Comprehensive Pan-Genomic Characterization of Adrenocortical Carcinoma

Tom Giordano

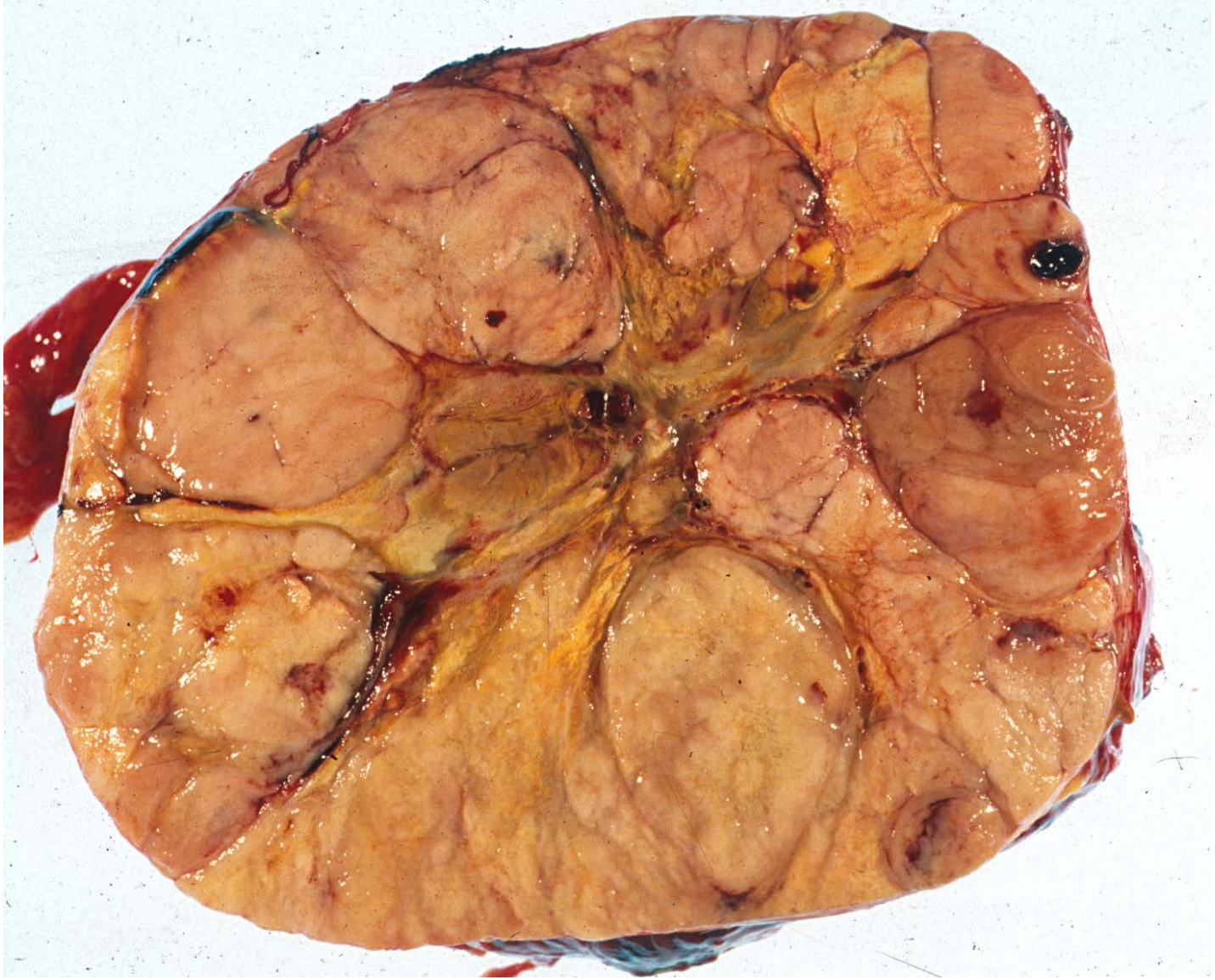
Update on behalf of the ACC AWG

University of Michigan
Medical School

Adrenocortical Carcinoma

- Rare; 1-2 cases per million
  - 500 cases in US per year
- Variable outcome, dependent on grade and stage
- Associated endocrinopathies
  - e.g. hypercortisolism (Cushing syndrome)
- Limited therapeutic options
- Centers with multidisciplinary clinics
  - Michigan, MD Anderson, NIH

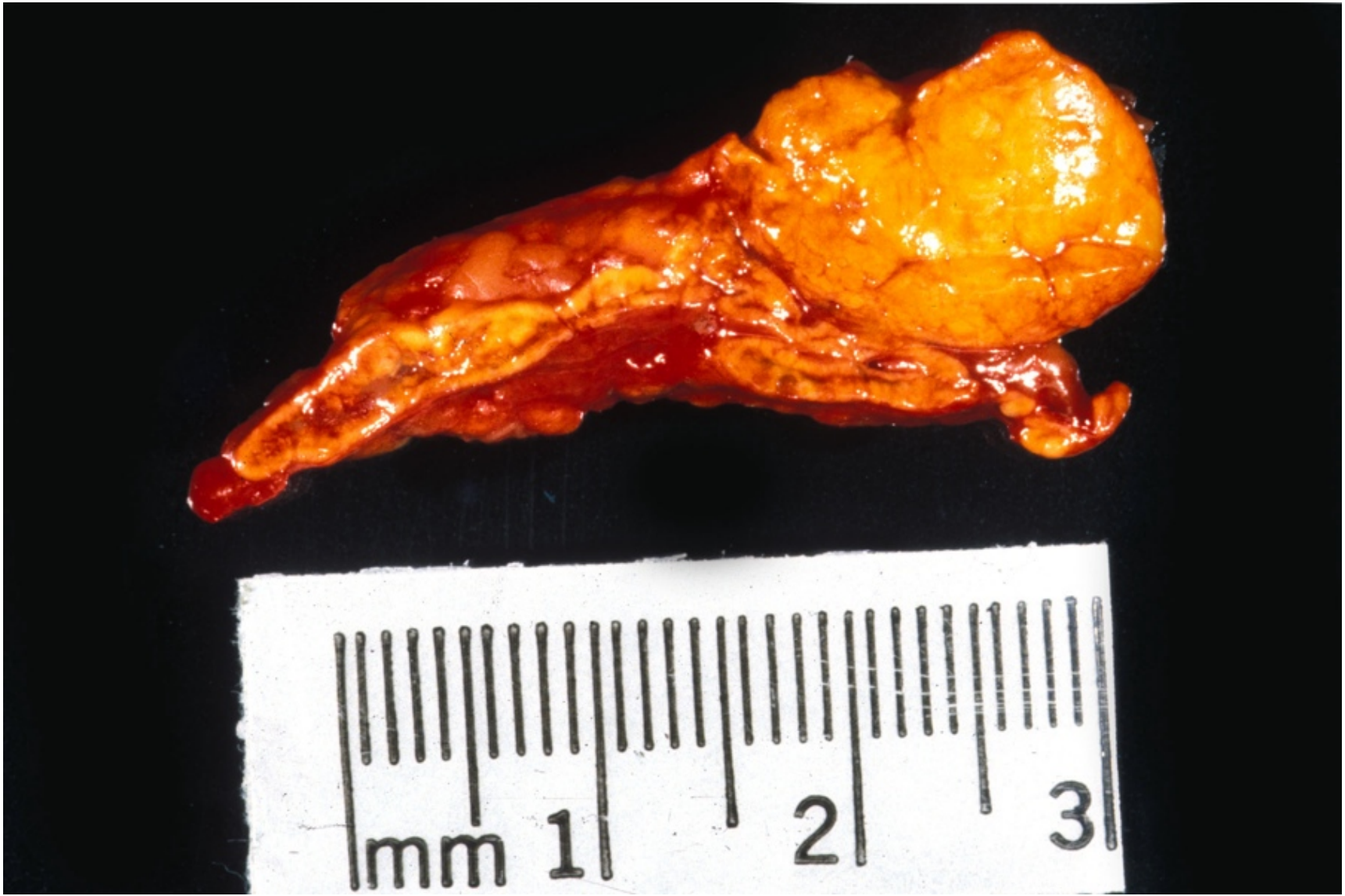
Adrenal Cortical Carcinoma (ACC)



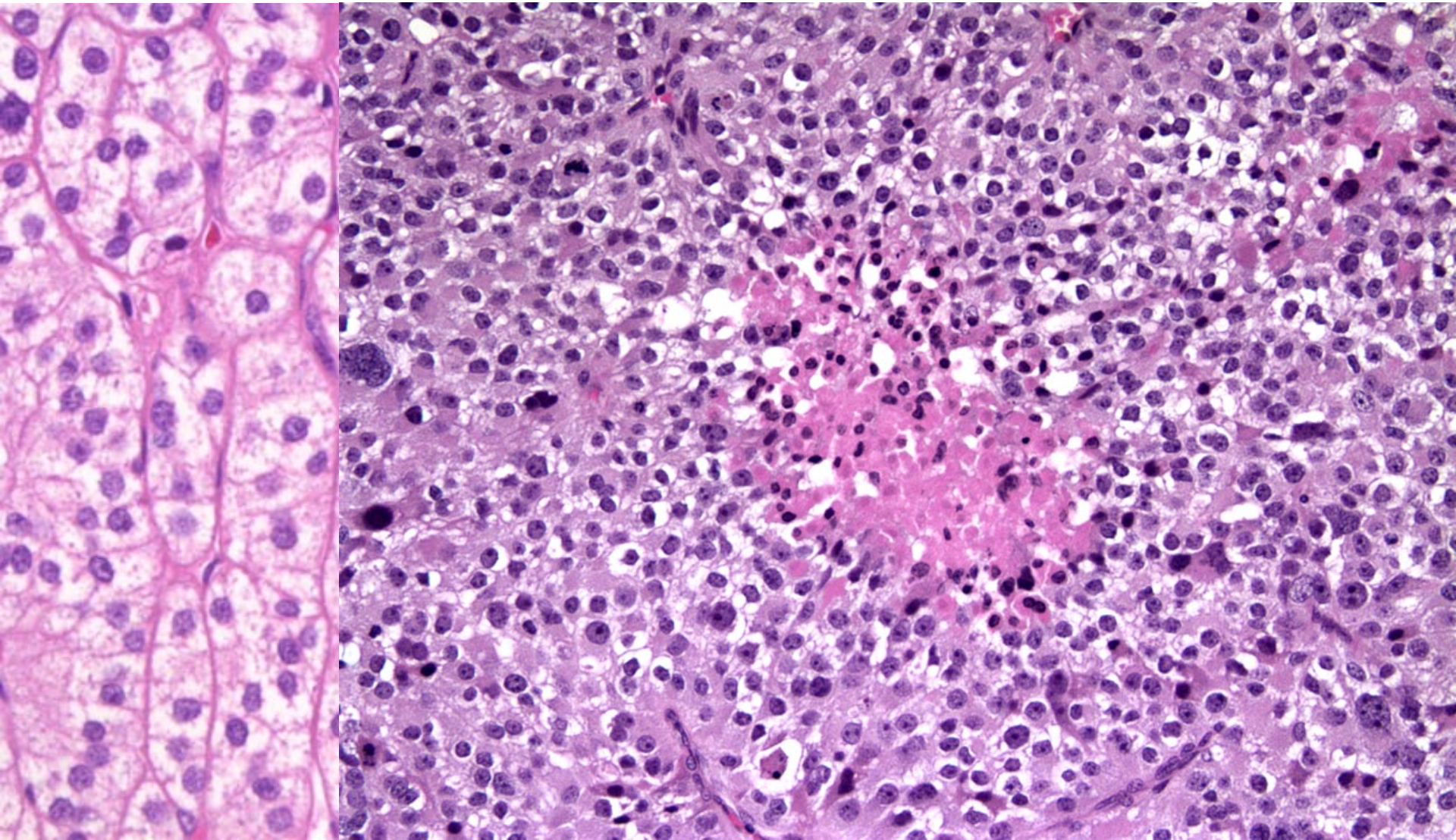
Very large -

20 cm tumor

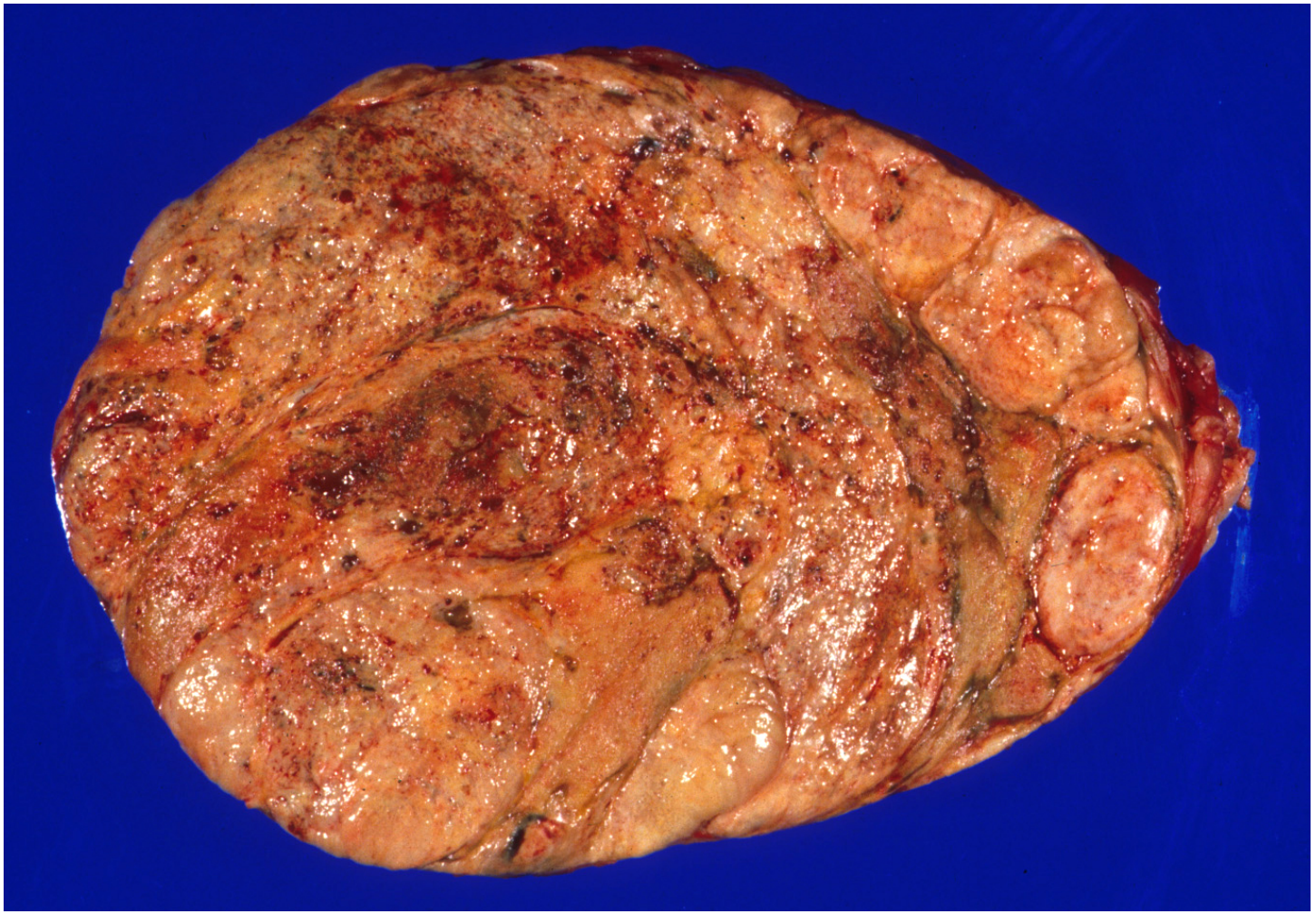
Adenoma to Carcinoma Progression



Histopathology



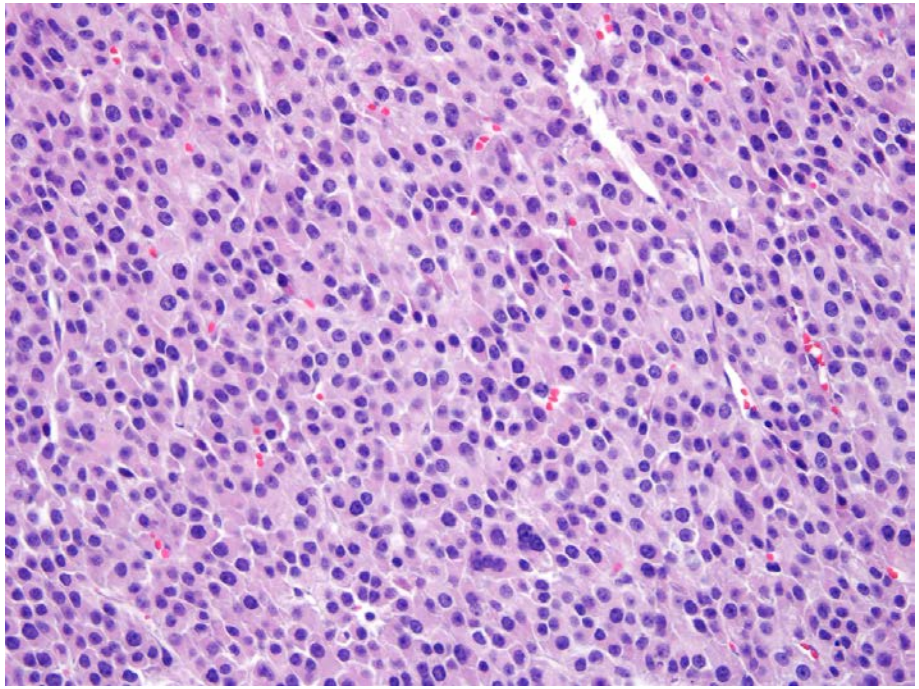
Resection - Only Curative Treatment



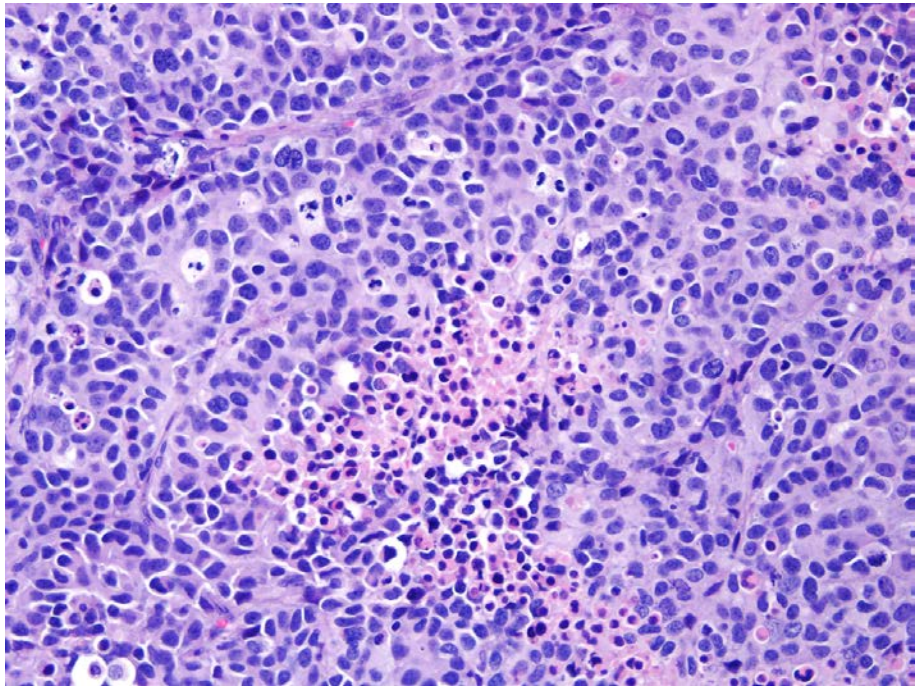
Stage

- Stage I
  - Less than 5 cm and confined to the adrenal
  - Rare cases
- Stage II
  - Greater than 5 cm and confined to the adrenal
- Stage III
  - Any size; locally invasive
- Stage IV
  - Any size; distant metastatic disease

Grade:
Two Mitotic Grades

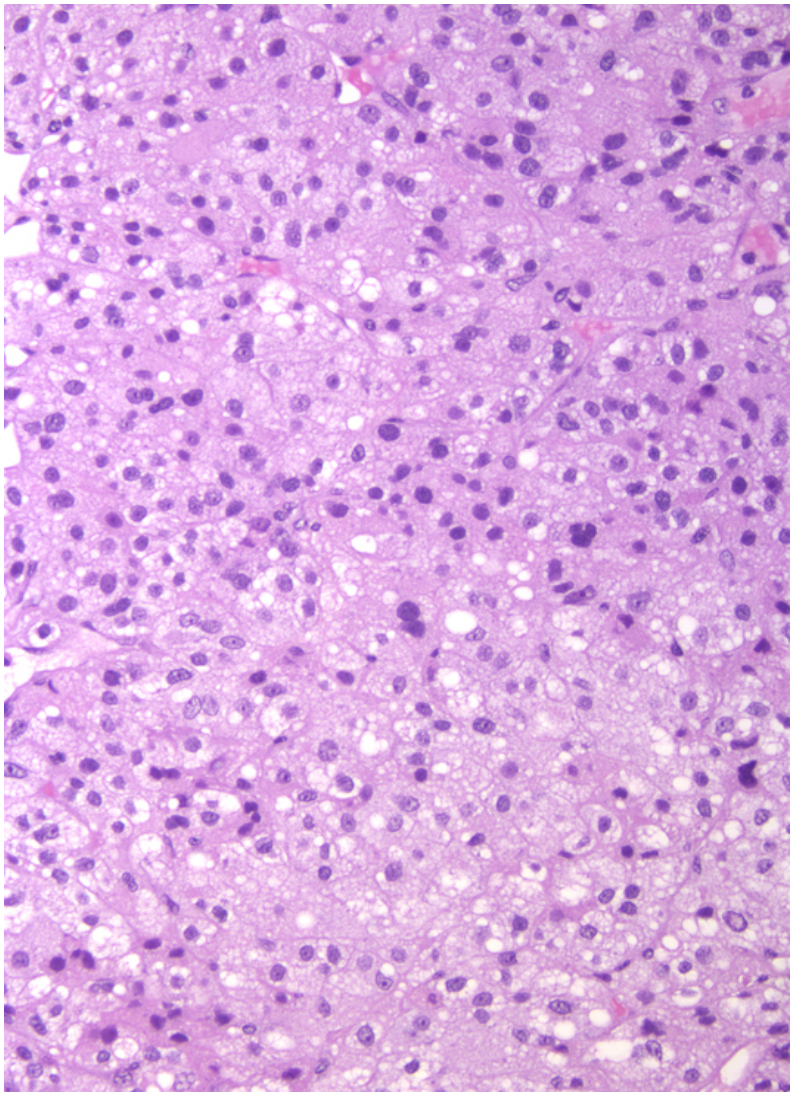


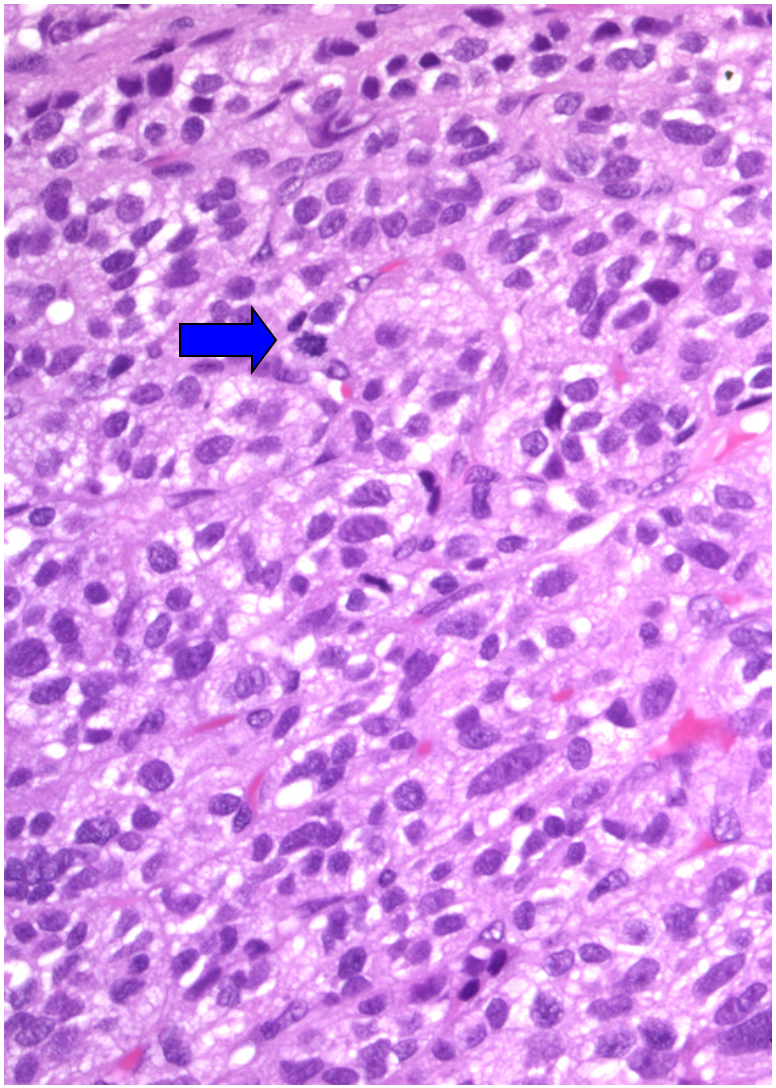
Low: less than 20 mitoses/50 hpfs

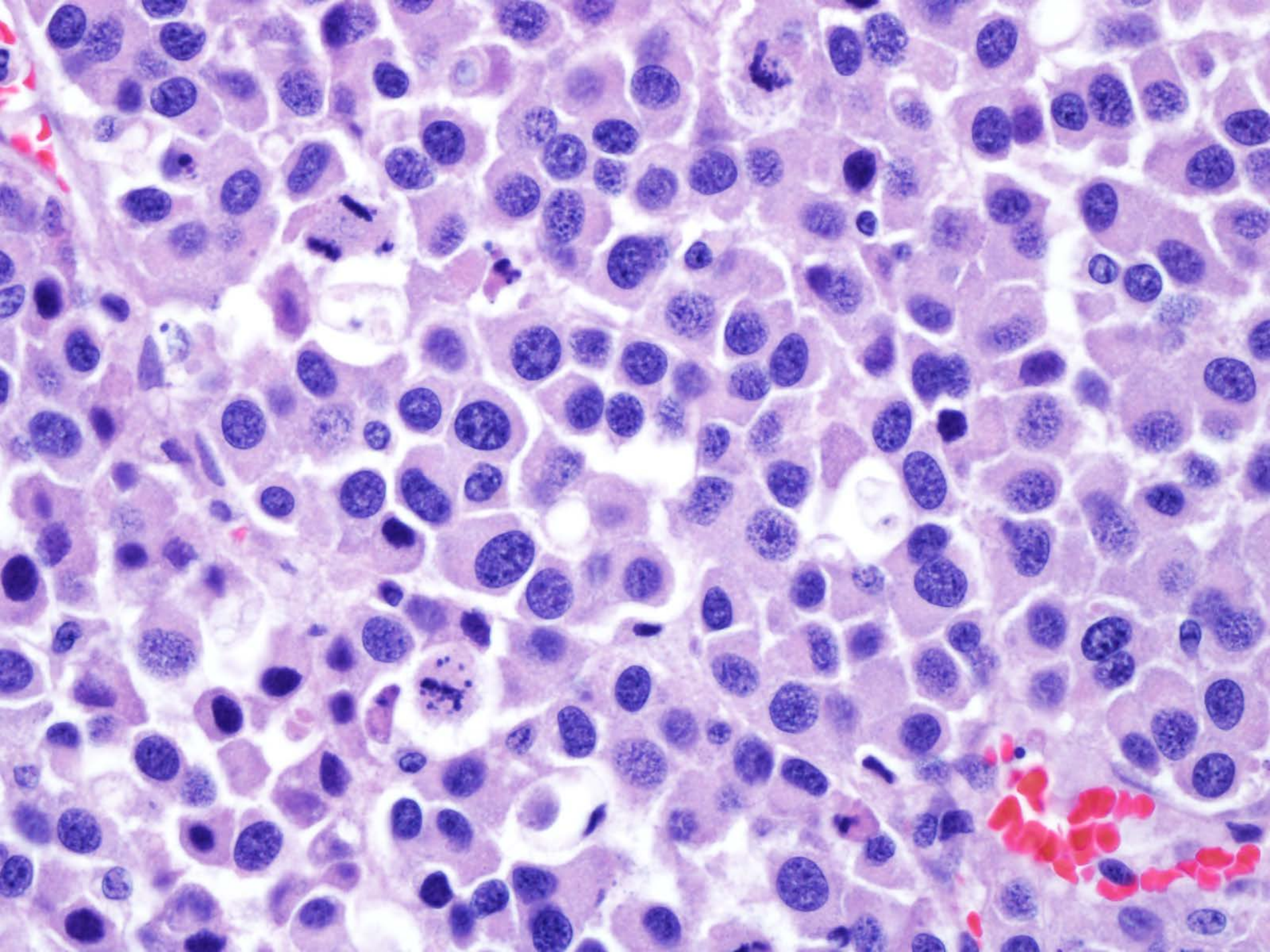


High: 20 or more mitoses/50 hpfs

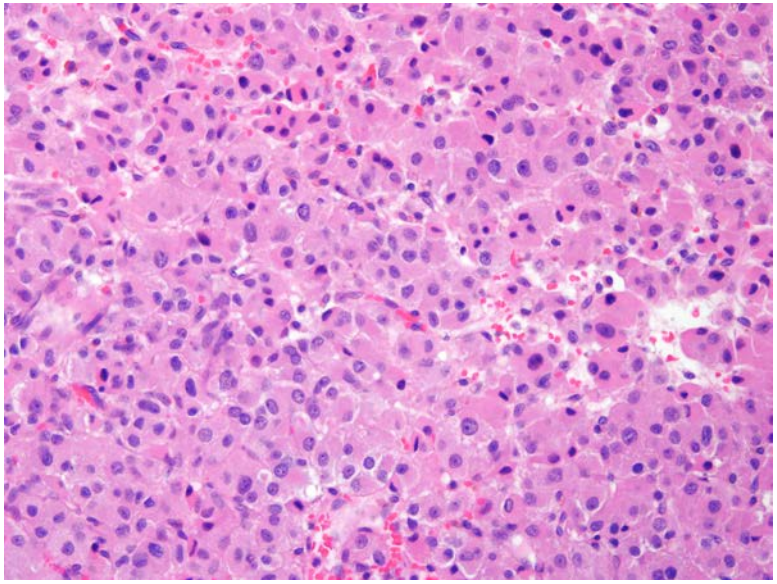
Range of Morphologies

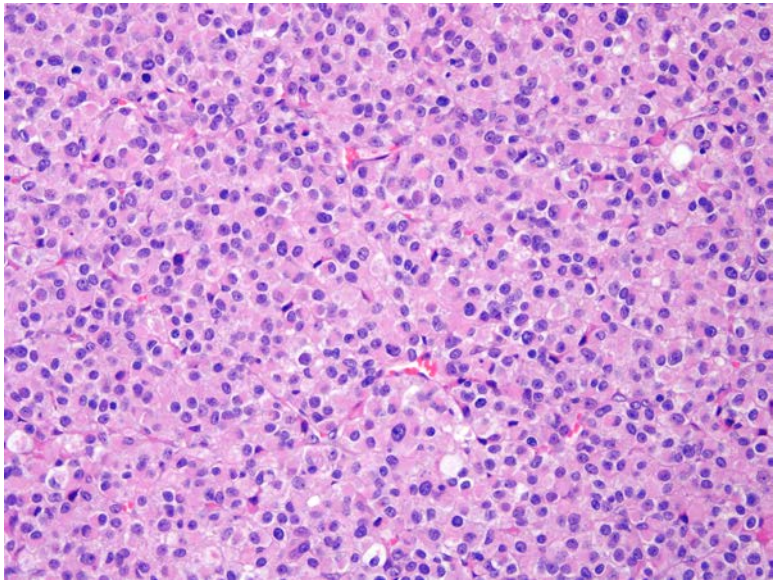


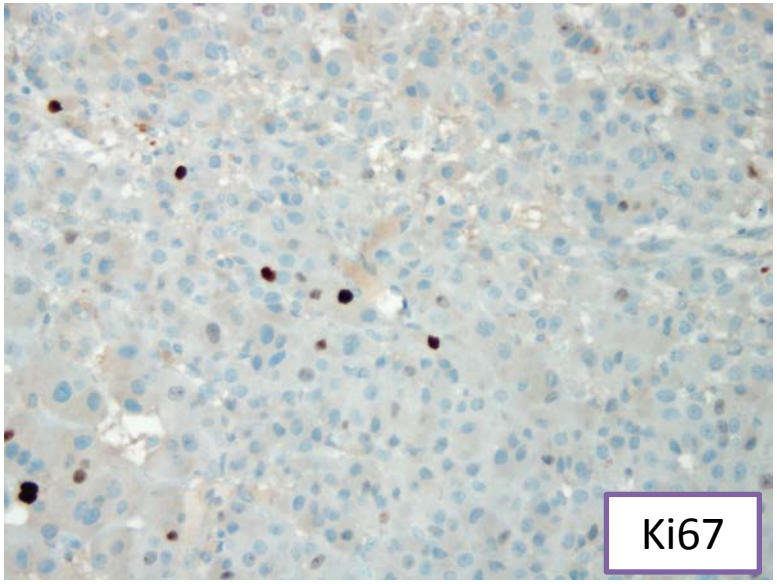


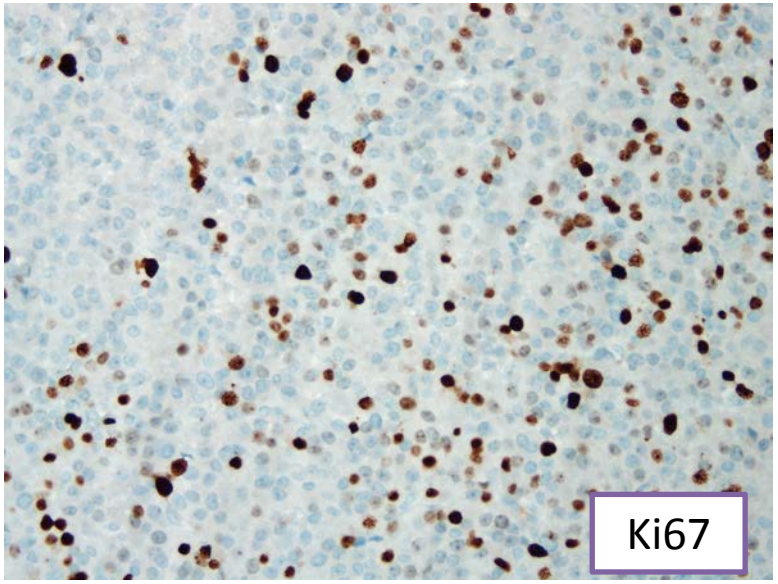


Intratumoral Heterogeneity





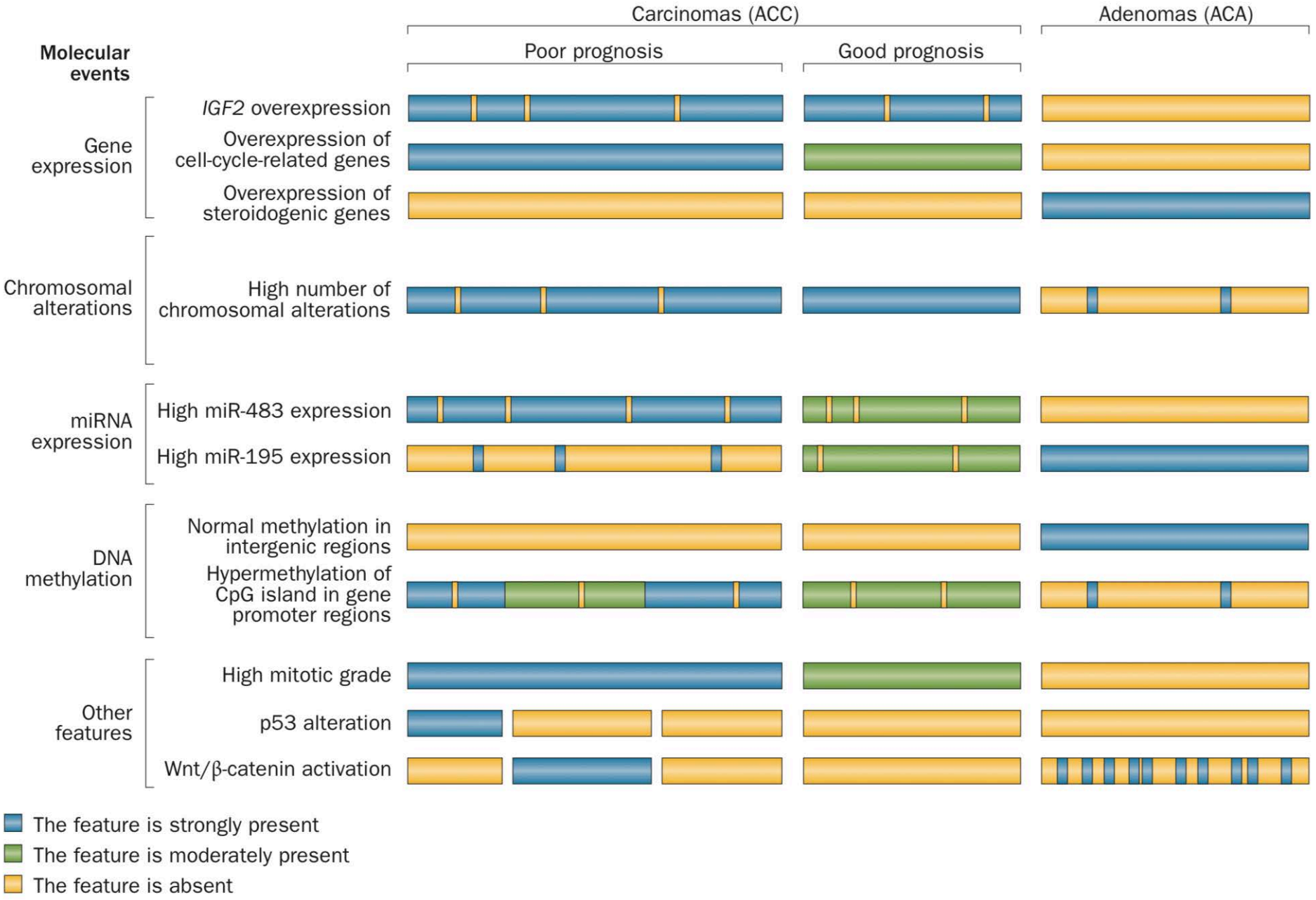




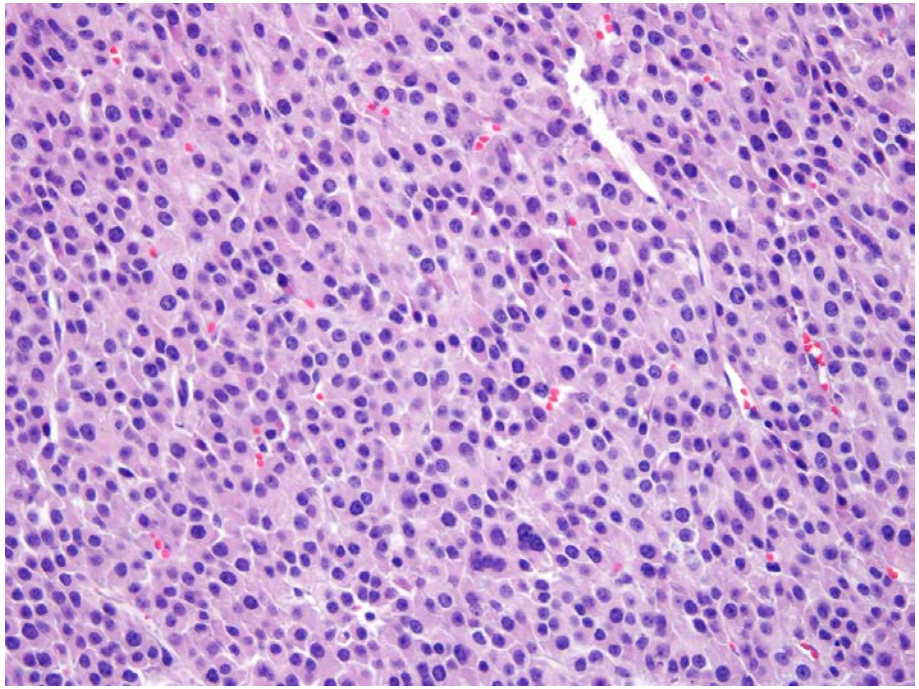
Challenges

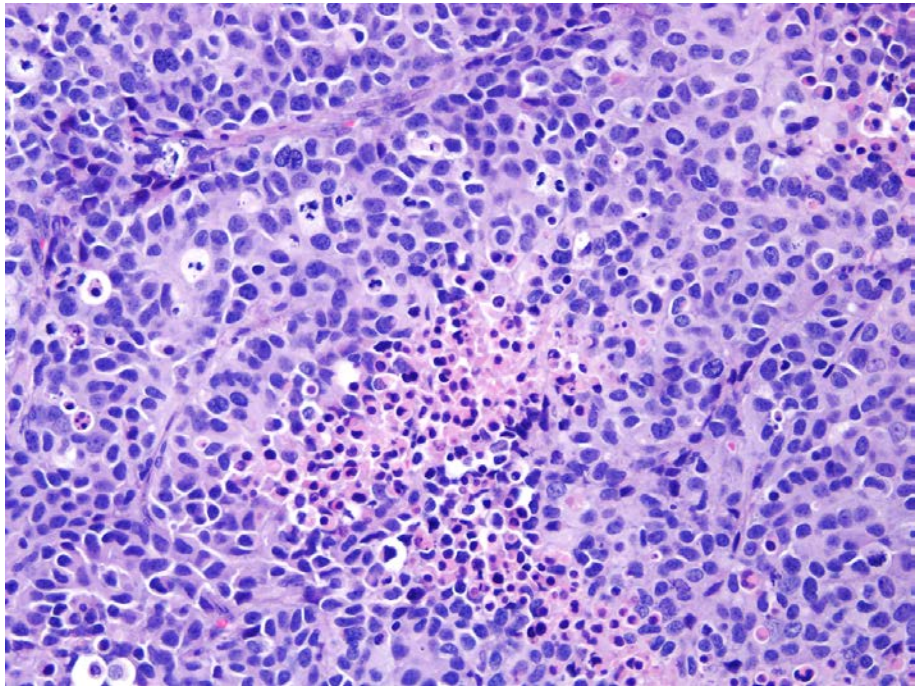
- Diagnostically difficult intermediate cases
- Overall prognosis assessment
- Prediction and risk assessment
  - Risk of local recurrence
  - Risk of metastatic disease
  - Response to therapy
- Limited therapeutic options

Emerging Molecular Classification



Profiling Results in Agreement with Mitotic Grade

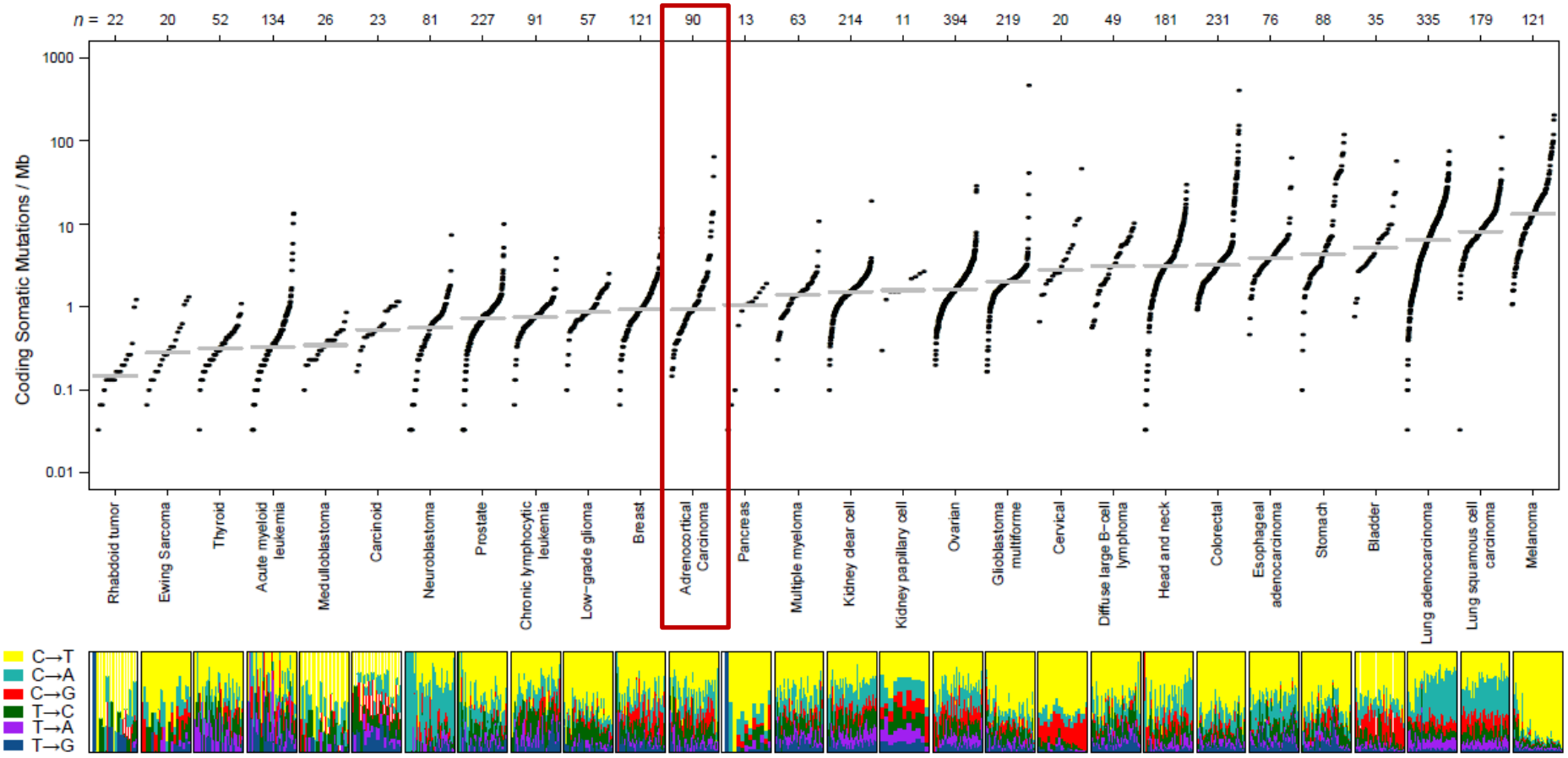




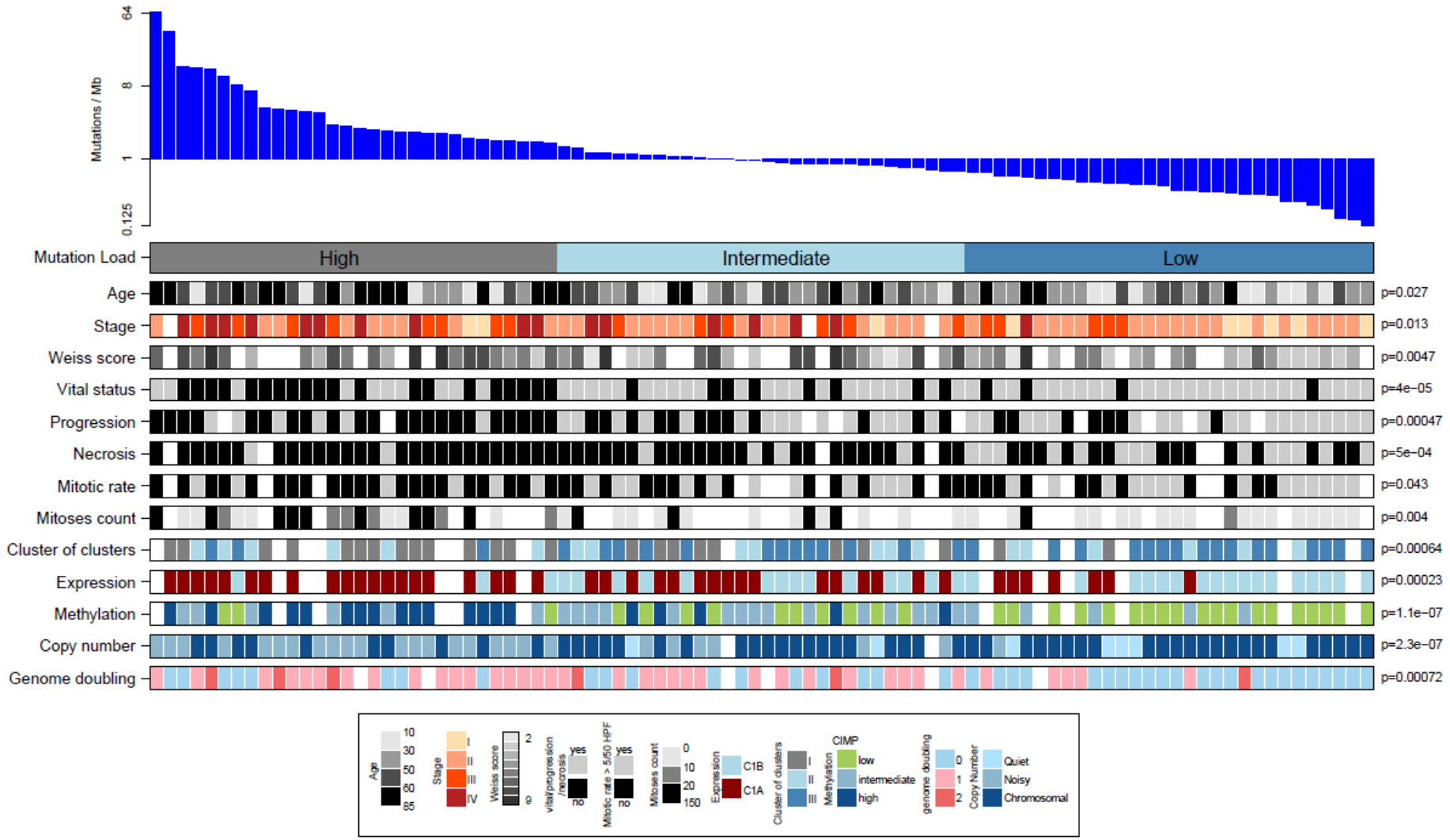
TCGA ACC Cohort & Data

- Global cohort; NA, SA, EU, & AUS
- Whole exome sequencing, n = 91
- mRNA sequencing, n=78
- miRNA sequencing, n=79
- DNA copy number, n=89
- DNA methylation, n=79
- RPPA, n=45
- Clinical data
- Pathology data

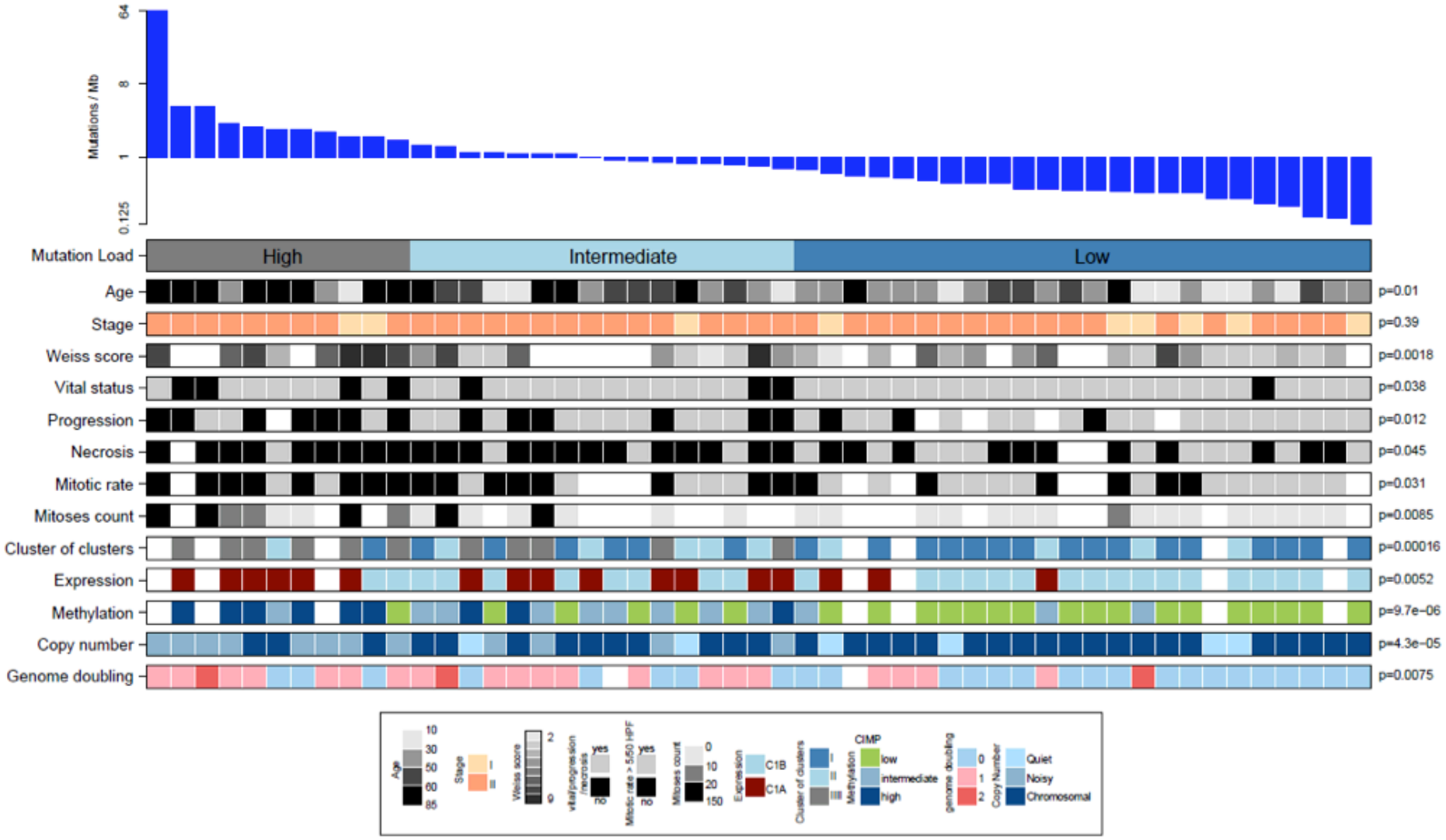
ACC Mutation density



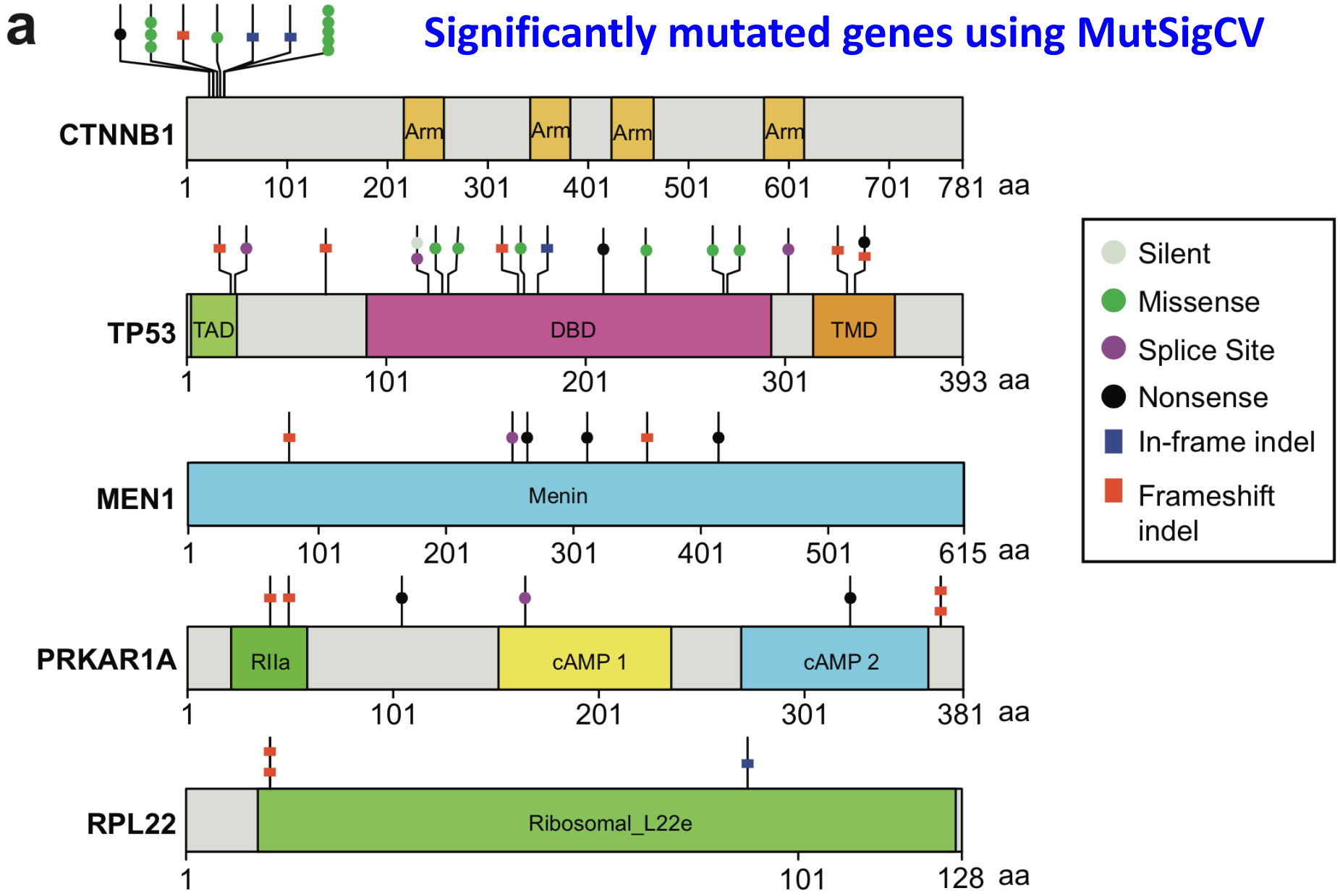
Mutation Density Correlates, all stages



Mutation Density Correlates, stage I and II only



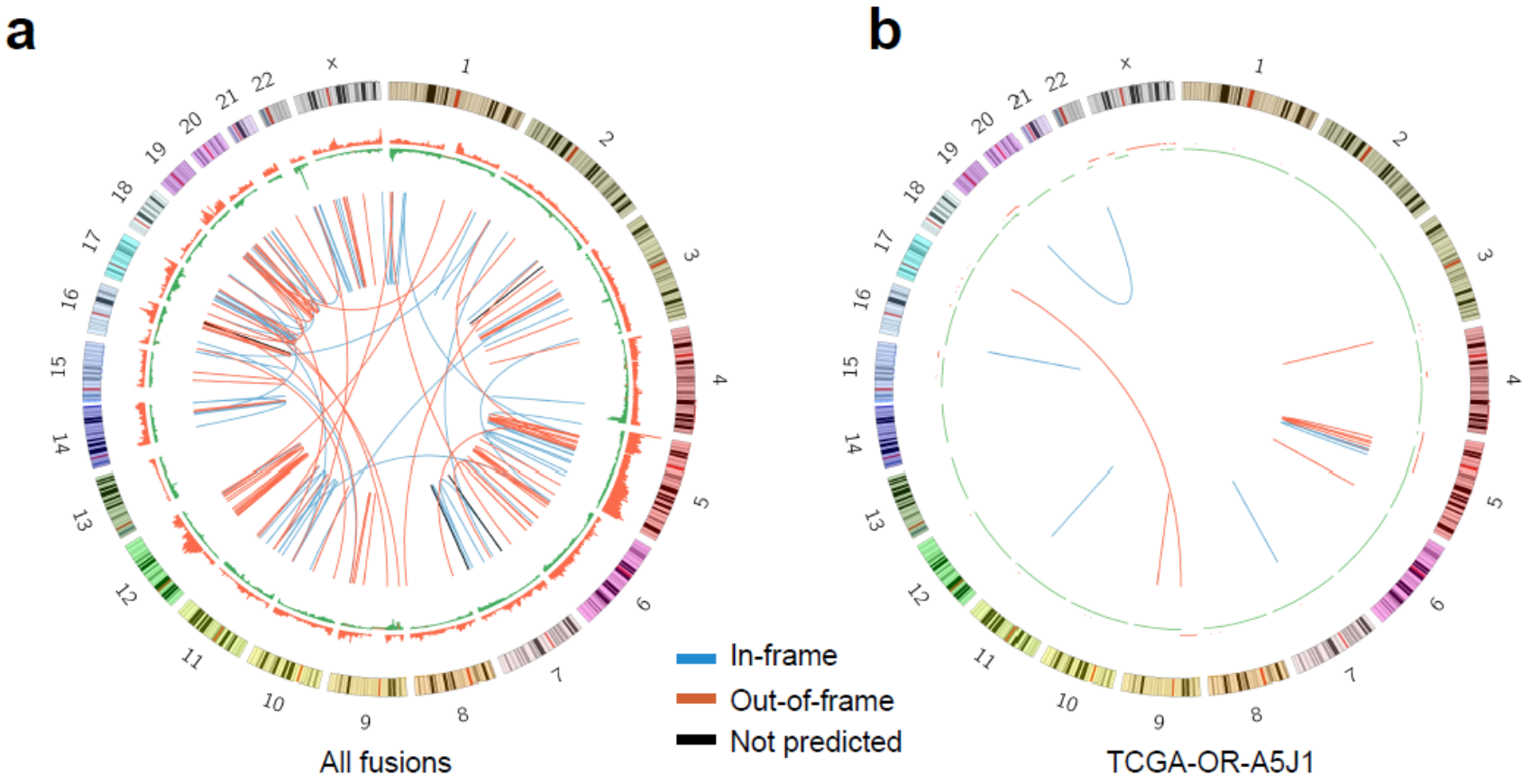
Whole exome sequencing: Significantly mutated genes using MutSigCV



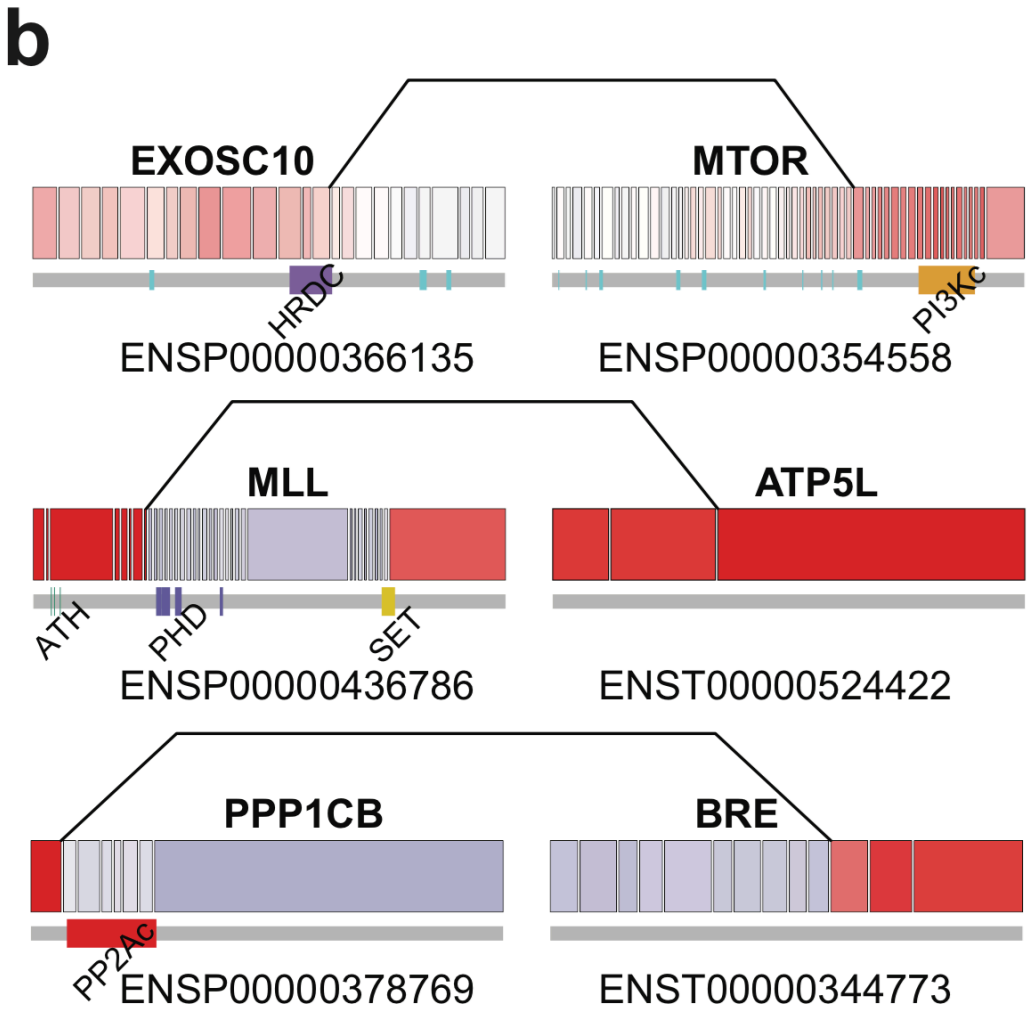
Hunt for Gene Fusions

- Excited about the prospect of finding recurrent gene fusions
- Used two methods to detect fusions
- Found 156 fusion events in 48 of 78 tumors
- Copy number data indicated a breakpoint in 65% of cases

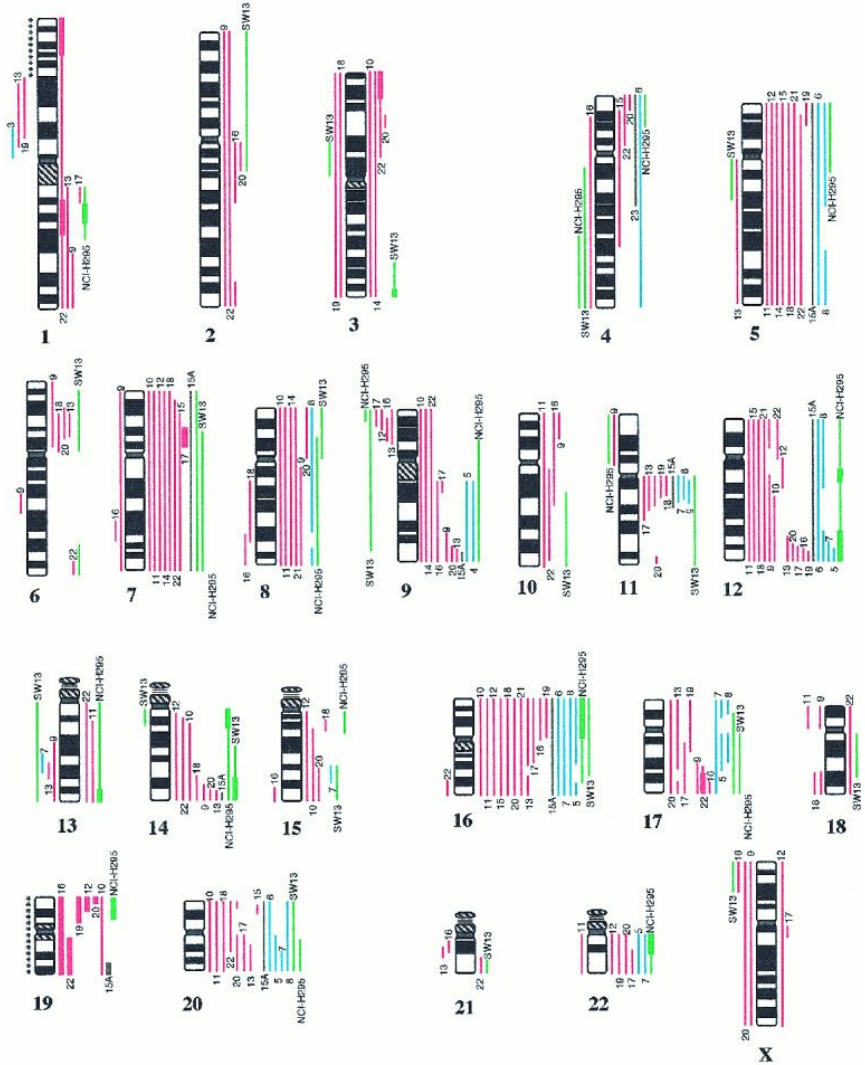
No Recurrent Fusions



Some Private Fusions involve known Cancer Genes

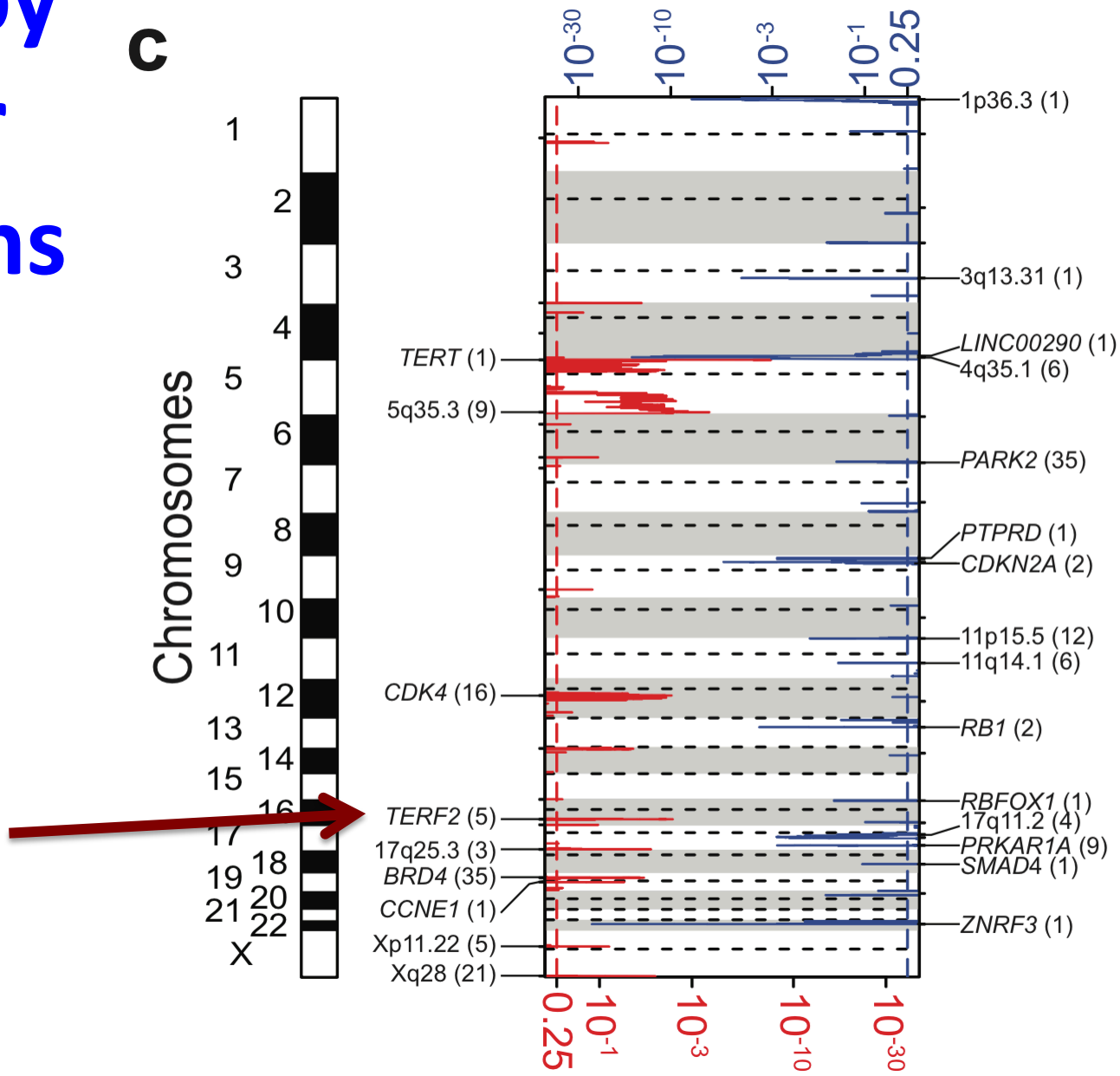


Copy Number Alterations circa 2000



Genes, Chromosomes and Cancer
Volume 28, Issue 2, pages 145-152, 22 MAY 2000 DOI: 10.1002/(SICI)1098-2264(200006)28:2<145::AID-GCC3>3.0.CO;2-7
http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1098-2264(200006)28:2<145::AID-GCC3>3.0.CO;2-7/full#fig1

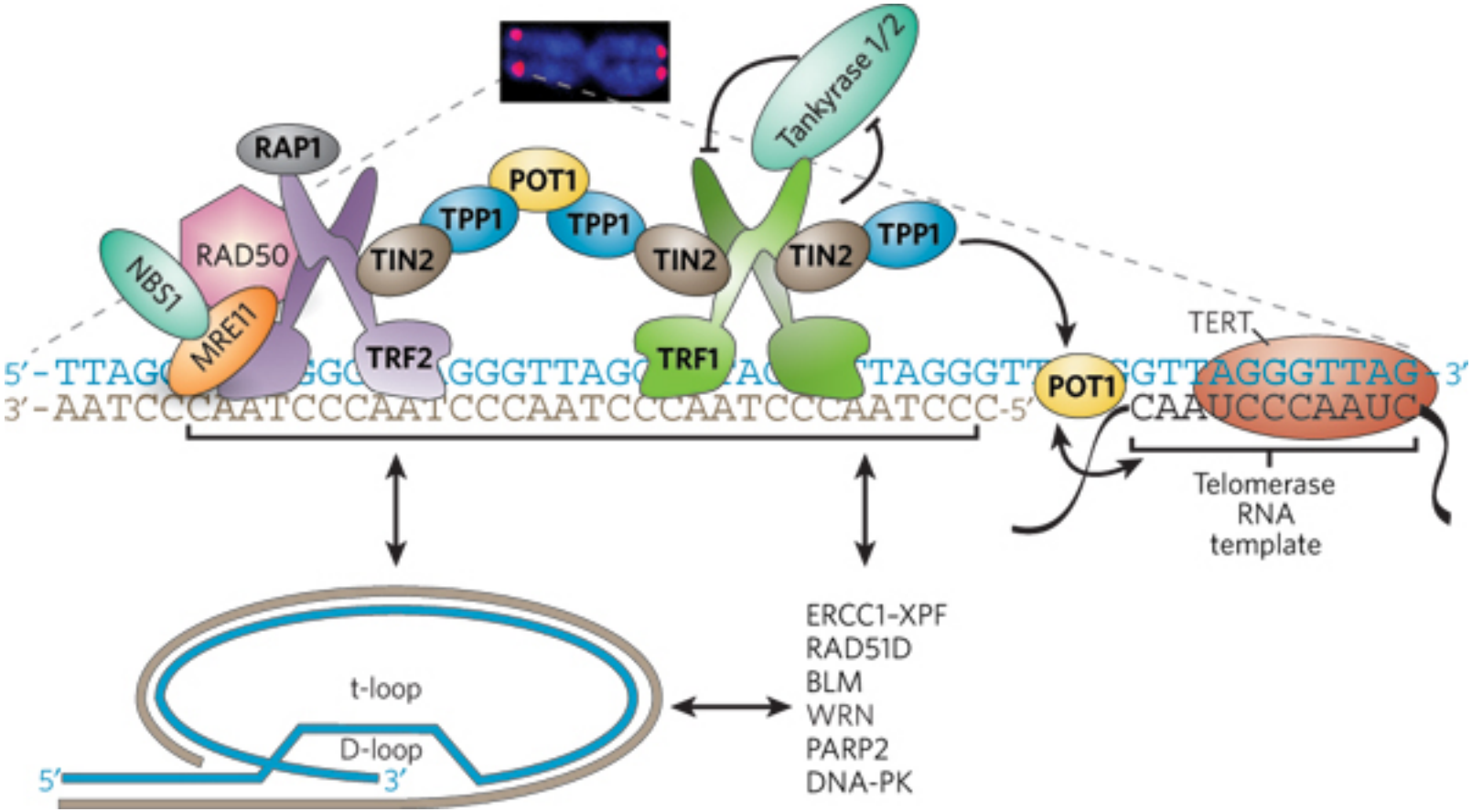
Focal copy number alterations



Novel *TERF2* amplification

Maybe unique within TCGA

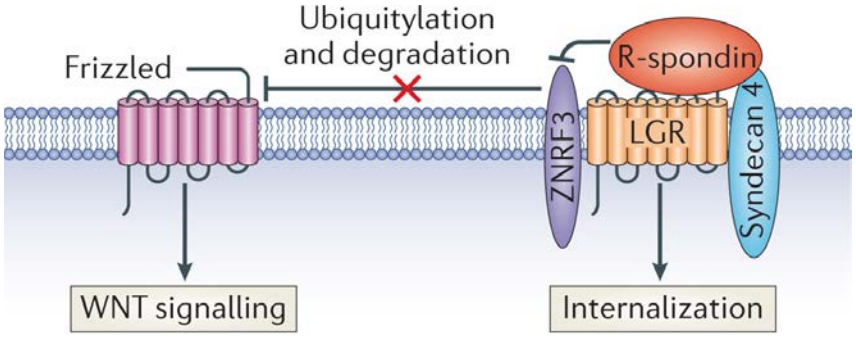
TERF2/TRF2 –
Telomeric Repeat Binding Protein 2



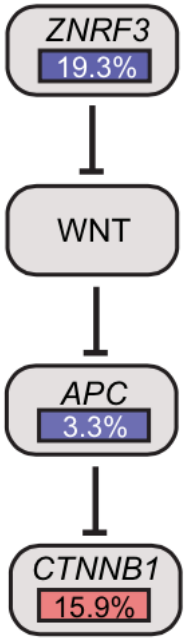
Nature **447**, 924-931

ZNRF3 deletion

- Negative regulator of Wnt signaling pathway
- Leads to degradation of Wnt receptor complex proteins
- Deletion of ZNRF3 may represent an alterative way to activate Wnt pathway in ACC
- About 20% of ACCs

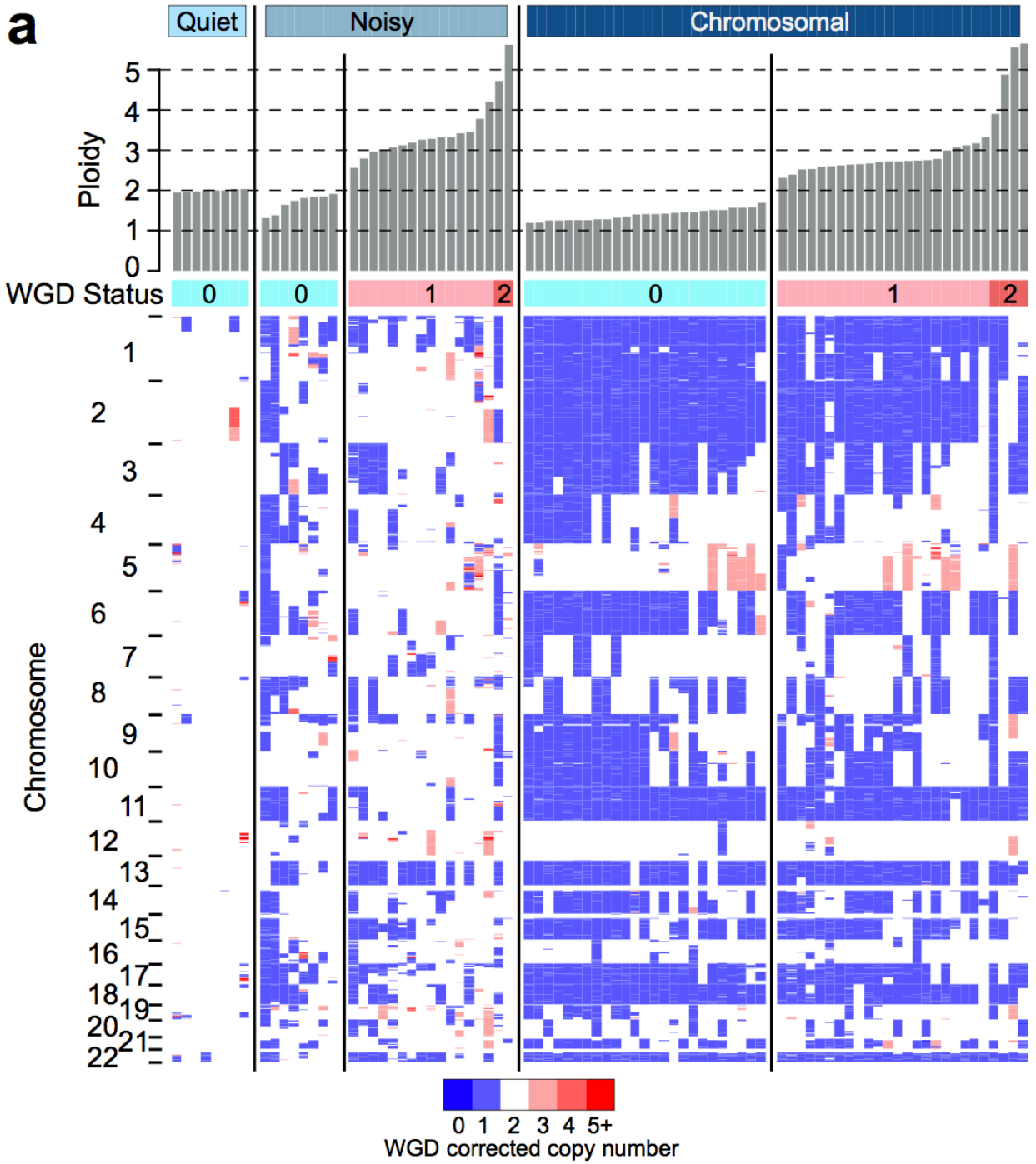


Nature Reviews | Molecular Cell Biology



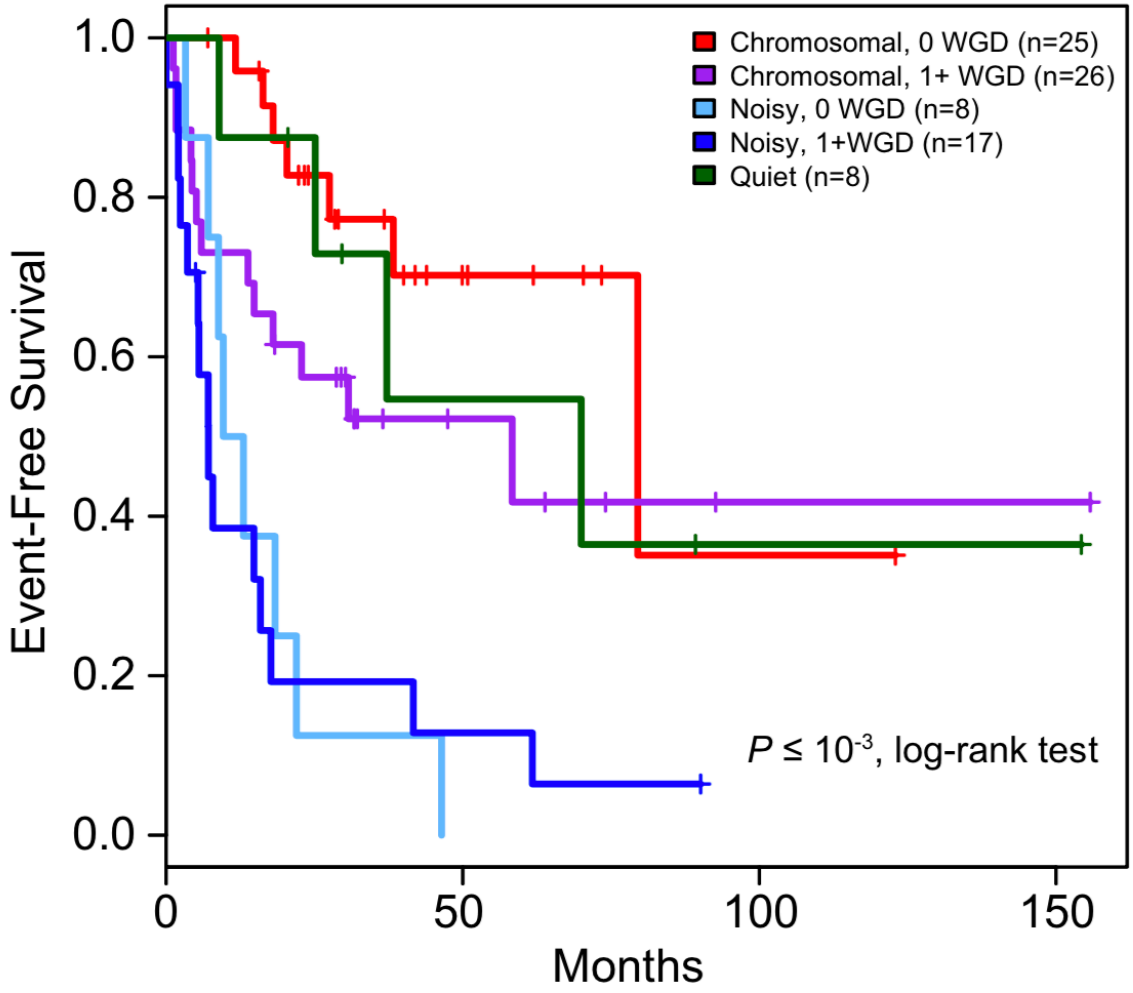
Copy number defines different classes of ACC…

Roel Verhaak, Siyuan Zhang, Andy Cherniack, Brad Murray, others



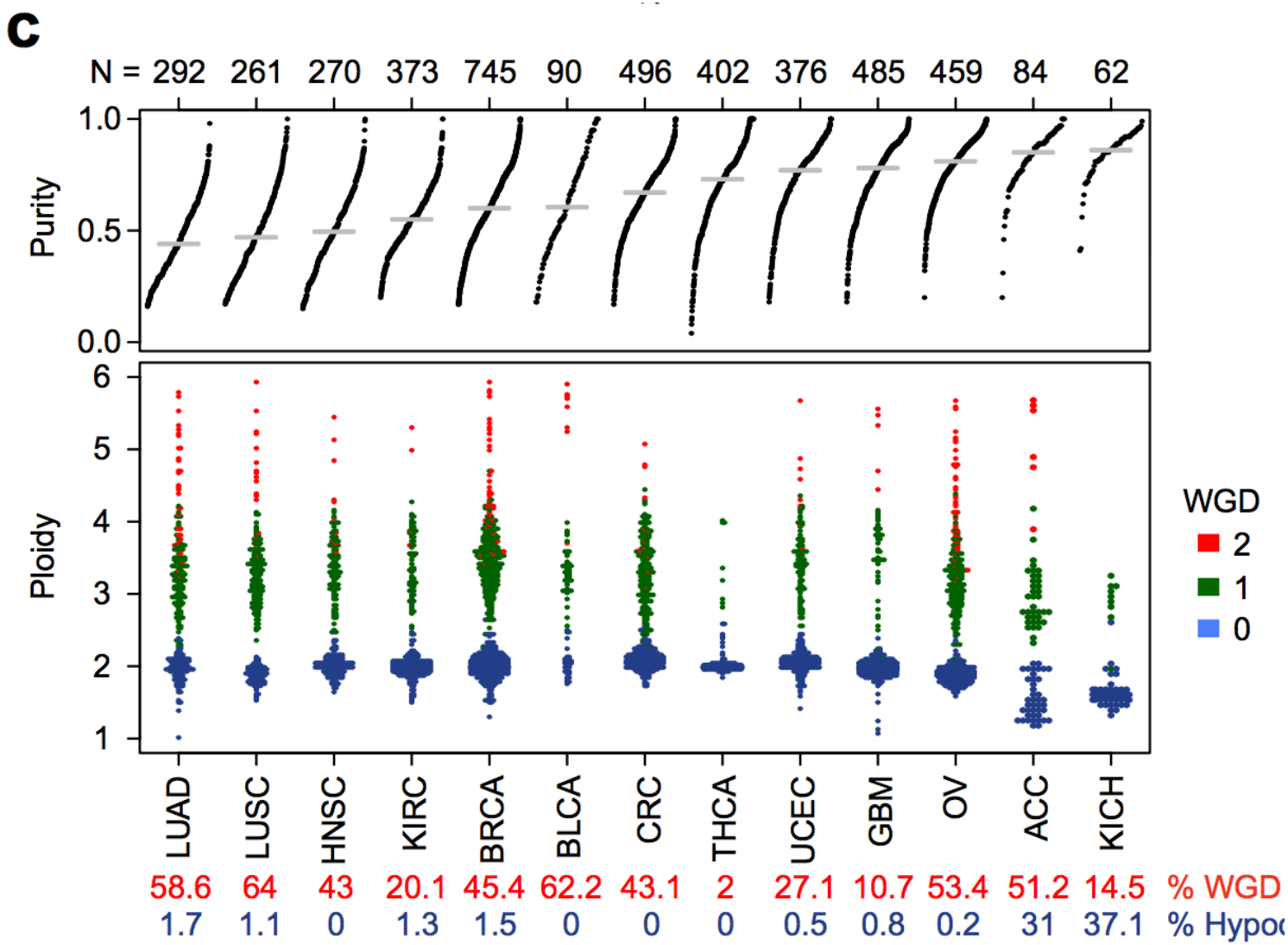
With different survival

b



***Noisy* tumors most aggressive**

PanCancer Context, purity and ploidy

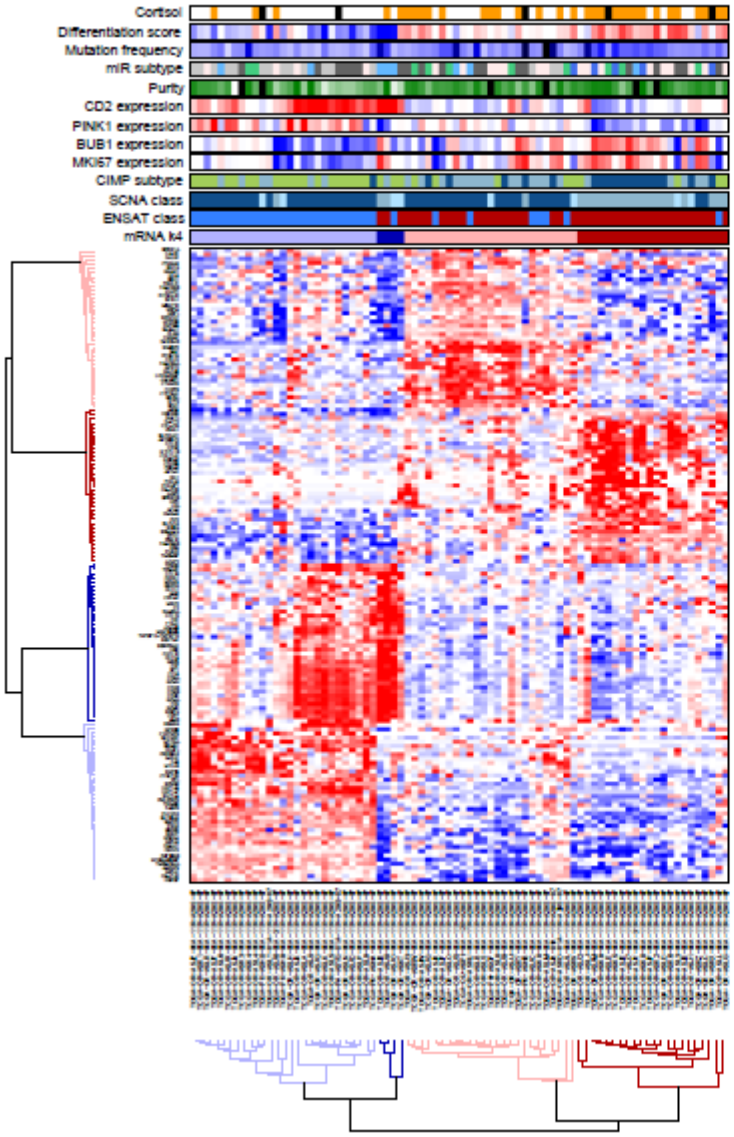


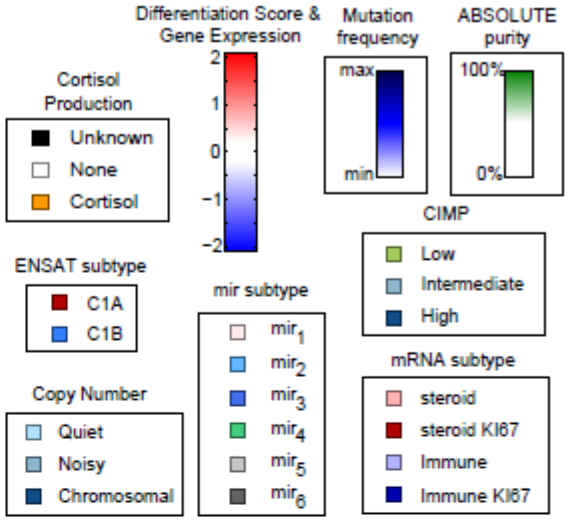
Transcriptome

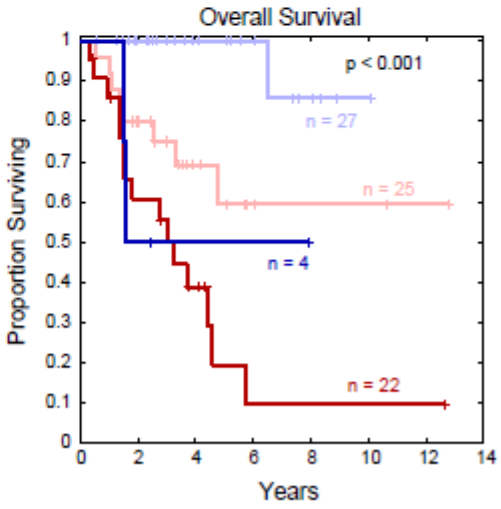
2 large classes

4 granular classes

profound differences between classes

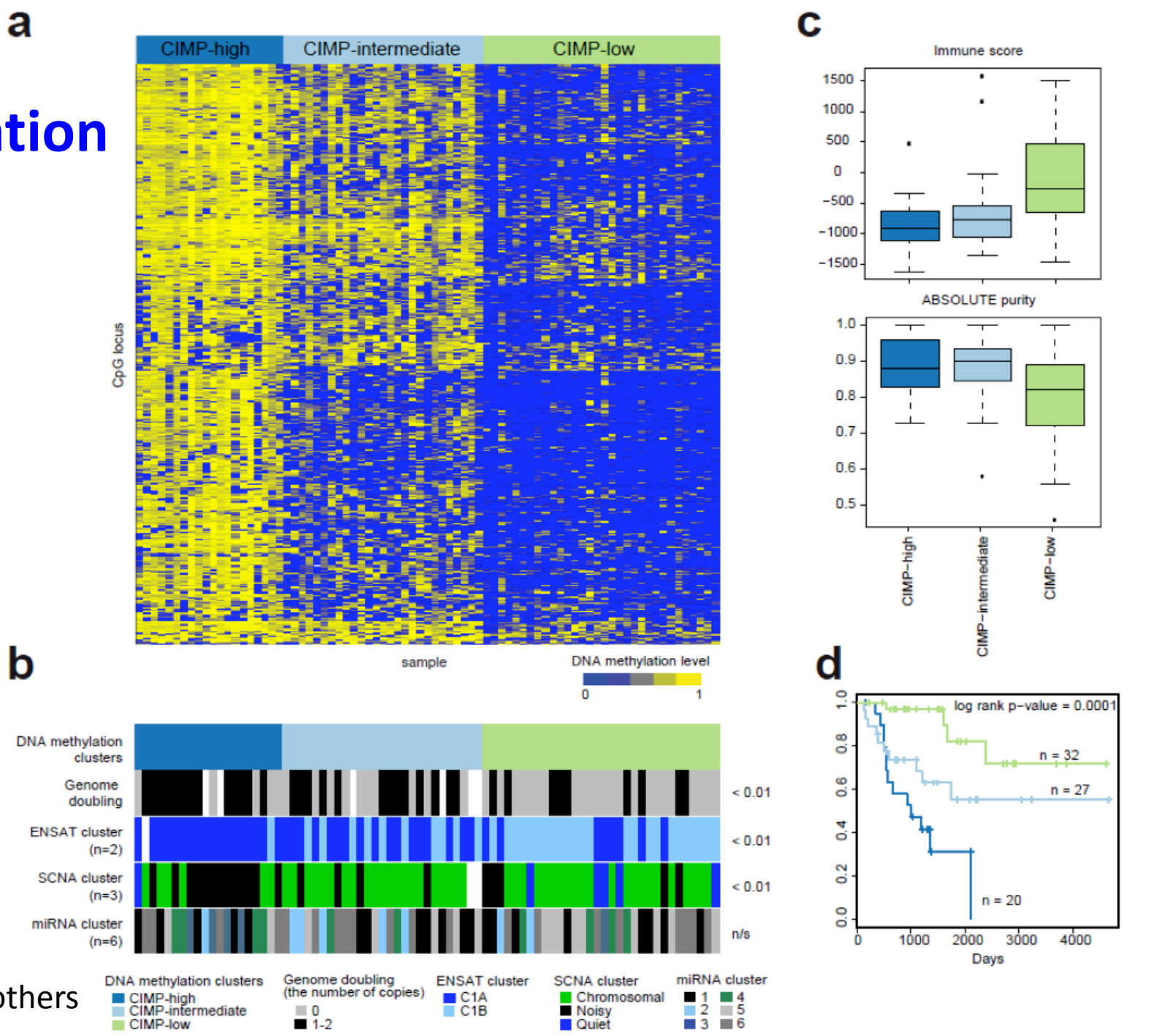






Richard Moffett, others

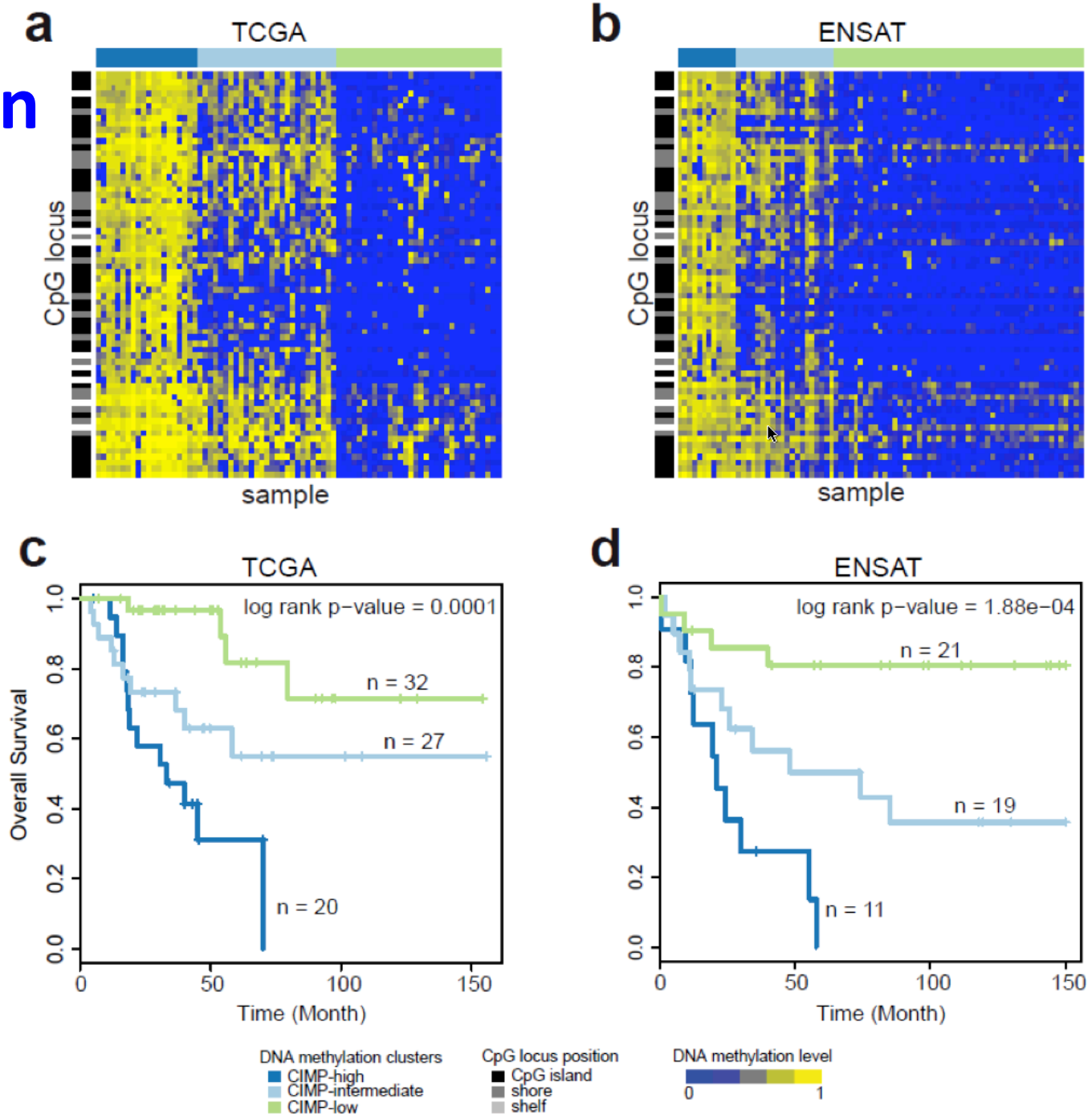
Methylation



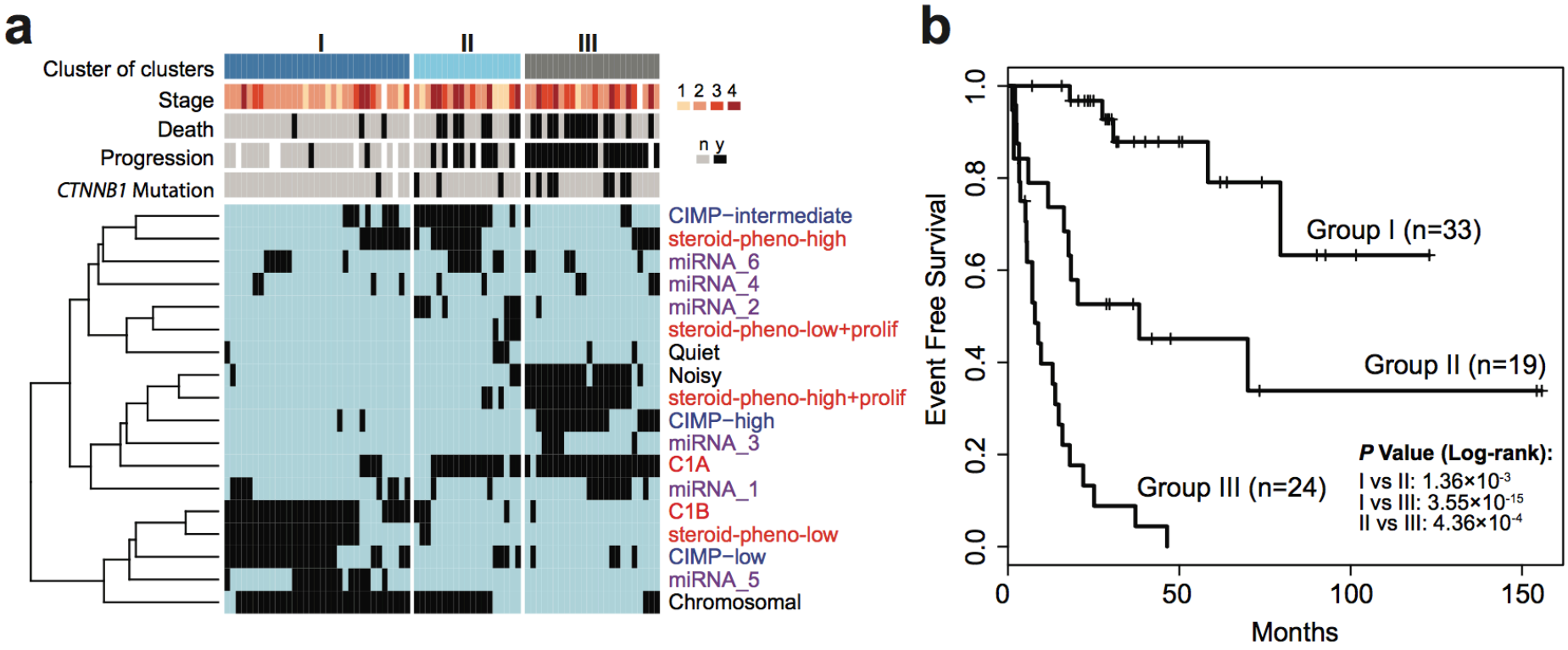
Luda Danilova, others

Methylation validation

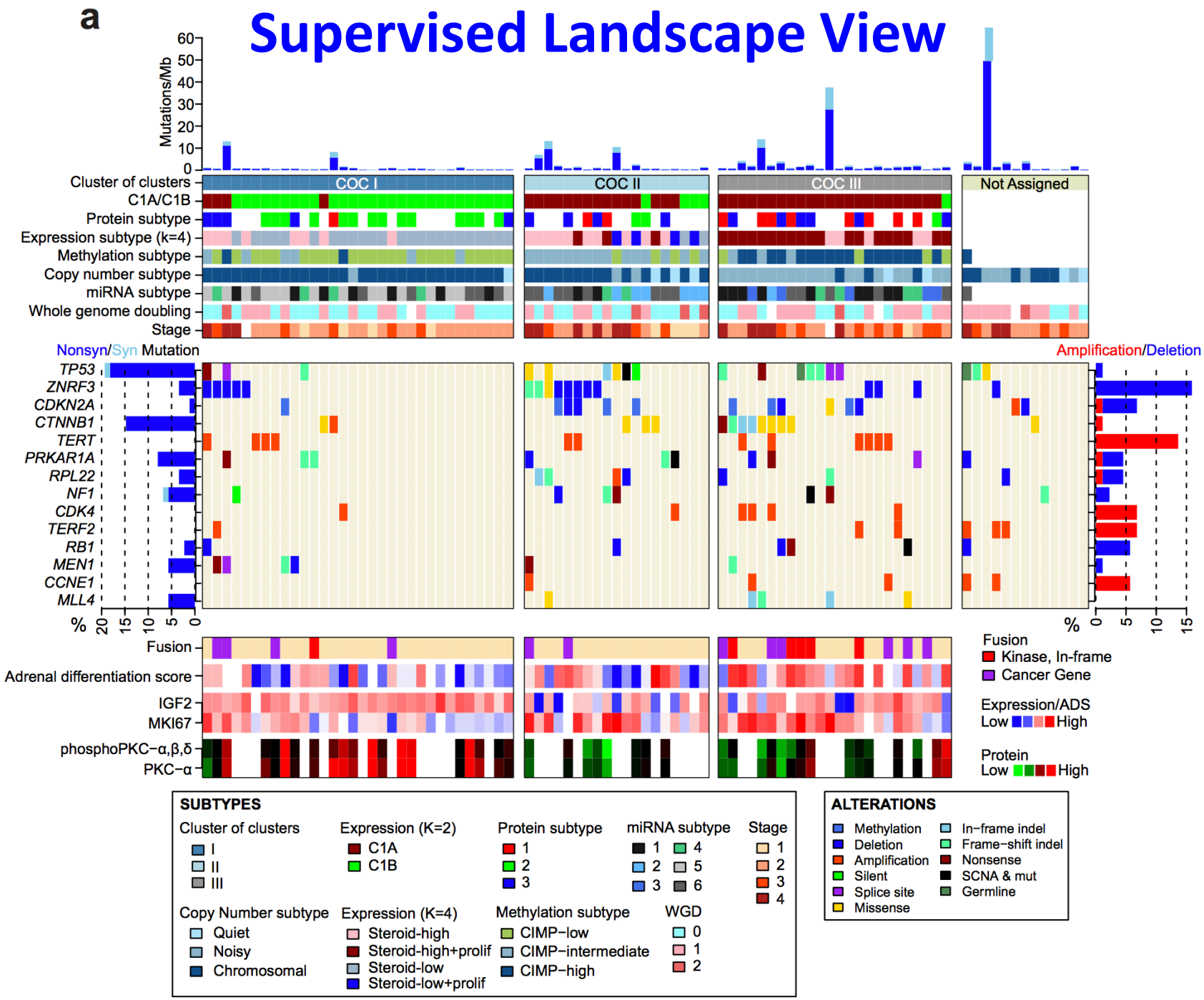
68-probe methylation signature



Cluster of Cluster



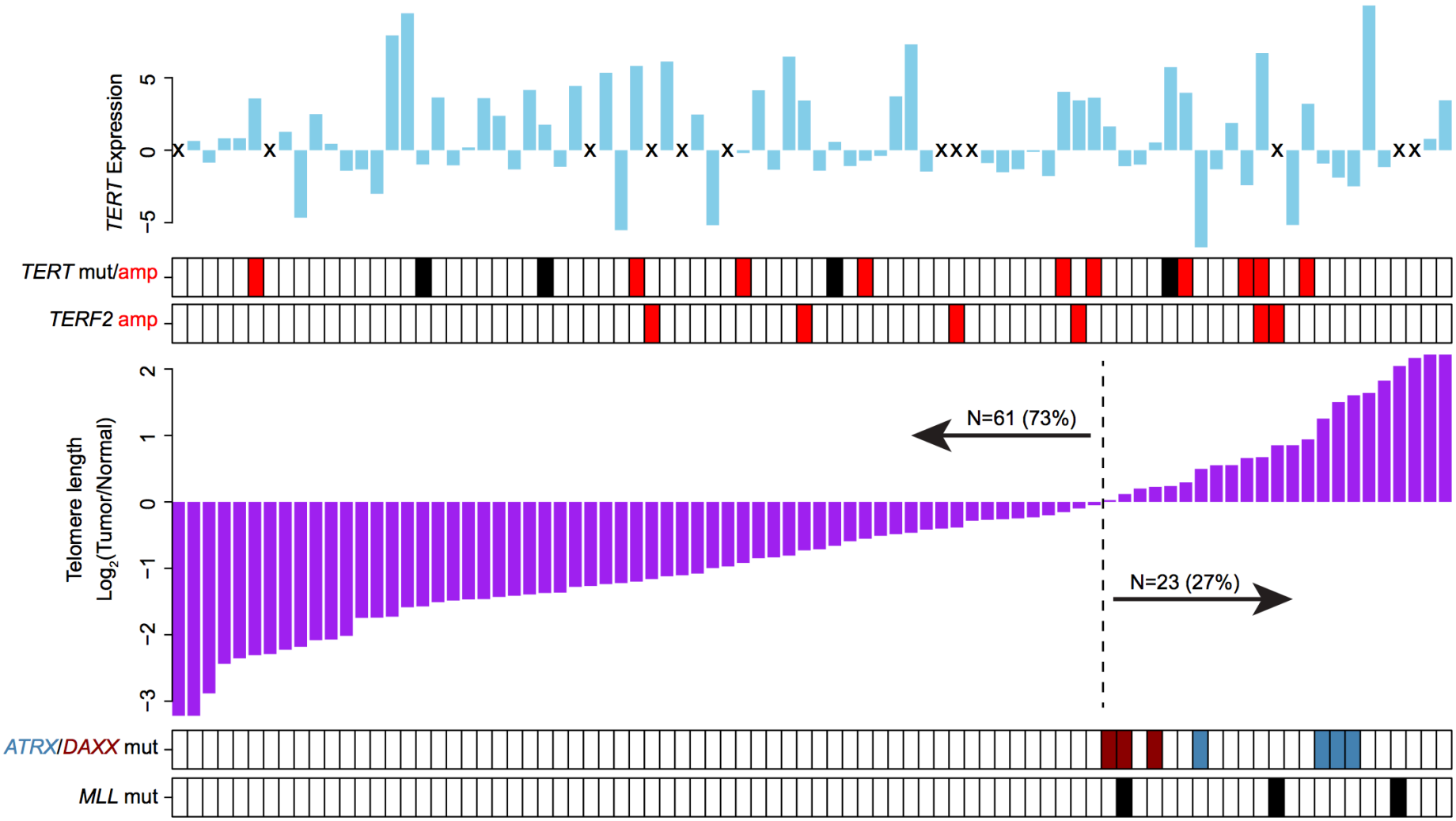
Most *CTNNB1* mutations in Groups II and III


a
Supervised Landscape View
Mutations/Mb
60
50
40
30
20
10
0
Cluster of clusters
COC I
COC II
COC III
Not Assigned
C1A/C1B
Protein subtype
Expression subtype (k=4)
Methylation subtype
Copy number subtype
miRNA subtype
Whole genome doubling
Stage
Nonsyn/Syn Mutation
Amplification/Deletion
TP53
ZNRF3
CDKN2A
CTNNB1
TERT
PRKAR1A
RPL22
NF1
CDK4
TERF2
RB1
MEN1
CCNE1
MLL4
%
20
15
10
5
0
%
0
5
10
15
Fusion
Adrenal differentiation score
IGF2
MKI67
phosphoPKC−α,β,δ
PKC−α
Fusion
Kinase, In-frame
Cancer Gene
Expression/ADS
Low
High
Protein
Low
High
SUBTYPES
Cluster of clusters
I
II
III
Expression (K=2)
C1A
C1B
Protein subtype
1
2
3
miRNA subtype
1
2
3
4
5
6
Stage
1
2
3
4
Copy Number subtype
Quiet
Noisy
Chromosomal
Expression (K=4)
Steroid-high
Steroid-high+prolif
Steroid-low
Steroid-low+prolif
Methylation subtype
CIMP−low
CIMP−intermediate
CIMP−high
WGD
0
1
2
ALTERATIONS
Methylation
Deletion
Amplification
Silent
Splice site
Missense
In−frame indel
Frame−shift indel
Nonsense
SCNA & mut
Germline

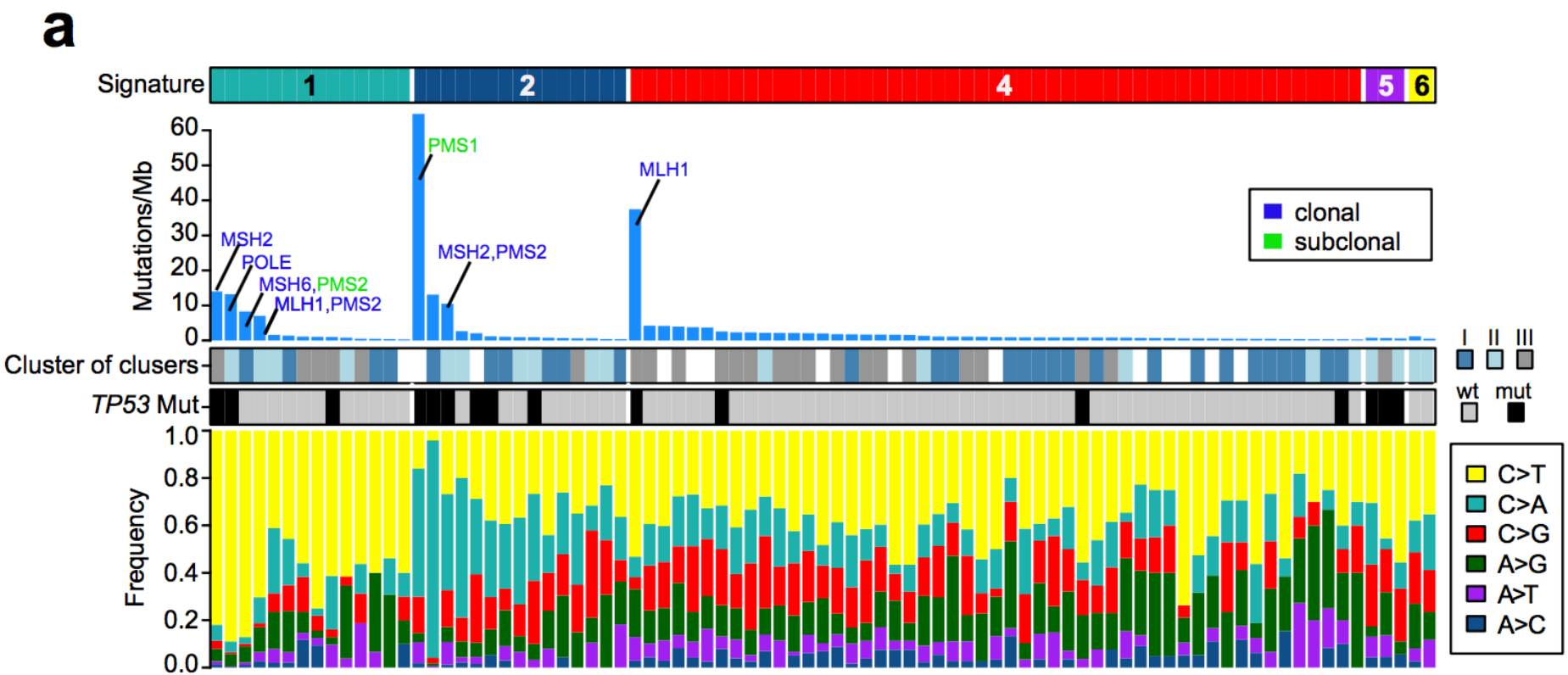
Integrative Analyses

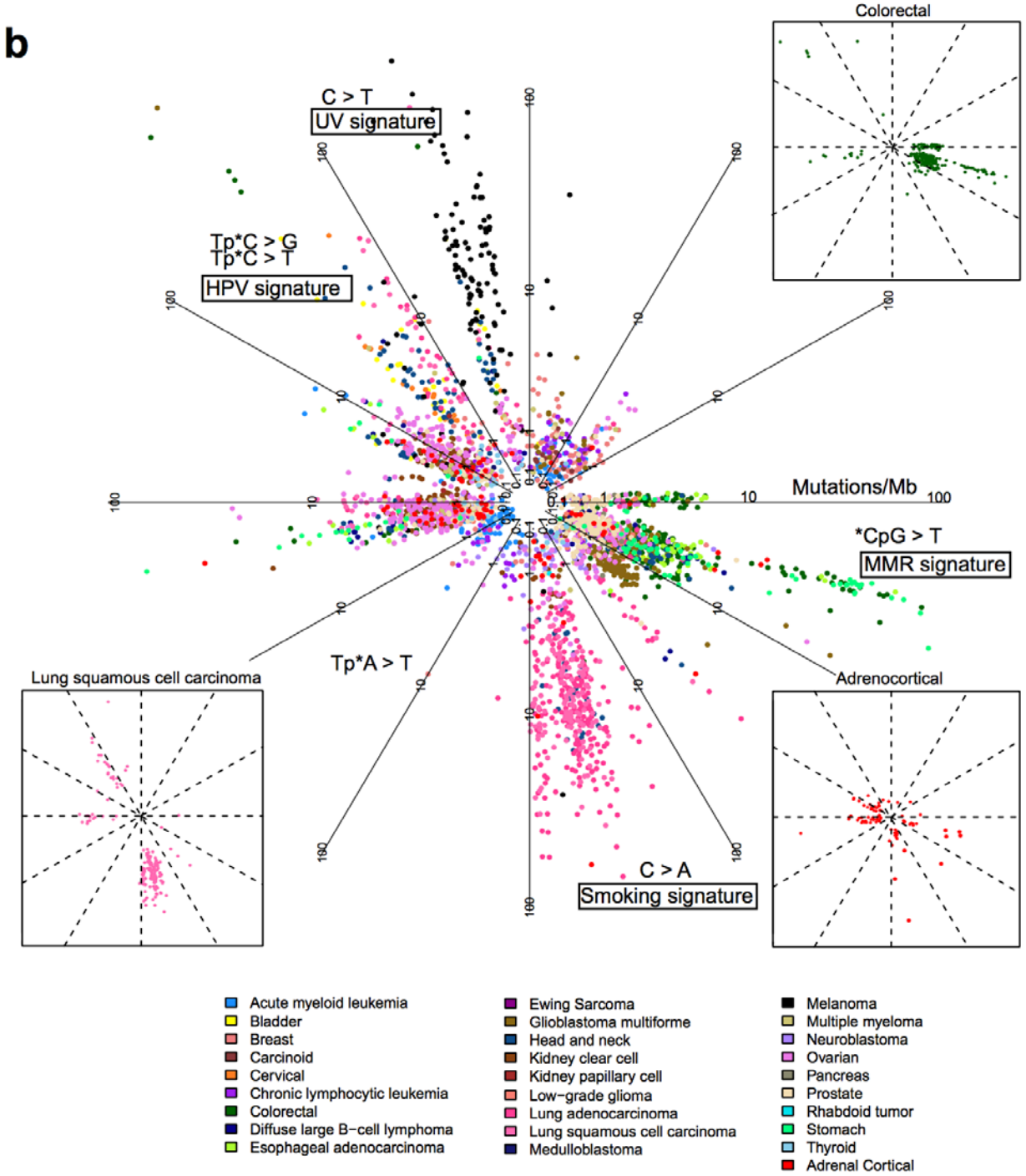
- Telomere length
- Adrenocortical differentiation
- HotNets
- PHIAL
- OncoSign
- PanCancer oncogenic processes

Telomere Length – ALT in play



Pan-cancer mutation signature analysis




b
C > T
UV signature
Tp*C > G
Tp*C > T
HPV signature
Mutations/Mb
*CpG > T
MMR signature
Tp*A > T
C > A
Smoking signature
Colorectal
Lung squamous cell carcinoma
Adrenocortical
Acute myeloid leukemia
Bladder
Breast
Carcinoid
Cervical
Chronic lymphocytic leukemia
Colorectal
Diffuse large B−cell lymphoma
Esophageal adenocarcinoma
Ewing Sarcoma
Glioblastoma multiforme
Head and neck
Kidney clear cell
Kidney papillary cell
Low−grade glioma
Lung adenocarcinoma
Lung squamous cell carcinoma
Medulloblastoma
Melanoma
Multiple myeloma
Neuroblastoma
Ovarian
Pancreas
Prostate
Rhabdoid tumor
Stomach
Thyroid
Adrenal Cortical

Highlights

- Created a outstanding genomic resource for adrenal cancer research
- Discovered novel somatic alterations
- Expanded role of WNT pathway alterations
- Copy number / whole genome doubling
- COC analysis with integrated view
  - Overall 3 classes of tumors
- Pan-cancer analysis
- Paper under review

Looking forward

- Pathology
  - Looking for ways to deliver the 3 class solution to routine cases
- Therapy
  - Supports the view that combined inhibition of IGF2 and Wnt pathways for the largest subset of cases
  - Other pathways in smaller subsets

People

Roel Verhaak

Siyuan Zheng

Many More People

- Siyuan Zheng, Andrew D. Cherniack, Ninad Dewal, Richard A. Moffitt, Luda Danilova, Bradley A. Murray, Antonio M. Lerario, Tobi Else, Theo A. Knijnenburg, Giovanni Ciriello, Seungchan Kim, Guillaume Assie, Olena Morozova, Rehan Akbani, Juliann Shih, Katherine A. Hoadley, Toni K. Choueiri, Jens Waldmann, Ozgur Mete, A. Gordon Robertson, Matthew Meyerson, Michael J. Demeure, Felix Beuschlein, Anthony J. Gill, Ana C. Latronico, Maria C. Fragosa, Leslie . Cope, Electron Kebebew, Mouhammed A. Habra, Timothy G. Whitsett, Kim Bussey, William E. Rainey, Sylvia L. Asa, Jérôme Bertherat, Martin Fassnacht, David A.Wheeler, Cancer Genome Atlas Research Network, Gary D. Hammer*, Thomas J. Giordano*, Roel G. W. Verhaak

- Plus many more (TSSs, etc.) from TCGA network
- TCGA program office
- **Kenna Shaw for listening and supporting the project**