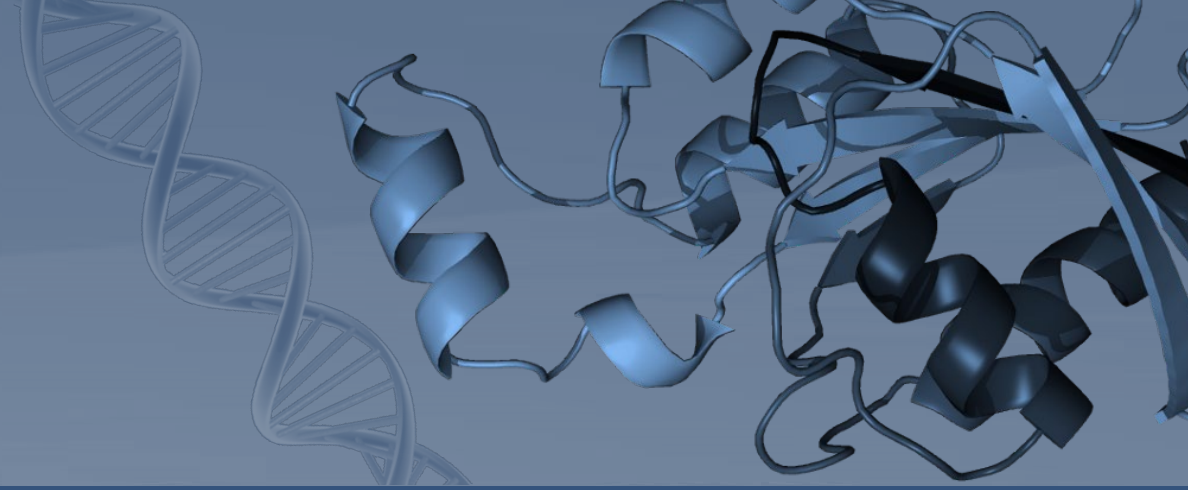




OFFICE OF CANCER CLINICAL  
PROTEOMICS RESEARCH

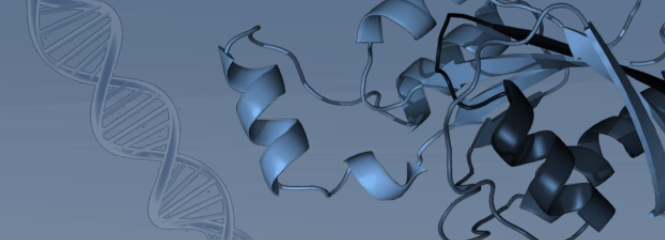


# Proteogenomic Characterization of Endometrial Cancer



Emily Kawaler

CPTAC Endometrial Cancer Working Group  
CPTAC Imaging Special Interest Group Webinar  
January 14, 2020



# Endometrial Cancer

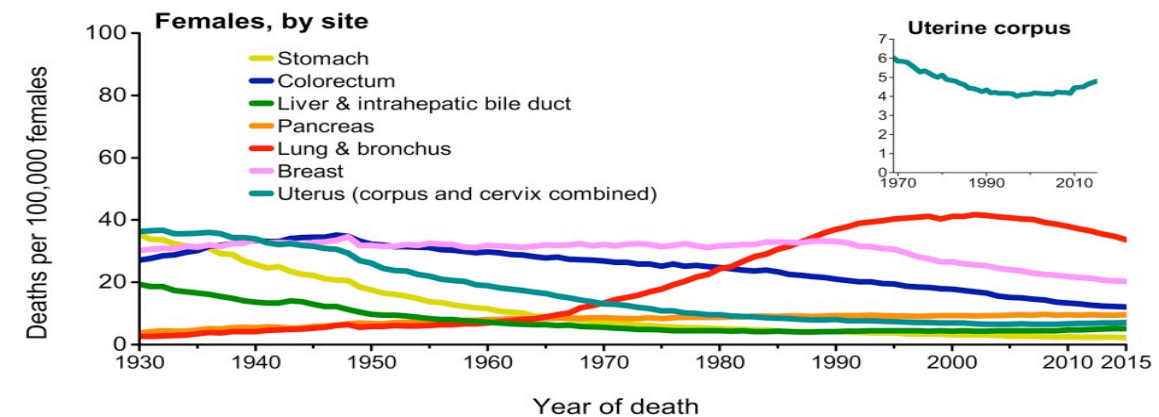
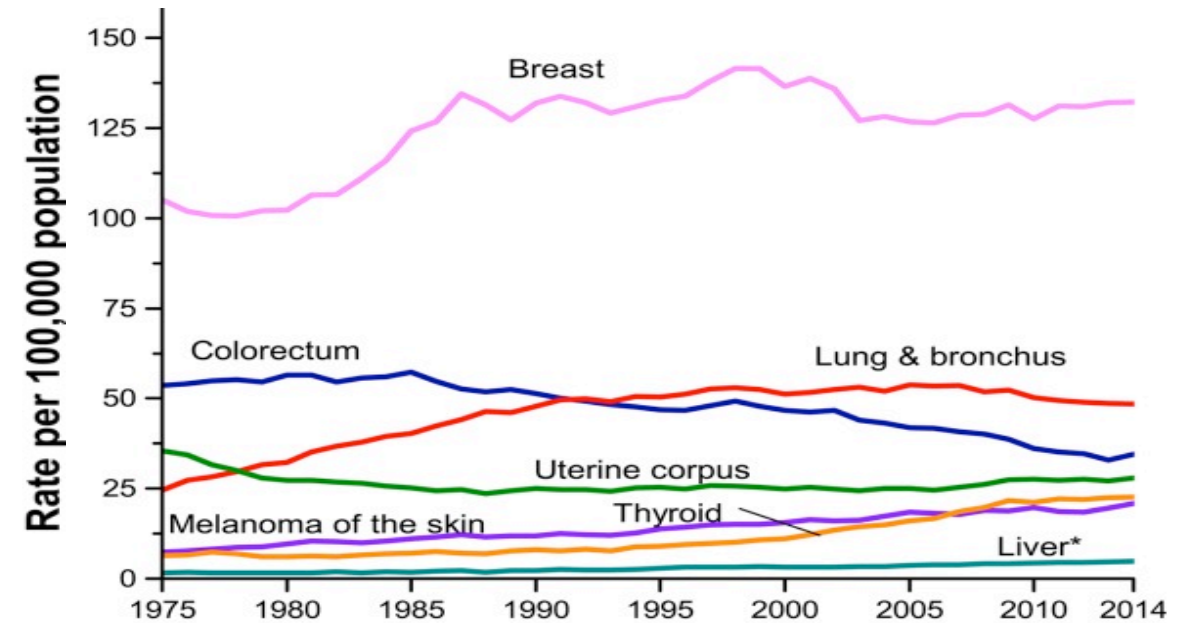


## Estimated New Cases

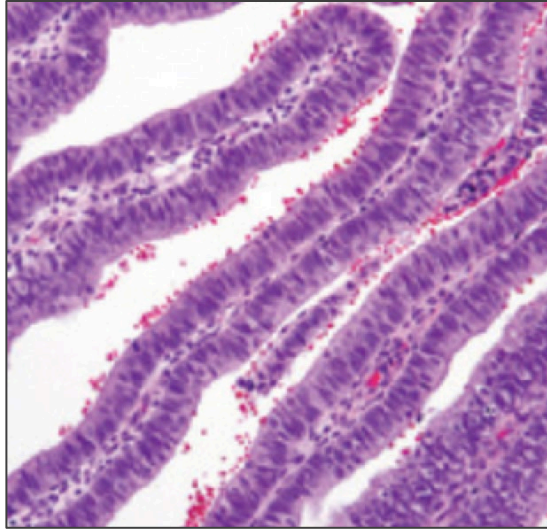
			Males	Females			
Prostate	164,690	19%			Breast	266,120	30%
Lung & bronchus	121,680	14%			Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%			Colon & rectum	64,640	7%
Urinary bladder	62,380	7%			Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%			Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%			Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%			Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%			Pancreas	26,240	3%
Leukemia	35,030	4%			Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%			Kidney & renal pelvis	22,660	3%
<b>All Sites</b>	<b>856,370</b>	<b>100%</b>			<b>All Sites</b>	<b>878,980</b>	<b>100%</b>

## Estimated Deaths

			Males	Females			
Lung & bronchus	83,550	26%			Lung & bronchus	70,500	25%
Prostate	29,430	9%			Breast	40,920	14%
Colon & rectum	27,390	8%			Colon & rectum	23,240	8%
Pancreas	23,020	7%			Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%			Ovary	14,070	5%
Leukemia	14,270	4%			Uterine corpus	11,350	4%
Esophagus	12,850	4%			Leukemia	10,100	4%
Urinary bladder	12,520	4%			Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%			Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%			Brain & other nervous system	7,340	3%
<b>All Sites</b>	<b>323,630</b>	<b>100%</b>			<b>All Sites</b>	<b>286,010</b>	<b>100%</b>

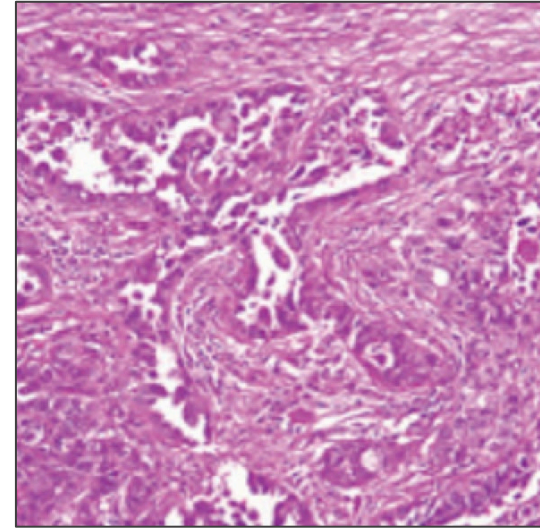


# Histologic Subtypes



## ENDOMETRIOID

- ~85% of cases
- Usually discovered at a lower grade, lower stage
- Best prognosis

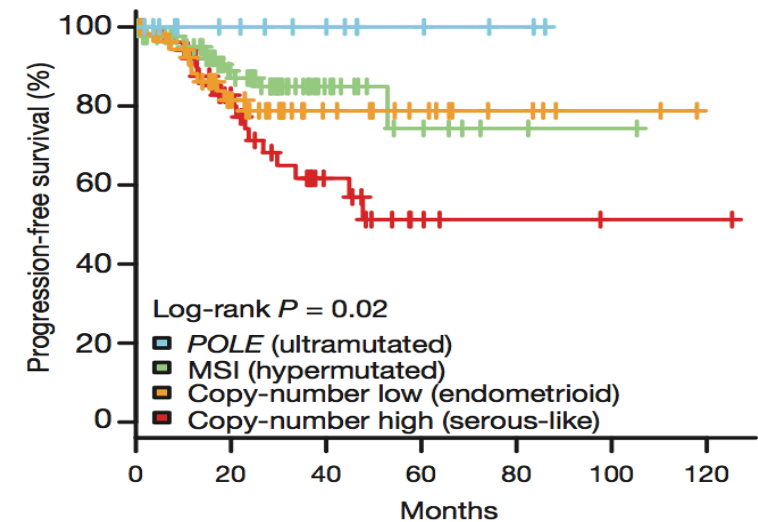
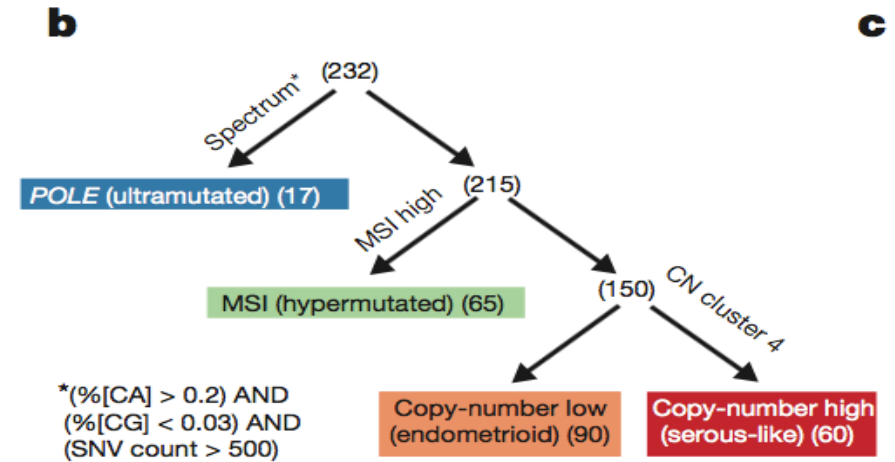


## SEROUS

- ~15% of cases, ~40% of deaths
- Usually discovered at a later stage
- More aggressive, poor survival rate

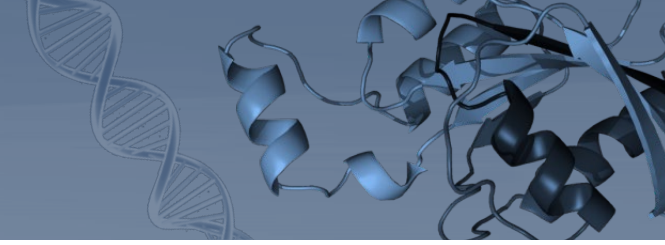
# TCGA Molecular Subtyping

- **POLE**: mutations in exonuclease domain of *POLE*, ultramutated
- **MSI**: hypermutated, most have MLH1 promoter methylation, heavy meth throughout, low SCNA
- **Copy Number Low**: most MSS endometrioid cancers
- **Copy Number High**: Mostly serous, some high-grade endometrioid



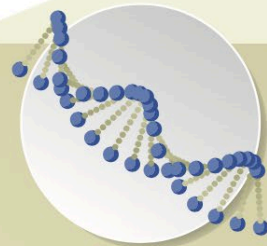


# Data Overview



## CPTAC Endometrial Carcinoma Cohort

- 83 endometrioid tumors
- 12 serous tumors
- 49 normal uterine samples
  - 18 normal endometrium
  - 25 mixed endometrium-myometrium
  - 6 myometrium



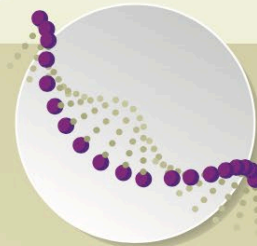
### Whole genome and exome sequencing

Somatic mutation

Copy number variation

POLE status

MSI status



### RNA sequencing

Gene expression

circRNA expression

Splice variant

miRNA expression



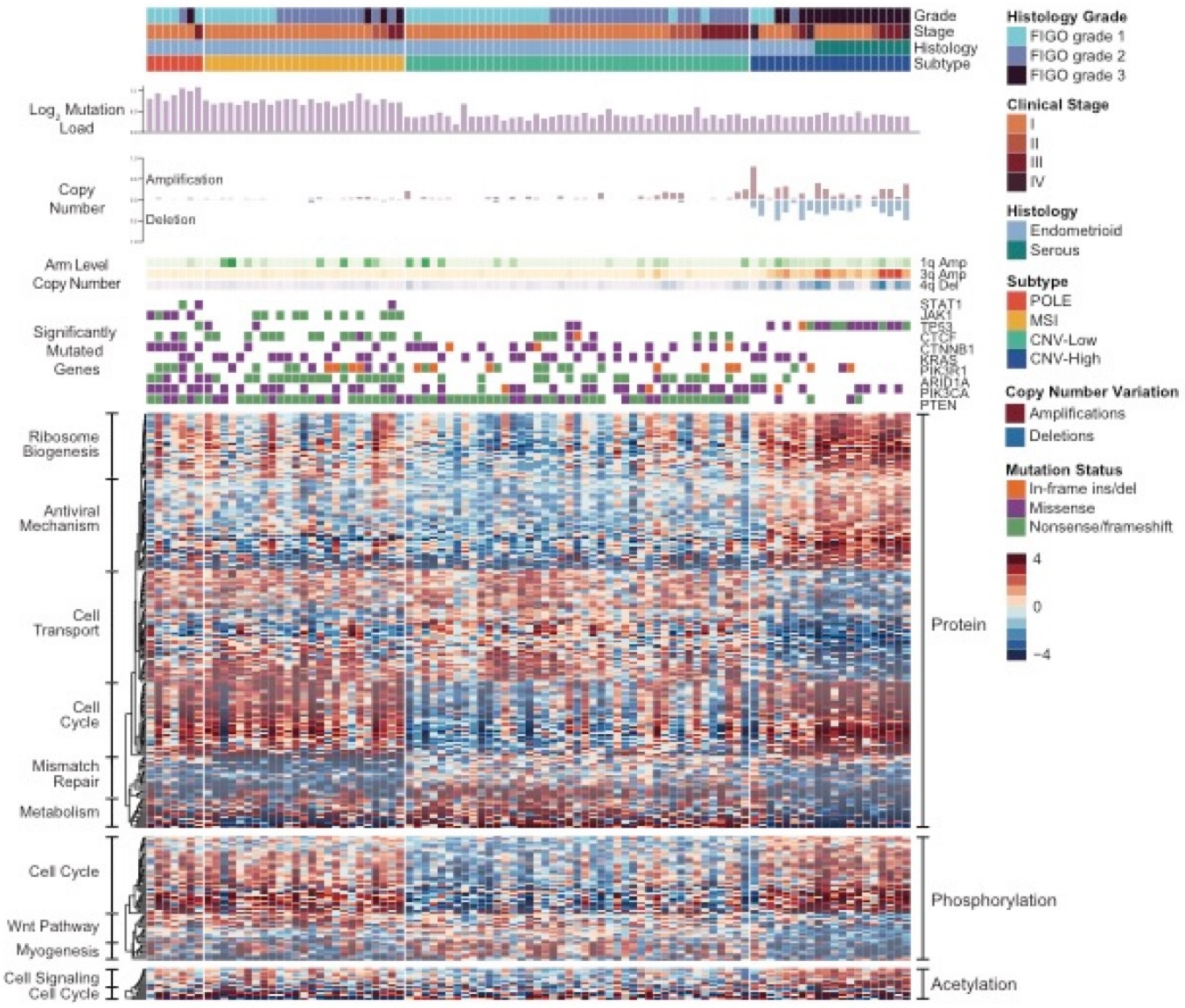
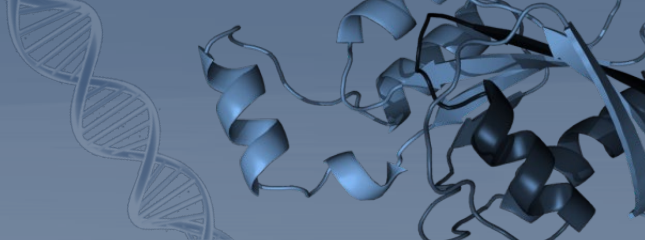
### MS protein analysis

Protein

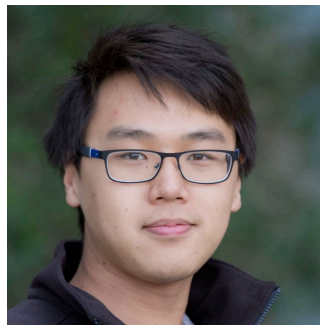
Protein phosphorylation

Protein acetylation

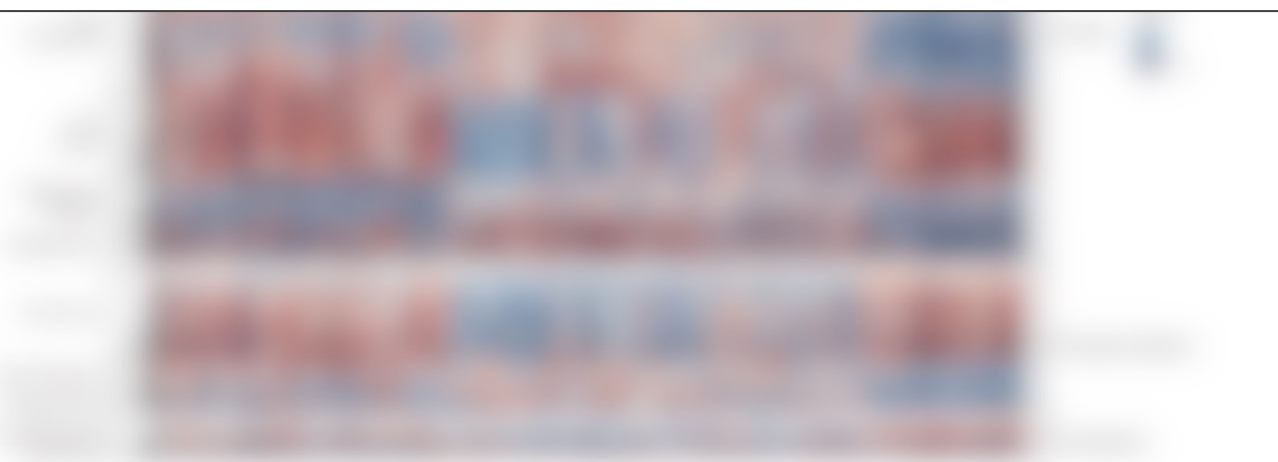
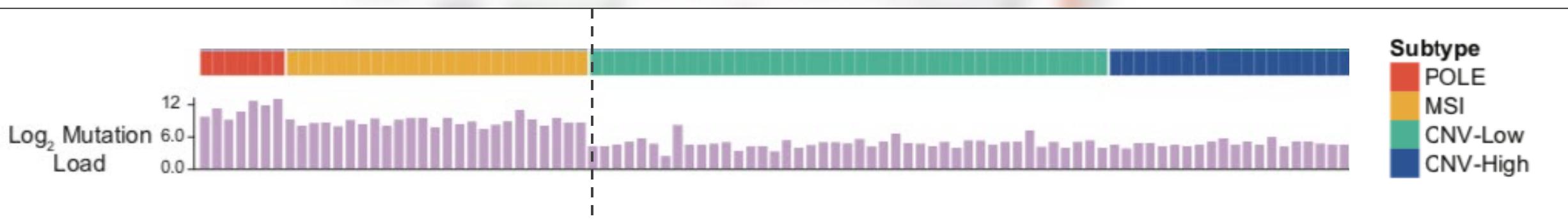
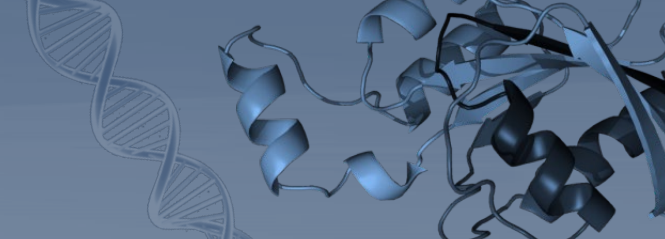
# Data At A Glance



Daniel Cui Zhou

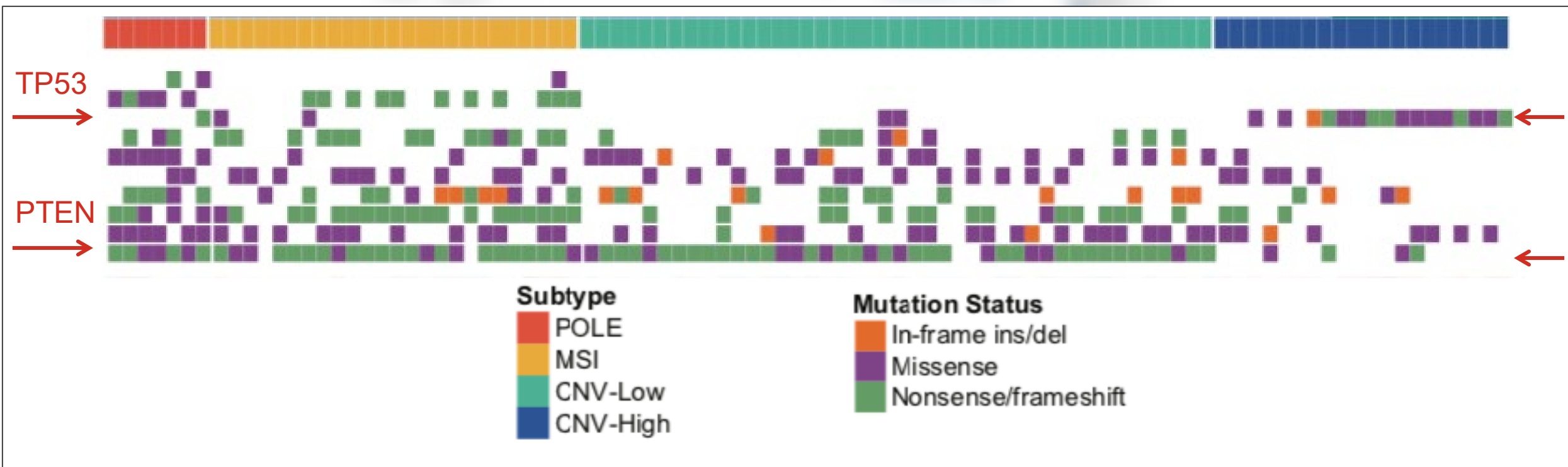
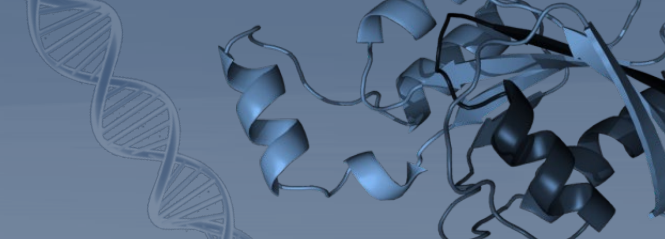


# Data At A Glance



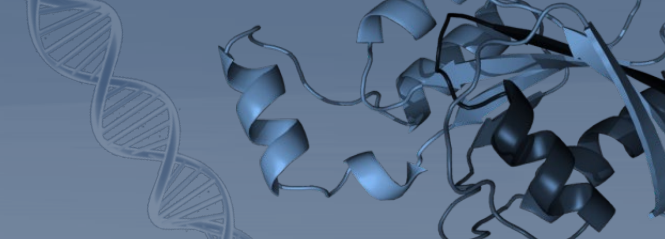


# Data At A Glance

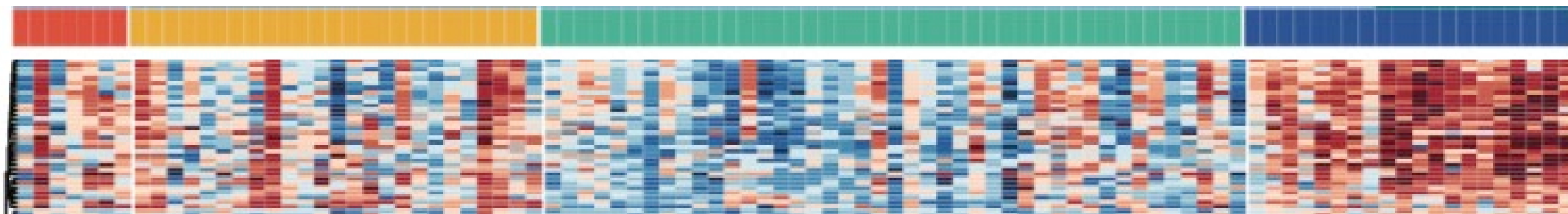




# Data At A Glance



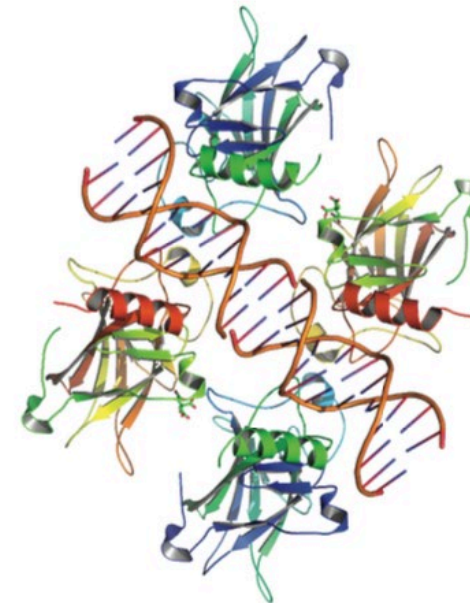
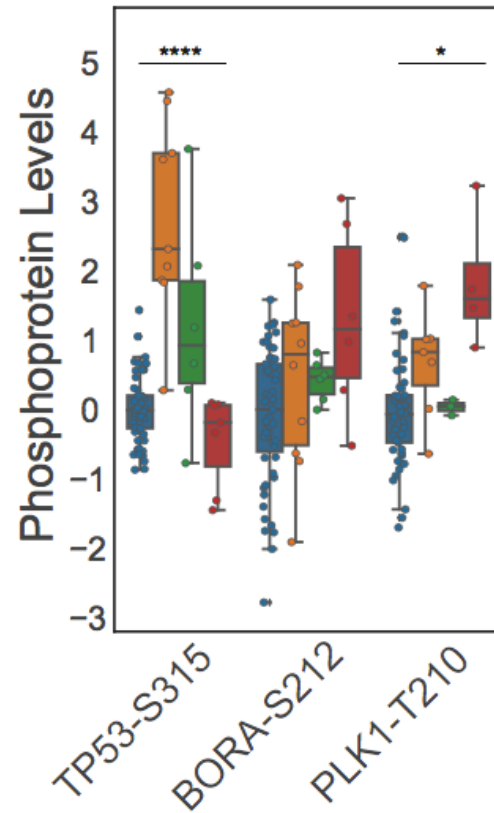
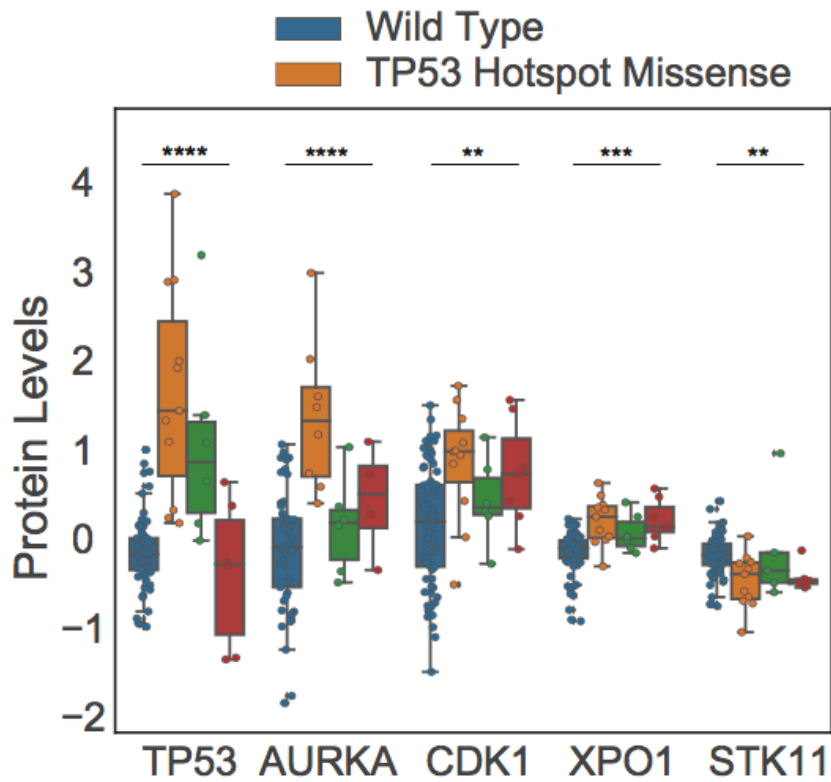
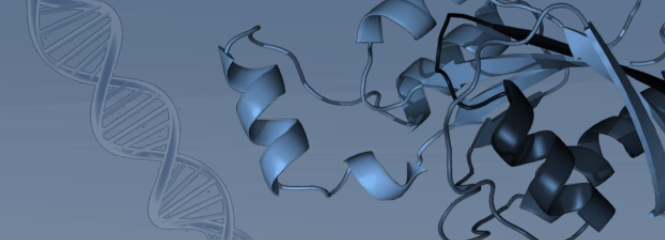
Ribosome  
Biogenesis



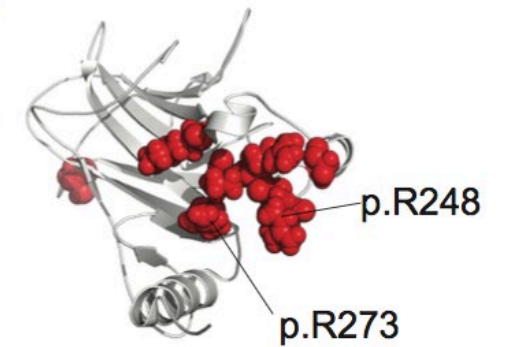
**Subtype**  
POLE  
MSI  
CNV-Low  
CNV-High

**Expression**  
4  
0  
-4

# Effects of *TP53* Mutations



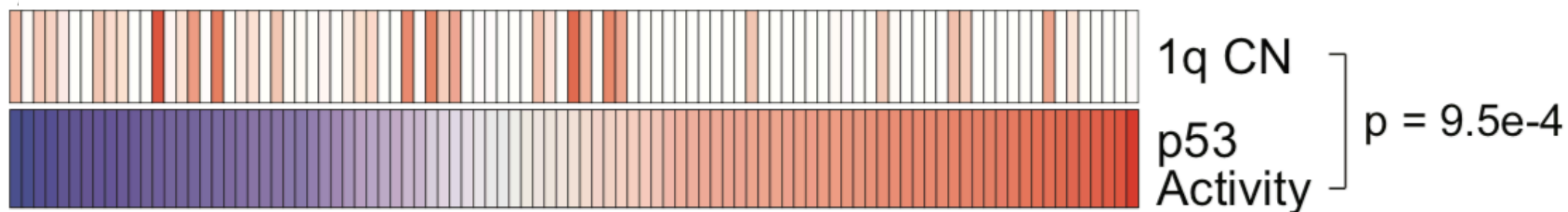
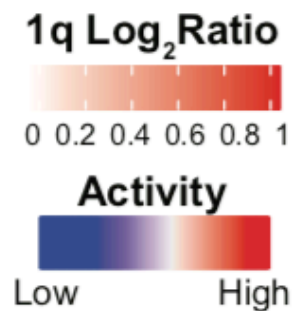
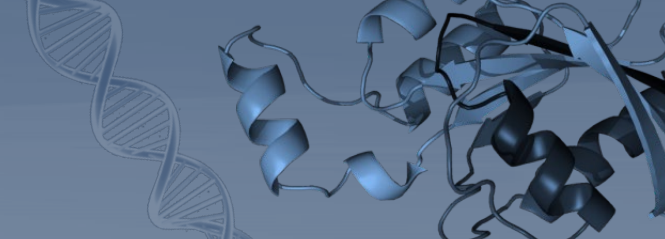
p53 Tetramer  
Bound to DNA



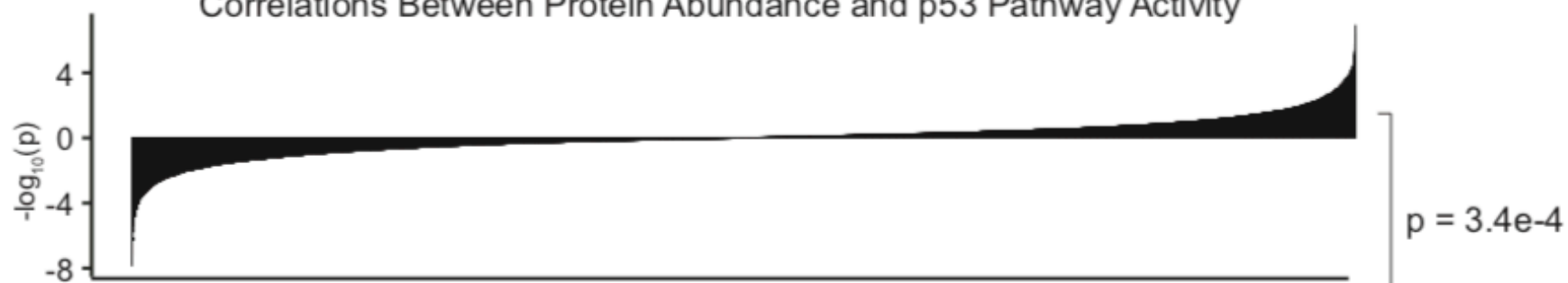
Samuel Payne



# p53 Activity and Chromosome 1q Gain



Correlations Between Protein Abundance and p53 Pathway Activity



1q Genes



1q Genes Correlated with CN Gain



p = 1.1e-4

Epigenetic Modifiers on 1q

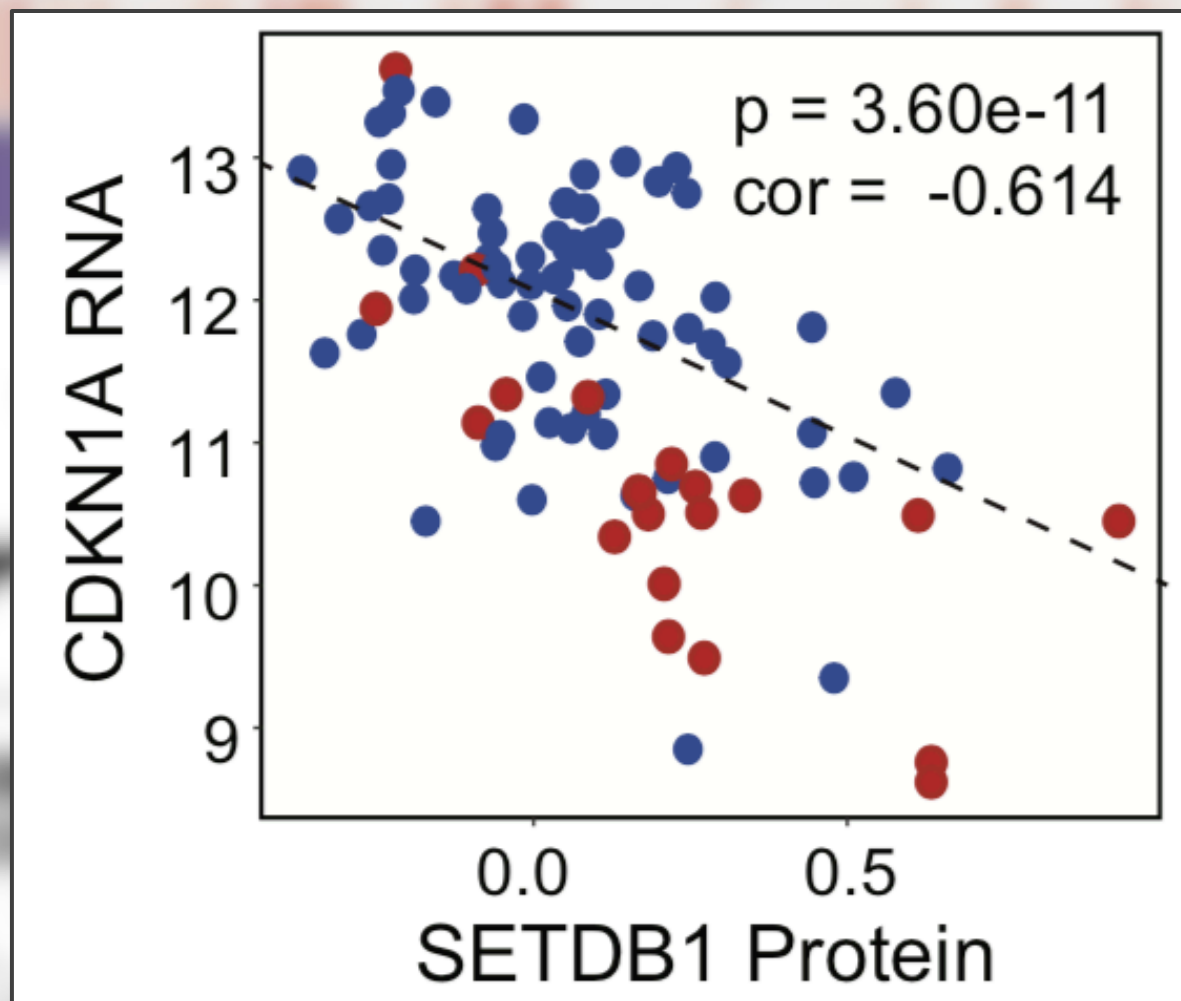
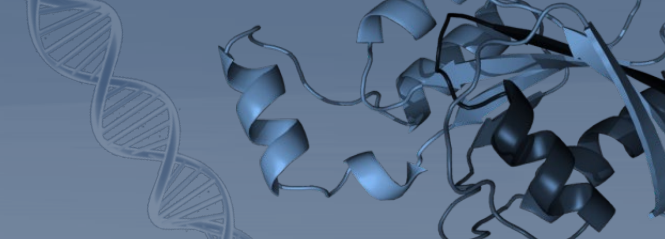
SETDB1  
PARP1  
SDE2  
GATAD2



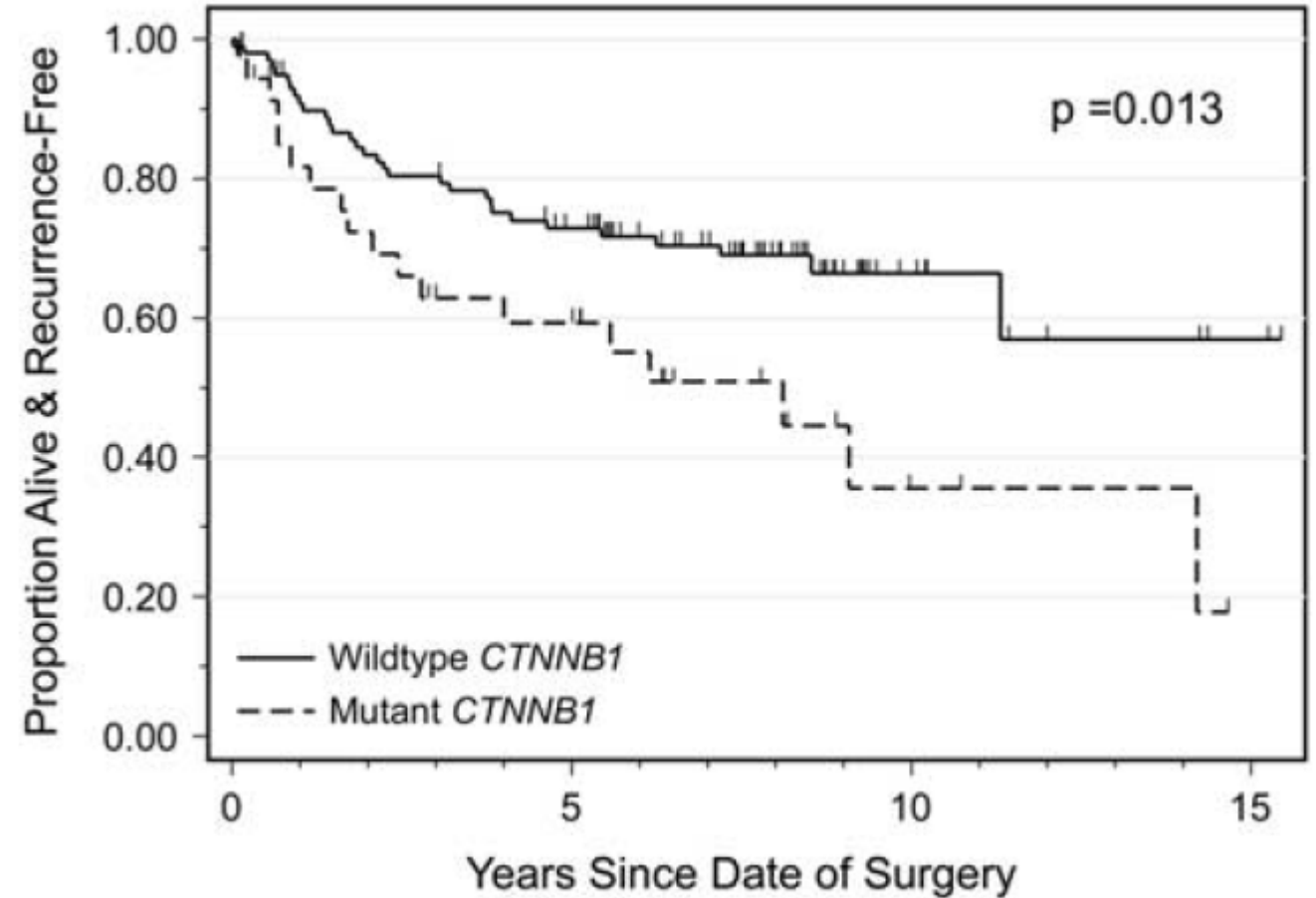
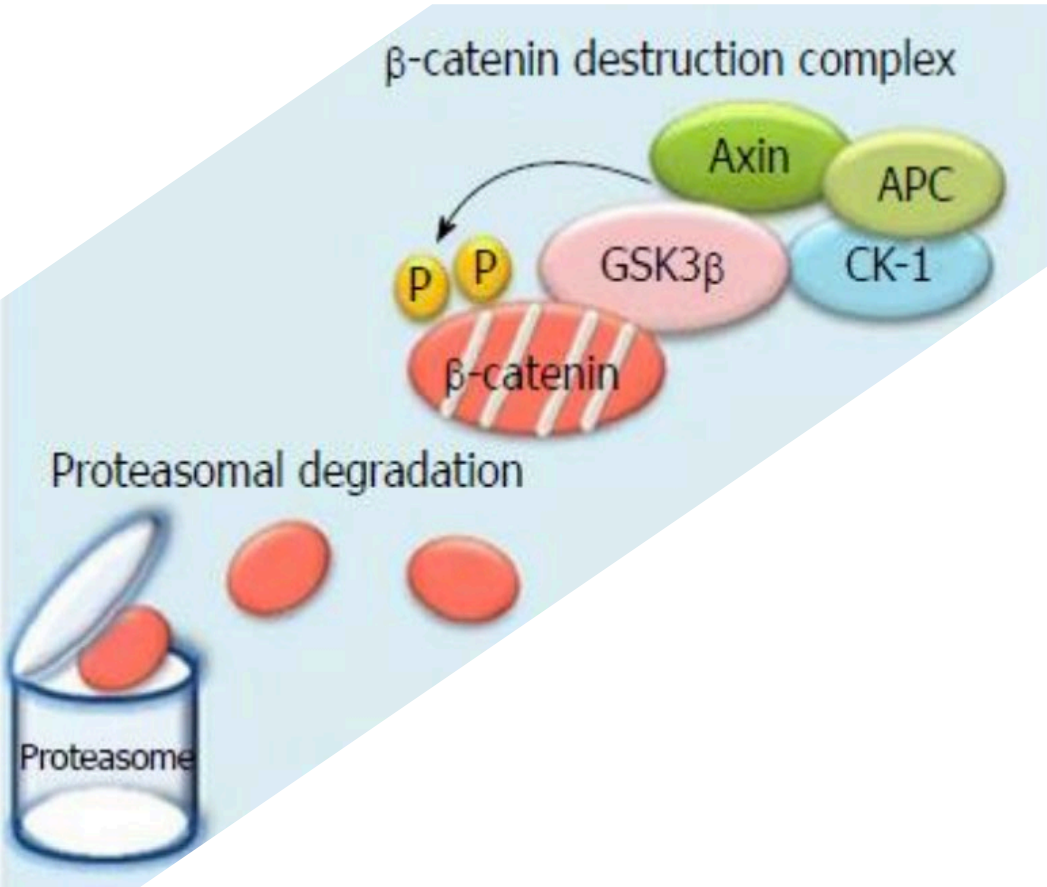
Chen Huang



# p53 Activity and Chromosome 1q Gain



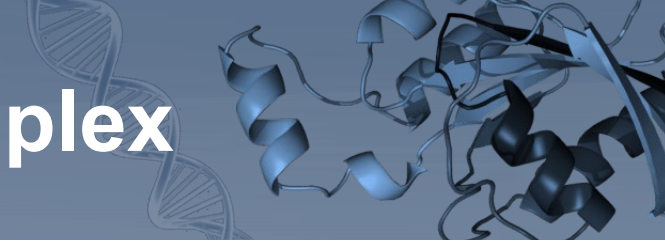
# Effects of *CTNNB1* Hotspot Mutations



Huang et al. Mechanism of combined use of vitamin D and puerarin in anti-hepatic fibrosis by regulating the Wnt/ $\beta$ -catenin signalling pathway. *World J Gastroenterol* 2018; 24(36): 4178-4185

Kurnit et al. *CTNNB1* (beta-catenin) mutation identifies low grade, early stage endometrial cancer patients at increased risk of recurrence. *Mod Pathol* 2017 Jul;30(7):1032-1041.

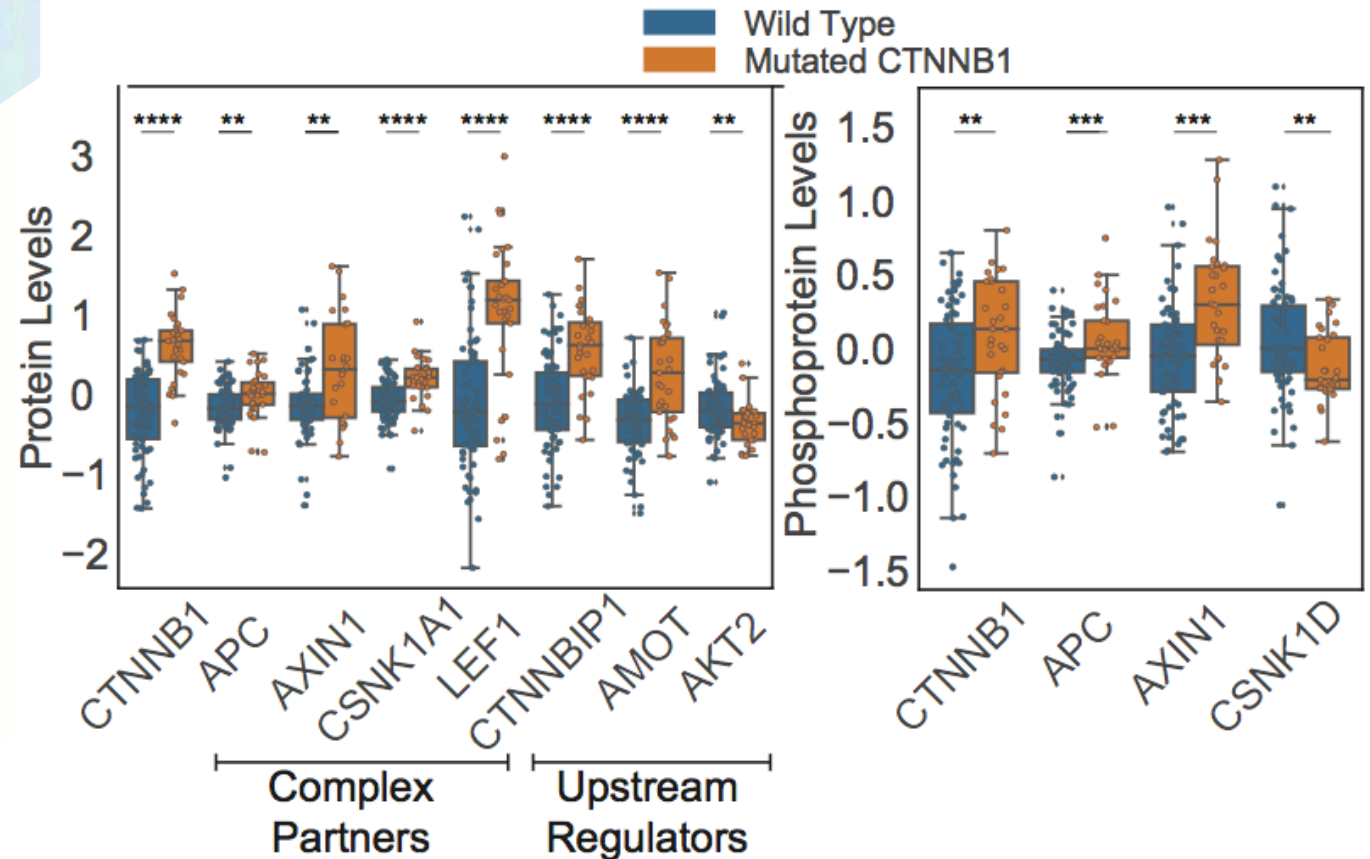
# CTNNB1 Mutations and the Destruction Complex



$\beta$ -catenin destruction complex



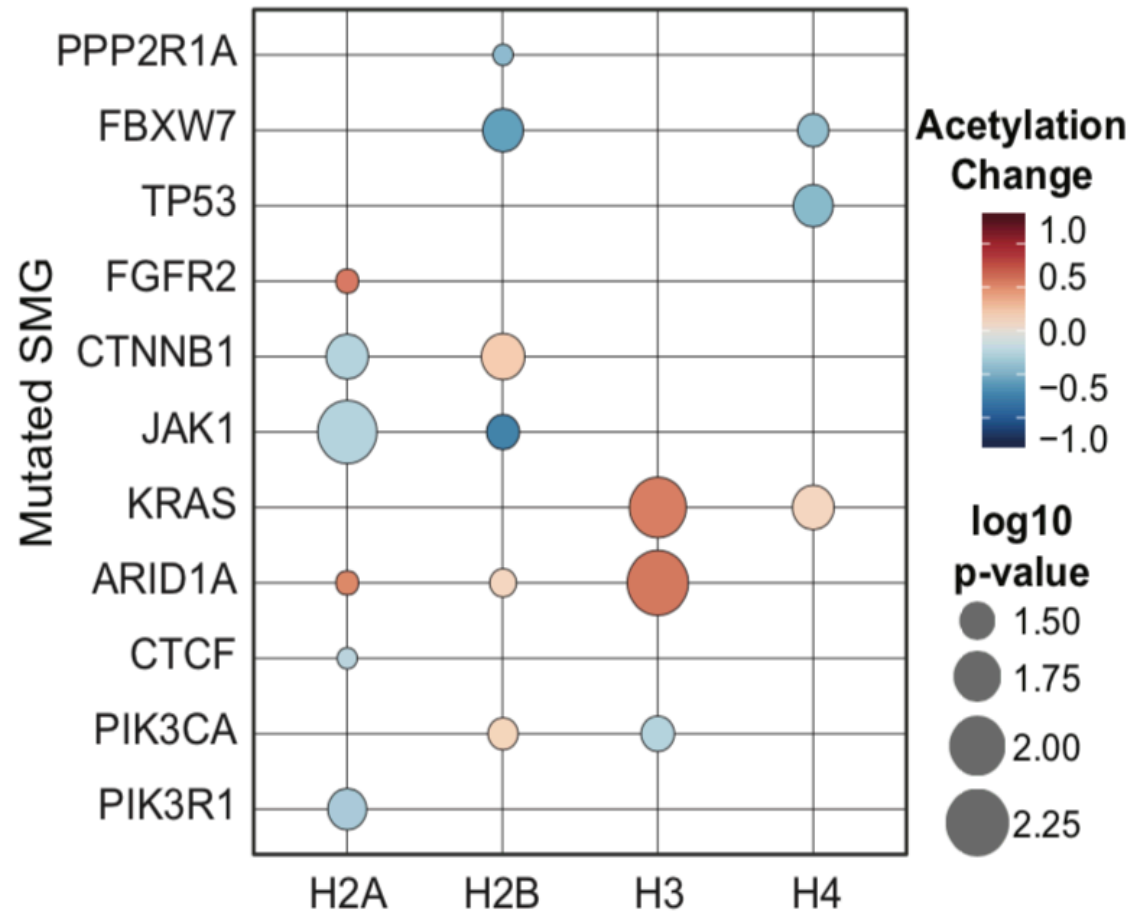
Proteasomal degradation



Huang et al. Mechanism of combined use of vitamin D and puerarin in anti-hepatic fibrosis by regulating the Wnt/ $\beta$ -catenin signalling pathway. *World J Gastroenterol* 2018; 24(36): 4178-4185



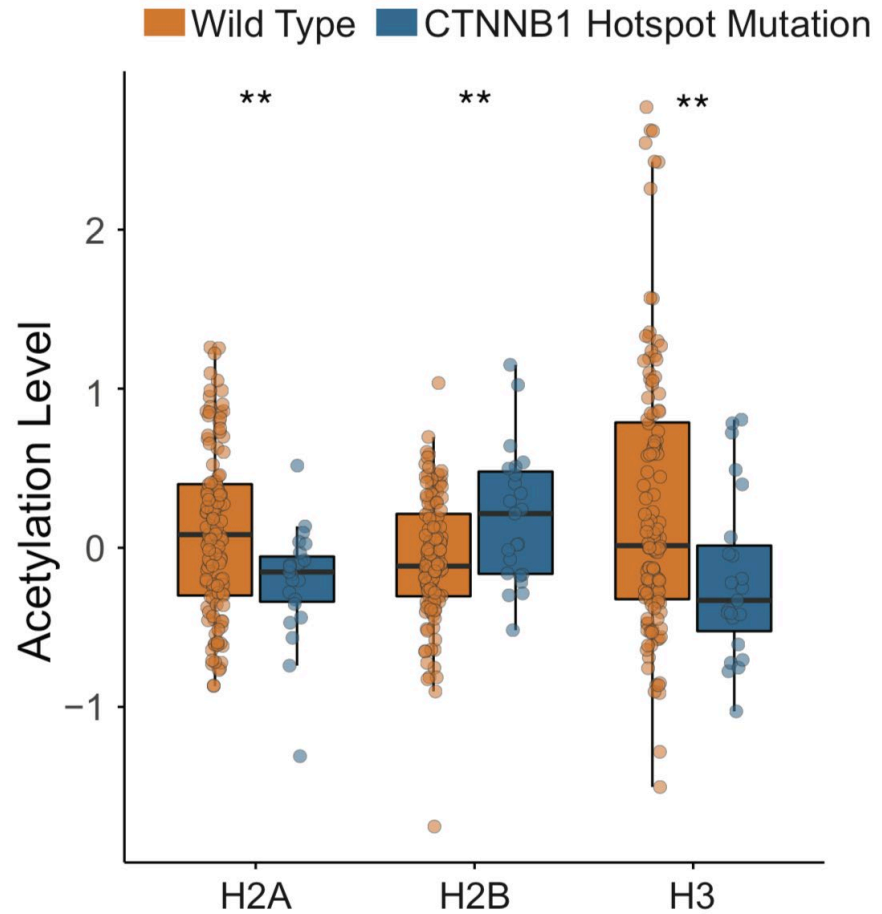
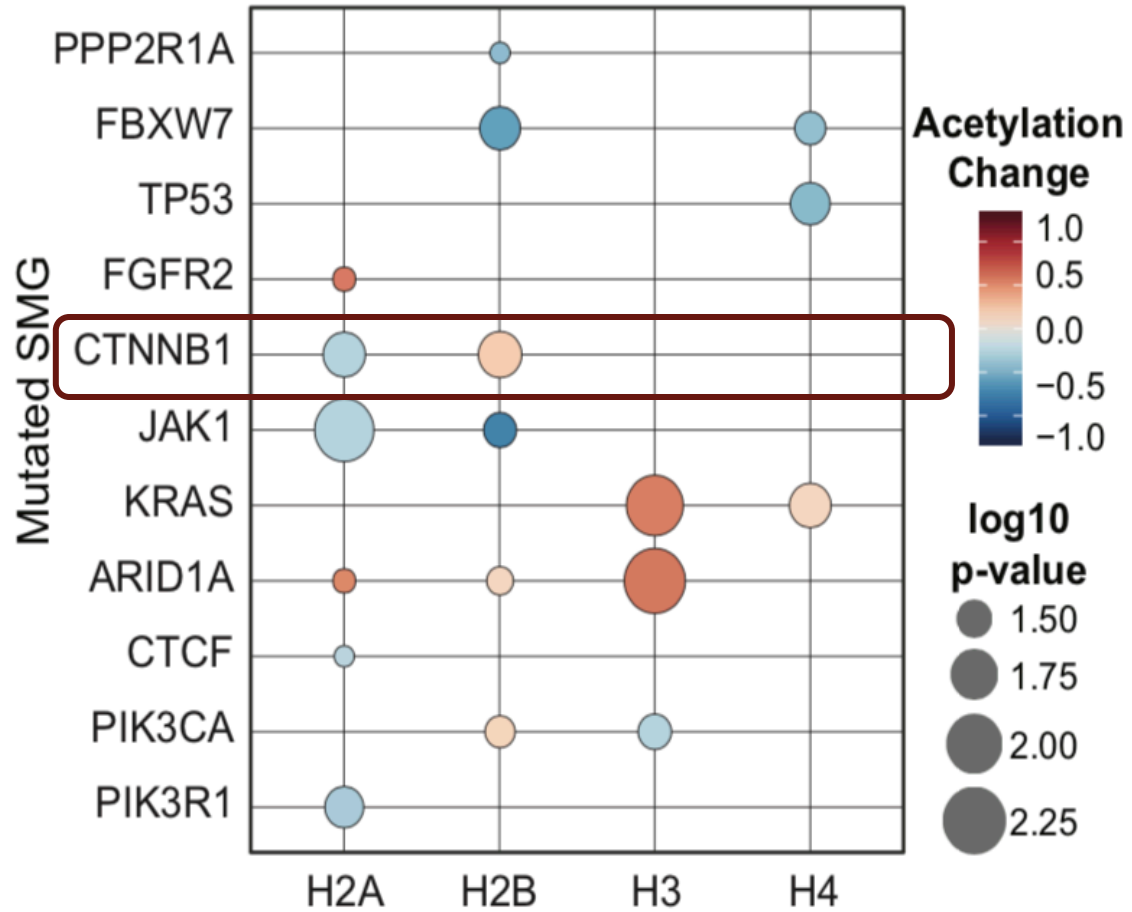
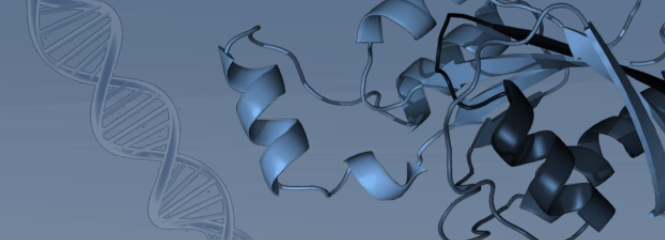
# Acetylation and *CTNNB1* Mutations



Alla Karpova



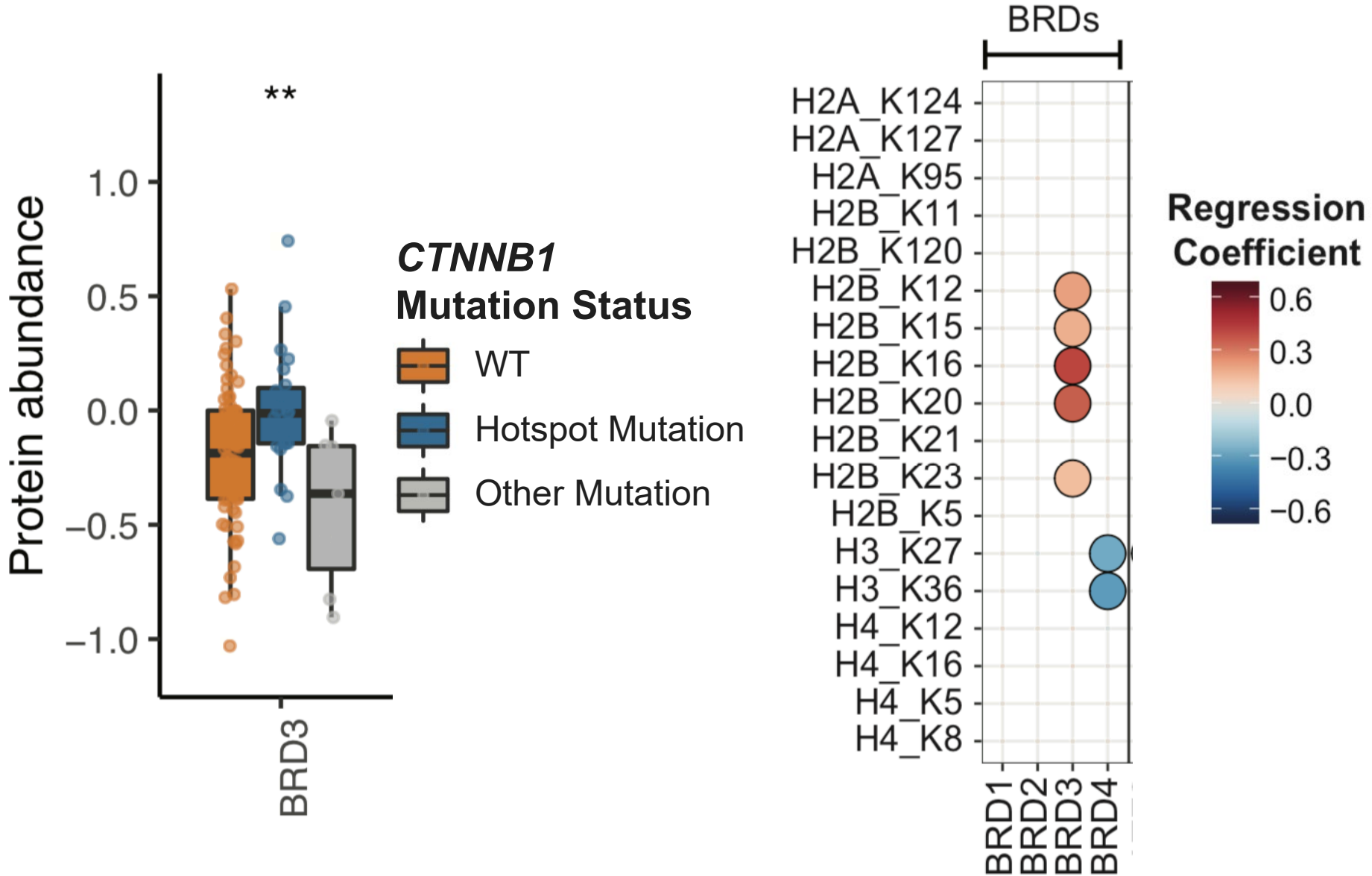
# Acetylation and *CTNNB1* Mutations



Alla Karpova

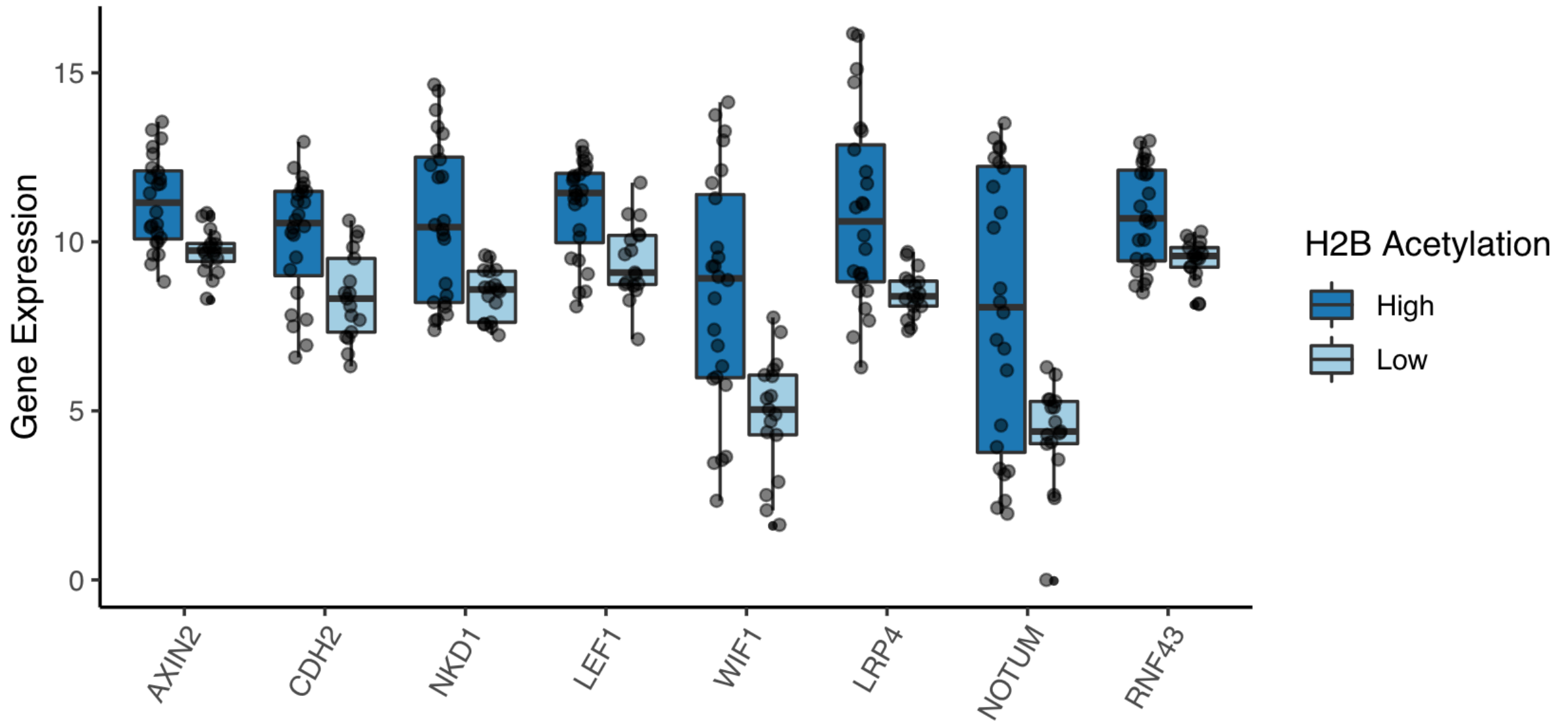


# CTNNB1 Mutations and Histone H2B Acetylation

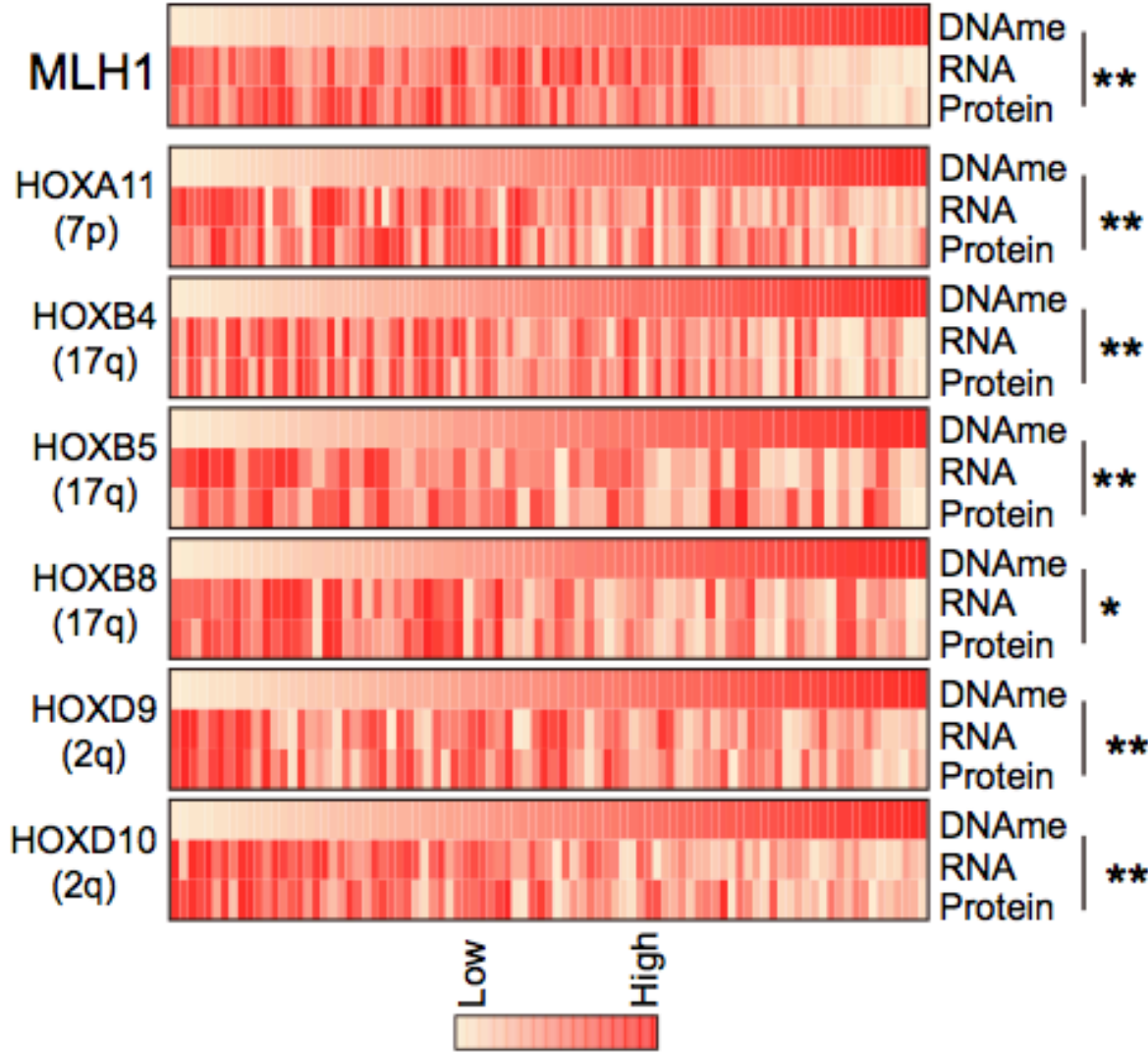
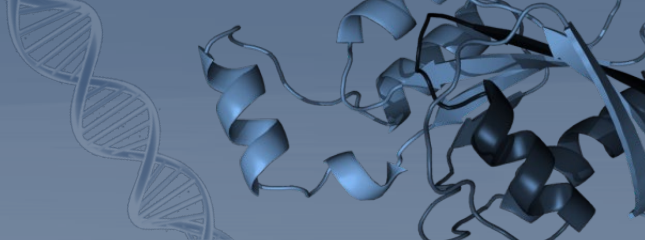




# Acetylation, *CTNNB1* Mutations, and the Wnt Pathway

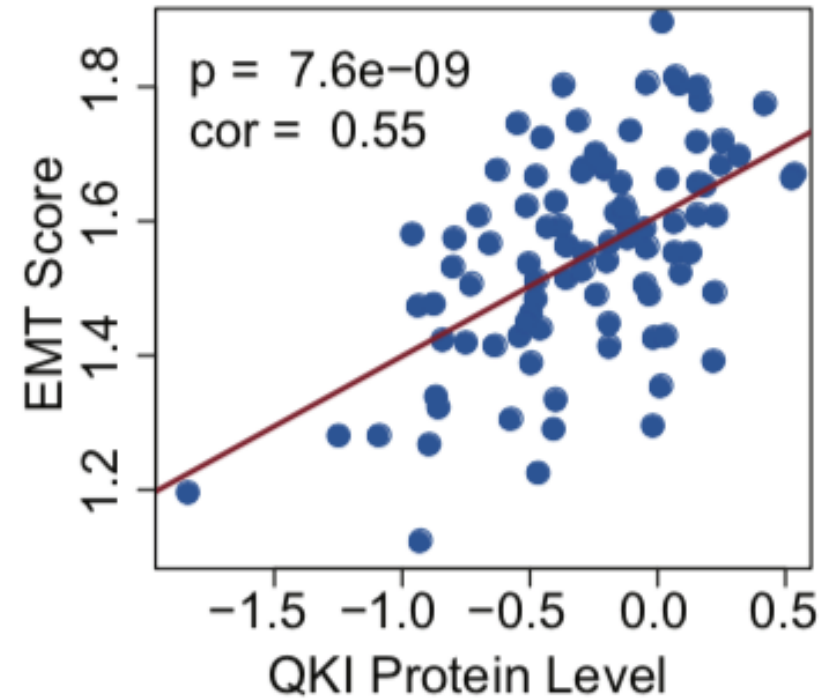
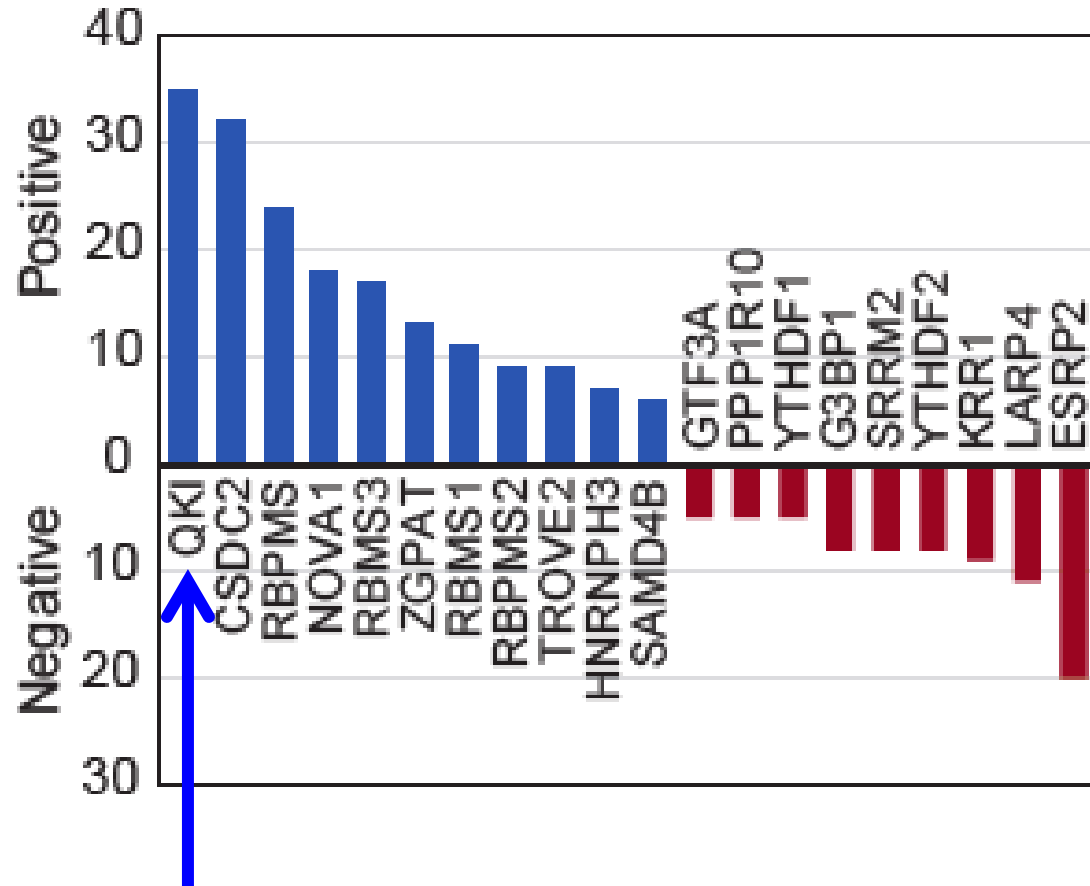
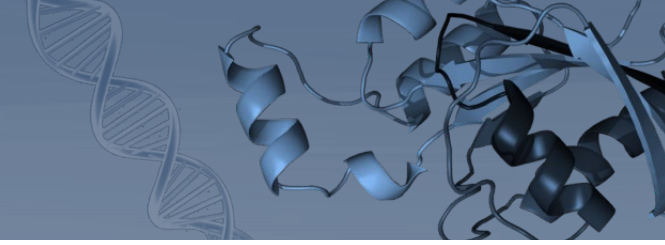


# DNA Methylation and HOX Proteins



Chen Huang

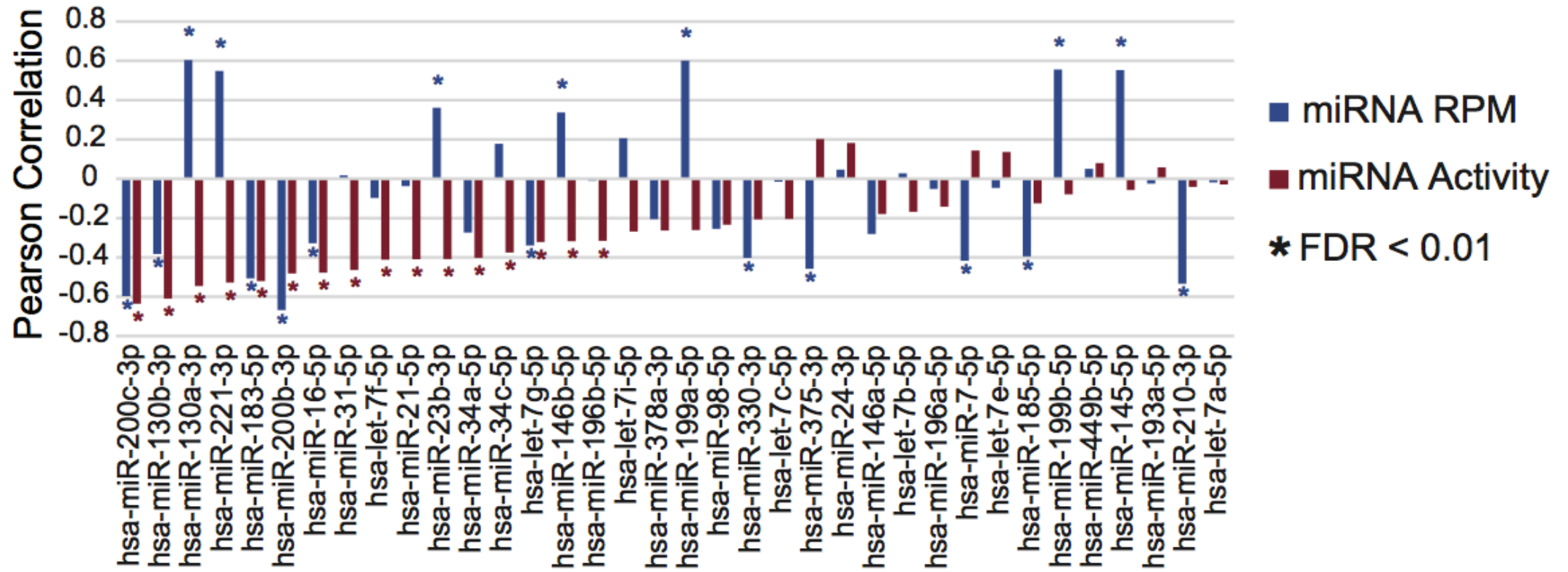
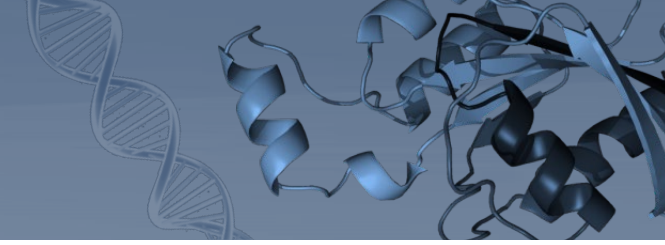
# Circular RNA and the EMT Pathway



Yongchao Dou

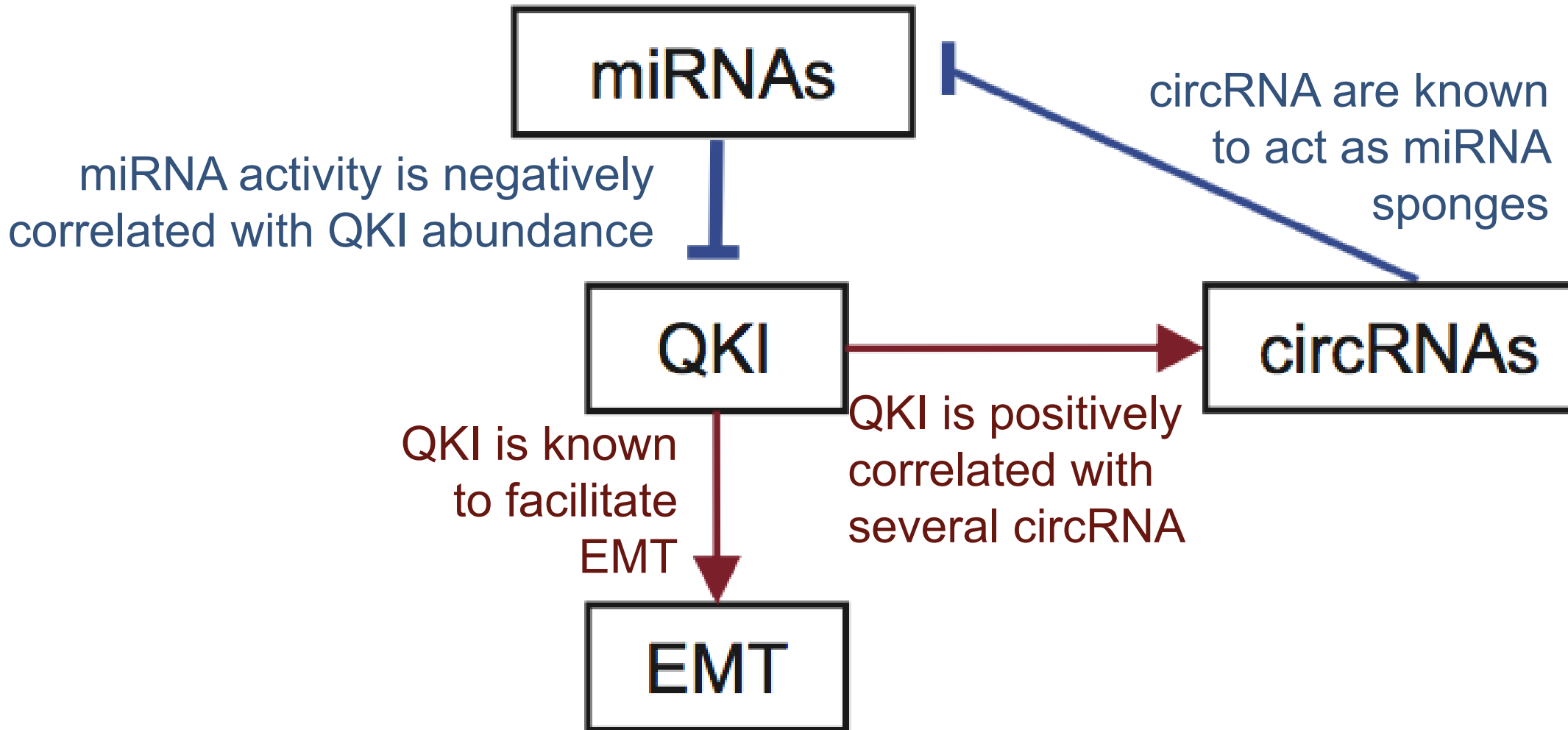
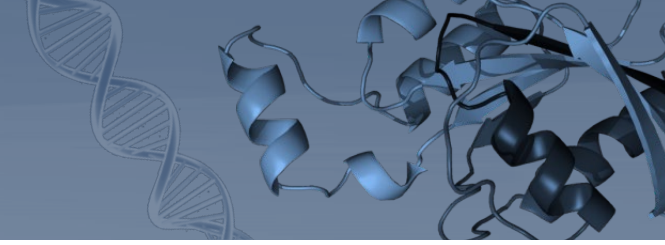


# Circular RNA and the EMT Pathway



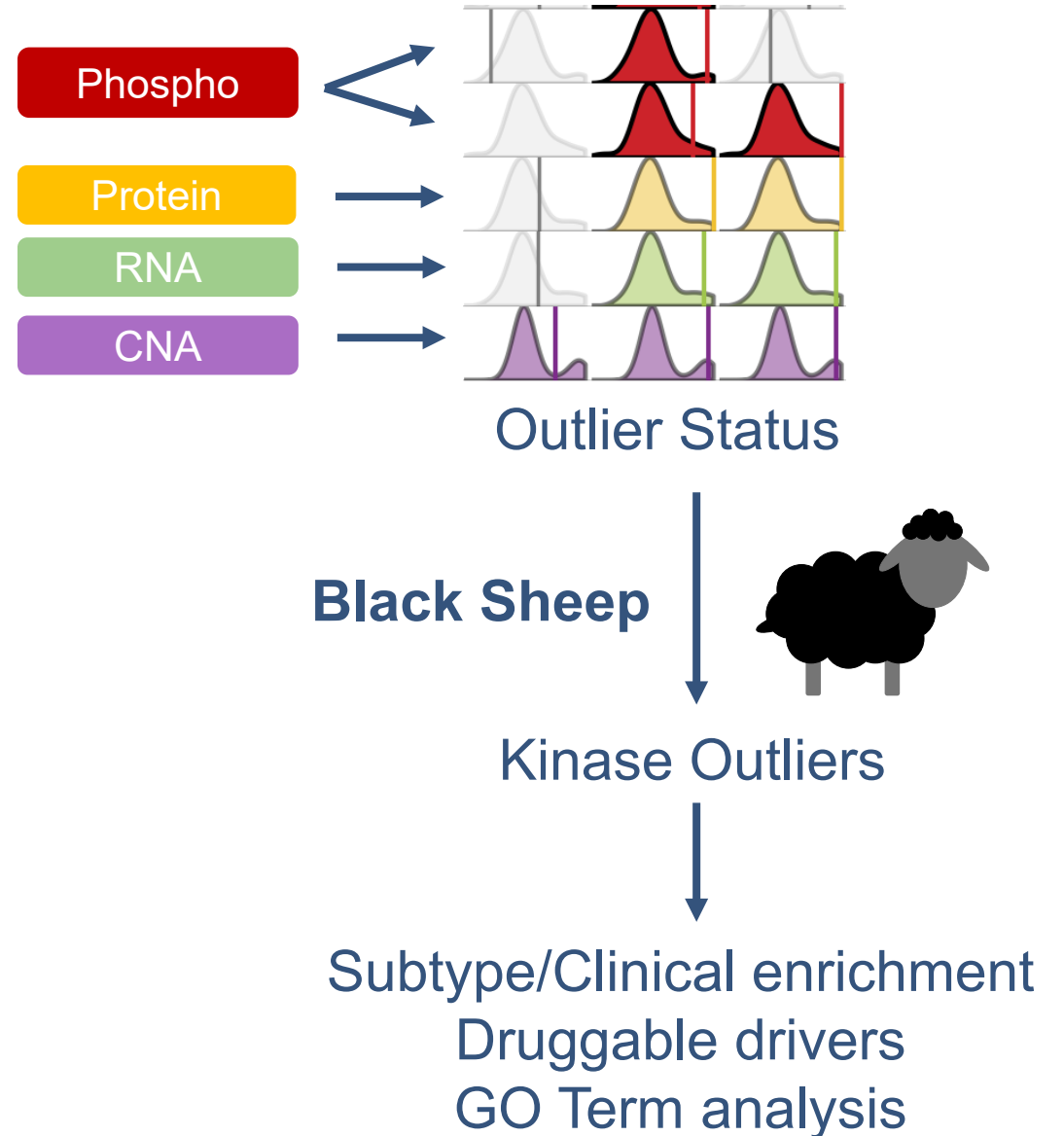


# Circular RNA and the EMT Pathway

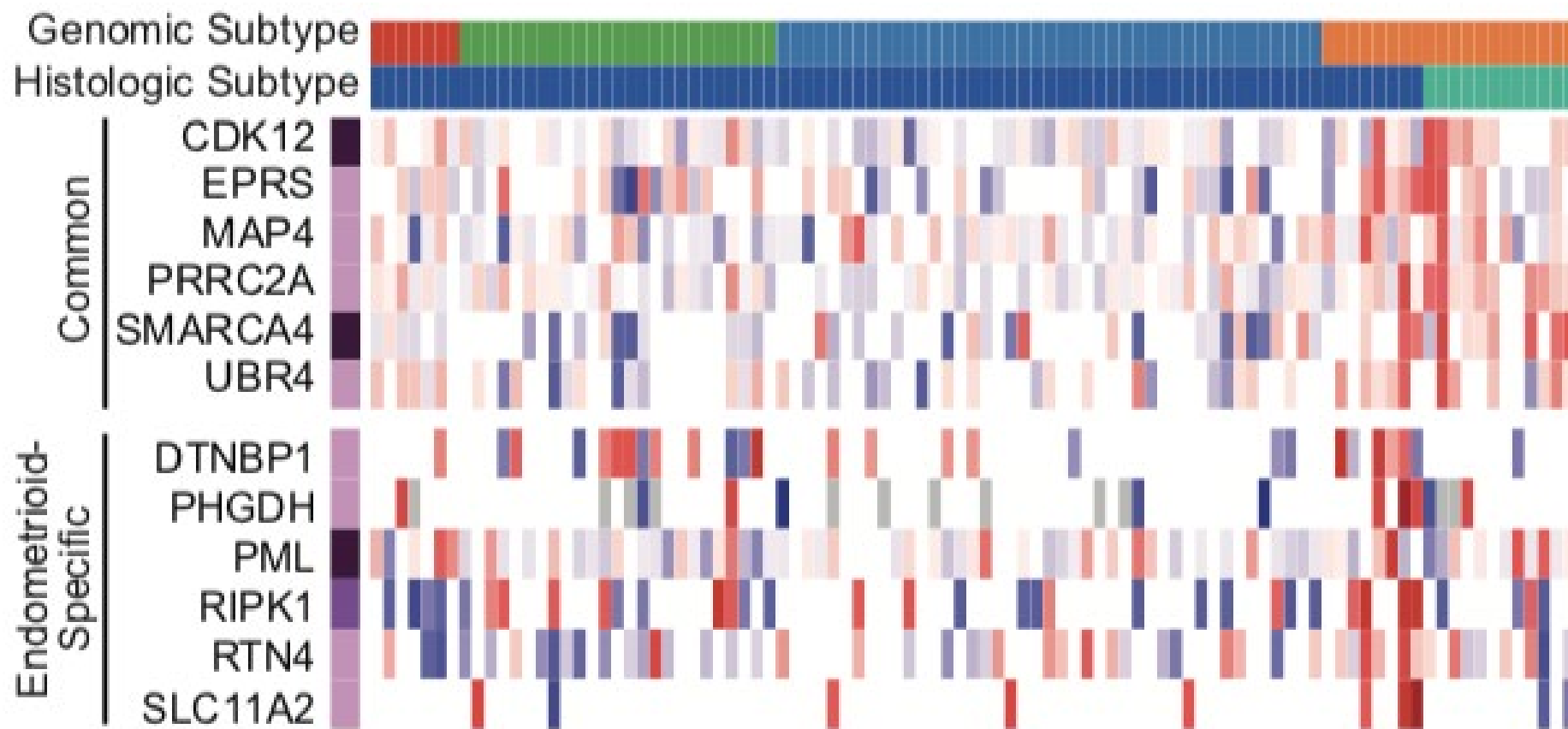


# Identifying Aberrant Kinases Using Black Sheep

- **Methods:**
  - Create distributions of normalized phosphosite expression across samples
  - Flag outliers ( $>X$  IQR from median)
  - Repeat for CNA, RNA and protein expression if desired
- **Why focus on kinases?**
  - Play key roles in cancer development and progression
  - Many highly selective and effective therapies directed against kinases



# Phosphoproteomic Analysis of CNV-High Patients



Drug Type

Pre-clinical  
Anti-neoplastic  
FDA-approved

Phospho Fraction Outliers



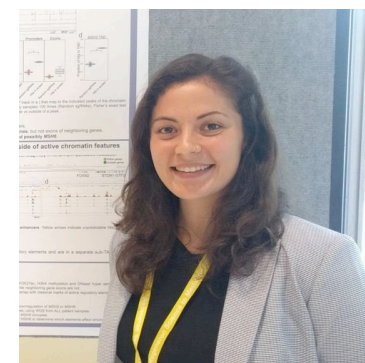
Genomic Subtype

POLE  
MSI-H  
CNV-High  
CNV-Low

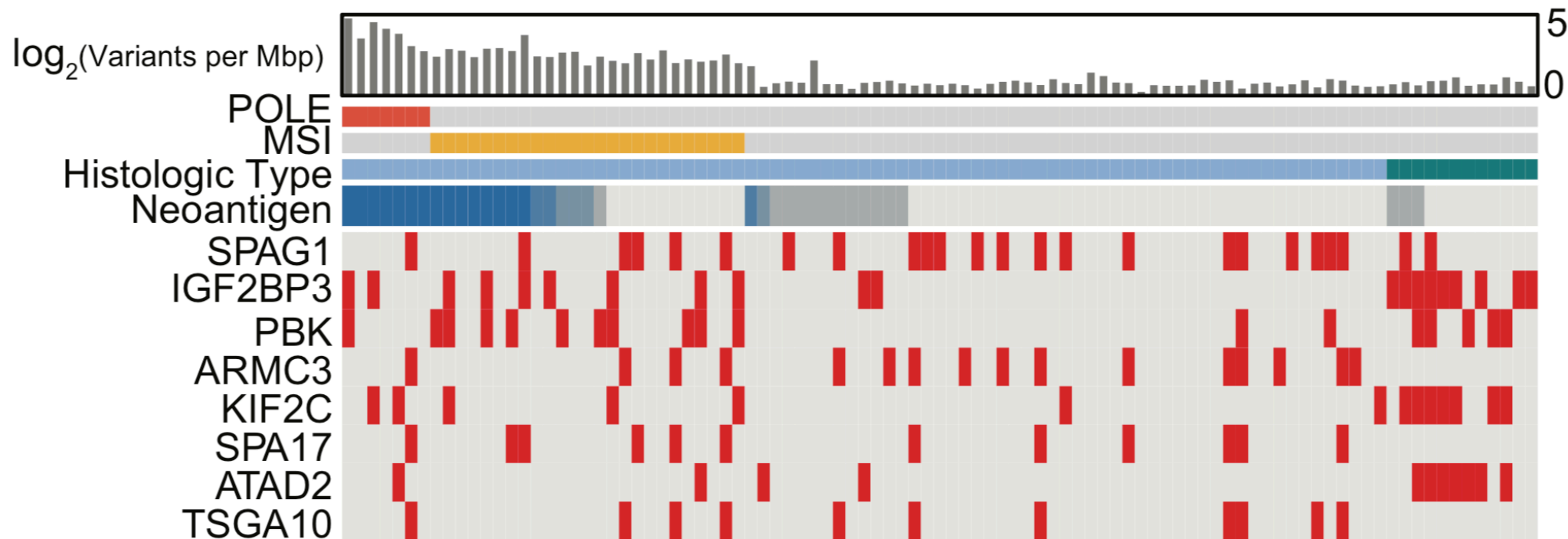
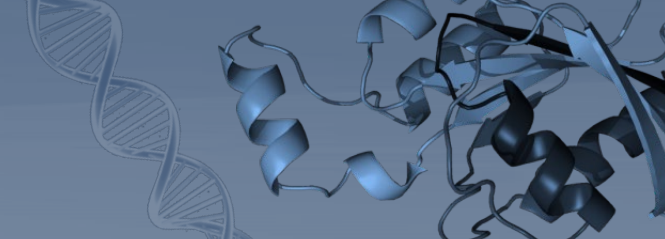
Histologic Type

Endometrioid  
Serous

Lili  
Blumenberg



# C/T Antigens and Putative Neoantigens



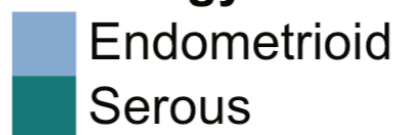
## POLE Subtype



## MSI Status



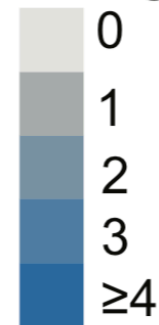
## Histology



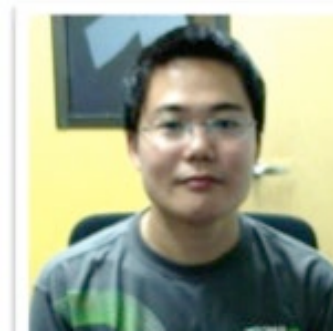
## CT Antigen



## Neoantigen Count

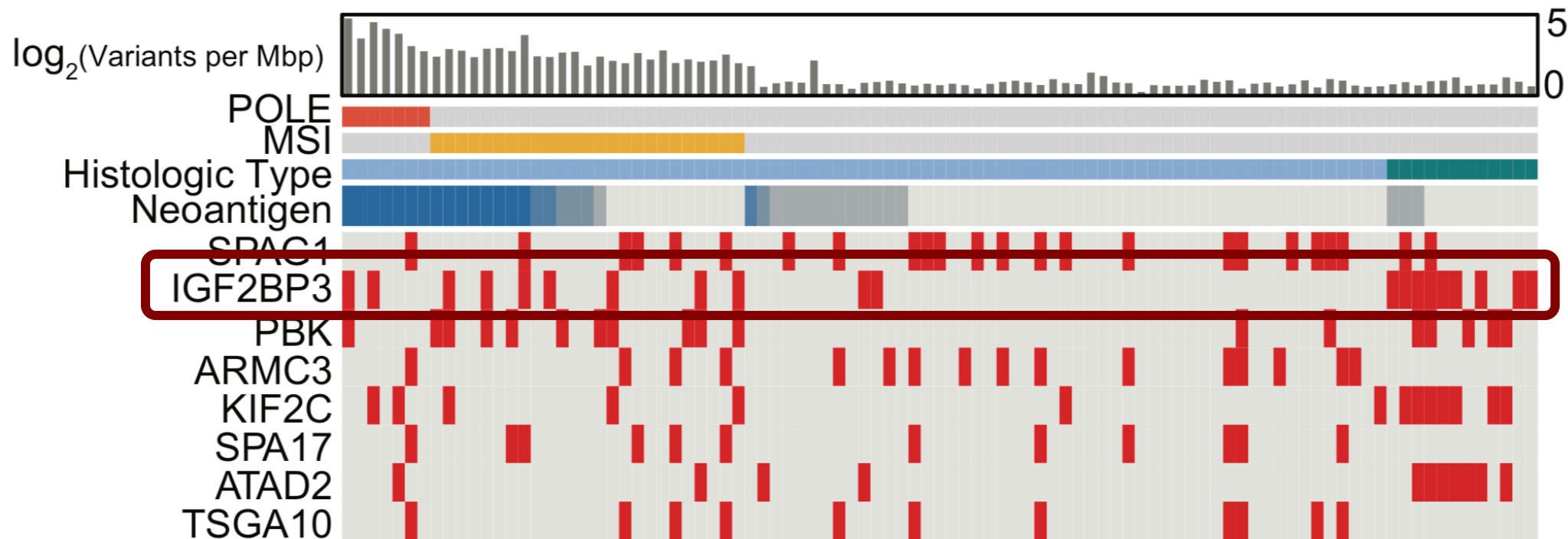
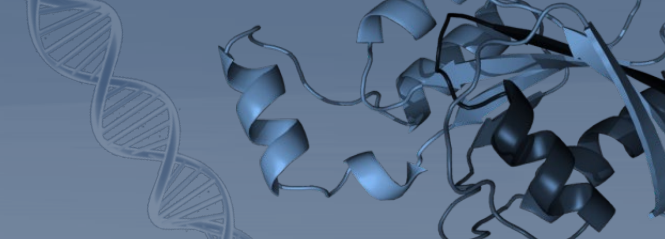


Yongchao  
Dou





# C/T Antigens and Putative Neoantigens



### POLE Subtype

Yes  
No

### MSI Status

MSI-H  
MSS

### Histology

Endometrioid  
Serous

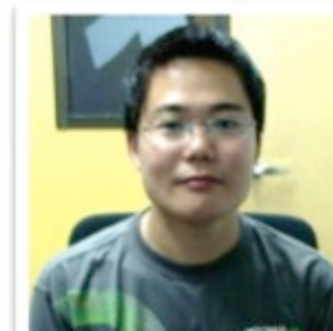
### CT Antigen

Present  
Not Present

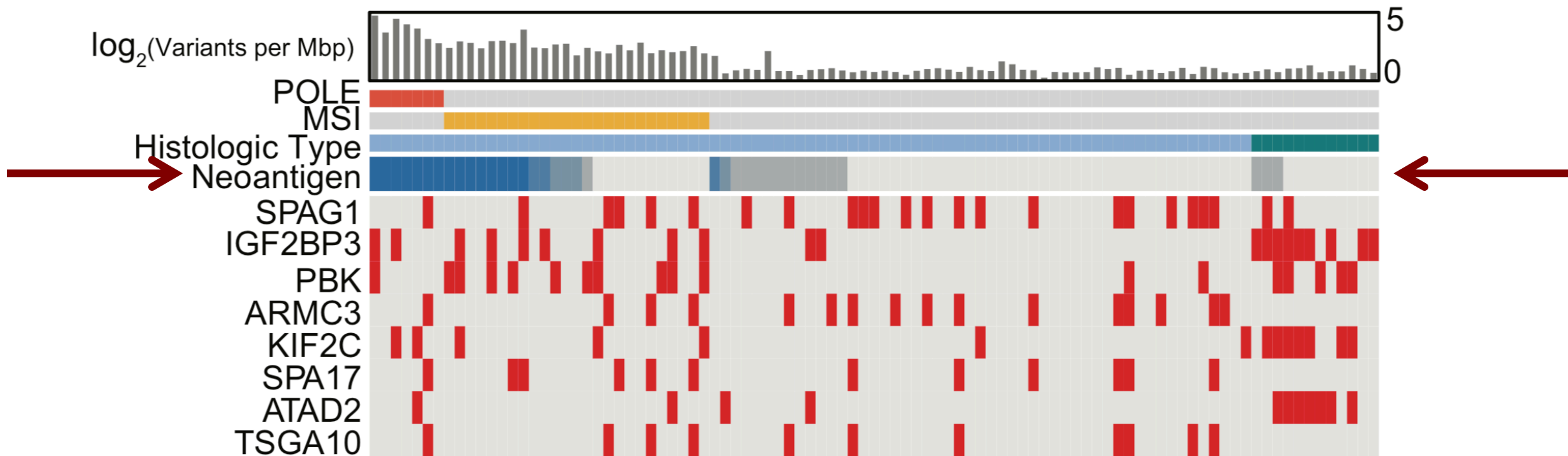
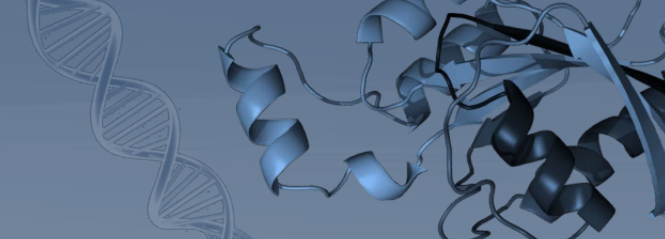
### Neoantigen Count

0  
1  
2  
3  
≥4

Yongchao  
Dou



# C/T Antigens and Putative Neoantigens



## POLE Subtype

Yes

No

## MSI Status

MSI-H

MSS

## Histology

Endometrioid

Serous

## CT Antigen

Present

Not Present

## Neoantigen Count

0

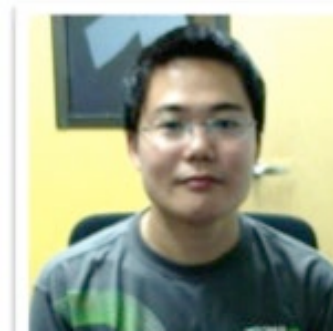
1

2

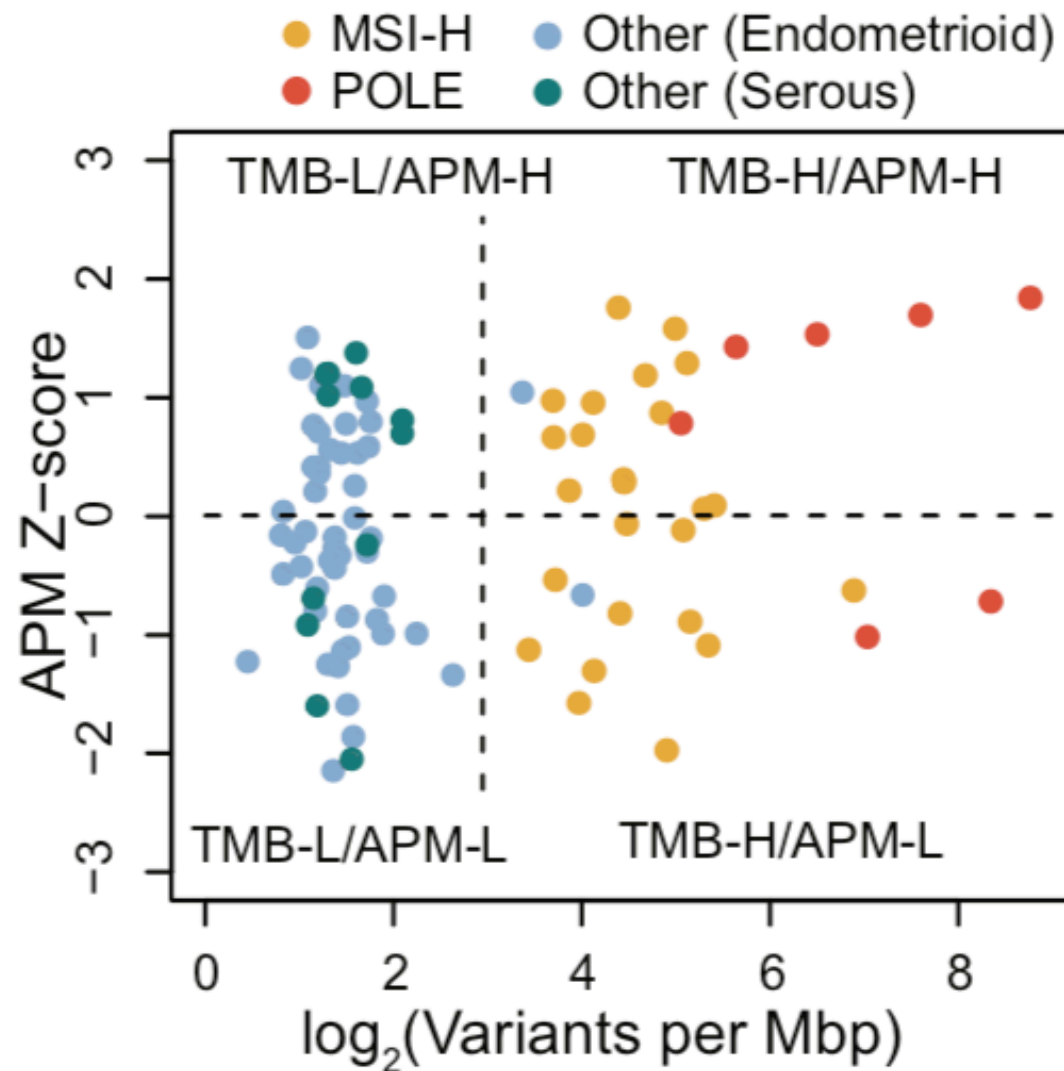
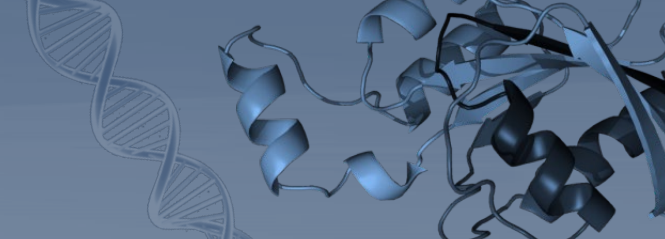
3

≥4

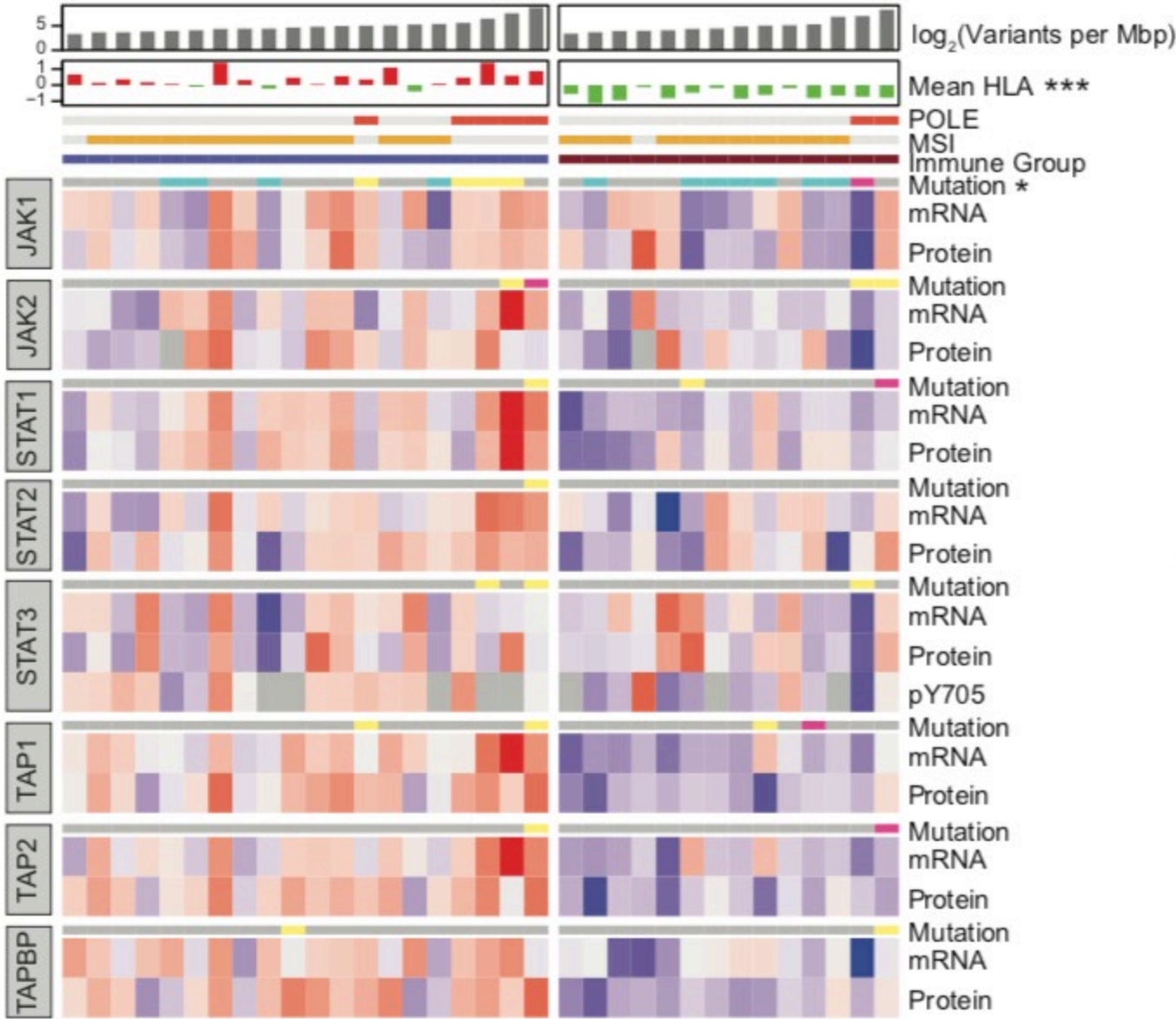
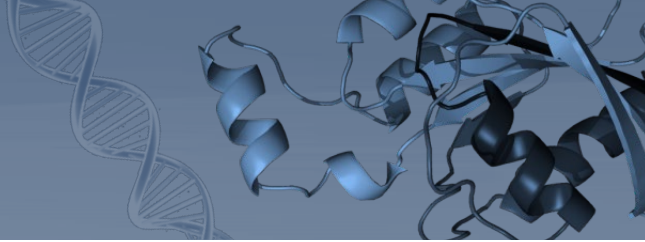
Yongchao  
Dou



# Tumor Immune Subgroups



# Markers of Immune Evasion



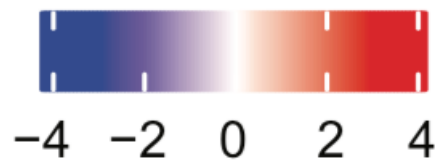
## Immune Group



## Mutation



## Expression



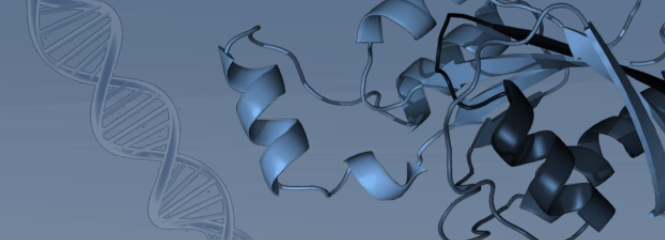


# Major Takeaways

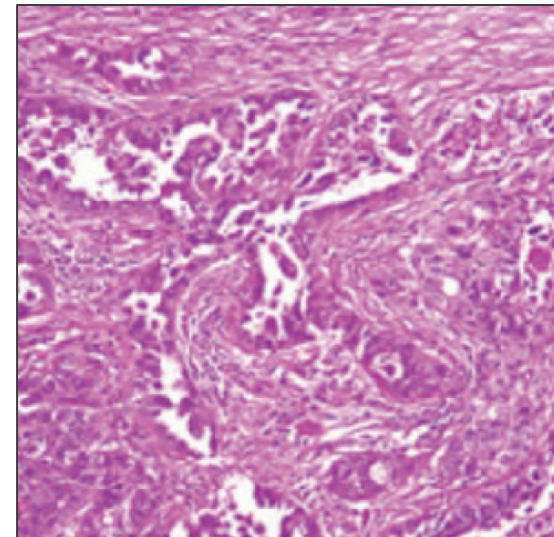
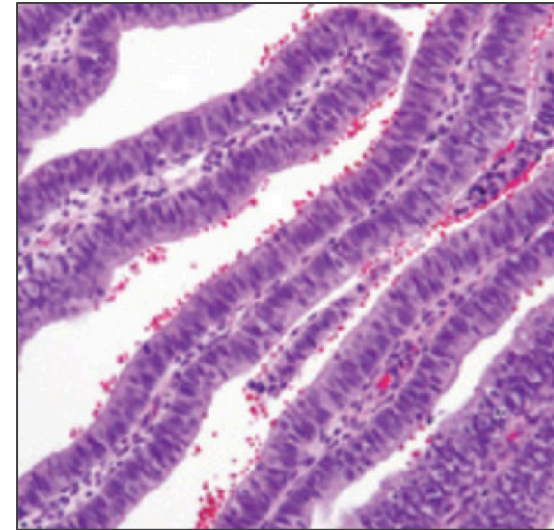


- Comprehensive proteogenomic characterization of 95 endometrial carcinomas
- Proteomic, phosphoproteomic, and acetylotomic co-identification of CTNNB1 complex partners and upstream regulators via mutation association analyses
- Proteomics data identifies putative EMT regulator QKI via circRNA
- Multi-omic analysis pinpoints potential therapeutic targets in clinically significant patient subsets
- Immune groupings identify immunotherapy candidates

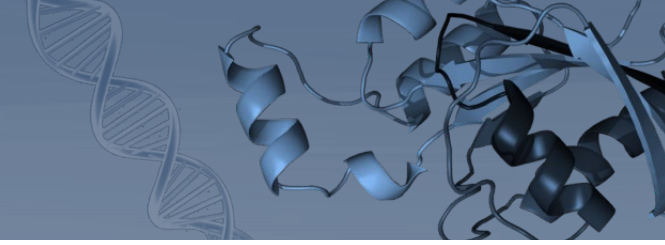
# How Can Imaging Help?



- Differentiation between serous and endometrioid
- Differentiation between genomic subtypes
- Annotation of specific features characteristic of certain subgroups



# Where Is The Data?



## CPTAC-UCEC

	<b>Radiology Image Statistics</b>	<b>Pathology Image Statistics</b>
Modalities	CT, MR, PT, CR, DX, SR	Pathology
Number of Patients	60	250
Number of Studies	84	N/A
Number of Series	1,257	N/A
Number of Images	121,109	888
Images Size (GB)	46.9	154

## TCGA-UCEC

<b>Image Statistics</b>	
Modalities	CT, CR, MR, PT
Number of Patients	65
Number of Studies	226
Number of Series	912
Number of Images	75,829
Images Size (GB)	36.1

<https://www.cancerimagingarchive.net/>

Path images for 560 more patients: <https://portal.gdc.cancer.gov/projects/TCGA-UCEC>

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