Comprehensive Molecular Characterization of Gastric Cancer:

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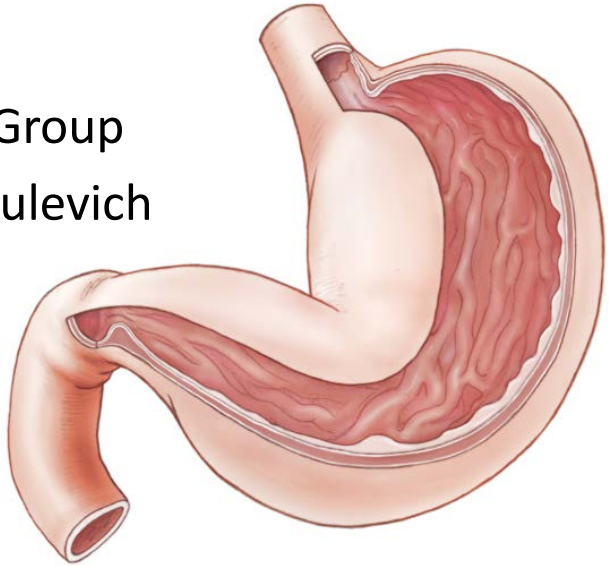
On Behalf of the STAD Working Group
Co-Chairs: Peter Laird & Ilya Shmulevich

TCGA Symposium
May 13, 2014



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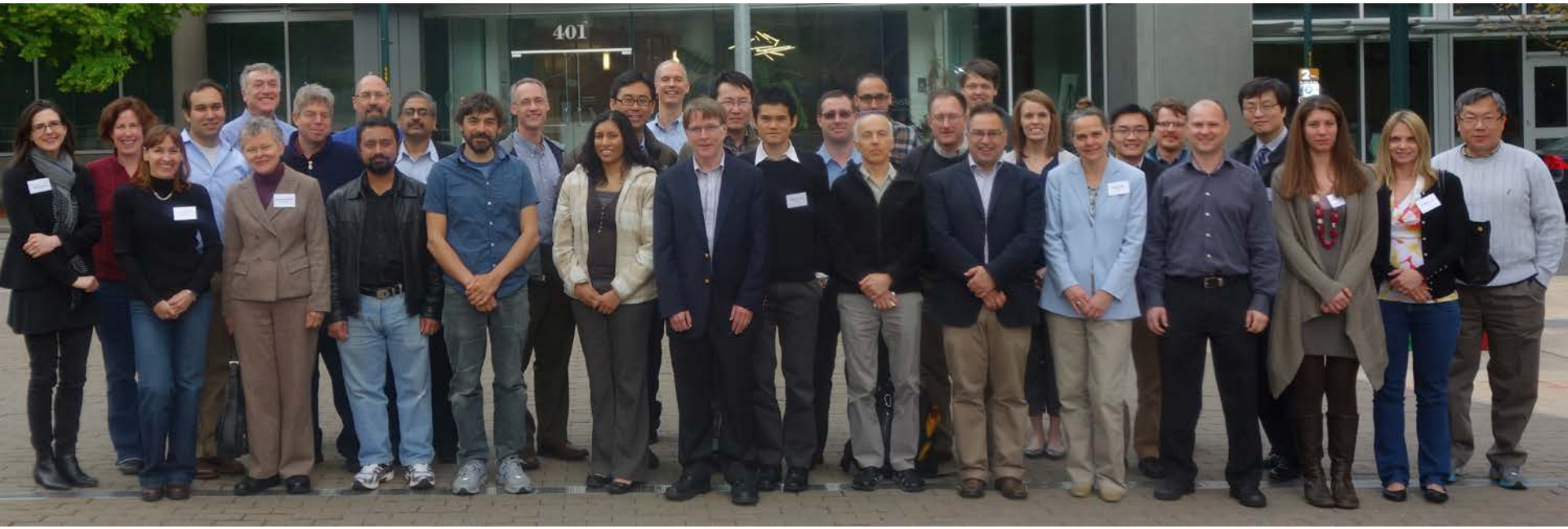
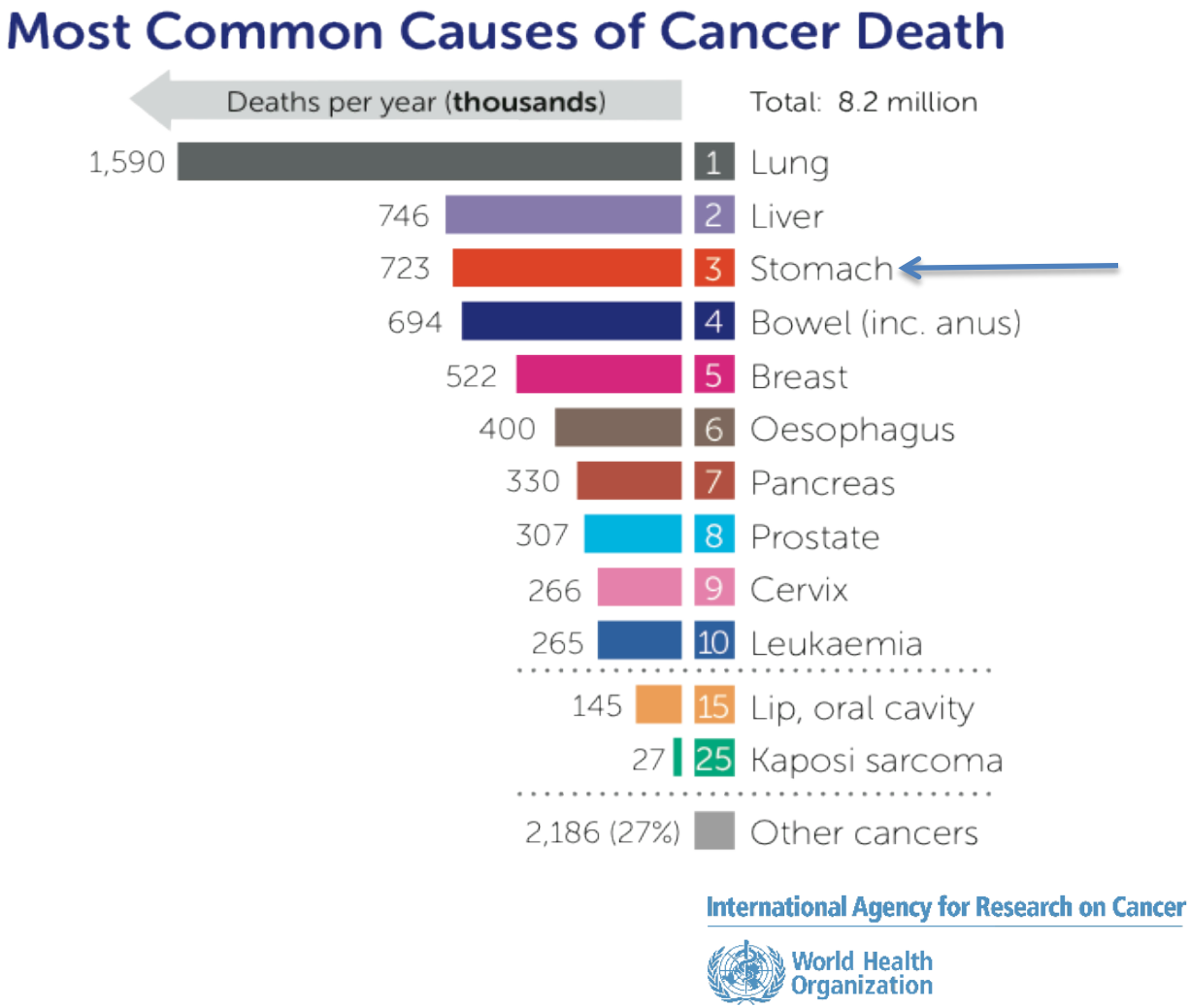
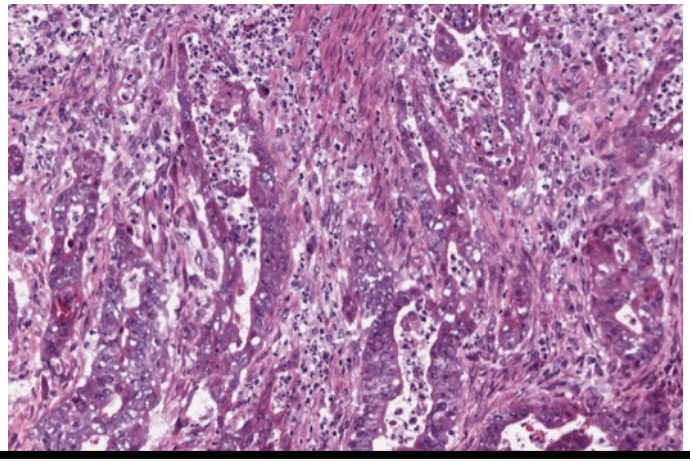
TCGA Stomach-Esophageal Working Group

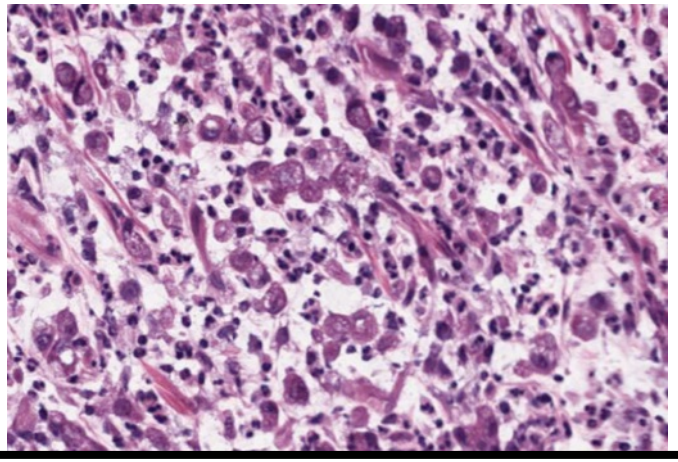


Gastric Cancer: ~723,000 deaths annually



Histopathology: Lauren's classification

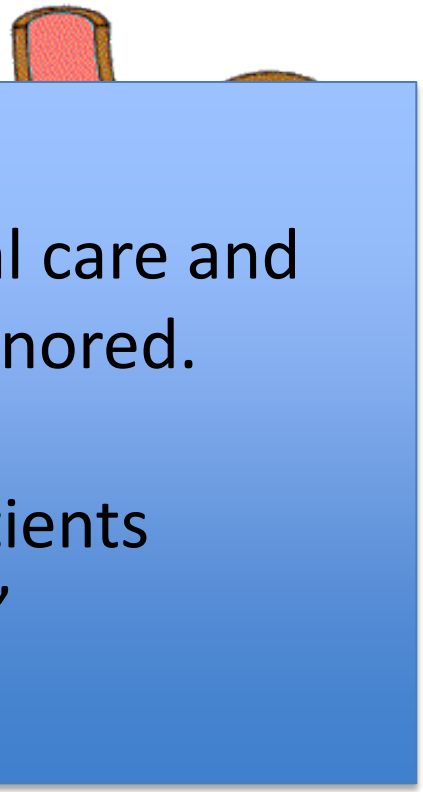




	Intestinal	Diffuse
Morphology	**Glandular** structure	**Poorly cohesive**, or dispersed single cells
Frequent sites of metastasis	Liver	Ovary, Peritoneum
Other remarks	Associated with atrophic gastritis, intestinal metaplasia	Familial variant involving ***CDH1*** germline mutation

Gastric Adenocarcinoma: What Disease are We Trying to Study?

- Histologic
  -
- A
  -
- G
  -
- M
  - MSI vs MSS, ERBB2+…..



But when it comes time to clinical care and clinical trials, all of this gets ignored.

"We did a trial of xxxx in patients with stomach cancer…."

Goals for the Gastric TCGA

- To better classify tumors
  - And to use a schema that can be applied in a more 'real world' setting
- To identify key pathways in distinct tumor types
- To identify targets/biomarkers for distinct tumors, tumor types

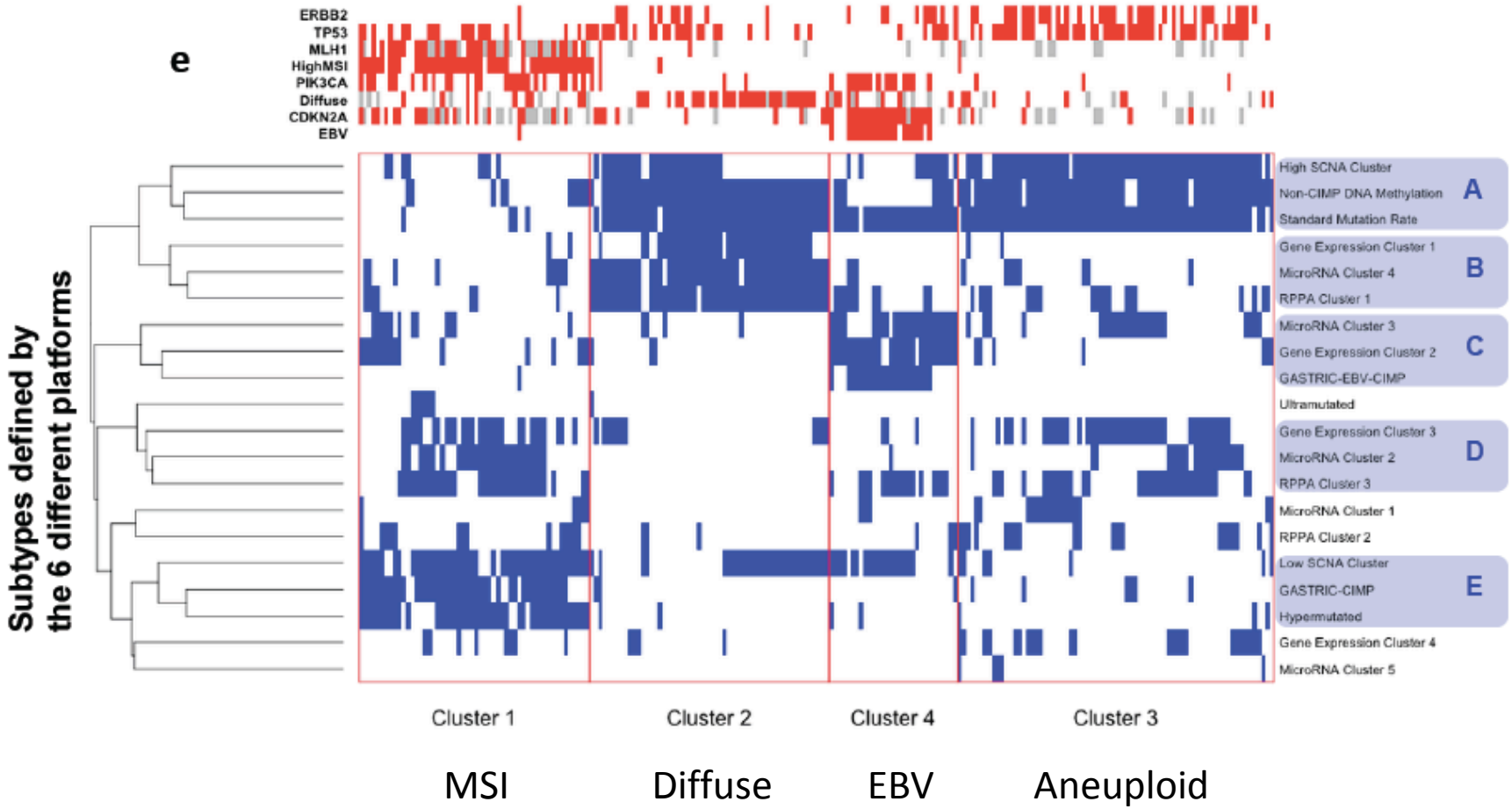
Comprehensive Molecular Characterization of Gastric Cancer – Data Types

Clinical Data
295 Cases
Copy Number Variation 293 Cases
Whole Exome Seq 289 Cases
RNA-seq
265 Cases
DNA Methylation Arrays 295 Cases

Developing Classification

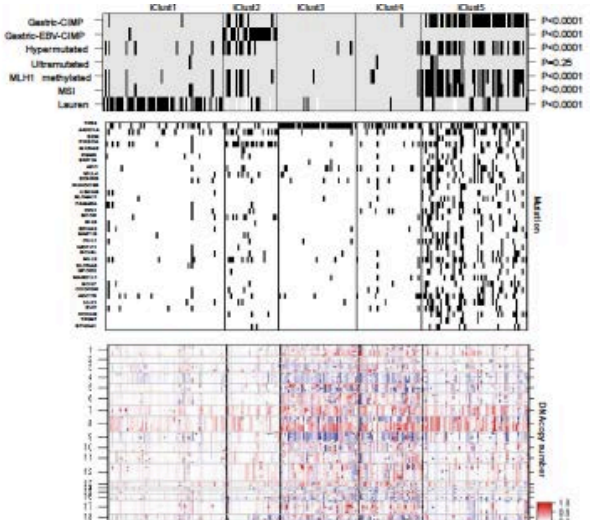
- Use Agnostic Molecular Classification
  - Cluster of Cluster Assignments
  - iCluster
- Identify key identifying features of molecular clusters of tumors
- Use identifying features to categorize tumors using a decision tree
  - Analysis based upon assignments from decision tree rather than based upon initial clustering

Cluster of Cluster Assignments….

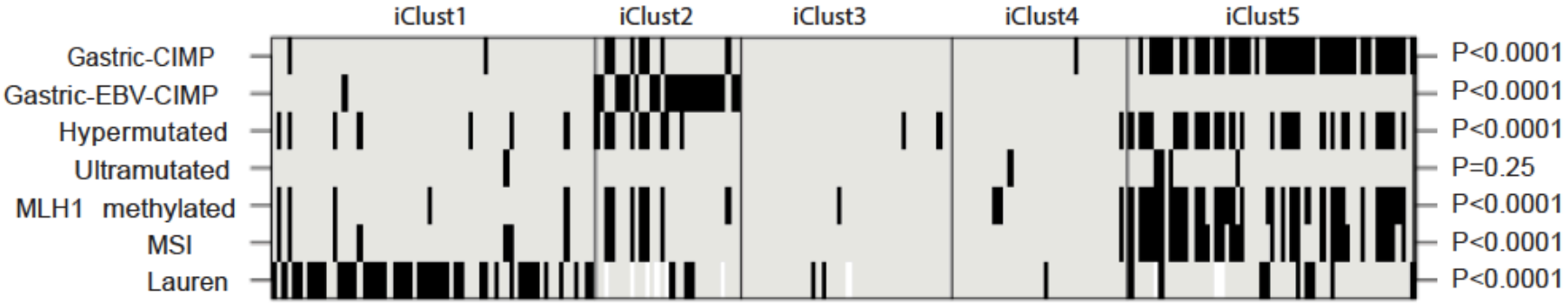


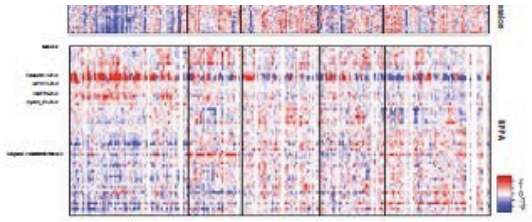
Vesteinn Thorsson

iCluster



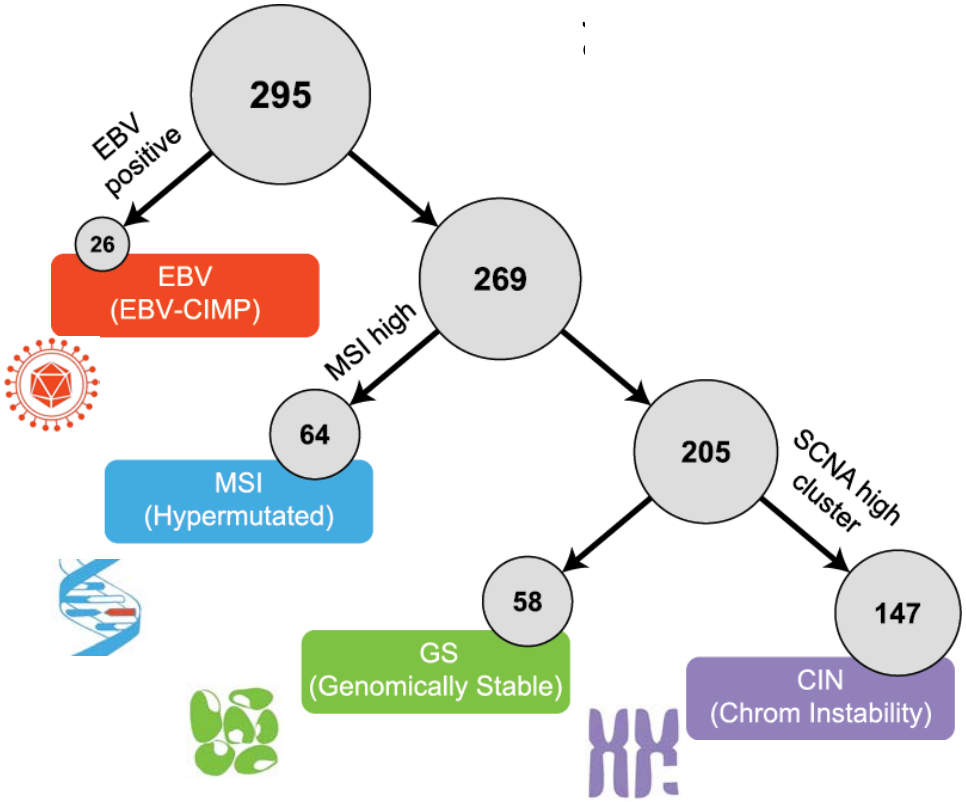
Diffuse EBV Aneuploid MSI





Ronglai Shen

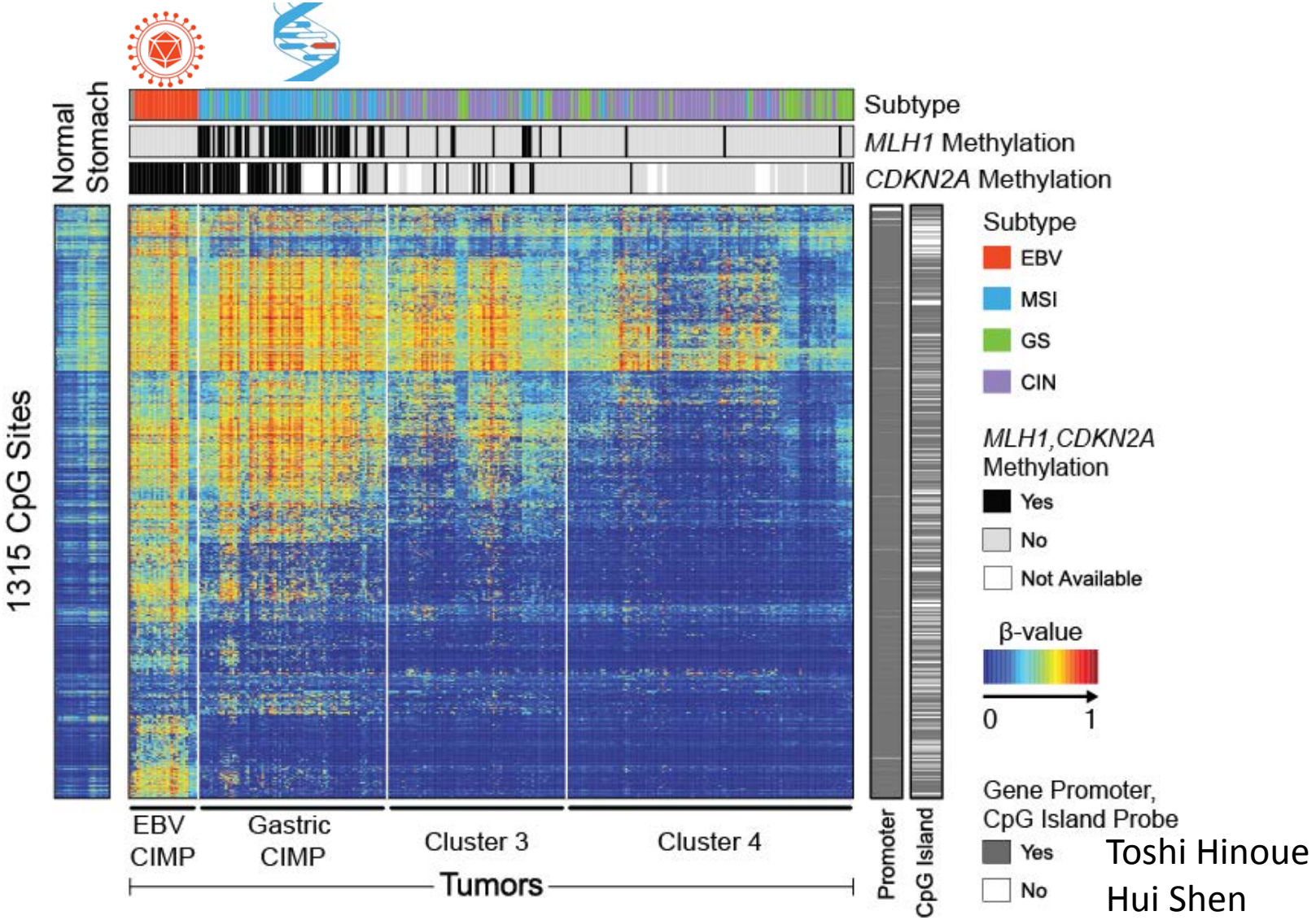
Genome-Guided Classification Correlations



Vesteinn Thorsson, Toshi Hinoue

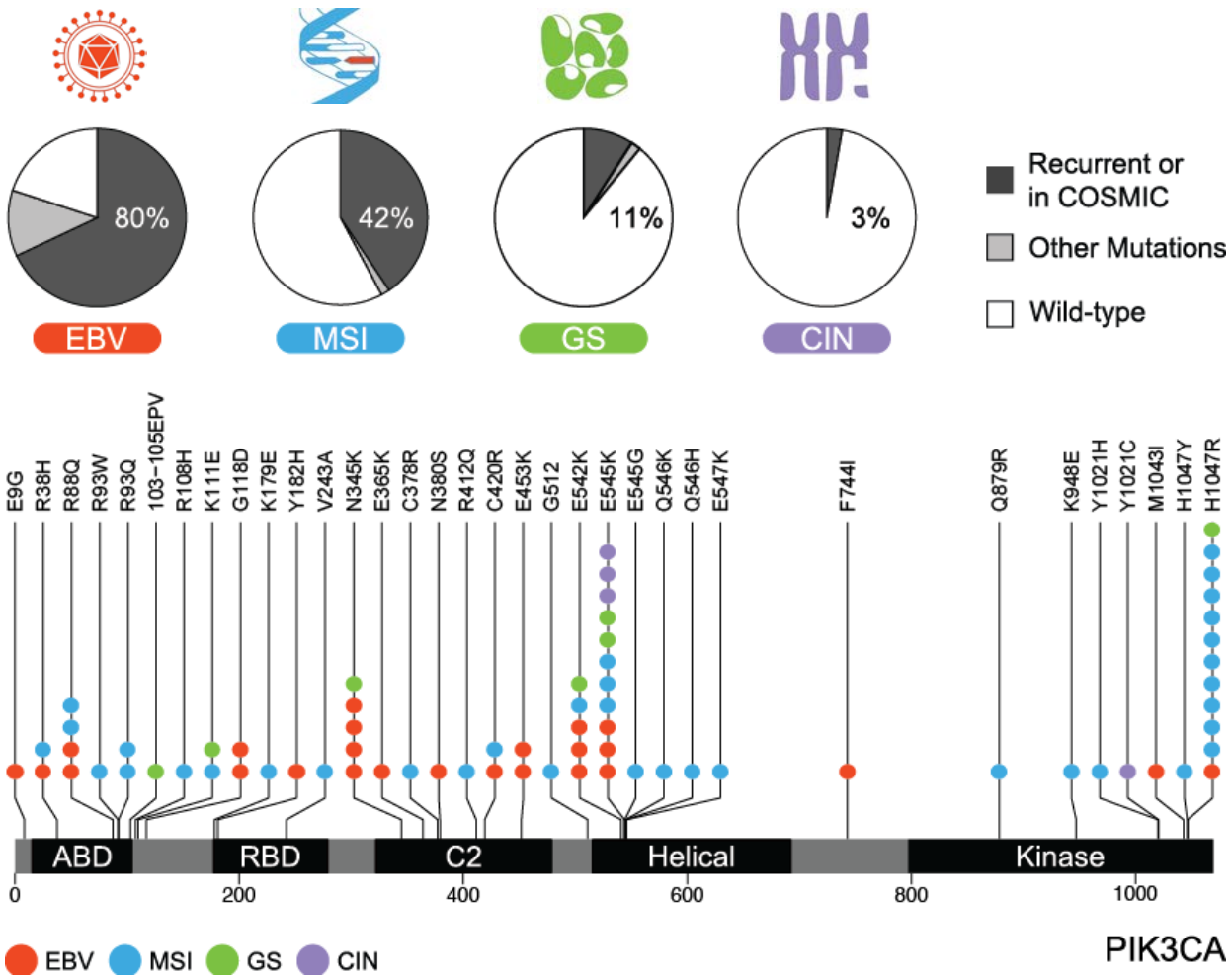
Example of Value of TCGA Integrated Analysis: Features of EBV-Positive GC

Distinct CIMP Profiles Differentiate EBV+ and MSI+ Gastric Cancer



Toshi Hinoue
Hui Shen

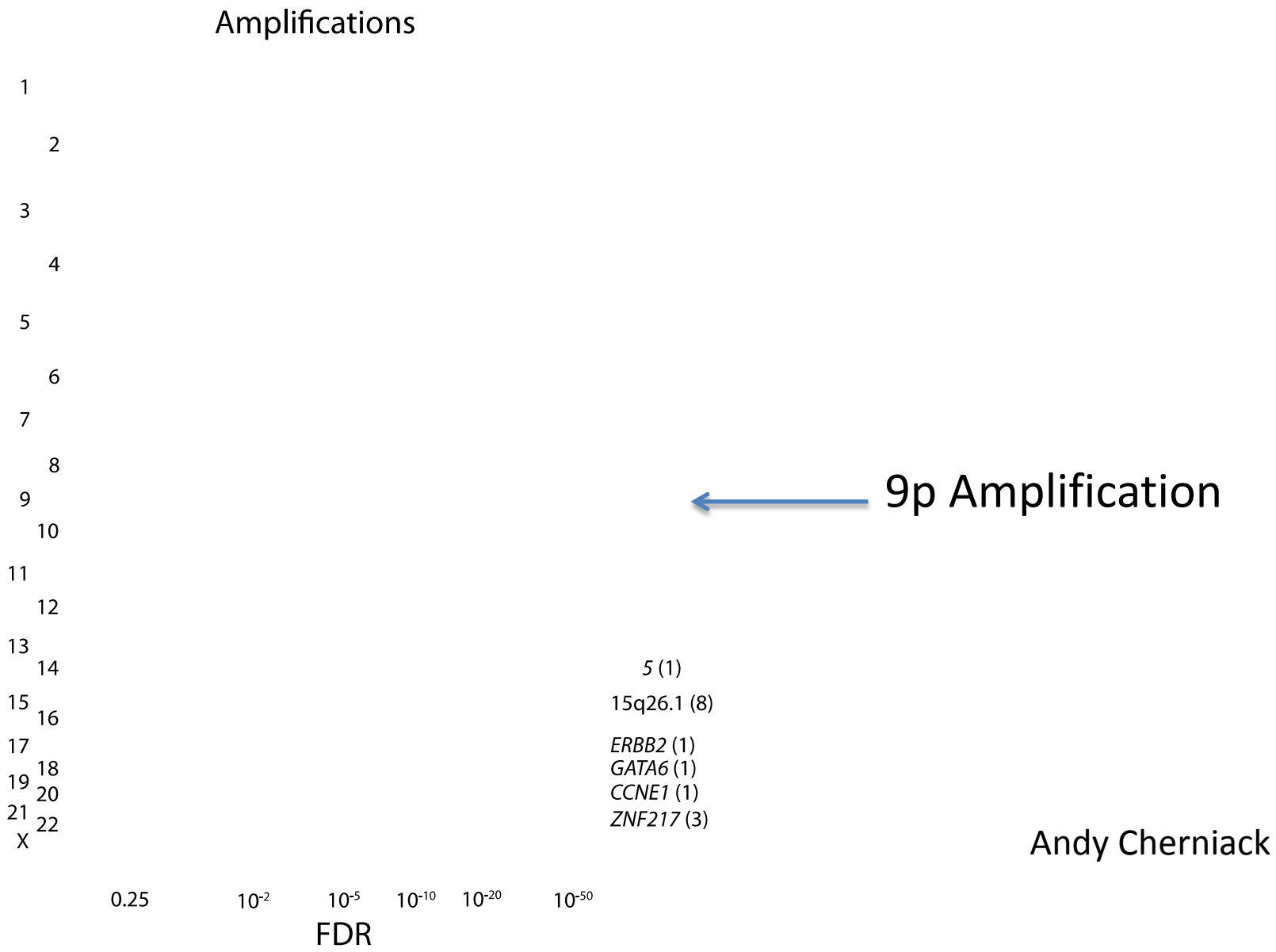
Dramatic Rates of *PIK3CA* Mutation in EBV+ GC



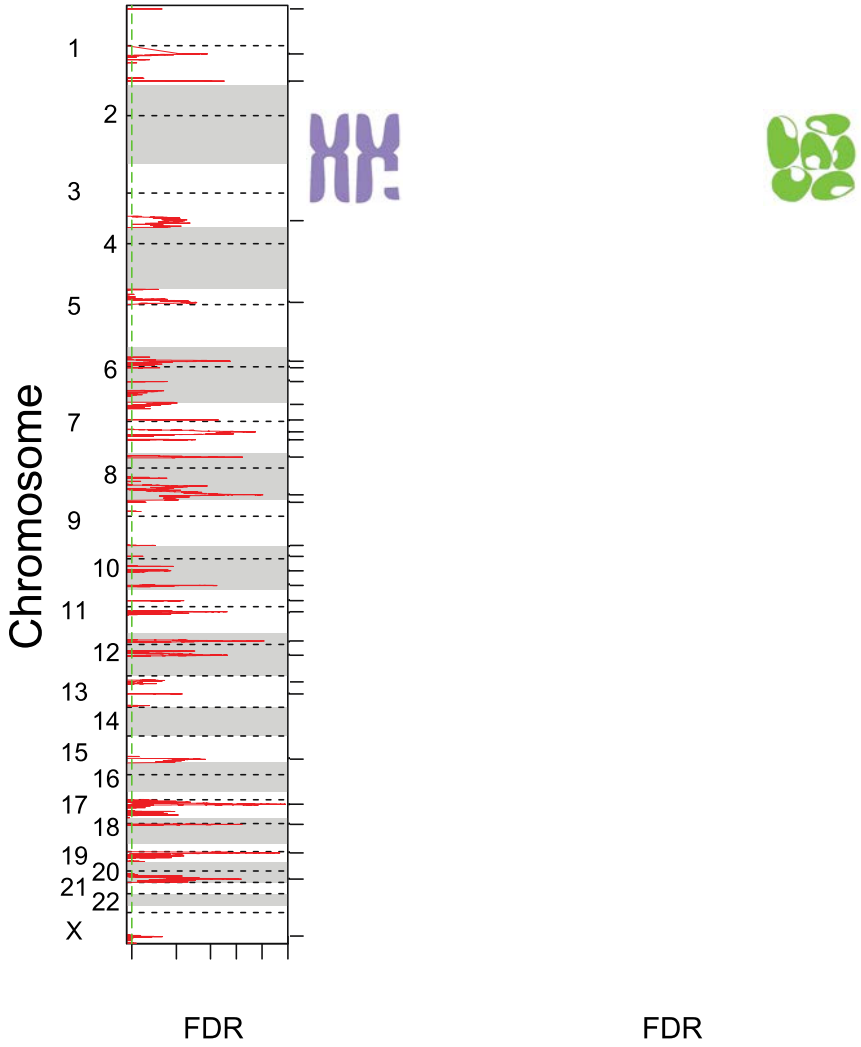
Amaro Taylor-Weiner

EBV and Identification of New Genomic Lesions in GC: Novel Amplifications

Focal Copy-Number Amplification Peaks Across 289 Gastric Cancers

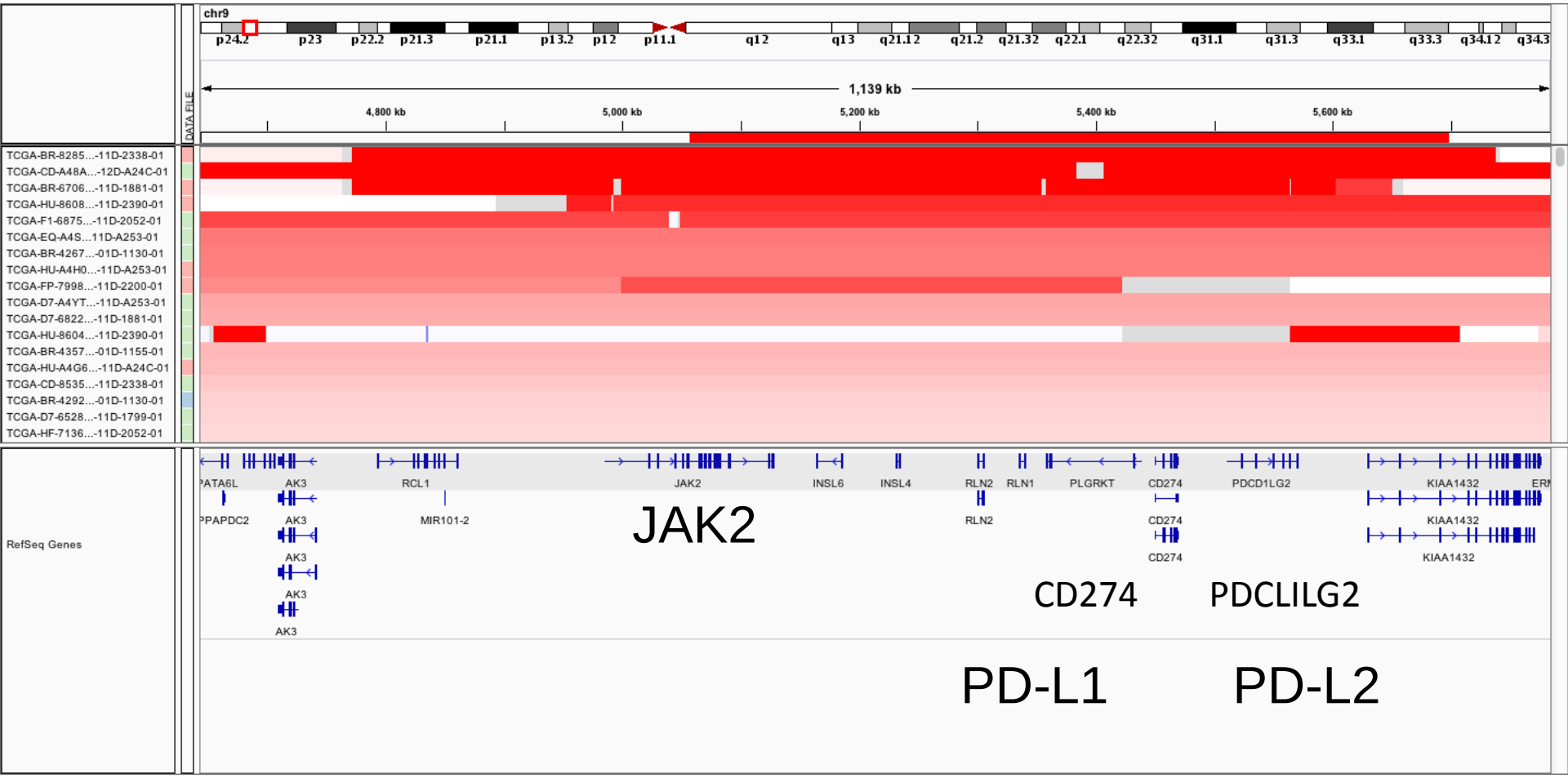


Focal Amplification Peaks Across Molecular Subtypes

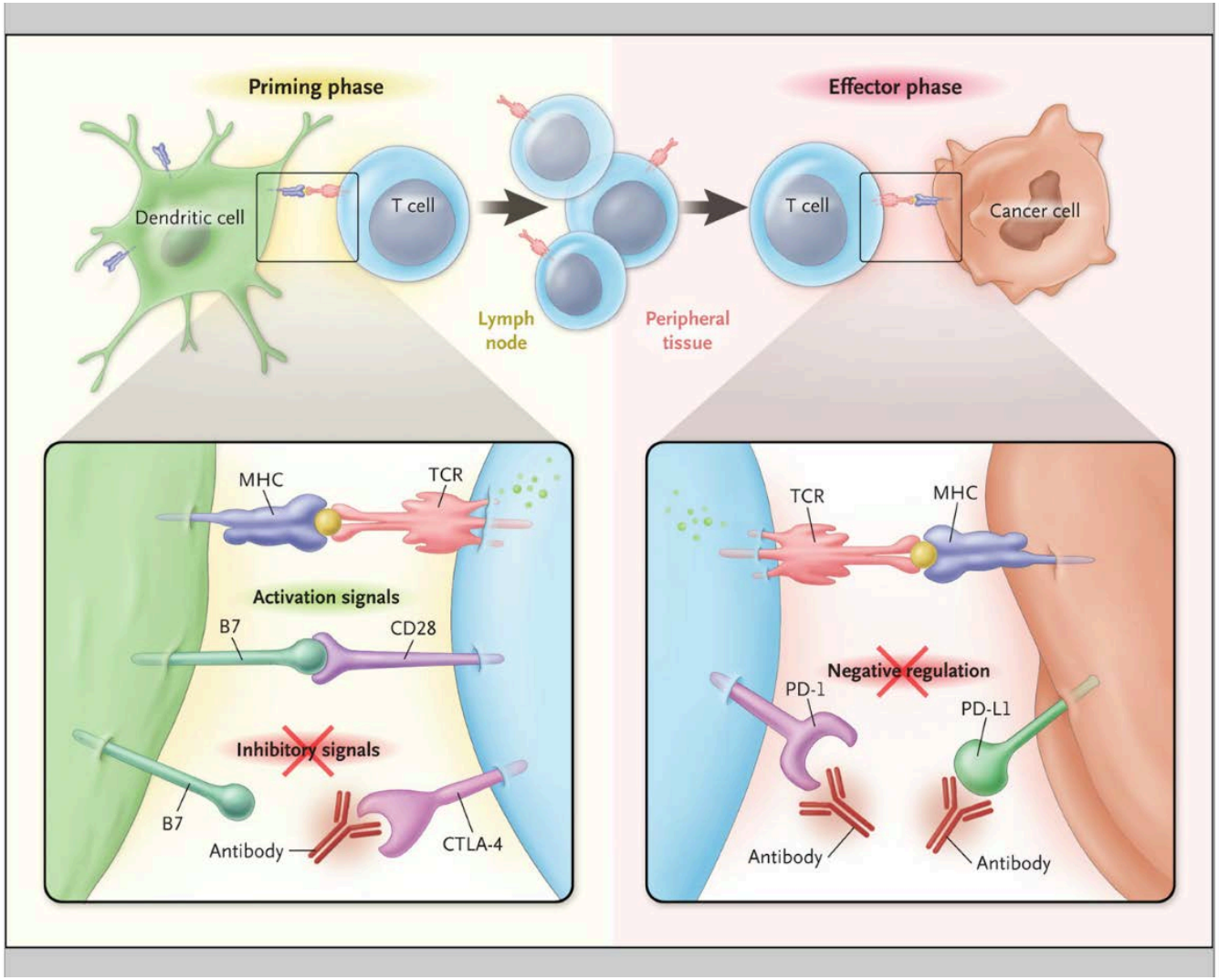


Andy Cherniack

Detailed Look at 9p24.1 Locus of Amplification

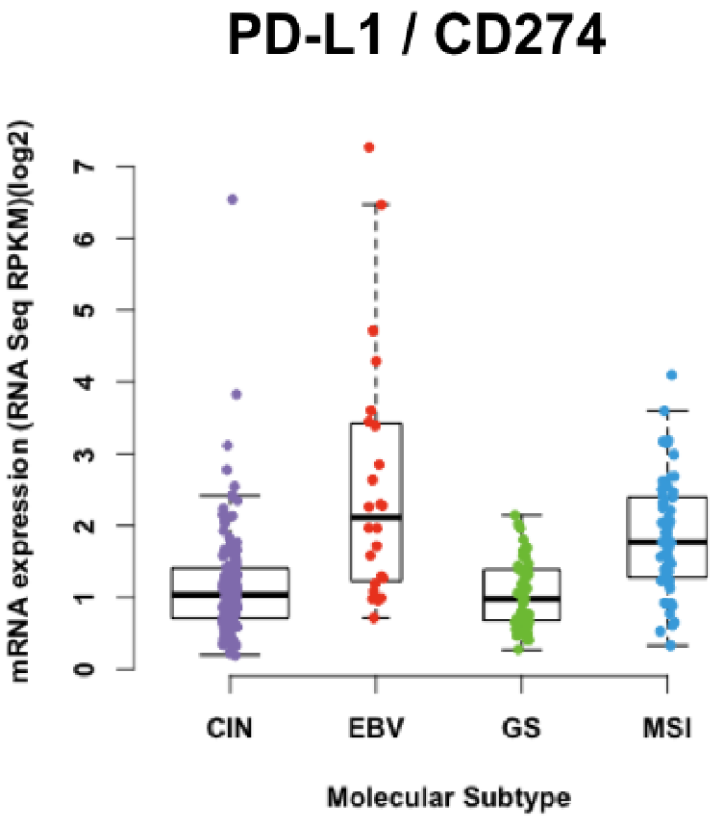


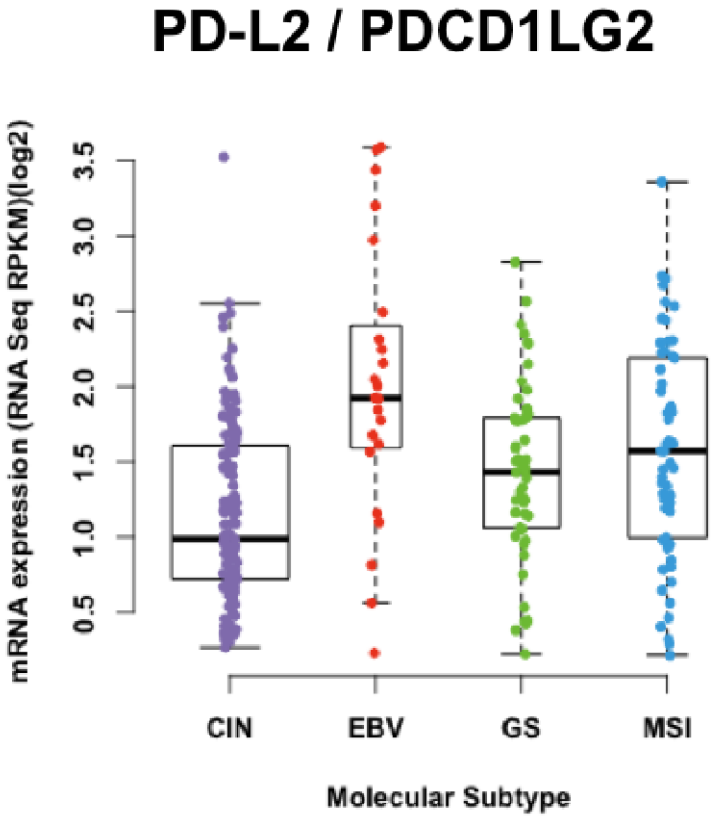
Basics of immune checkpoints



Ribas et al

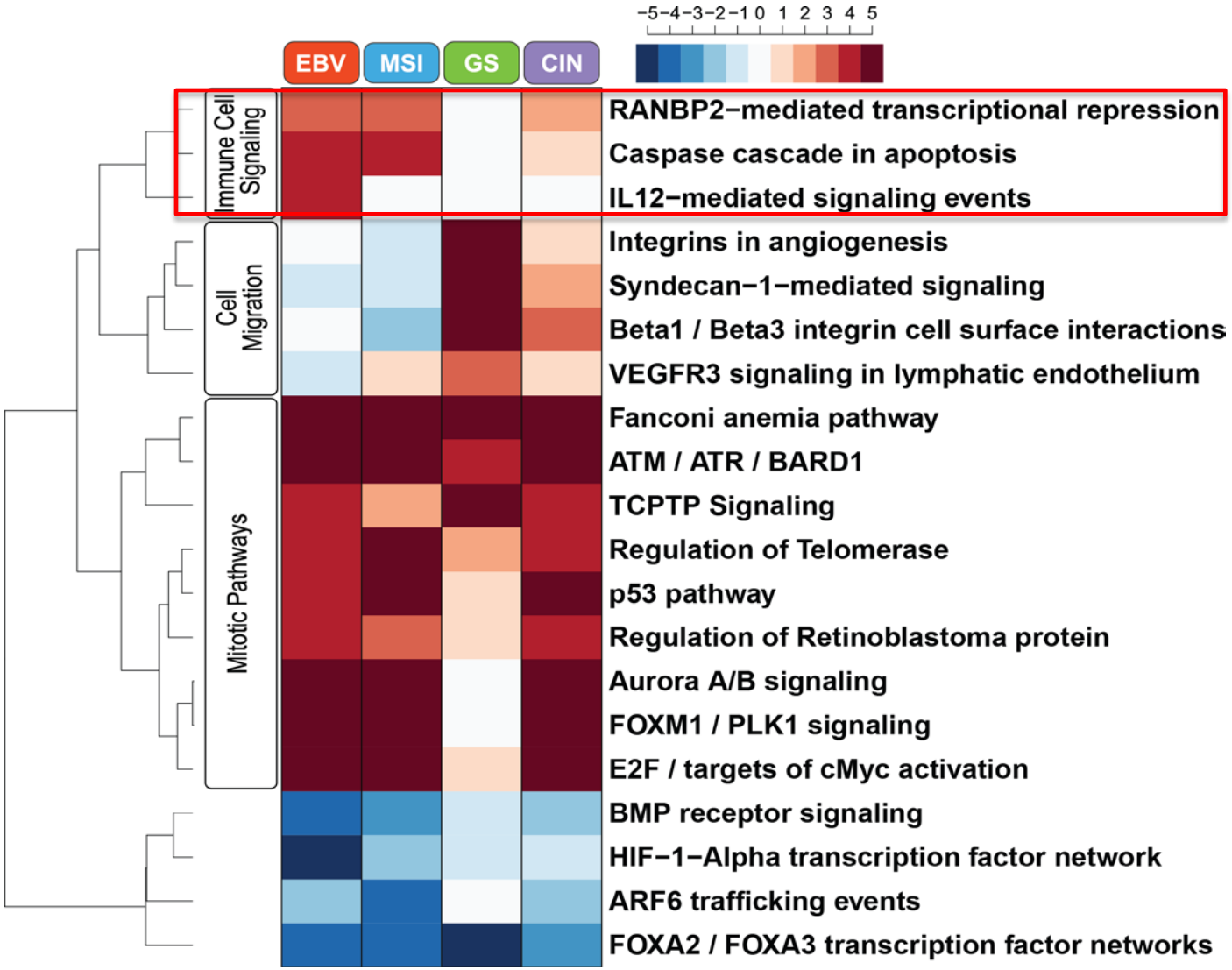
Elevated PD-L1 and PD-L2 Expression in EBV+ Gastric Cancer





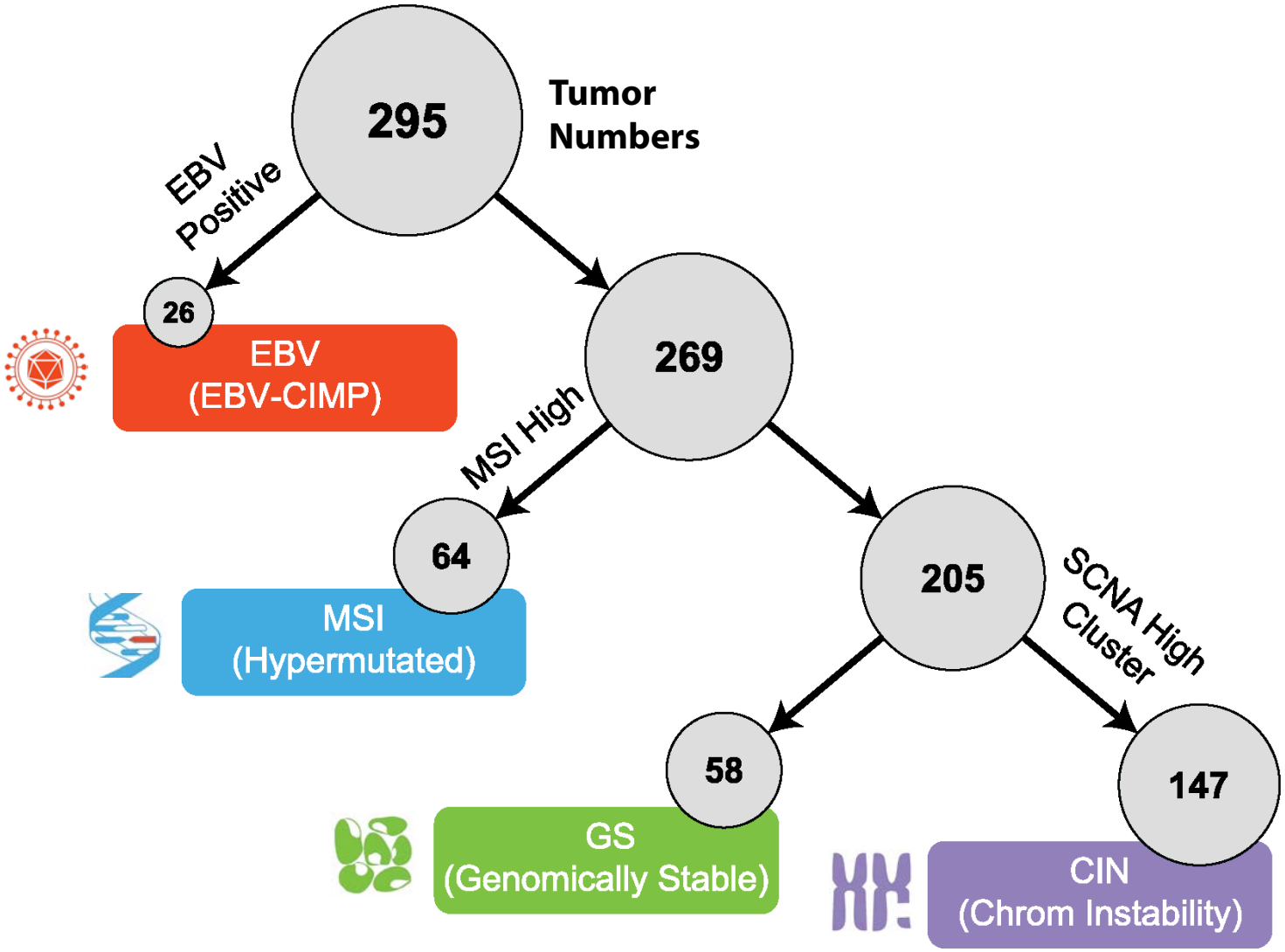
Andy Cherniack
Vesteinn Thorsson

Expression Signatures of Immune Cell Signaling Enriched in EBV+

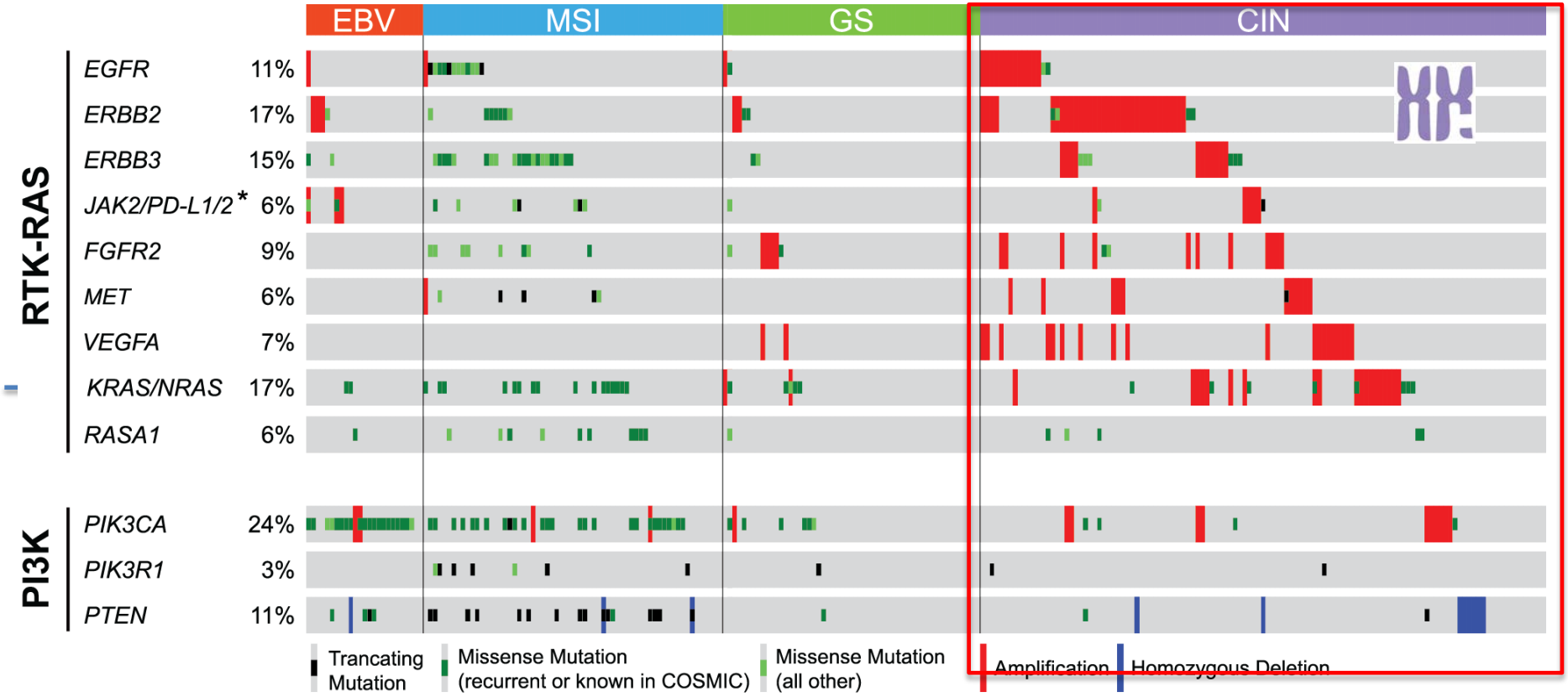


Sheila Reynolds
Christina Curtis

Molecular Classification Scheme for Gastric Cancer

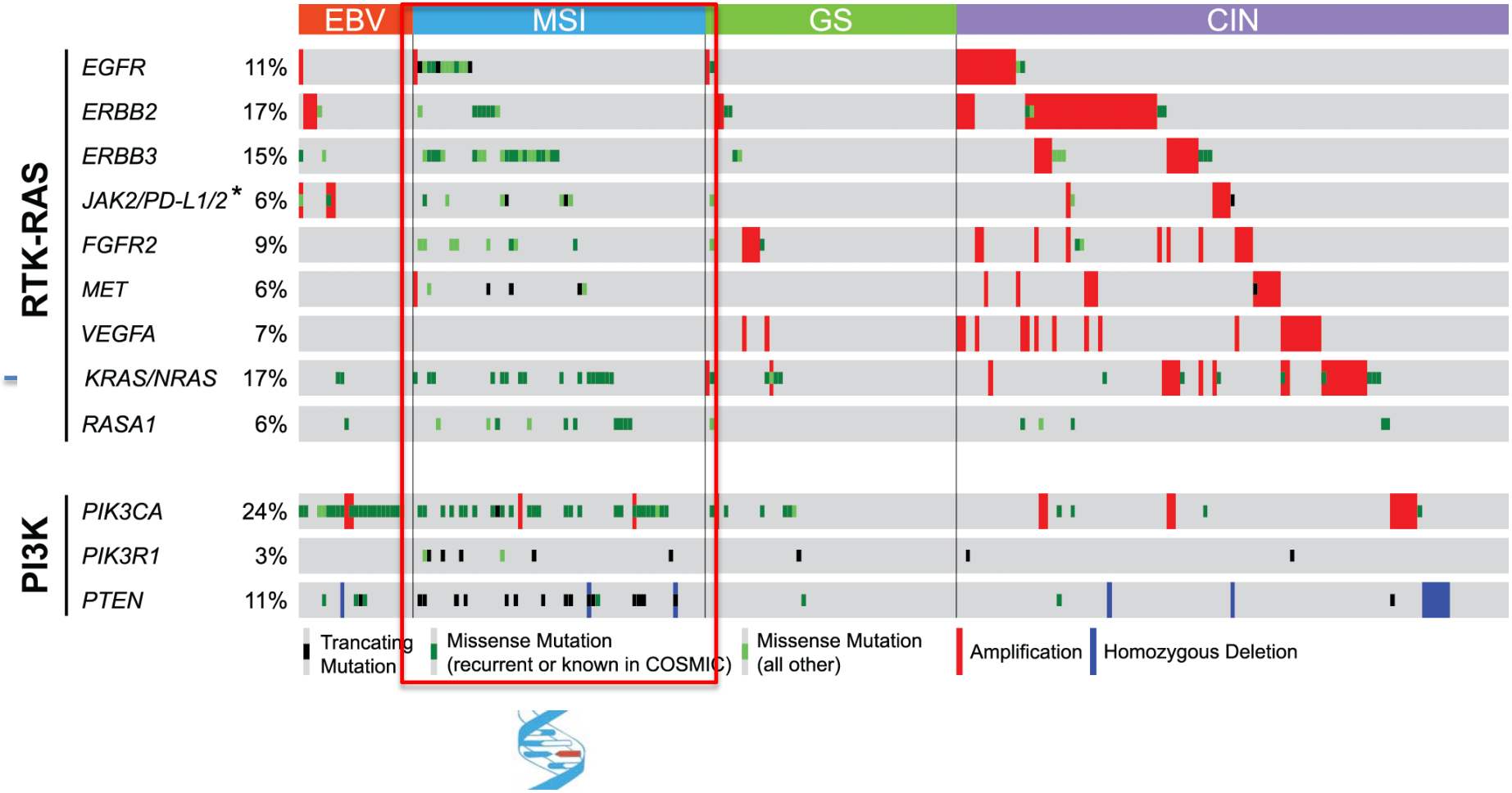


CIN Tumors: Highly Recurrent Amplification of Oncogenes



Nils Wilheim

MSI Tumors: Recurrent Mutations of Oncogenes



Nils Wilheim

Recurrent Oncogenic Mutations in ERBB2/ERBB3

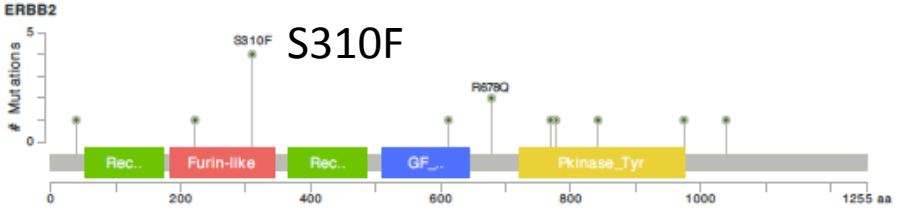
RESEARCH ARTICLE

Activating HER2 Mutations in HER2 Gene Amplification Negative Breast Cancer

Ron Bose[1,2], Shyam M. Kavuri[1], Adam C. Searleman[1], Wei Shen[1], Dong Shen[3], Daniel C. Koboldt[3], John Monsey[1], Nicholas G... Elaine R. Mardis[2,3,4], and M...

Oncogenic *ERBB3* Mutations in Human Cancers

Bijay S. Jaiswal,[1] Noelyn M. Kljavin,[1] Eric W. Stawiski,[1,9] Emily Chan,[2] Chaitali Parikh,[1] Steffen Durinck,[1,9] Subhra Chaudhuri,[1] Kanan Pujara,[1] Joseph Guillory,[1] Kyle A. Edgar,[3] Vasantharajan Janakiraman,[1] Rolf-Peter Scholz,[10] Krista K. Bowman,[4,7] Maria Lorenzo,[8] Hong Li,[8] Jiansheng Wu,[8] Wenlin Yuan,[1] Brock A. Peters,[1] Zhengyan Kan,[1] Jeremy Stinson,[1] Michelle Mak,[1] Zora Modrusan,[1] Charles Eigenbrot,[4] Ron Firestein,[5] Howard M. Stern,[5] Krishnaraj Rajalingam,[10] Gabriele Schaefer,[6] Mark A. Merchant,[2] Mark X. Sliwkowski,[6] Frederic J. de Sauvage,[1] and Somasekar Seshagiri[1,*]



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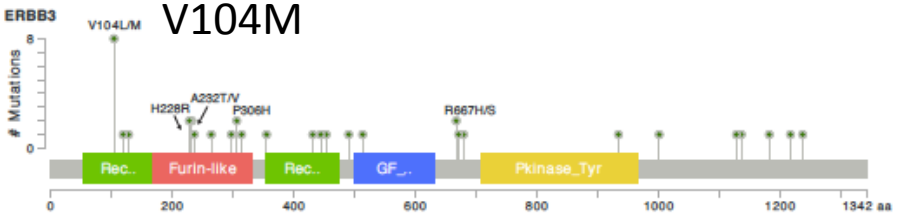
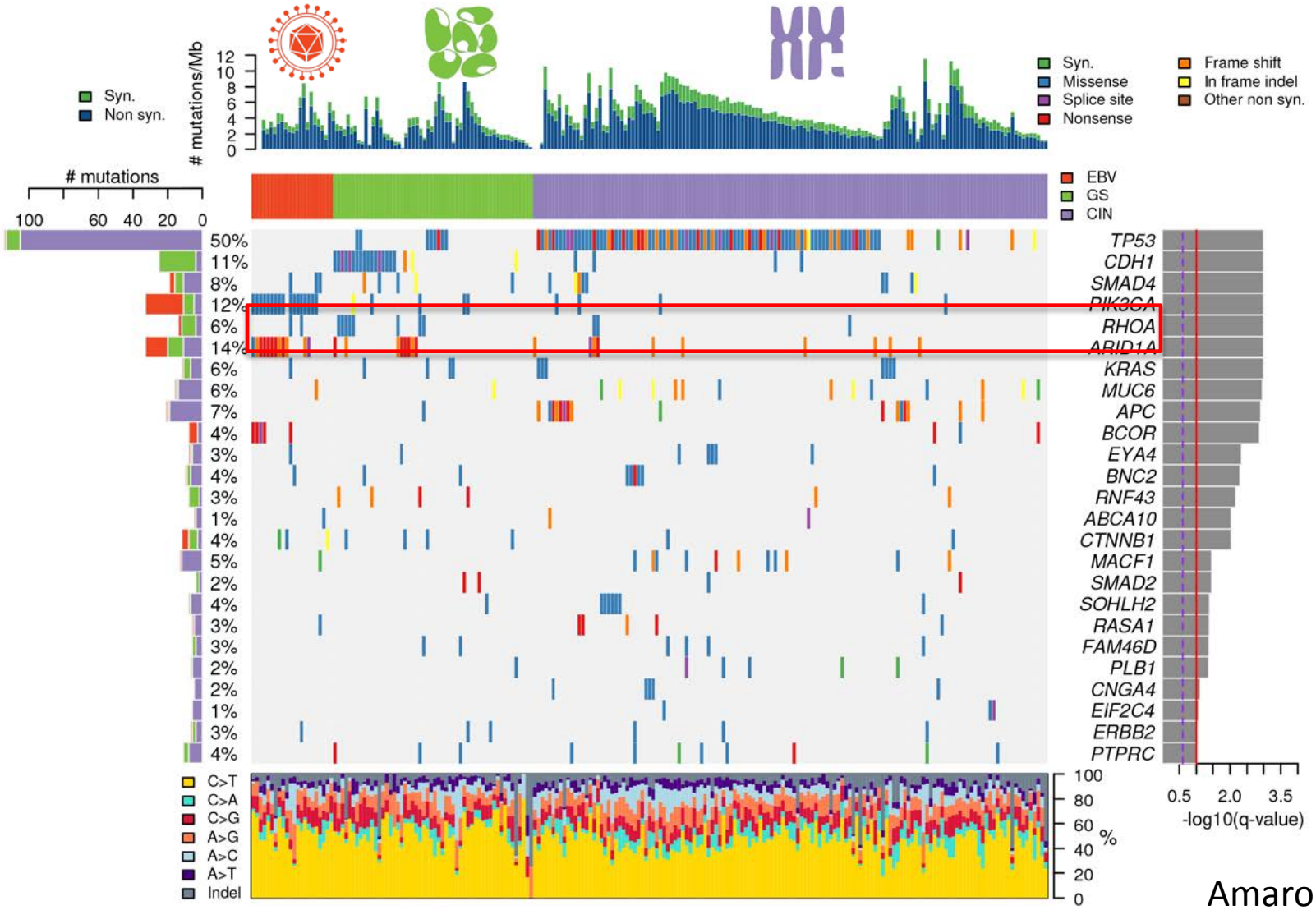


V104M

What About Genomically-Stable (i.e. Diffuse) Gastric Cancer

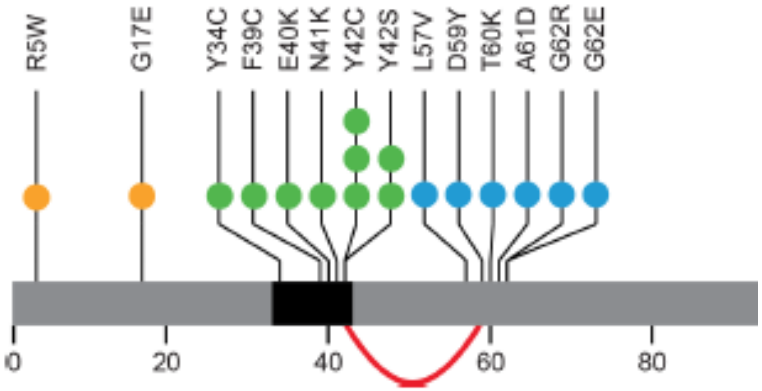
Significantly Mutated Genes in Gastric Cancer (Excluding Hypermutators)

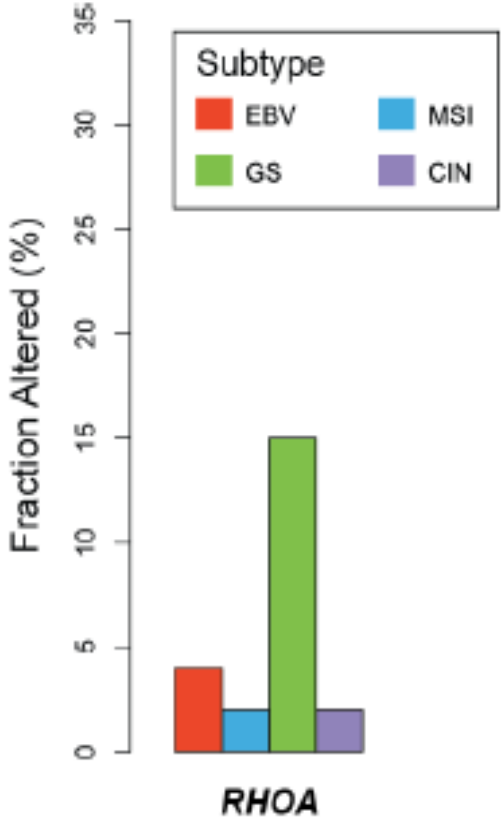


RHOA

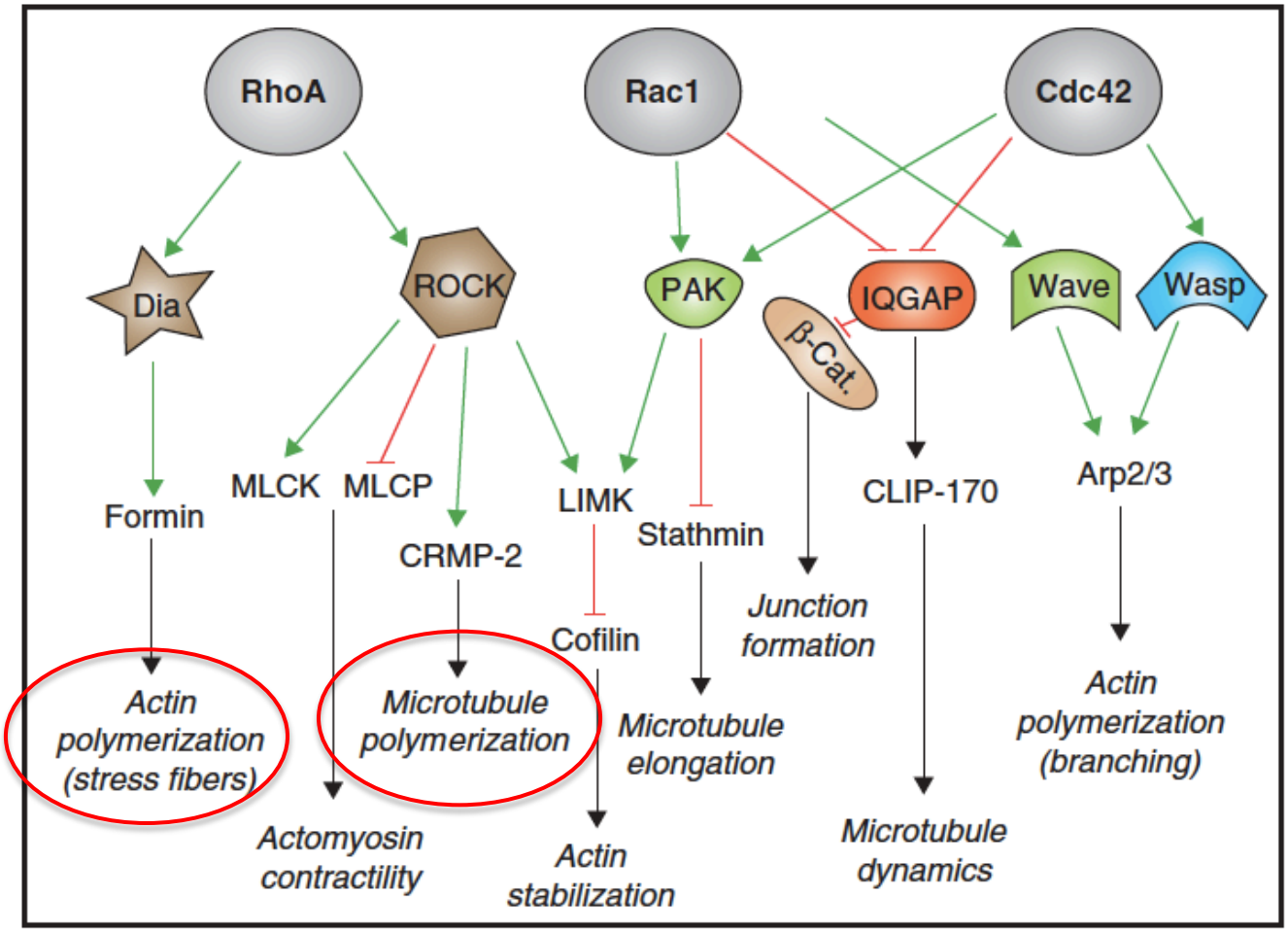
Amaro Taylor-Weiner

Highly Recurrent *RHOA* GTPAse Mutations in Diffuse/Genomically Stable GC



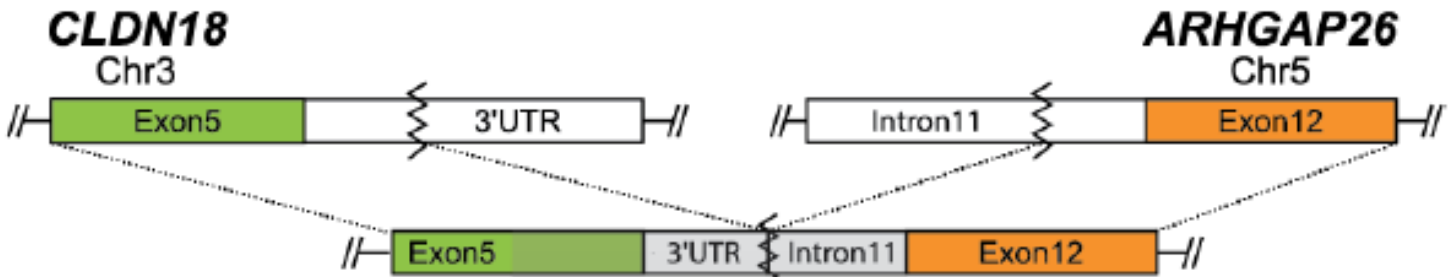


RHOA: Roles in Invasion and Migration Could Contribute to 'Diffuse' Growth Phenotype



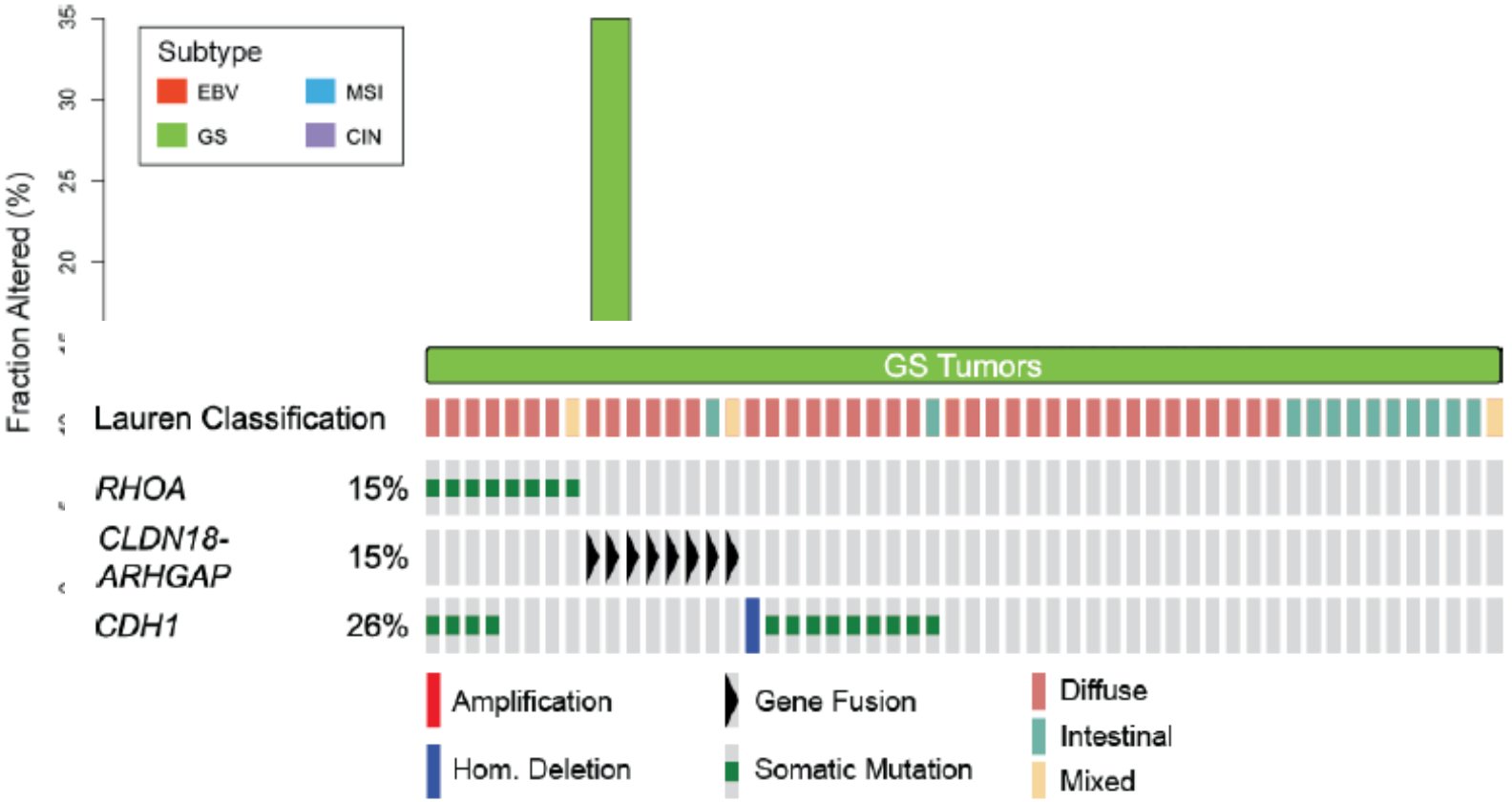
Citi et al *Molecular Membrane Biology* 2011

New Recurrent Fusion Gene Impacts RhoA Pathway and Adhesion



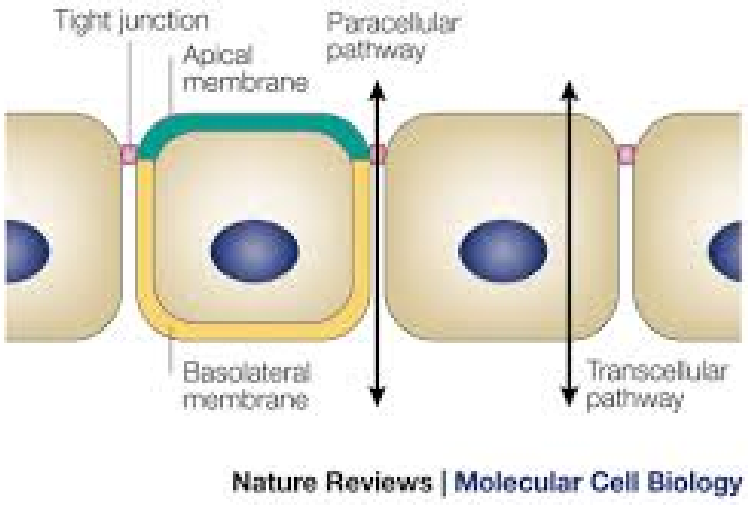
Angeliki Pantazi
Andy Mungall
Reanne Bowlby

Both RhoA and ARHGAP Fusions Enriched in Diffuse/GS Type GC



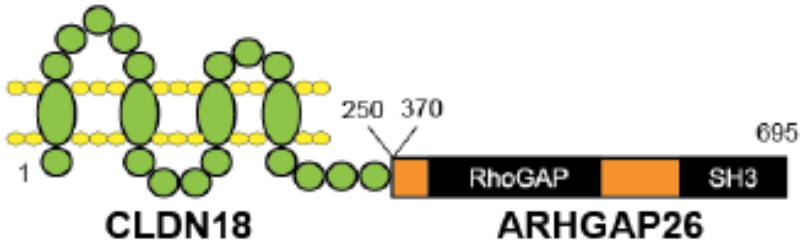
CLDN18-ARHGAP26….What are these genes?

Claudin 18: Component of tight junctions, cellular <u>adhesion</u> complex

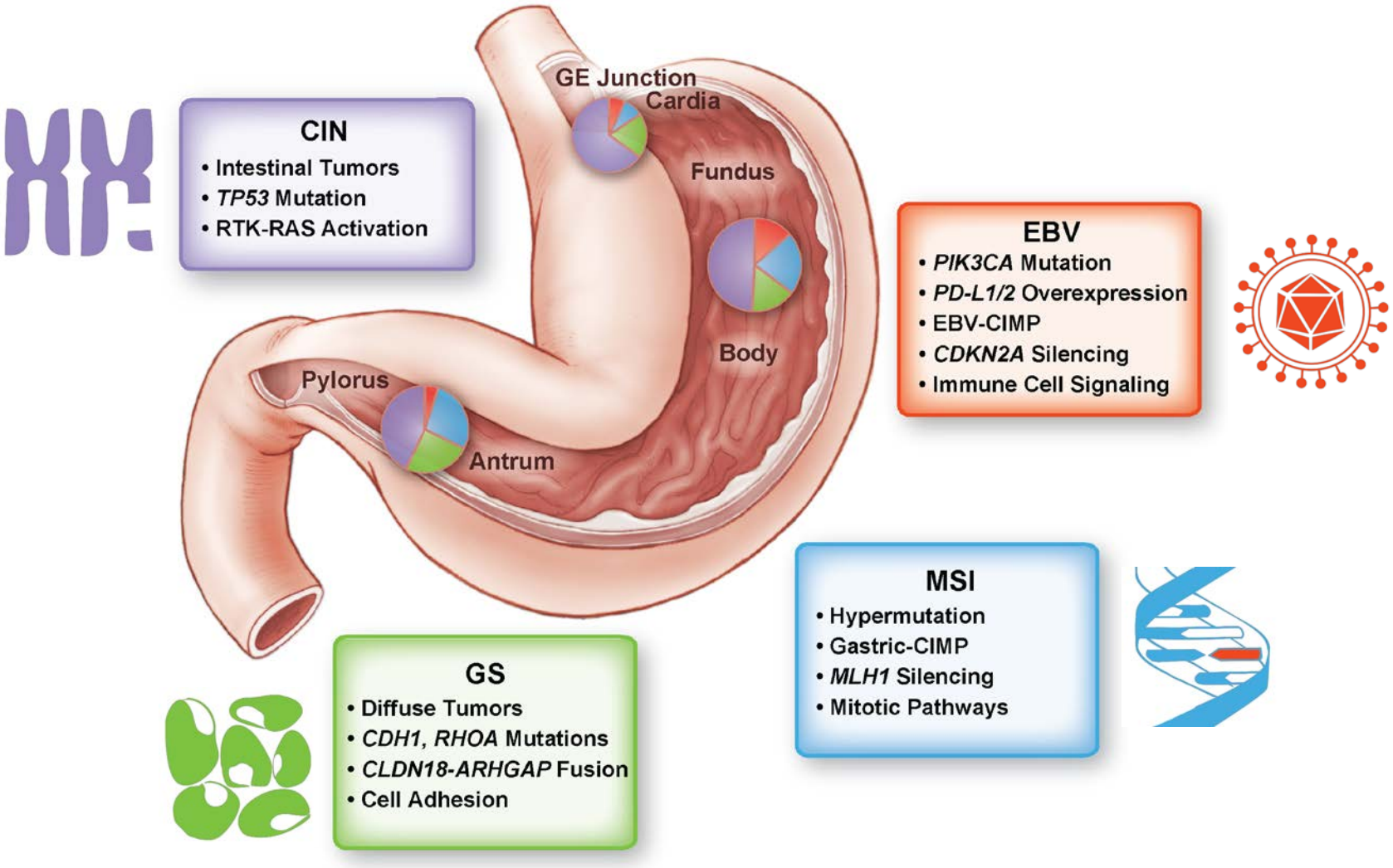


ARHGAP26: a RHO-GAP, GTPase activating protein, something that should act to <u>reduce</u> RHOA activity…

???



Molecular Subtypes of GC and Key Features



Ryo Sakai

TCGA Stomach Analysis Working Group

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Tracy Hall
Troy Shelton
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Wei Xu
Wei Zhang
Wenbin liu
Zhining Wang

Special Thanks: ***Ryo Sakai, Allison Kudla***

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