Chromophobe Renal Cell Carcinoma

TCGA KICH AWG

Chairs: Chad Creighton, W. Kim Rathmell

Introduction

- Chromophobe renal cell carcinoma (ChRCC) represents ~5% of cancers arising from the kidney nephron
- Due in part to its relative rarity, this disease has been understudied at the molecular level
- Comprehensively profiled by TCGA, as the first of its Rare Tumor Projects

Data summary

Data Type	Platforms	Cases	Data access
Whole exome DNA sequence	Illumina	66	Controlled
Whole genome DNA sequence	Illumina	50	Controlled
Mitochondria DNA sequence	Illumina (LR-PCR)	61	Controlled
DNA copy number/genotype	Affymetrix SNP 6	66	Controlled
mRNA expression	Illumina	66	Controlled - BAM files Open - expression files
miRNA expression	Illumina	66	Controlled - BAM files Open - expression files
CpG DNA methylation	Illumina 450K	66	Open

66 tumor cases for comprehensive profiling

50 cases with whole genome sequencing

61 cases with mitochondria genome sequencing

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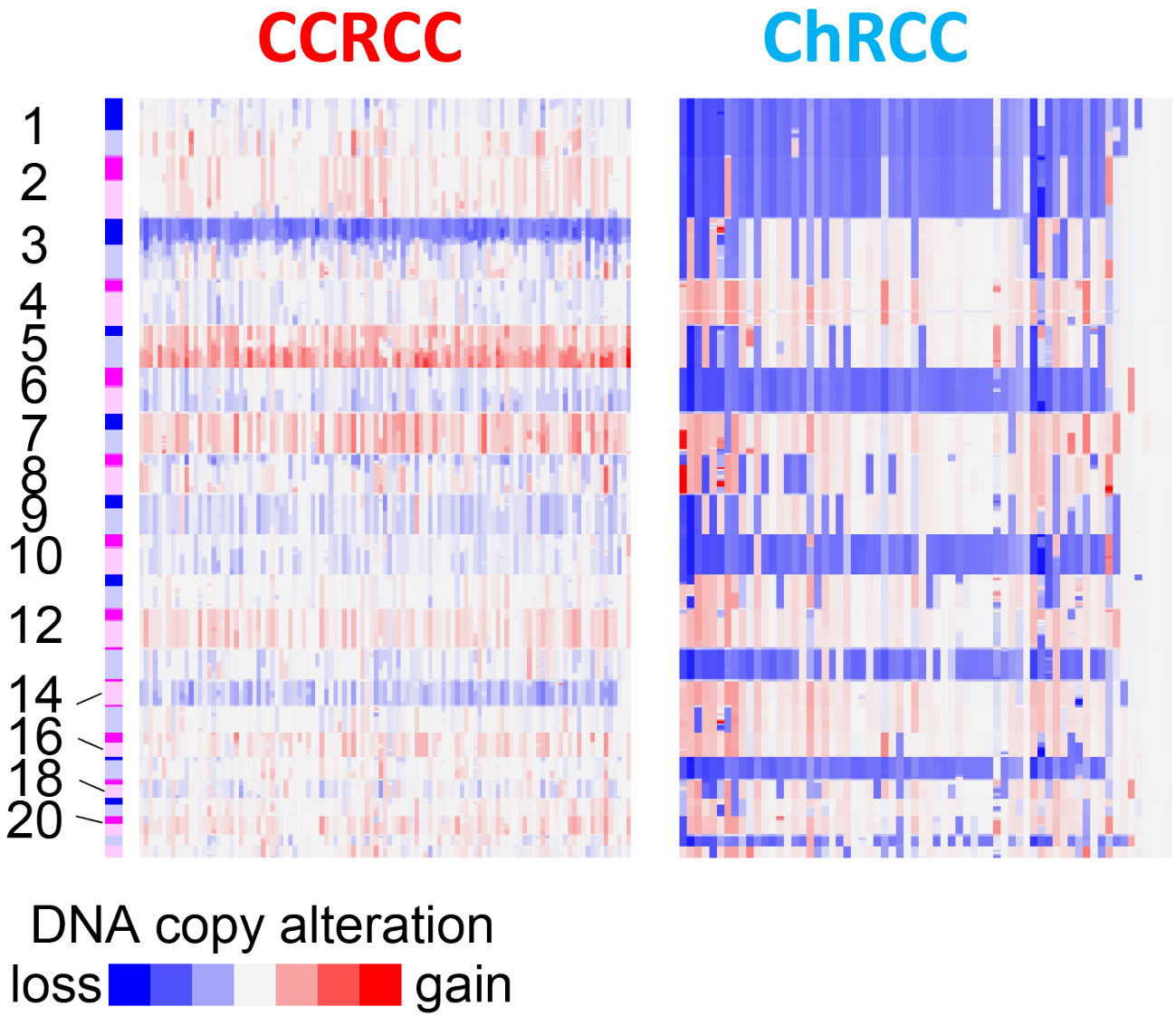
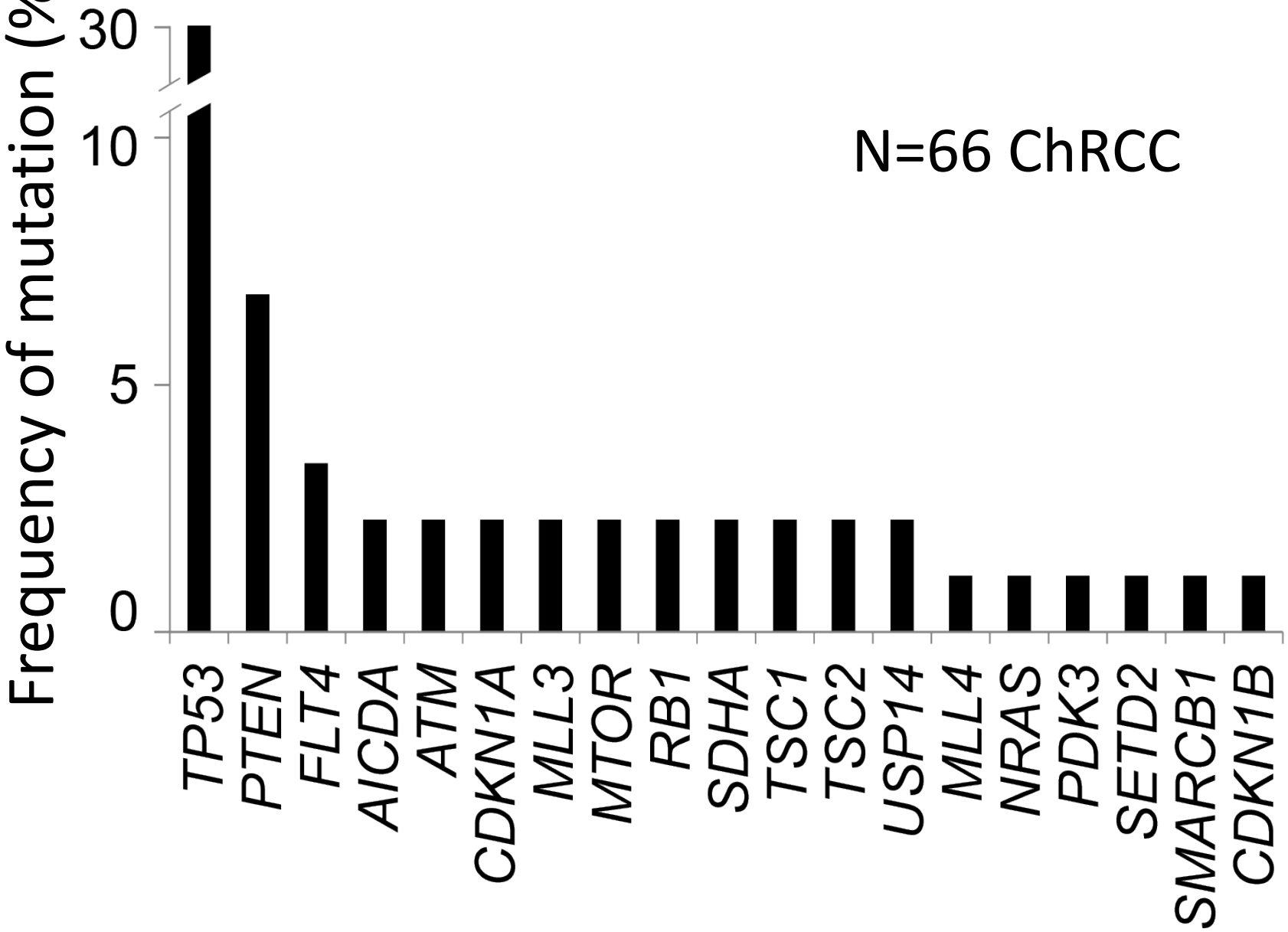
Somatic alterations (copy and whole exome)

DNA copy alterations



Somatically mutated genes

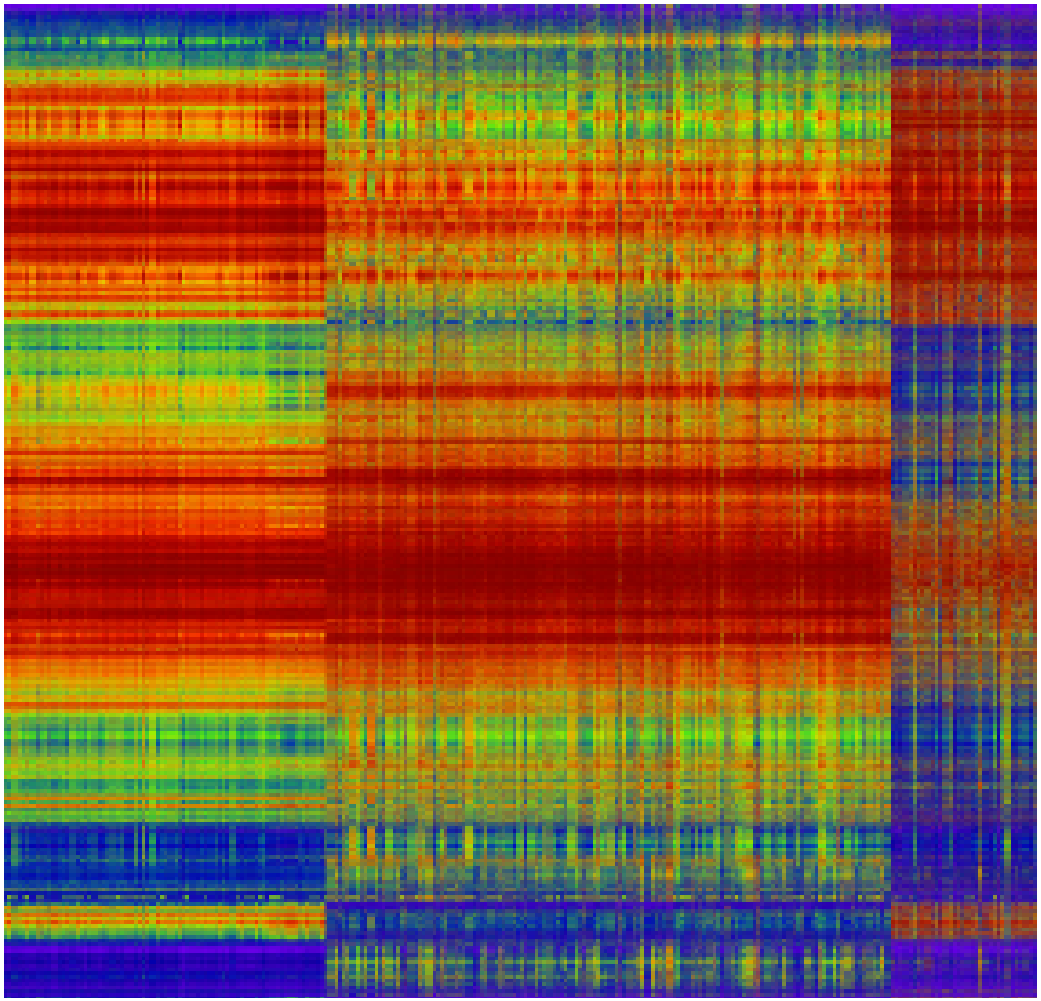


DNA methylation and RNA expression

DNA methylation

low high

64,000 differential loci in total



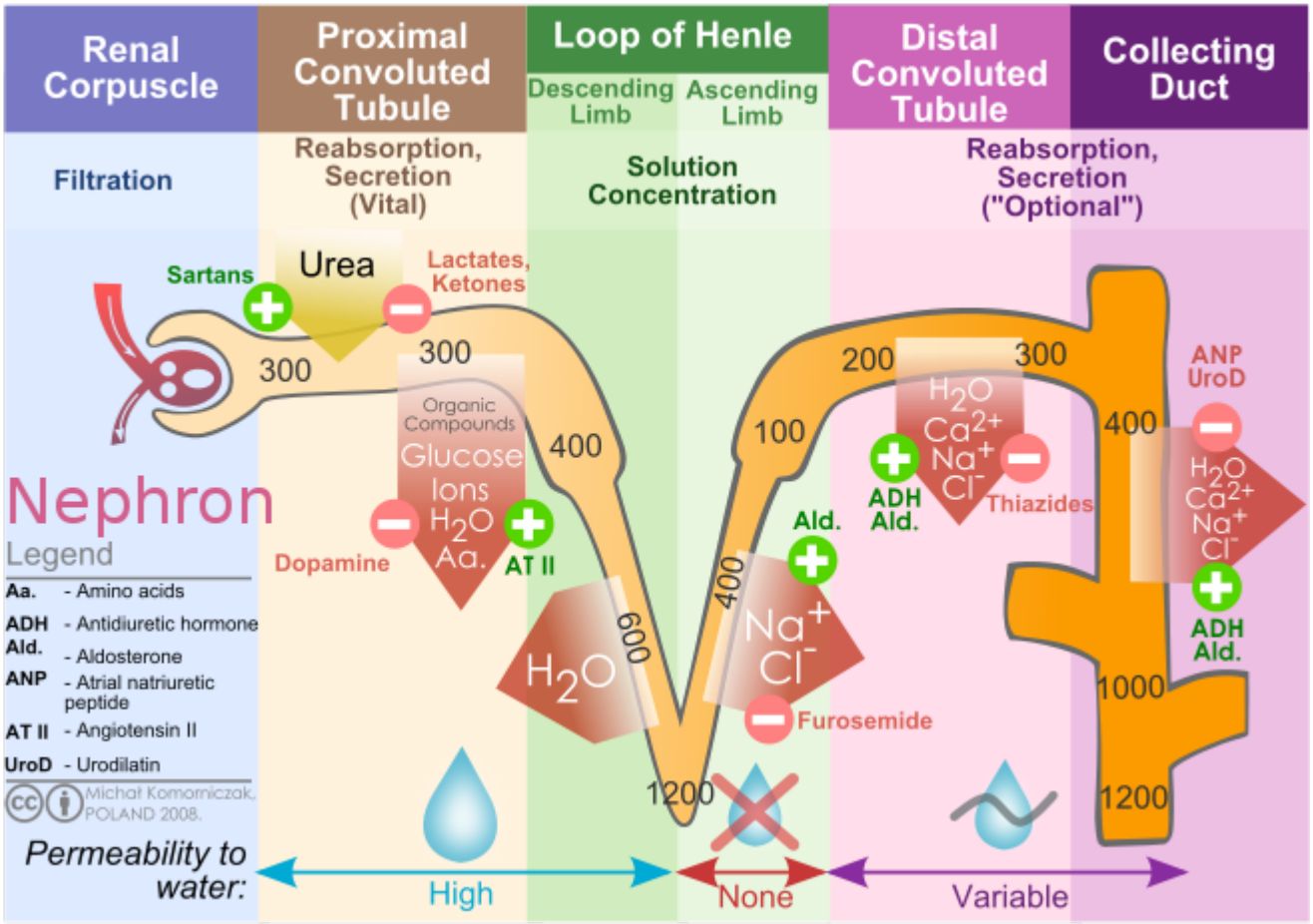
normal **CCRCC** **ChRCC**

Widespread differences between ChRCC and CCRCC

Shen H
Laird P

Anatomy of the kidney nephron

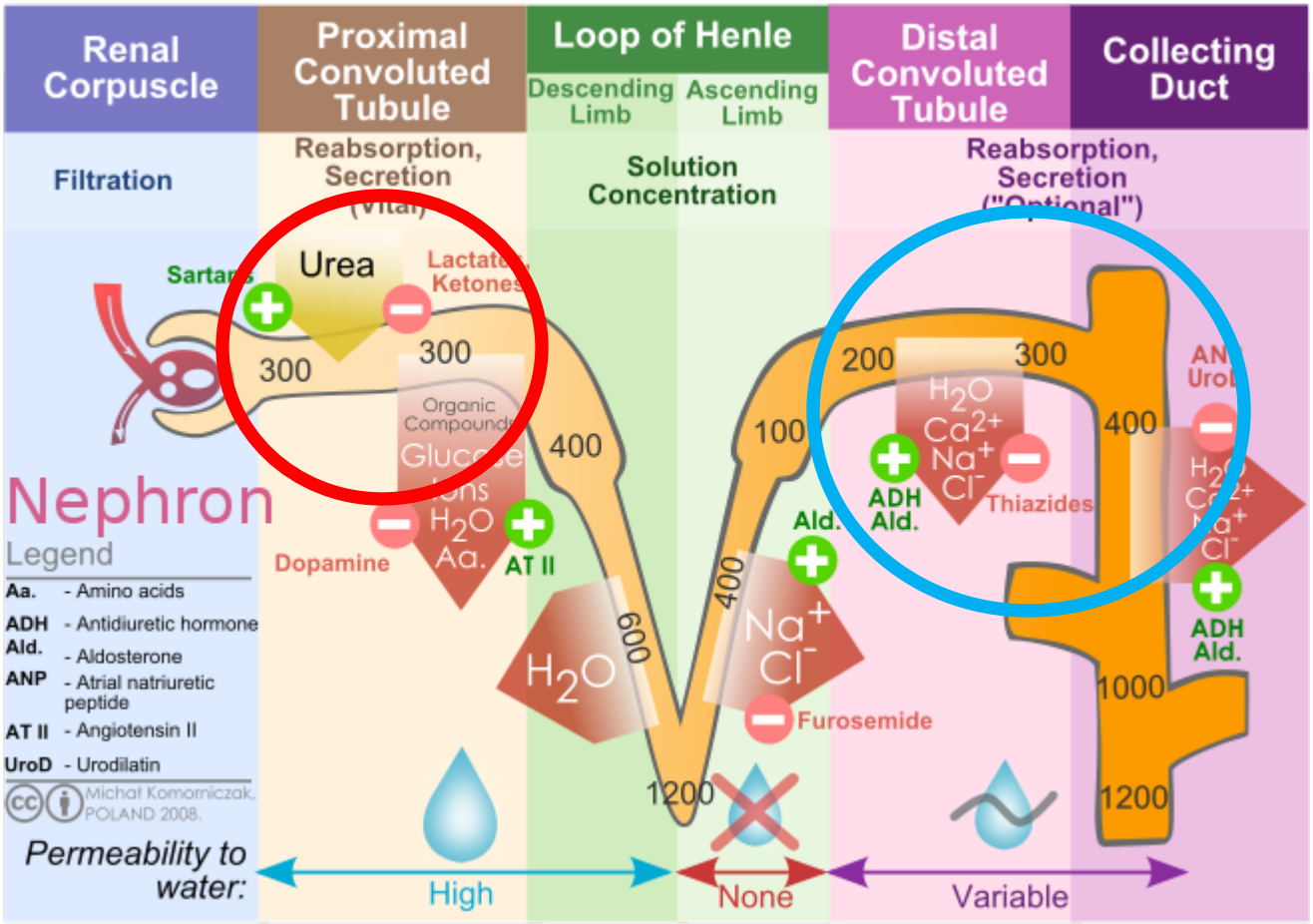
proximal **distal**



http://en.wikipedia.org/wiki/File:Kidney_nephron_molar_transport_diagram.svg

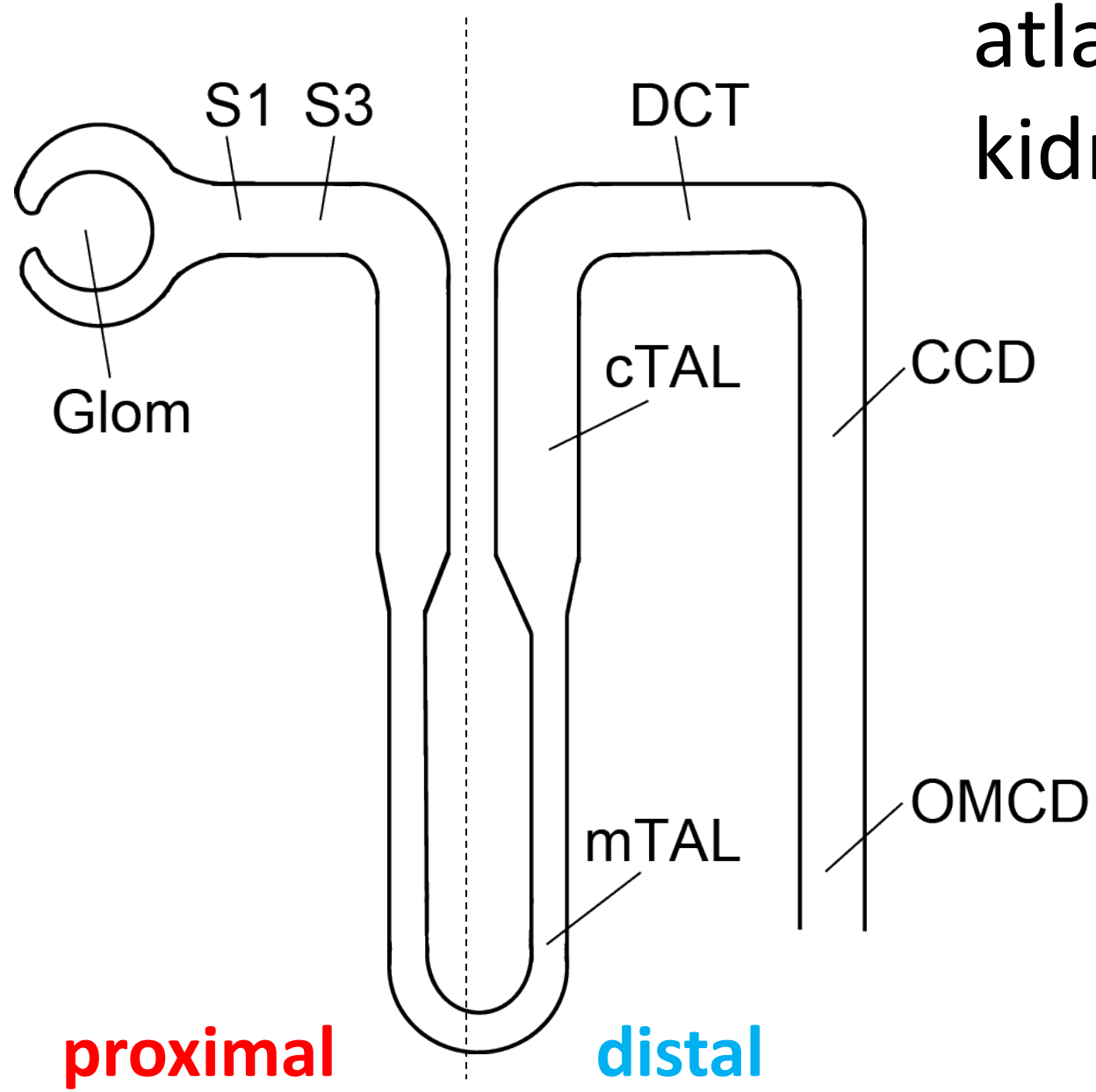
Anatomy of the kidney nephron

proximal **distal**



CCRCC? **ChRCC?**

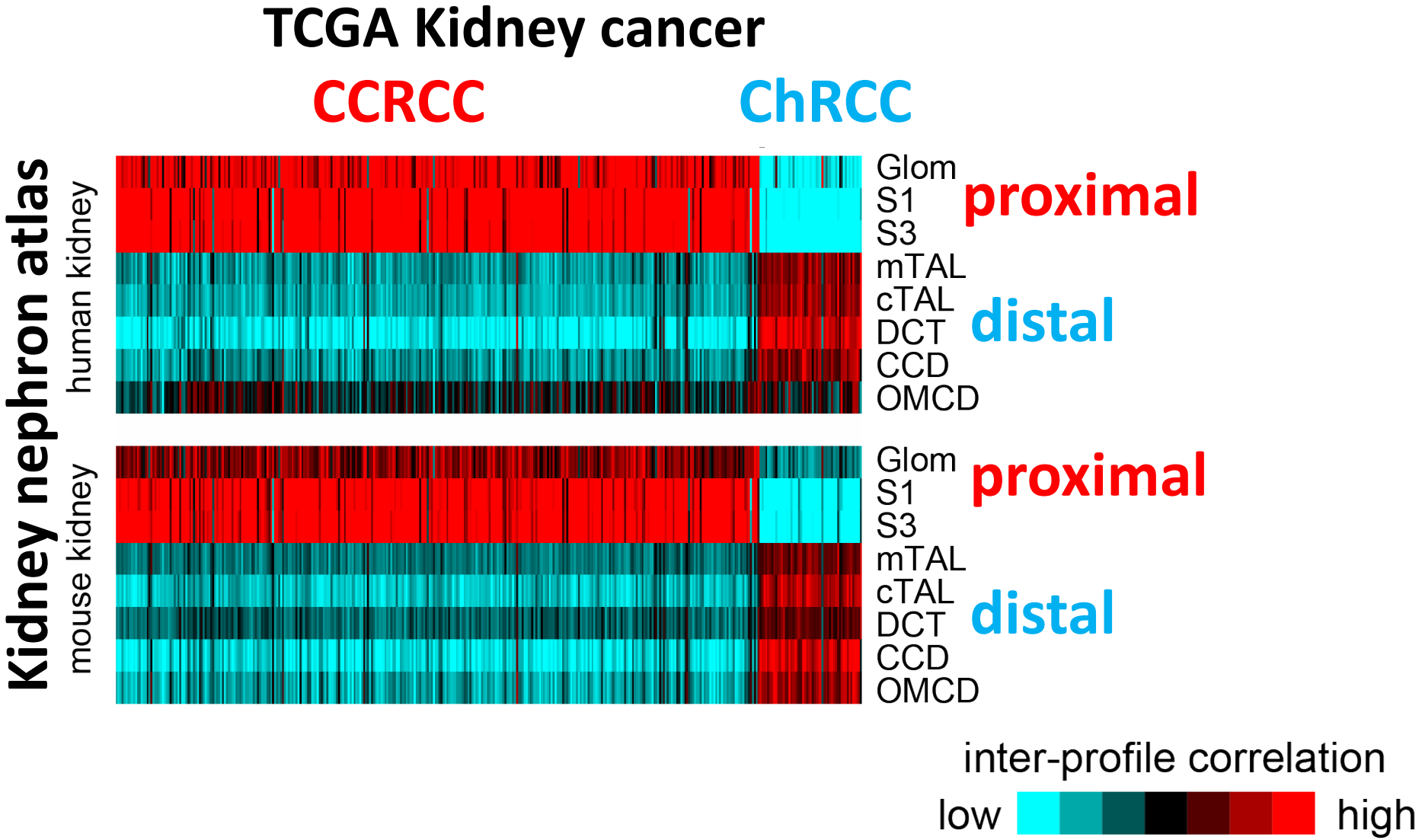
Gene expression atlas of the kidney nephron



Published mRNA profiling dataset of micro-dissected regions (mouse and human)

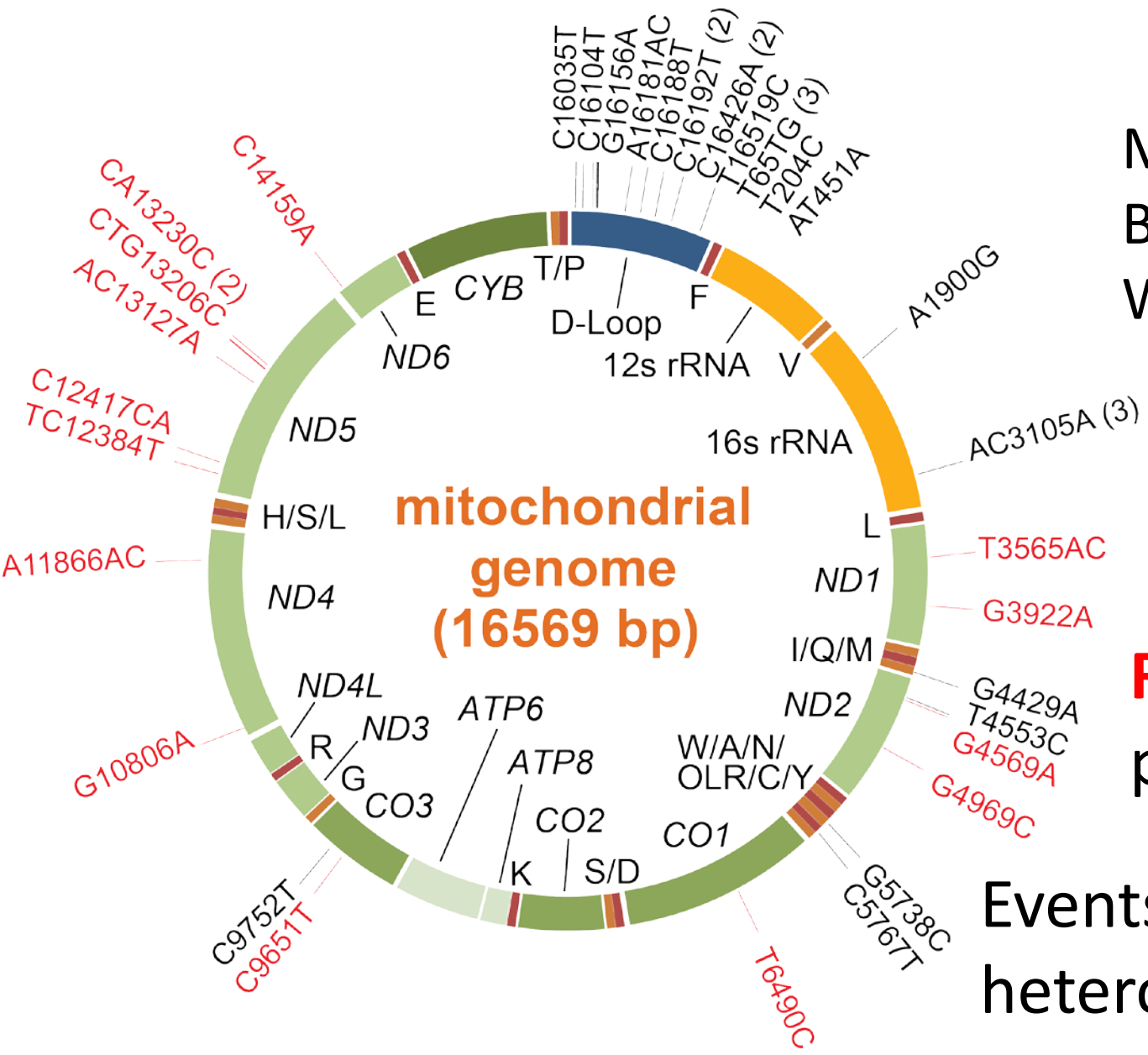
Cheval et al.
PLOS One 2012

ChRCC versus CCRCC expression differences reflect distal versus proximal nephron



Mitochondrial DNA alterations

mtDNA somatic mutations in ChRCC



Muzny D,
Buhay C
Wang M

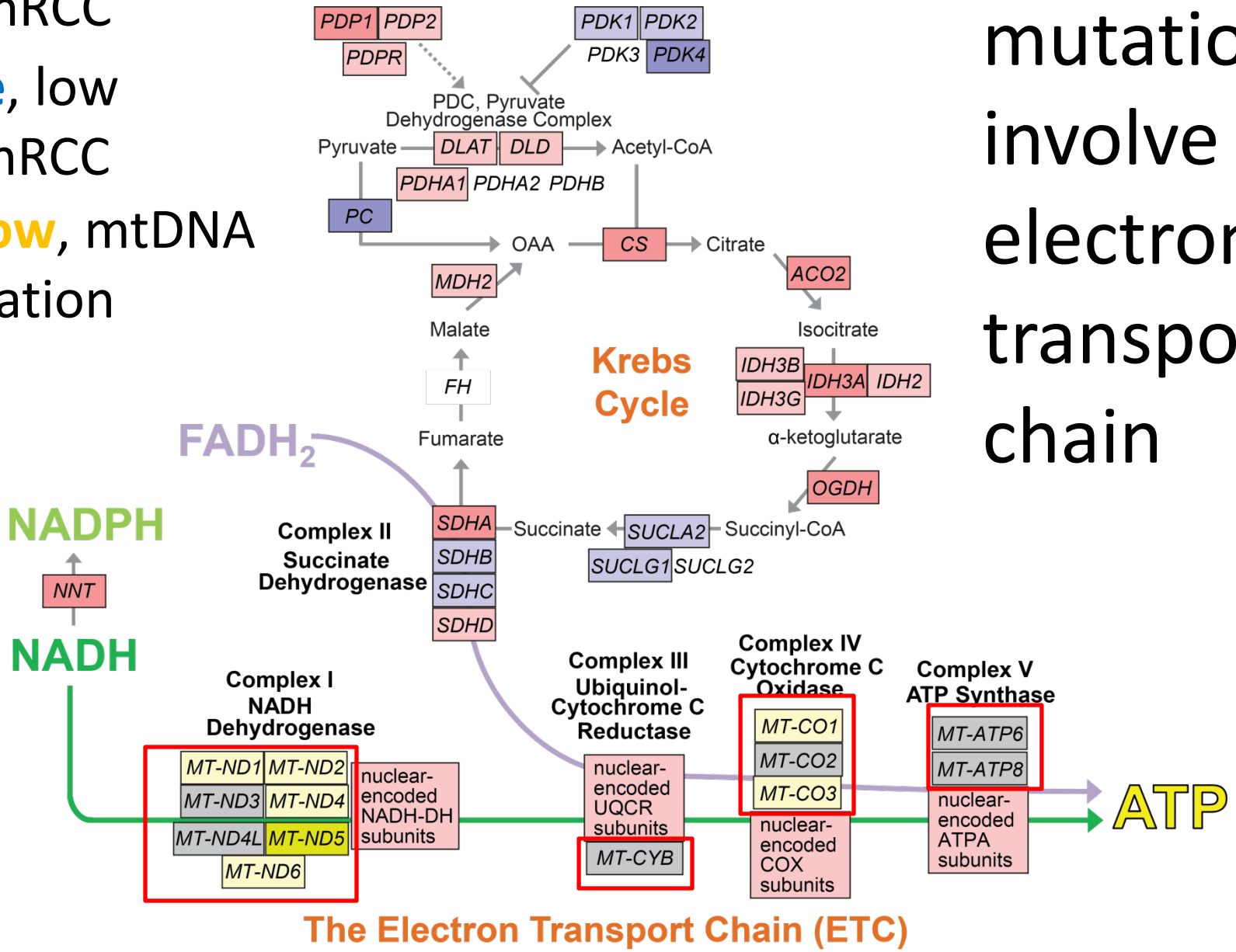
Red, affects protein coding

Events with >50% heteroplasmy shown

Red, high in ChRCC

Blue, low in ChRCC

Yellow, mtDNA mutation



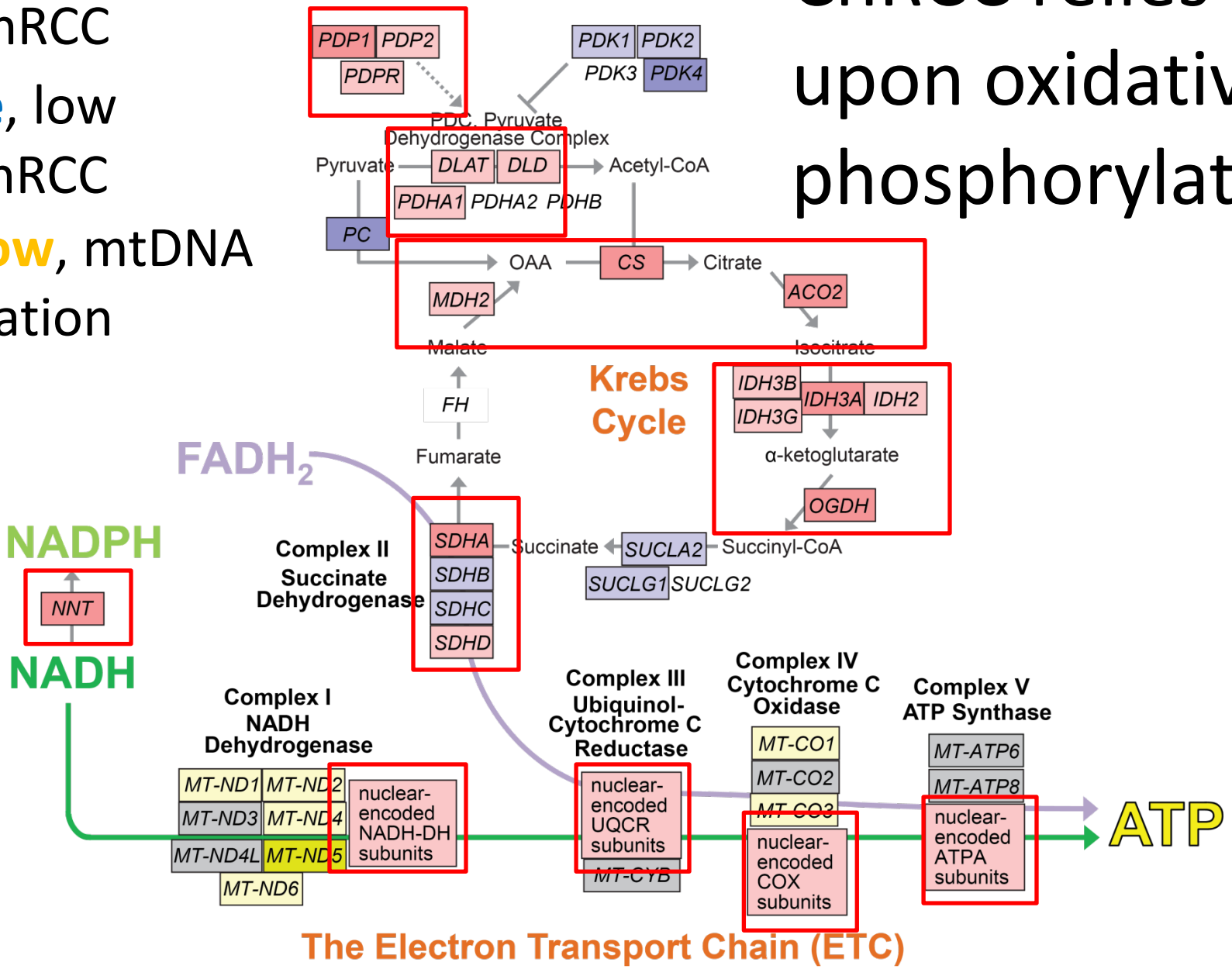
mtDNA mutations involve the electron transport chain

Red, high in ChRCC

Blue, low in ChRCC

Yellow, mtDNA mutation

ChRCC relies upon oxidative phosphorylation



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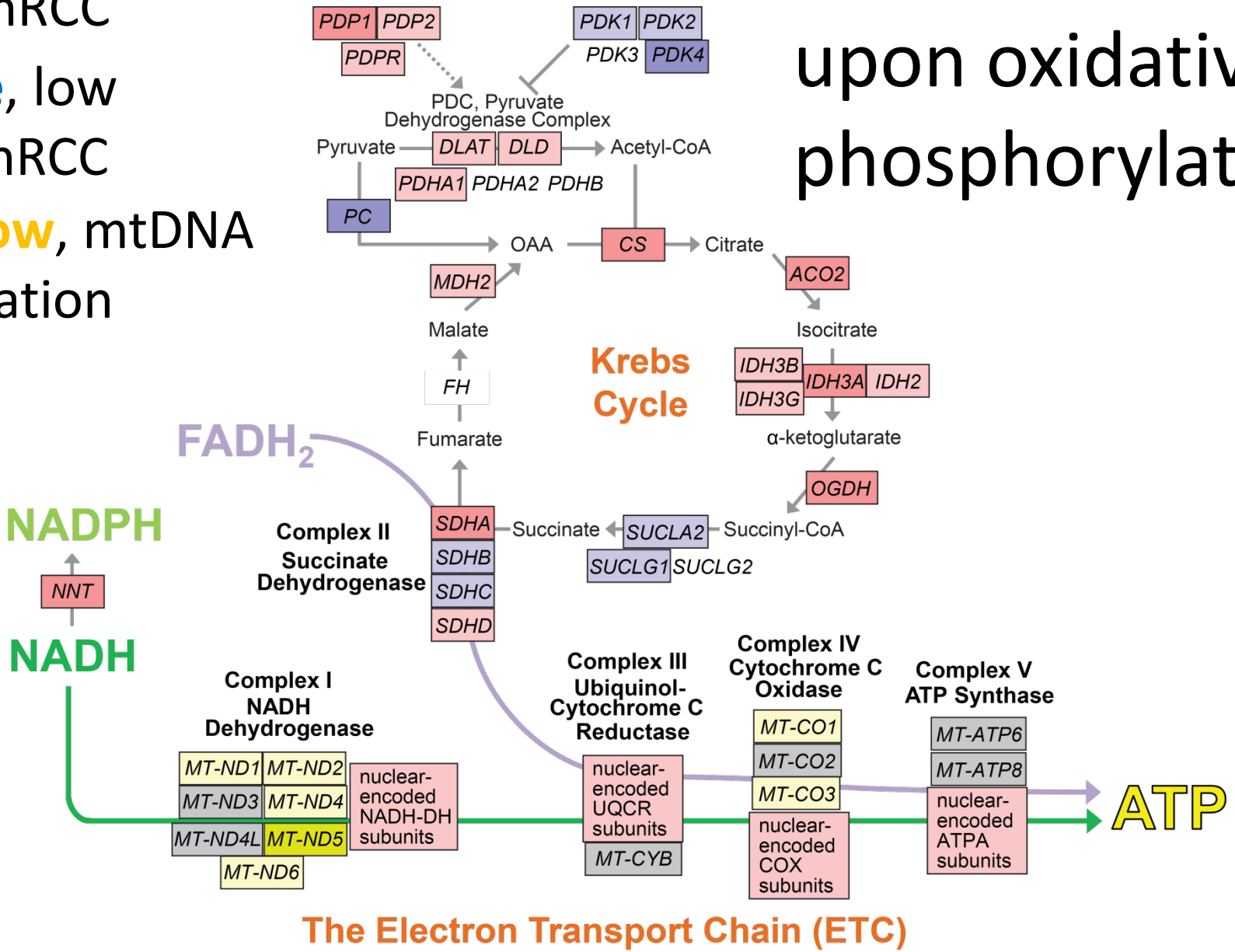
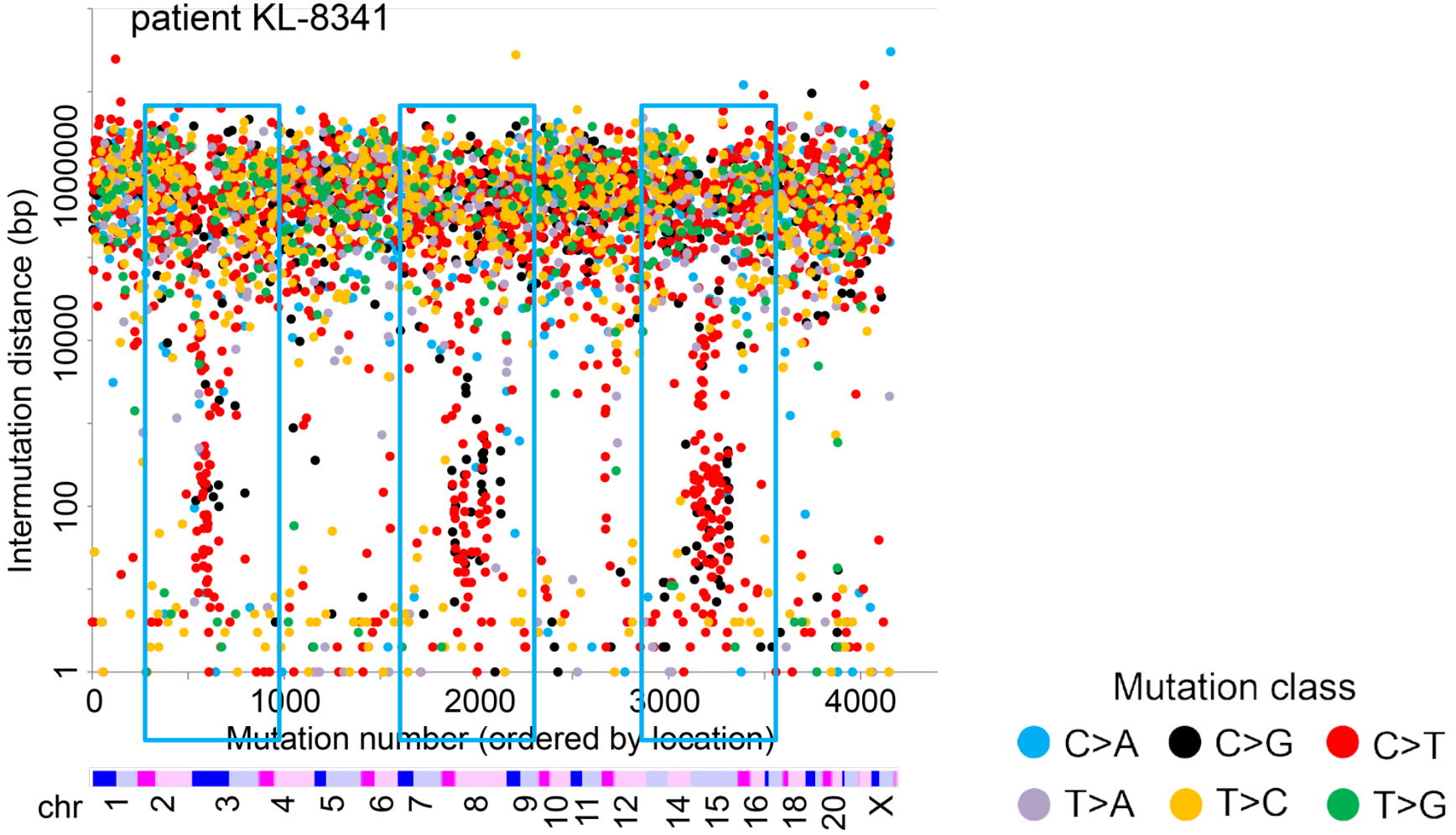


Whole Genome Analysis

Kataegis observed in ChRCC

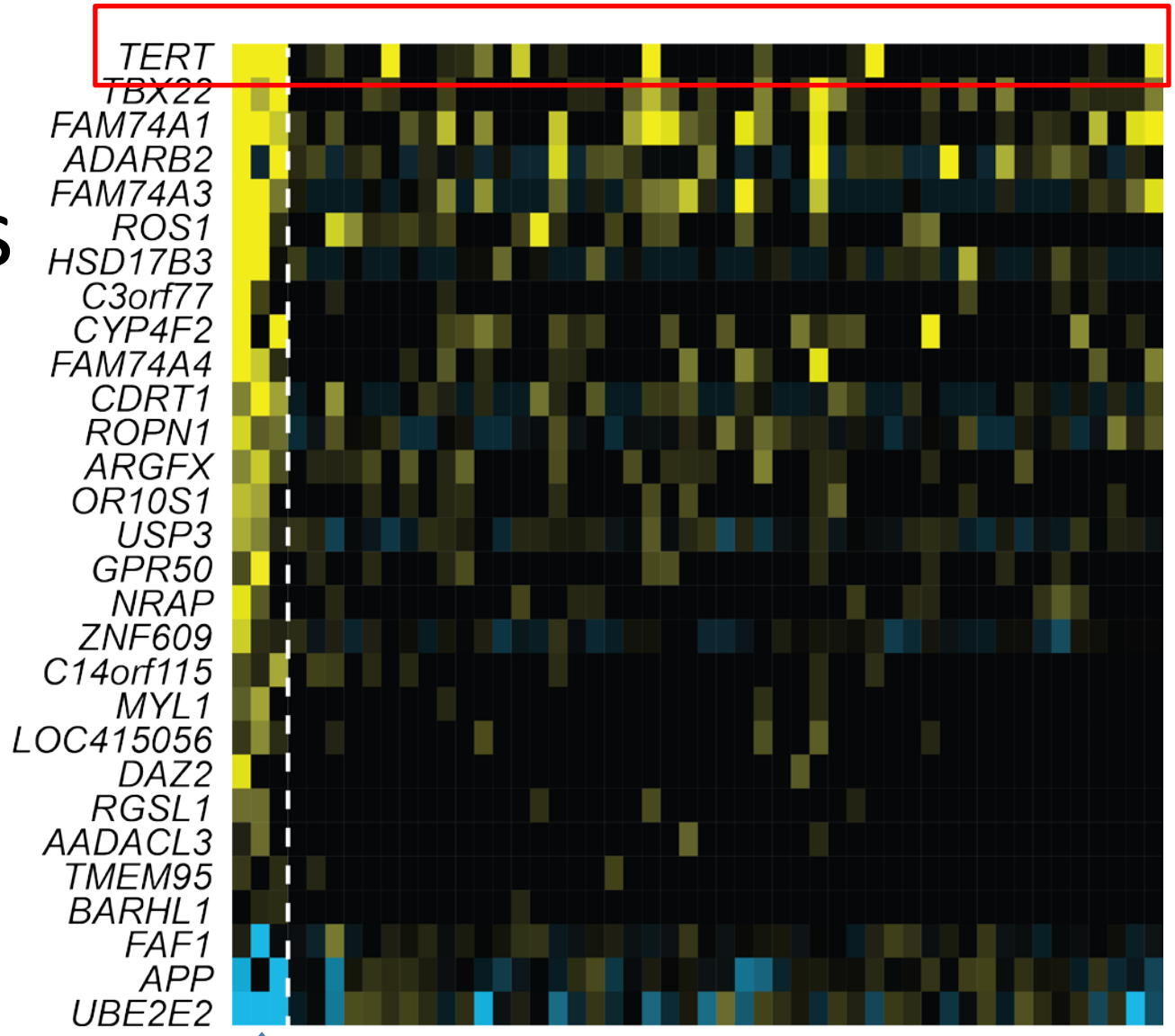


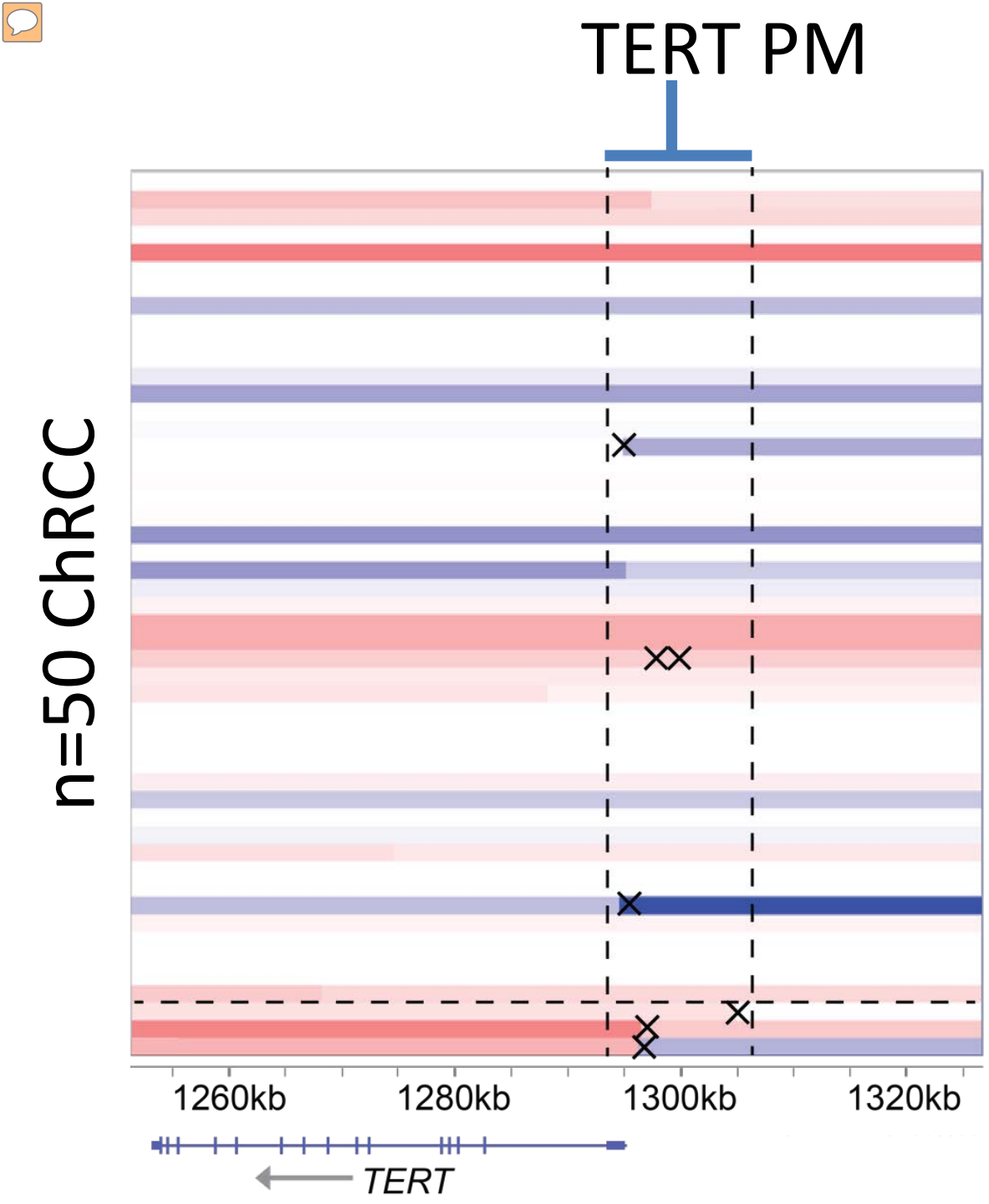
Davis C, Wheeler D

mRNA correlates of kataegis

Creighton C,
Davis C

Includes TERT





Structural breakpoints within TERT promoter region

Copy gain

Copy loss

Breakpoint X

Davis C

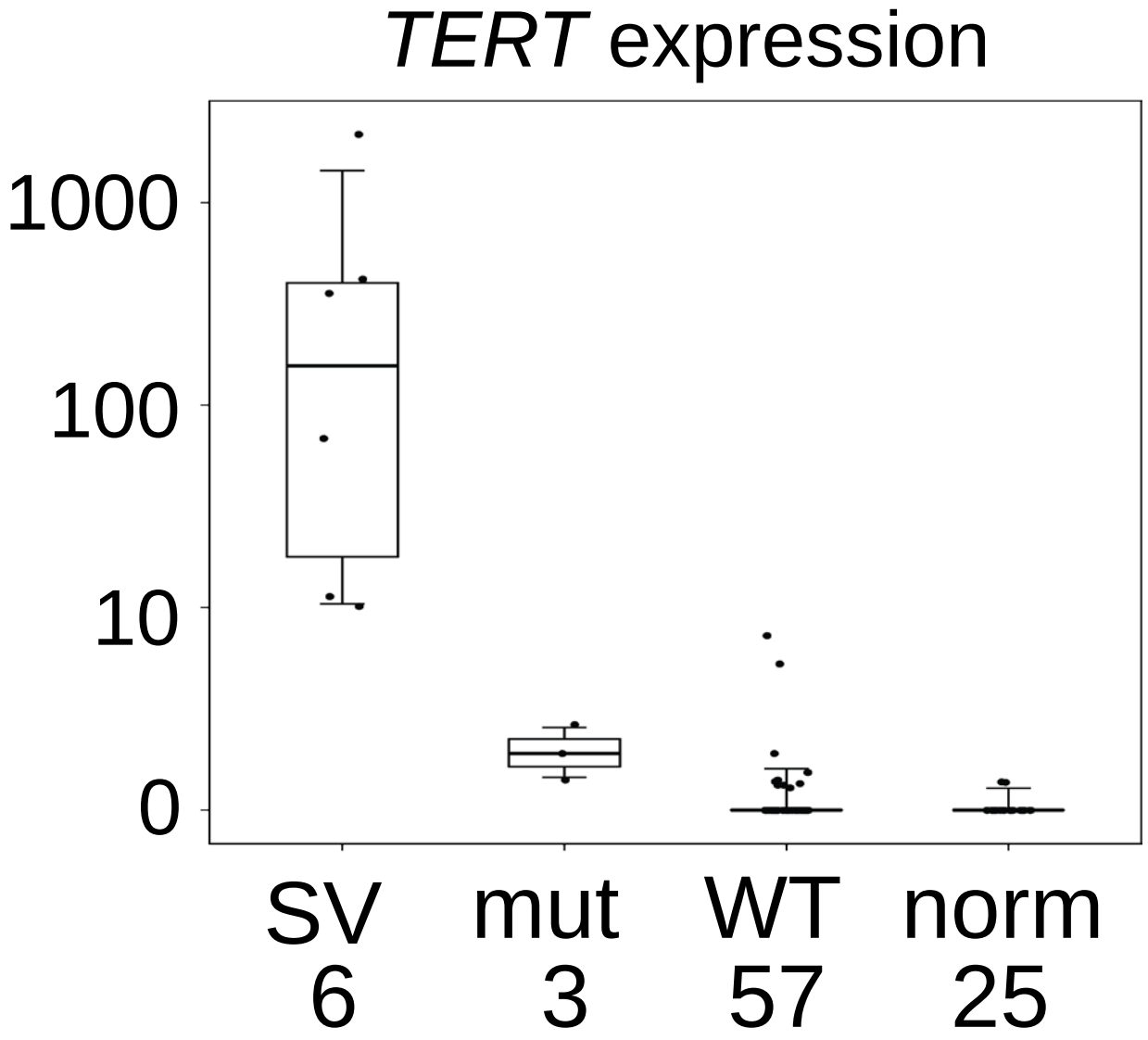
Structural variants associated with TERT promoter region by WGS analysis

	breakpoint A			breakpoint B			
case	***chr:pos***	***ori***	***gene***	***chr:pos***	***ori***	***gene***	***event type***
KL-8341	5:1116986	-1		5:1296148	1	TERT PM	tandem dup.
KN-8435	5:272199	1	PDCD6	5:1296716	1	TERT PM	inversion
KM-8438	5:1348783	-1		5:1295372	1	TERT PM	deletion
KL-8346	5:1125430	-1		5:1295604	1	TERT PM	tandem dup.
KL-8323	5:49560803	1		5:1299528	-1	TERT PM	tandem dup.
KL-8323	5:49563017	-1		5:1297603	1	TERT PM	del-insertion
KM-8443	13:52688659	1	NEK5	5:1305300	1	TERT PM	Inter-chr transl.

Davis C, Wang L, Park P

Meerkat algorithm

TERT promoter-associated SVs correlate with high TERT expression



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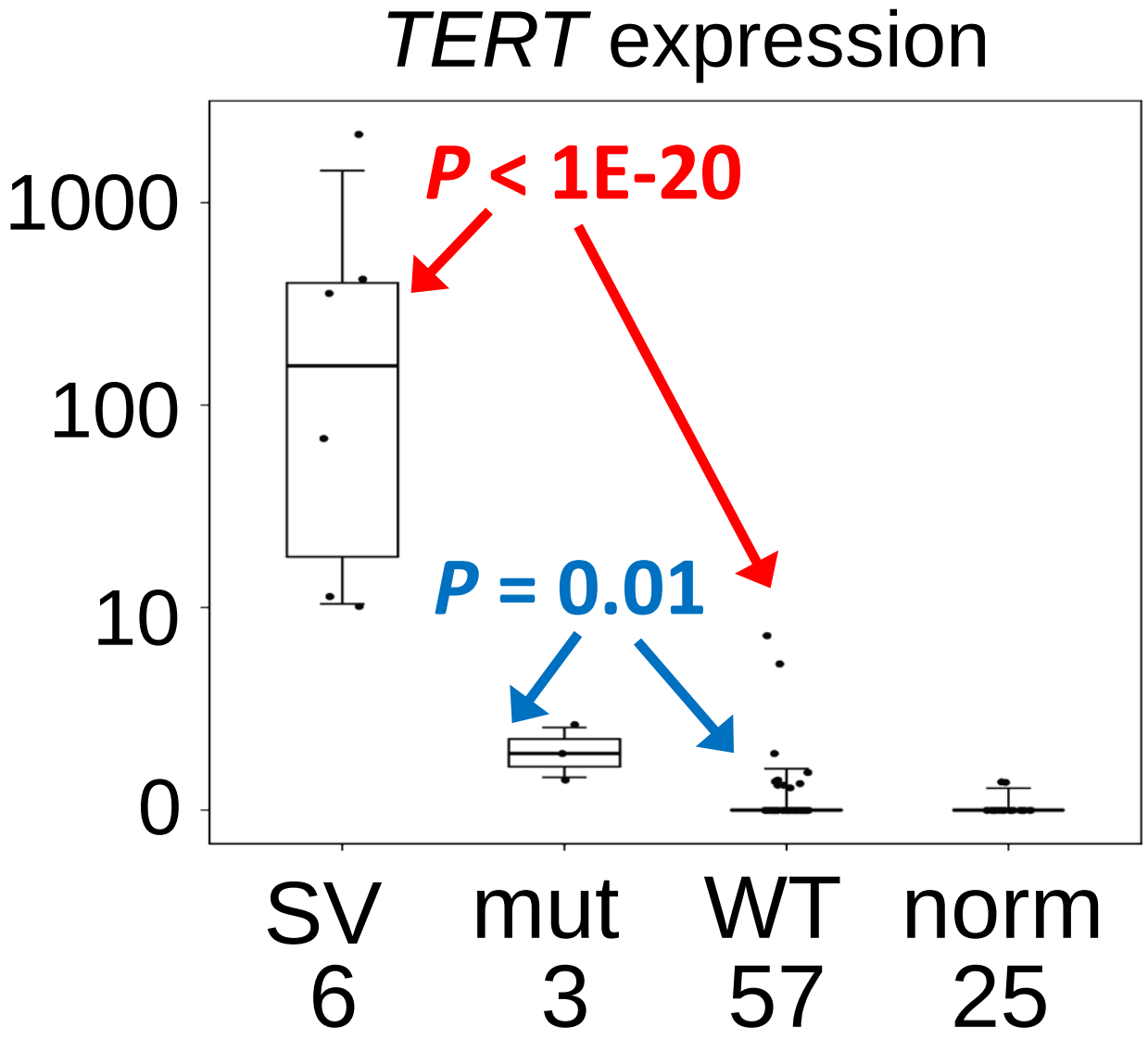
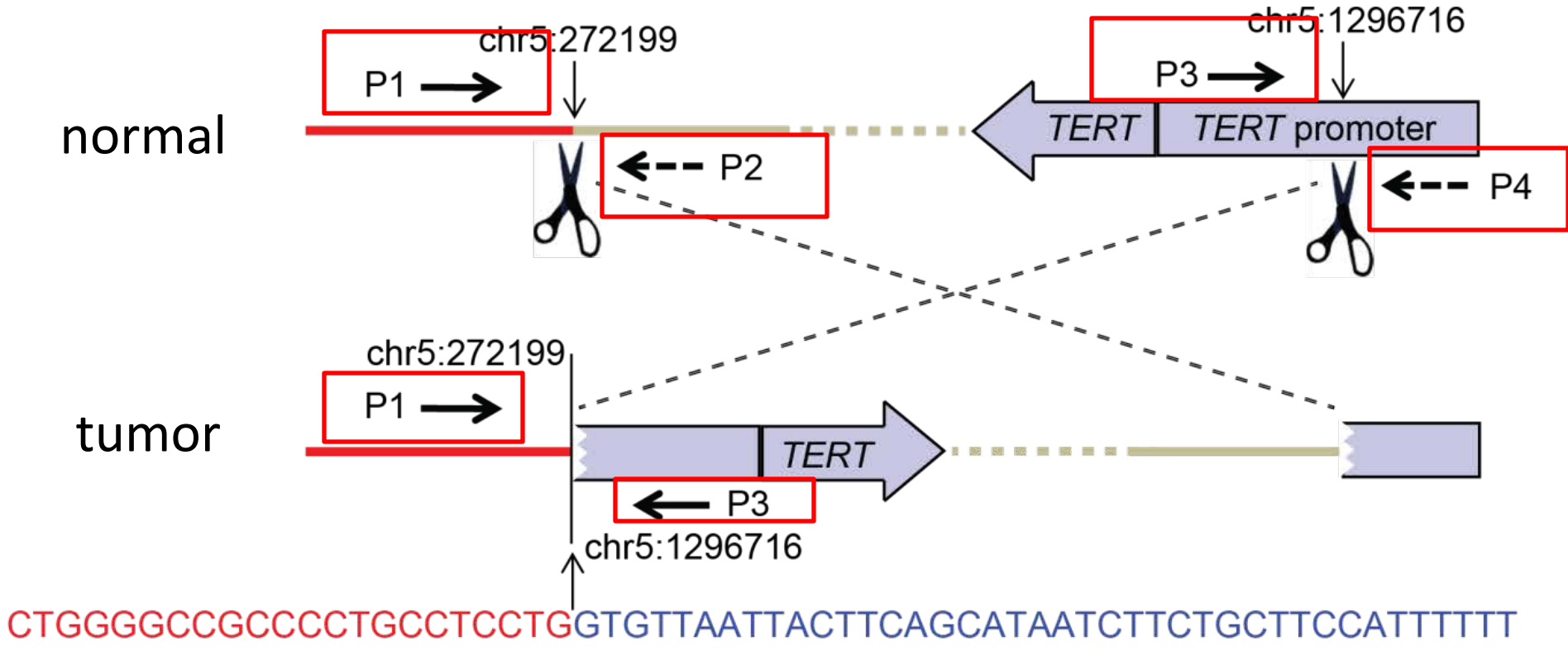


Validation of TERT PM-associated SVs

KN-8435 (inversion)



Wang M, Muzny D

Validation of TERT PM-associated SVs

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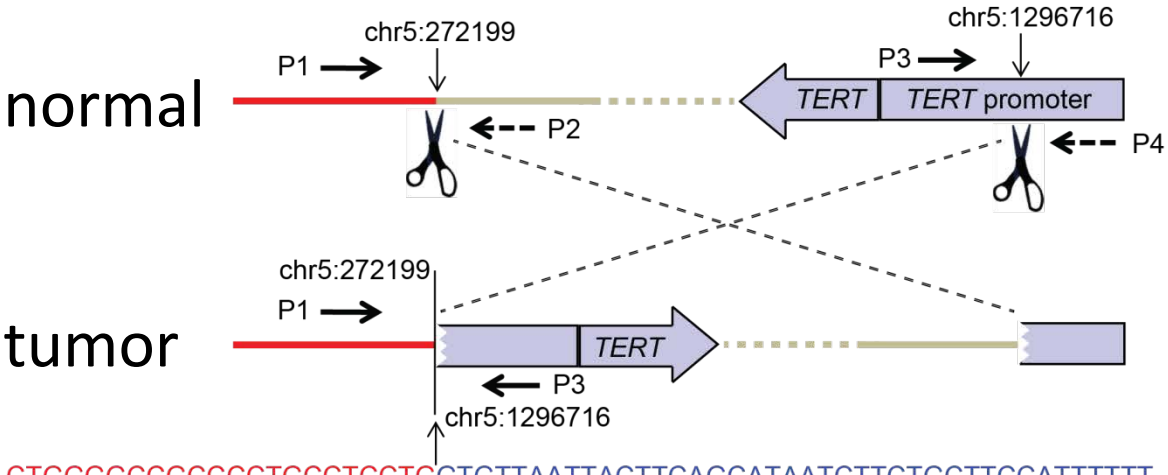

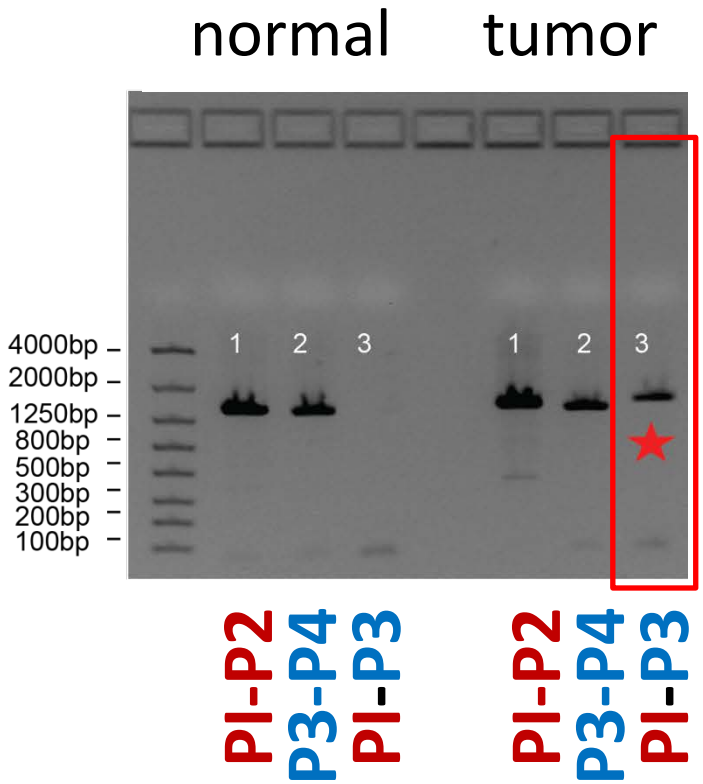

Wang M, Muzny D

Conclusions

- Comprehensive molecular analysis of a rare cancer type as a platform for discovery
- Global molecular patterns may provide clues as to a cancer's cell of origin
- mtDNA sequencing incorporated into multi-platform molecular characterization of cancer
- Discovery of recurrent genomic rearrangements involving TERT promoter region

KICH Analysis Working Group

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Preethi Gunaratne	Baylor
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Andy Chu	BCGSC
Andrew Mungall	BCGSC
Payal Sipahimalani	BCGSC
Andrew Cherniack	Broad
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Eric Wallen	UNC
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Kate Hacker	UNC
Gyan Bhanot	Rutgers
Peter Laird	USC

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