



Genomic Aberrations in GBM from the TCGA pilot project

Subclasses and Targets

Copy Number Platforms

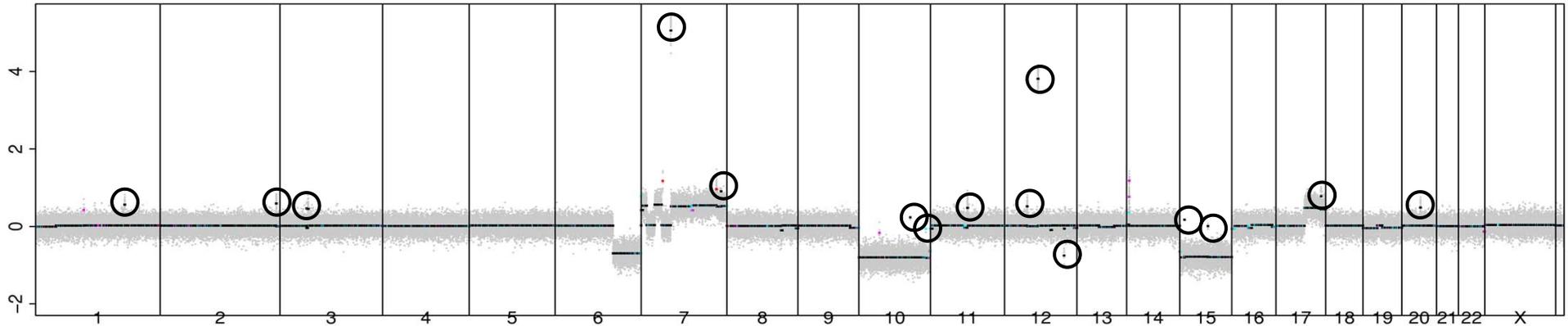
Broad – Affymetrix SNP 6.0

Harvard – Agilent Whole Genome

MSKCC – Agilent Whole Genome, Custom High-density

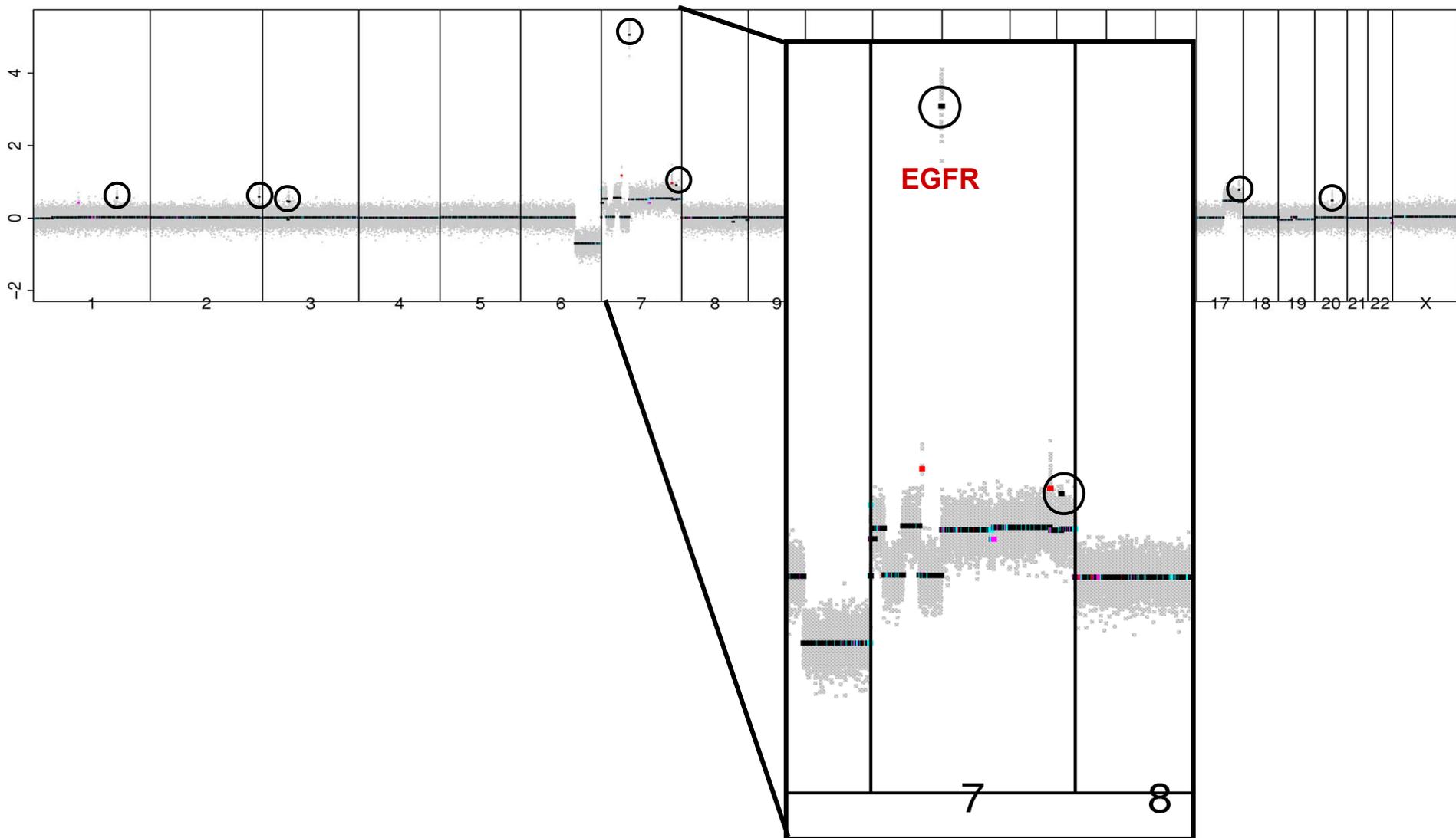
Stanford – Illumina Infinium SNP

Example tumor profile, Agilent, MSKCC



- Example profile, focal CNA events marked by circles

EGFR amplicon

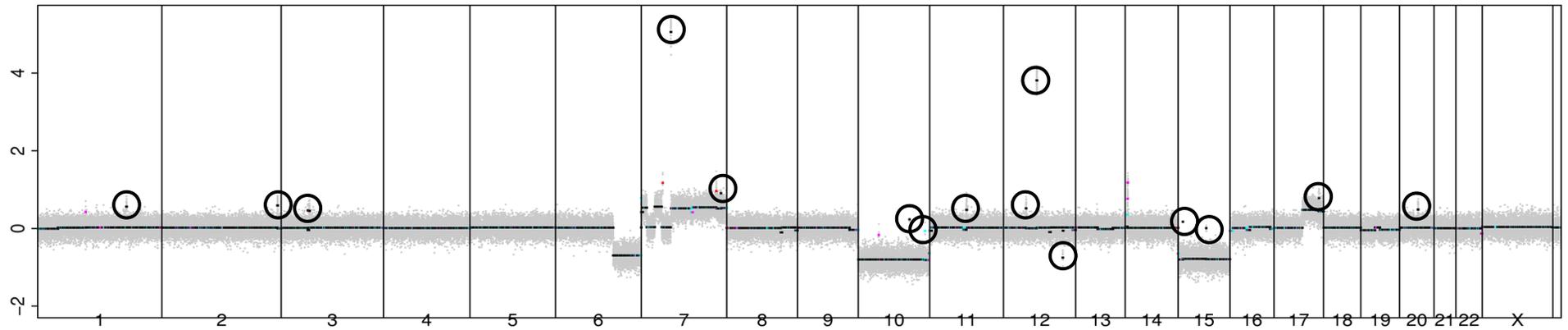


High concordance between centers

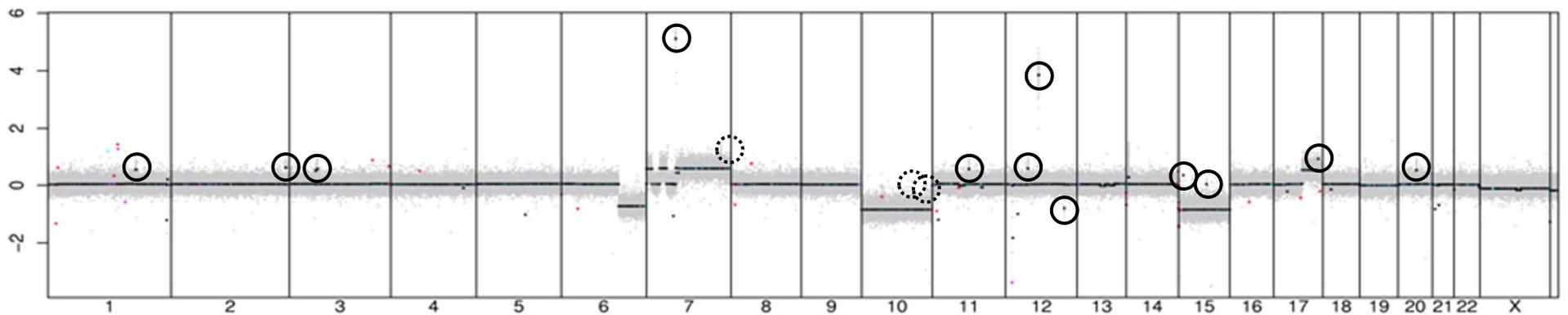
THE CANCER GENOME ATLAS



MSKCC



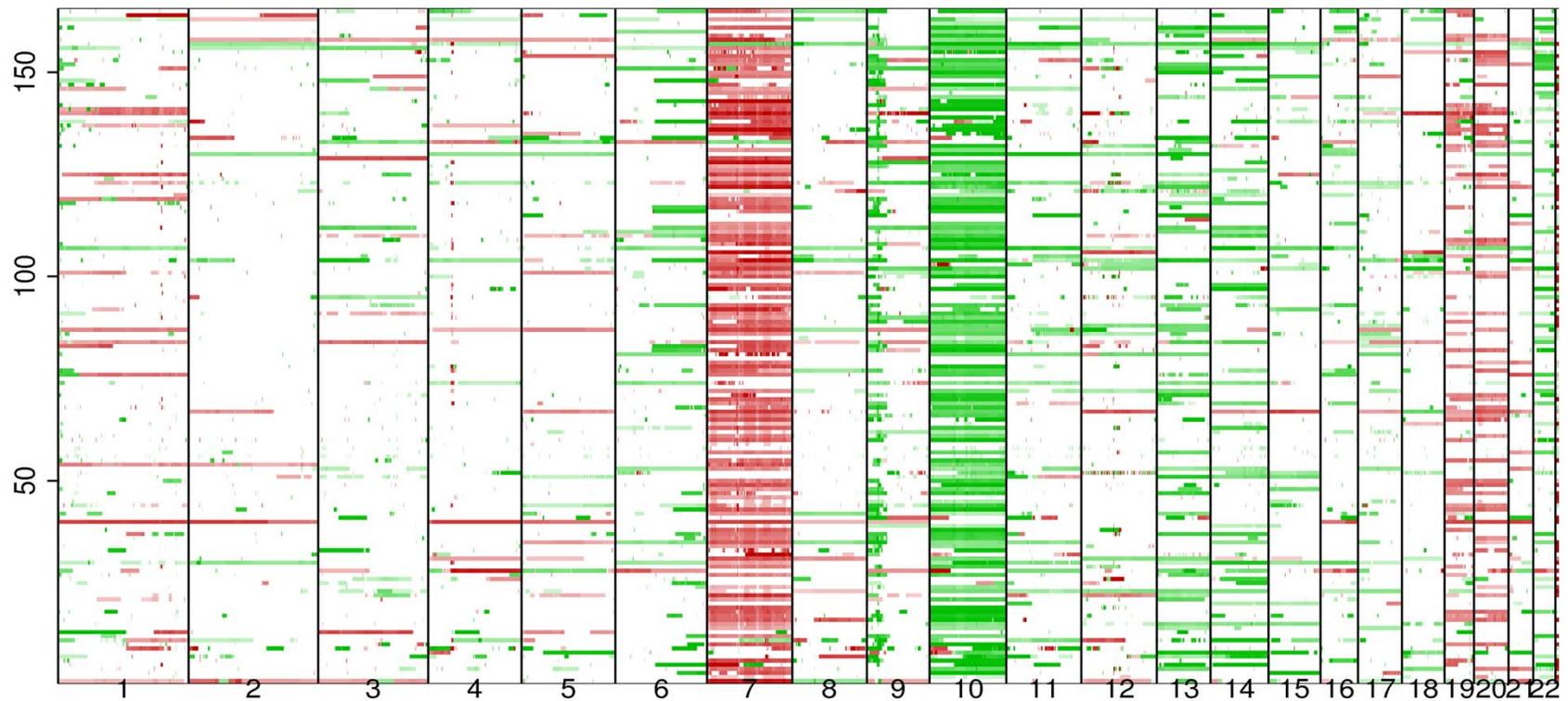
Harvard



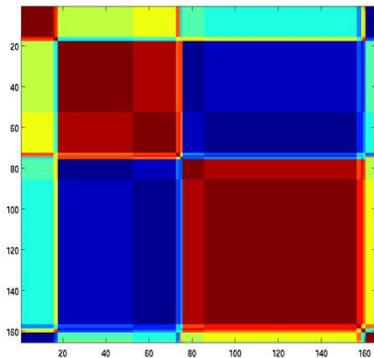
Copy number profiling



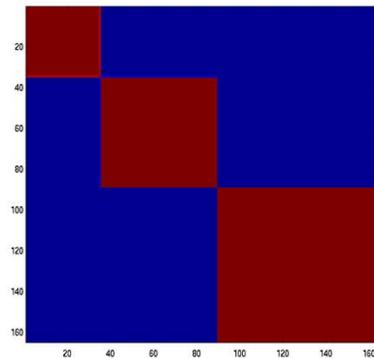
- 165 tumors profiled to date



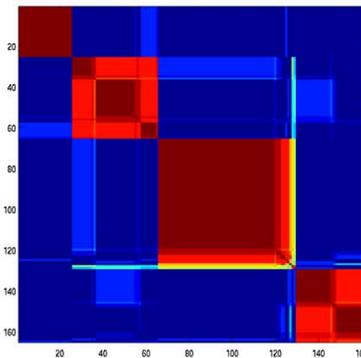
Subclass Discovery by Non-negative Matrix Factorization (NMF)



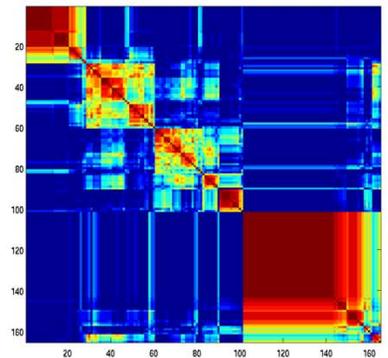
2-way



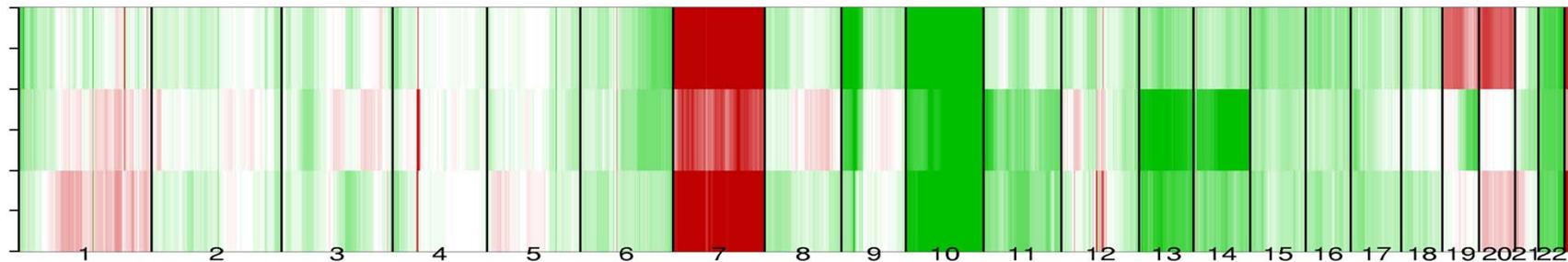
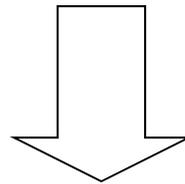
3-way



4-way



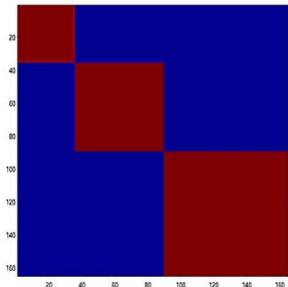
5-way



3 kinds of genomic profile found
(NMF cluster medians)

Subclass Discovery by NMF

3-way grouping



3-way grouping

+7 -9p -10



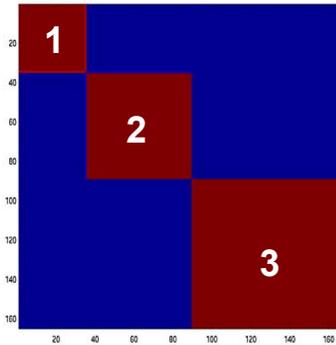
Clustering by transcriptome



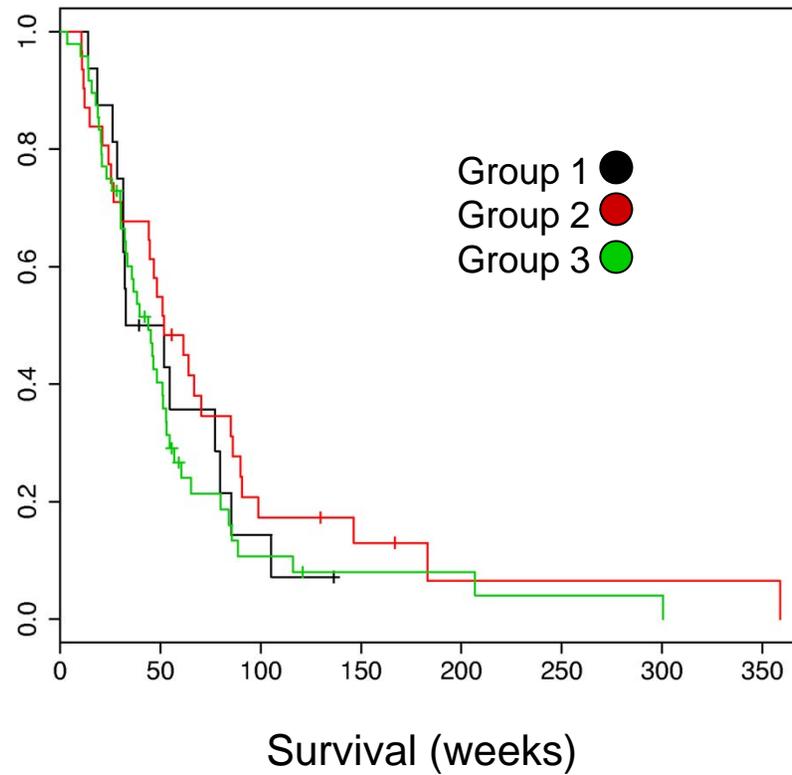
- Copy number profiles clustered by matching transcriptome data (Neil Hayes & Katherine Hoadley, UNC)
- Possible overlap of -13/14 and +19/20 subclasses



3-way NMF groups show no survival difference



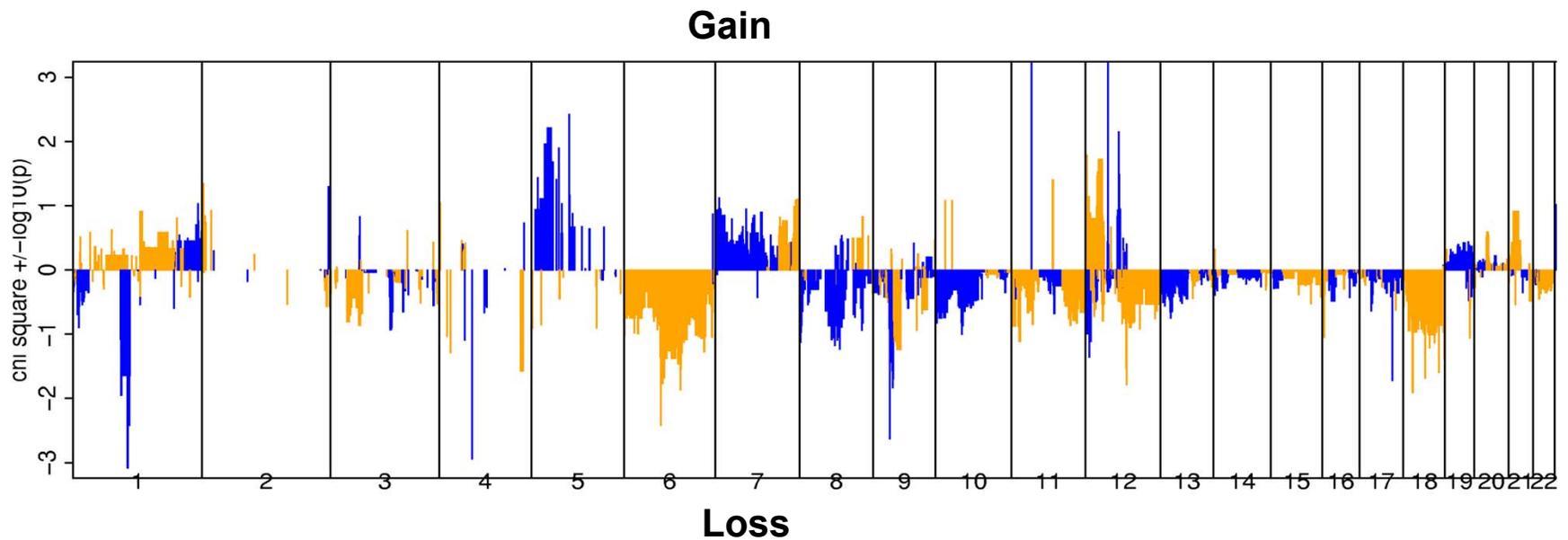
3-way grouping



Survival as a function of regional gain and loss



better survival / **poorer survival**

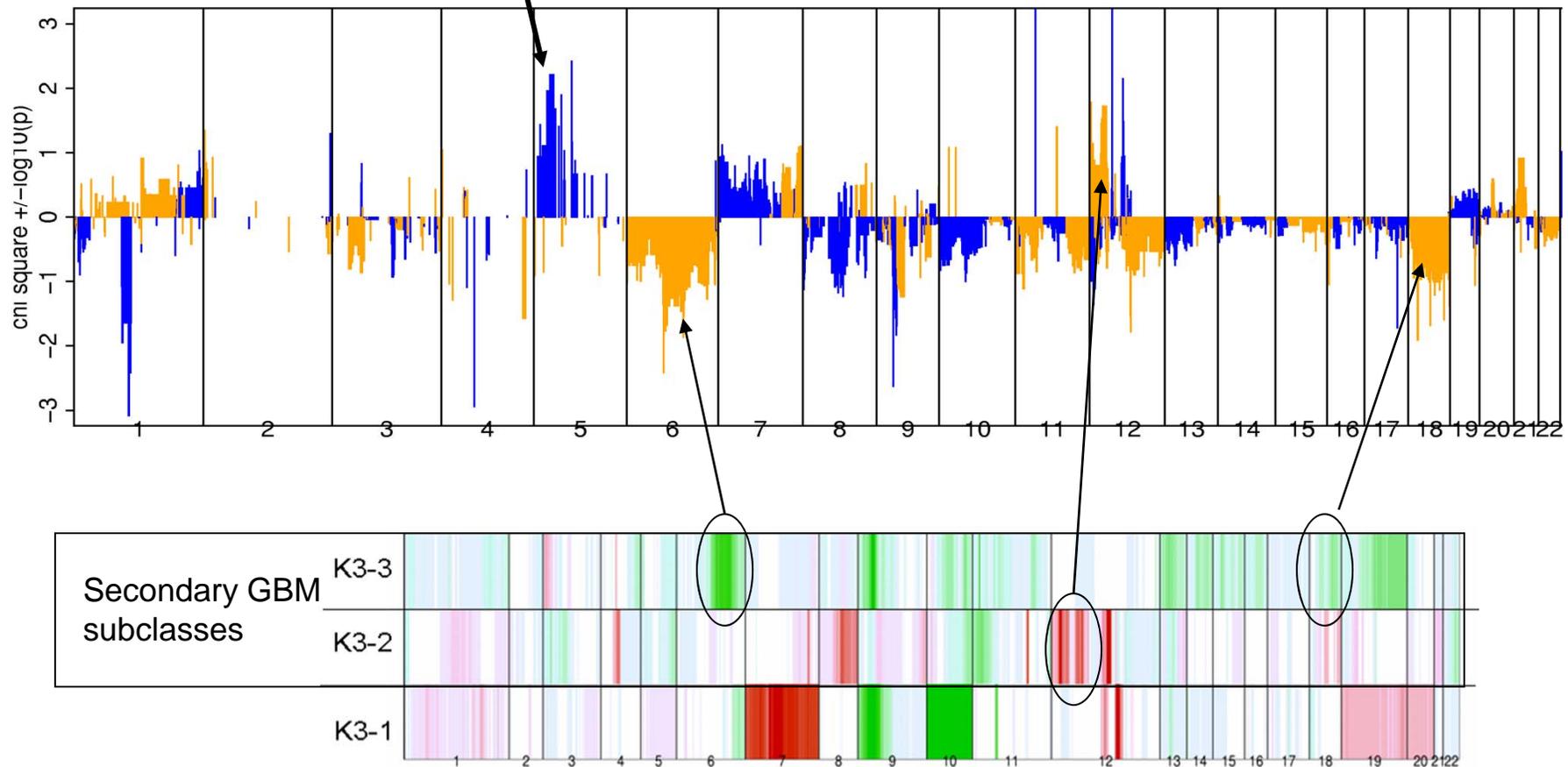


Survival-associated gain/loss: correlation with reported regions



+5p

Overexpressed Skp2 within 5p amplification detected by array-based comparative genomic hybridization is associated with poor prognosis of glioblastomas. Saigusa et al.; Cancer Sci., 2005

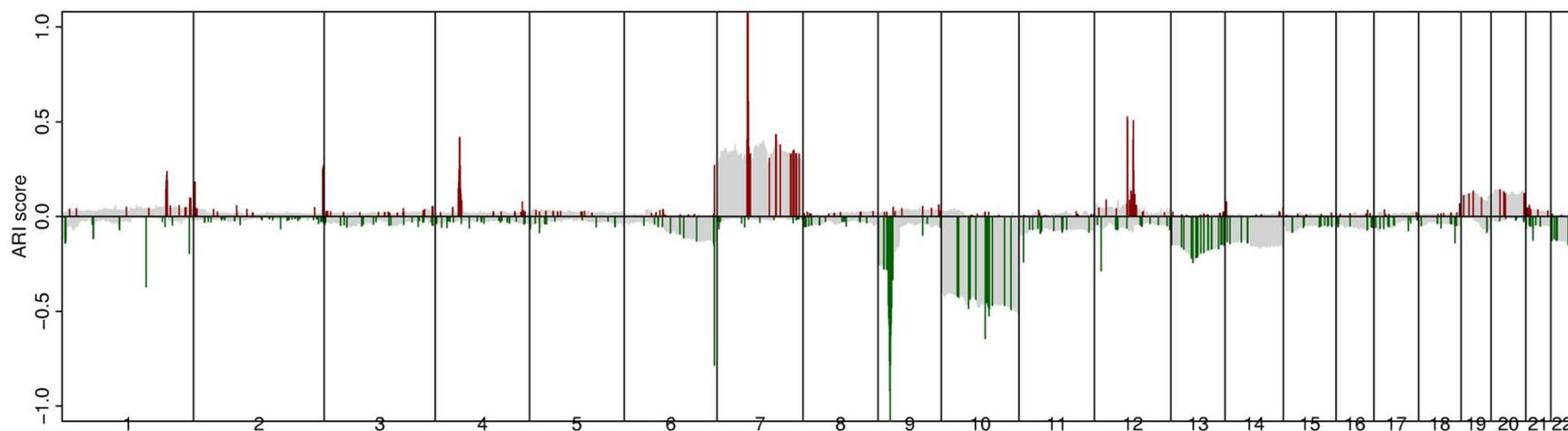


Regions of Interest for CNA



Derive ROI from copy number profiles
by 3 essential features:

- 1. Amplitude
 - 2. Recurrence
 - 3. Focality
- } → ARI = “aberration recurrence index”
- AFI = “aberration focality index”



ROI selected for most focally-altered 2% of genome

Focal amplifications

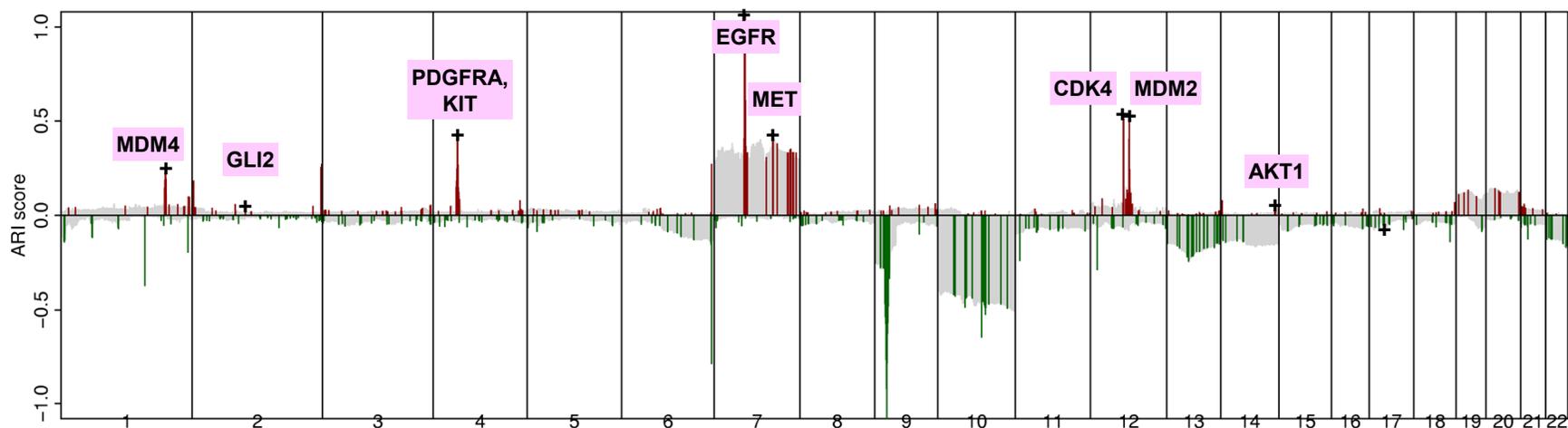


226 genes,

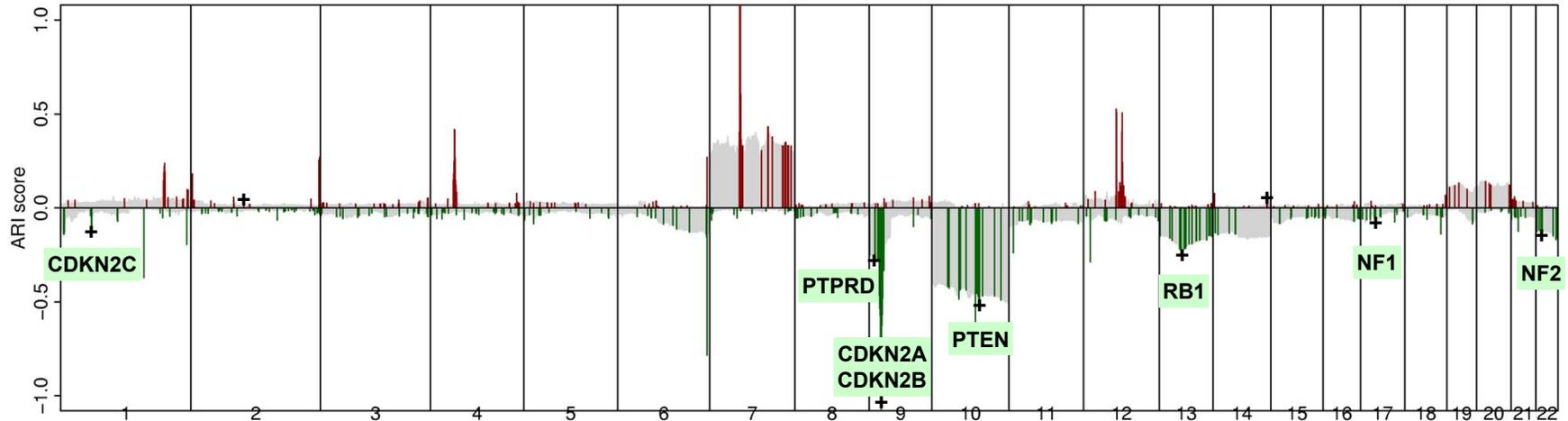
enriched for “oncogene” CANDID score, $p < 0.05$

Top 20 include: EGFR, PDGFRA, KIT, MET, AKT1, AKT3,
PIK3C2B, MDM2, MDM4, CDK4, GLI2

Others: GFI1B, PLAG1, RALGDS



Focal deletions



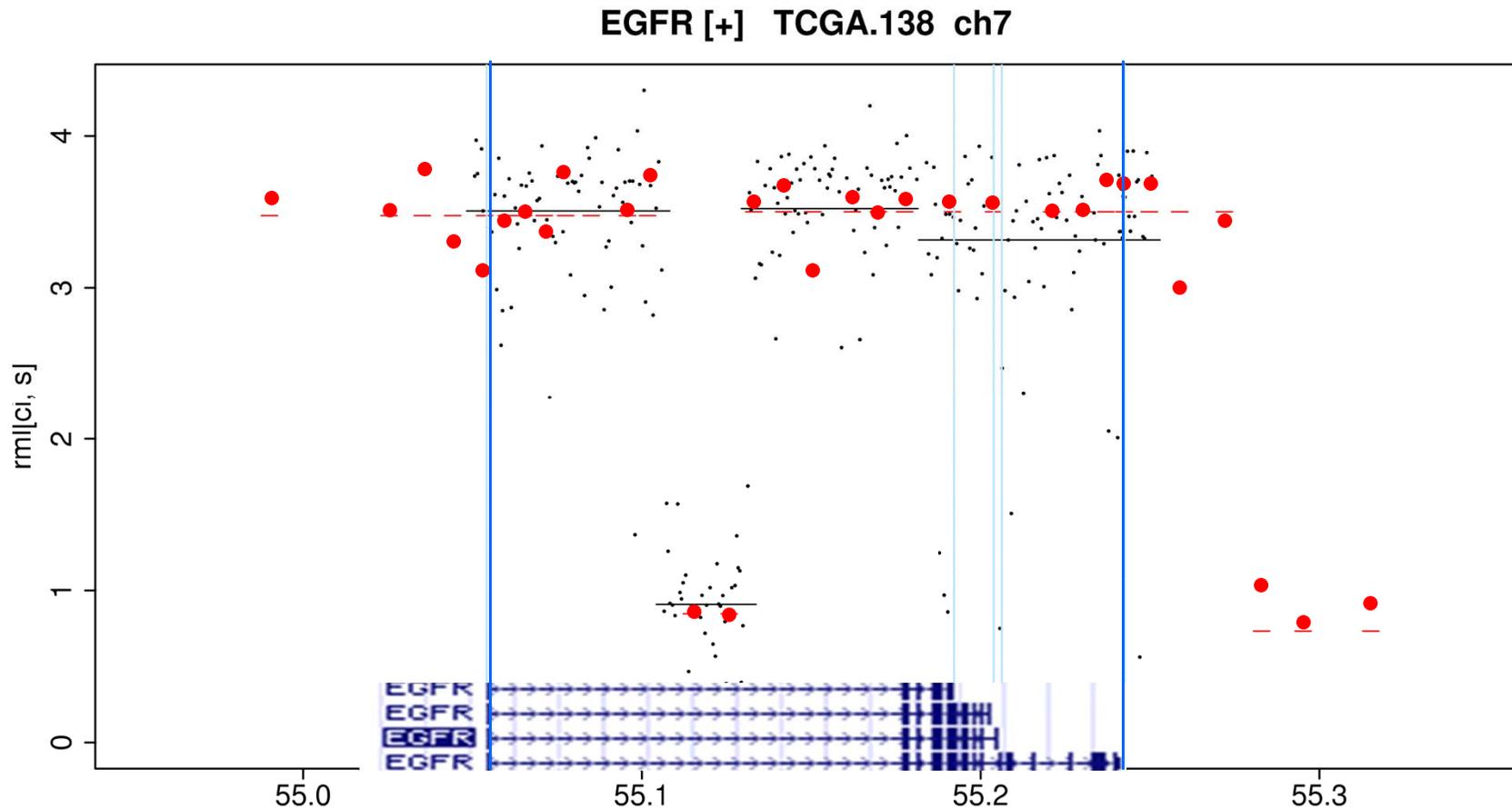
219 genes,

enriched for “tumor suppressor” CANDID score, $p < 0.013$

Top 20 include: PTEN, CDKN2A/B/C, NF1, NF2, RB1, PTPRD

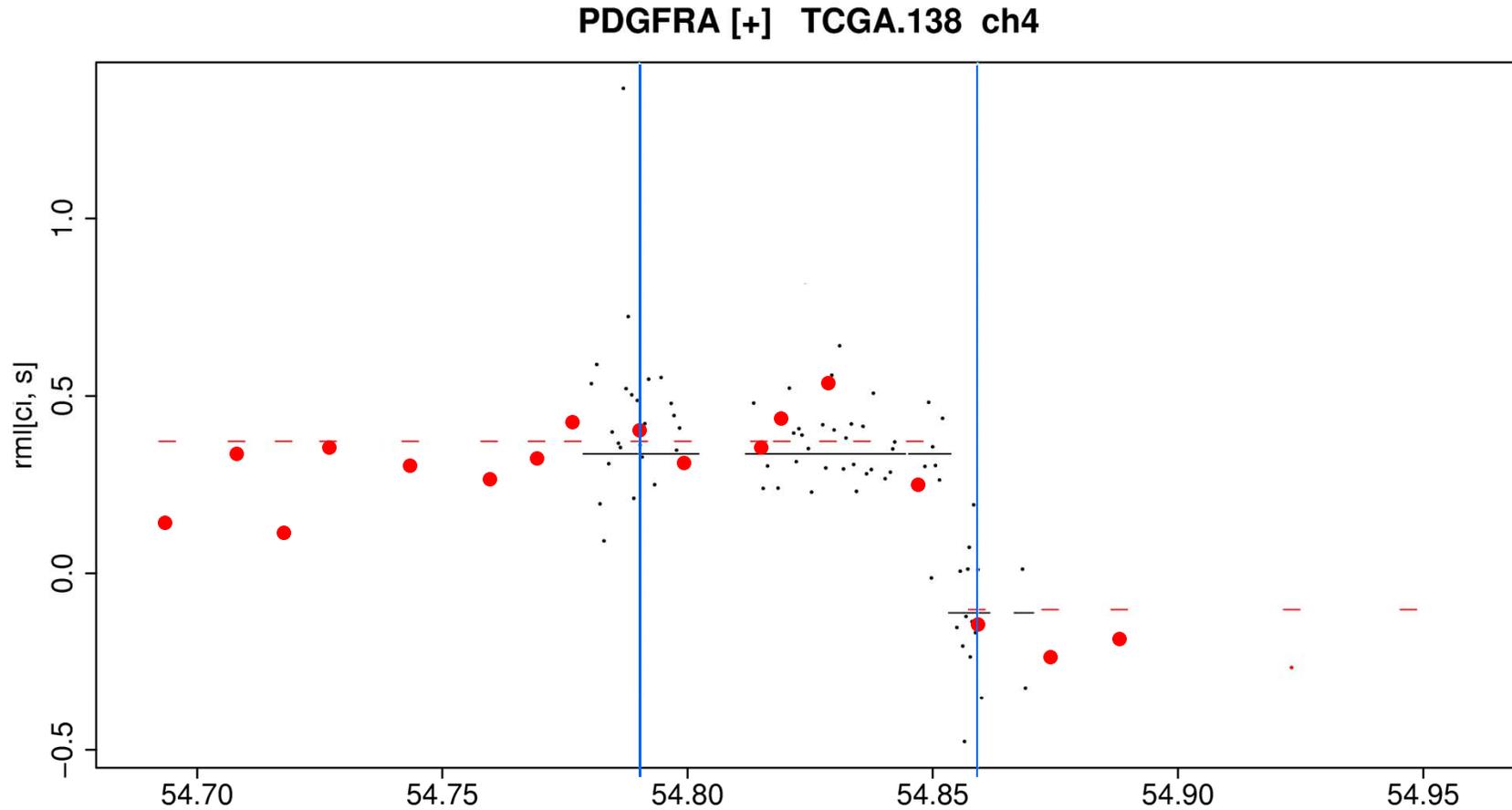
Others: PTPRD, WWOX, APAF1, FBXW7, BMPR2

High-density custom array for intragenic deletions, translocations



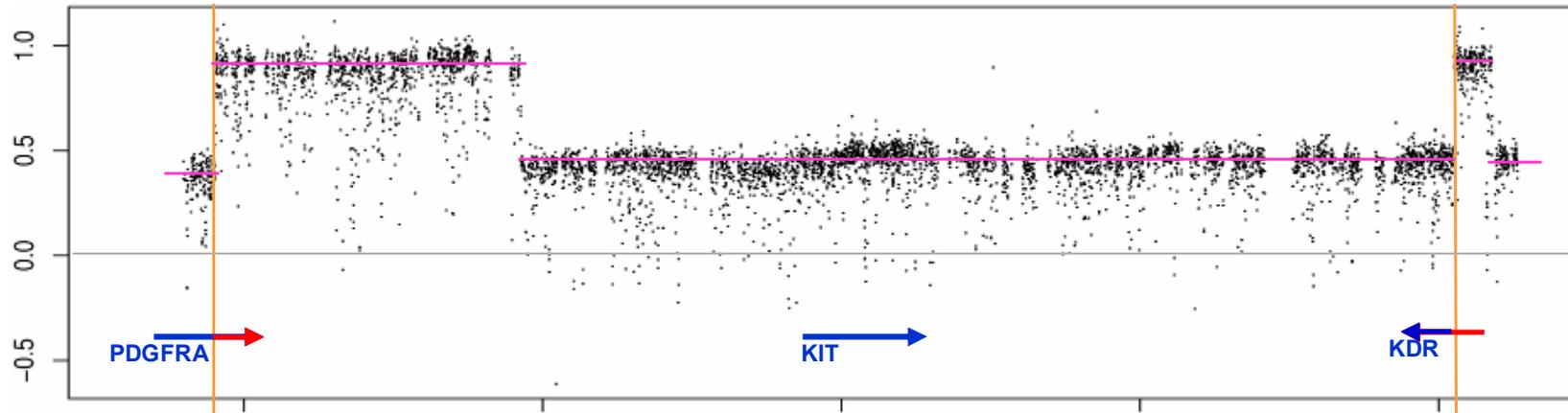
Custom array: 650bp resolution vs **whole genome 8,170bp**

High-density custom array for intragenic deletions, translocations



Custom array: 580bp resolution vs **whole genome 10,000bp**

Novel TK fusion protein in GBM: KDR-PDGFR α

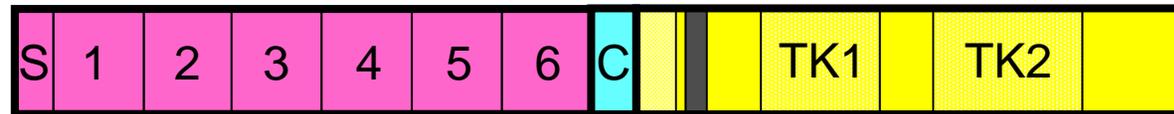


KDR

PDGFRA

3,879

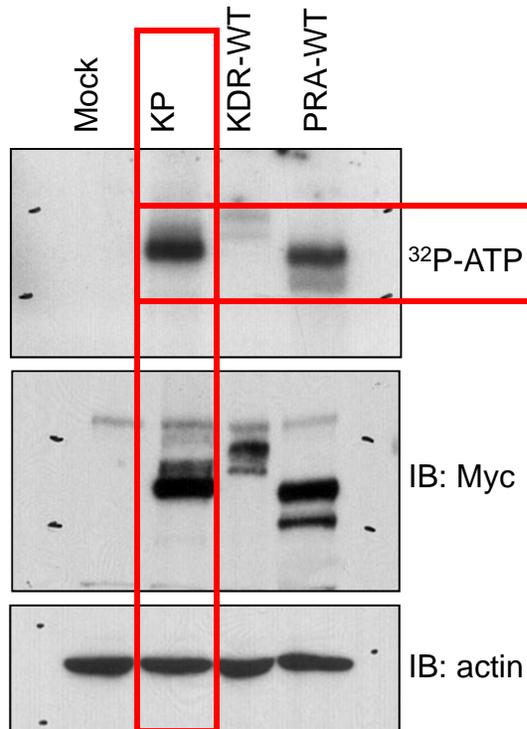
KDR-PDGFR α



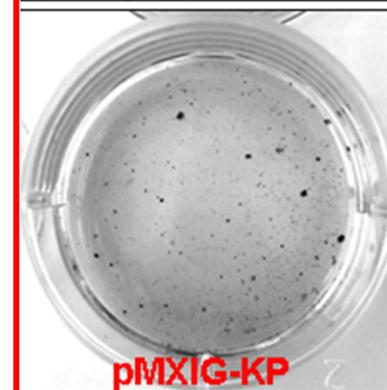
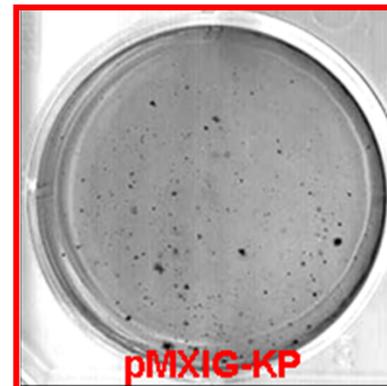
KDR-PDGFR- α fusion protein (3,882bp): KDR (1,987bp) + Cryptic exon (38bp) + PDGFRA (1,860bp)

Ig-like domain: immunoglobulin like domain, **S:** signal sequence, **TM:** transmembrane domain, **JM:** juxtamembrane domain, **TK:** tyrosine kinase domain, **C:** cryptic exon

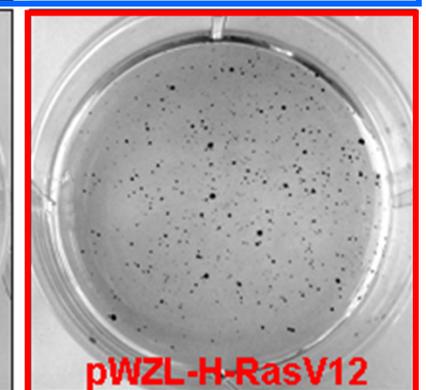
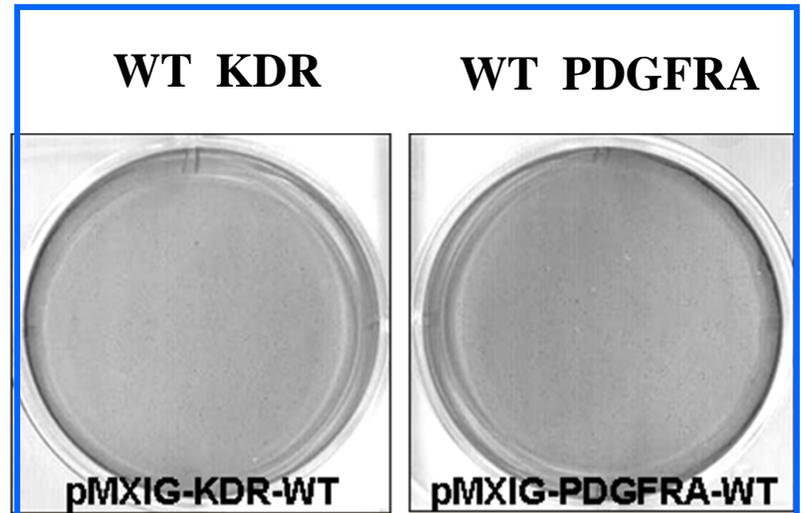
The KP fusion kinase is constitutively phosphorylated and transforming



pMXIG-NIH3T3 cell (p6)
Serum Starve O/N



K-P Fusion



HRas V12

Tatsuya Ozawa