TCGA Clear Cell Renal Cell Carcinoma Project

TCGA KIRC AWG

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Background

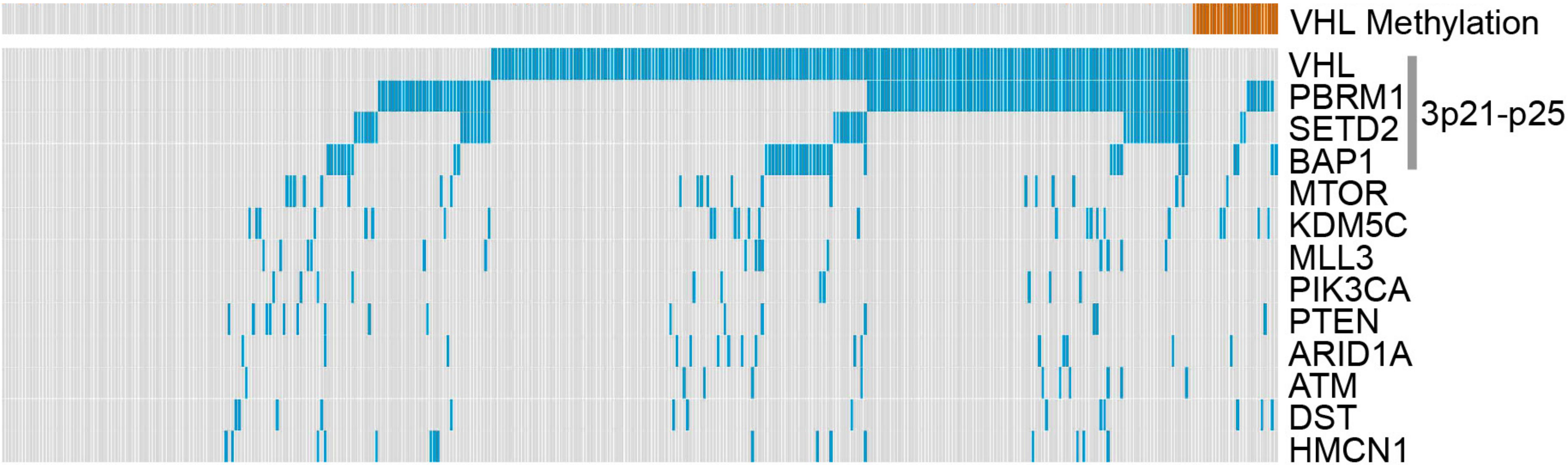
- Genetic changes underlying clear cell renal cell carcinoma (ccRCC) include alterations in genes controlling cellular oxygen sensing (e.g. *VHL*) and the maintenance of chromatin states (e.g. *PBRM1*).
- For 446 ccRCC cases, TCGA evaluated clinical and pathological features, genomic alterations, DNA methylation profiles, and RNA and proteomic signatures.

Data summary

Data Type	Platforms	Cases	Data access
Whole exome DNA sequence	Illumina and SOLiD	430	Controlled
Whole genome DNA sequence	Illumina	33	Controlled
DNA copy number/genotype	Affymetrix SNP 6	441	Controlled
mRNA expression	Illumina	417	Controlled - BAM files Open - expression files
miRNA expression	Illumina	414	Controlled - BAM files Open - expression files
CpG DNA methylation	Illumina 27K	192	Open
	Illumina 450K	253	Open
Protein expression	RPPA	411	Open
Freeze 1.4 (Core)	All Platforms	372	
Freeze 1.4 (Extended)	At least one platform	74	
Total Cases		446	

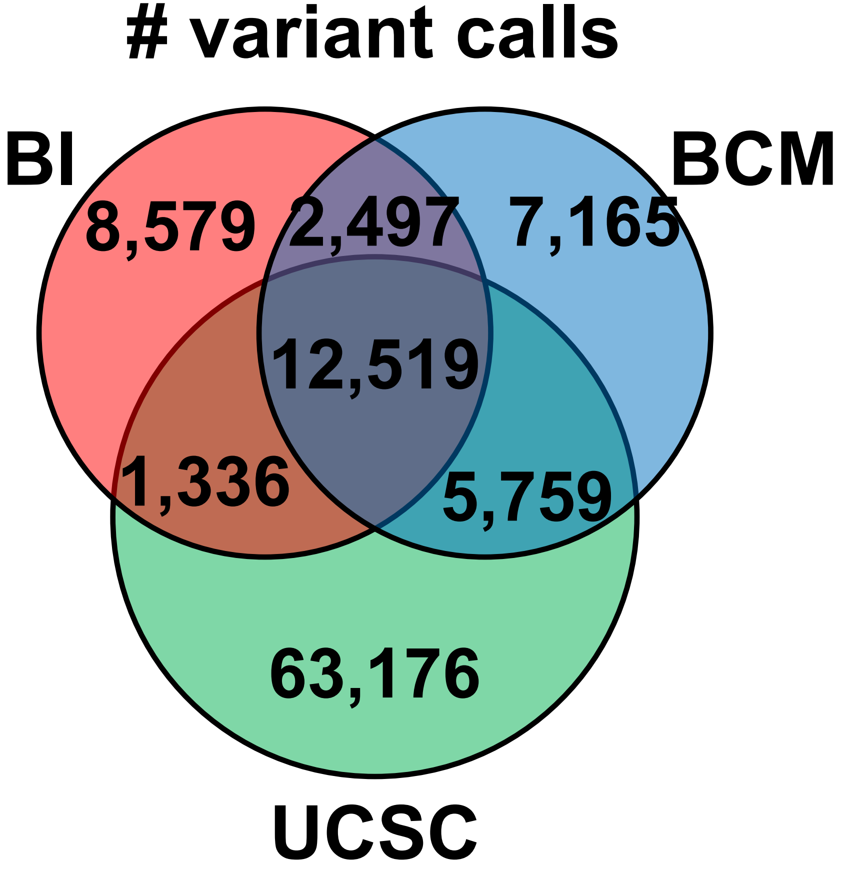
Significantly mutated genes

372 ccRCC tumor samples



Verhaak R, Wheeler D, TCGA

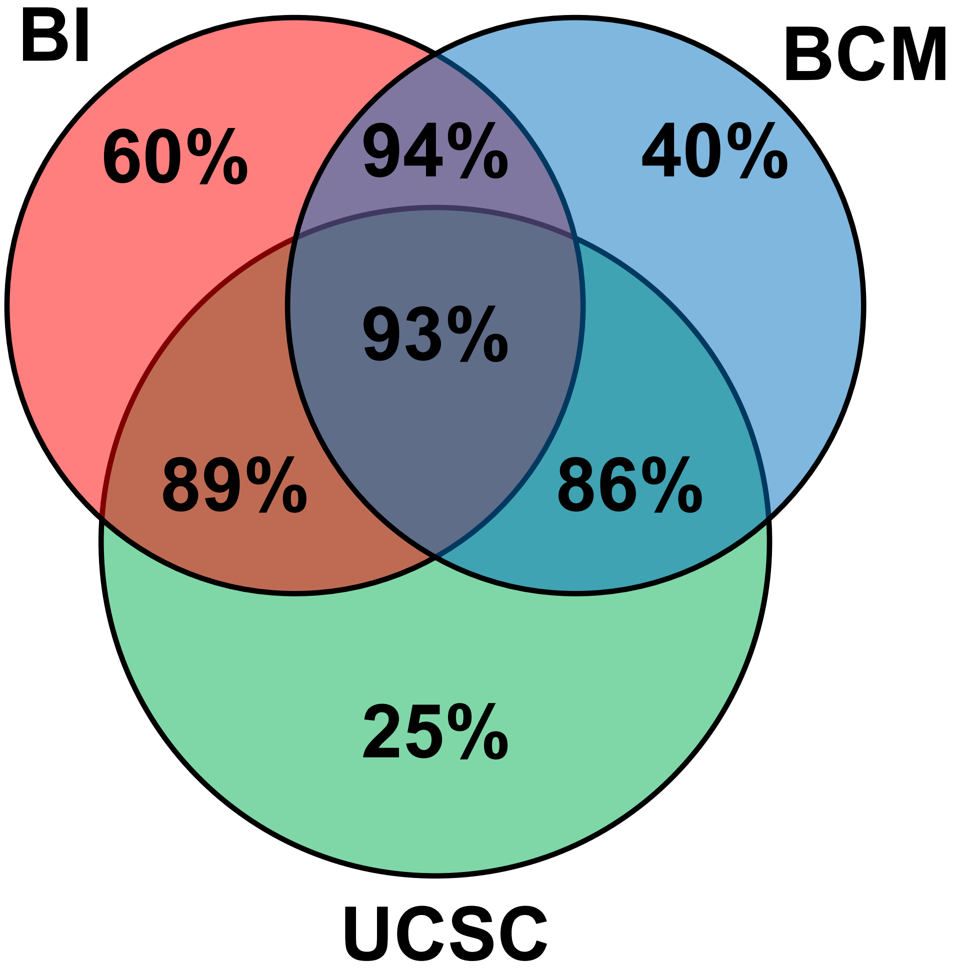
Somatic mutations called by three centers



Poster #114

Howe C, Liu X, Chang K, Wheeler D, TCGA

Corresponding validation rates



Poster #114

Howe C, Liu X, Chang K, Wheeler D, TCGA

Significantly mutated genes

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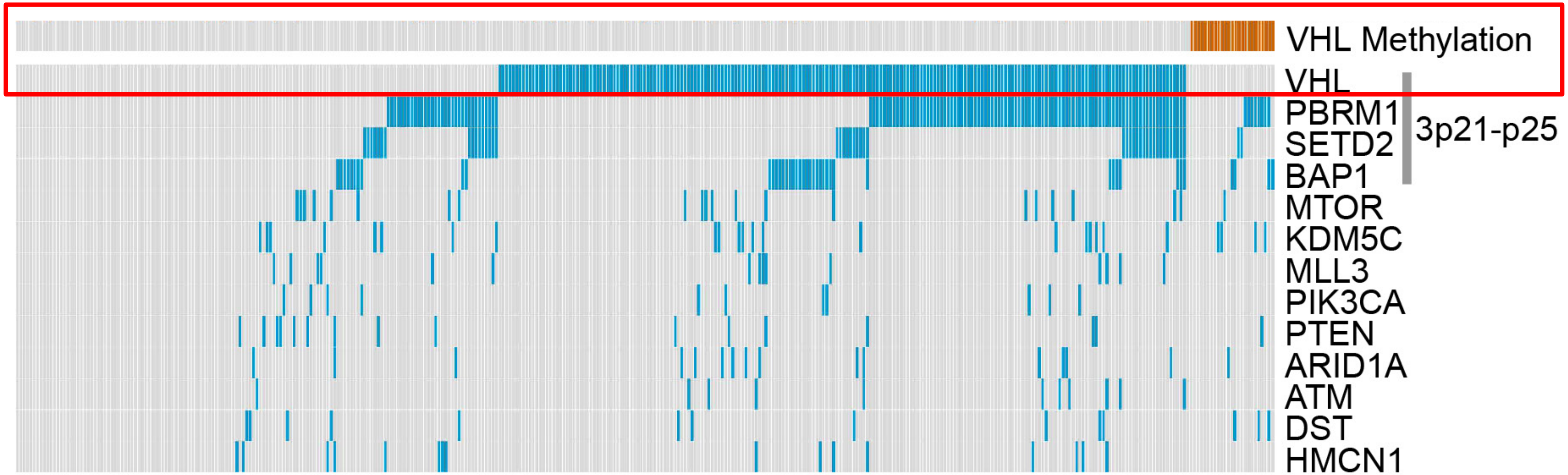
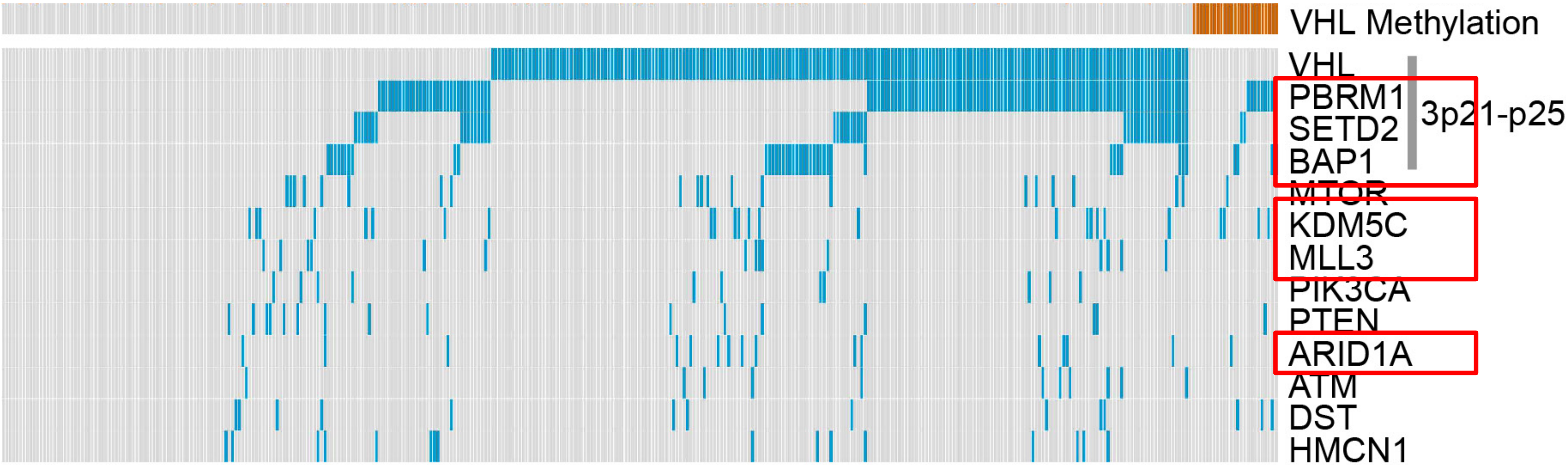


Frequent VHL alterations
(91% copy, 55% mutation, 7% methylation)

Verhaak R, Wheeler D, TCGA

Significantly mutated genes

372 ccRCC tumor samples

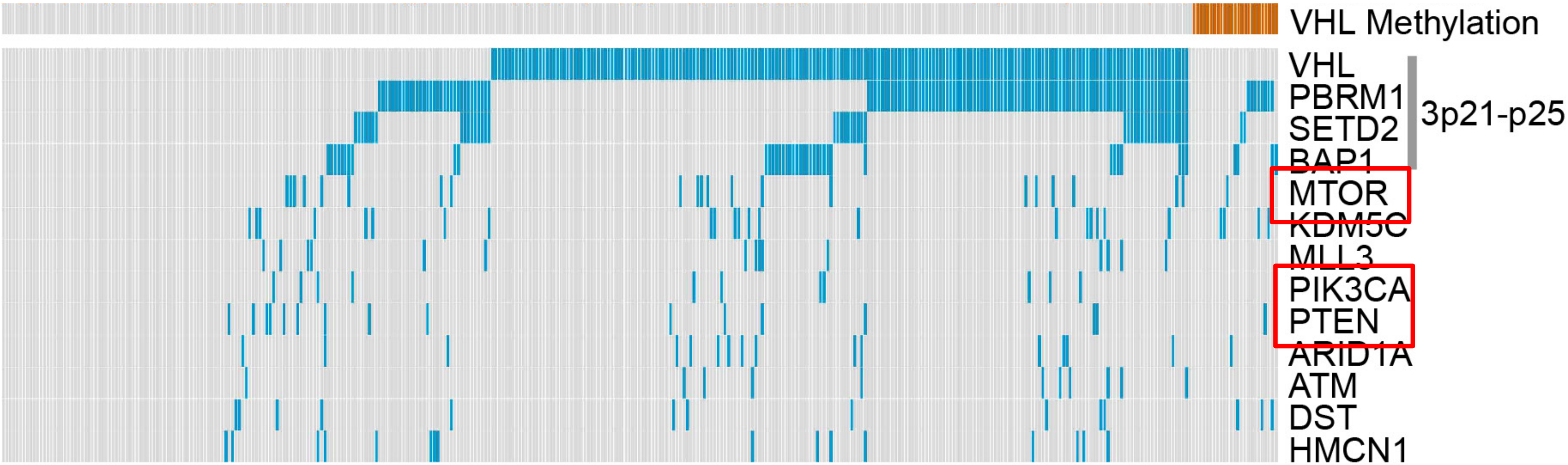


Mutations in chromatin regulators PBRM1, SETD2, BAP1, ARID1A

Verhaak R, Wheeler D, TCGA

Significantly mutated genes

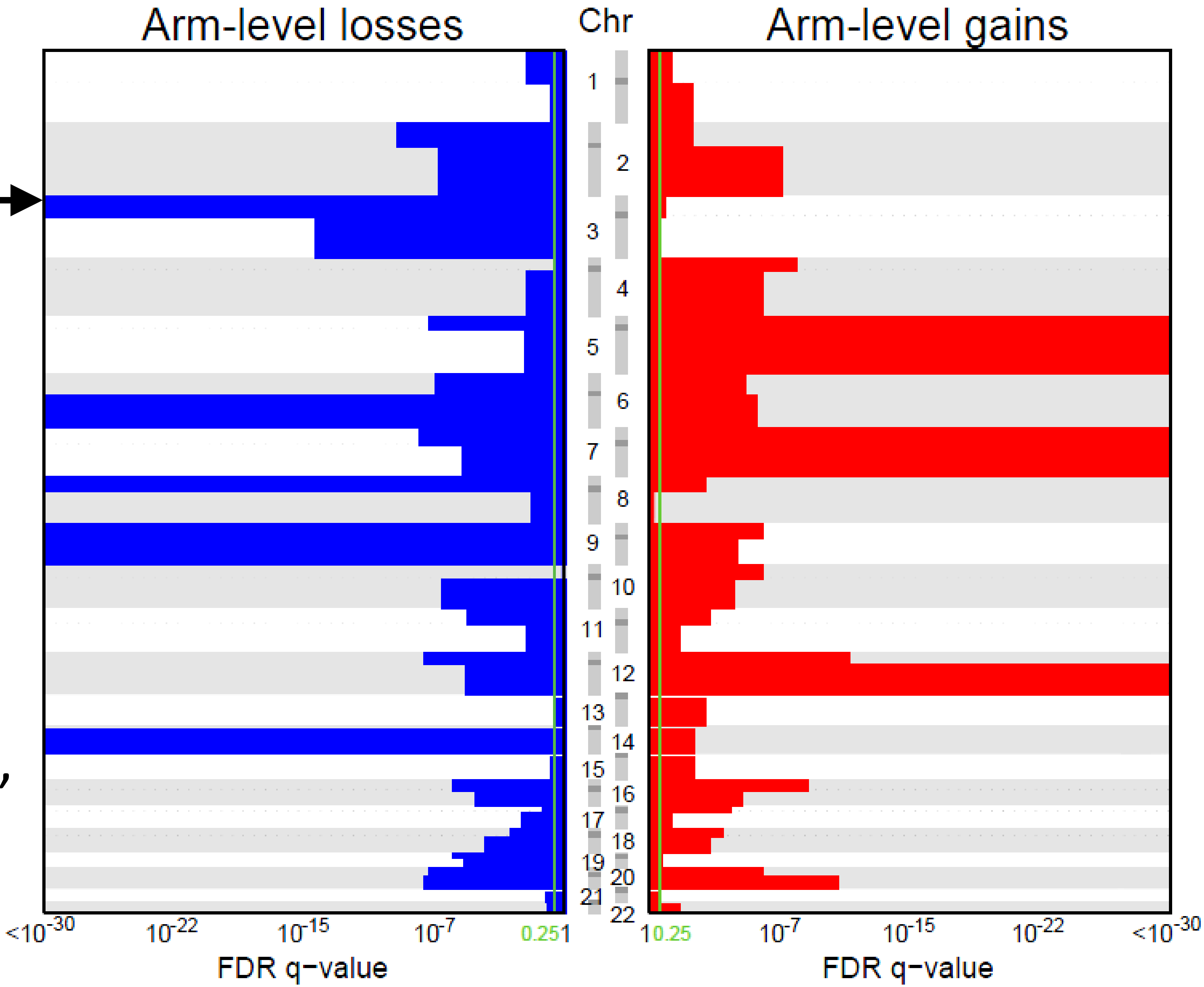
372 ccRCC tumor samples



Mutations in PI3K pathway regulators

Verhaak R, Wheeler D, TCGA

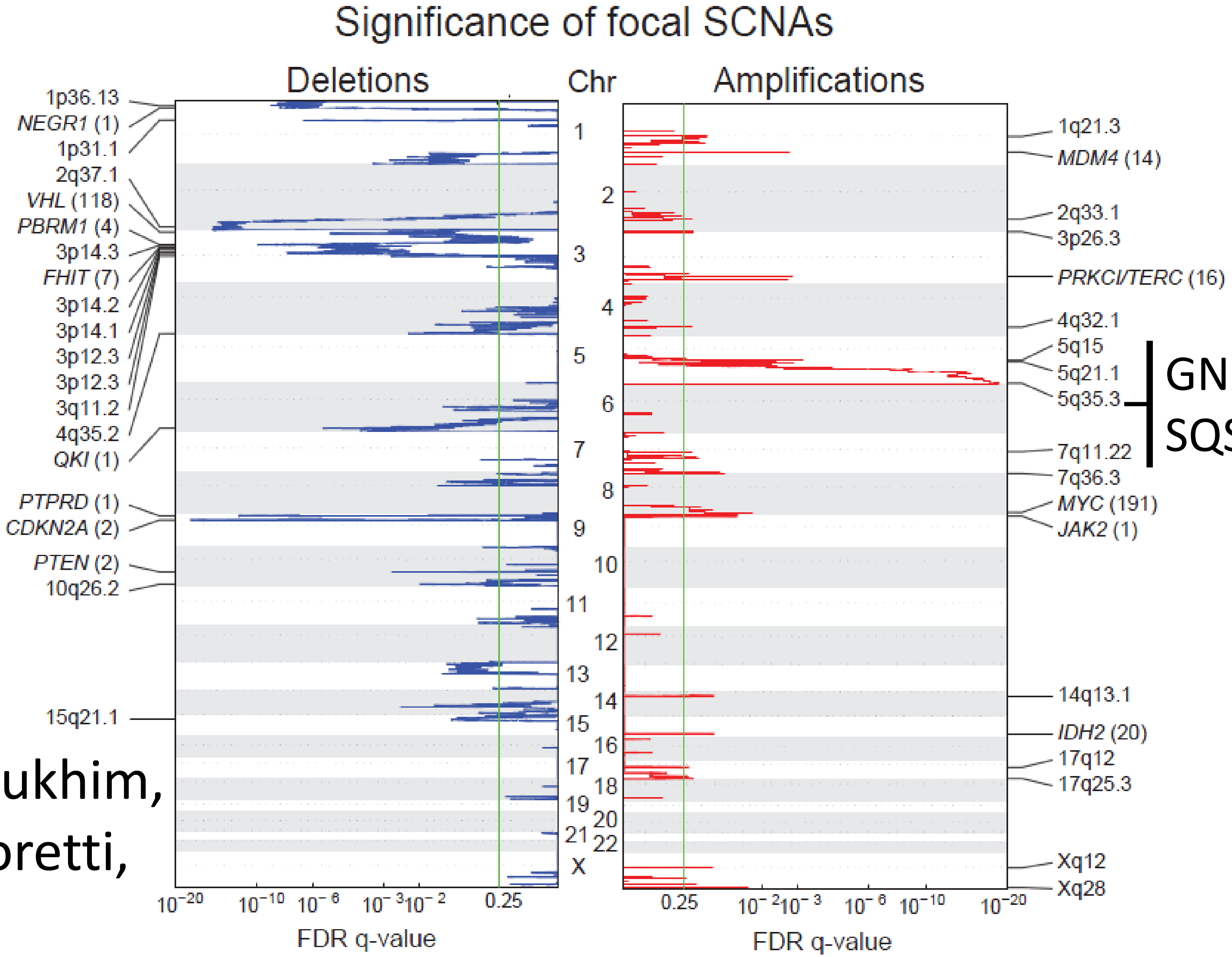
Copy number alterations



VHL
PBRM1
SETD2
BAP1

R Beroukhim,
S Signoretti,
TCGA

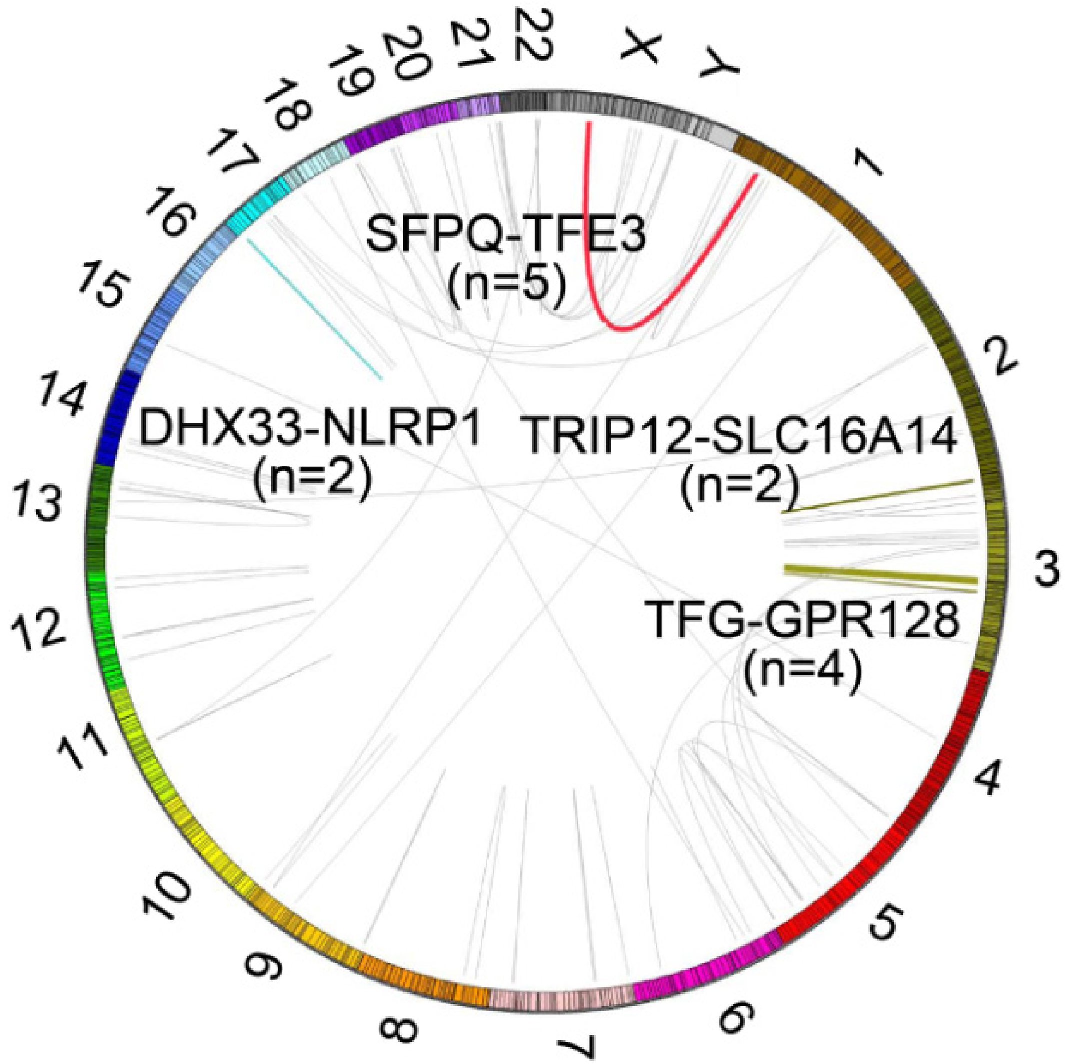
Copy number alterations



GNB2L1
SQSTM1

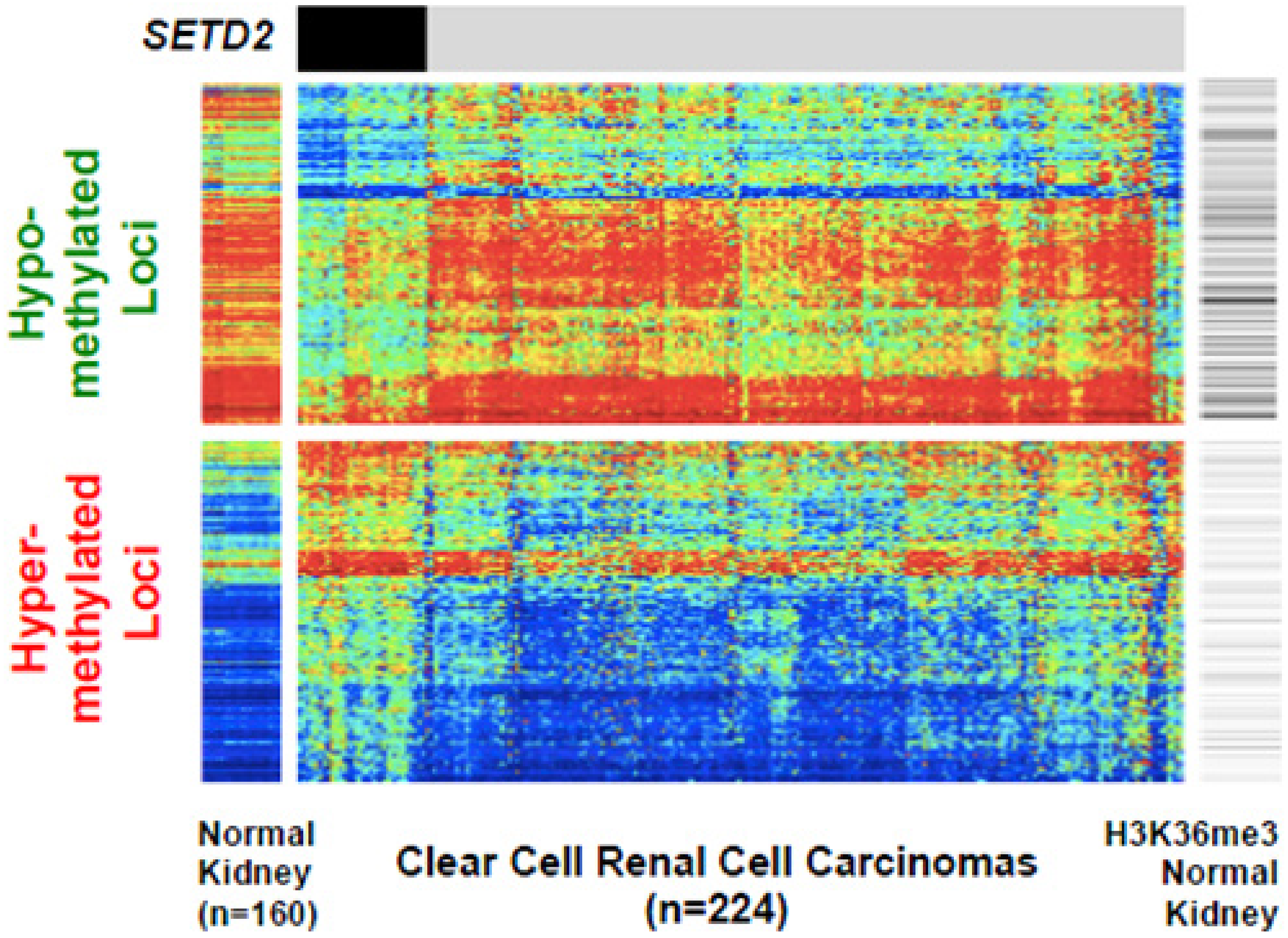
R Beroukhim,
S Signoretti,
TCGA

Recurrent fusion RNA transcripts



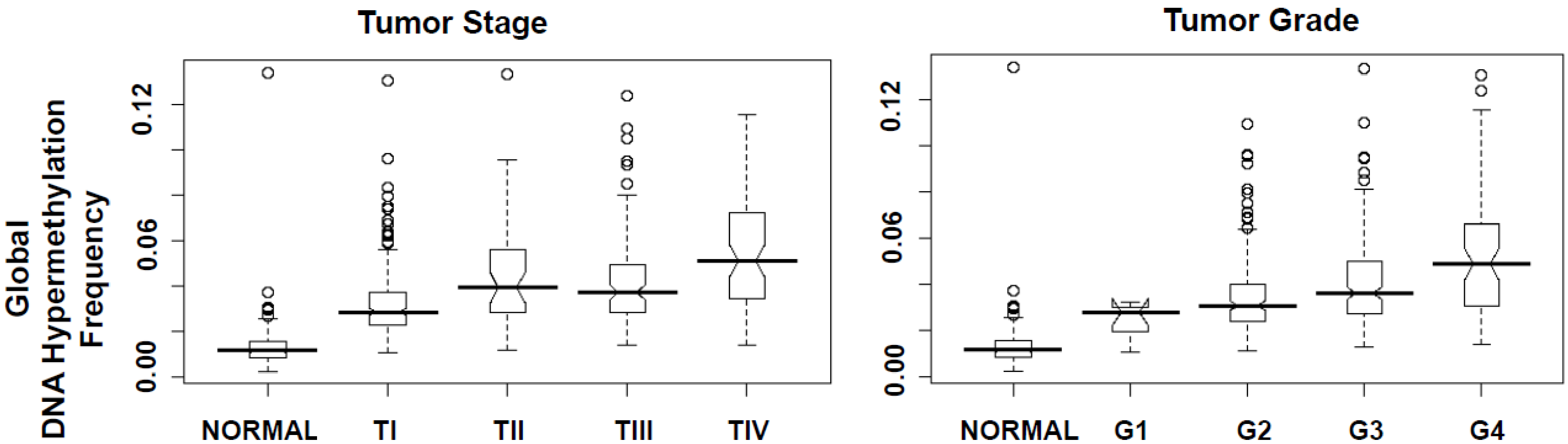
R Verhaak,
W Torres-Garcia,
TCGA

Widespread DNA hypomethylation associated with mutation of *SETD2*



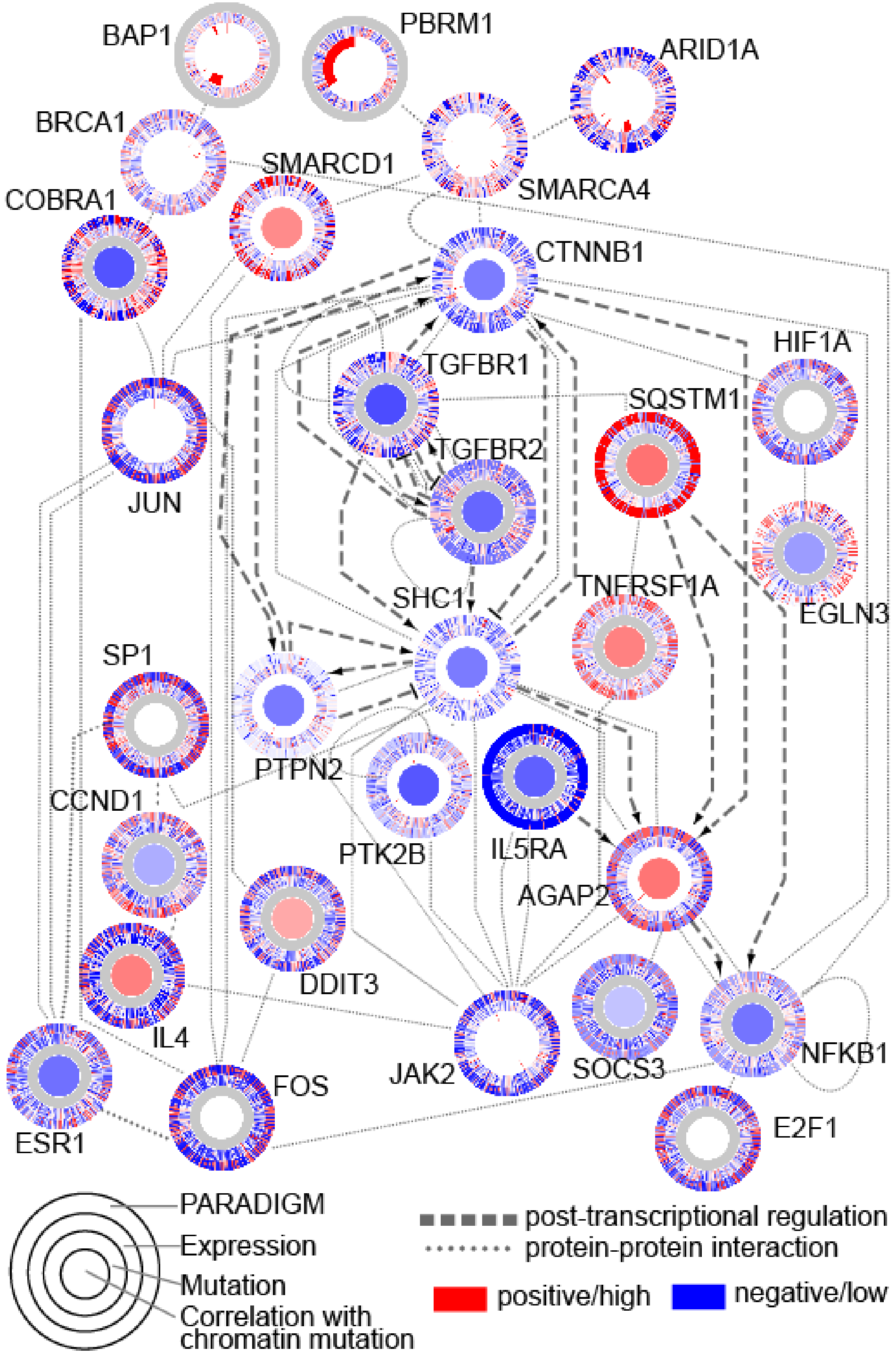
Shen H, Laird P, TCGA

DNA hypermethylation increases with advancing tumor stage and grade



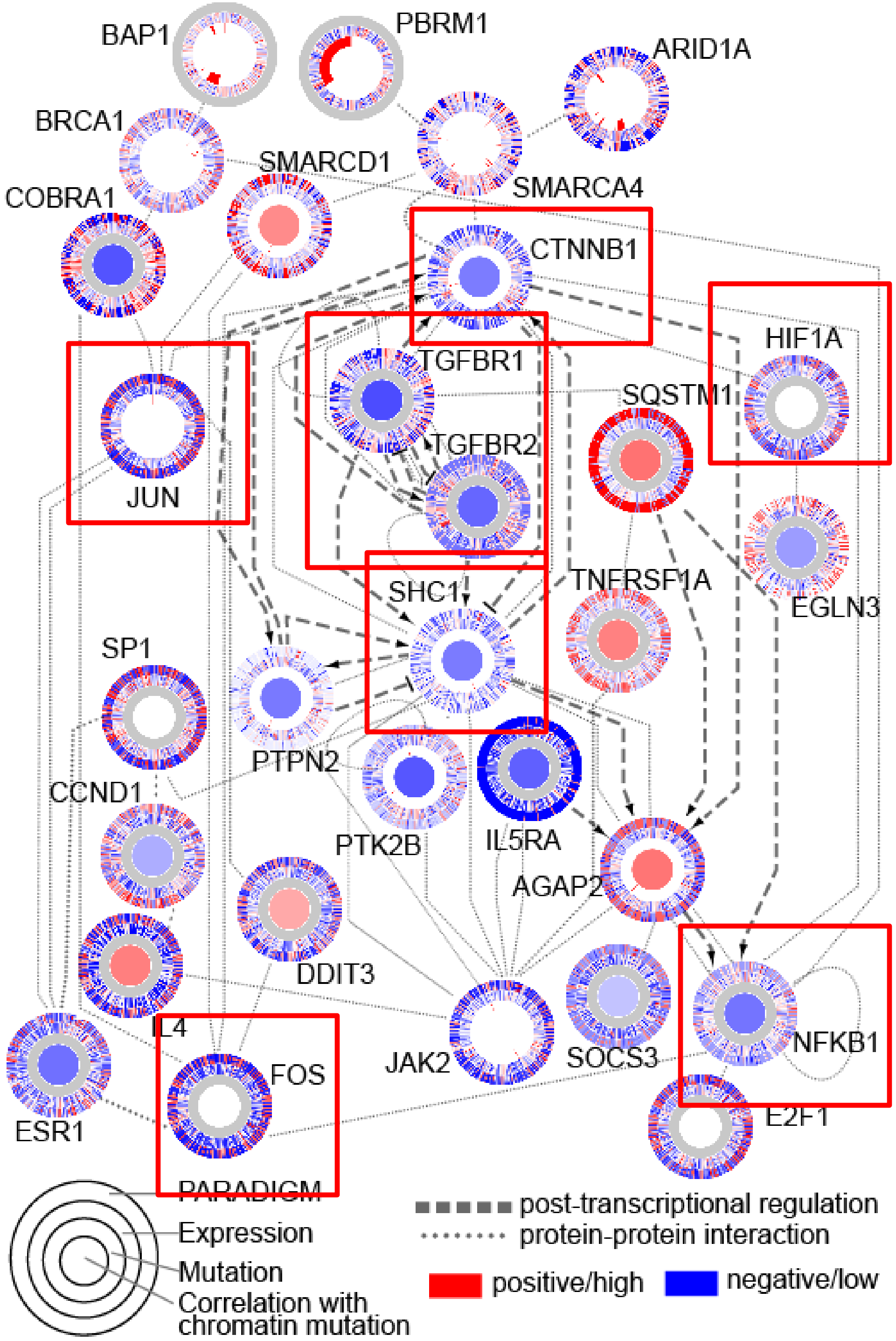
Shen H, Laird P, TCGA

Mutations involving the SWI/SNF chromatin remodeling complex show far-reaching effects on other pathways



Paull E, Stuart J, Raphael B, TCGA

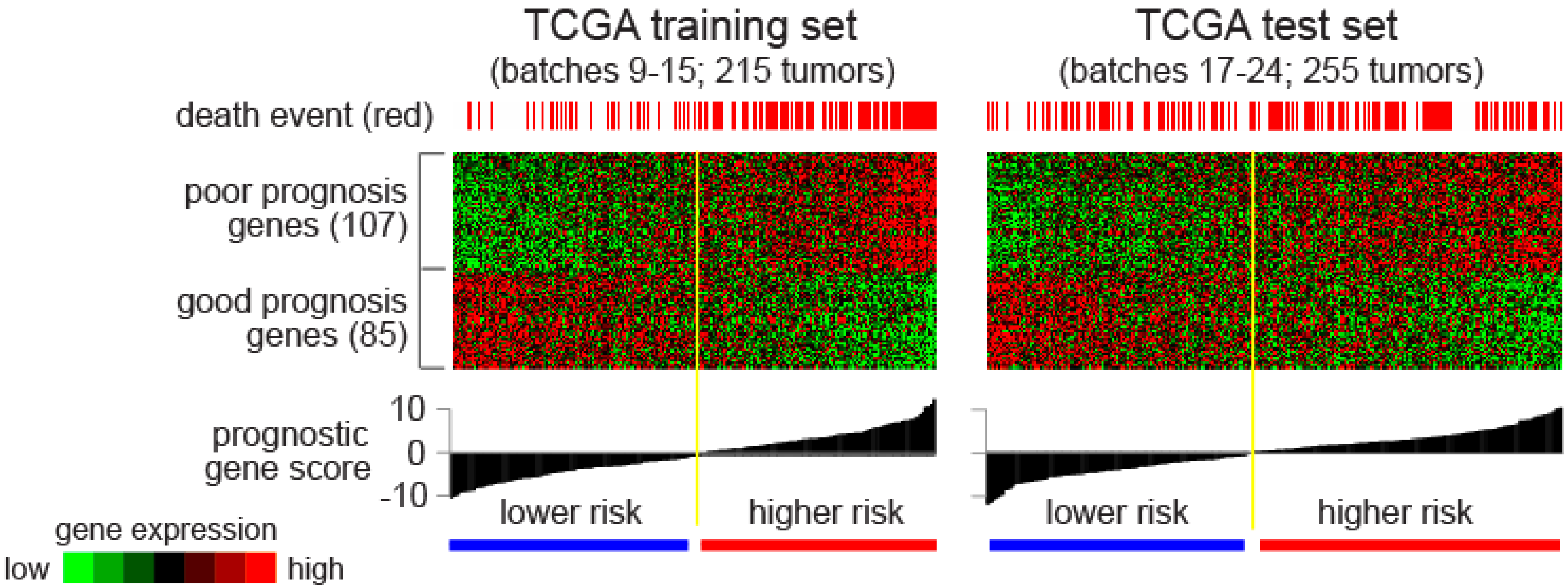
Mutations involving the SWI/SNF chromatin remodeling complex show far-reaching effects on other pathways



Paull E, Stuart J, Raphael B, TCGA

Molecular signatures and pathways of aggressive ccRCC

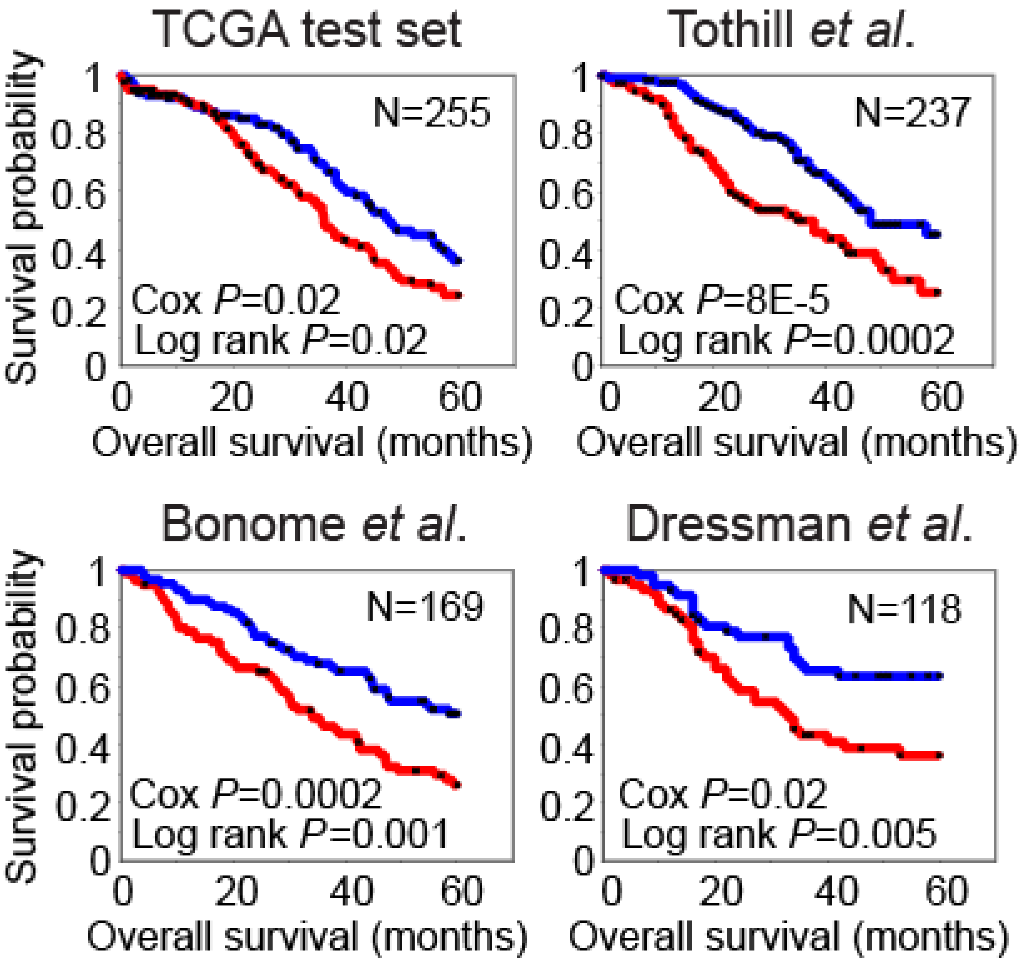
A gene expression signature of survival in high grade serous ovarian cancer



- Defined using a training dataset
- Applied to multiple test datasets in predicting higher risk versus lower risk patients

Creighton CJ and TCGA consortium, Nature 2011

A gene expression signature of survival in high grade serous ovarian cancer



Creighton CJ and TCGA consortium, Nature 2011

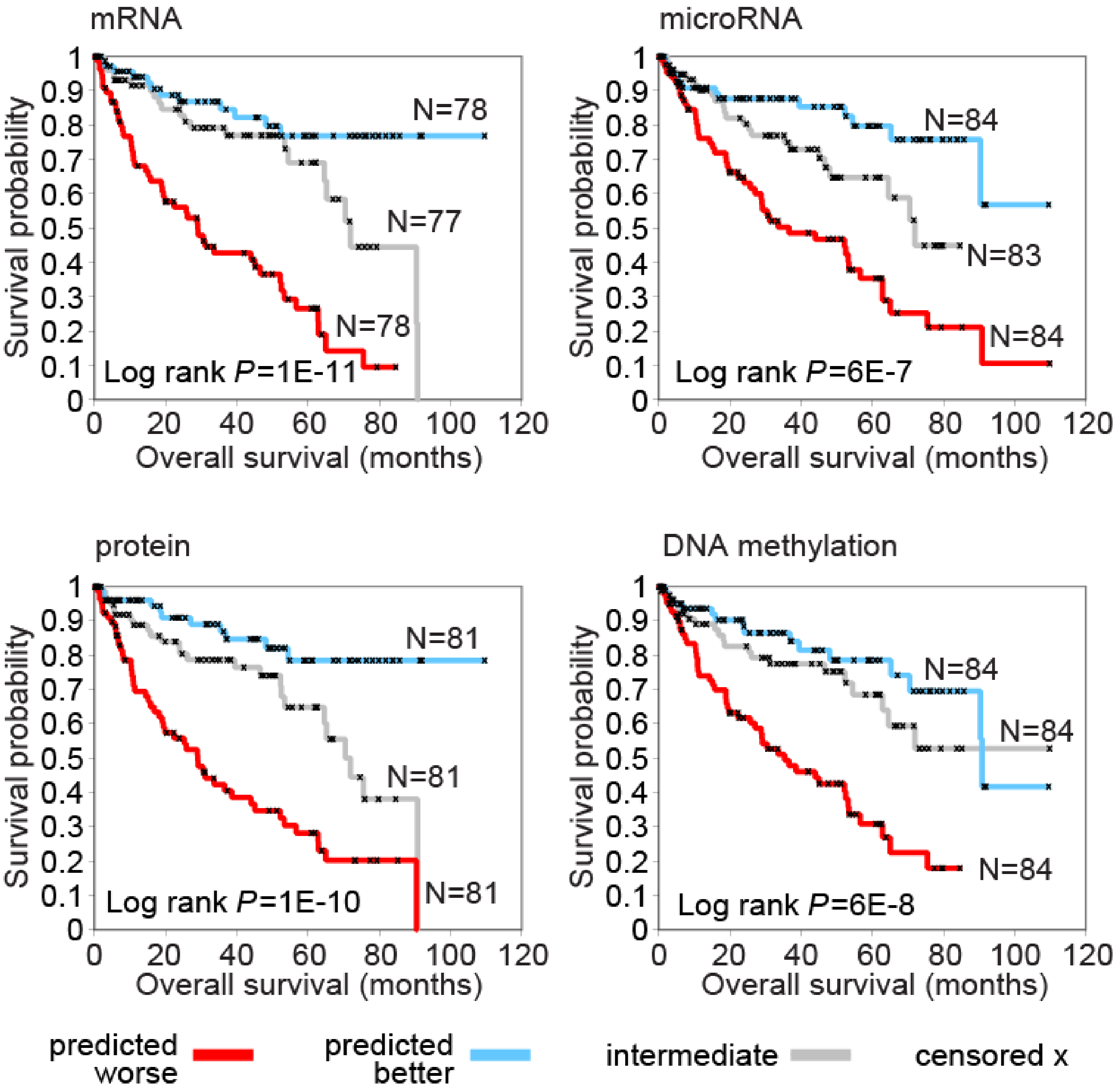
Molecular signatures of survival in ccRCC

Discovery and validation subsets

Data Type	Platform	N - discovery	N - validation
mRNA	RNA-seq	184	233
microRNA	miR-seq	163	251
DNA methylation	Illumina array	192	252
protein	RPPA	168	243

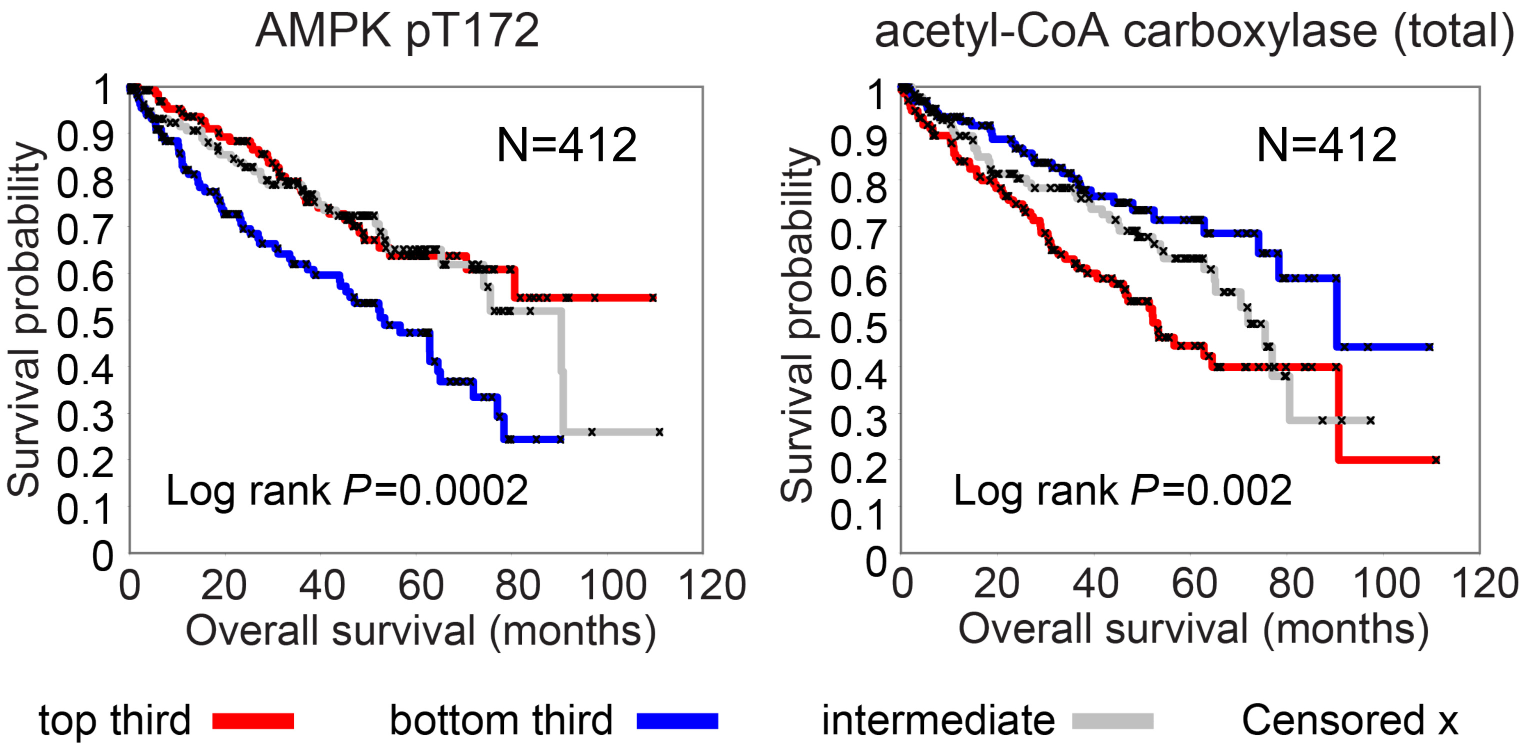
Creighton CJ and TCGA consortium

Molecular signatures of survival in ccRCC



Creighton CJ and TCGA consortium

Protein survival correlates in ccRCC include AMPK and acetyl-CoA carboxylase



AMPK pT172

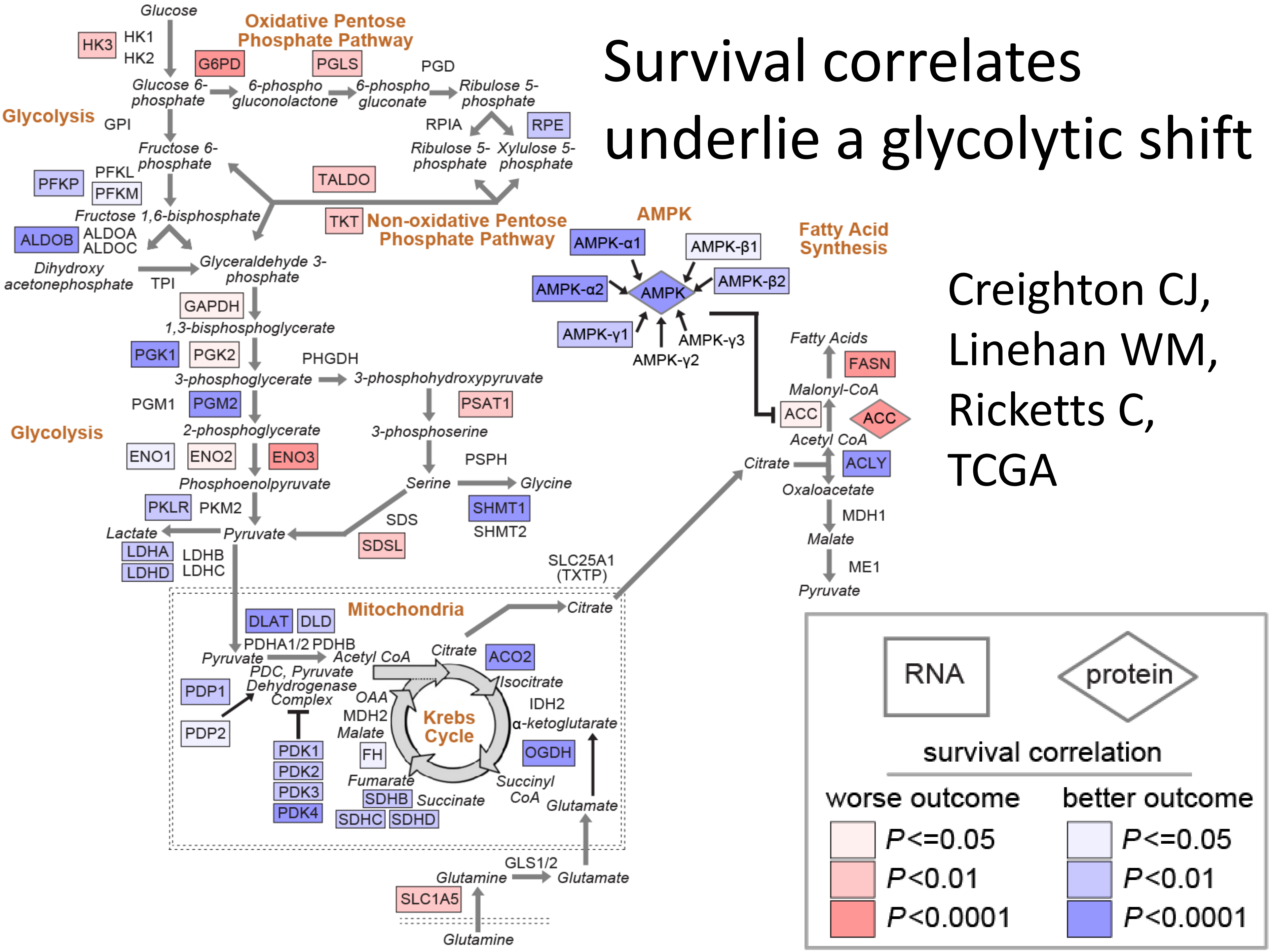
acetyl-CoA carboxylase (total)

LOW AMPK, HIGH acetyl-coA carboxylase = worse outcome

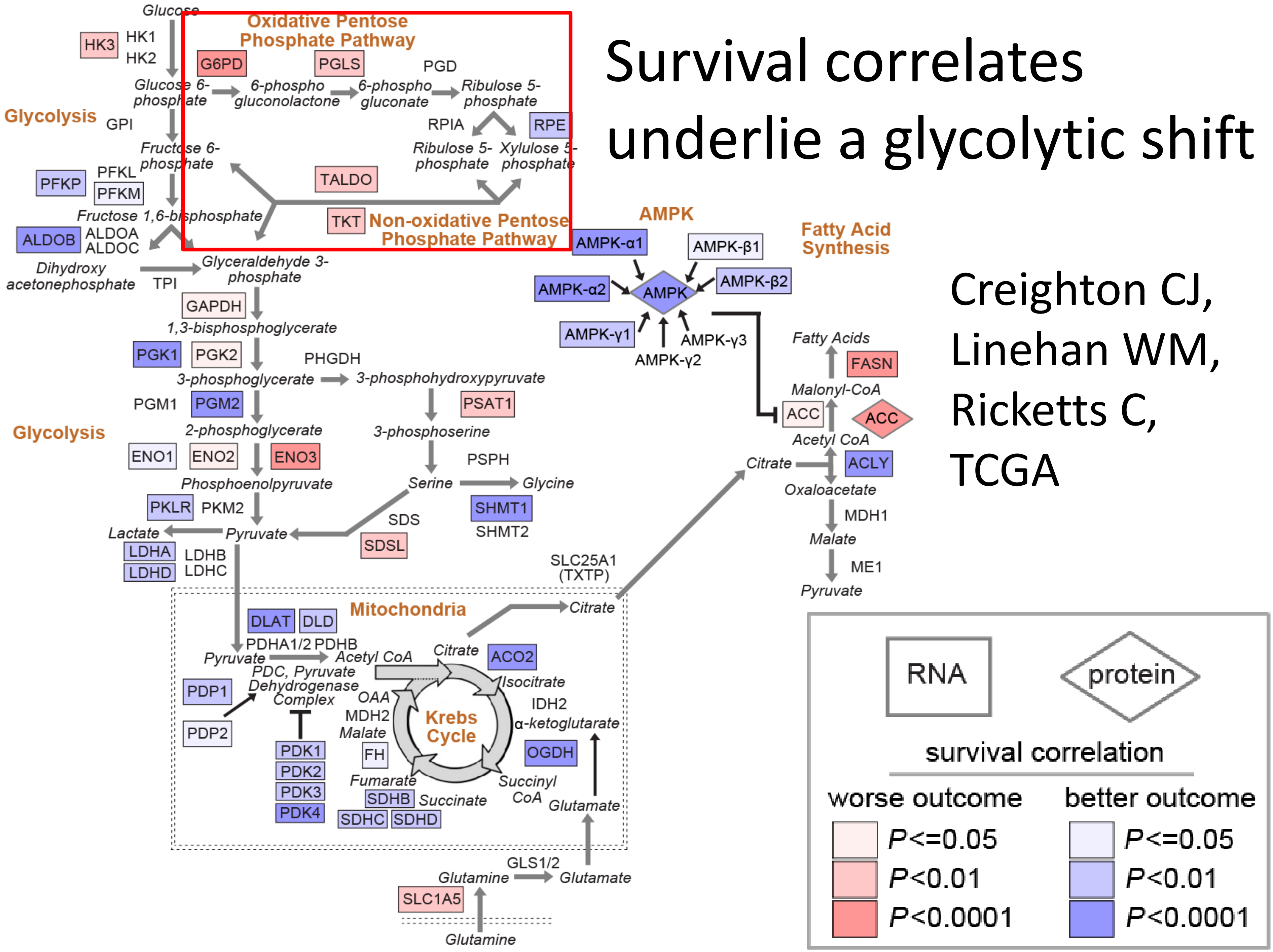
AMPK ↓ → Acetyl-coA carboxylase ↑ → aerobic glycolysis

Survival correlates underlie a glycolytic shift

Creighton CJ,
Linehan WM,
Ricketts C,
TCGA



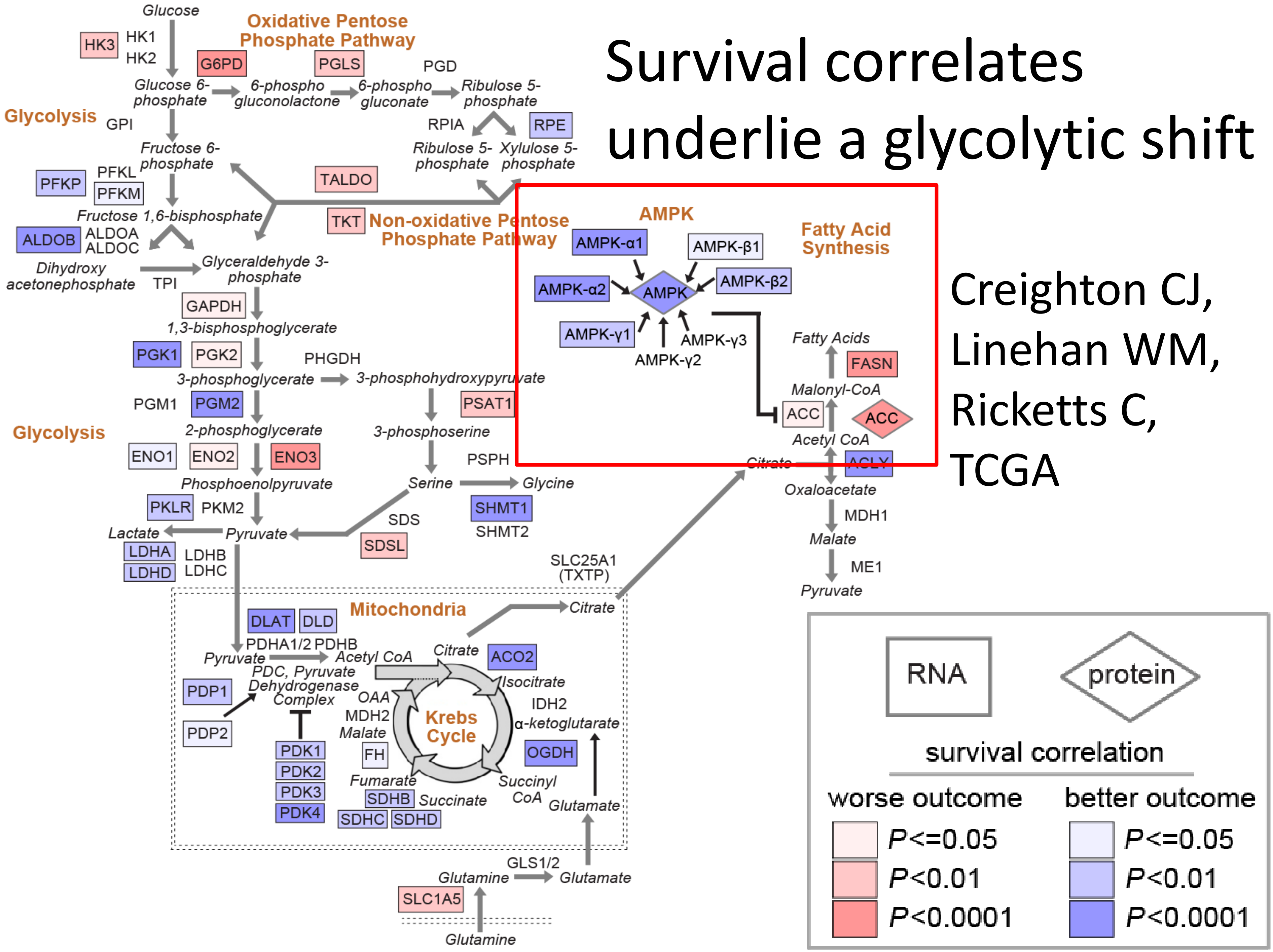
Survival correlates underlie a glycolytic shift



Creighton CJ, Linehan WM, Ricketts C, TCGA

Survival correlates underlie a glycolytic shift

Creighton CJ, Linehan WM, Ricketts C, TCGA



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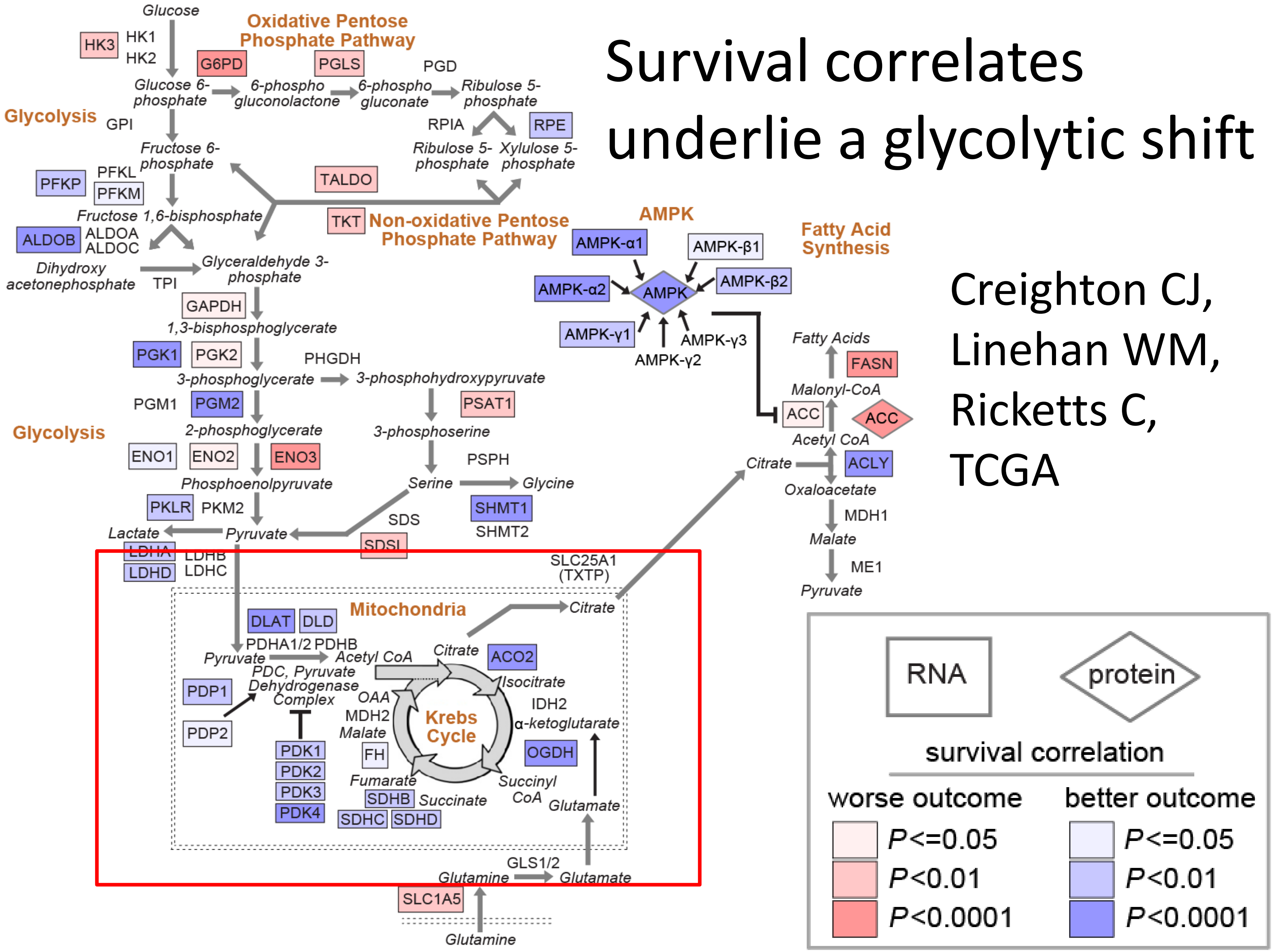

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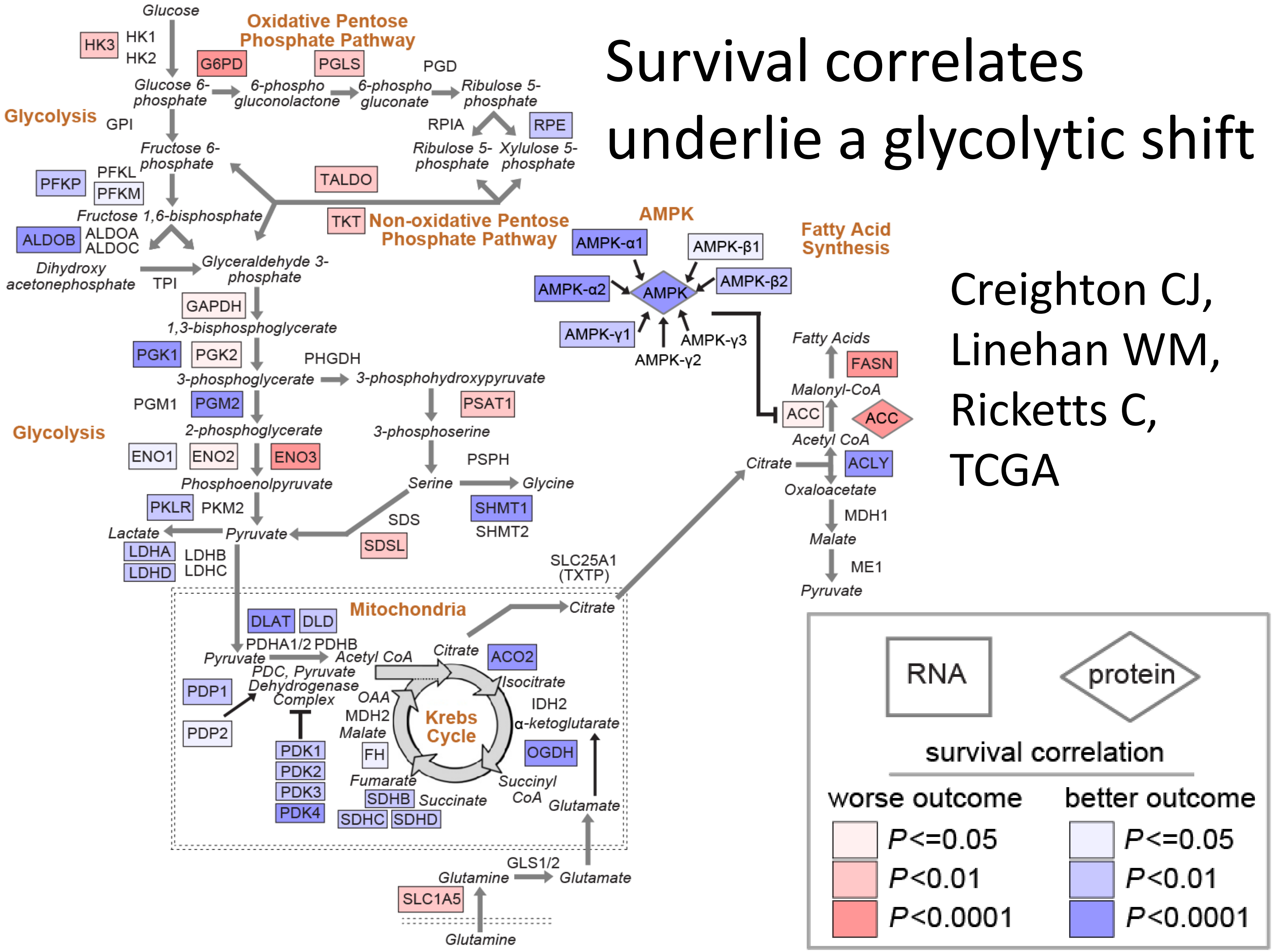
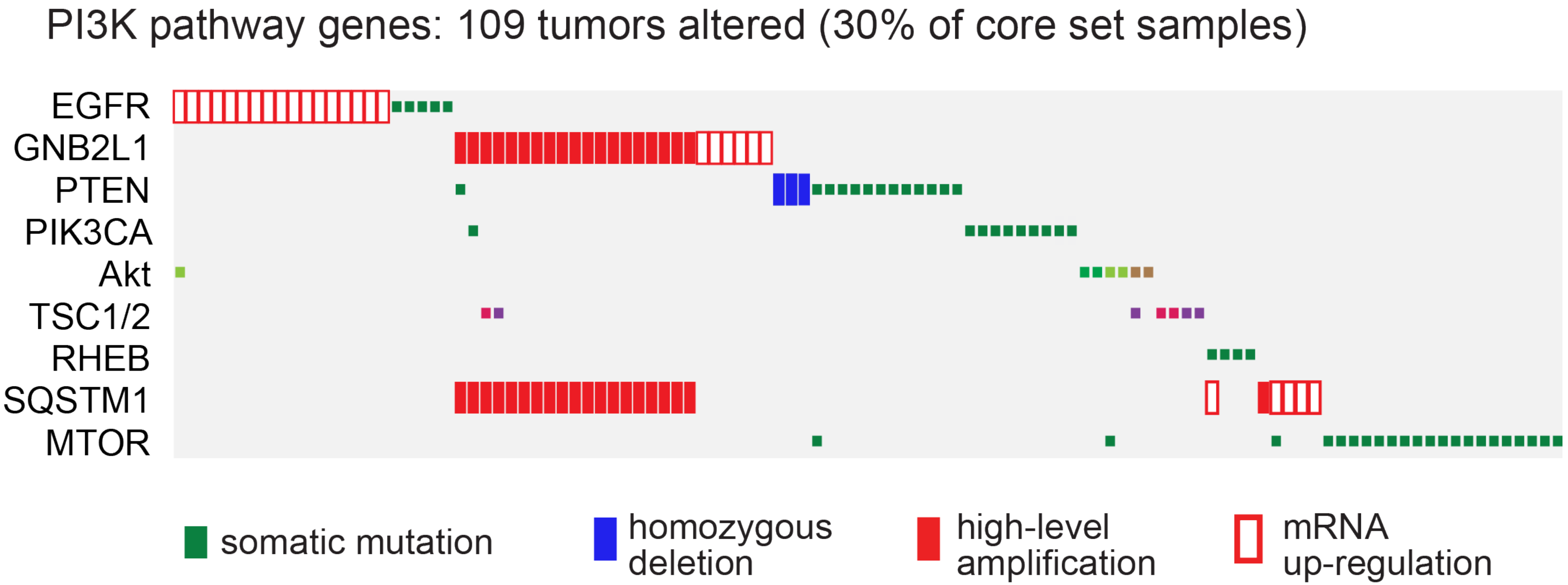


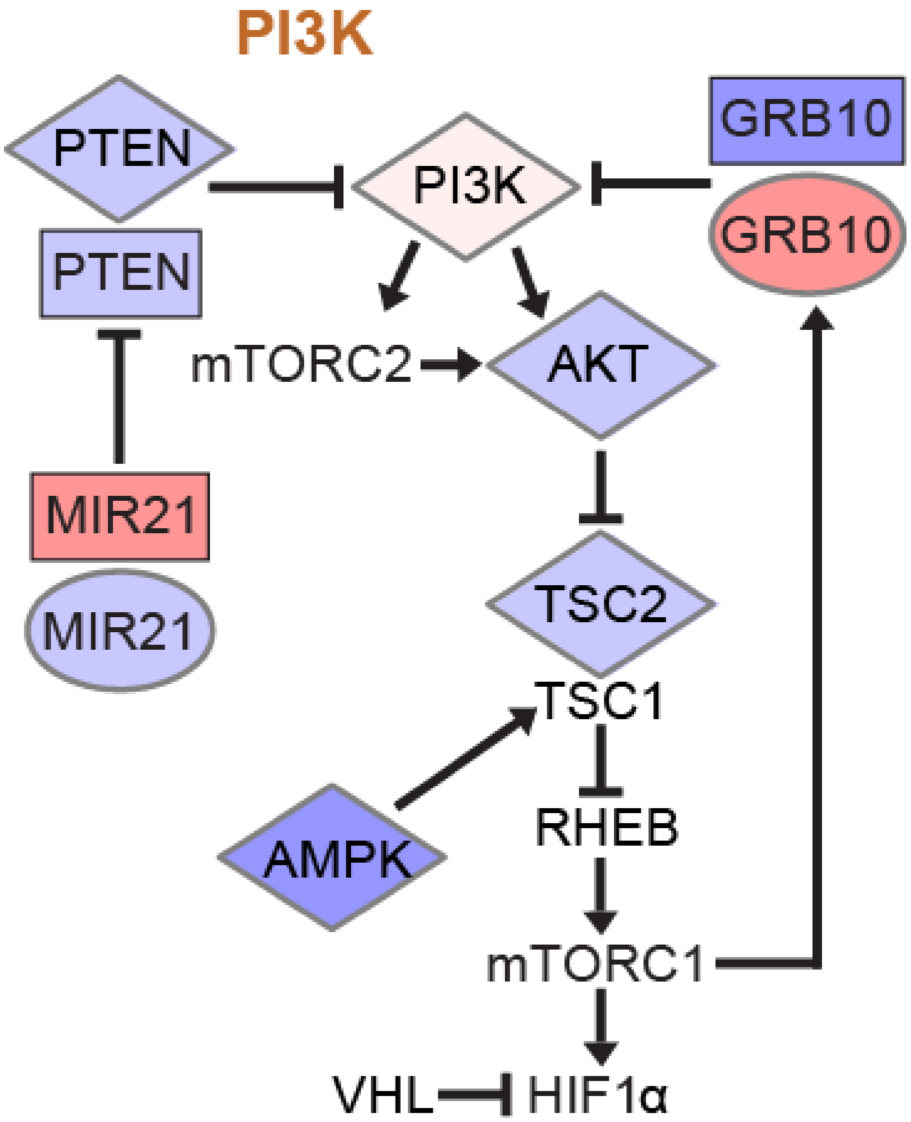
The PI3K pathway is highly targeted at the genetic and genomic levels



PI3K pathway genes: 109 tumors altered (30% of core set samples)

Anderson J, Ciriello G, Schultz N, Sander C, TCGA

Promoter methylation of miR-21 and *GRB10* contributes to PI3K pathway deregulation



Creighton CJ,
Robertson AG,
Laird P,
TCGA

Survival correlation

Worse outcome 🟥

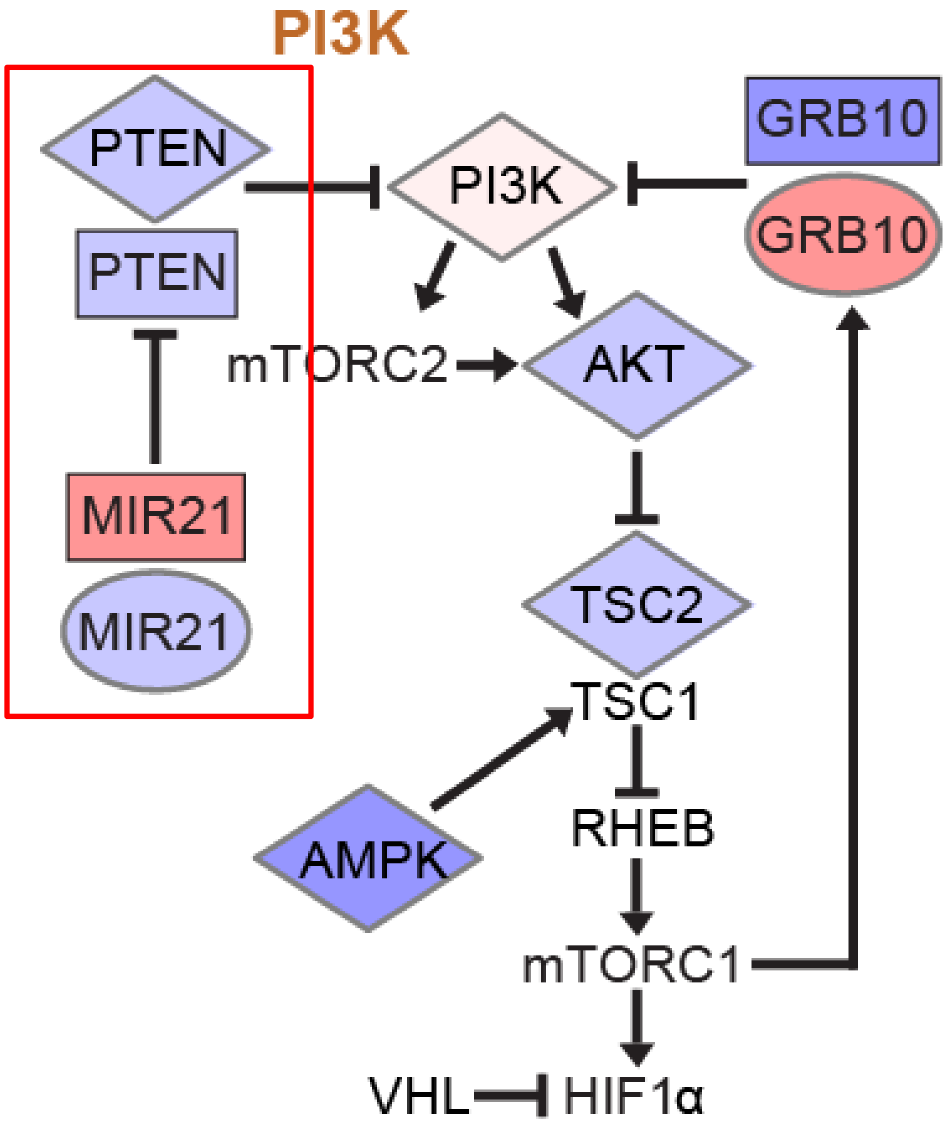
Better outcome 🟦

RNA

protein

meth.

Promoter methylation of miR-21 and *GRB10* contributes to PI3K pathway deregulation



miR21 meth ↓

miR21 expr ↑

PTEN expr ↓

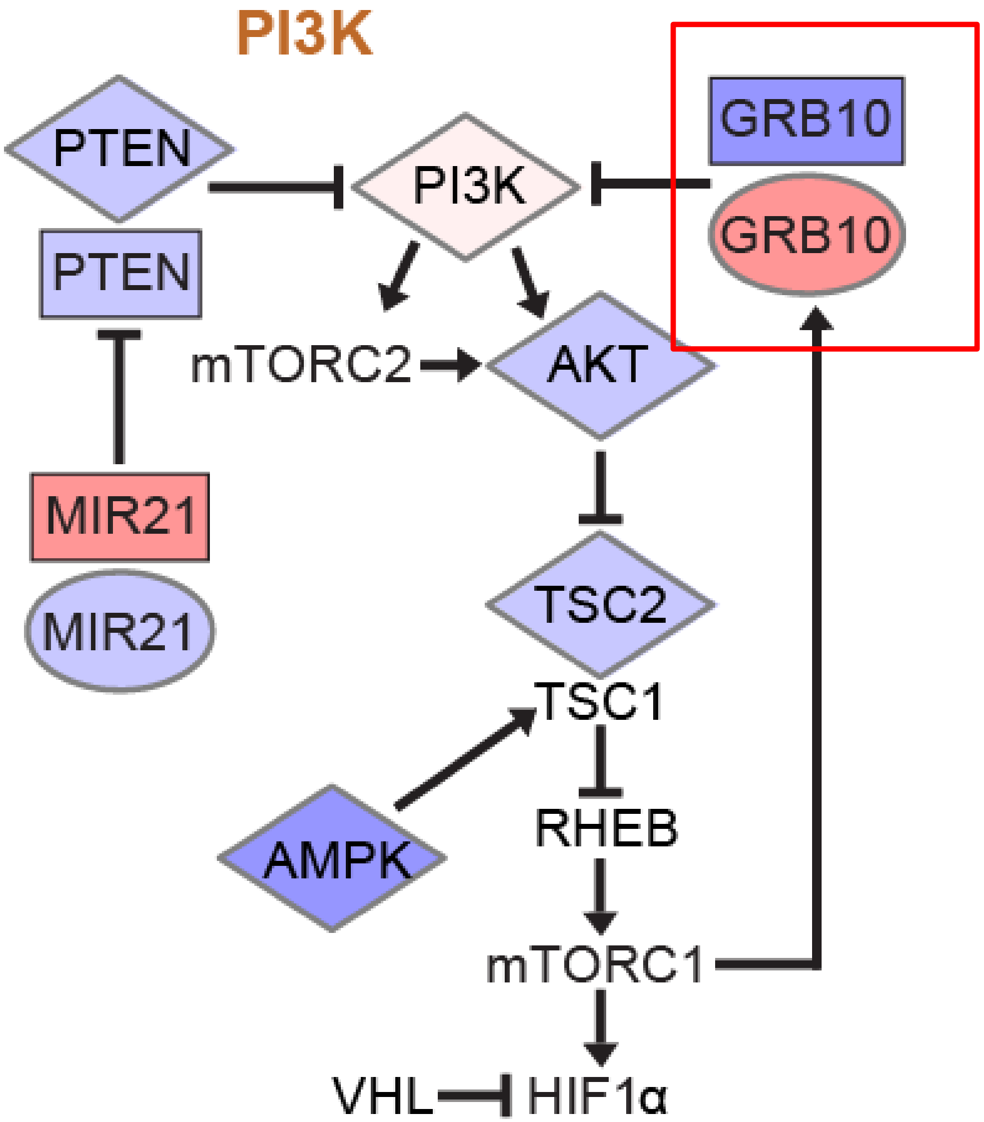
<u>Survival correlation</u>

Worse outcome 🟥

Better outcome 🟦

RNA protein meth.

Promoter methylation of miR-21 and *GRB10* contributes to PI3K pathway deregulation



GRB10 meth ↑

GRB10 expr ↓

PI3K activity ↑

Survival correlation

Worse outcome 🟥

Better outcome 🟦

RNA

protein

meth.

Conclusions

- Integrative analyses highlights the importance of both *VHL/HIF* pathway and chromatin remodeling/histone methylation pathway
- Frequent targeting of PI3K pathway at genetic, genomic, and epigenetic levels
- A metabolic shift to aerobic glycolysis appears involved with more aggressive disease

Kidney Cancer Disease Working Group

(apologies for any omissions)

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