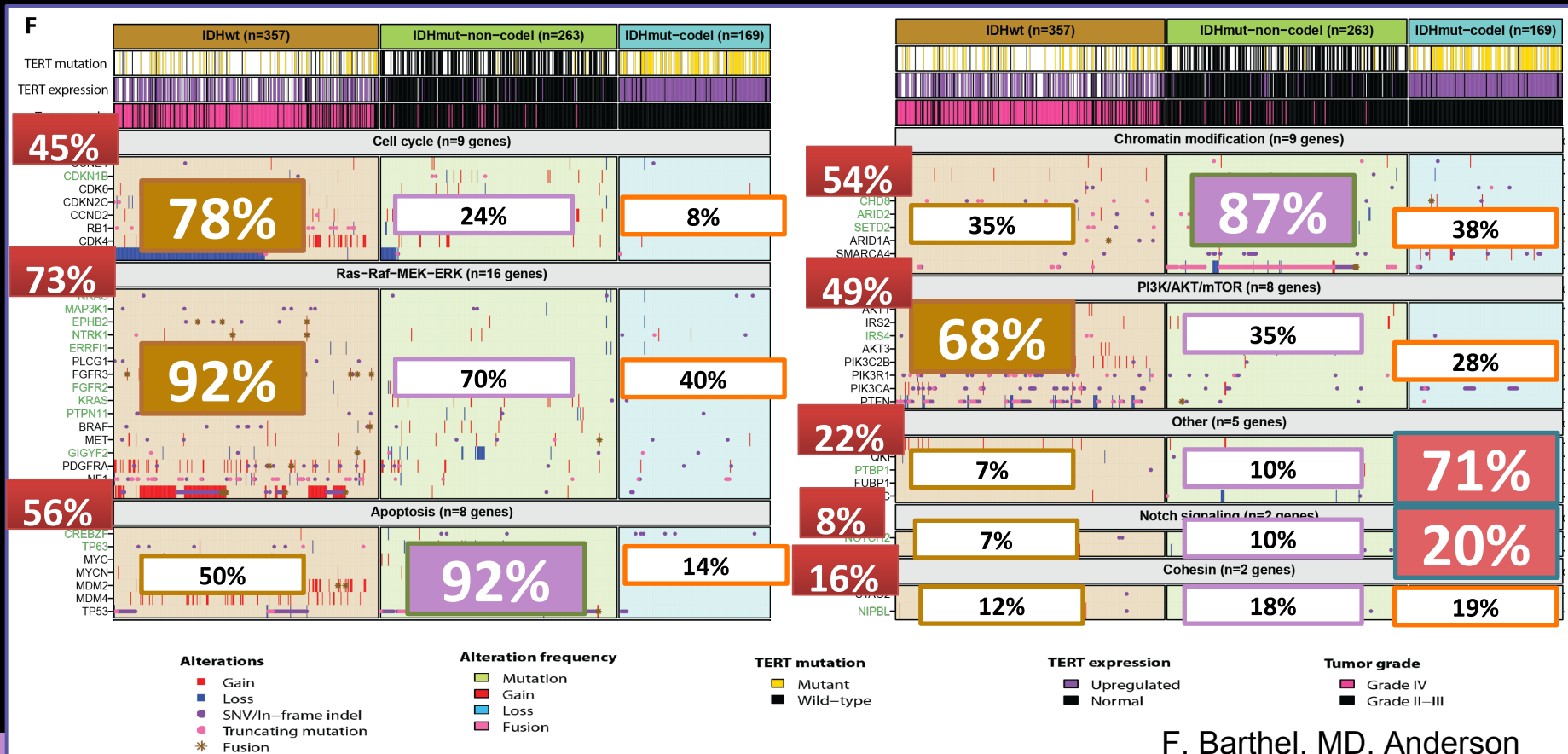
TERT expression

- Upregulated
- Normal

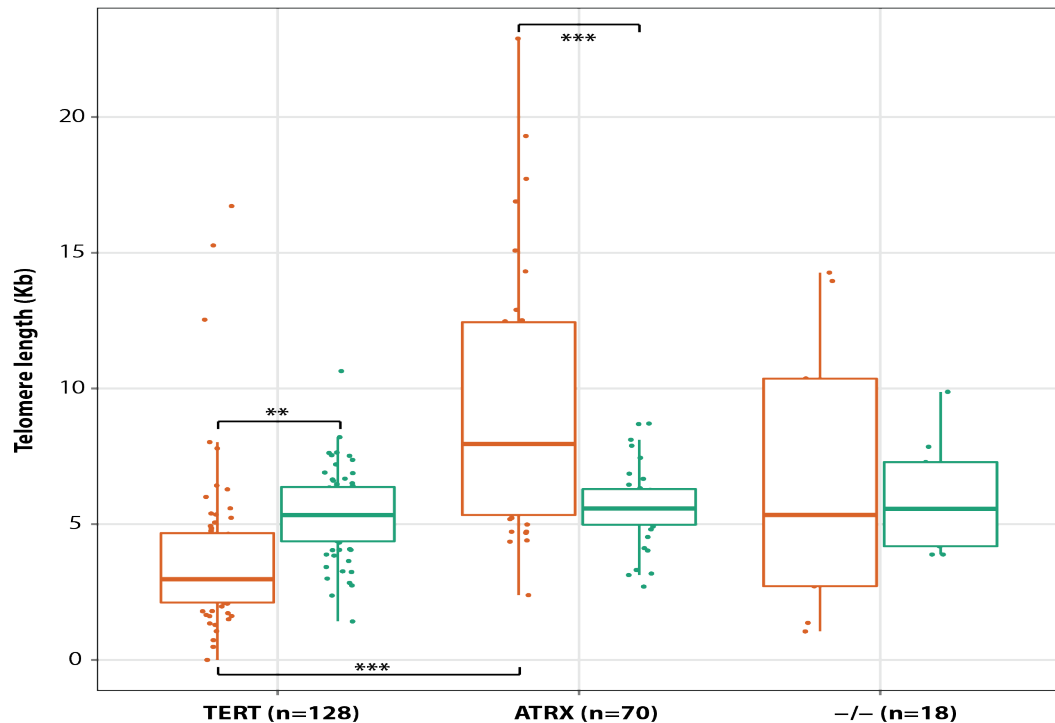
Tumor grade

- Grade IV
- Grade II-III

Genomic Landscape of Gliomas by Pathways



ATRX mutant tumor samples show longer telomeres in tumor than TERT mutant tumor samples

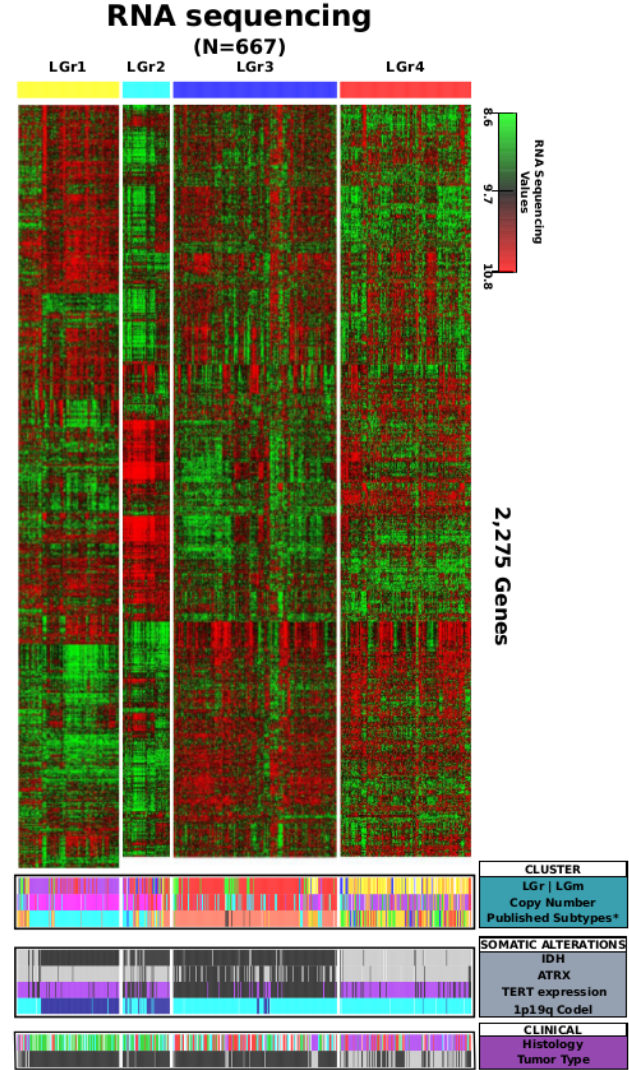


	Normal (Kb)	Tumor (Kb)
TERT	5.4 ± 1.6	3.8 ± 3.0
ATRX	5.6 ± 1.5	9.4 ± 4.9
-/-	5.8 ± 2.0	6.9 ± 4.9

*** P < 0.0001

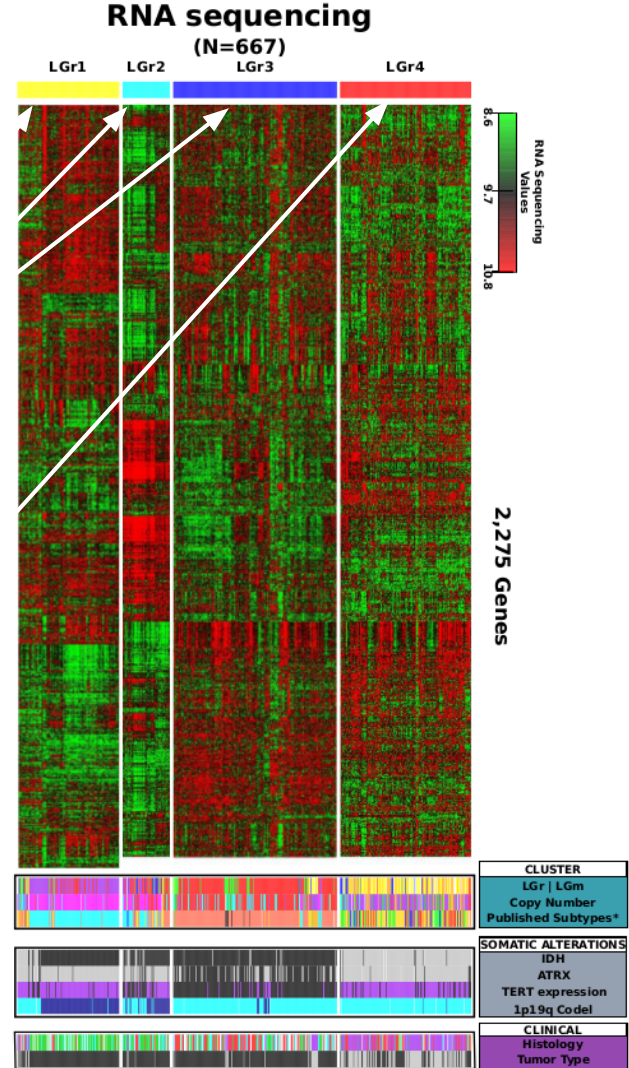
** P < 0.001

RNA sequencing Cluster reveals 4 distinct clusters



RNA sequencing Cluster reveals 4 distinct clusters

- LGr1-3 dominated by IDHmut
- LGr4 dominated by IDHwt

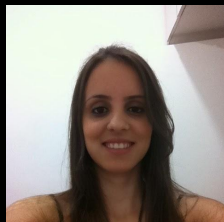


DNA methylation reveals 2 macro groups with 3 clusters per group

Tumor Type	LGm1	LGm2	LGm3	LGm4	LGm5	LGm6
GBM	18	11	4	128	205	50
LGG	45	253	123	23	45	27

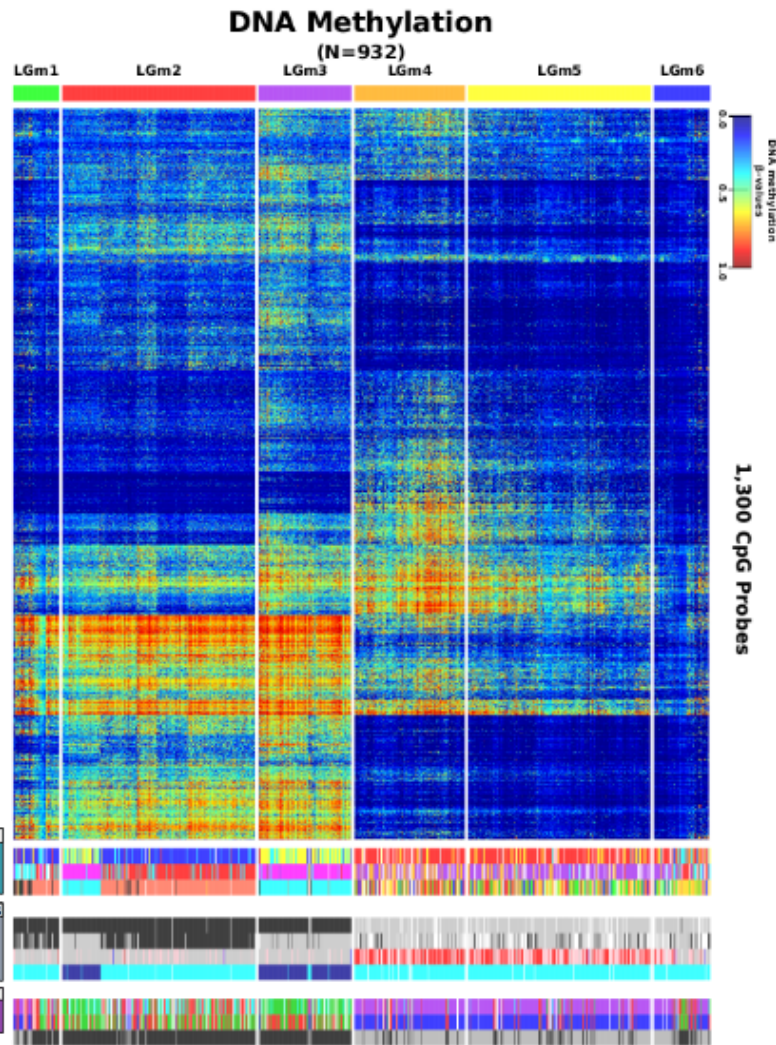
IDHmut

IDHwt



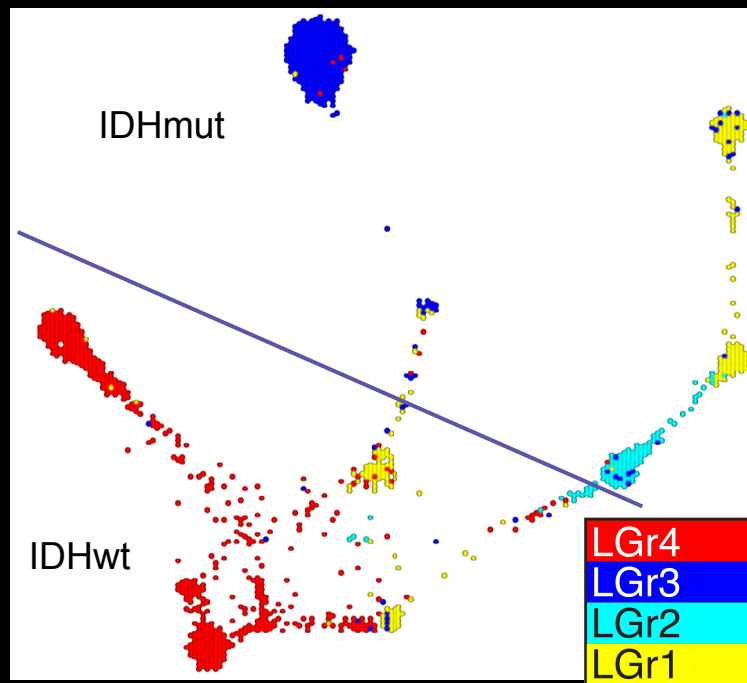
Thais Sabedot, USP

CLUSTER
LGm LGm
Copy Number
Published Subtypes*
SOMATIC ALTERATIONS
IDH
ATRX
TERT expression
3p19q Code1
CLINICAL
Histology
Tumor Type

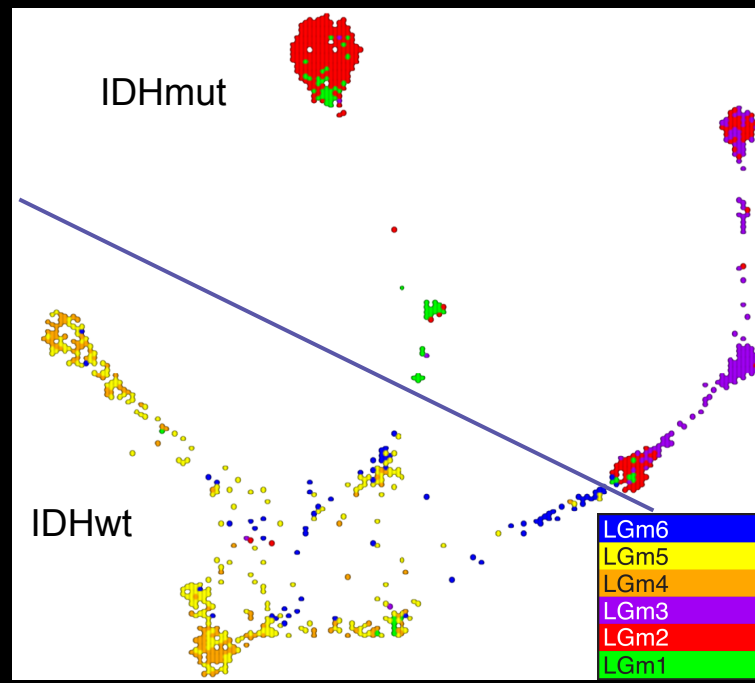


Tumor Map (exp+dna methylation)

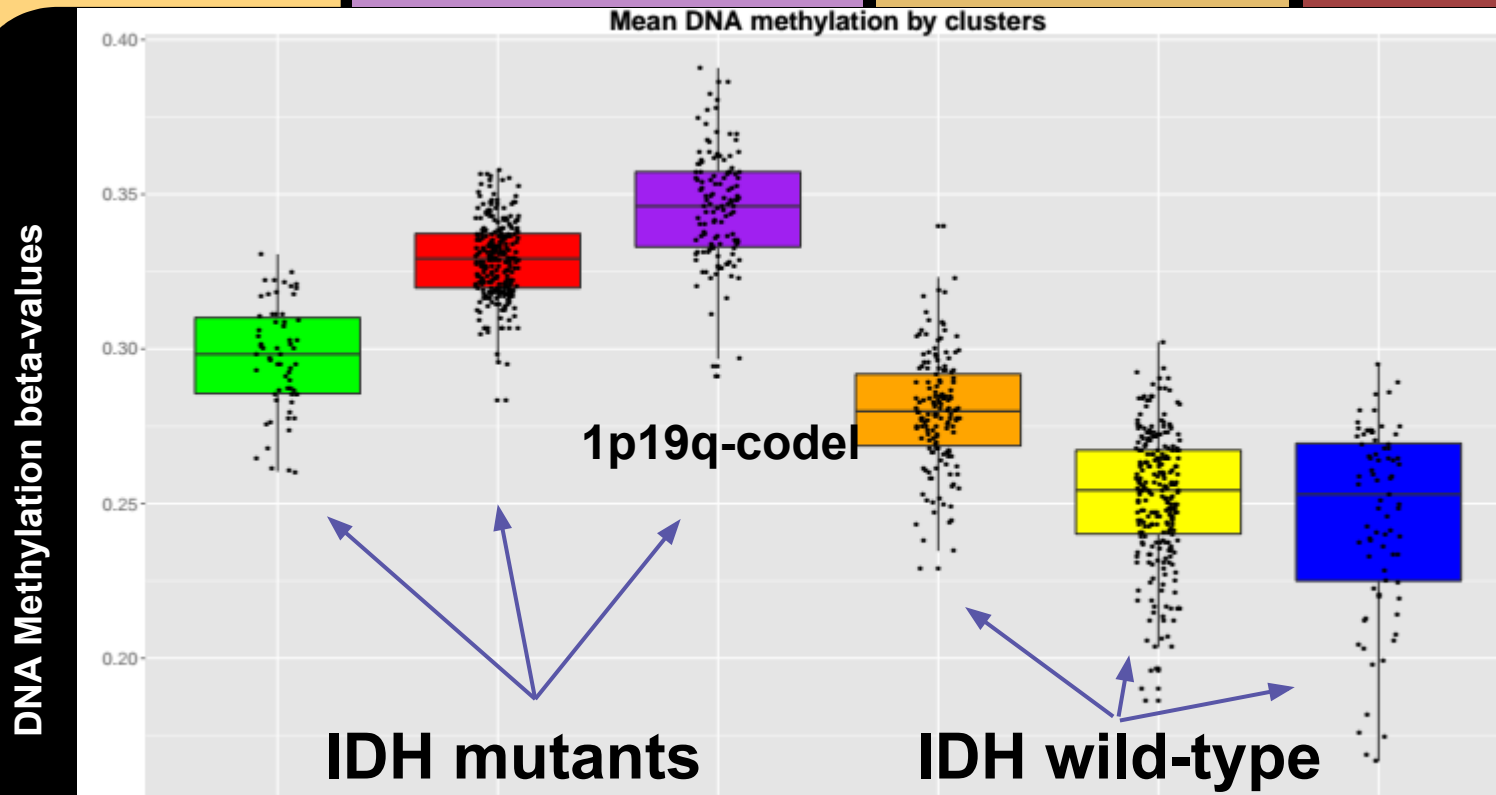
Expression



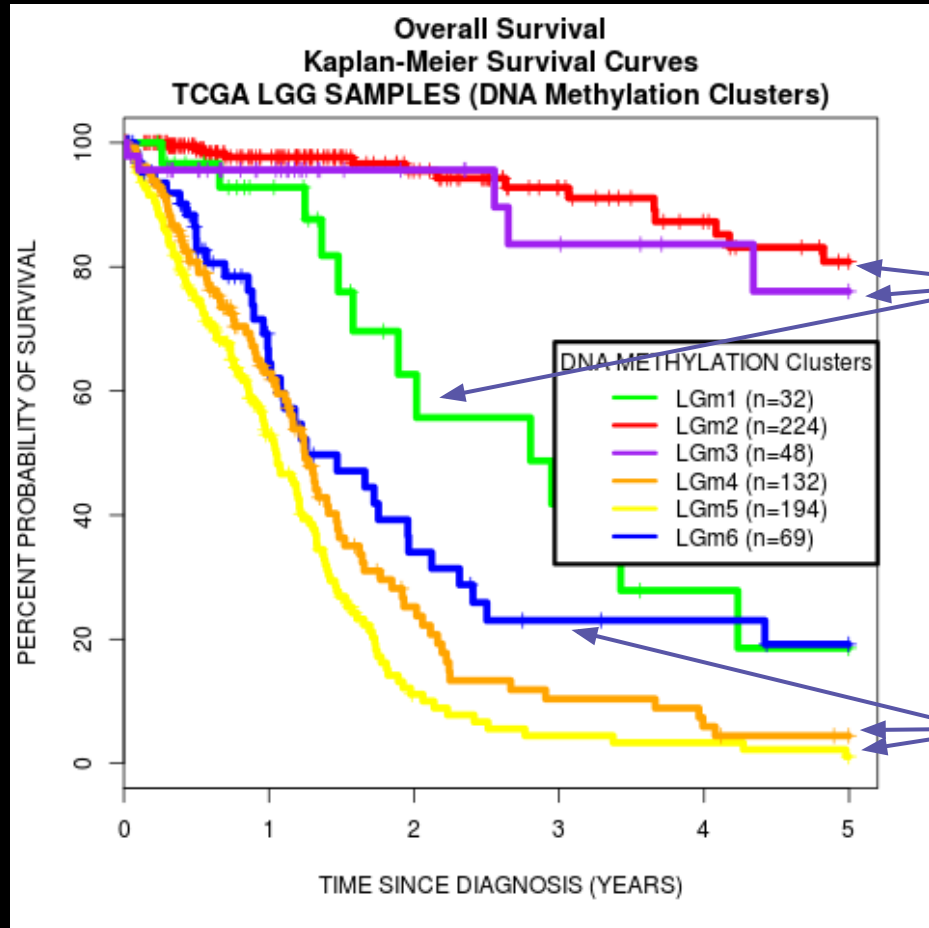
DNA methylation



DNA methylation profiles across IDH status



Kaplan-Meier Survival Curves separated by IDH status



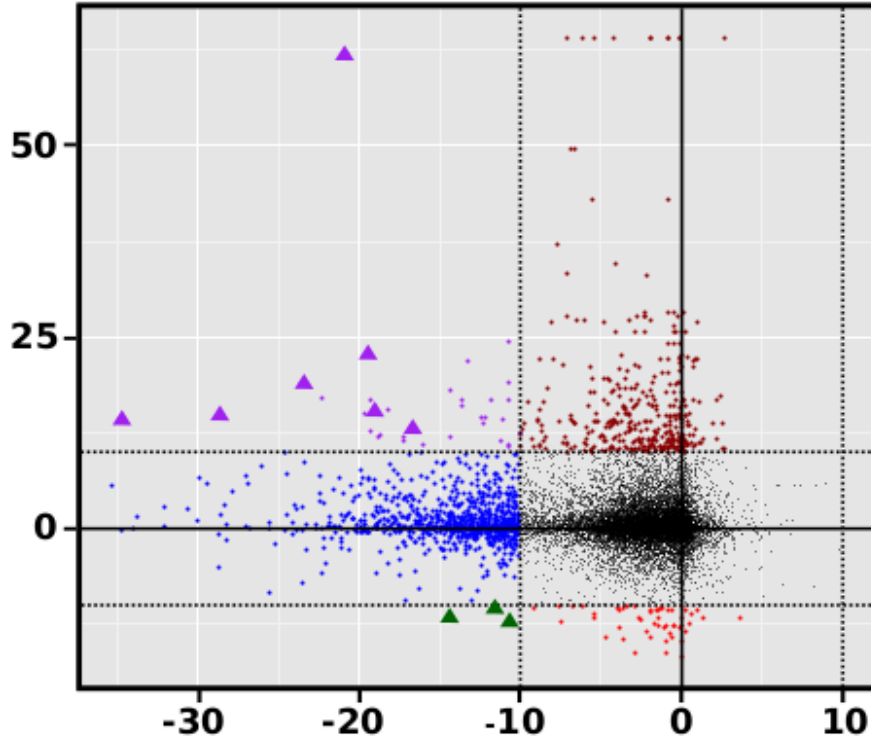
**B**

Starburst plot

LGM1 non-codons vs. LGM2 non-codons

Gene Expression

Fold Change < 0 , $\text{Log}_{10}(\text{FDR-corrected p value})$
Fold Change ≥ 0 , $-\text{Log}_{10}(\text{FDR-corrected p value})$



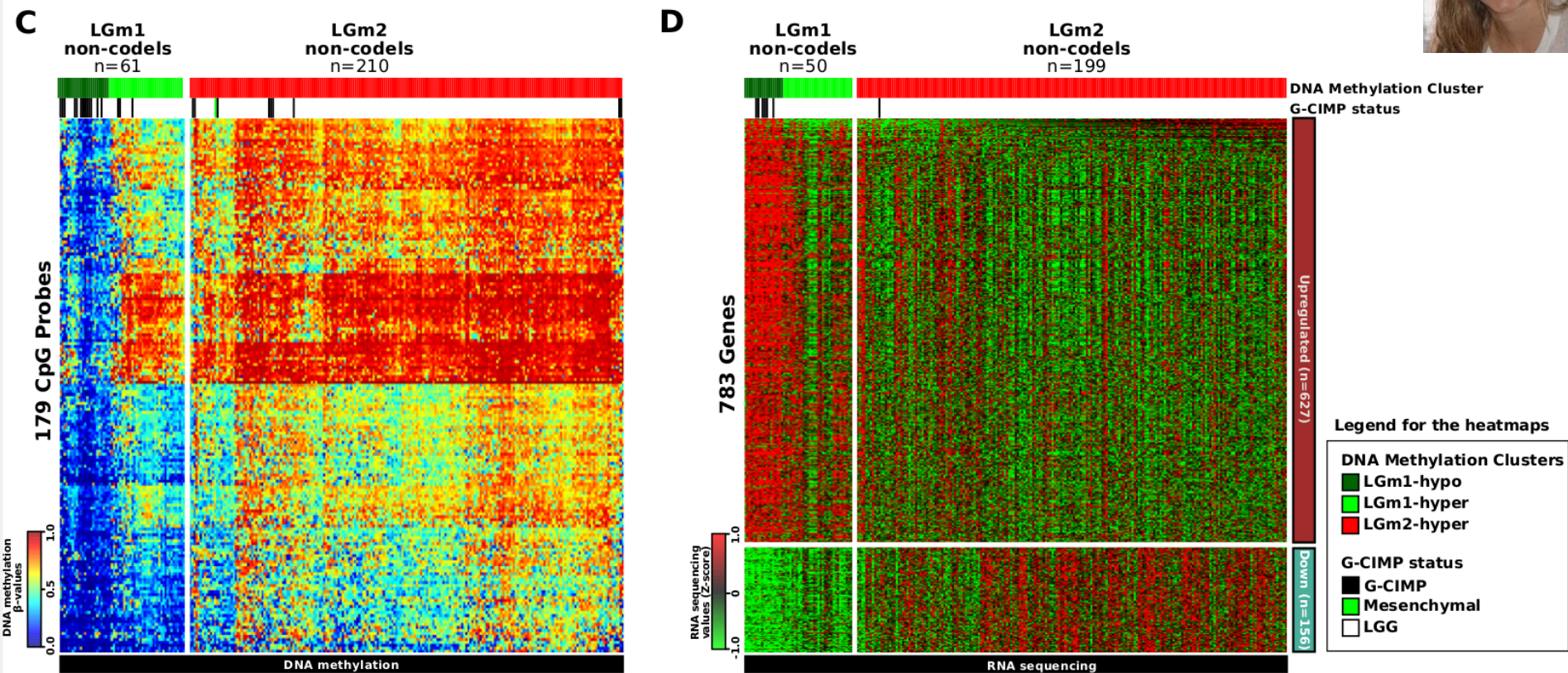
DNA Methylation

$\beta\text{-value} < 0$, $\text{Log}_{10}(\text{FDR-corrected p value})$
 $\beta\text{-value} \geq 0$, $-\text{Log}_{10}(\text{FDR-corrected p value})$

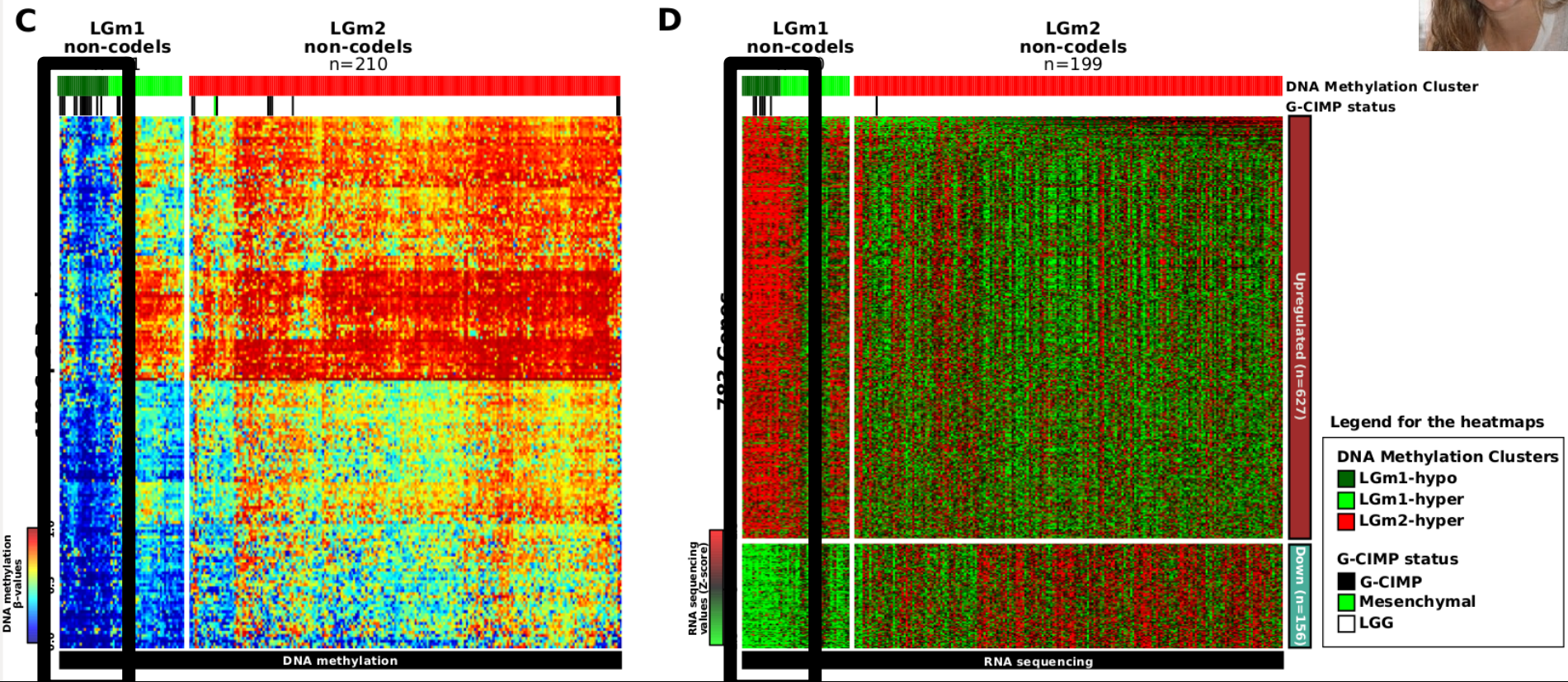
Relation to LGM1

- ▲ Up & Hypo & $\text{Diff}(\beta\text{-values}) < -0.25$
- Up & Hypo
- ▲ Down & Hypo
- Hypomethylated
- Upregulated
- Downregulated
- Not significant
- $\text{FDR} = 10^{-10}$

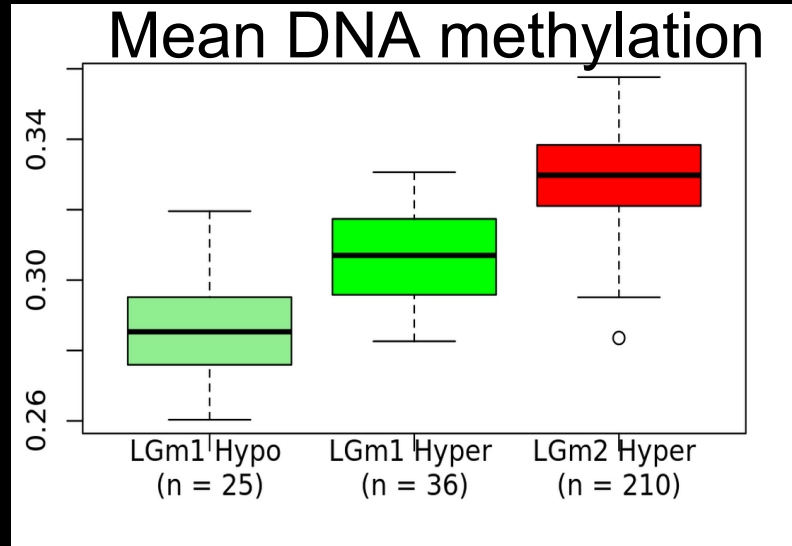
Two subgroups of LGm1



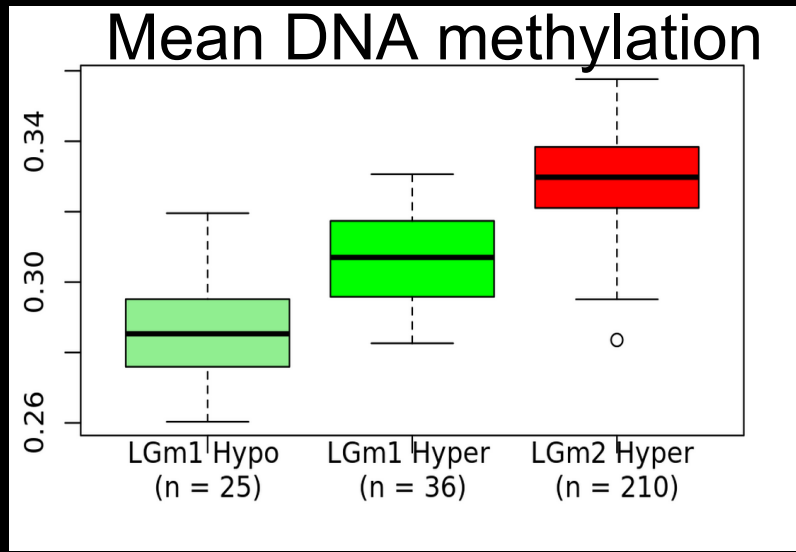
Two subgroups of LGm1



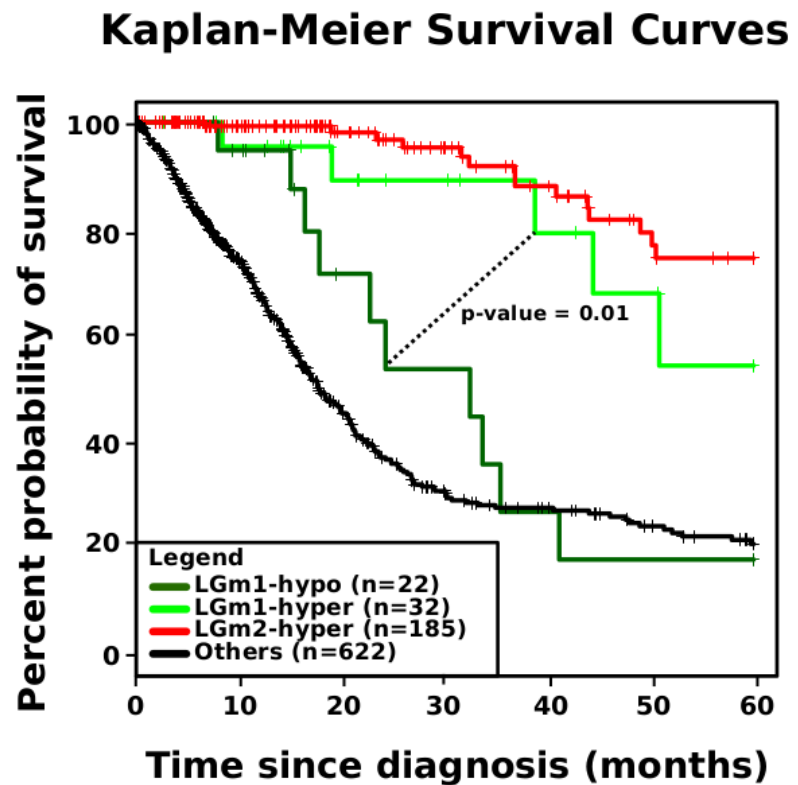
Distinct Epigenome and Survival



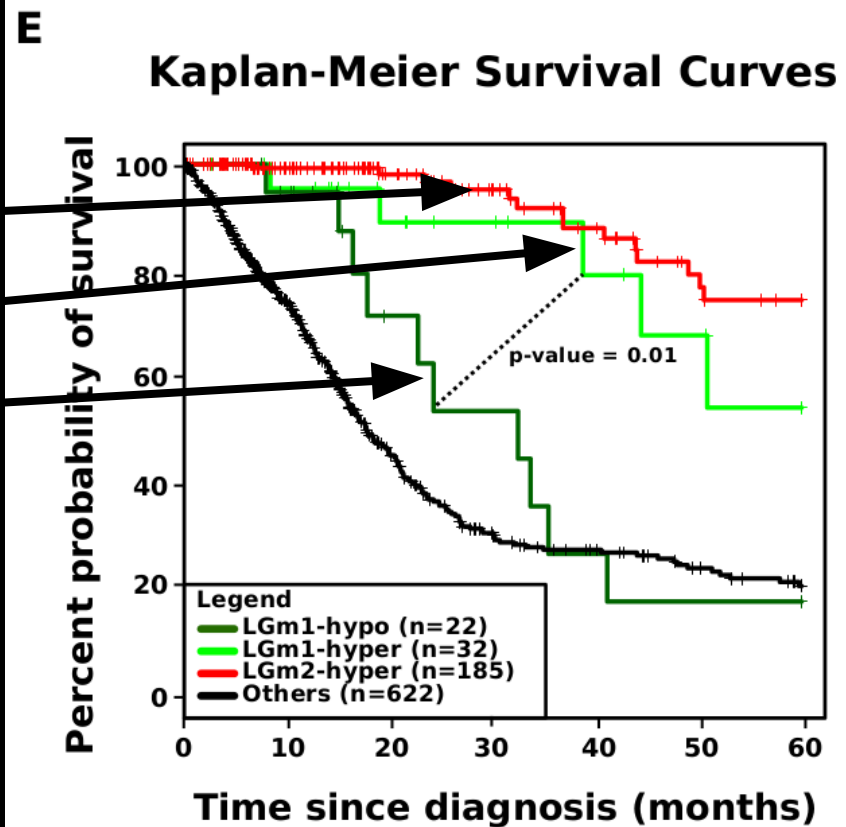
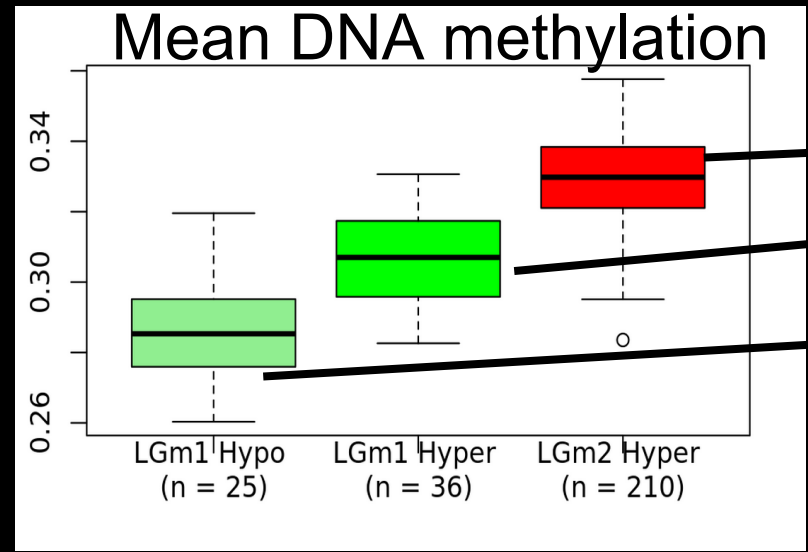
Distinct Epigenome and Survival



E



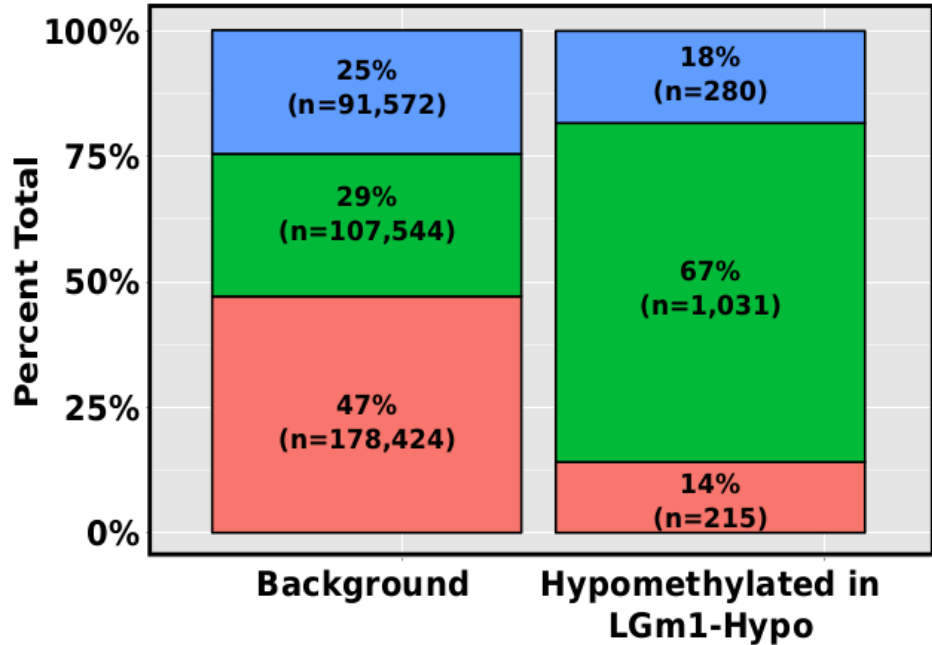
Distinct Epigenome and Survival



Genomic Signatures Defines Subtype

F

LGm1-Hypo Differentially Methylated
CpG Probes across known genomic features



CpG Island (Irizarry's HMM)

Open Sea

Shores (flanking CpG Island - 2000bp)

Enriched DNA Motif Analysis


p-value = 1e-6; 2.7 Fold


p-value = 1e-18; 1.7 Fold


p-value = 1e-9; 2.2 Fold

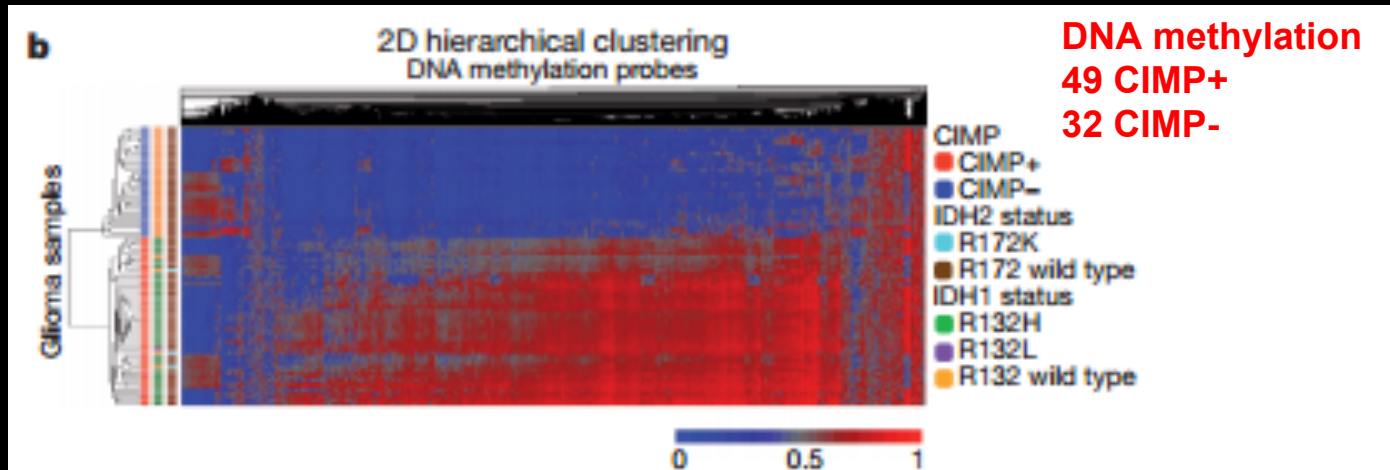
Non-TCGA Data - Validation

LETTER

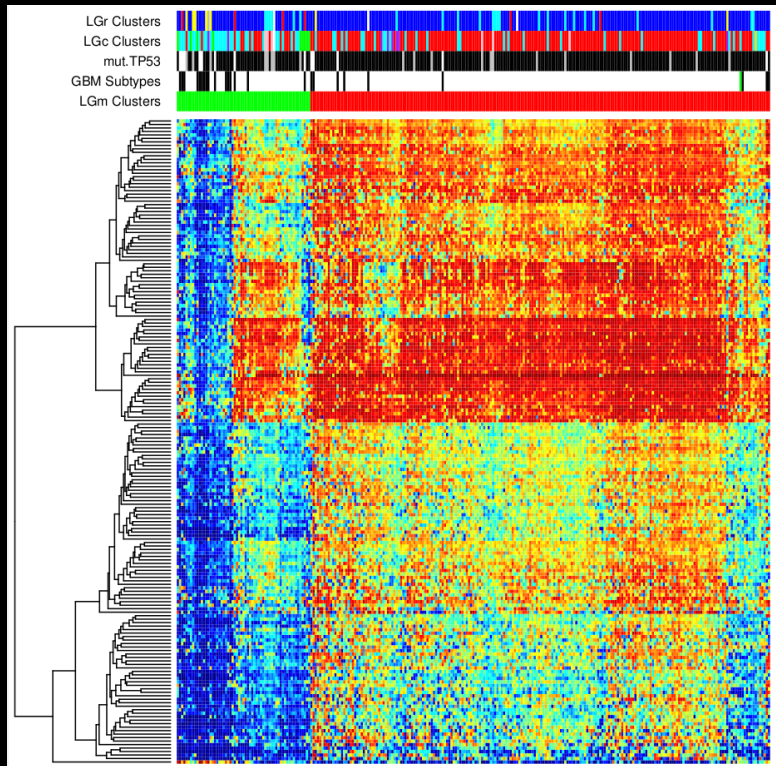
doi:10.1038/nature10866

IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype

Sevin Turcan^{1*}, Daniel Rohle^{1,2*}, Anuj Goenka^{1,3*}, Logan A. Walsh¹, Fang Fang¹, Emrullah Yilmaz¹, Carl Campos¹, Armida W. M. Fabius¹, Chao Lu^{4,5}, Patrick S. Ward^{4,5}, Craig B. Thompson⁴, Andrew Kaufman¹, Olga Guryanova¹, Ross Levine¹, Adriana Heguy¹, Agnes Viale⁶, Luc G. T. Morris^{1,7}, Jason T. Huse^{1,8}, Ingo K. Mellinghoff^{1,2,9,10} & Timothy A. Chan^{1,2,3,10}



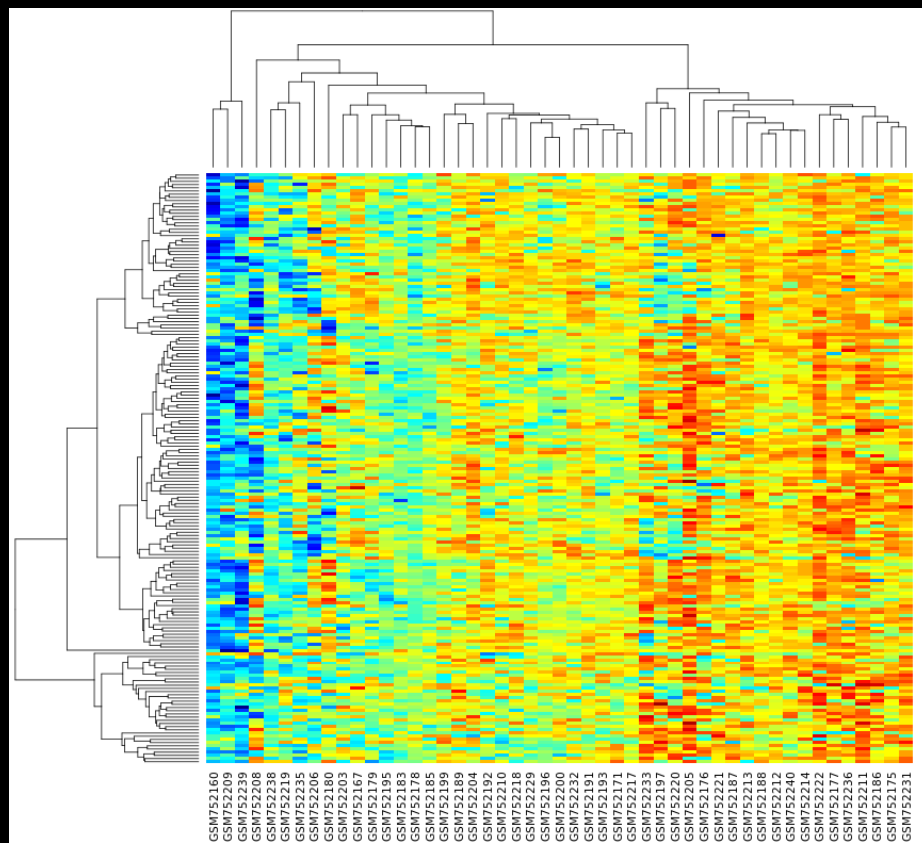
TCGA LGG+GBM AWG



LGm1 Hyper = 36
 LGm2 Hyper = 210
 LGm1 Hypo = 25

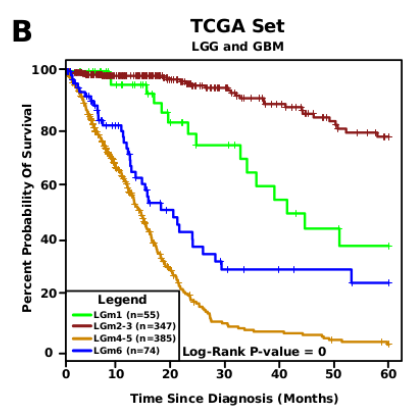
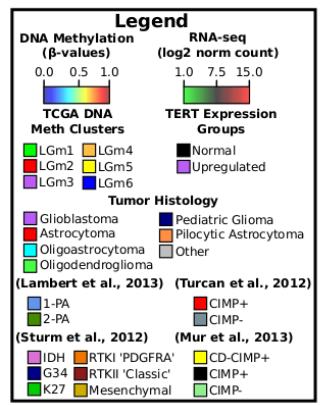
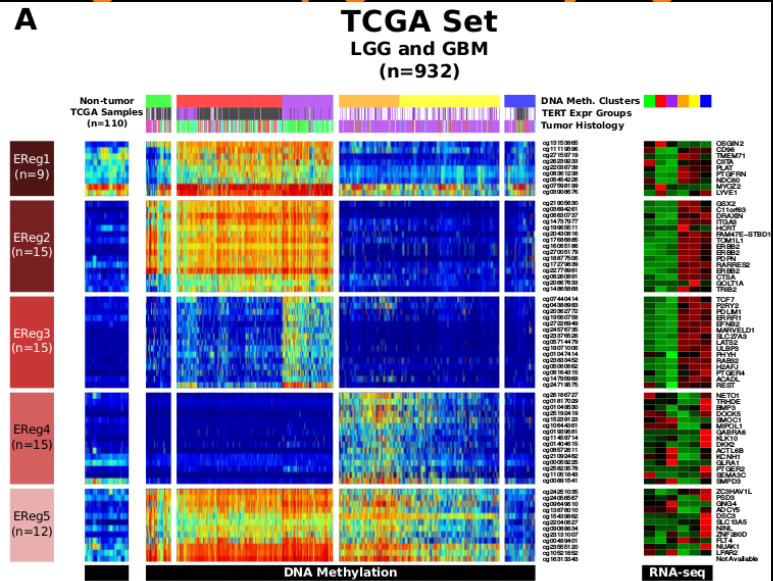
LGm1+2+3 = 454
 25 out of 454 are hypomethylated (5.5%)

Turcan et al. 2012 - Infinium 450K probe



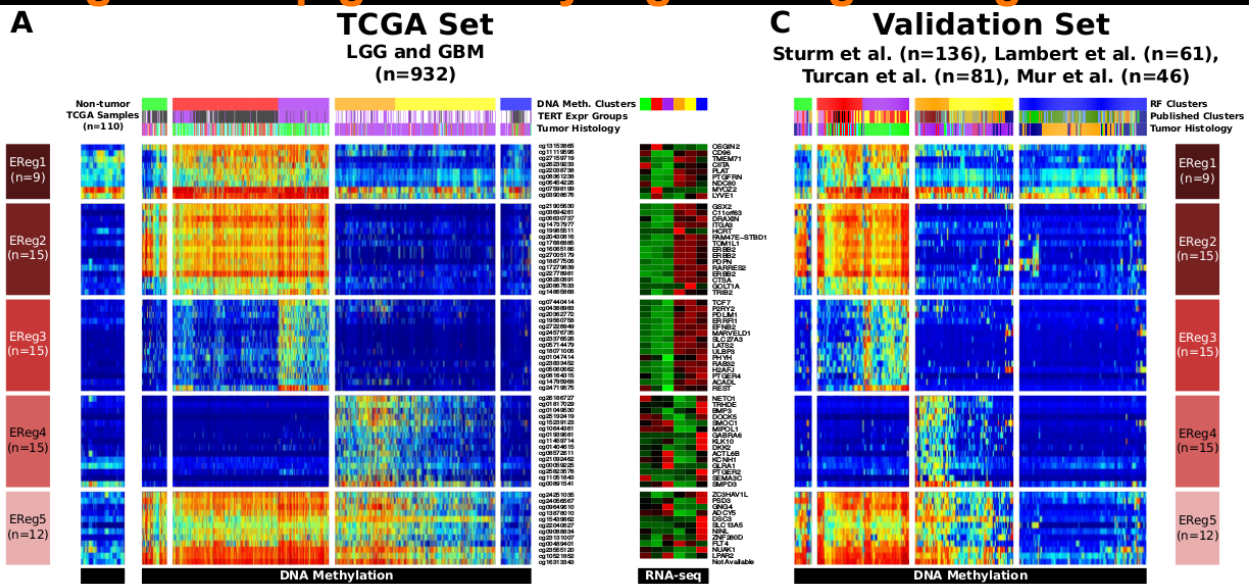
3 out of 49 are hypomethylated (6%)

Prognostic epigenetically regulated gene signatures



Thais Sabedot, USP

Prognostic epigenetically regulated gene signatures

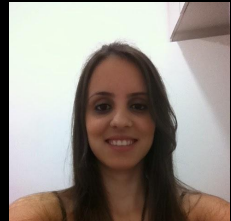
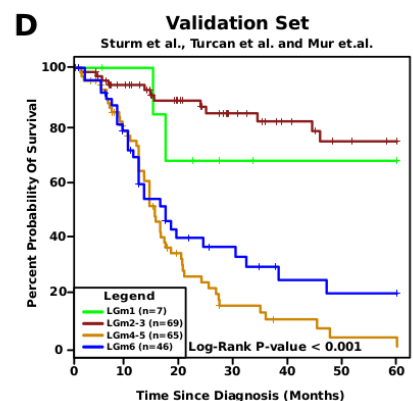
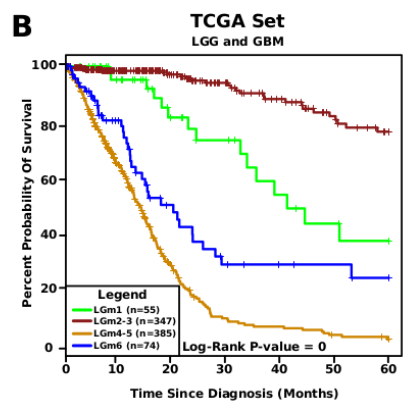
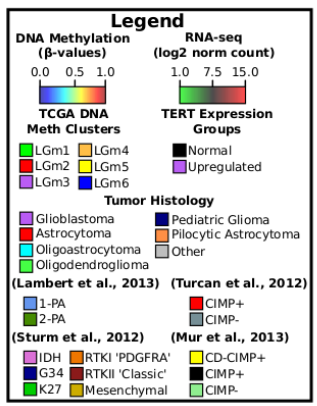


Sturm, 2012
a 136 GBM
(59 pediatric; 77 adult)

Lambert, 2013
61 Pilocytic astrocytoma

Turcan, 2012
81 LGG

Mur, 2013
46 oligodendroglial tumors



Thais Sabedot, USP

Summary

- ★ We identified several novel genes that likely contribute to gliomagenesis
- ★ We showed that mutations in TERT and ATRX have an impact on telomere length
- ★ We identified molecularly tumor subtypes that defy traditional histology
- ★ We identified epigenetically regulated genes that can predict patient outcome

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TCGA LGG/GBM AWG

