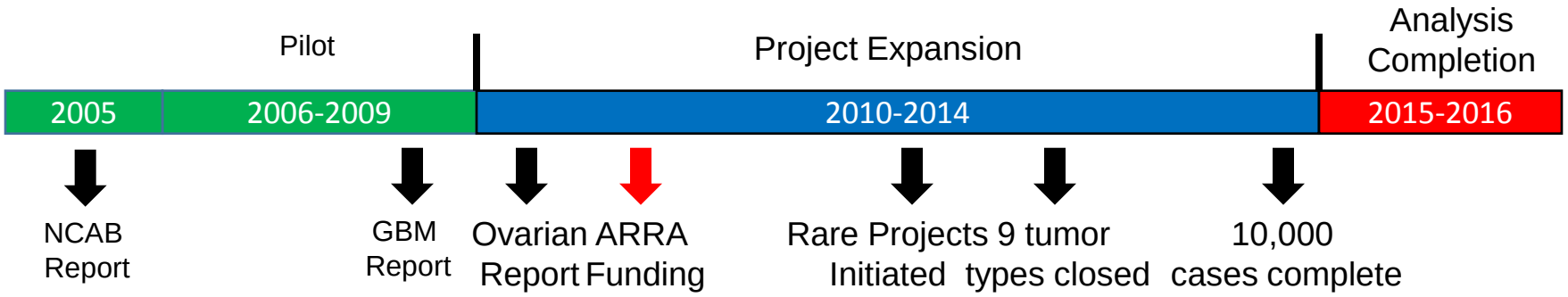
TCGA analysis of glioblastoma

Kenneth Aldape

- GBM as the test-case an initial entry for TCGA and initial description of first cohort of TCGA samples
- Some comments on expression profiling and transcriptomal subtypes in GBM
- Integrated analyses and thoughts on present and future approaches towards understanding diffuse gliomas

TCGA timeline
GBM was initial entry



- **Pilot Project: GBM ~500 cases**
  - Establish infrastructure for effective team science
  - Develop a scalable "pipeline"
  - Demonstrate the feasibility of a large-scale, high throughput approach to identifying the molecular 'parts-list'
  - Make the data publicly and broadly available to the cancer community while protecting patient privacy

TCGA analytic mandate:
No Platform Left Behind

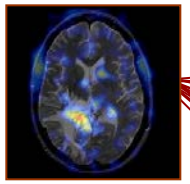
~25* forms of cancer

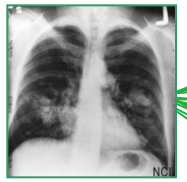
glioblastoma

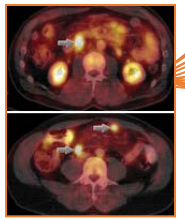
squamous carcinoma (lung)

Serous cystadenocarcinoma (ovarian)

etc. etc. etc.







Biospecimen Core Resource with more than 150 Tissue Source Sites

6 Cancer Genomic Characterization Centers

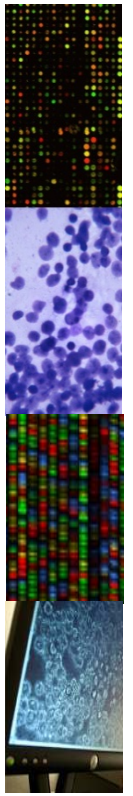
3 Genome Sequencing Centers

7 Genome Data Analysis Centers

Data Coordinating Center

Multiple data types

- Clinical diagnosis
- Treatment history
- Histologic diagnosis
- Pathologic report/images
- Tissue anatomic site
- Surgical history
- Gene expression/RNA sequence
- Chromosomal copy number
- Loss of heterozygosity
- Methylation patterns
- miRNA expression
- DNA sequence
- RPPA (protein)
- Subset for Mass Spec



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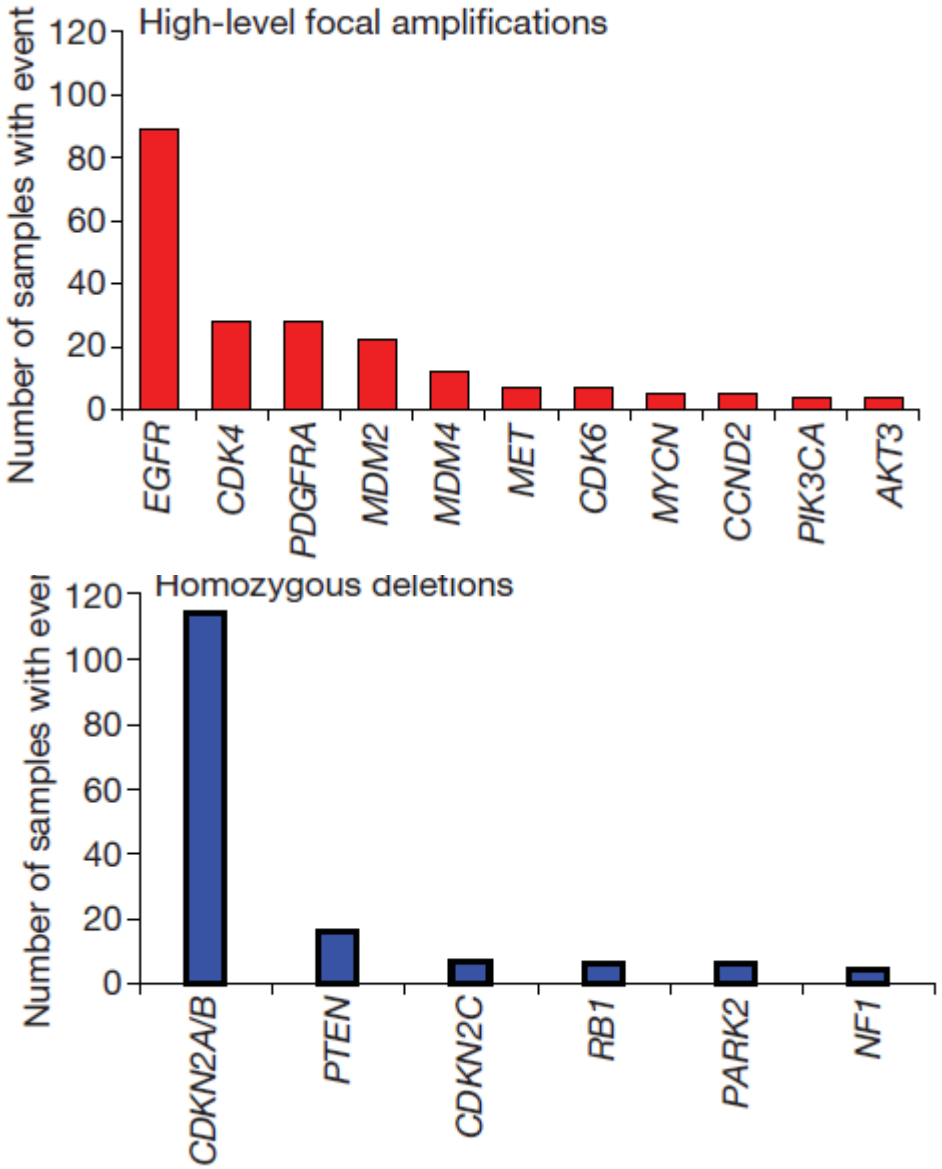
ARTICLES

Comprehensive genomic characterization defines human glioblastoma genes and core pathways

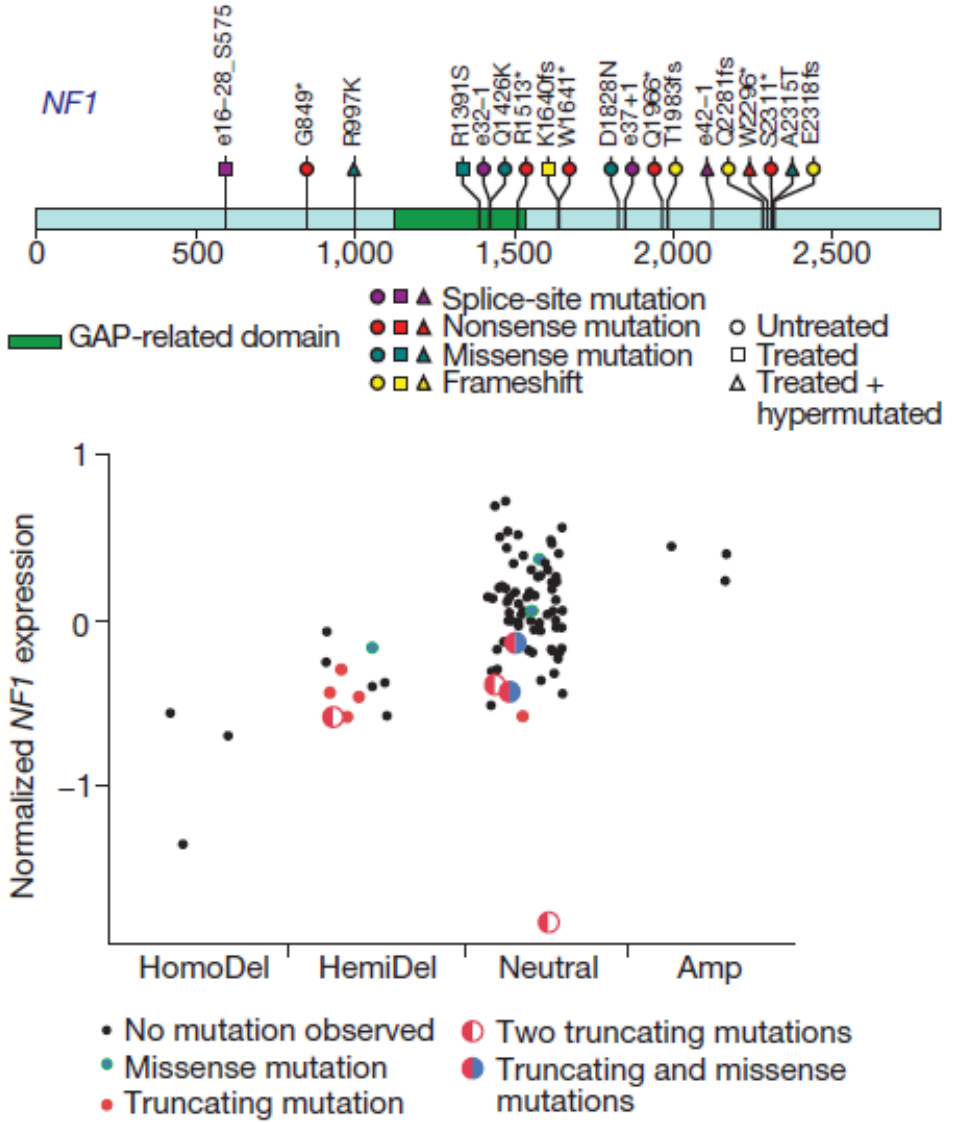
The Cancer Genome Atlas Research Network*

- Initial TCGA paper
- Catalogued known and previously described alterations
- Some novel findings (e.g. somatic NF1 mutations)
- Provided a resource for the neuro-oncology community
- Proof-of-principle/successful implementation of TCGA project

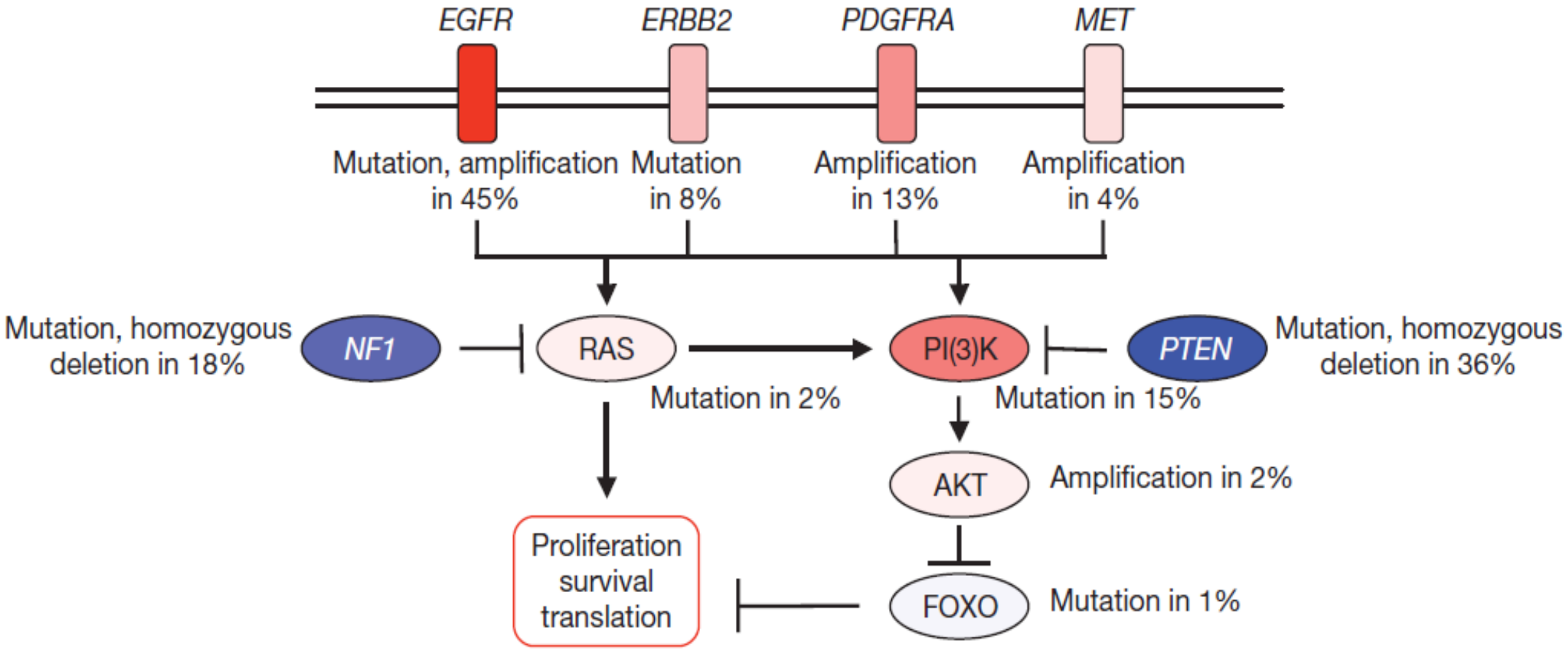
Amplifications and homozygous deletions



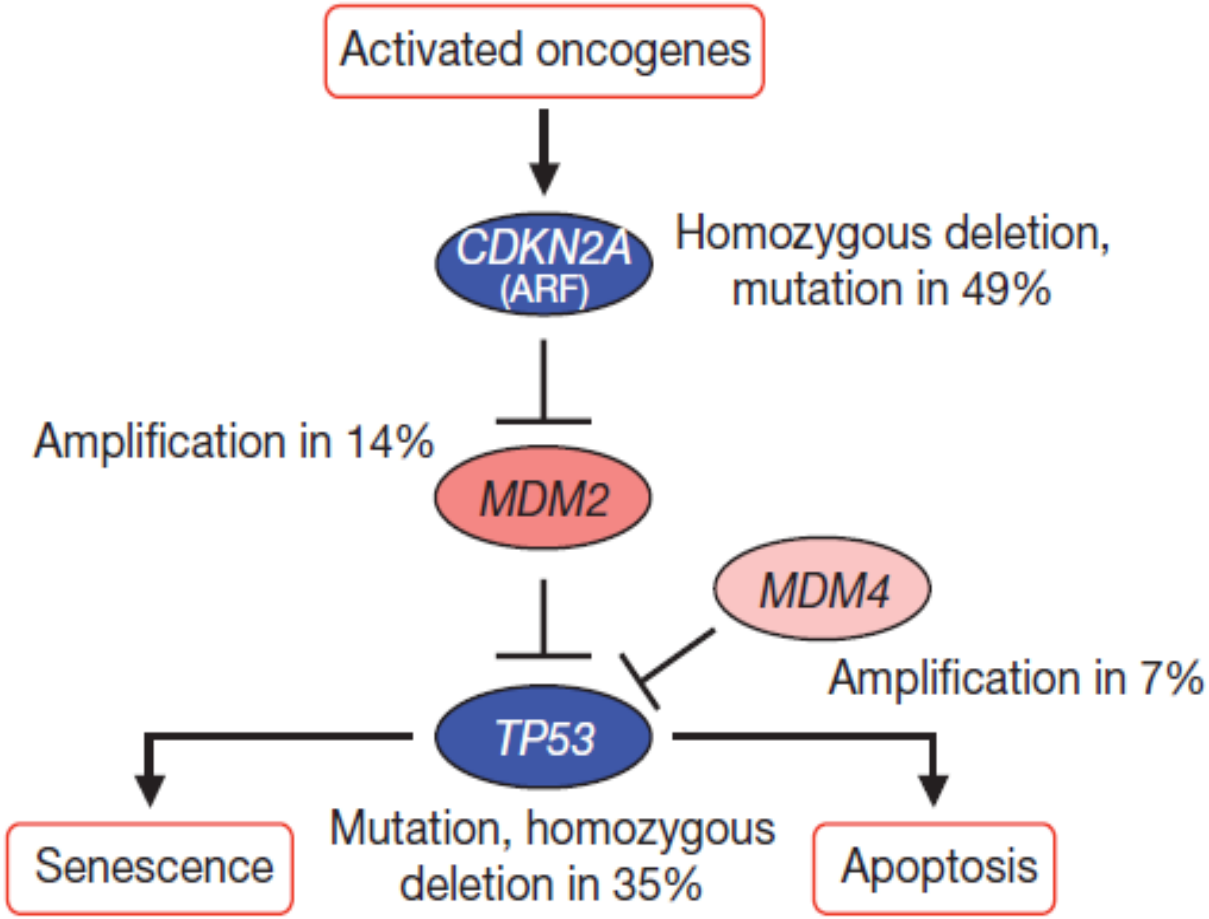
NF1 inactivation in GBM



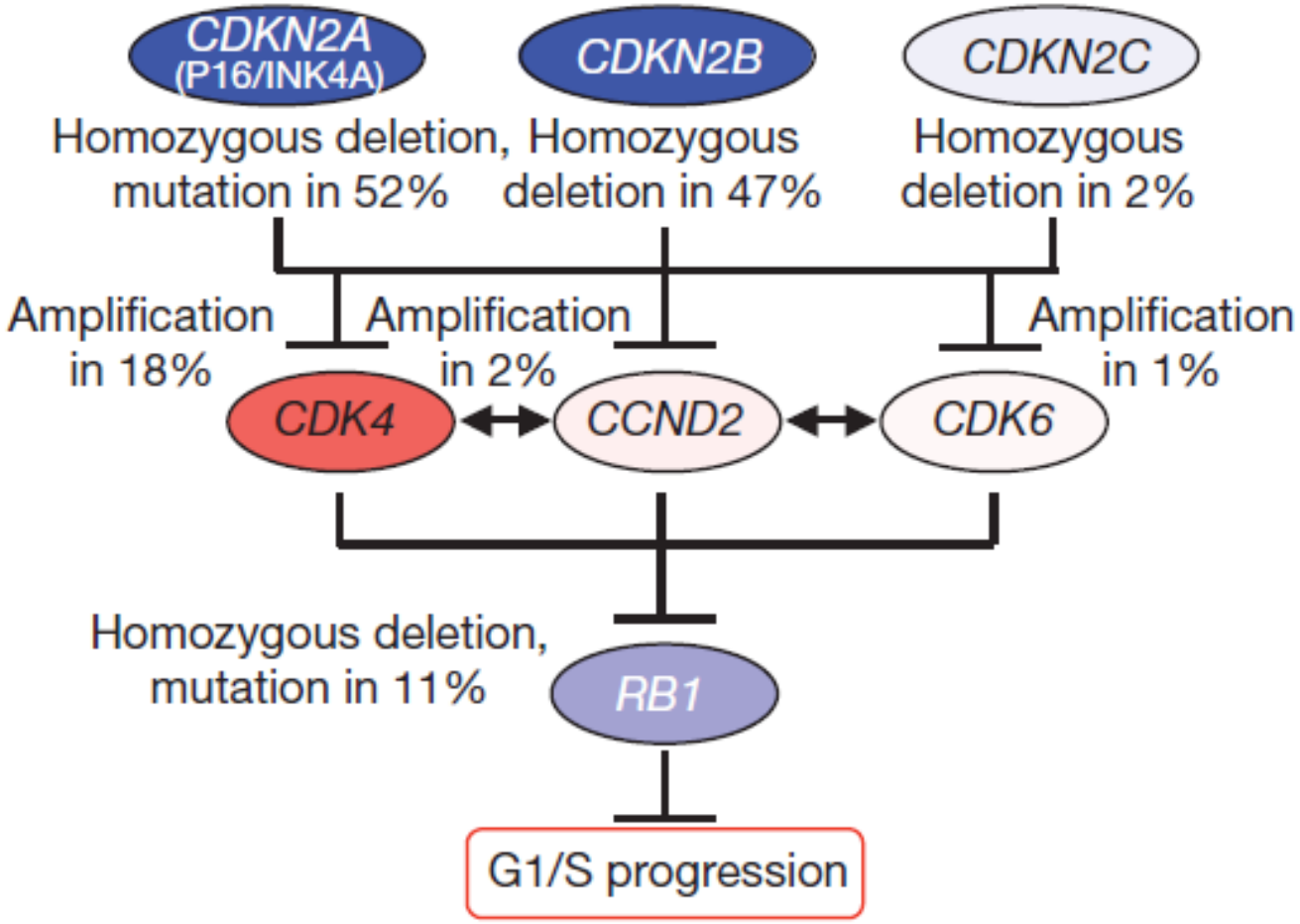
Genomic alteration present predicted to cause aberrant RTK/Ras signaling in 88% of cases



Altered p53 pathway in signaling in 87% of cases



Altered RB pathway in signaling in 78% of cases



An Integrated Genomic Analysis of Human Glioblastoma Multiforme

D. Williams Parsons,[1,2*] Siân Jones,[1*] Xiaosong Zhang,[1*] Jimmy Cheng-Ho Lin,[1*] Rebecca J. Leary,[1*] Philipp Angenendt,[1*] Parminder Mankoo,[3] Hannah Carter,[3] I-Mei Siu,[4] Gary L. Gallia,[4] Alessandro Olivi,[4] Roger McLendon,[5] B. Ahmed Rasheed,[5] Stephen Keir,[5] Tatiana Nikolskaya,[6] Yuri Nikolsky,[7] Dana A. Busam,[8] Hanna Tekleab,[8] Luis A. Diaz Jr.,[1] James Hartigan,[9] Doug R. Smith,[9] Robert L. Strausberg,[8] Suely Kazue Nagahashi Marie,[10] Sueli Mieko Oba Shinjo,[10] Hai Yan,[5] Gregory J. Riggins,[4] Darell D. Bigner,[5] Rachel Karchin,[3] Nick Papadopoulos,[1] Giovanni Parmigiani,[1] Bert Vogelstein,[1†] Victor E. Velculescu,[1†] Kenneth W. Kinzler[1†]

Gene	Point mutations*		Amplifications†		Homozygous deletions†		Fraction of tumors with any alteration (%)	Passenger probability‡
	No. of tumors	Fraction of tumors (%)	No. of tumors	Fraction of tumors (%)	No. of tumors	Fraction of tumors (%)		
CDKN2A	0/22	0	0/22	0	11/22	50	50	<0.01
TP53	37/105	35	0/22	0	1/22	5	40	<0.01
EGFR	15/105	14	5/22	23	0/22	0	37	<0.01
PTEN	27/105	26	0/22	0	1/22	5	30	<0.01
NF1	16/105	15	0/22	0	0/22	0	15	0.04
CDK4	0/22	0	3/22	14	0/22	0	14	<0.01
RB1	8/105	8	0/22	0	1/22	5	12	0.02
IDH1	12/105	11	0/22	0	0/22	0	11	<0.01
PIK3CA	10/105	10	0/22	0	0/22	0	10	0.10
PIK3R1	8/105	8	0/22	0	0/22	0	8	0.10

Cell

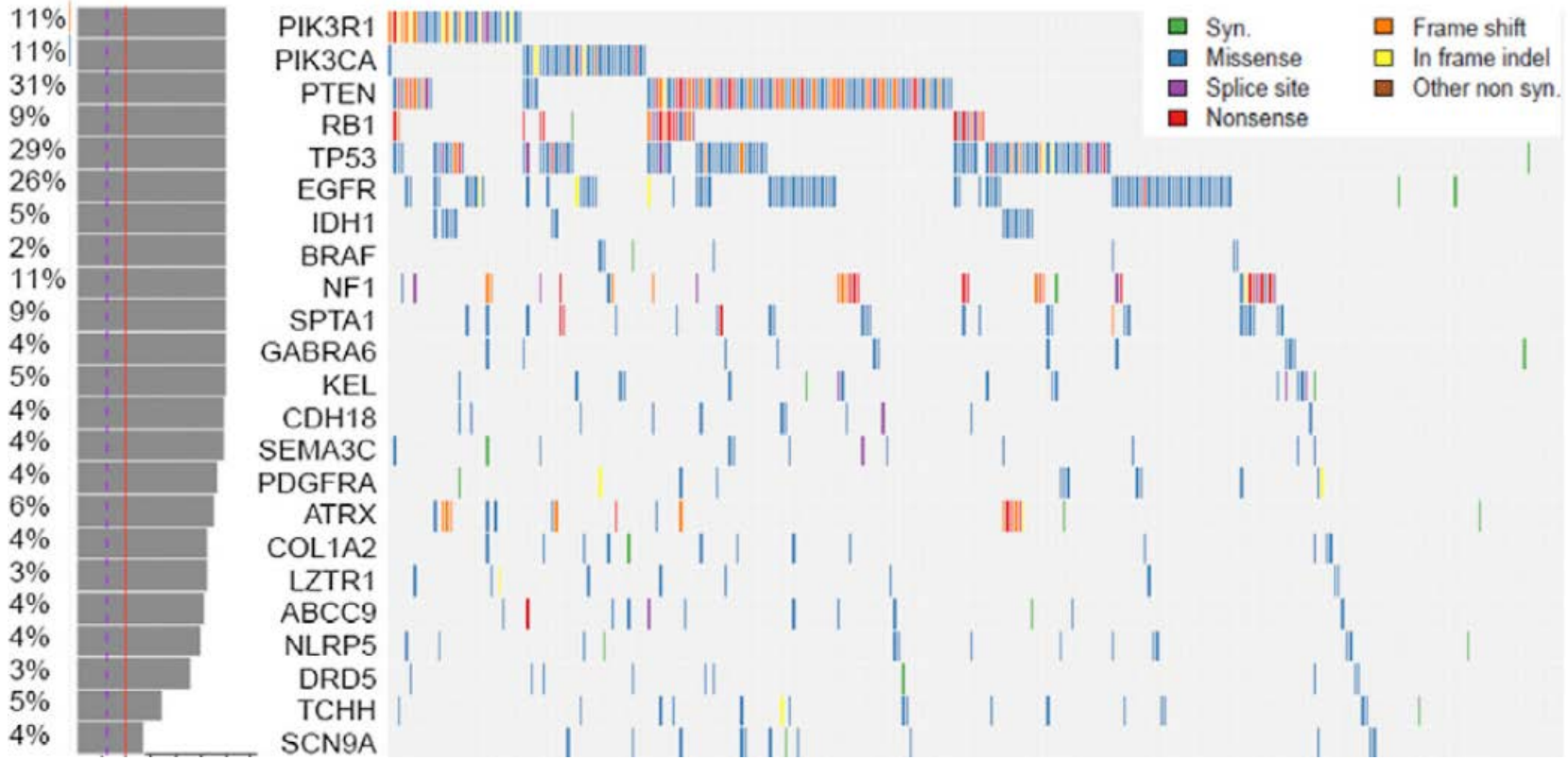
Resource

The Somatic Genomic Landscape of Glioblastoma

Cameron W. Brennan,[1,2,40,*] Roel G.W. Verhaak,[3,11,40] Aaron McKenna,[4,40] Benito Campos,[5,6] Houtan Noushmehr,[7,8] Sofie R. Salama,[9] Siyuan Zheng,[3] Debyani Chakravarty,[1] J. Zachary Sanborn,[9] Samuel H. Berman,[1] Rameen Beroukhim,[4,5] Brady Bernard,[10] Chang-Jiun Wu,[11] Giannicola Genovese,[11] Ilya Shmulevich,[10] Jill Barnholtz-Sloan,[12] Lihua Zou,[4] Rahulsimham Vegesna,[3] Sachet A. Shukla,[5] Giovanni Ciriello,[13] W.K. Yung,[14] Wei Zhang,[15] Carrie Sougnez,[4] Tom Mikkelsen,[16] Kenneth Aldape,[15] Darell D. Bigner,[17] Erwin G. Van Meir,[18] Michael Prados,[19] Andrew Sloan,[20] Keith L. Black,[21] Jennifer Eschbacher,[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,[30] Daniel J. Weisenberger,[7] 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,[13] John Weinstein,[3] Matthew Meyerson,[4,5] Stacey Gabriel,[4] Peter W. Laird,[7] David Haussler,[9,39] Gad Getz,[4] Lynda Chin,[4,11,*] and TCGA Research Network

- Identification of additional significantly mutated genes in GBM, including LZTR1, ATRX, KEL and QKI
- pattern of mutations, not attributable to chance, among genes implicated in regulation of chromatin modification.
- Additional changes the structure of the gene EGFR
- Characterization of rearrangements of chromosome 12 that contains the oncogenes MDM2 and CDK4;
- highly frequent point mutations in a non-coding region of the TERT gene.

The number of individual genes mutated at high frequency in GBM is small



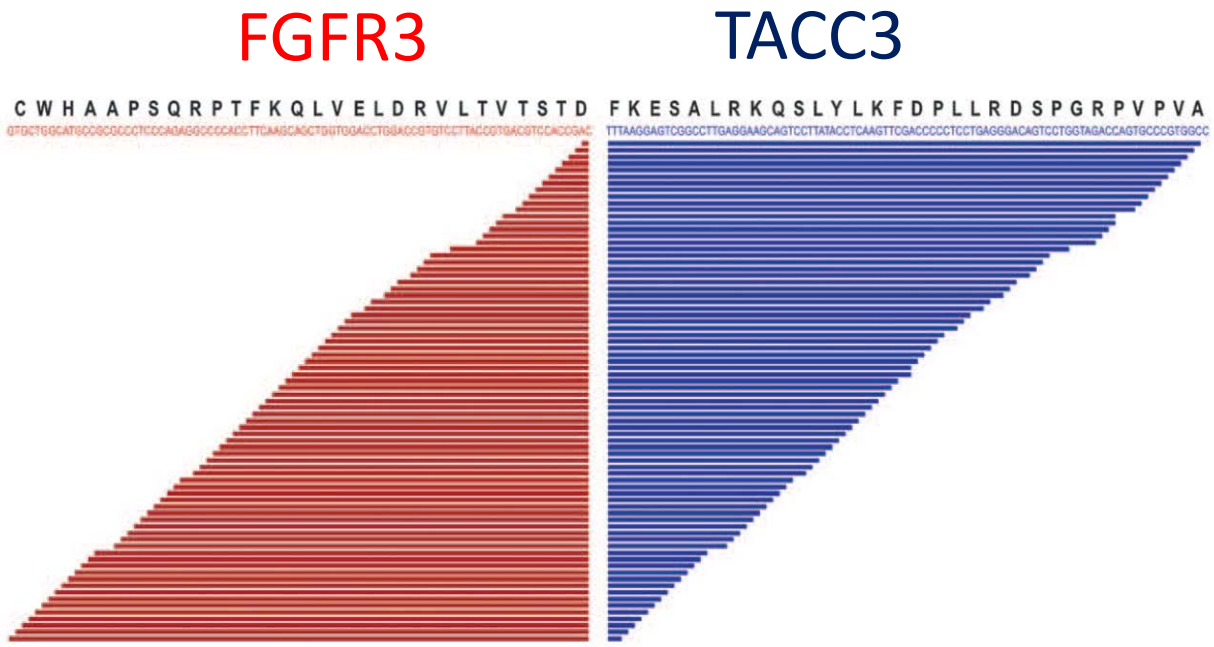
Mutual exclusivity of mutations in:

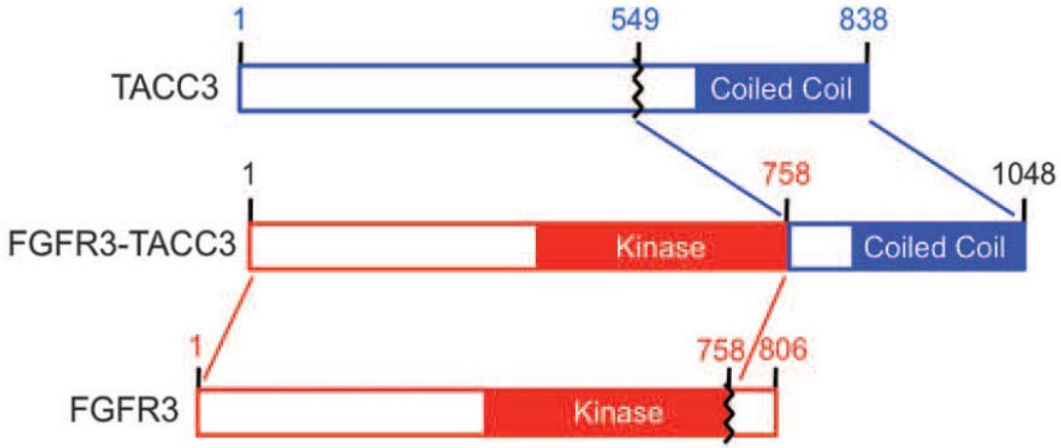
- p53 pathway (MDM2, MDM4, and TP53); vs.
- Rb pathway (CDK4, CDK6, CCND2, CDKN2A/B, and RB1); vs.
- PI3K pathway (PIK3CA, PIK3R1, PTEN, EGFR, PDGFRA, and NF1)

40% of tumors harbor at least one nonsynonymous mutation among the chromatin-modifier genes.

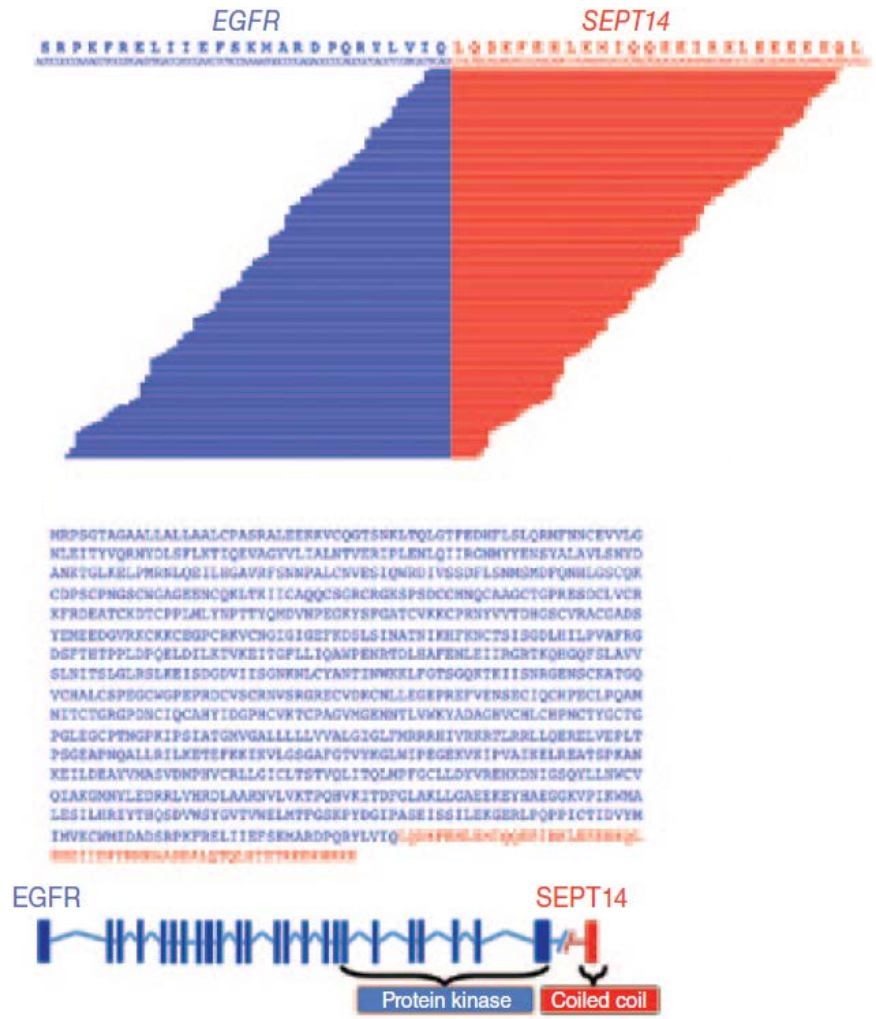
Transforming Fusions of *FGFR* and *TACC* Genes in Human Glioblastoma

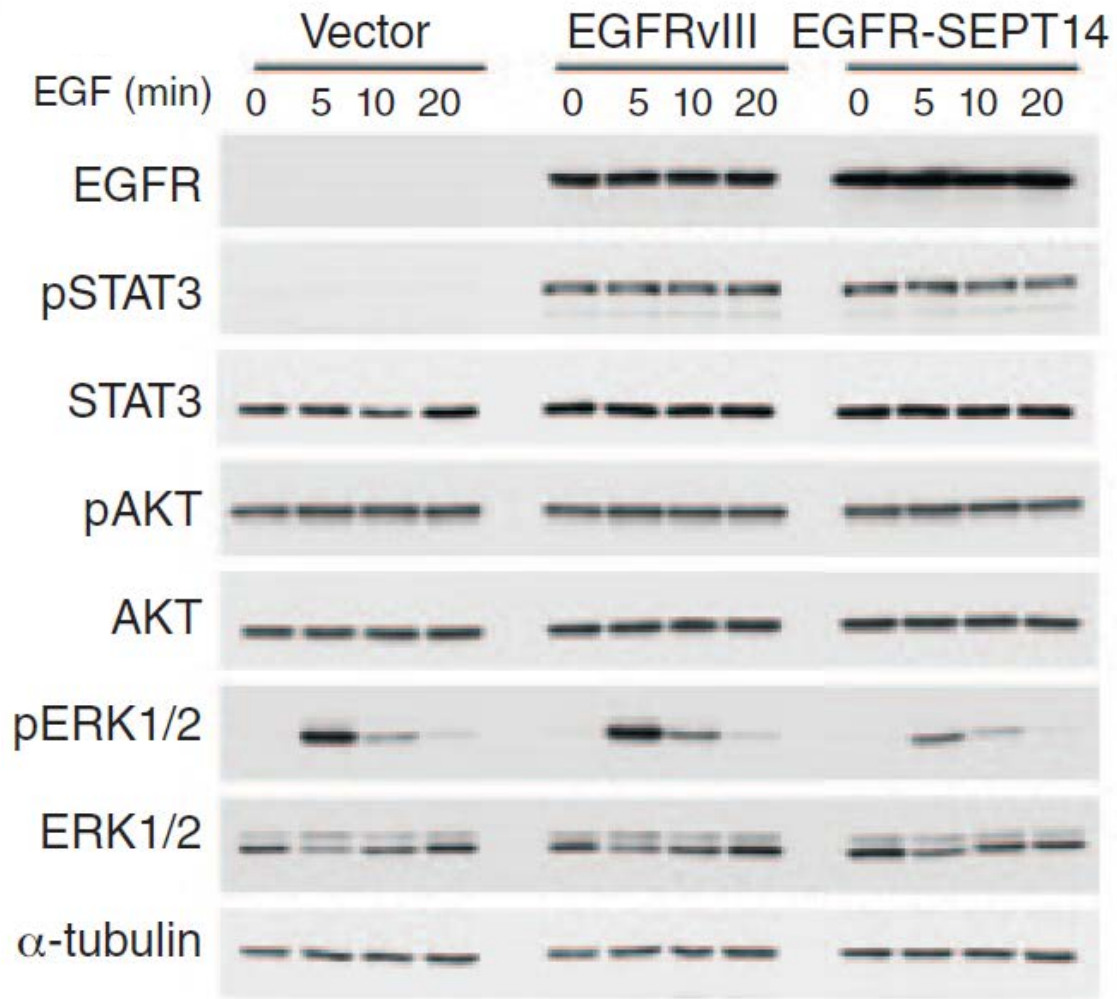
Devendra Singh,[1*] Joseph Minhow Chan,[2*] Pietro Zoppoli,[1*] Francesco Niola,[1*†] Ryan Sullivan,[1] Angelica Castano,[1] Eric Minwei Liu,[2] Jonathan Reichel,[2,3] Paola Porrati,[4] Serena Pellegatta,[4] Kunlong Qiu,[5] Zhibo Gao,[5] Michele Ceccarelli,[6] Riccardo Riccardi,[7] Daniel J. Brat,[8] Abhijit Guha,[9] Ken Aldape,[10] John G. Golfinos,[11] David Zagzag,[11,12] Tom Mikkelsen,[13] Gaetano Finocchiaro,[4] Anna Lasorella,[1,14,15]‡ Raul Rabadan,[2]‡ Antonio Iavarone[1,15,16]‡



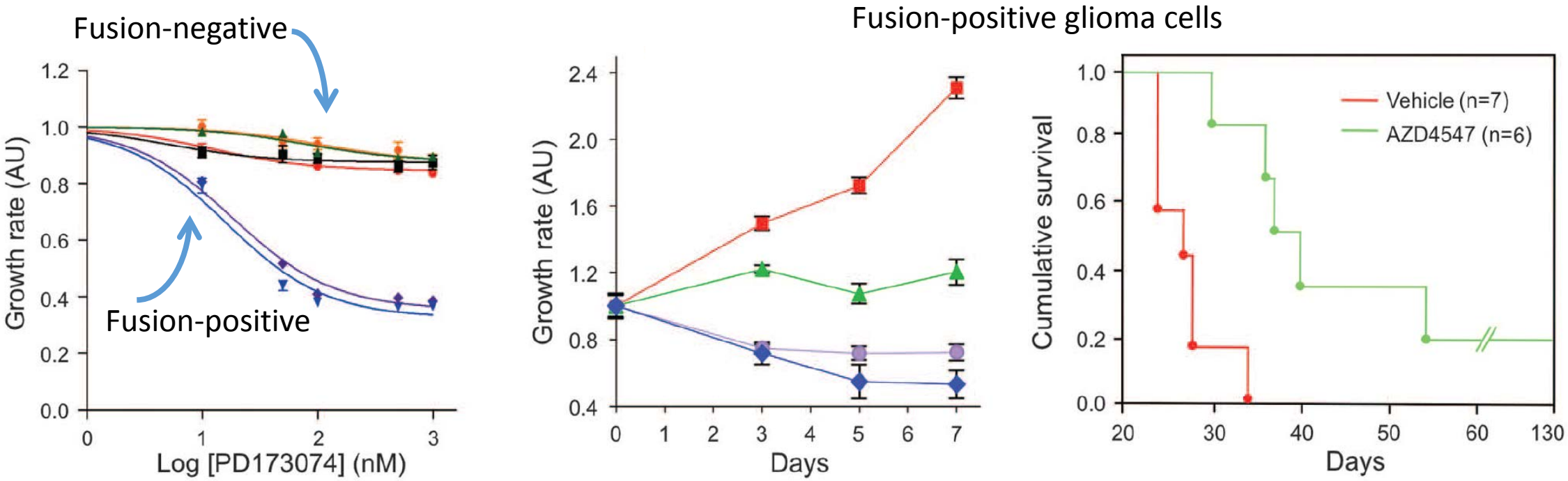


Fusion transcripts involving EGFR result in downstream STAT3 signaling





FGFR inhibitors are efficacious in fusion-positive glioma cells in preclinical model systems



FGFR-TACC fusions in glioma

- Fusion is present in ~3% if glioblastoma
- Clinical trial of FGFR inhibitor for fusion-positive cases
- Promising in concept, but raise logistical issues that challenge our previous paradigms of clinical trials designed for patient groups driven by histologic diagnosis
  - Targeted therapy for tumor-specific fusion gene as an attractive hypothesis, but
  - Challenge to enroll in trial where 97% of registered patients are ineligible

- GBM as the test-case an initial entry for TCGA and initial description of first cohort of TCGA samples
- Some comments on expression profiling and transcriptomal subtypes in GBM
- Integrated analyses and thoughts on present and future approaches towards understanding diffuse gliomas

Expression (mRNA) profiling

- Widely used
- Gene expression is dynamic
- Many parameters affect gene expression pattern when viewed as a snapshot and as an “average” in bulk tumor
- How stable and uniform are expression signatures in GBM?

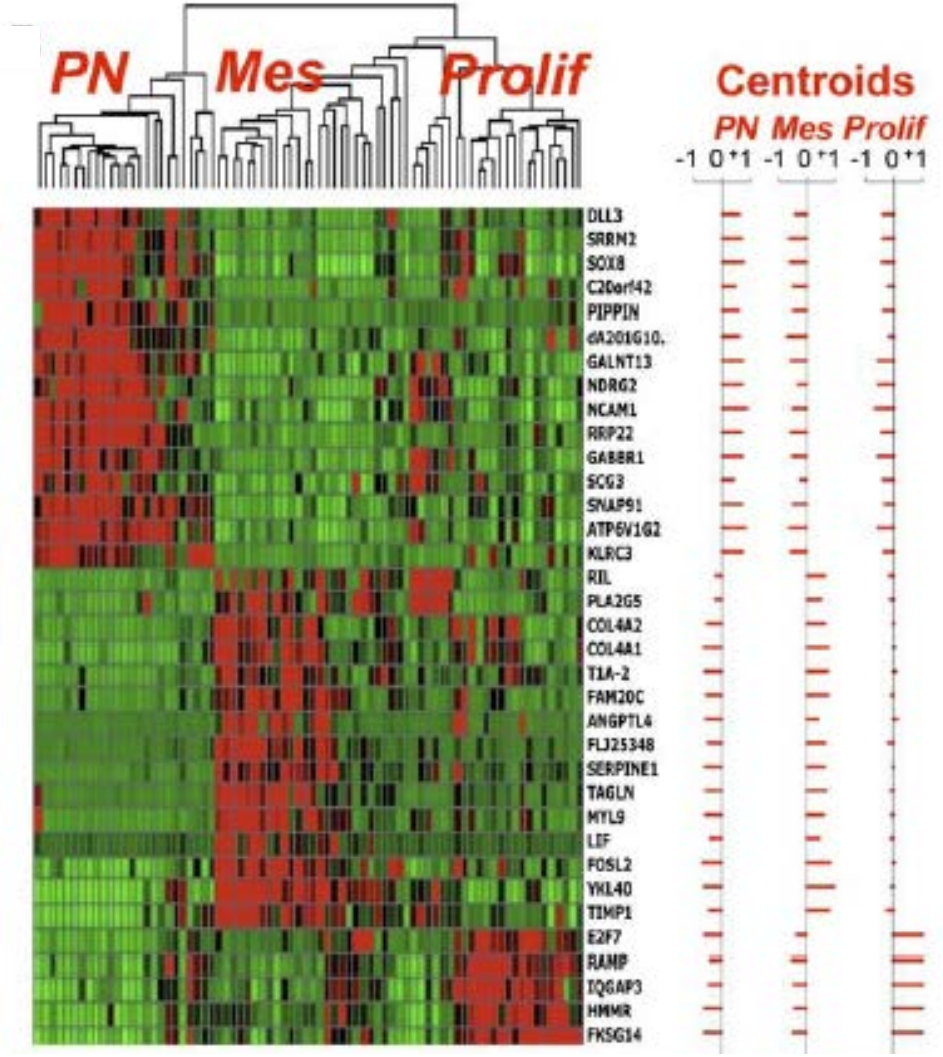
Transcriptomal subtypes of GBM

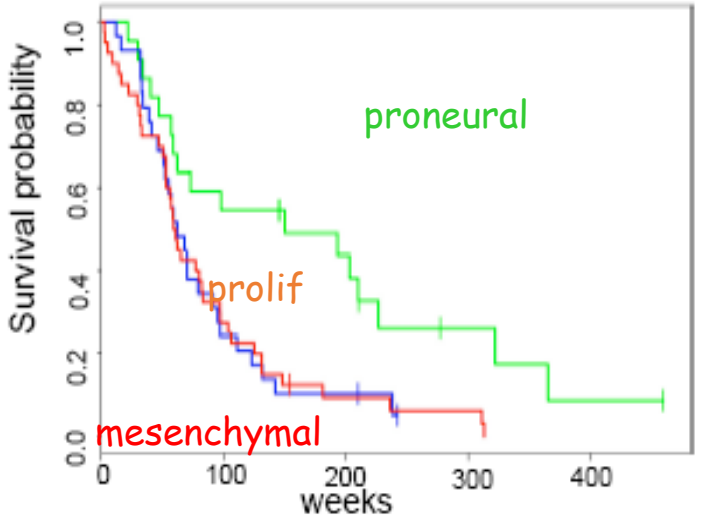
- mRNA microarray as the first of the genome-wide platforms available for routine testing
  - Most experience with this platform over the years

Cancer Cell
Article

Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis

Heidi S. Phillips,[1,*] Samir Kharbanda,[1] Ruihuan Chen,[1] William F. Forrest,[2] Robert H. Soriano,[3] Thomas D. Wu,[4] Anjan Misra,[5] Janice M. Nigro,[5] Howard Colman,[6] Liliana Soroceanu,[1] P. Mickey Williams,[3] Zora Modrusan,[3] Burt G. Feuerstein,[5] and Ken Aldape[7]

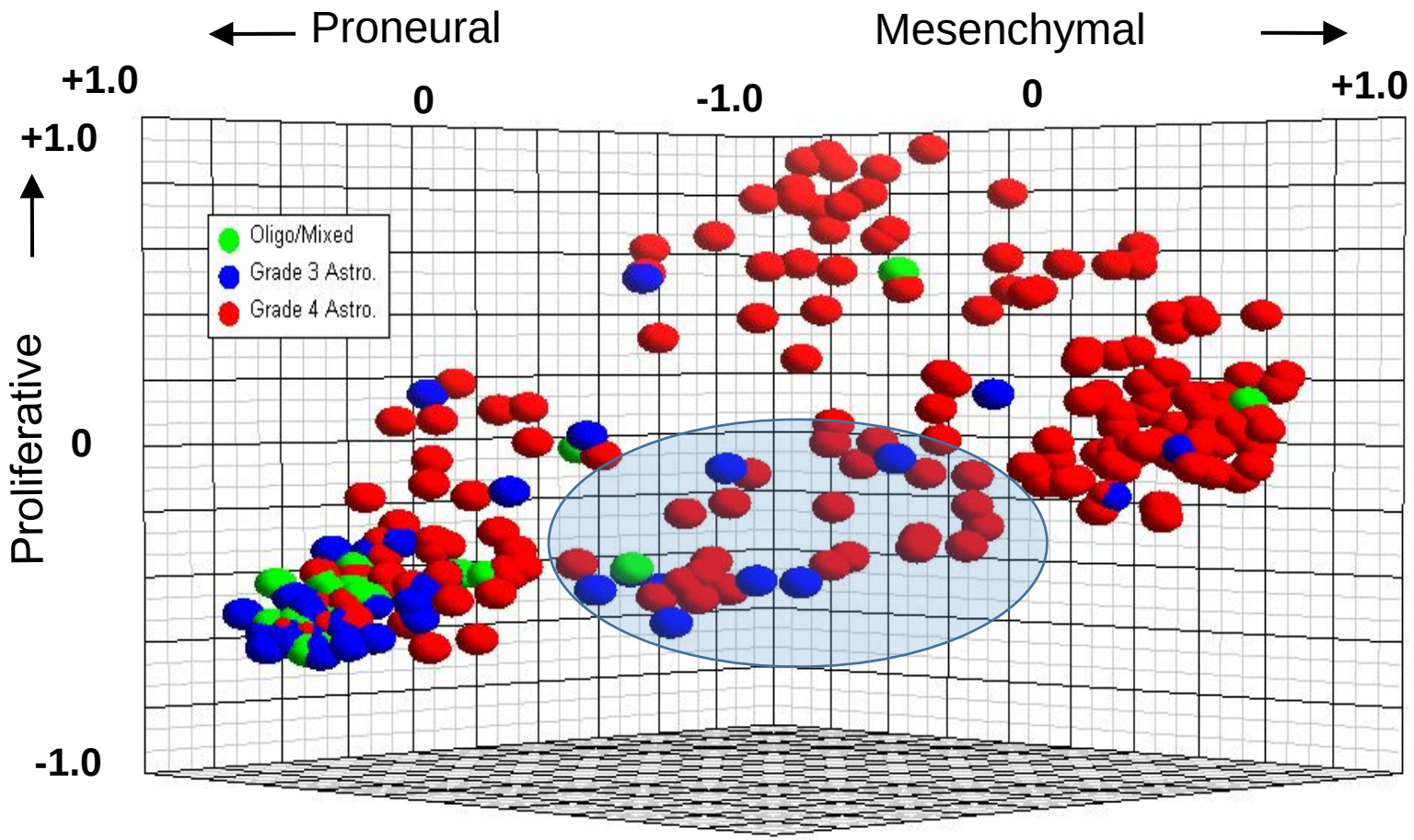




In retrospect:

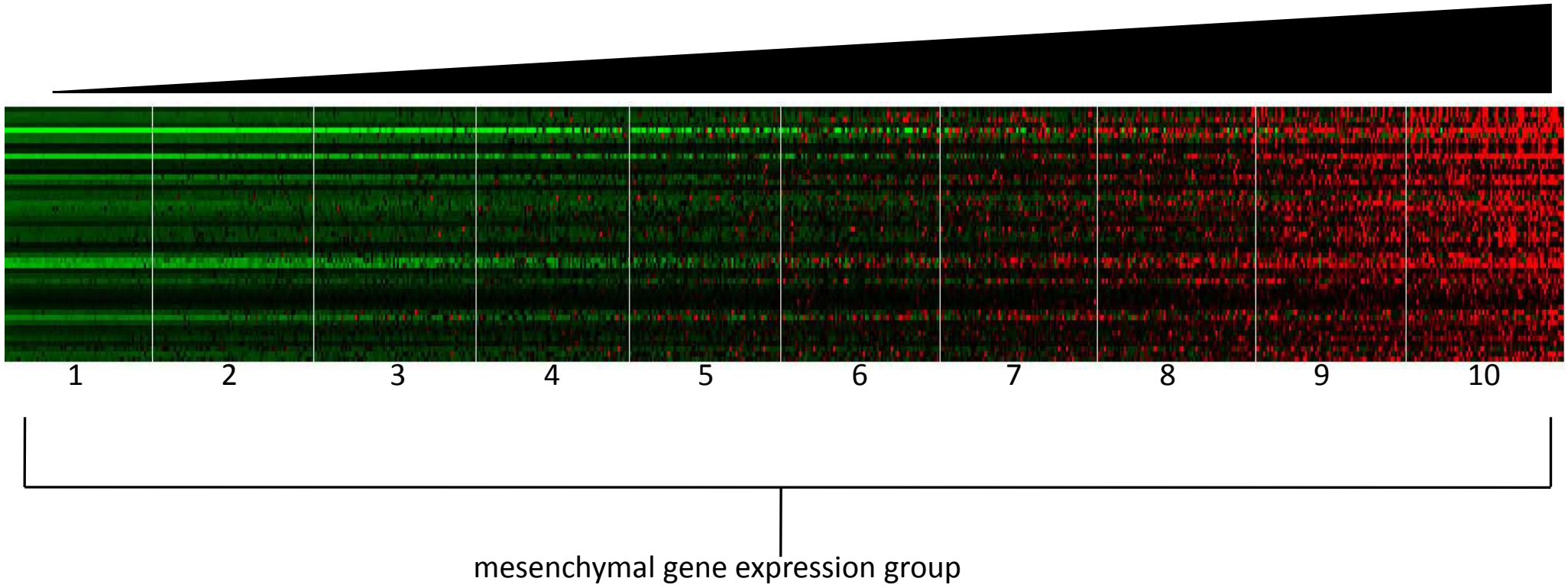
- inclusion of AA with GBM--IDH-mutant tumors (invariably proneural) accentuated the differences between IDHmut/proneural tumors and IDHwt/mesenchymal tumors
- “proliferative” tumors represented an “other” category

Expression Signatures stratify tumors by grade



..but there is some “noise”!

the mesenchymal phenotype is a continuum

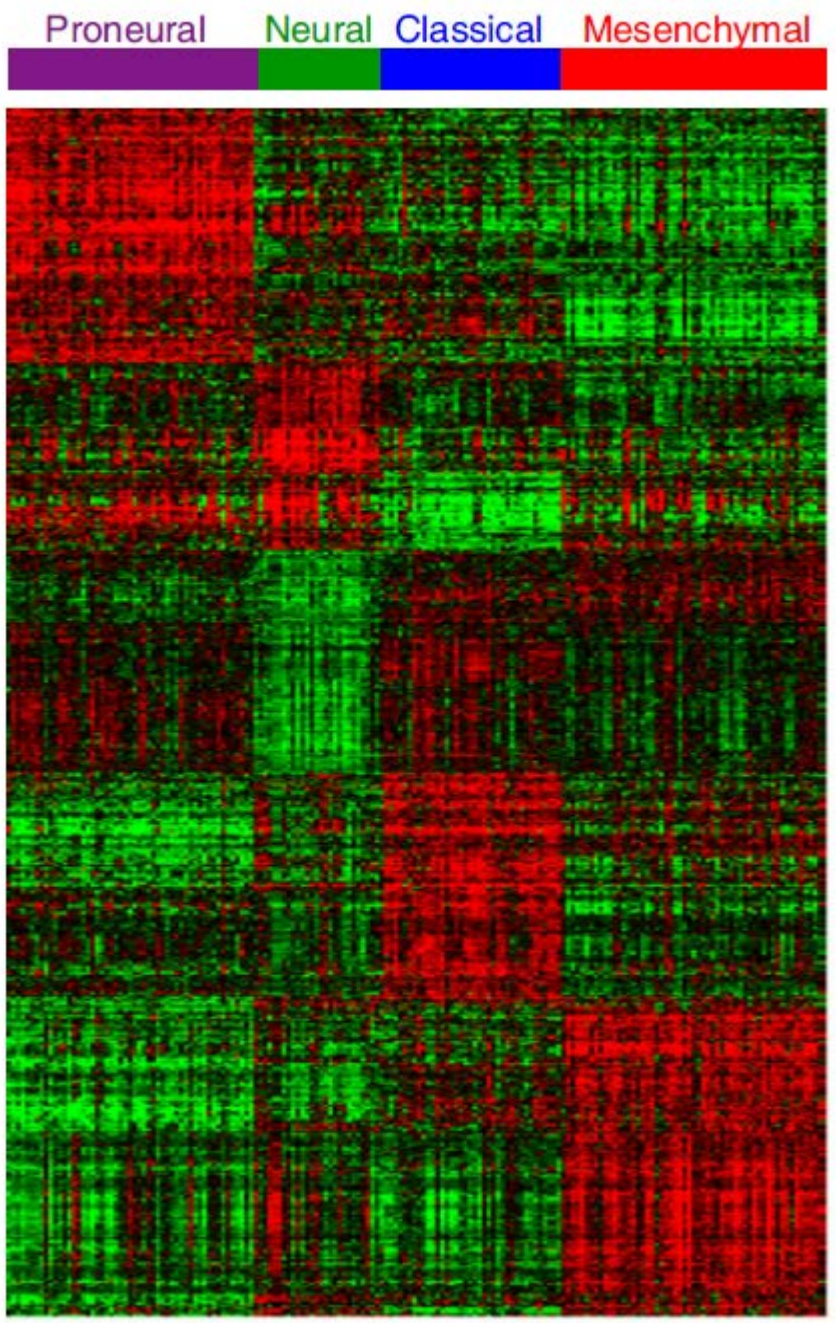


Cancer Cell
Article

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,[4,5] Matthew D. Wilkerson,[4,5] C. Ryan Miller,[4,6] 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,[11] Heidi S. Feiler,[11] J. Graeme Hodgson,[12] C. David James,[12] Jann N. Sarkaria,[13] Cameron Brennan,[14] Ari Kahn,[15] Paul T. Spellman,[11] Richard K. Wilson,[9] Terence P. Speed,[7,16] Joe W. Gray,[11] Matthew Meyerson,[1,2] Gad Getz,[1] Charles M. Perou,[3,4,8] D. Neil Hayes,[4,5,*] and The Cancer Genome Atlas Research Network

- 4 subtypes
- Mesenchymal, proneural
- Classical subtype-associated with EGFR amplification/rearrangement
- IDH1 mutation

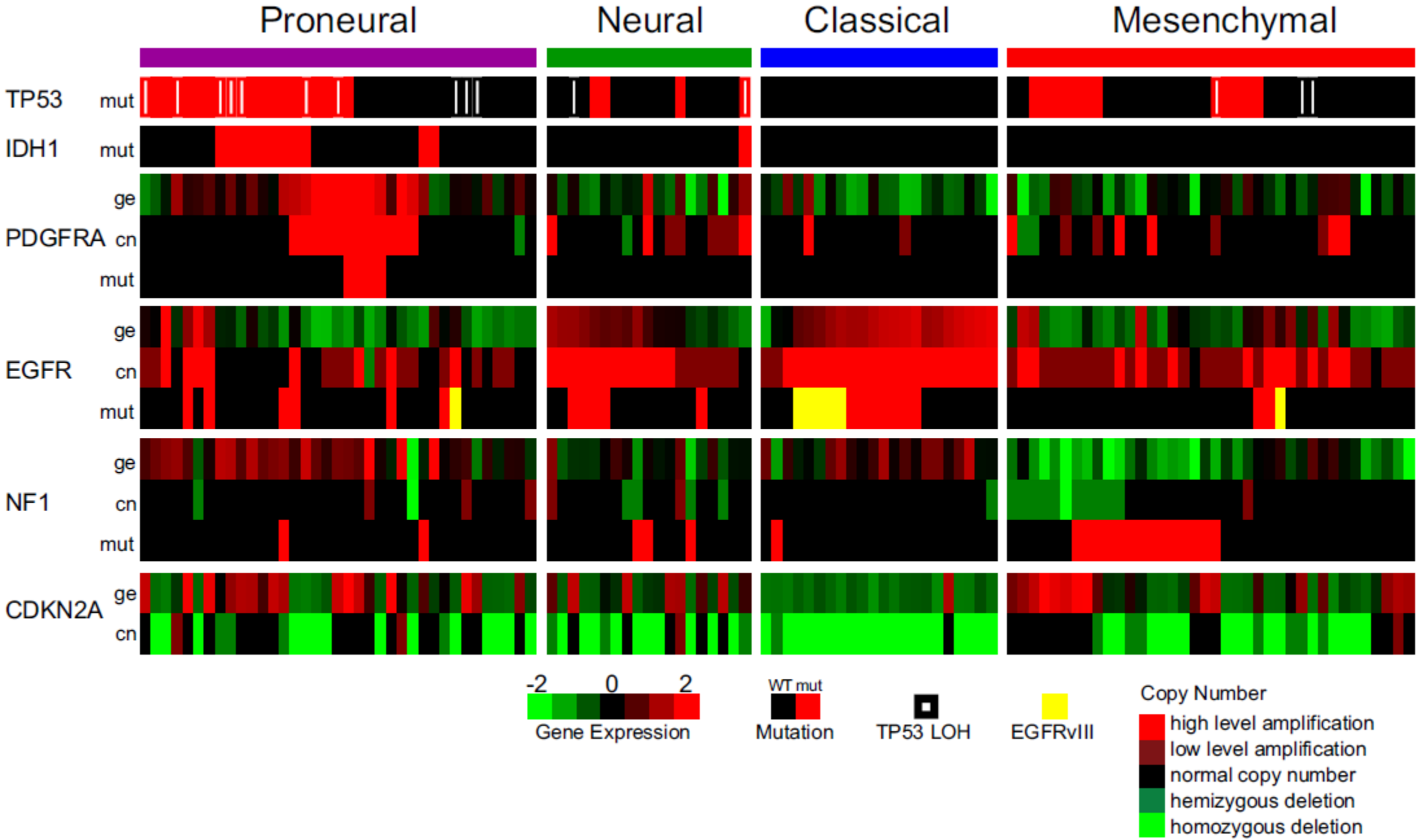


Multiplatform analysis to better characterize transcriptomal subtypes

Mutations	proneural	neural	classical	mesenchymal
TP53	54%	21%	0%	32%
PTEN	16%	21%	23%	32%
NF1	5%	16%	5%	37%
EGFR	16%	26%	32%	5%
IDH1	30%	5%	0%	0%
PIK3R1	19%	11%	5%	0%
RB1	3%	5%	0%	13%
ERBB2	5%	16%	5%	3%
EGFRvIII	3%	0%	23%	3%
PIK3CA	8%	5%	5%	3%
PDGFRA	11%	0%	0%	0%

Multiplatform analysis to better characterize transcriptomal subtypes

Mutations	proneural	neural	classical	mesenchymal
TP53	54%	21%	0%	32%
PTEN	16%	21%	23%	32%
NF1	5%	16%	5%	37%
EGFR	16%	26%	32%	5%
IDH1	30%	5%	0%	0%
PIK3R1	19%	11%	5%	0%
RB1	3%	5%	0%	13%
ERBB2	5%	16%	5%	3%
EGFRvIII	3%	0%	23%	3%
PIK3CA	8%	5%	5%	3%
PDGFRA	11%	0%	0%	0%


Proneural
Neural
Classical
Mesenchymal
TP53
mut
IDH1
mut
PDGFRA
ge
cn
mut
EGFR
ge
cn
mut
NF1
ge
cn
mut
CDKN2A
ge
cn
-2
0
2
Gene Expression
WT mut
Mutation
TP53 LOH
EGFRvIII
Copy Number
high level amplification
low level amplification
normal copy number
hemizygous deletion
homozygous deletion

Current status of expression subtypes/analysis in GBM

- Transcriptional drivers
- Plasticity of subtype switching
- Intratumoral heterogeneity

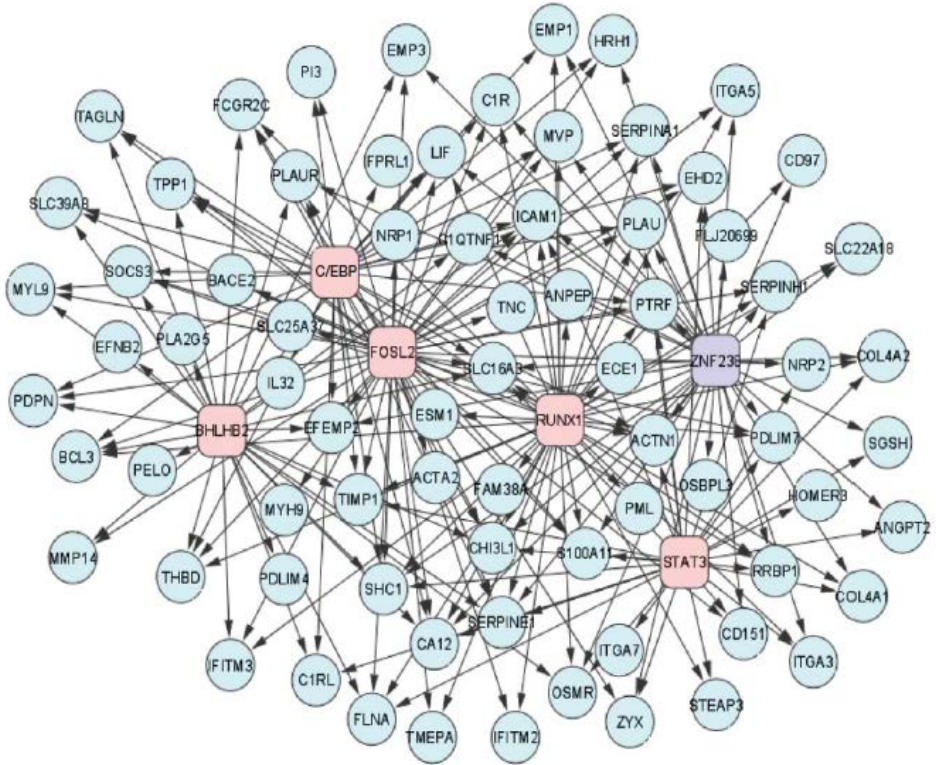
The transcriptional network for mesenchymal transformation of brain tumours

nature

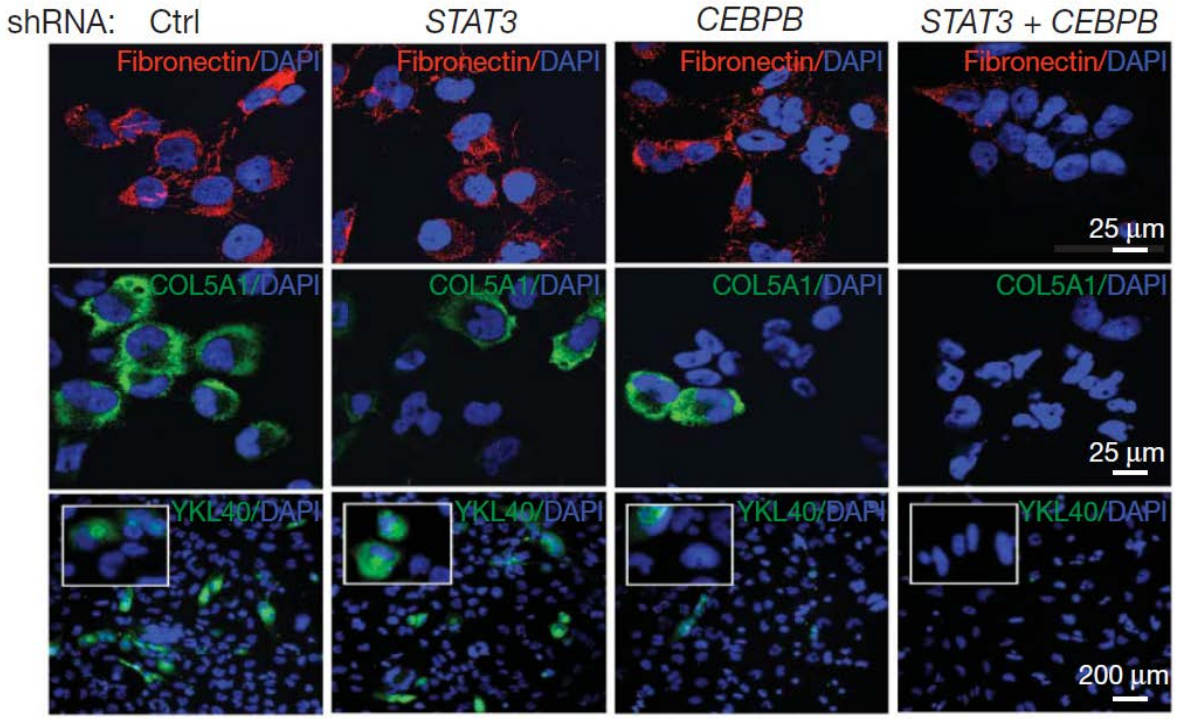
ARTICLES

Maria Stella Carro[1]*†, Wei Keat Lim[2,3]*†, Mariano Javier Alvarez[3,4]*, Robert J. Bollo[8], Xudong Zhao[1], Evan Y. Snyder[9], Erik P. Sulman[10], Sandrine L. Anne[1]†, Fiona Doetsch[5], Howard Colman[11], Anna Lasorella[1,5,6], Ken Aldape[12], Andrea Califano[1,2,3,4] & Antonio Iavarone[1,5,7]

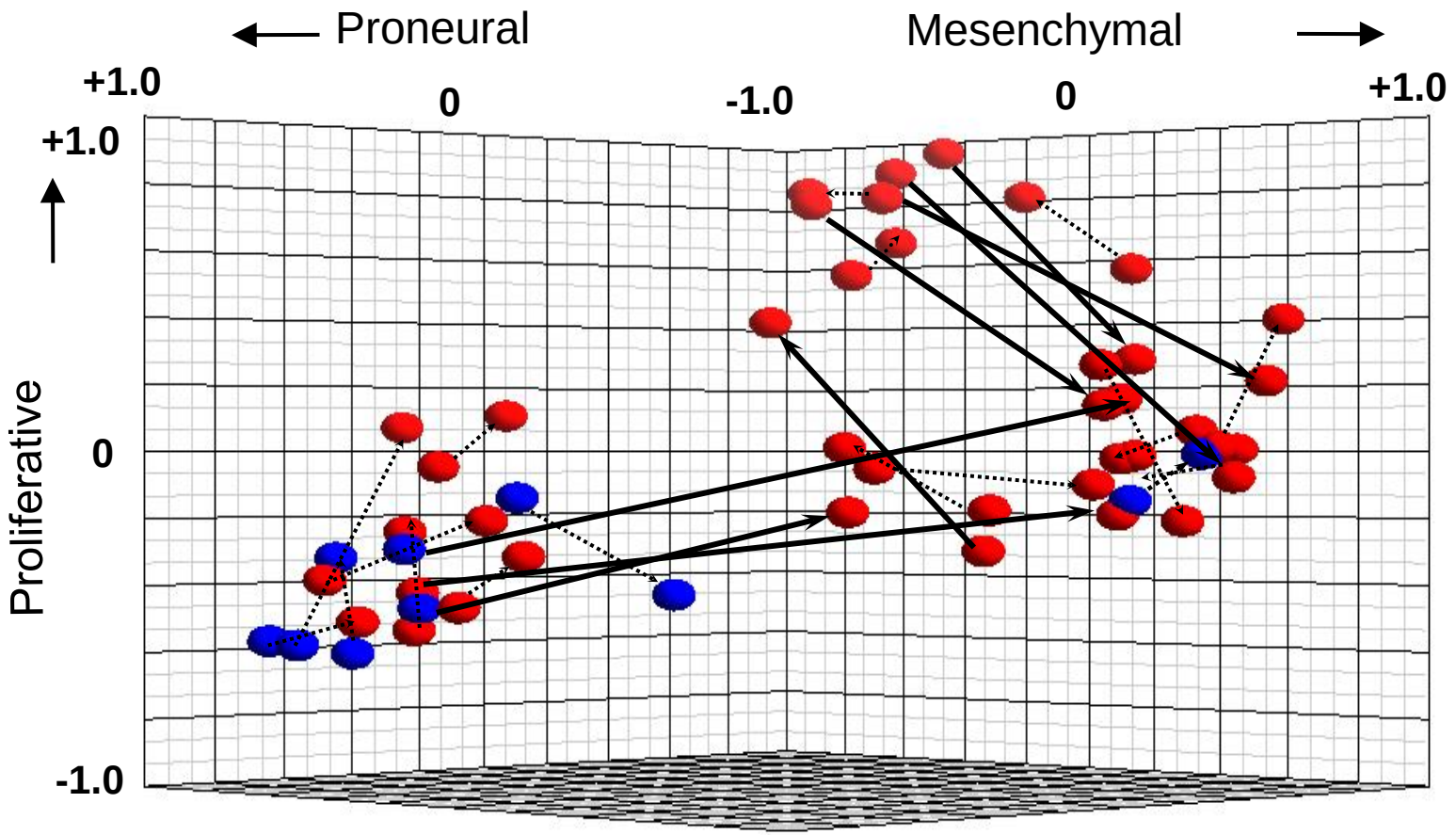
STAT3 and CEBP-β at center of transcriptional network for MES gene expression in human tumors



STAT3 and CEBP-β drive MES differentiation in glioma cells



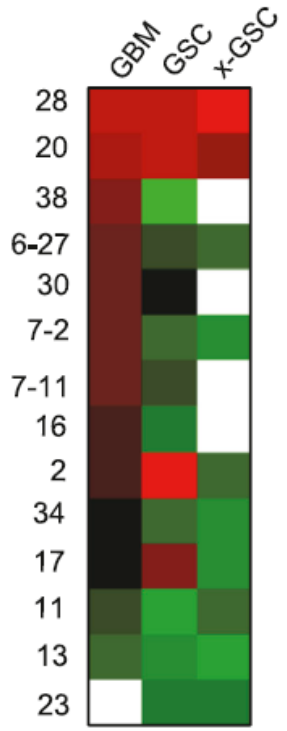
Potential for transcriptomal class switching was noted by comparison of matched primary-recurrent pairs

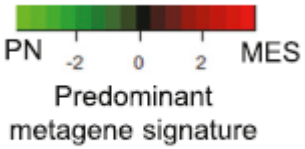


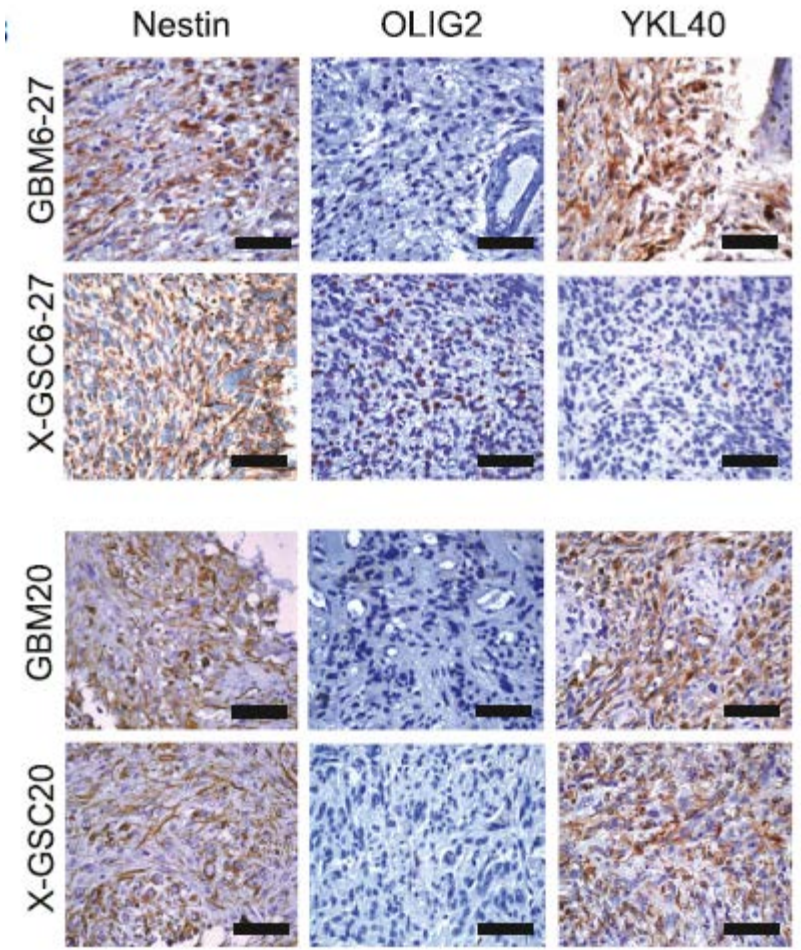
Cancer Cell
Article

Mesenchymal Differentiation Mediated by NF-κB Promotes Radiation Resistance in Glioblastoma

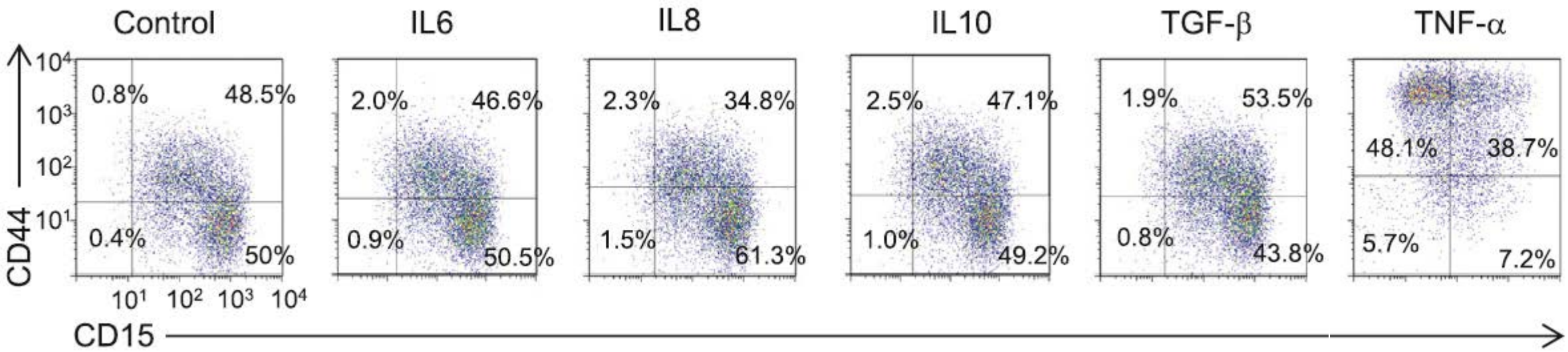
Krishna P.L. Bhat,[1,16,*] Veerakumar Balasubramaniyan,[5,16] Brian Vaillant,[7,16] Ravesanker Ezhilarasan,[2,16] Karlijn Hummelink,[1] Faith Hollingsworth,[1] Khalida Wani,[1] Lindsey Heathcock,[1] Johanna D. James,[1] Lindsey D. Goodman,[2] Siobhan Conroy,[6] Lihong Long,[1] Nina Lelic,[8] Suzhen Wang,[3] Joy Gumin,[4] Divya Raj,[5] Yoshinori Kodama,[9] Aditya Raghunathan,[10] Adriana Olar,[1] Kaushal Joshi,[11] Christopher E. Pelloski,[12] Amy Heimberger,[4] Se Hoon Kim,[13] Daniel P. Cahill,[8] Ganesh Rao,[4] Wilfred F.A. Den Dunnen,[6] Hendrikus W.G.M. Boddeke,[5] Heidi S. Phillips,[14] Ichiro Nakano,[11] Frederick F. Lang,[4] Howard Colman,[15,17] Erik P. Sulman,[2,17,*] and Kenneth Aldape[1,17,*]







TNF-α promotes mesenchymal change in GBM neurospheres



How uniform are transcriptomal profiles within a single tumor?

Sciencexpress

Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma

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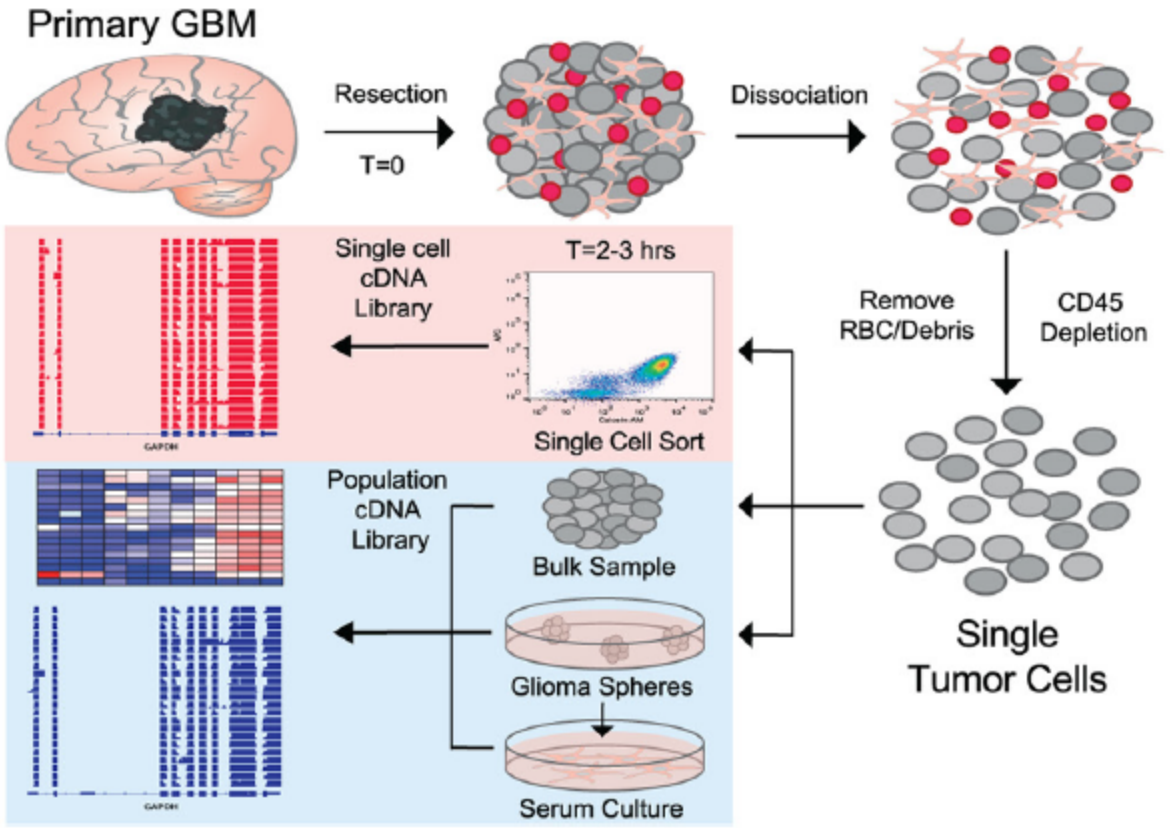
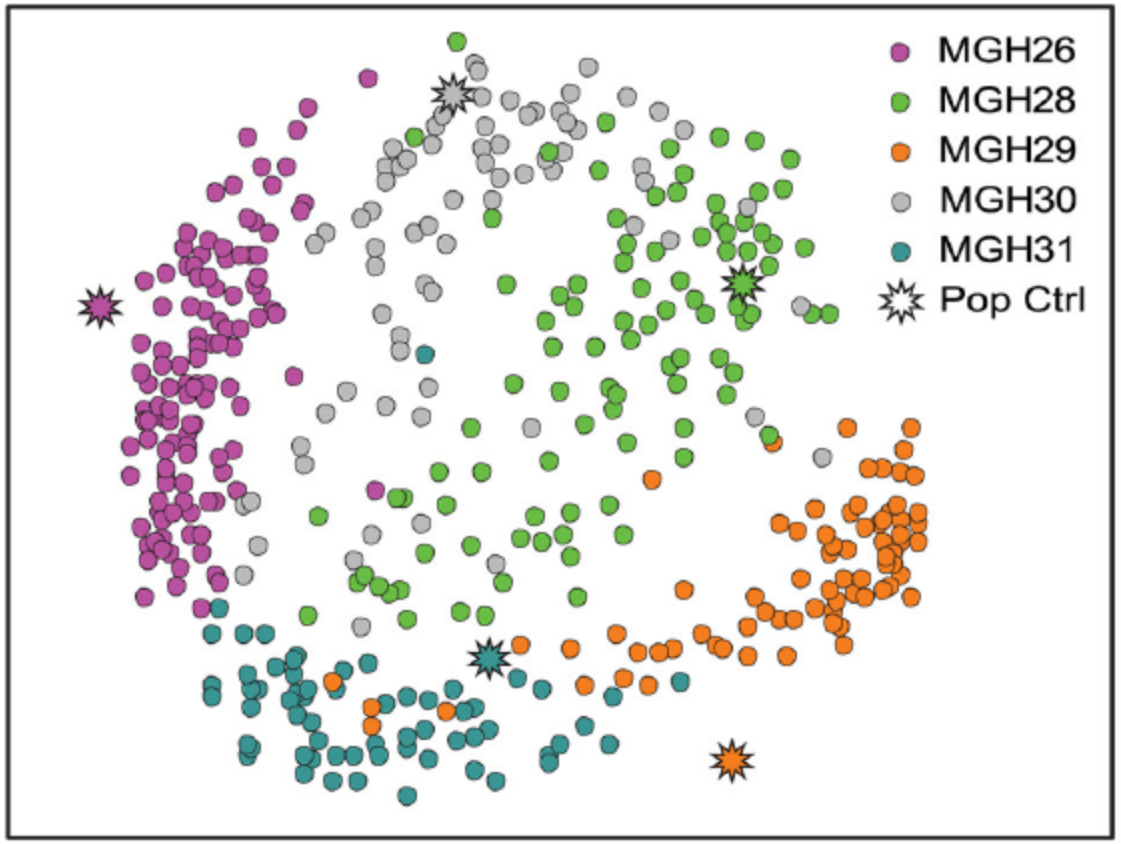
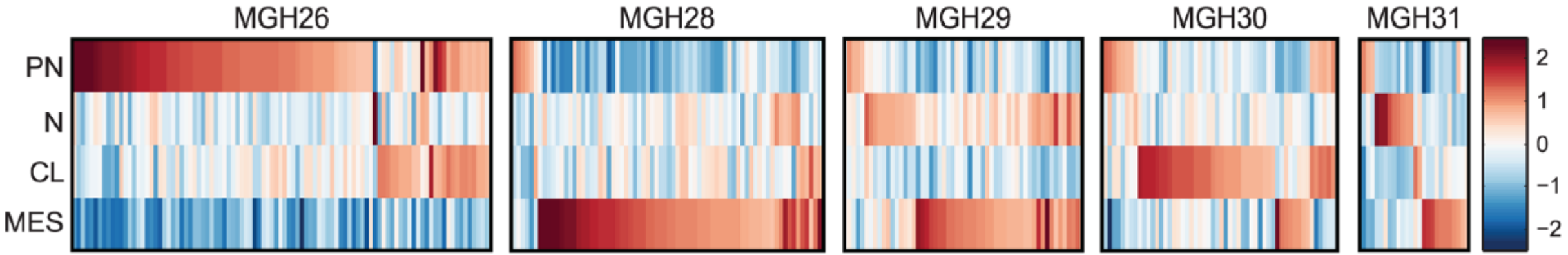
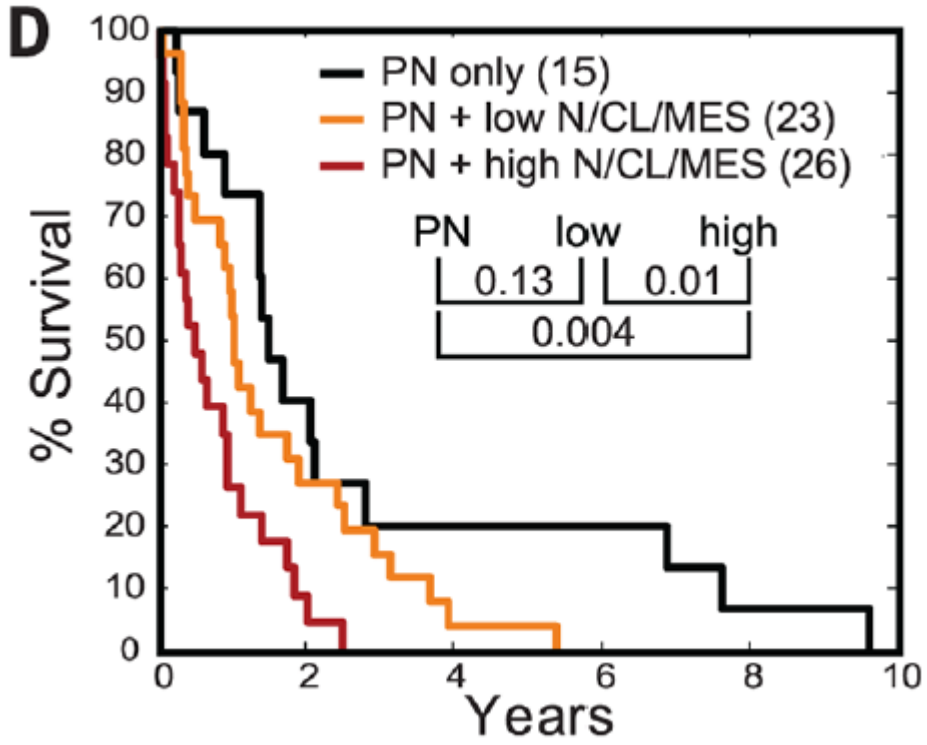
single-cell RNA sequencing (RNA-seq) to profile 430 cells from five primary glioblastoma tumor samples







- Transcriptomal phenotype: intra-tumoral heterogeneity
- Some cells show strong “hybrid” signatures
- Degree of transcriptomal heterogeneity may be important



Expression subtypes in GBM

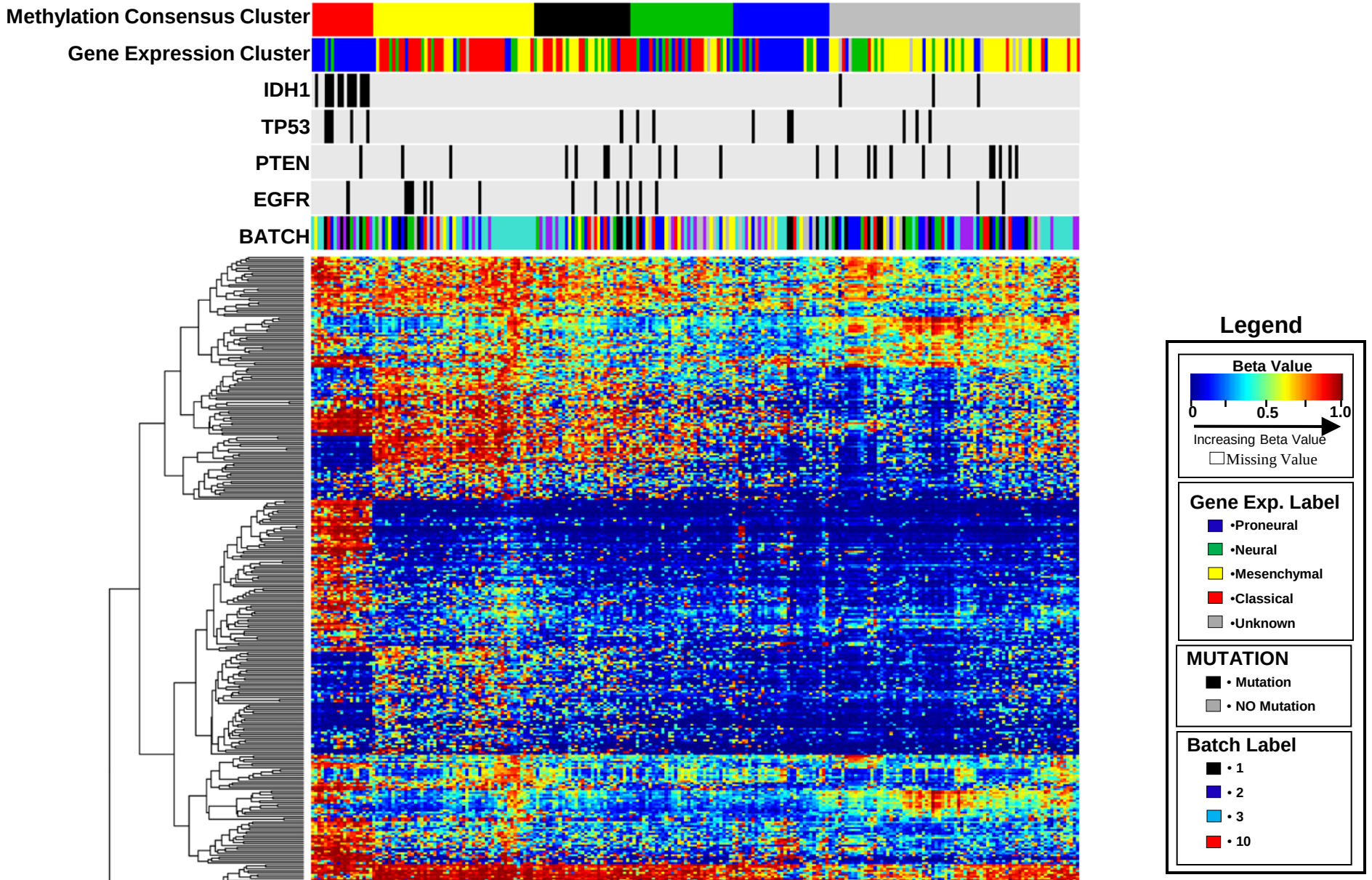
- A range of expression subtypes can be discerned in bulk tumor GBM samples
- dynamic process with plasticity: microenvironmental/intratumoral determinants
  - Can change over time
  - Non-uniform within a tumor
- Useful to understand biology
  - IDH mutation and proneural signature
  - NF1 mutation and mesenchymal signature
- Probably not robust as a classification tool in the clinic
- Consider re-analysis of expression analysis based in IDH status (mut vs wt) rather than by histologic grade (GBM vs grade II-III)

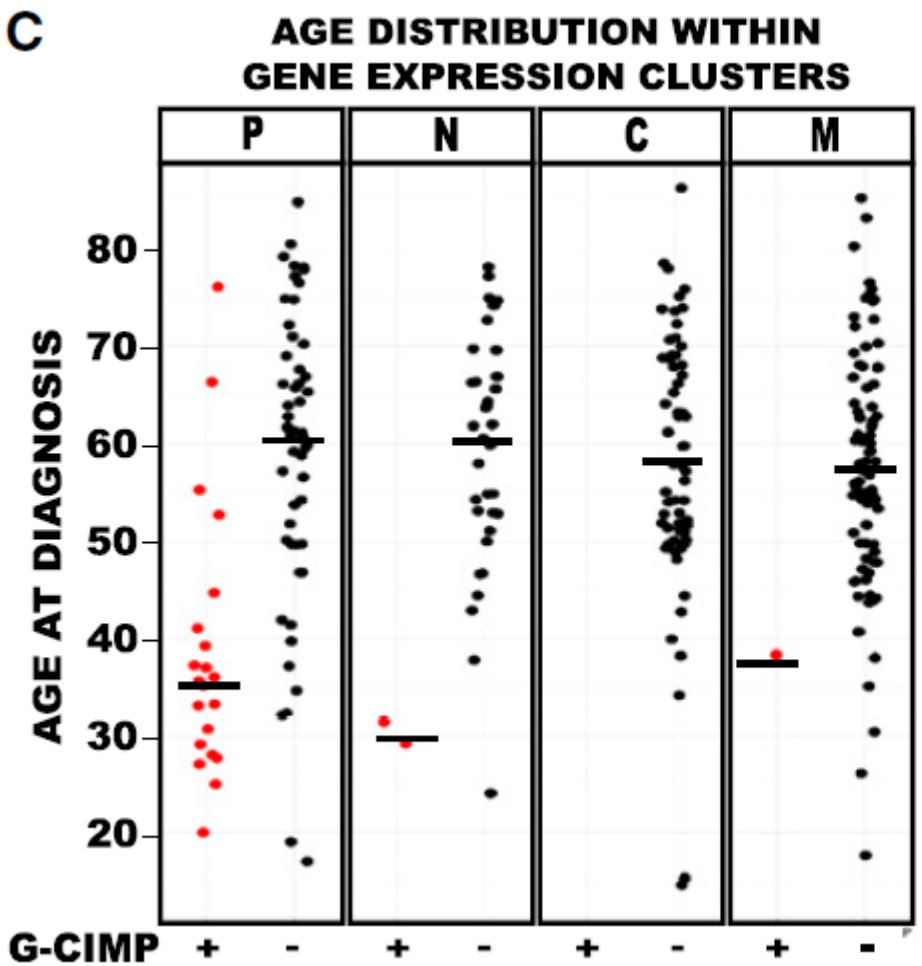
- GBM as the test-case an initial entry for TCGA and initial description of first cohort of TCGA samples
- Some comments on expression profiling and transcriptomal subtypes in GBM
- Integrated analyses and thoughts on present and future approaches towards understanding diffuse gliomas

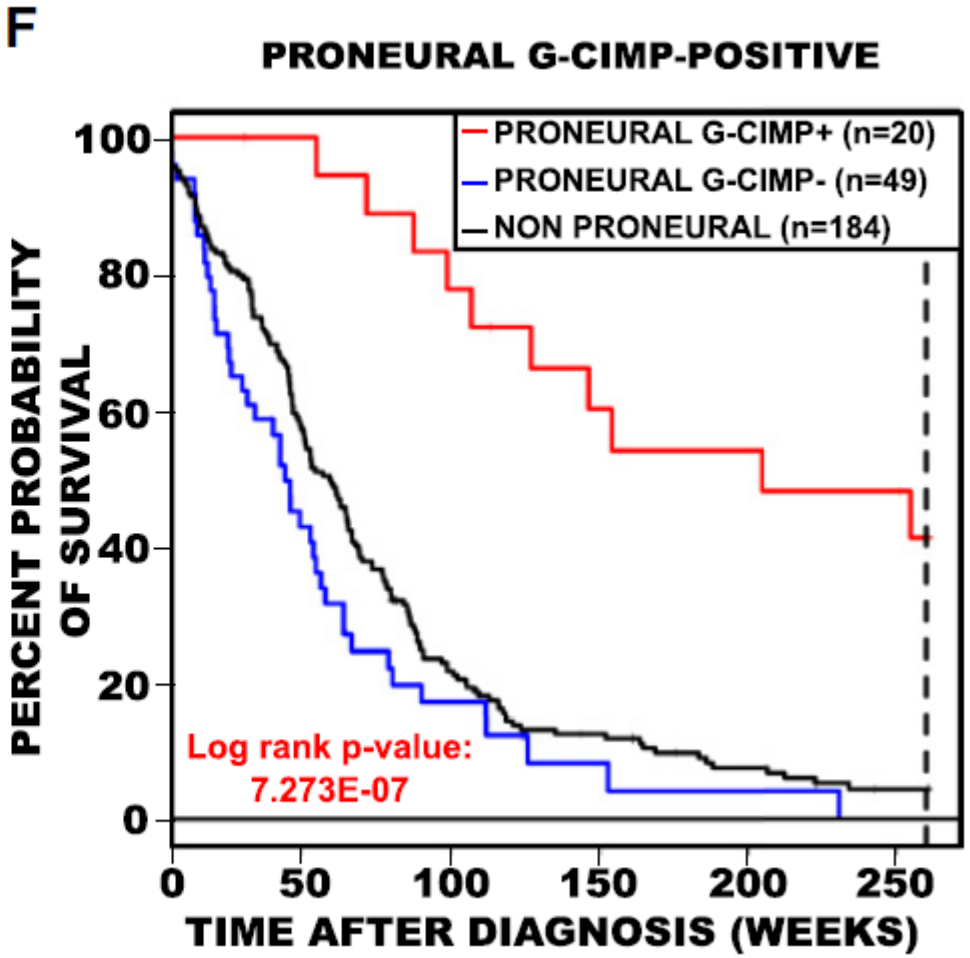
Cancer Cell
Article

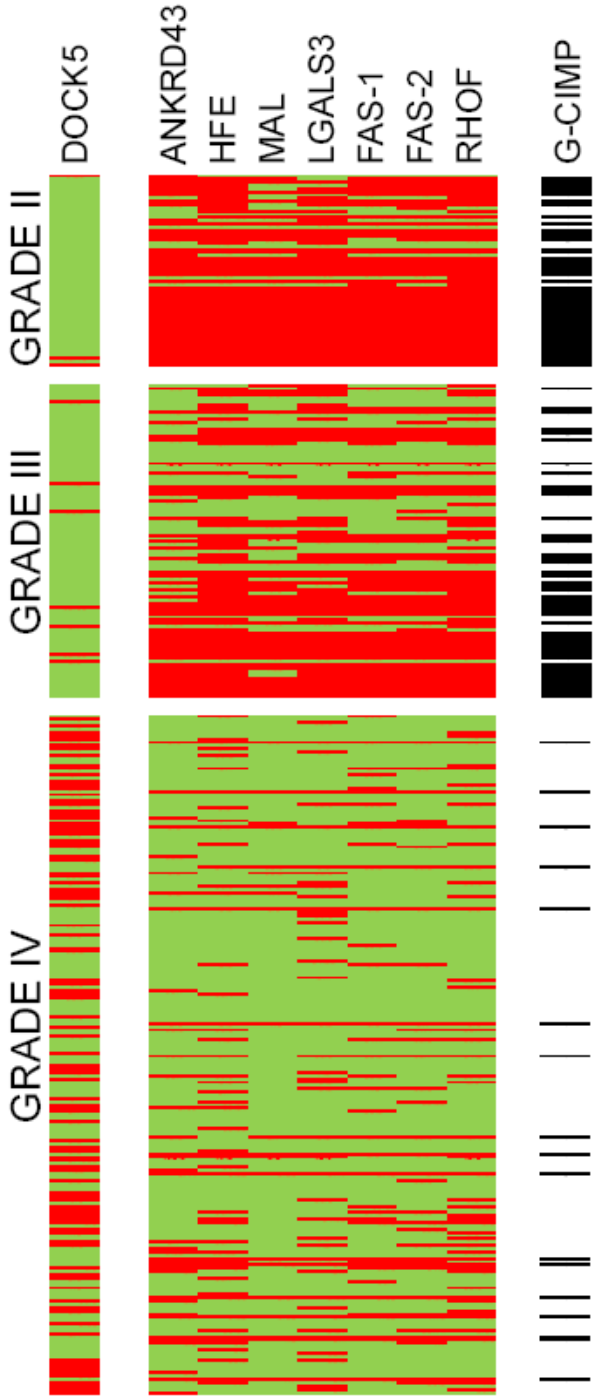
Identification of a CpG Island Methylator Phenotype that Defines a Distinct Subgroup of Glioma

Houtan Noushmehr,[1,13] Daniel J. Weisenberger,[1,13] Kristin Diefes,[2,13] Heidi S. Phillips,[3] Kanan Pujara,[3] Benjamin P. Berman,[1] Fei Pan,[1] Christopher E. Pelloski,[4] Erik P. Sulman,[4] Krishna P. Bhat,[2] Roel G.W. Verhaak,[5,6] 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


Methylation Consensus Cluster
Gene Expression Cluster
IDH1
TP53
PTEN
EGFR
BATCH
Legend
Beta Value
0
0.5
1.0
Increasing Beta Value
Missing Value
Gene Exp. Label
•Proneural
•Neural
•Mesenchymal
•Classical
•Unknown
MUTATION
• Mutation
• NO Mutation
Batch Label
• 1
• 2
• 3
• 10


C
AGE DISTRIBUTION WITHIN
GENE EXPRESSION CLUSTERS
P
N
C
M
AGE AT DIAGNOSIS
80
70
60
50
40
30
20
G-CIMP
+
-
+
-
+
-
+
-


F
PRONEURAL G-CIMP-POSITIVE
PRONEURAL G-CIMP+ (n=20)
PRONEURAL G-CIMP- (n=49)
NON PRONEURAL (n=184)
PERCENT PROBABILITY
OF SURVIVAL
100
80
60
40
20
0
Log rank p-value:
7.273E-07
0
50
100
150
200
250
TIME AFTER DIAGNOSIS (WEEKS)

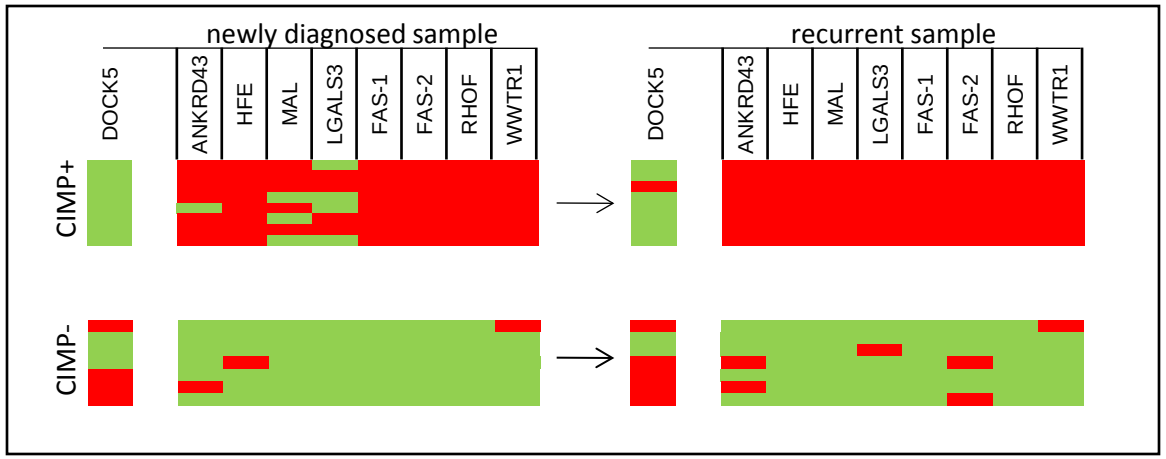


CIMP status is associated with tumor grade

	CIMP+	% CIMP+
grade II	68/84	83.0%
grade III	34/69	49.2%
grade IV	18/221	8.0%

CIMP status is a stable phenotype

- Characterize stability of CIMP status in matched primary-recurrent pairs.
- Time between primary and recurrent samples: 2-9 years
- CIMP status stable for both CIMP+ and CIMP- cases.



LETTER

doi:10.1038/nature10866

IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype

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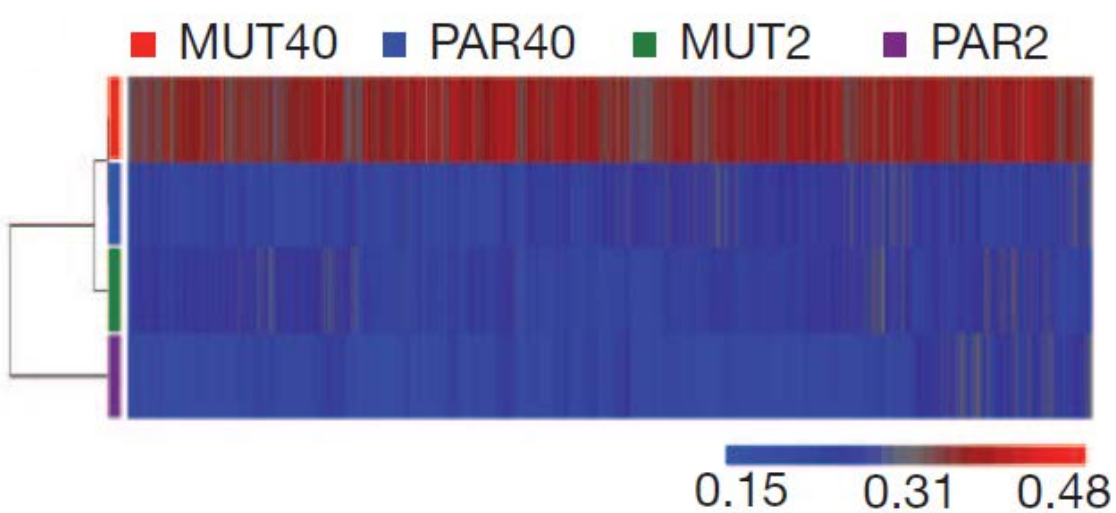

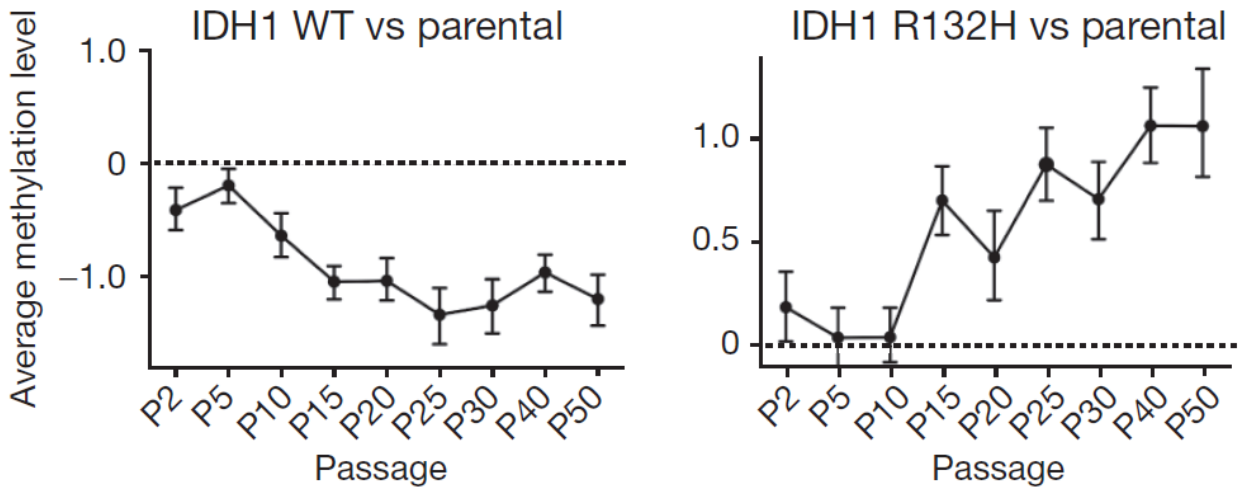

Integrated analyses

OPEN ACCESS Freely available online

PLoS one

Integrative Subtype Discovery in Glioblastoma Using iCluster

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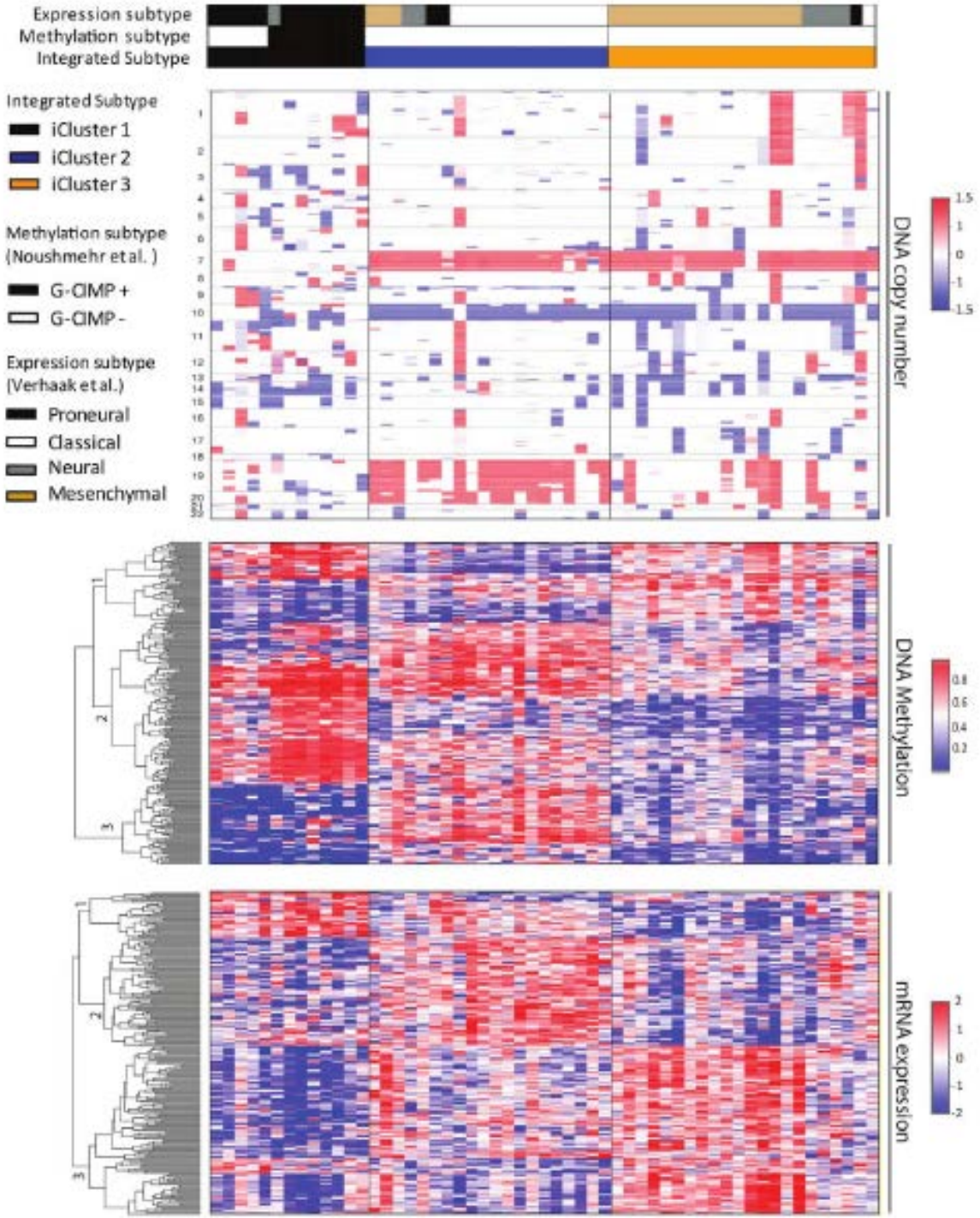
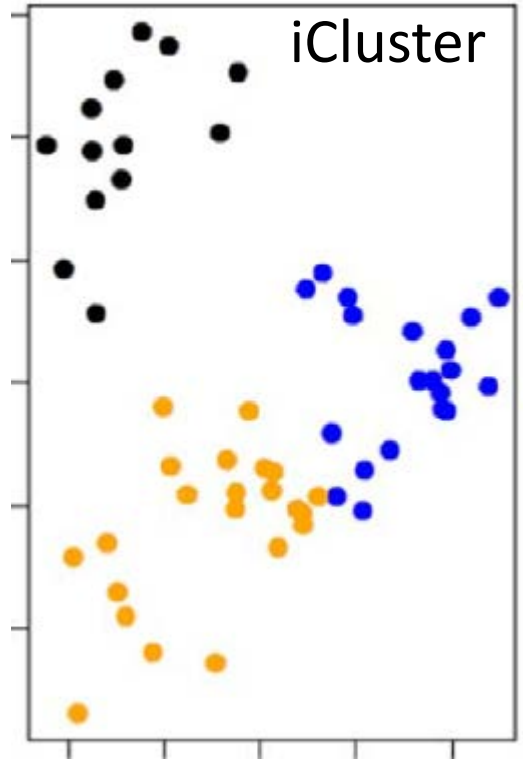
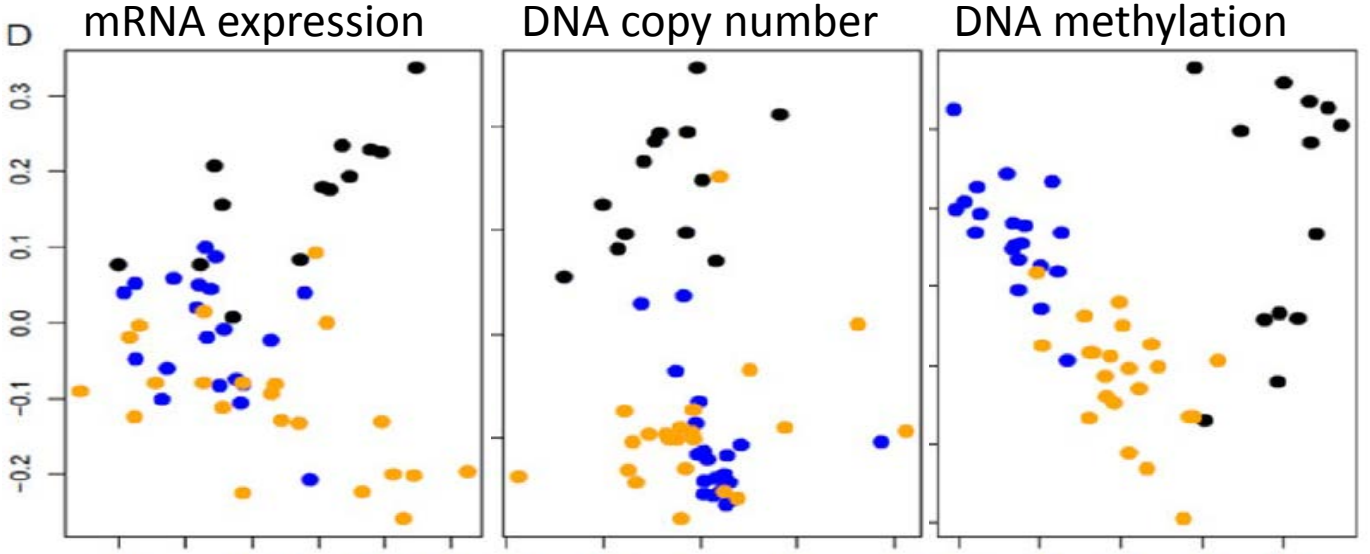


Integrative genomic studies increase reliability of classification compared to single platform studies





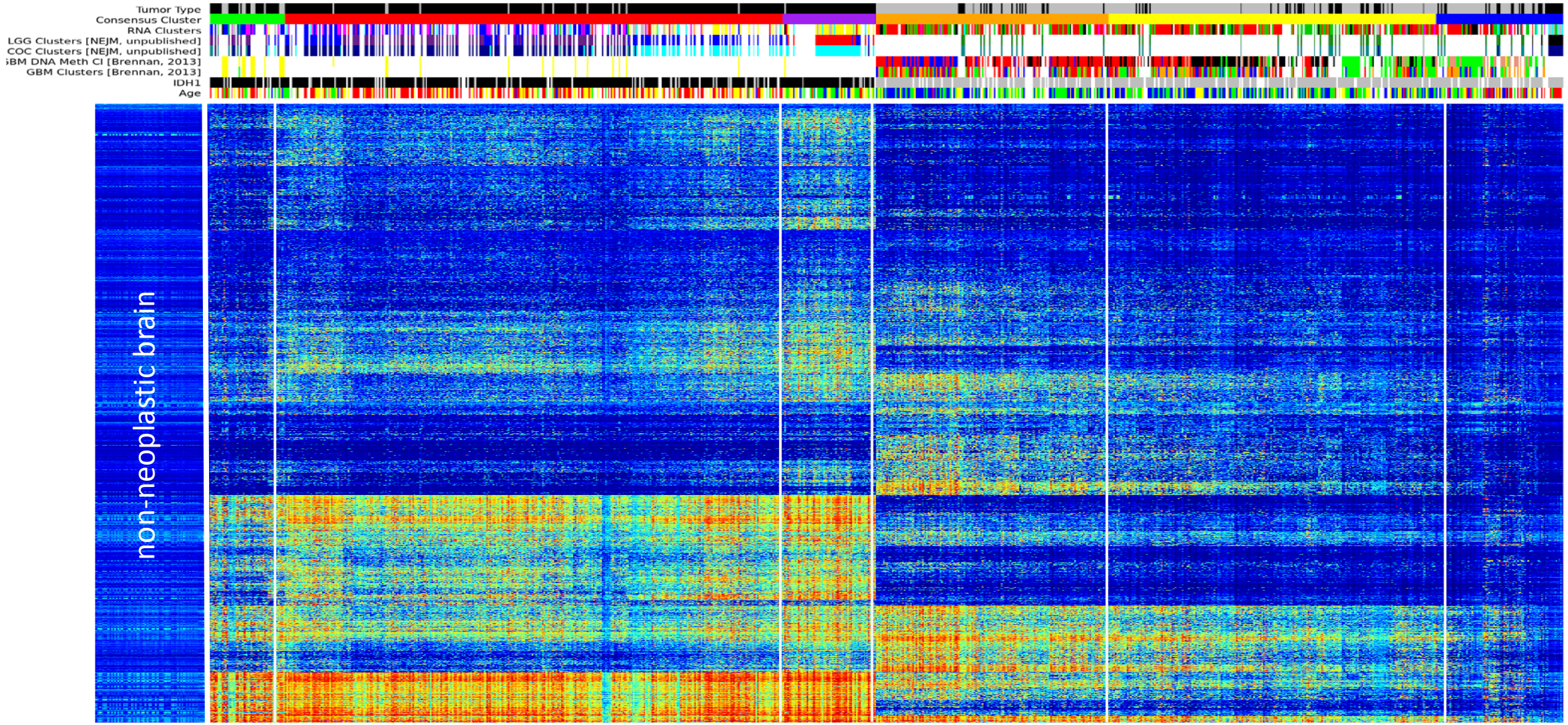
TCGA GBM-LGG integrated analysis effort

- What are the differences and similarities between IDH+ LGG and IDH+ GBM?

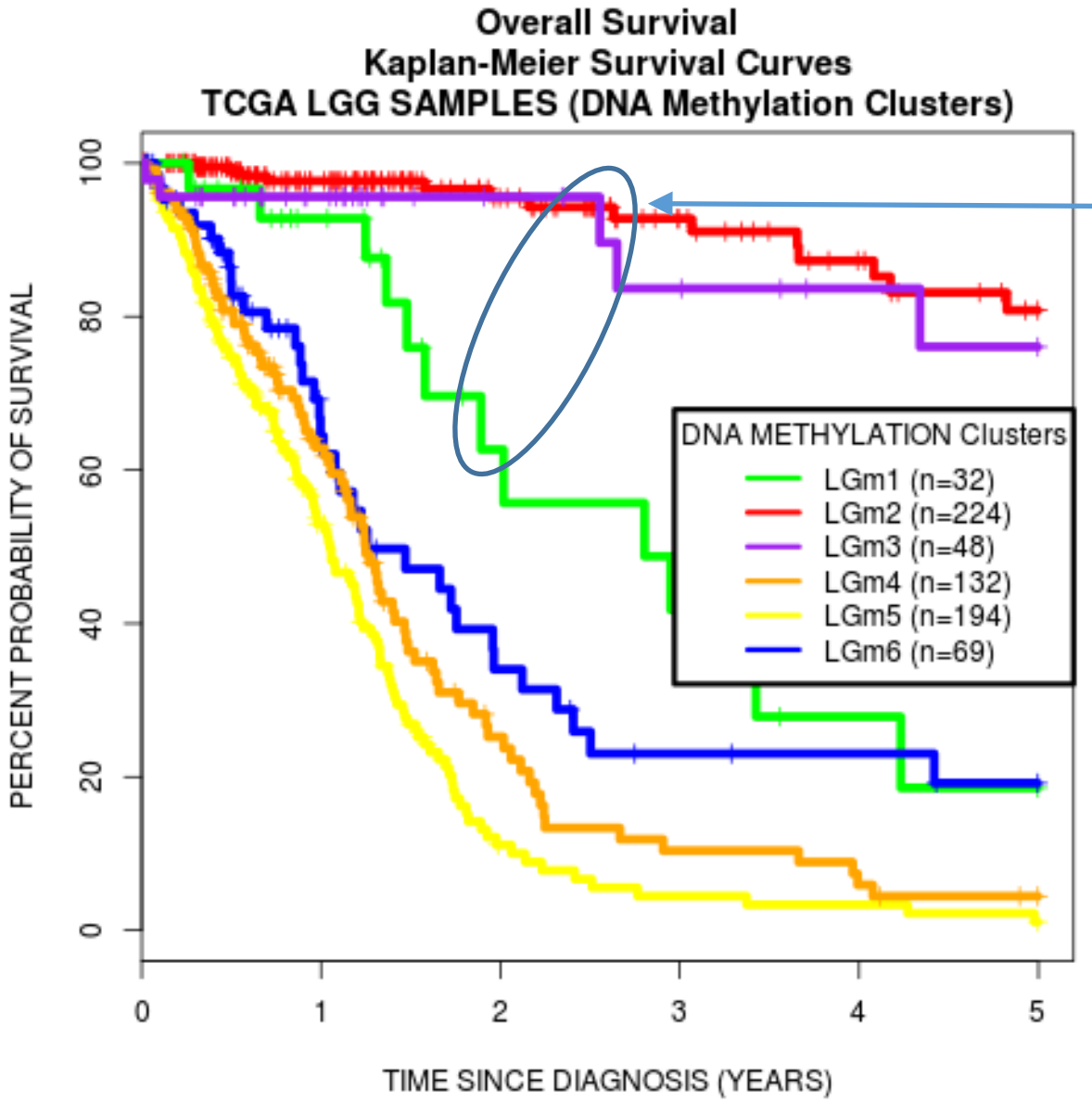
- What are the differences and similarities between IDH1-wt LGG and IDH1-wt GBM?

2 major methylation classes (G-CIMP+/G-CIMP-)

distribution according to IDH mutation status rather than histologic grade

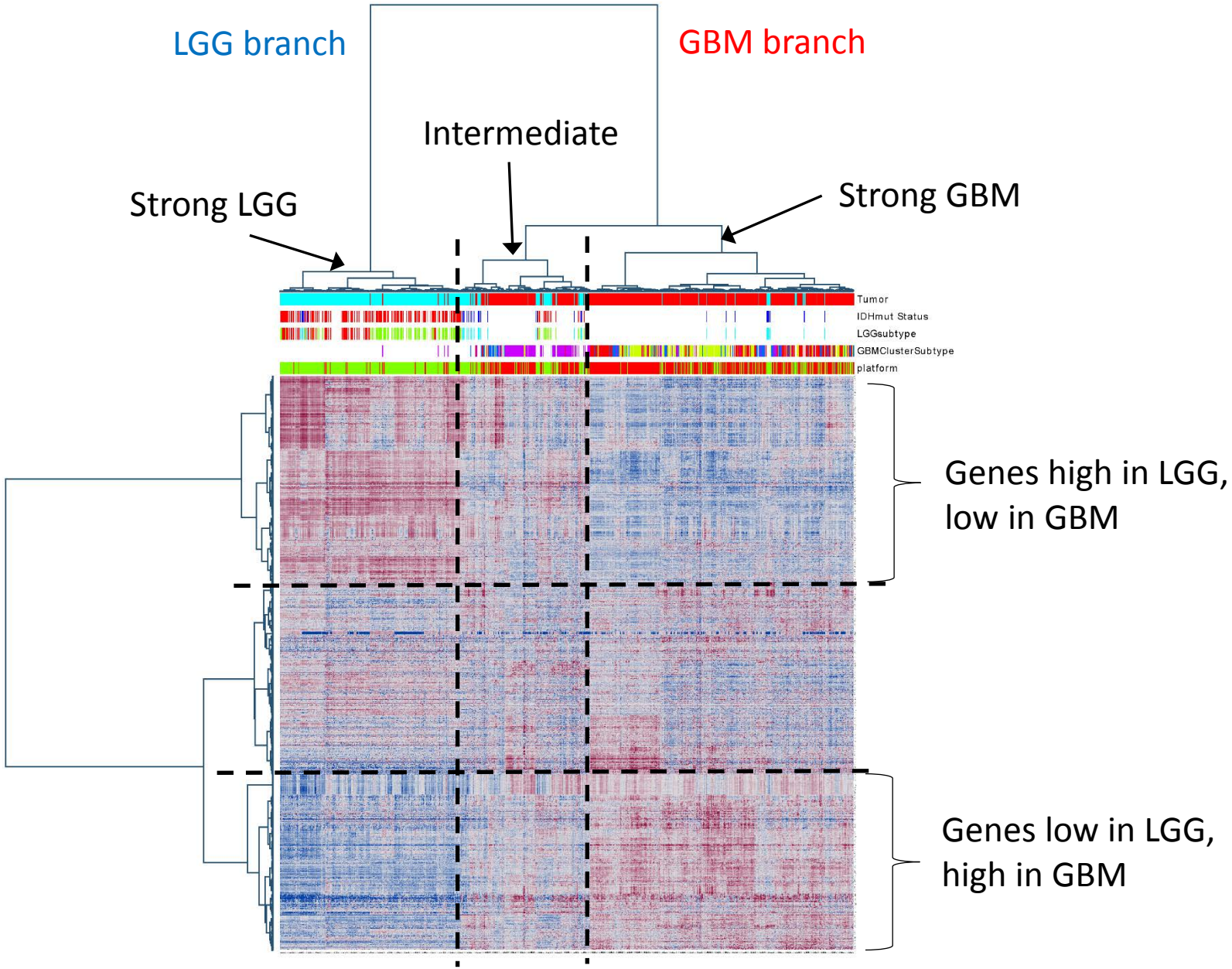


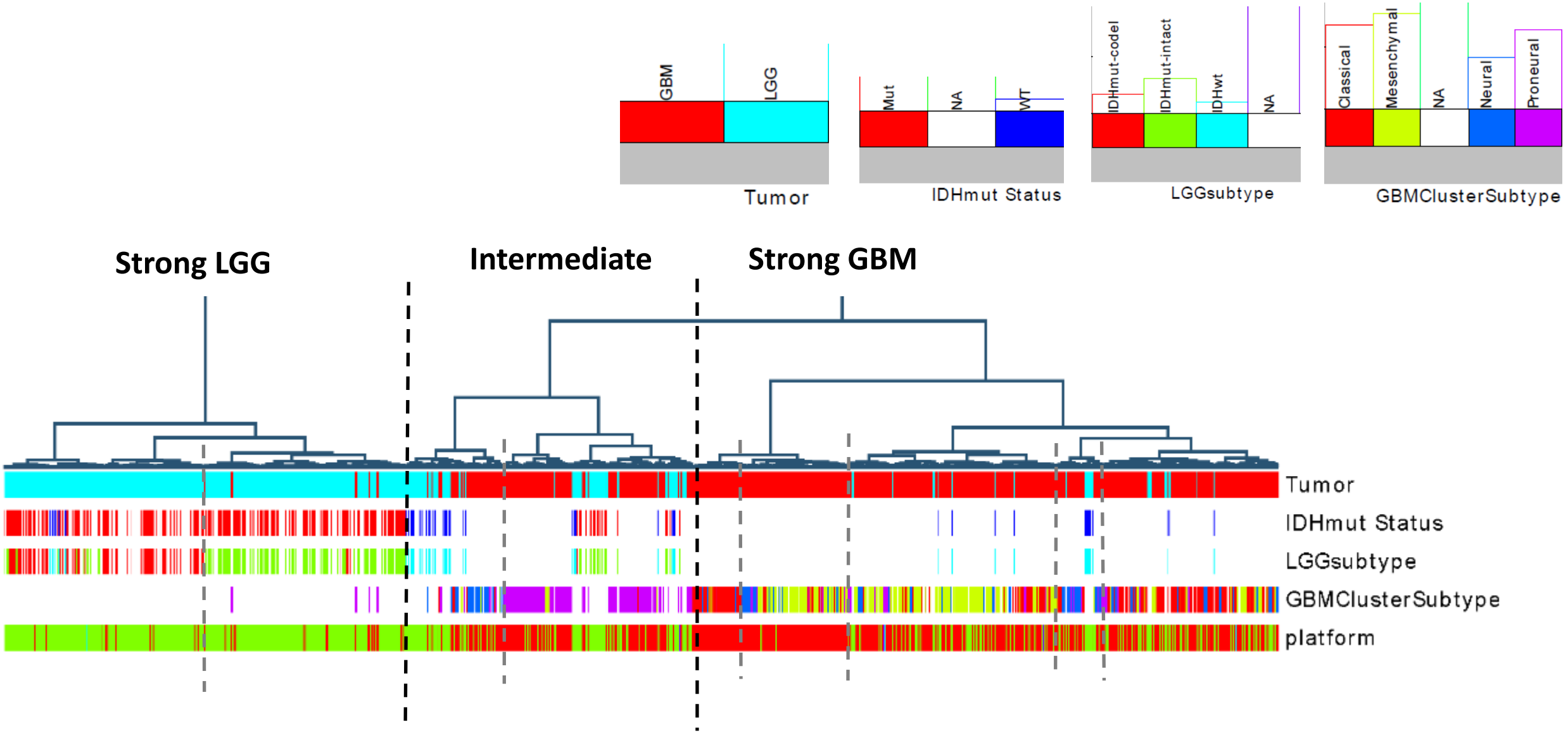
Kaplan-Meier Survival Curves based on methylation subclass



G-CIMP-positive tumors

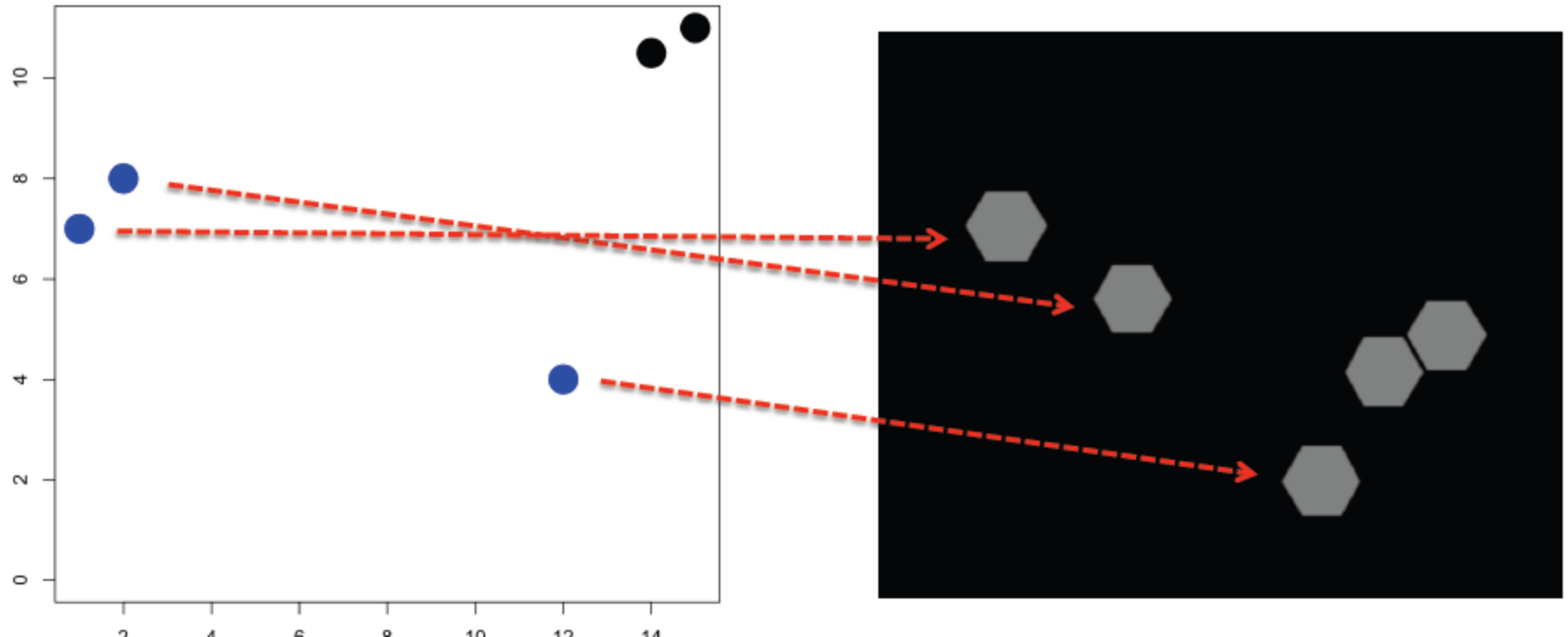
Combined LGG/GBM expression data



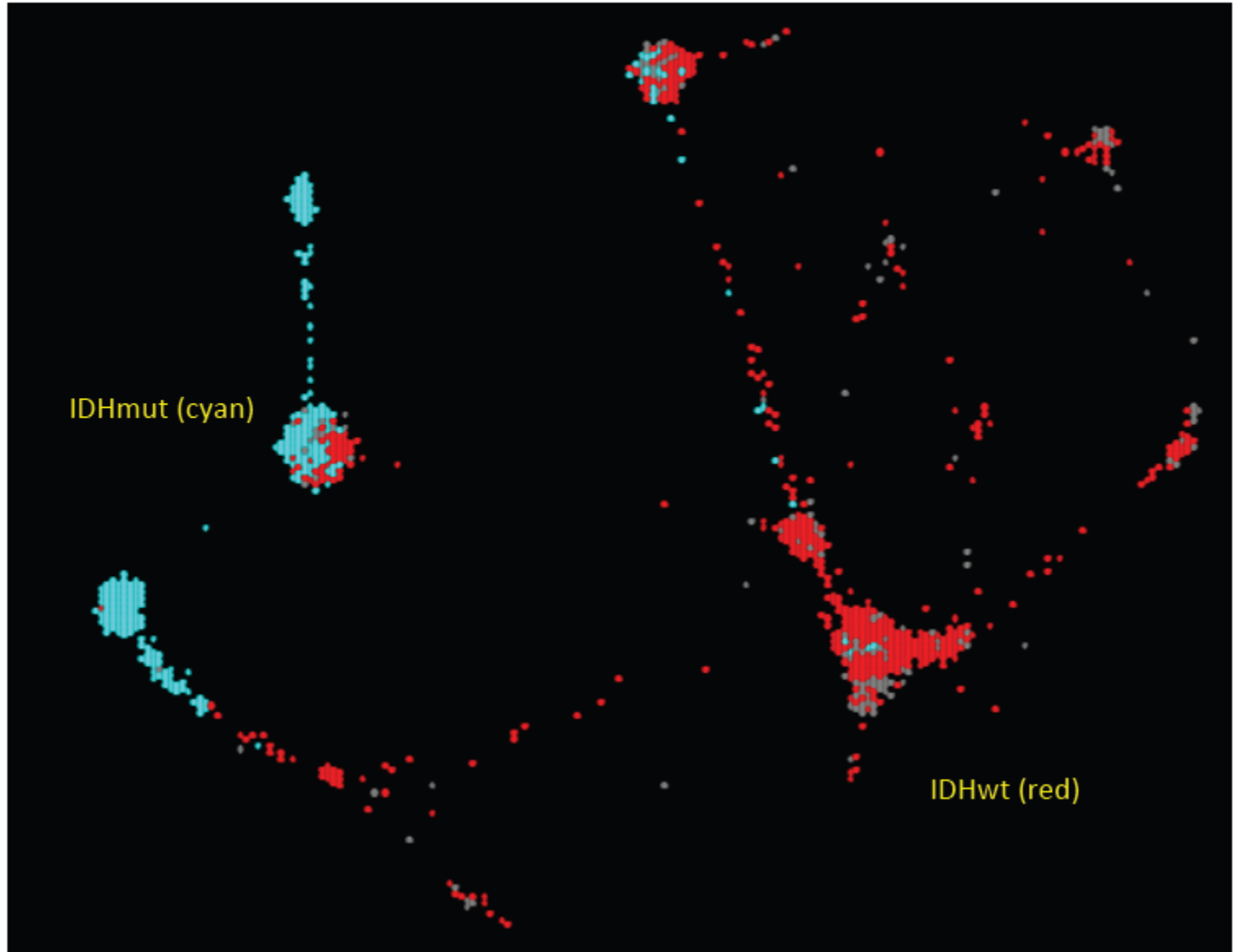

GBM
LGG
Tumor
Mut
NA
WT
IDHmut Status
IDHmut-codel
IDHmut-intact
IDHwt
NA
LGGsubtype
Classical
Mesenchymal
NA
Neural
Proneural
GBMClusterSubtype
Strong LGG
Intermediate
Strong GBM
Tumor
IDHmut Status
LGGsubtype
GBMClusterSubtype
platform

Tumor Map Data Visualization

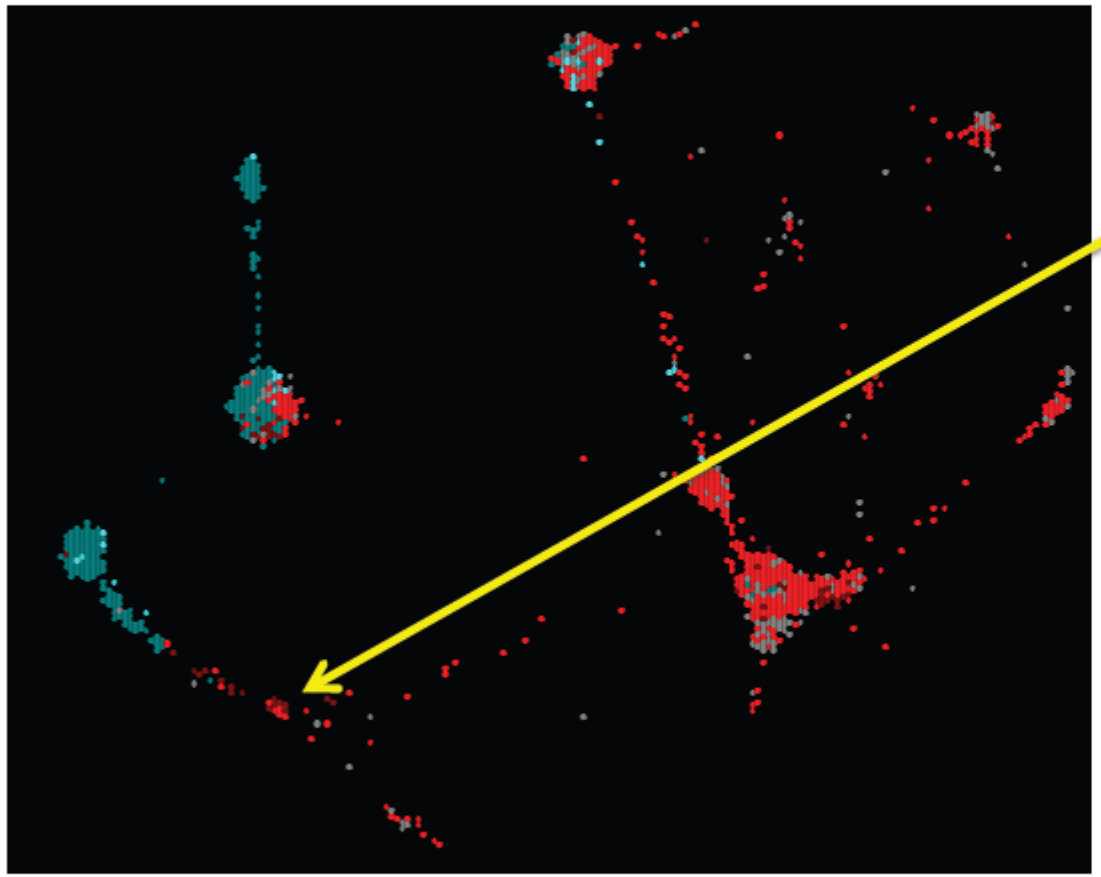
- Way to visualize high-dimensional data in more than 2 dimensions
  - Attributes and layers
- SOM-like relative distance layout logic
  - Samples that are close are laid out near from each other on the map
  - Samples that are distant are laid out at a distance on the map



Tumor Map Shows Separation of IDHmut and IDHwt Molecular Subtypes

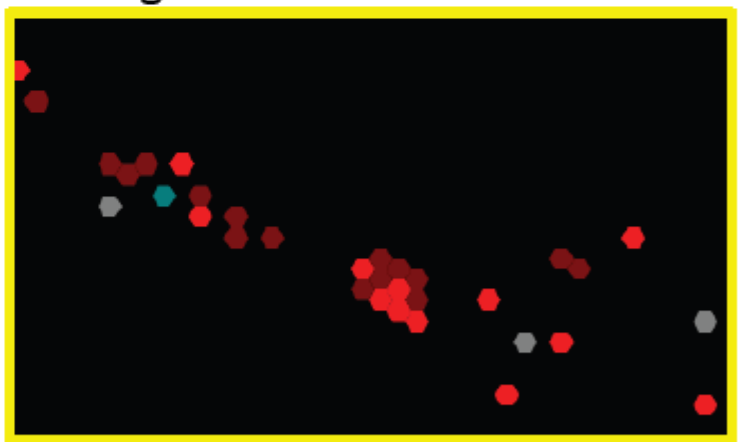


Tumor Map Shows Some LGG IDHwt Cluster with GBM IDHwt



LGG IDHwt mixed with GBM IDHwt

Mixing of LGG and GBM IDHwt:



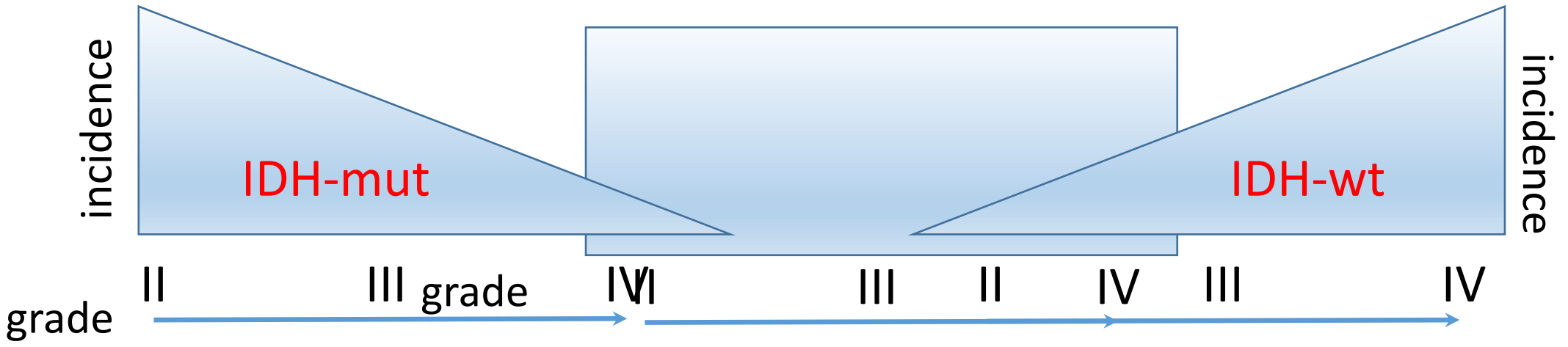
Dark red – **LGG** IDHwt
Bright red – **GBM** IDHwt

What have we learned from the TCGA glioma effort?

- Multiplatform genomic analyses if a powerful approach towards understanding glioma biology
  - allows inter-platform comparisons and detailed analysis of a large sample set
- IDH mutation as a fundamental

Understanding LGG and GBM in the context of IDH mutations

IDH mutation status	Traditional designation	Clinical presentation
Wild type	De novo pathway	Usually as GBM
Mutant	Secondary GBM pathway	Usually as lower grade



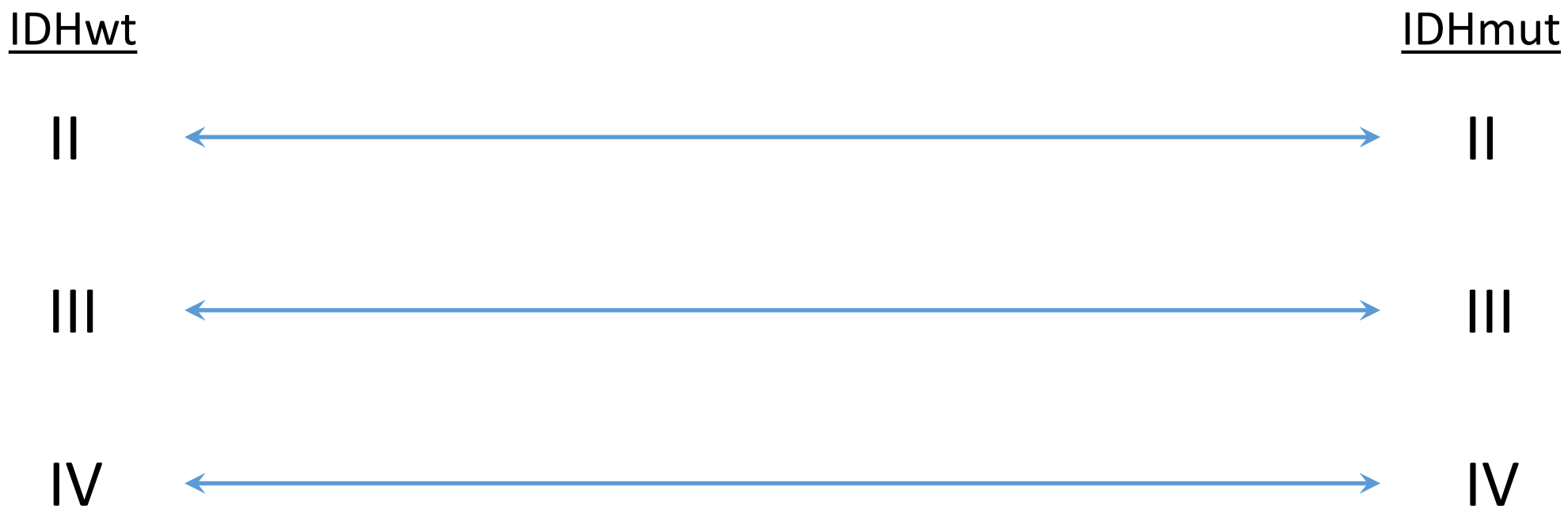
Re-thinking relationships among diffuse glioma entities

II

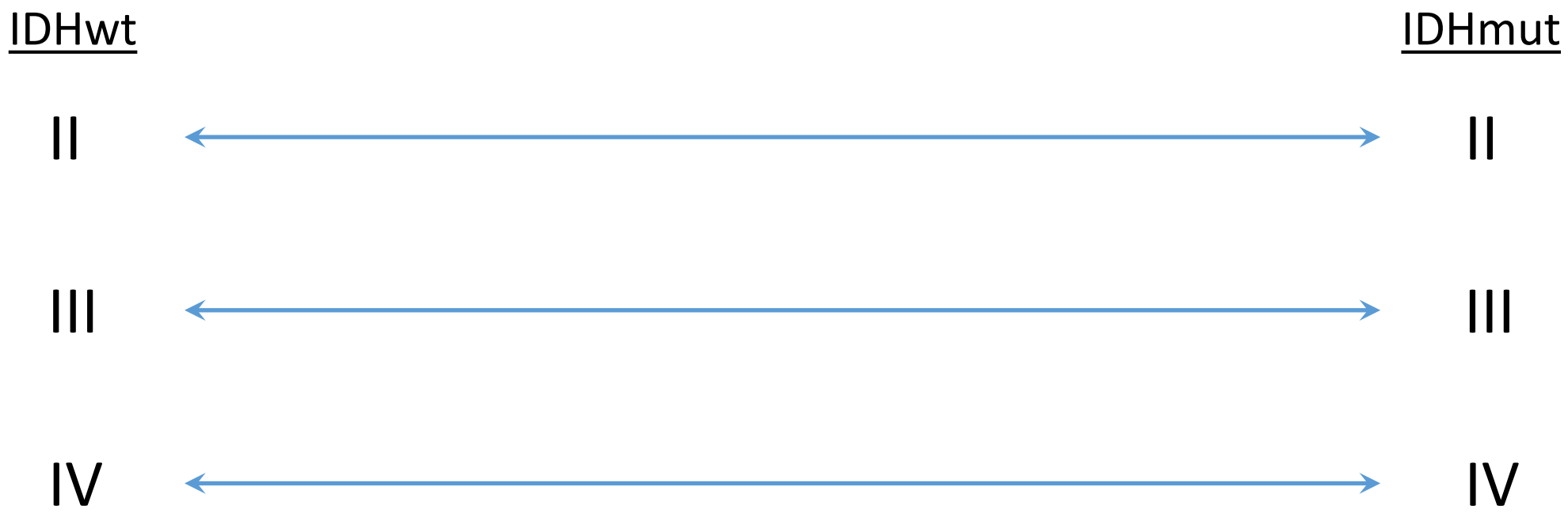
III

IV

Re-thinking relationships among diffuse glioma entities

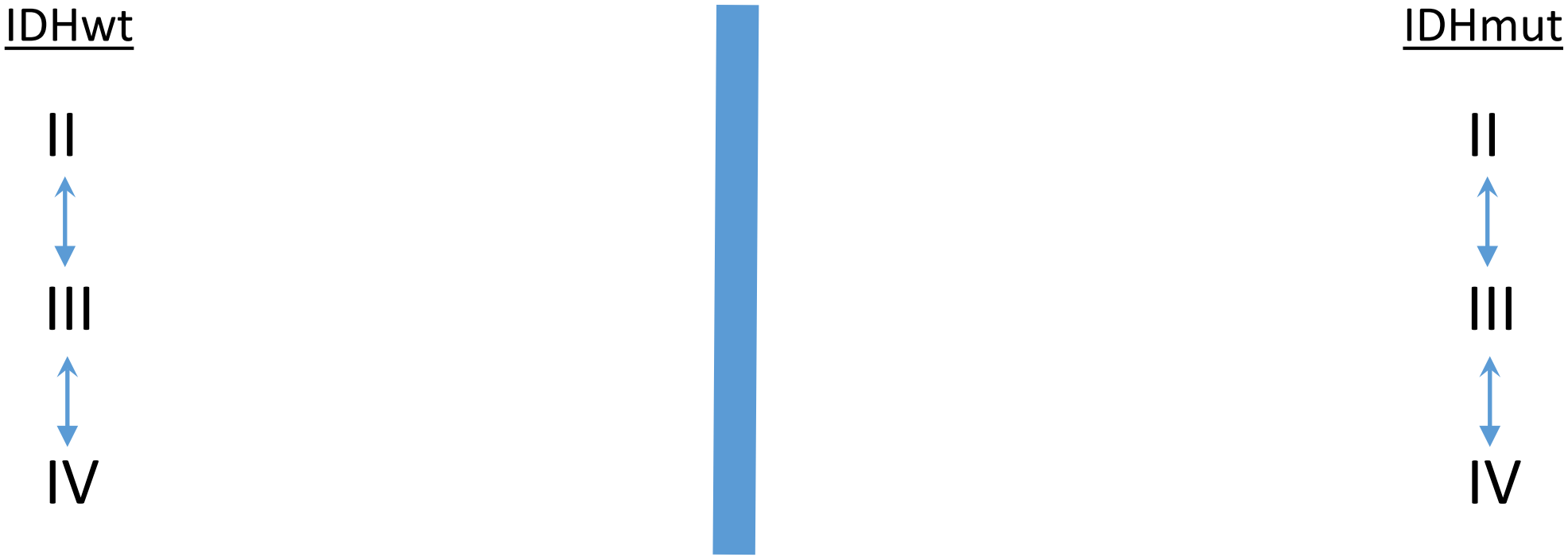


Re-thinking relationships among diffuse glioma entities



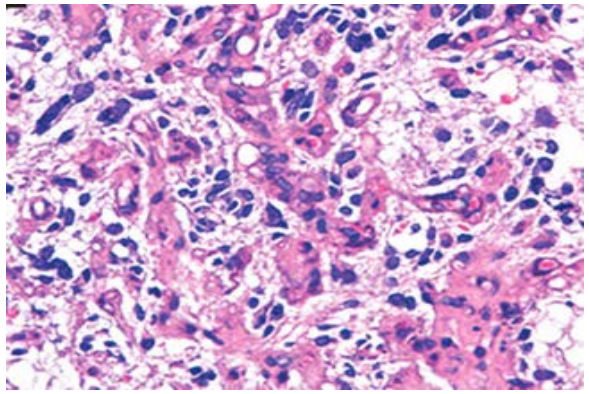
Re-thinking relationships among diffuse glioma entities

Re-thinking relationships among diffuse glioma entities

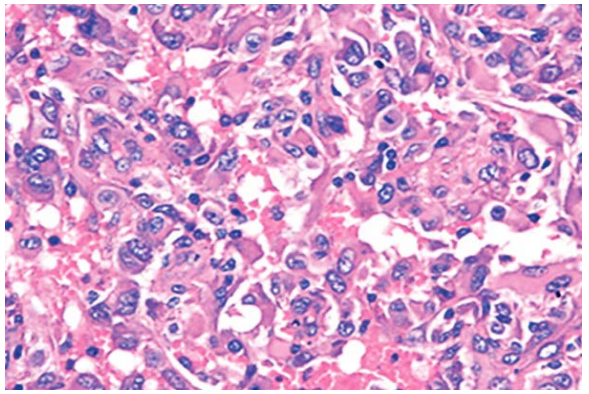


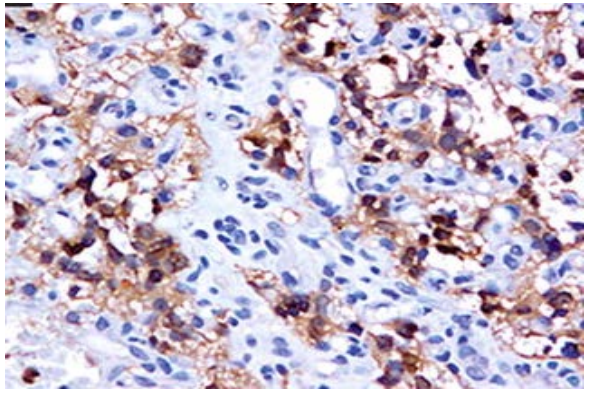
Histology can be deceiving?

GBM

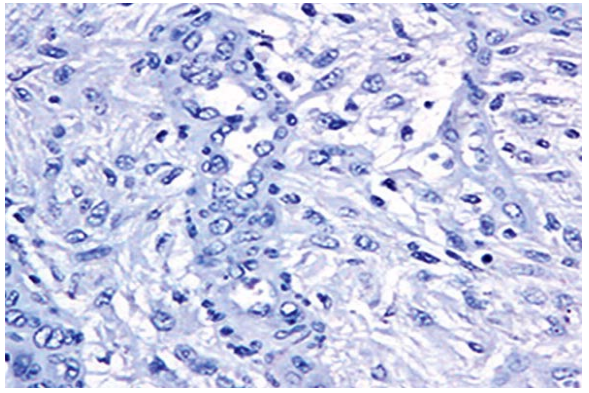


GBM





GBM-IDHmut



GBM-IDHwt

Some questions raised by TCGA data analysis of GBM and LGG

- What are the drivers of progression for IDH-mutant diffuse glioma?
- What is the relationship of IDHwt LGG to IDHwt GBM?
- Should IDHwt lower grade glioma be clinically considered and treated as GBM?

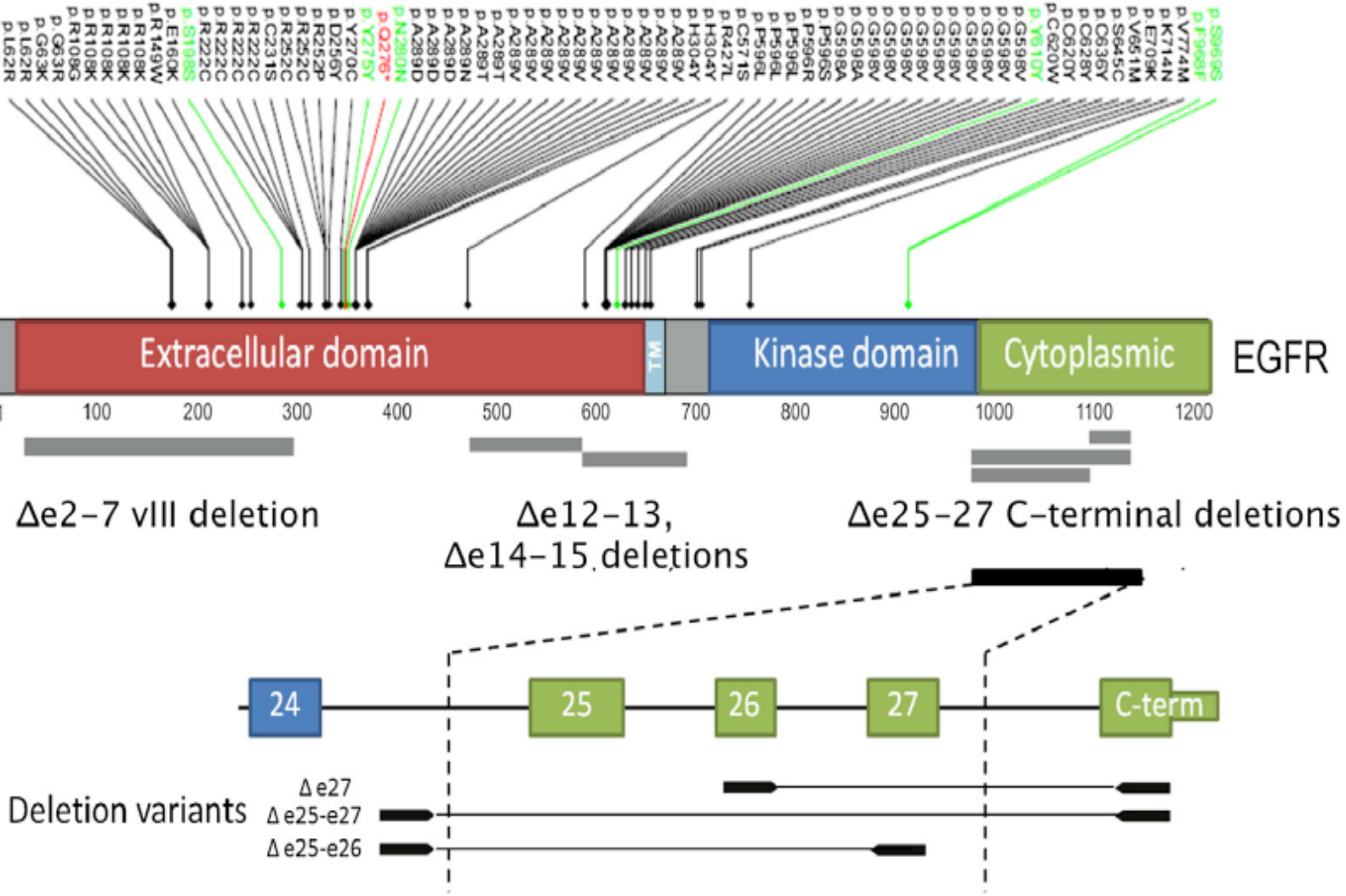
Next-generation TCGA project for diffuse glioma?

Past	Future
GBM vs. grade II-III glioma	IDHwt vs. IDHmut diffuse glioma
Retrospectively collected samples	Prospectively collected samples
Heterogeneous clinical f/u	Incorporated clinical f/u plan
Bulk tumor profiled	Incorporate single cell profiling
Adult patients	Children and adult patients
Pre-treatment sample only	Matched pre- and post-treatment samples
Tissue requirements limiting (frozen tissue/blood, etc)	Tissue requirements less restrictive (?FFPE/?better support for frozen tissue banking)
No companion biologic studies	Primary cultures/companion functional studies
Heterogeneous therapies	Cohorts of uniformly treated patients
Results without impact on patients under study	Real-time CLIA testing/integration with clinical trials

TCGA GBM effort

- Success of team science
- Large sample size with robust genome-wide platform analyses have allowed insights into glioma biology
  - Mutational spectrum
  - Refinement of transcriptomal subtypes
  - Targetable alterations including fusion transcripts
  - “primacy” of IDH mutation as and link to epigenetic changes
- Future efforts will undoubtedly focus on clinical relevance and implications of key genomic findings in glioma

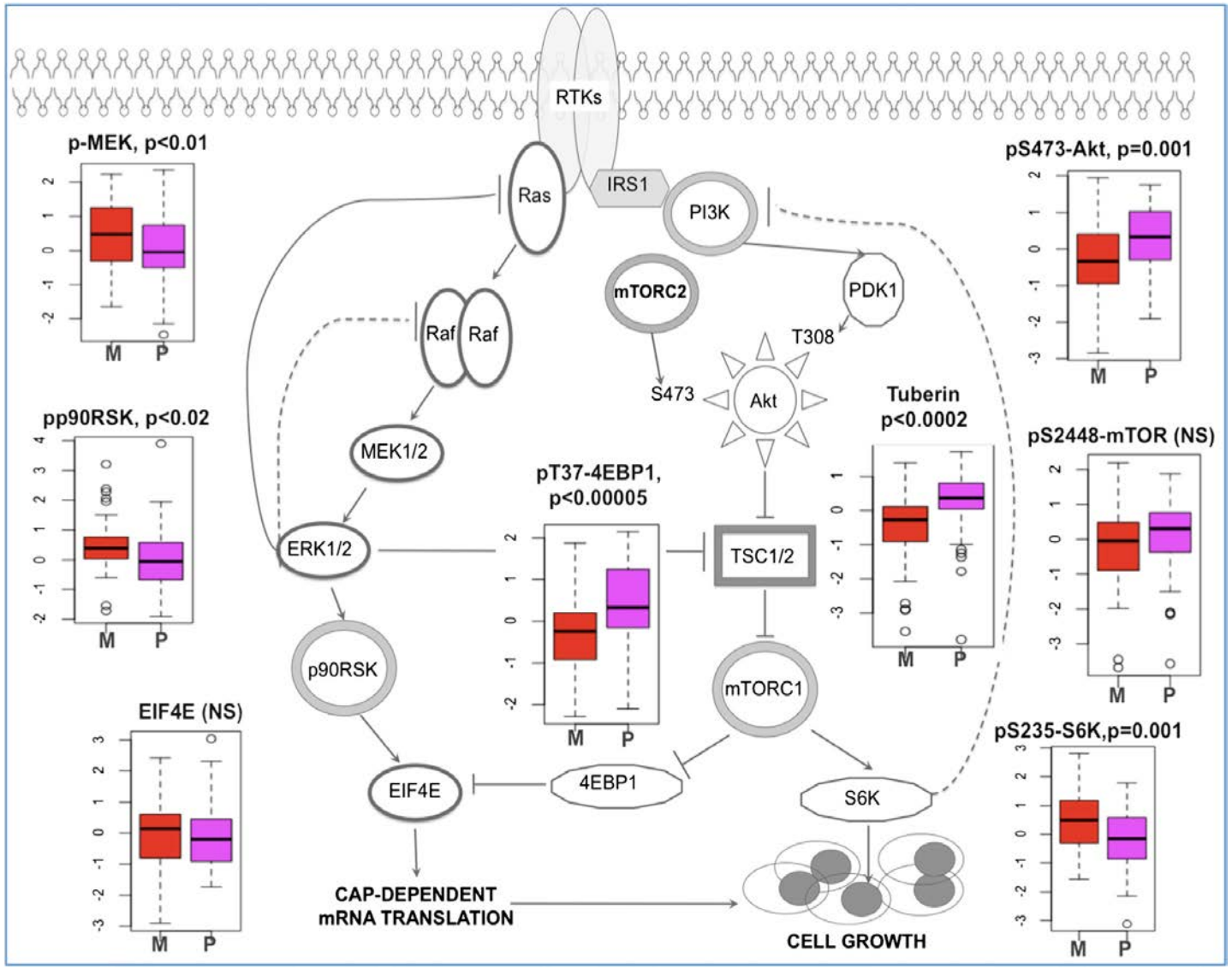
EGFR mutations/fusions characterized



57% of GBM with evidence of mutation, rearrangement, altered splicing, and/or focal amplification of EGFR.

- impact of specific genomic alterations on downstream pathway signaling is not linear not always predictably concordant with genotype.

Targeted proteomic profile



Intratumoral heterogeneity of receptor tyrosine kinases EGFR and PDGFRA amplification in glioblastoma defines subpopulations with distinct growth factor response

Nicholas J. Szerlip[a], Alicia Pedraza[b], Debyani Chakravarty[b], Mohammad Azim[c], Jeremy McGuire[c], Yuqiang Fang[d], Tatsuya Ozawa[e], Eric C. Holland[e,f,g,h], Jason T. Huse[d,h], Suresh Jhanwar[d], Margaret A. Leversha[c], Tom Mikkelsen[i], and Cameron W. Brennan[b,f,h,1]

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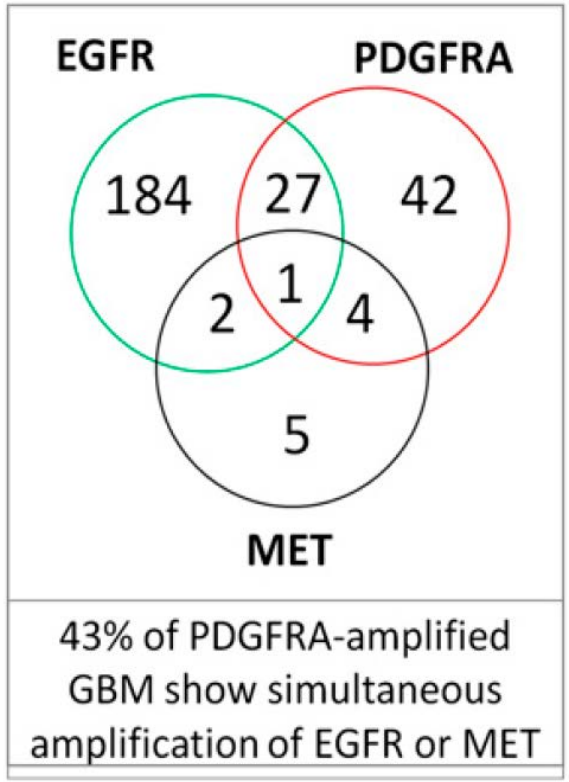
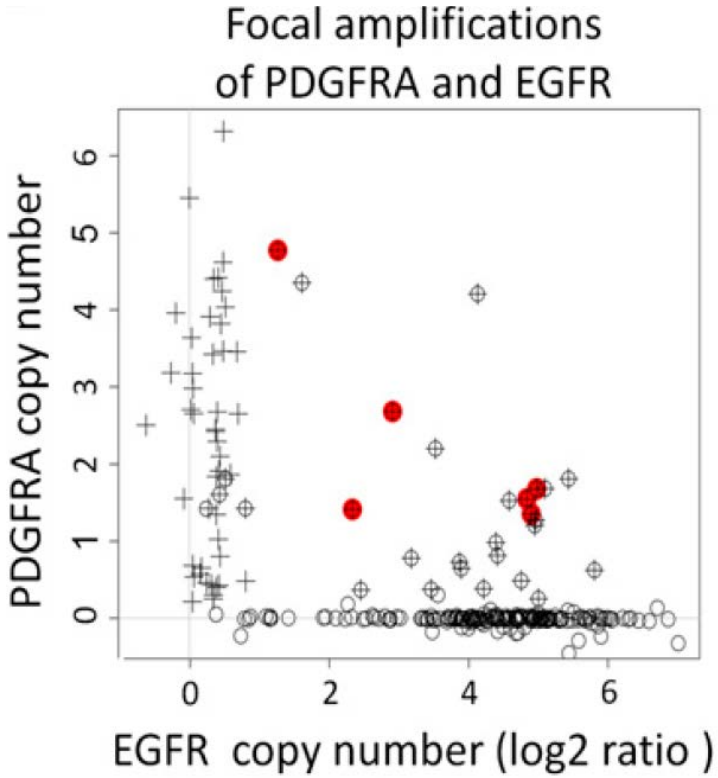


43% of PDGFRA-amplified GBM show simultaneous amplification of EGFR or MET



Cancer Cell
Article

Mosaic Amplification of Multiple Receptor Tyrosine Kinase Genes in Glioblastoma

Matija Snuderl,[1,6] Ladan Fazlollahi,[1,6] Long P. Le,[1] Mai Nitta,[1] Boryana H. Zhelyazkova,[1] Christian J. Davidson,[1] Sara Akhavanfard,[1] Daniel P. Cahill,[2,4] Kenneth D. Aldape,[3,4] Rebecca A. Betensky,[5] David N. Louis,[1] and A. John Iafrate[1,*]
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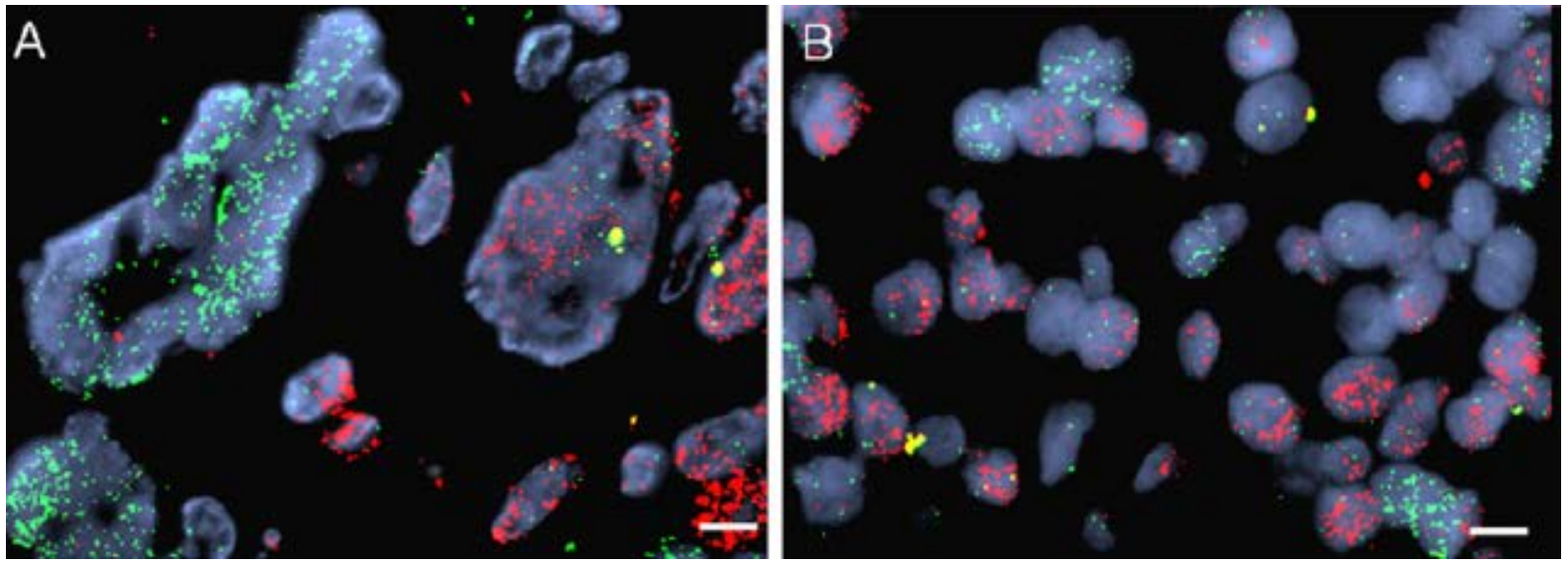
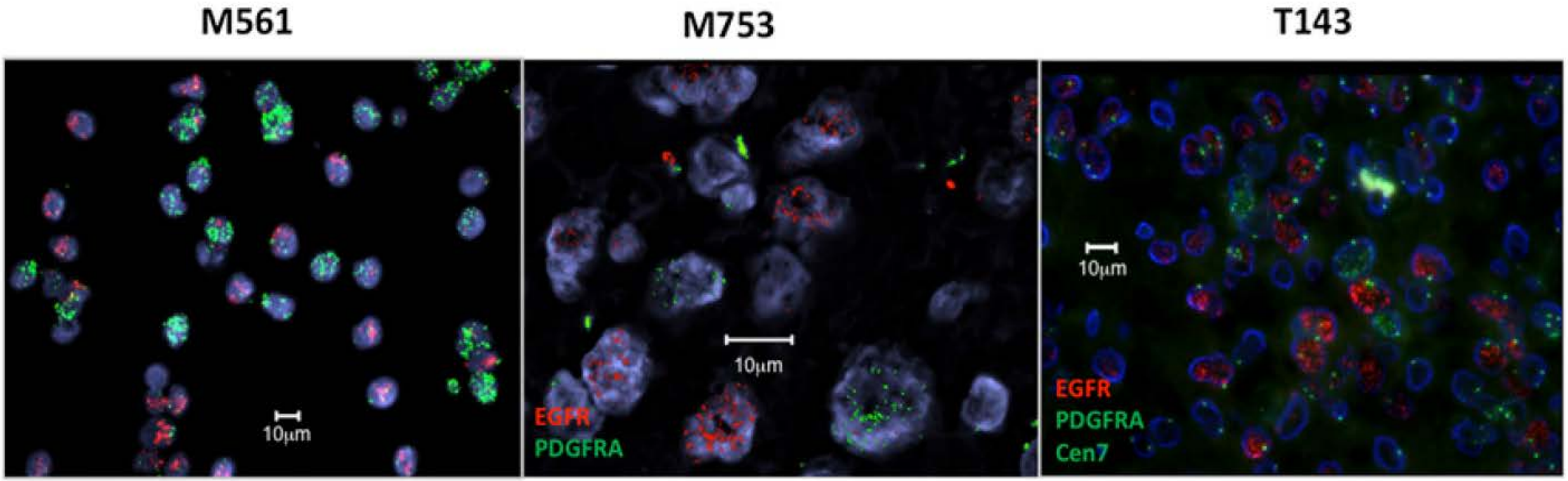
DOI 10.1016/j.ccr.2011.11.005



Intratumoral heterogeneity of RTK amplification in GBM



Implications of RTK co-amplification for clinical practice/clinical trials

- RTK co-amplification present in ~5% of GBM
- But co-amplification of alternate RTK present in 43% of PDGFRA-amplified tumors
  - Implications for targeted therapy trials with PDGFR inhibitors

TERT promoter mutation in GBM

- C228T mutation in 15/25 cases
- C250T variant was found in another six cases
- TERT promoter mutations at these two hot spots were correlated with upregulated TERT expression at the RNA level