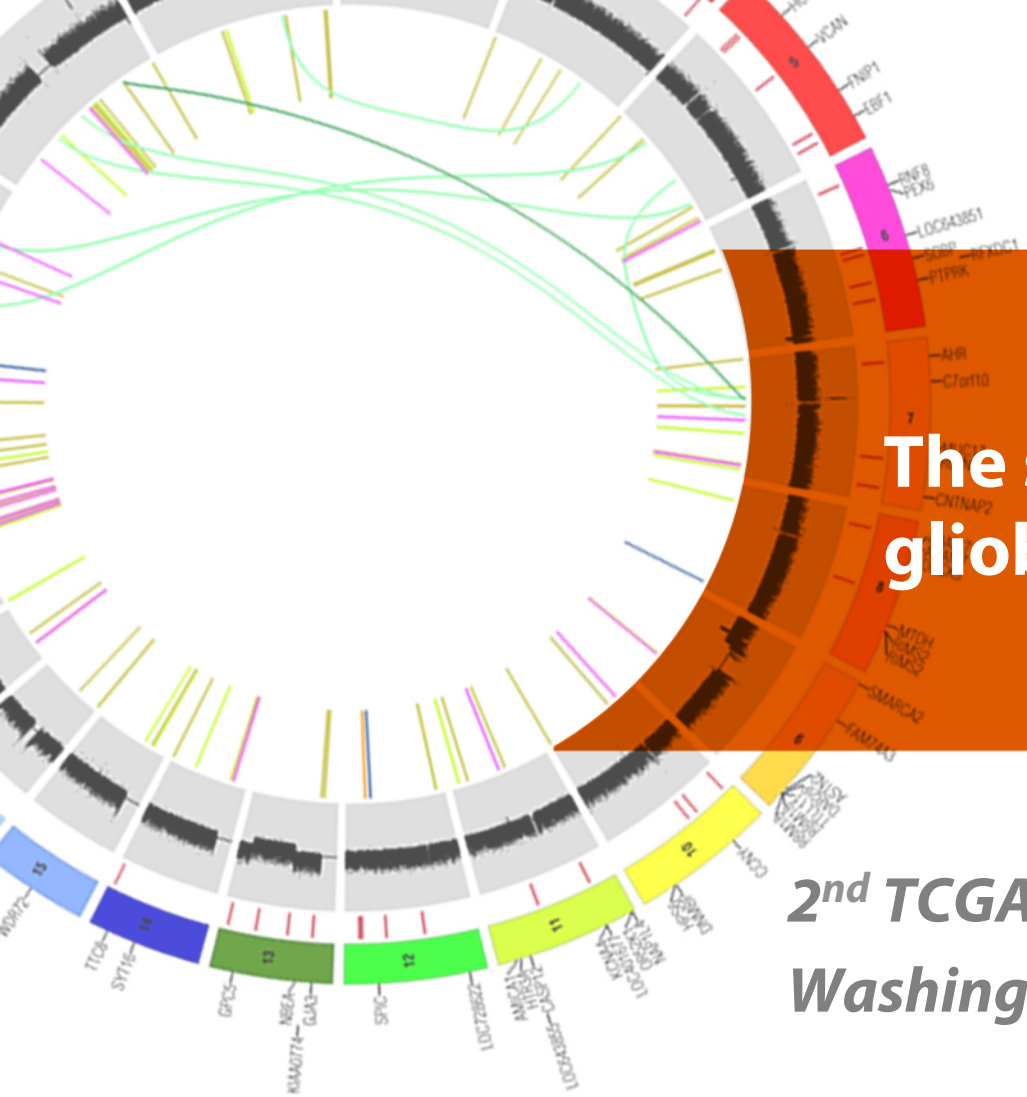


The Cancer Genome Atlas

The somatic landscape of glioblastoma multiforme

2nd TCGA Scientific Symposium

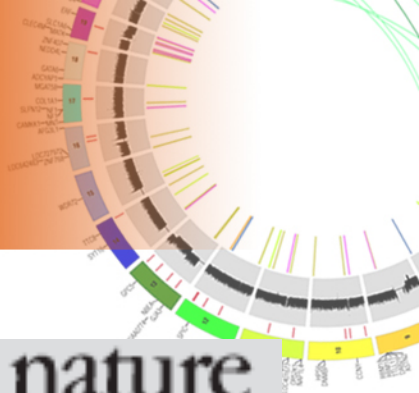
Washington, DC

*Roel Verhaak, PhD – **rverhaak@mdanderson.org***

UT MD Anderson Cancer Center, Houston, TX

A GBM marker study…?! I thought you guys did one already…..!!

A GBM marker study…?! I thought you guys did one already…..!!



nature
ARTICLES

Comprehensive genomic characterization defines human glioblastoma genes and core pathways

The Cancer Genome Atlas Research Network*

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

98 Cancer Cell *17*, 98–110, January 19, 2010 ©2010 Elsevier Inc.

Cancer Cell
Article

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

510 Cancer Cell *17*, 510–522, May 18, 2010 ©2010 Elsevier Inc.

Cancer Cell
Article

Comparison of 2008/2010 data set versus current data set

Data Type	Cases in 2008
DNA sequence of exome **600 genes*	91*
DNA sequence of whole genome	0
DNA copy number	206
Genotypes	206
mRNA expression profiling	206
mRNA sequencing	0
CpG DNA Methylation	242
miRNA expression profiling	205
Protein expression profiling	0
Clinical characteristics	206

Comparison of 2008/2010 data set versus current data set

Data Type	Cases in 2008	Cases in 2012
DNA sequence of exome **600 genes*	91*	**291**
DNA sequence of whole genome	0	**17**
DNA copy number	206	**578**
Genotypes	206	**413**
mRNA expression profiling	206	**544**
mRNA sequencing	0	**164**
CpG DNA Methylation	242	**545**
miRNA expression profiling	205	**491**
Protein expression profiling	0	**214**
Clinical characteristics	206	**543**

71 genes are significantly mutated in 291 GBMs

Gene	description	n	q	Frequency
TP53	tumor protein p53	100	<0.001	34.4%
EGFR	epidermal growth factor receptor	95	<0.001	32.6%
PTEN	phosphatase and tensin homolog	93	<0.001	32%
NF1	neurofibromin 1	40	<0.001	13.7%
PIK3CA	phosphoinositide-3-kinase, catalytic, alpha polypeptide	35	<0.001	12%
PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 alpha	34	<0.001	11.7%
SPTA1	spectrin, alpha, erythrocytic 1 (elliptocytosis 2)	29	<0.001	10%
RB1	retinoblastoma 1	27	<0.001	9.3%
ATRX	alpha thalassemia/mental retardation syndrome	17	0.0022	5.8%
TCHH	trichohyalin	17	0.027	5.8%
IDH1	isocitrate dehydrogenase 1	15	<0.001	5.2%
KEL	Kell blood group, metallo-endopeptidase	15	<0.001	5.2%
ABCC9	ATP-binding cassette, member 9	14	0.0033	4.8%
LZTR1	Leucine Zipper Transcription Regulator 1	10	<0.001	3.4%
PDGFRA	platelet-derived growth factor receptor alpha	13	<0.001	4.5%

71 genes are significantly mutated in 291 GBMs including many novel genes

Gene	description	n	q	Frequency
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ATRX	**alpha thalassemia/mental retardation syndrome**	**17**	**0.002**	**5.8%**
TCHH	**trichohyalin**	**17**	**0.027**	**5.8%**
IDH1	isocitrate dehydrogenase 1	15	<0.001	5.2%
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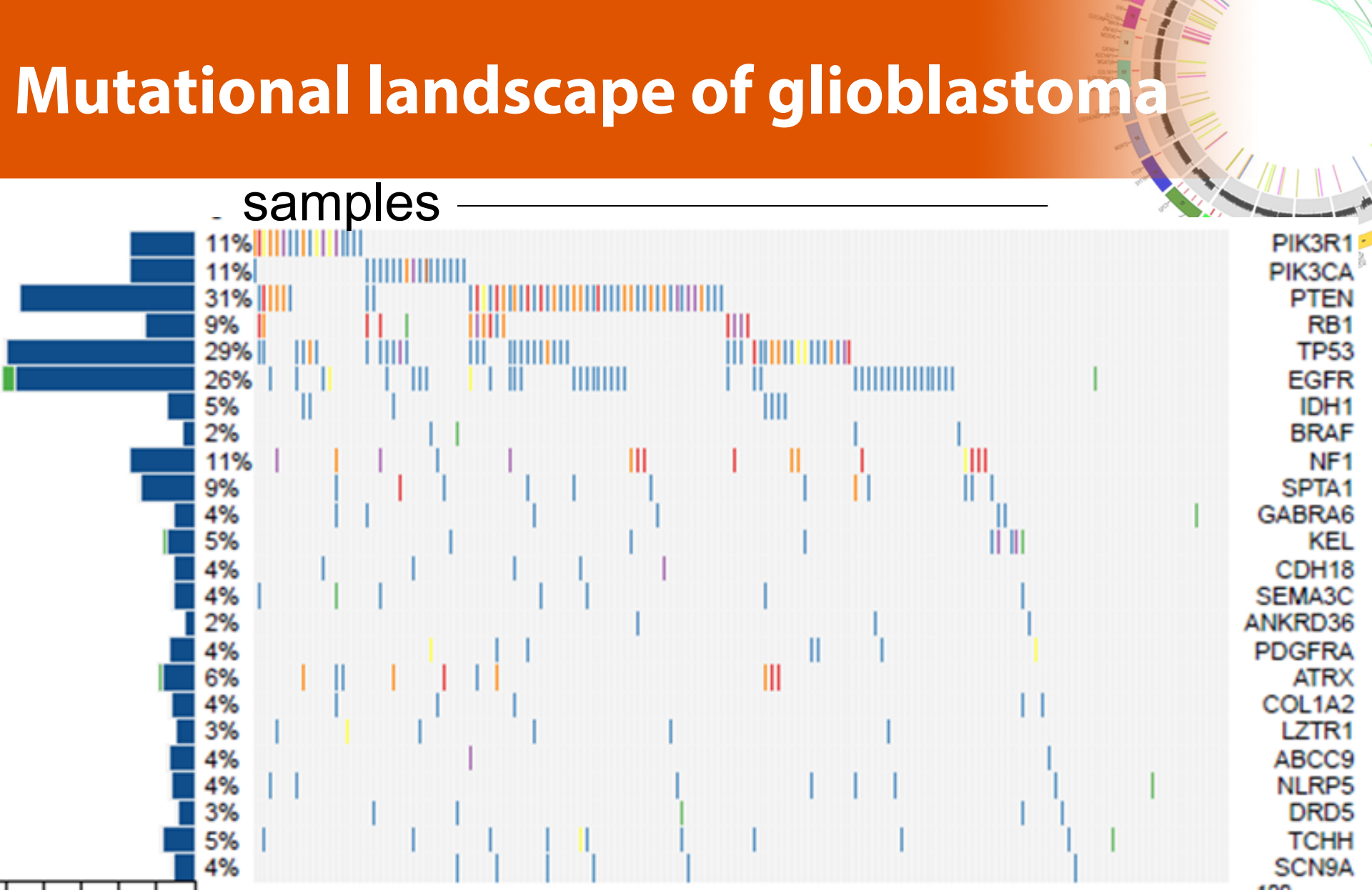
ABCC9	**ATP-binding cassette, member 9**	**14**	**0.0033**	**4.8%**
LZTR1	**Leucine Zipper Transcription Regulator 1**	**10**	**<0.001**	**3.4%**
PDGFRA	platelet-derived growth factor receptor alpha	13	<0.001	4.5%

Mutational landscape of glioblastoma

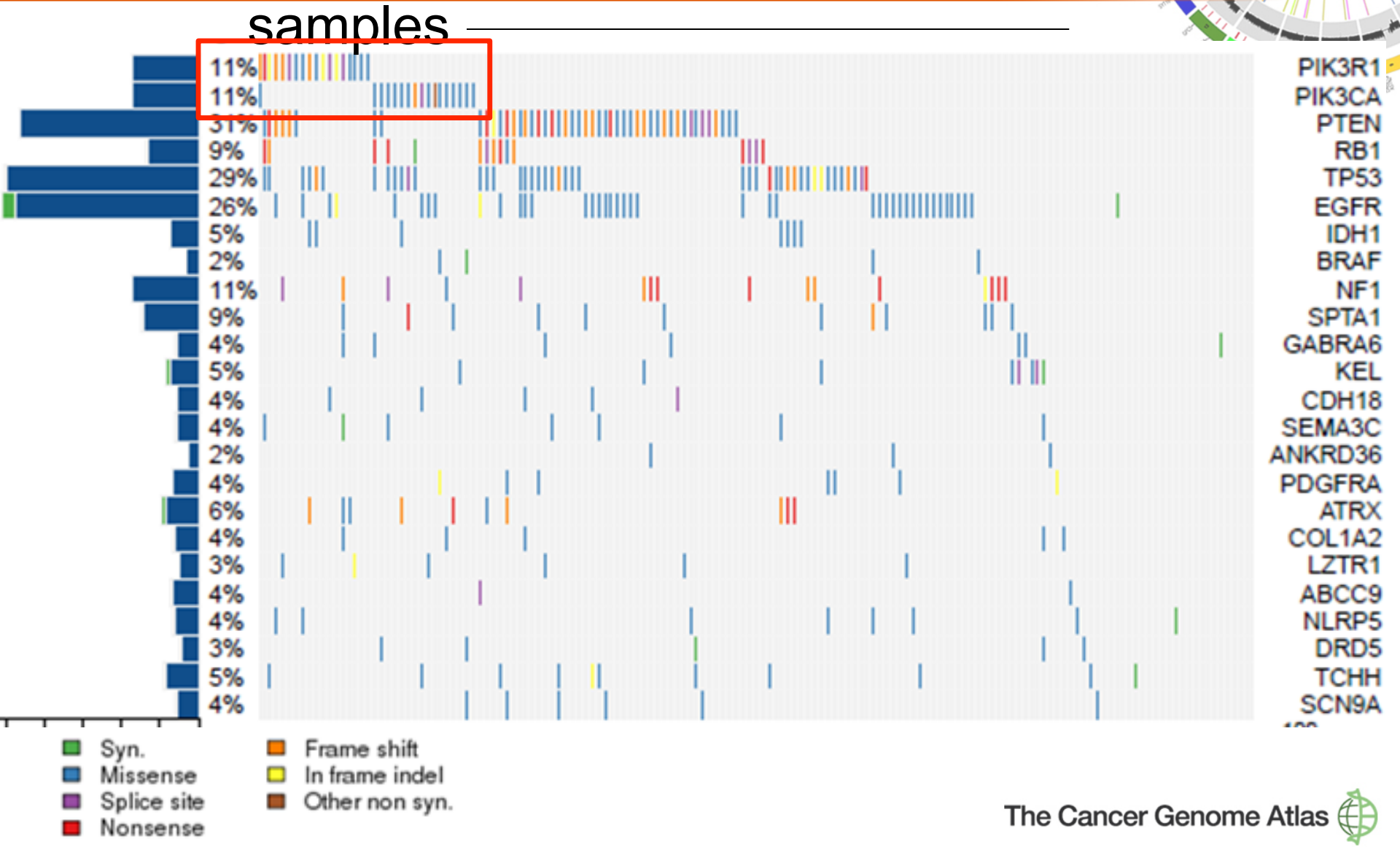


No 'significant gene' mutation found in ~10% of samples

Th

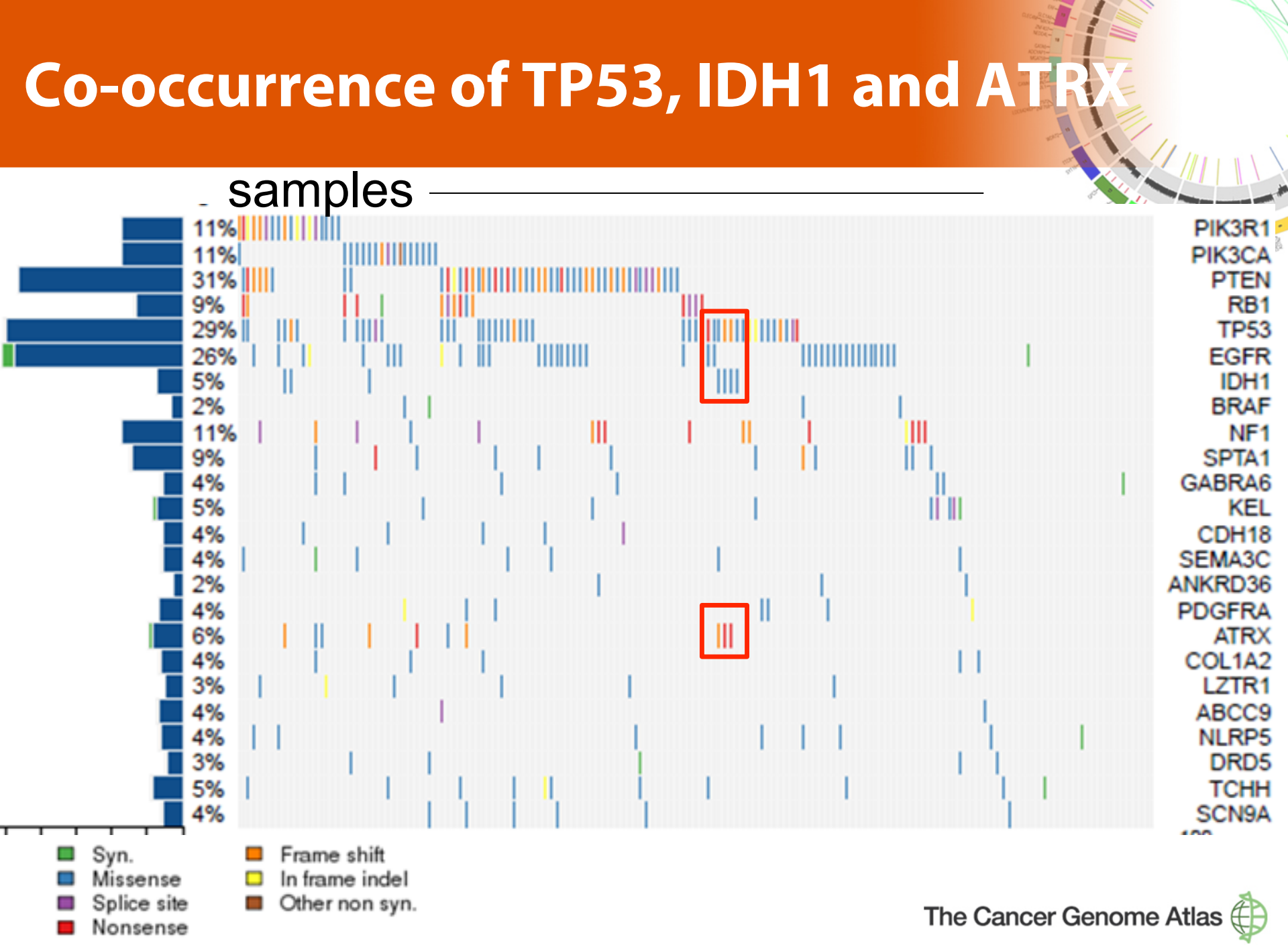
Aaron Mckenna
Broad Institute

Mutual exclusivity of PIK3CA and PIK3R1



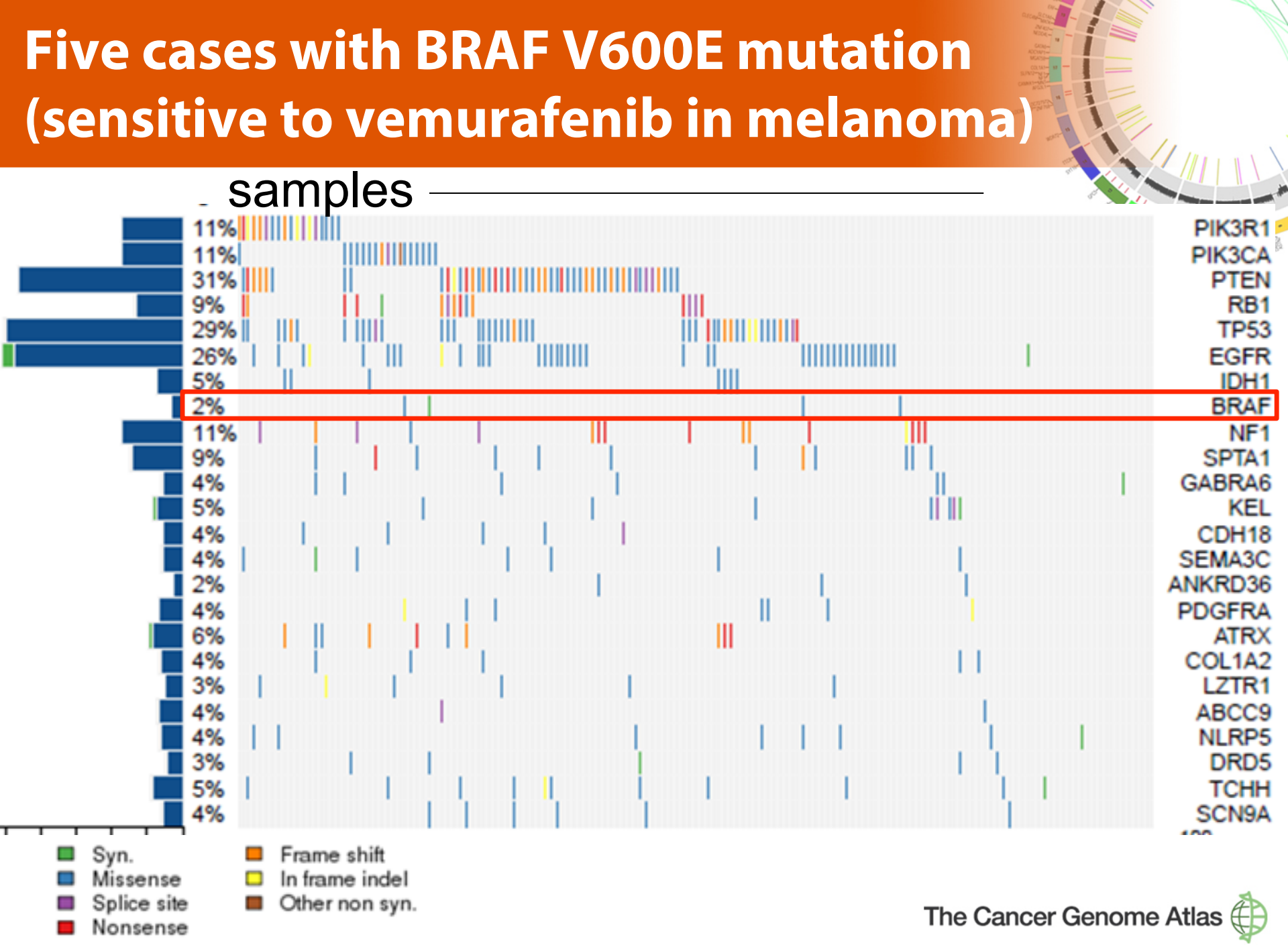
The Cancer Genome Atlas

Co-occurrence of TP53, IDH1 and ATRX

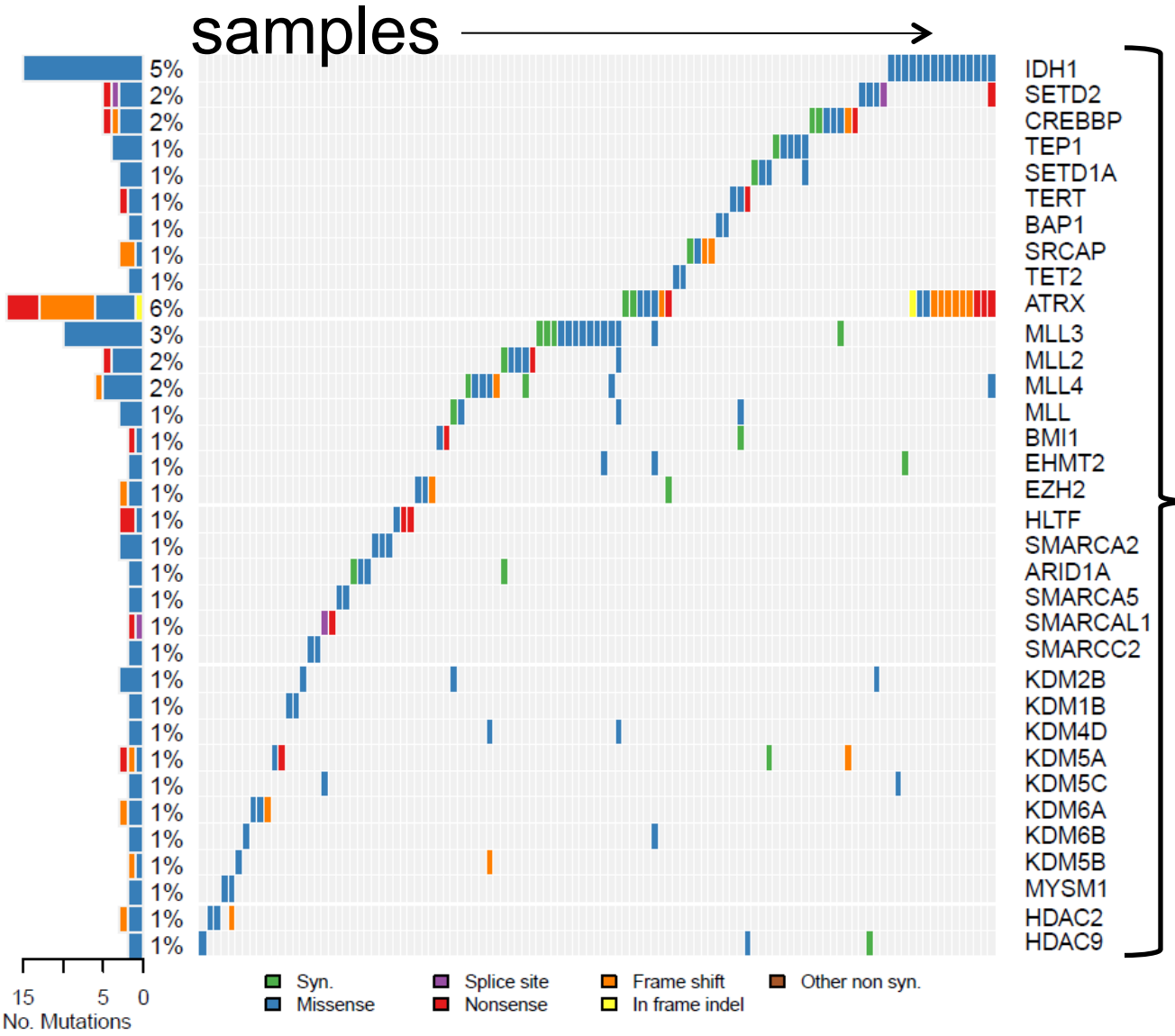


The Cancer Genome Atlas

Five cases with BRAF V600E mutation (sensitive to vemurafenib in melanoma)



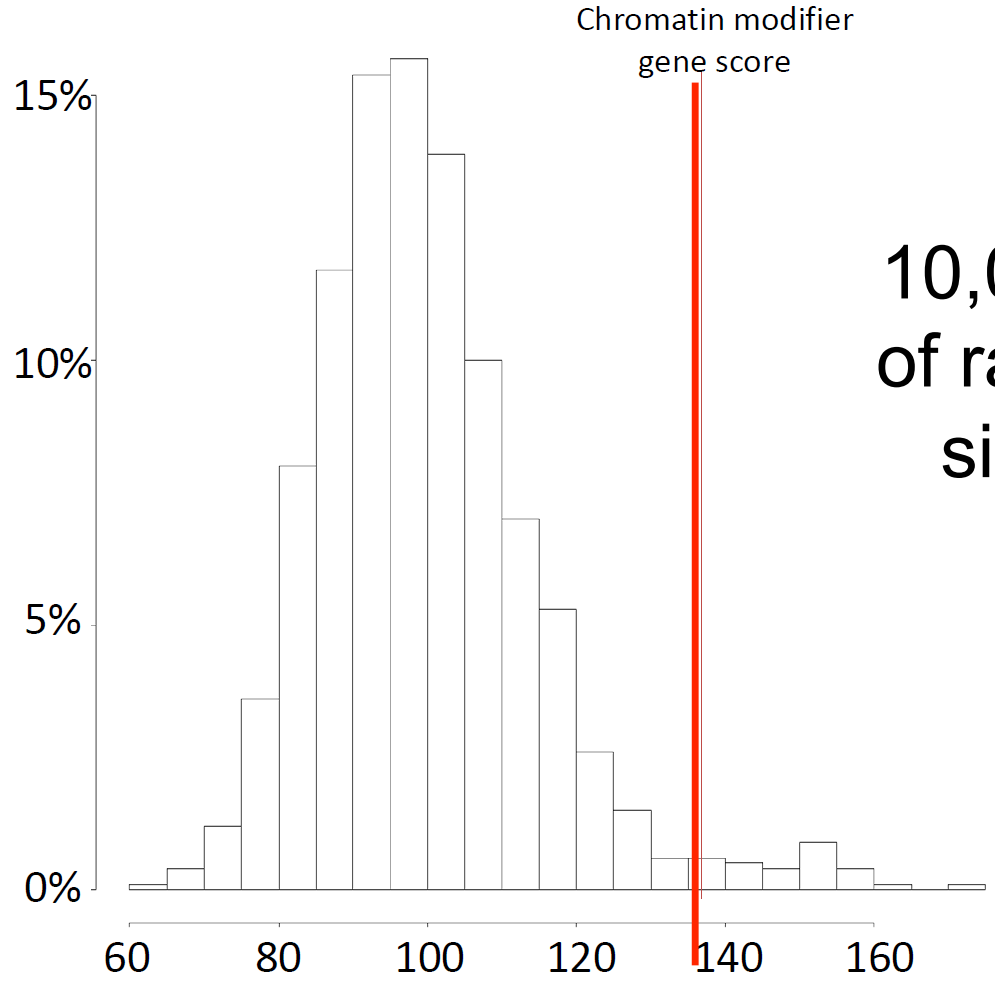
Mutatations in chromatin modifyer genes detected in 41% of GBM



Chromatin modifier genes

Lihua Zou
Dana-Farber

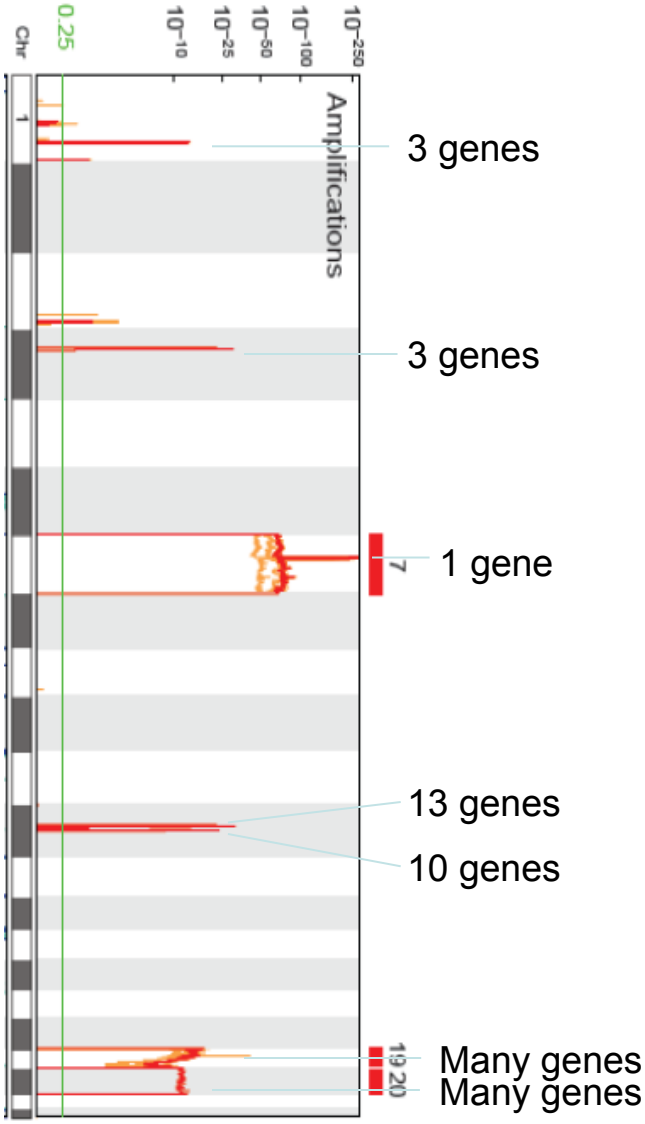
Permutations of similar sized gene sets suggest significance of chromatin remodeling mutations



10,000 permutations of randomly selected similar gene sets

Analysis of >540 samples allows precise definition of CNA target regions

2008:
200
GBMs



Rameen Beroukhim – DFCI

Analysis of >540 samples allows precise definition of CNA target regions

2008:
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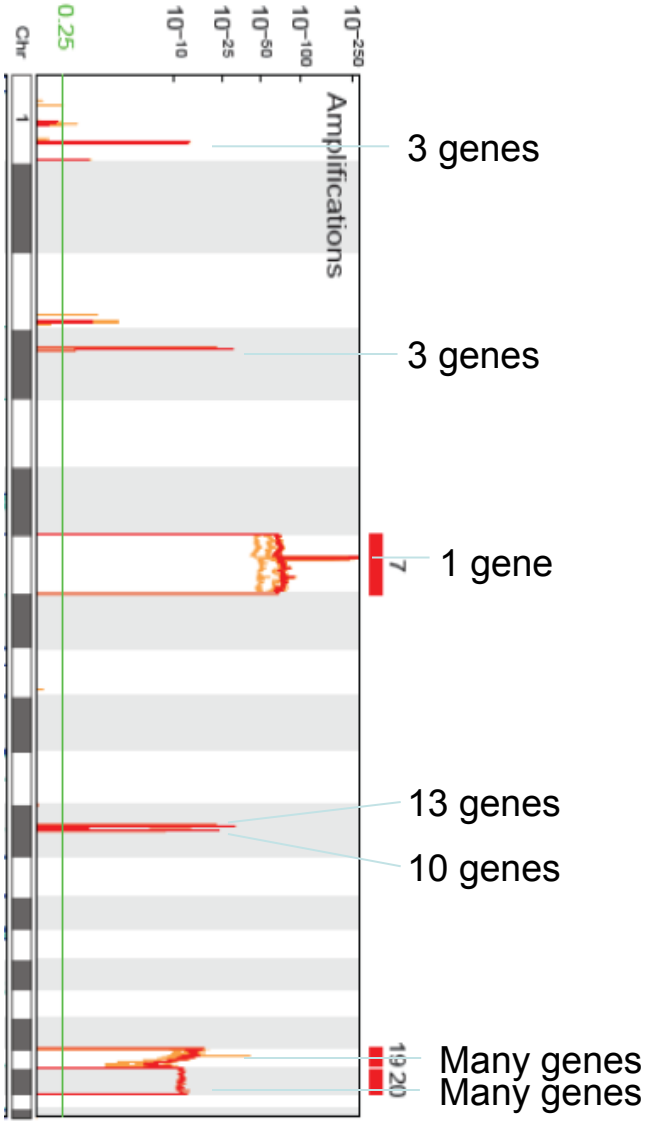
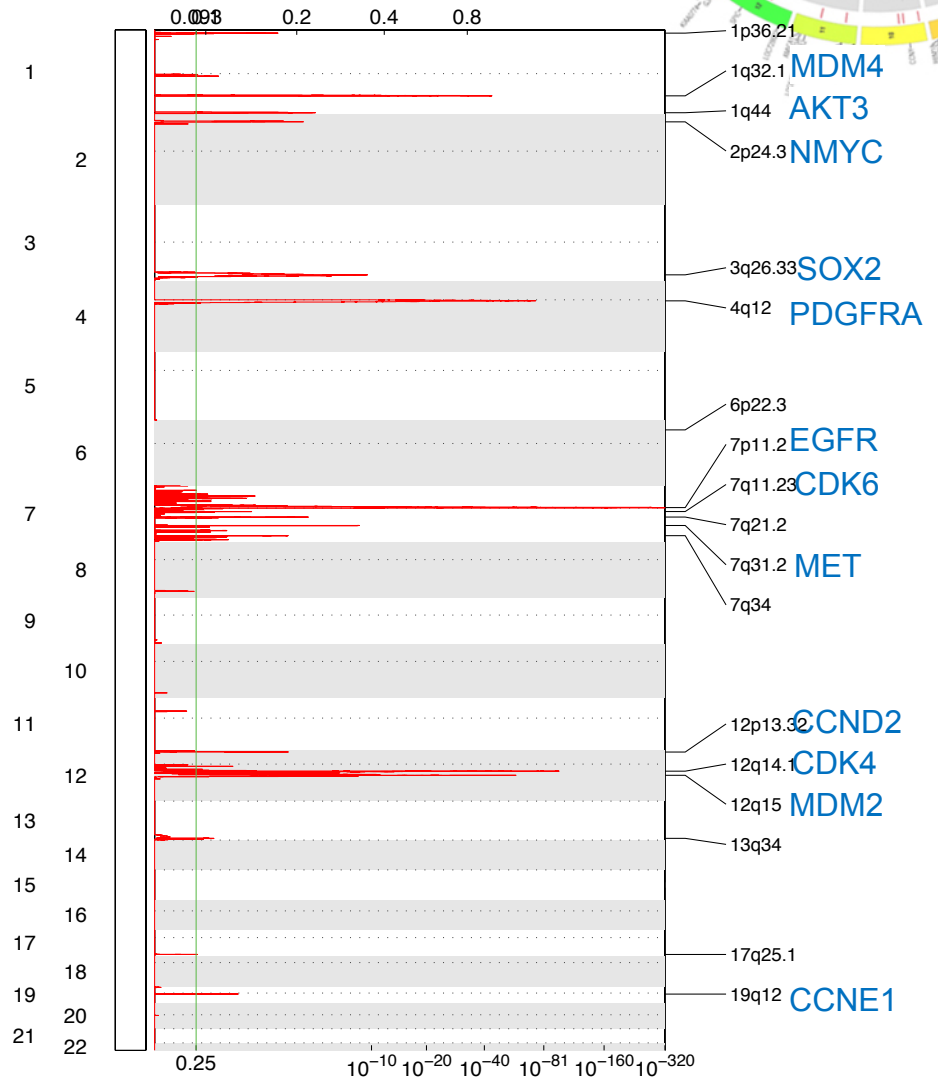
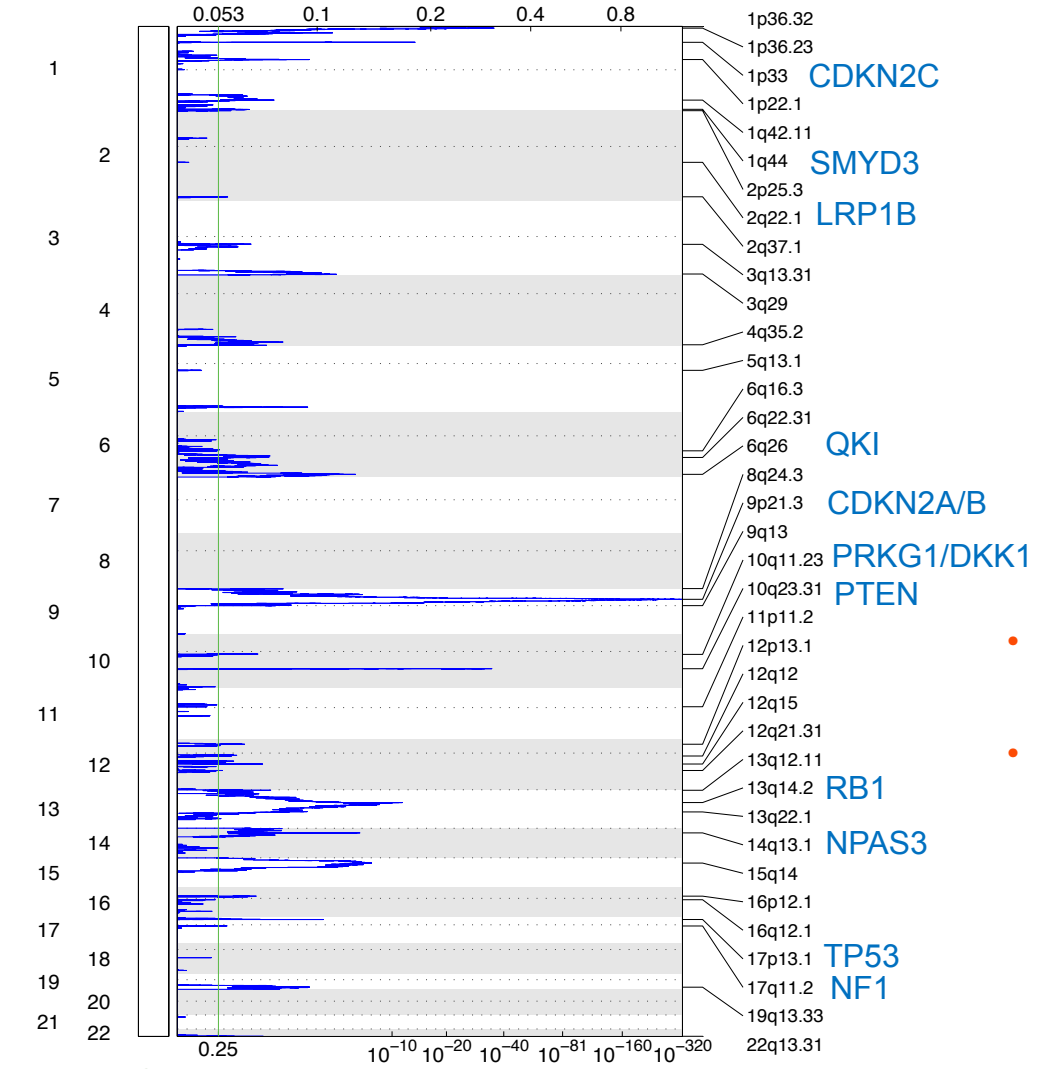




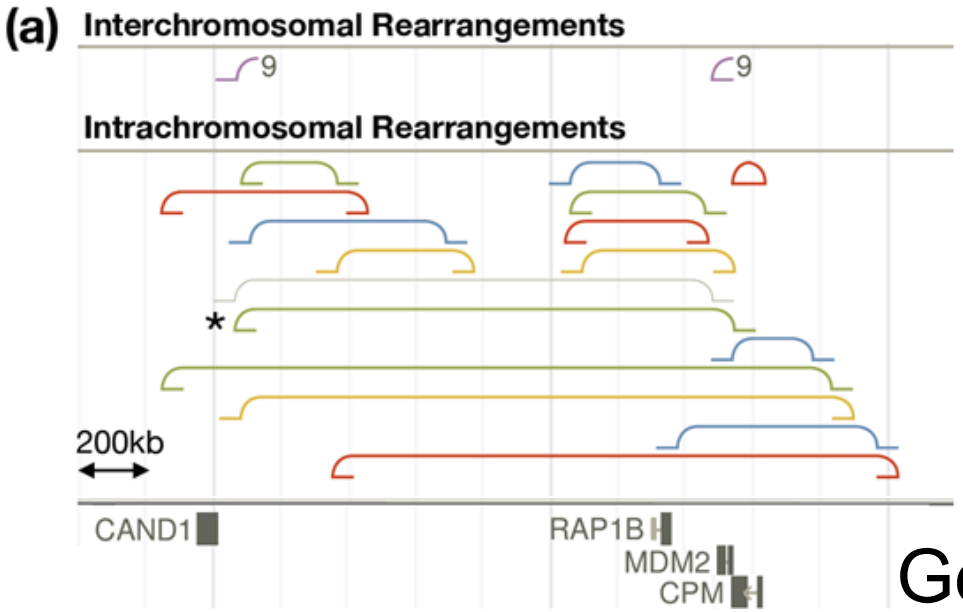
Focal copy number loss targets tumor suppressor genes



- PTEN, QKI, SMYD3, NPAS3 – single gene in focal deletion
- RB1 as one of two genes in focal deletion

Whole genome sequencing identifies complex rearrangements

Chr 12q15



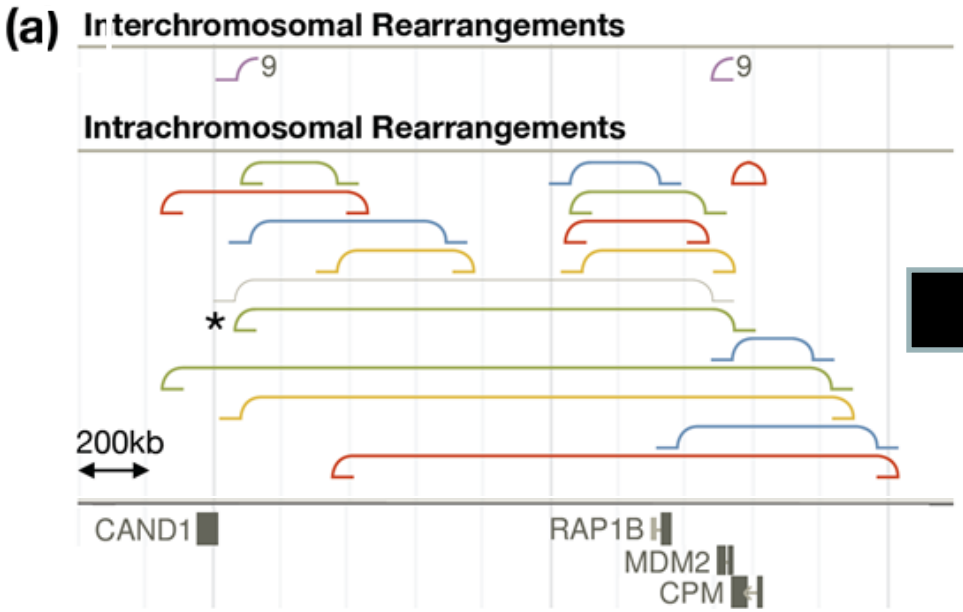
Genome rearrangements

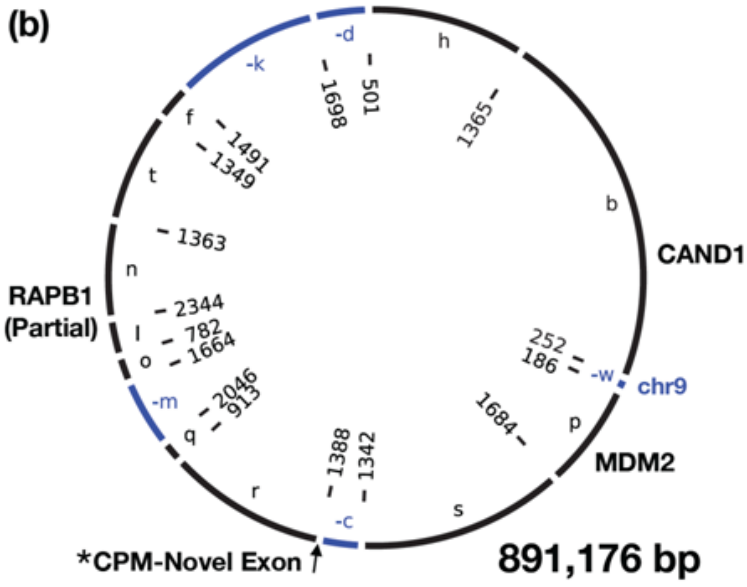
Genes

Zack Sanborn/
Sofie Salama
UCSC

Complex rearrangements can be assembled into double minutes

Chr 12q15

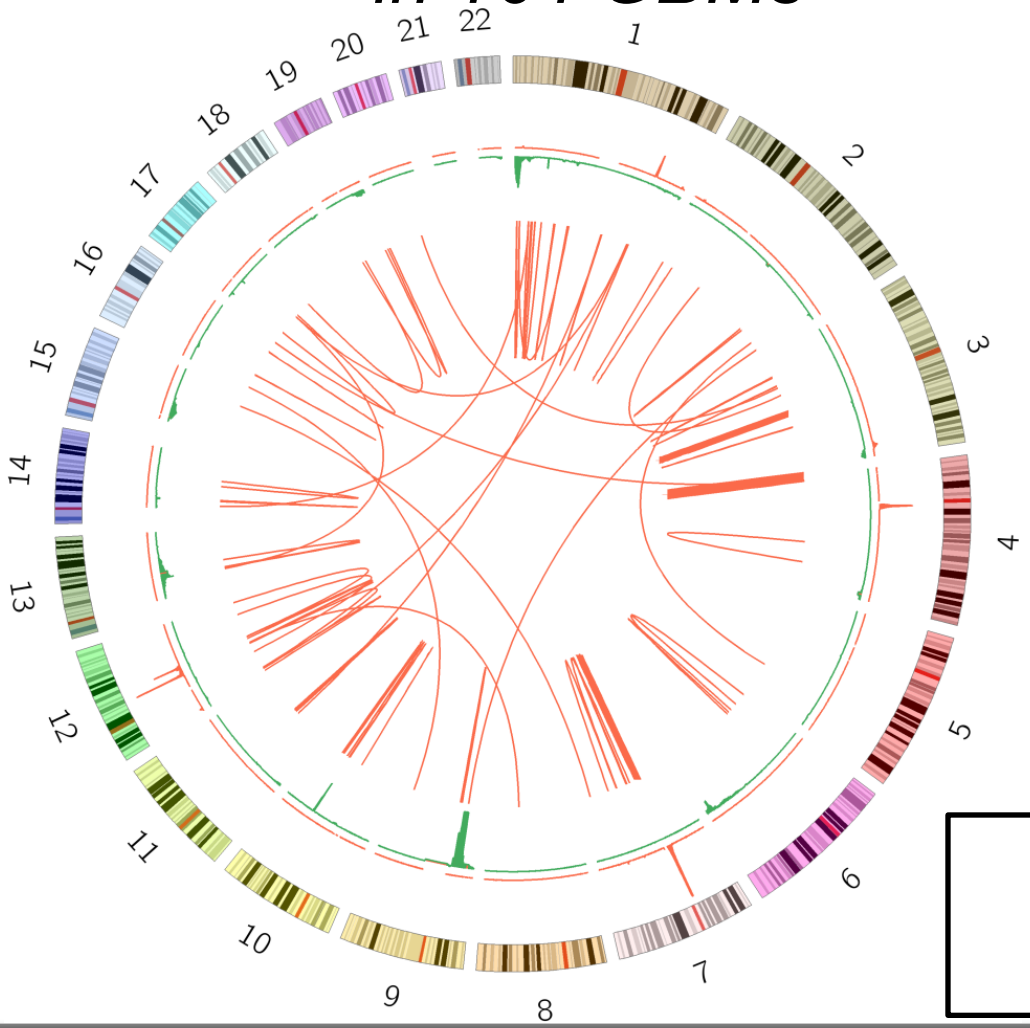




Double minute, confirmed by FISH

RNA sequencing identifies fusion transcripts across GBM

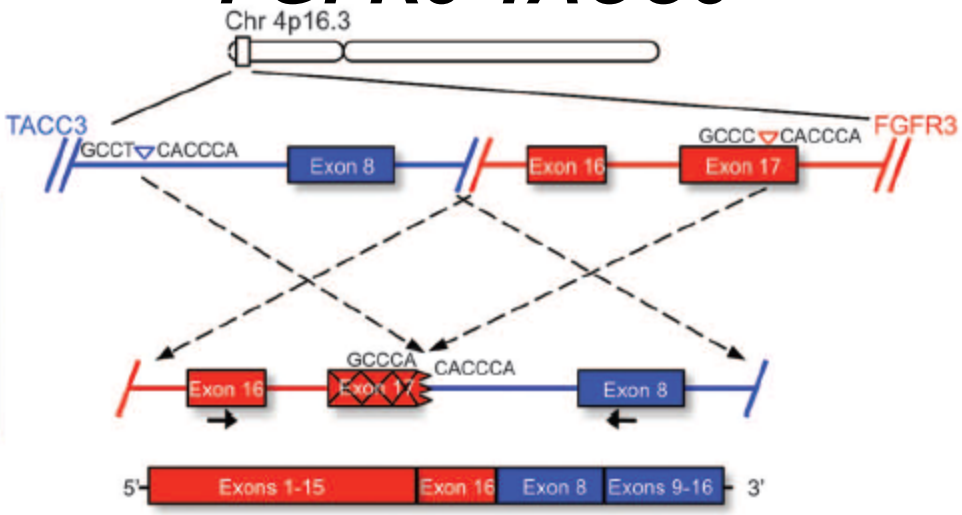
84 in frame fusion transcripts in 164 GBMs



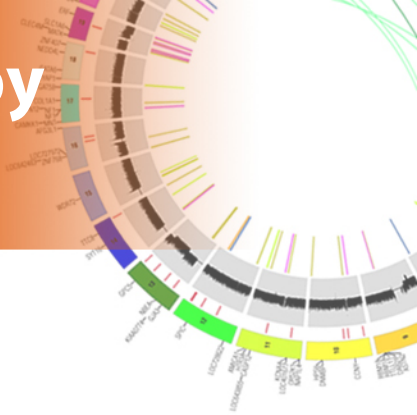
- 80 out of frame fusions
- 66 fusions involving a UTR

Siyuan Zheng
MD Anderson

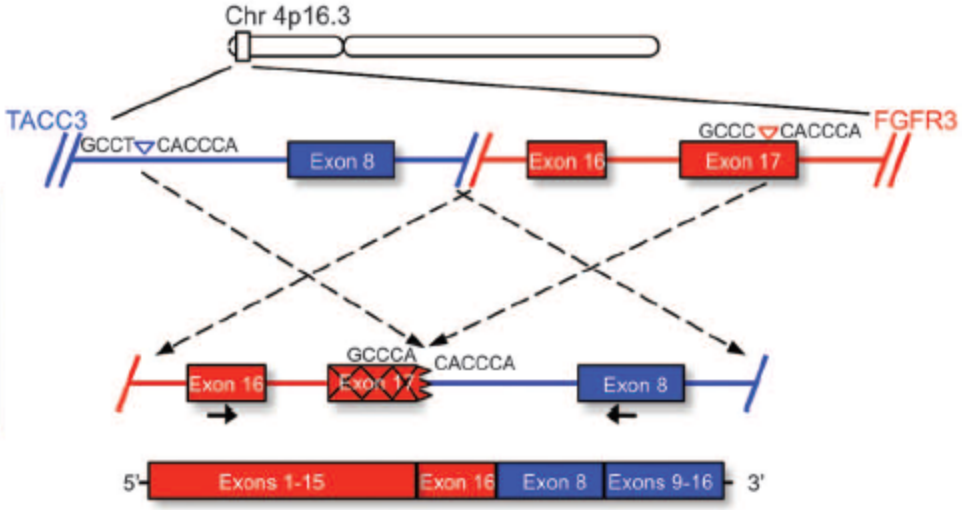
Fusion transcripts are frequently the result of local inversions



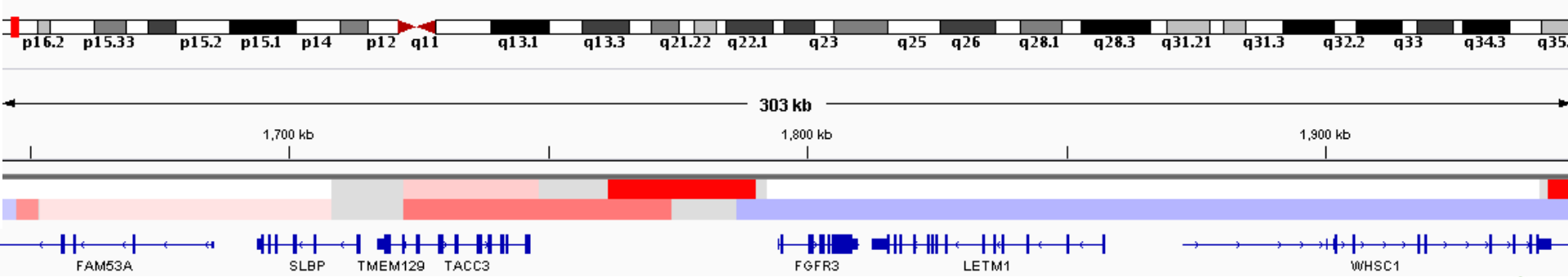
Genome breakpoints are associated with copy number difference



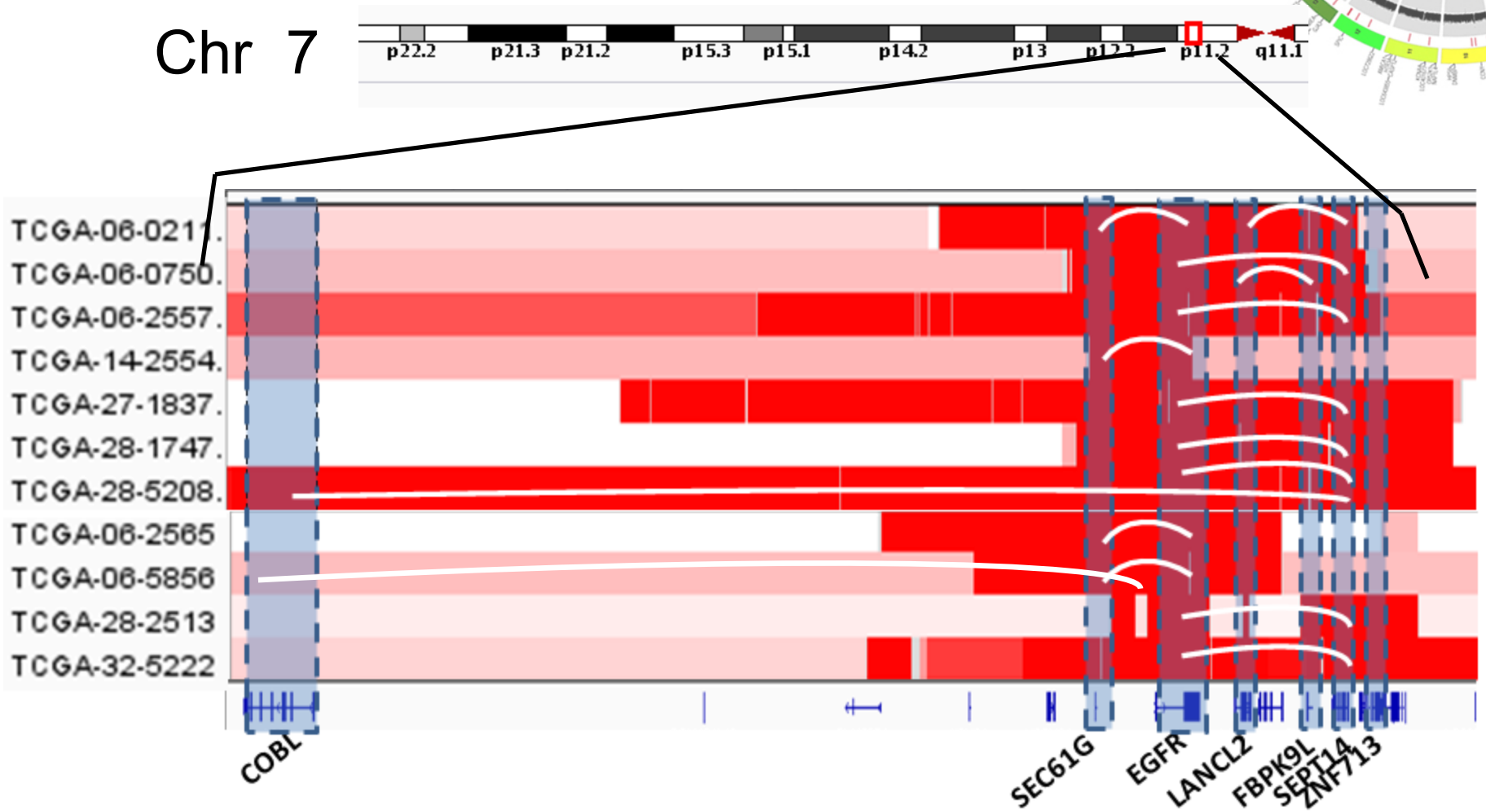
FGFR3-TACC3



Copy number profile of two FGFR3-TACC3 cases in TCGA

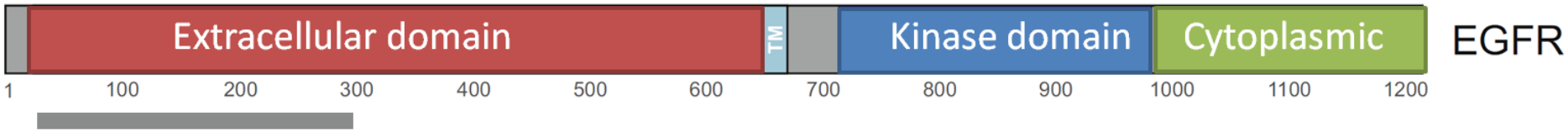


6.4% of GBM harbor transcript fusions involving EGFR



All fusions fall within the area of the EGFR amplification

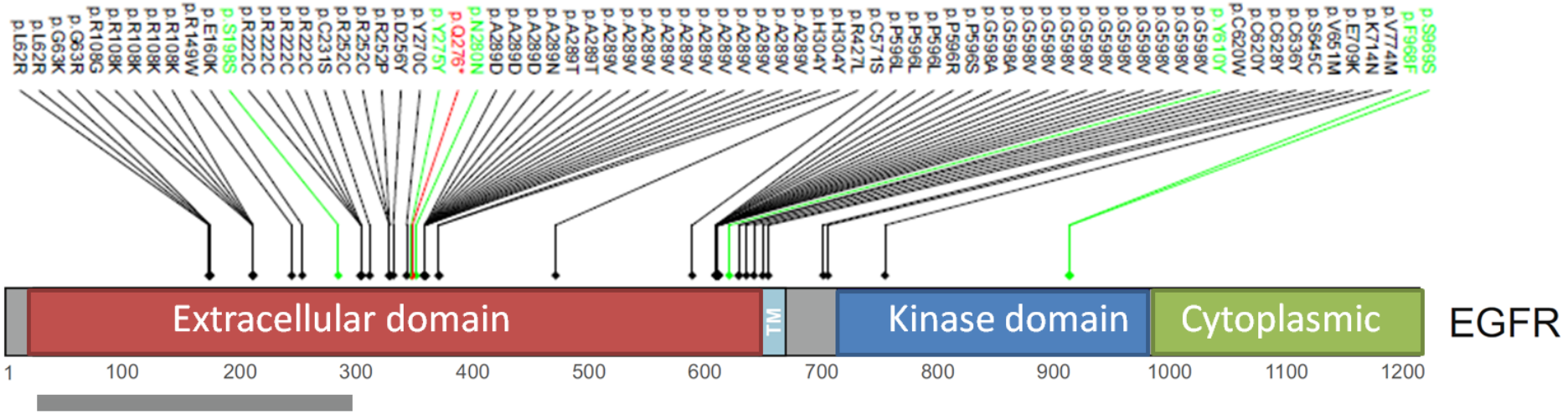
Intragenic rearrangements in EGFR are detected through RNA sequencing



Δ e2-7 *vIII* deletion *(10%)*

Siyuan Zheng
MD Anderson

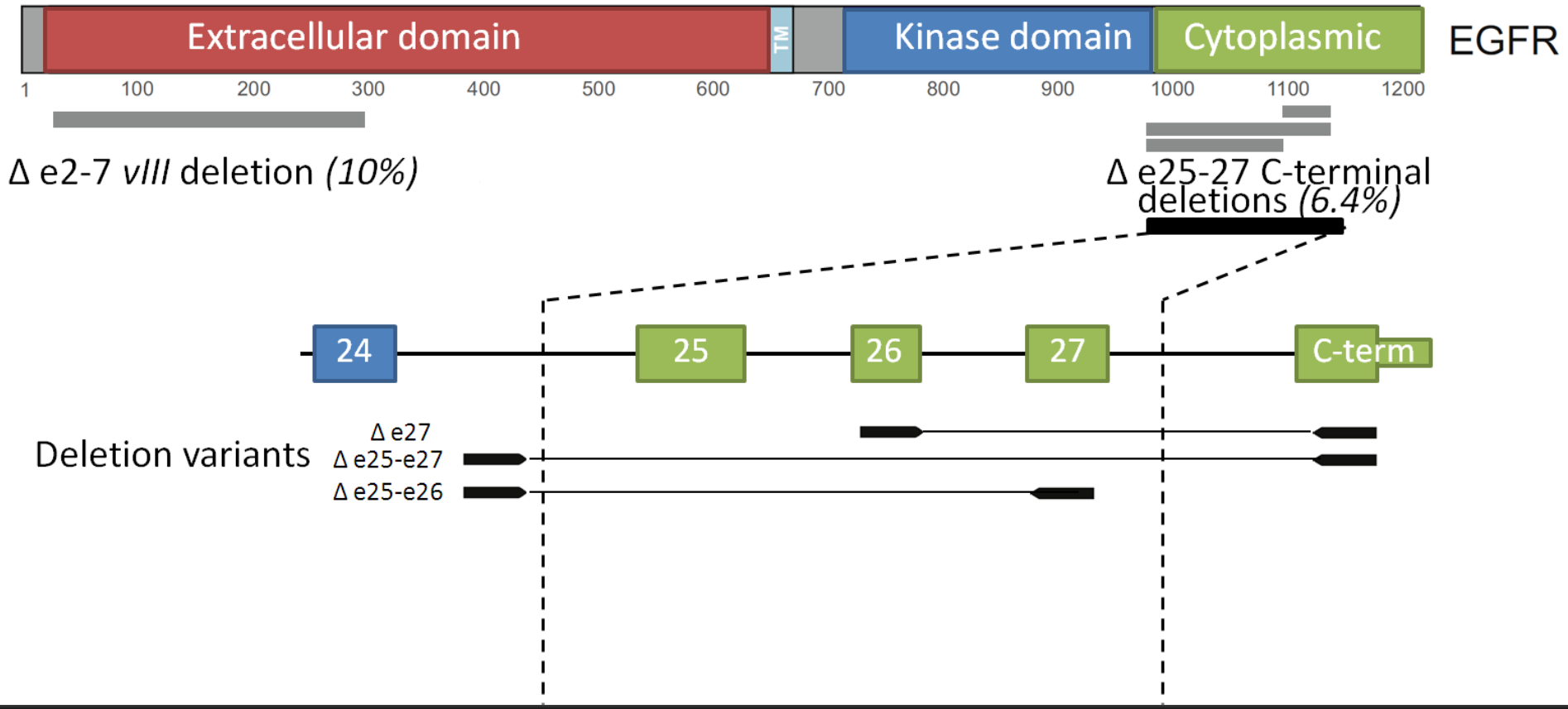
vIII occurs in the extracellular domain, area of most point mutations



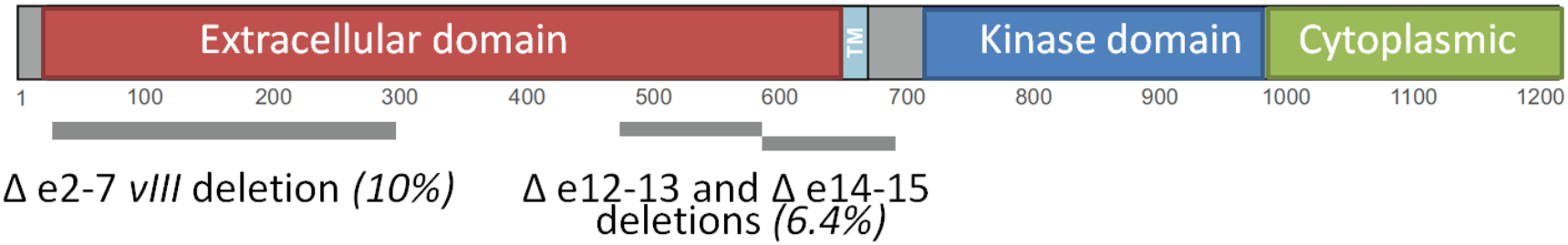
Δ e2-7 *vIII* deletion *(10%)*

Three different C-terminal deletions were found

RNA seq data cannot detect 'true' C-terminal deletions



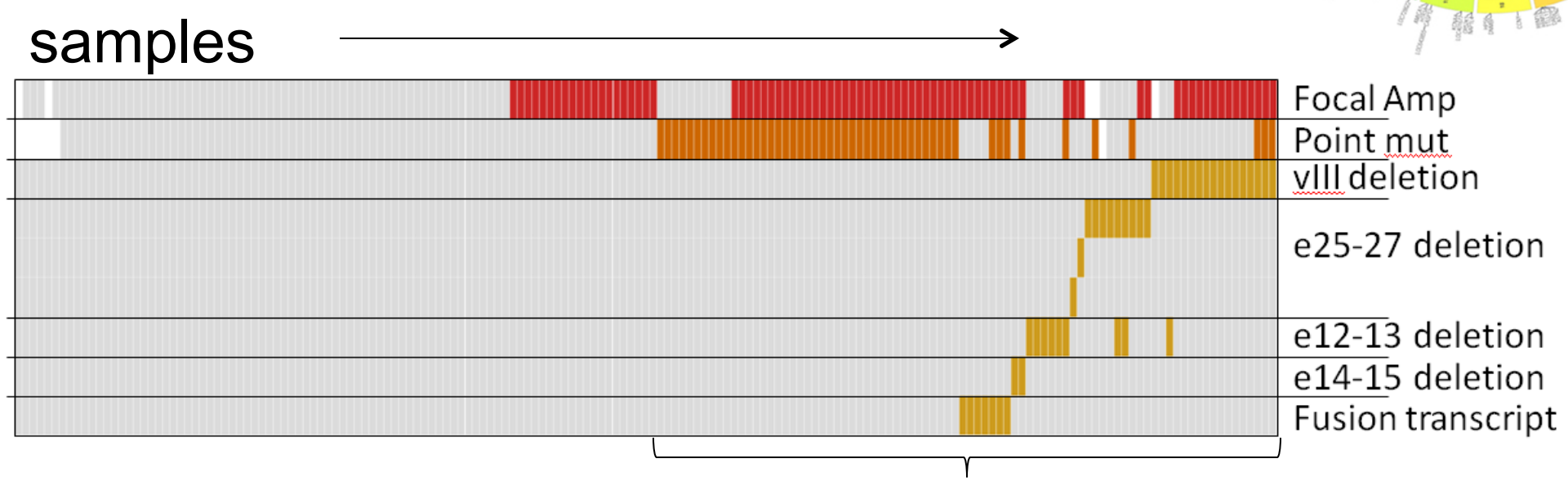
Two relatively unknown variants, exon-12 13 and exon 14-15, were detected



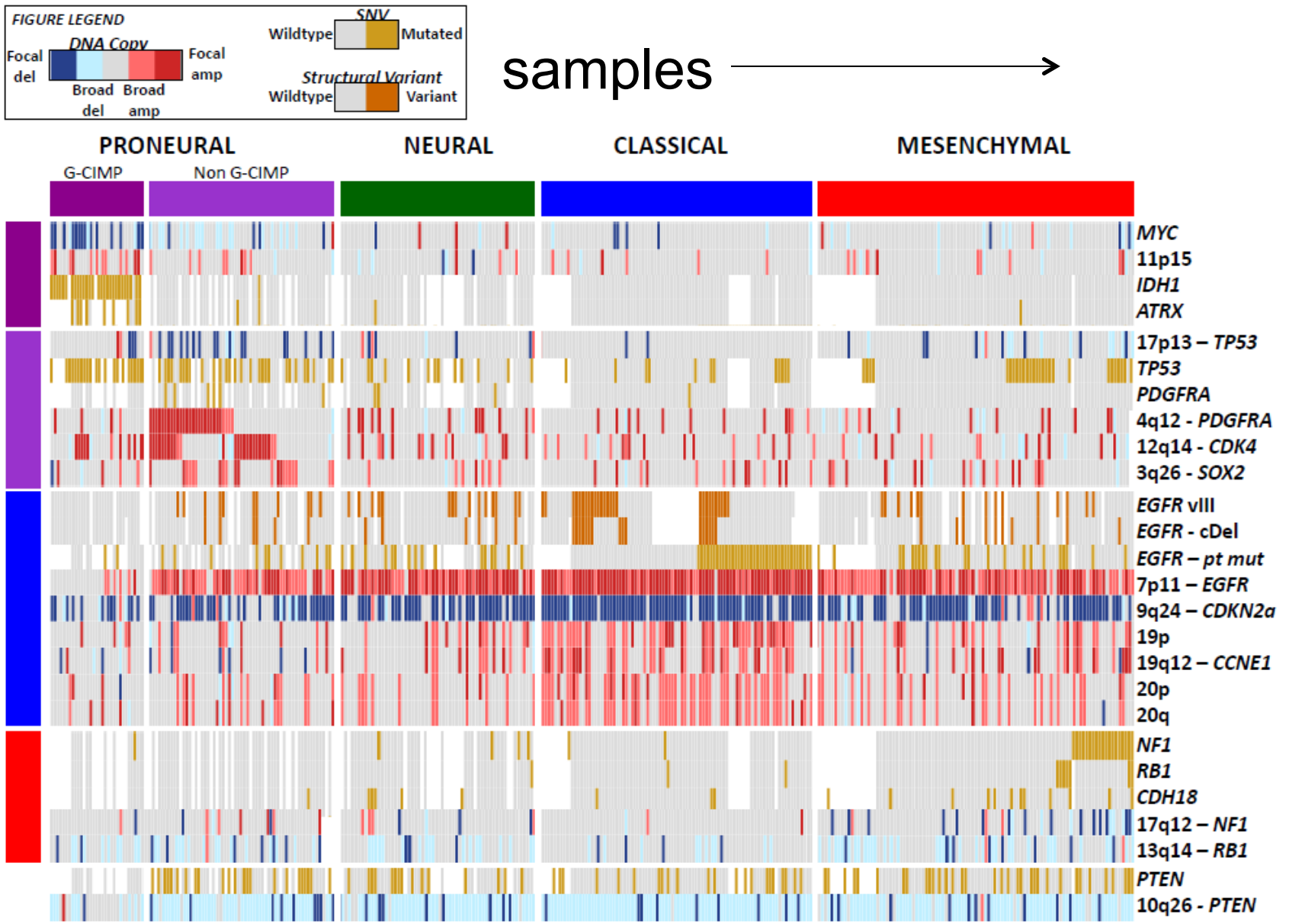
Δ e2-7 *vIII* deletion *(10%)*

Δ e12-13 and Δ e14-15 deletions *(6.4%)*

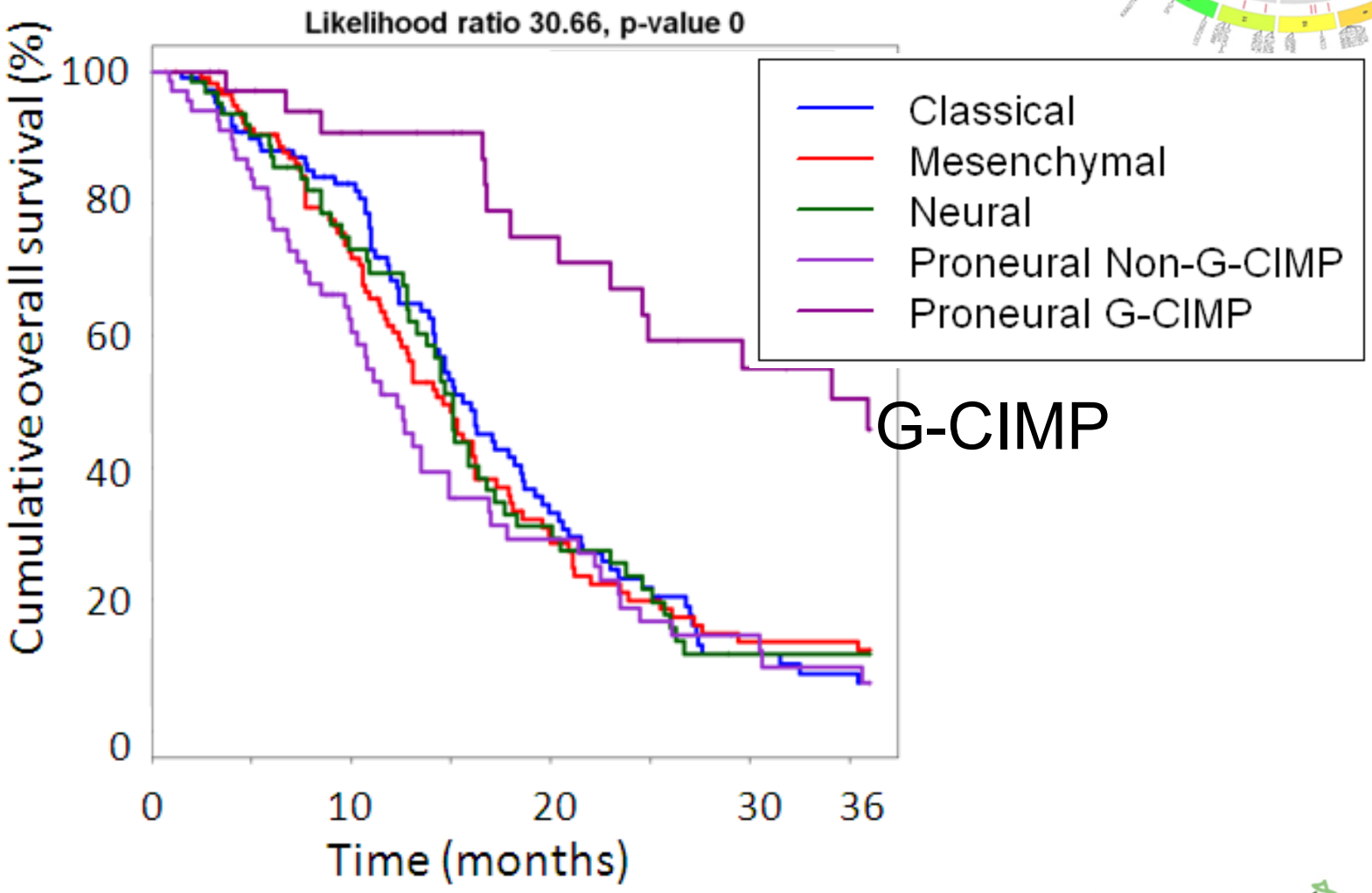
Approimately 45% of GBM harbors an EGFR point mutation or genomic rearrangement



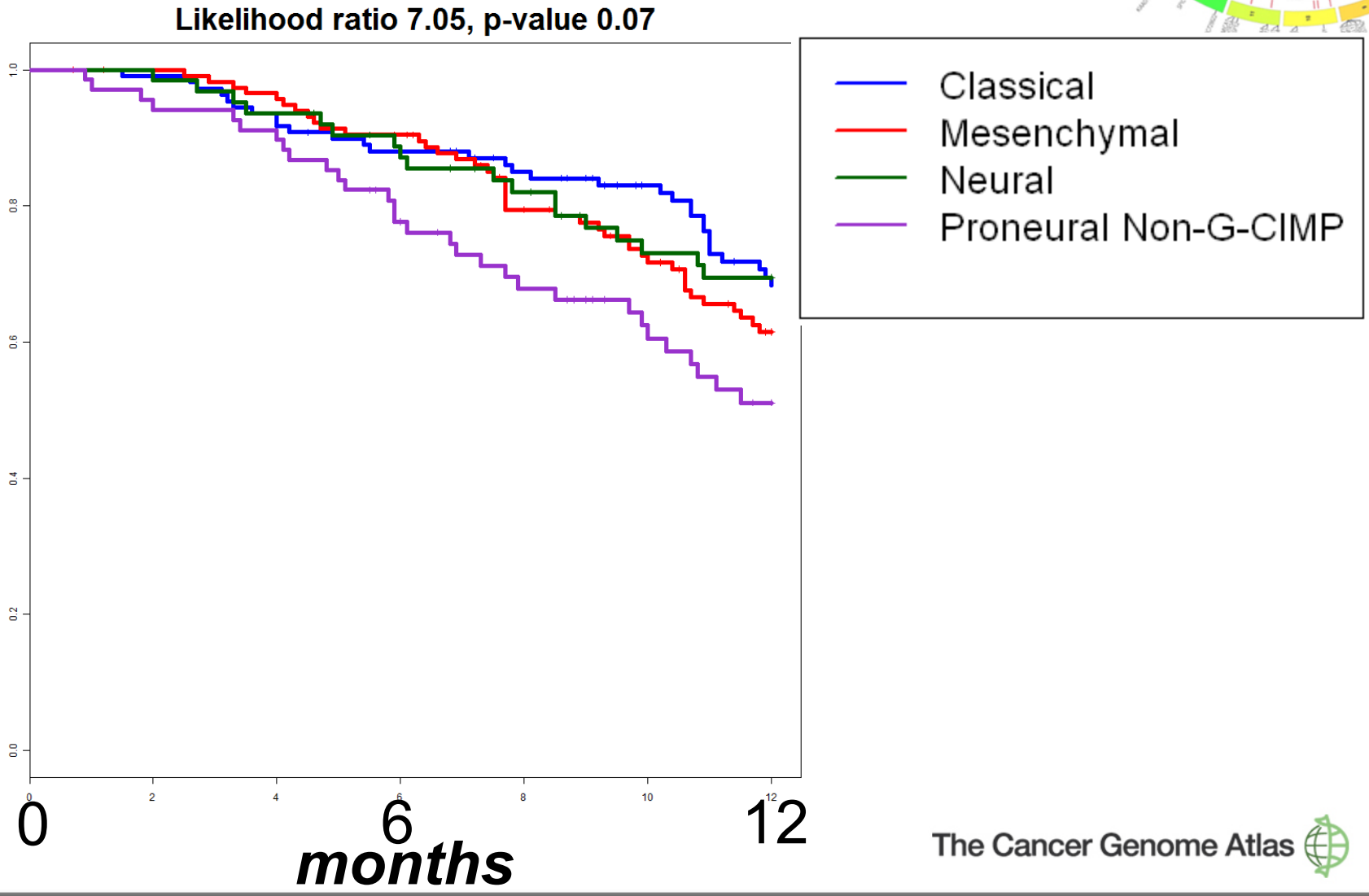
GBM expression subtypes related to genomic abnormalities in *MYC, EGFR, IDH1, …*



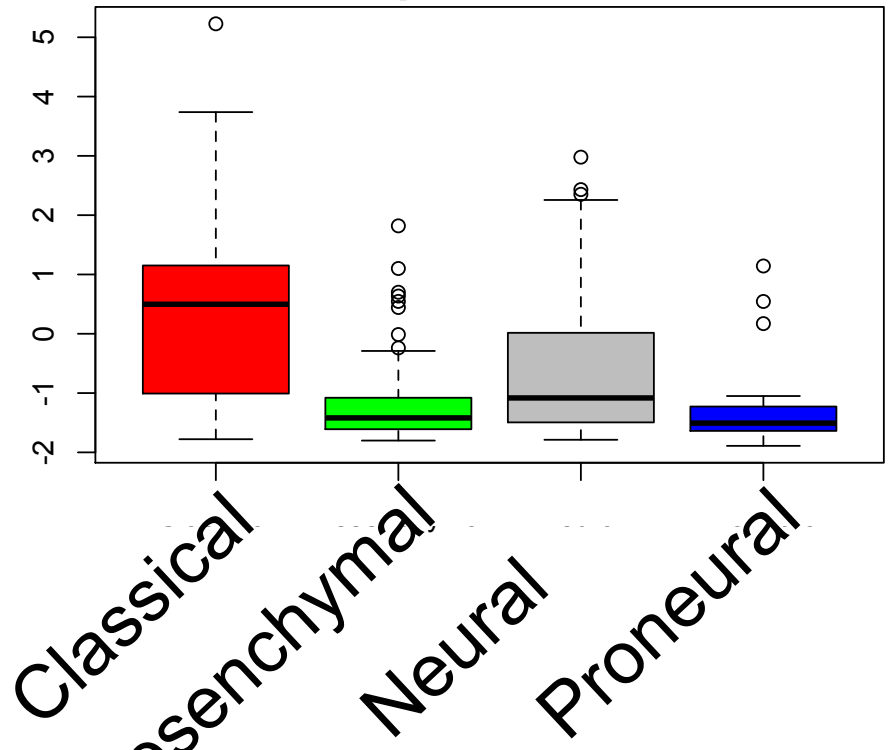
G-CIMP hypermethylators associate with better outcome

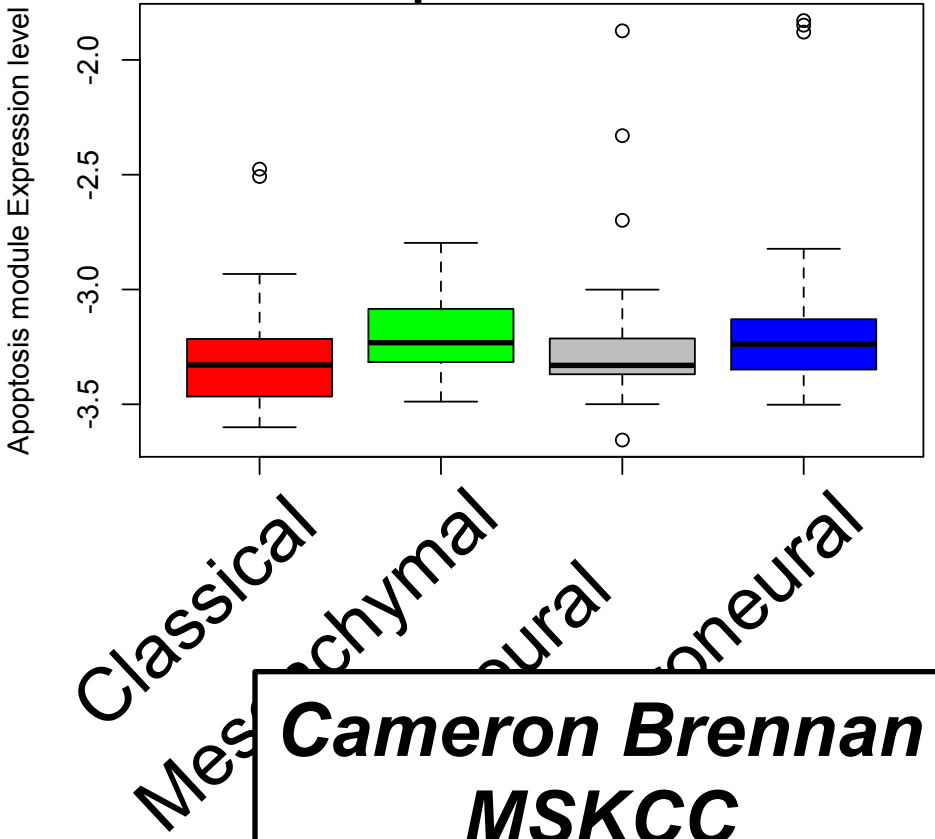


Proneural class performs WORSE than other subtypes when taking out GCIMP



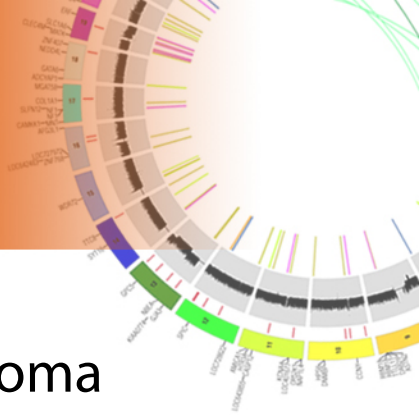
Protein expression levels associate with transcriptomal class





Cameron Brennan
MSKCC

Summary



- Comprehensive genomic profiling of ~ 600 samples characterizes the somatic alteration landscape of glioblastoma
- Novel significantly mutated genes detected: SPTA1, LZTR1, KEL, TCHH
- Whole genome and mRNA sequencing detects genomic rearrangements, most notably involving *EGFR*
- Proneural class may perform worse than other subtypes

Acknowledgements

TCGA GBM Working Group

Lynda Chin, Cameron Brennan, Aaron McKenna, Rameen Beroukhim, Scott L. Carter, Benito Campos , Kristian Cibulskis, Debyani Chakravarty, Gad Getz, David Haussler, Peter Laird, Matthew Meyerson, Michael Noble, Houtan Noushmehr, Sofie Salama, Zachary Sanborn, Sachet Shukla, Carrie Sougnez, Wei Zhang, Lihua Zou

TCGA GDAC at MD Anderson Cancer Center

Verhaak lab

Siyuan Zheng
Rahul Vegesna
Wandaliz Torres-Garcia
Hoon Kim
Kosuke Yoshihara
Ji-Yeon Yang
Emmanuel Martinez