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

MSKCC

Harvard
Copy number profiling

• 165 tumors profiled to date
Subclass Discovery by Non-negative Matrix Factorization (NMF)

3 kinds of genomic profile found
(NMF cluster medians)
Subclass Discovery by NMF
3-way grouping

3-way grouping

+7  -9p  -10

+19, +20

-13, -14
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

Survival (weeks)

Group 1
Group 2
Group 3
Survival as a function of regional gain and loss

better survival / poorer survival
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

\[ \text{ARI} = \text{“aberration recurrence index”} \]
\[ \text{AFI} = \text{“aberration focality index”} \]

ROI selected for most focally-altered 2% of genome
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 amplifications
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
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-PDGFRA

KDR-PDGFRA 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: criptic exon
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