

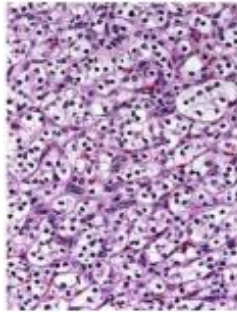
The molecular classification of kidney cancer

ESMO

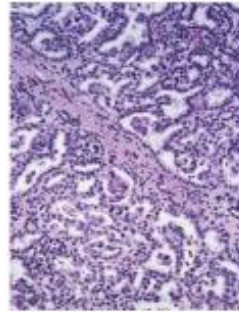
September 29, 2014

Andy Futreal
MD Anderson Cancer Center
&
Wellcome Trust Sanger Institute

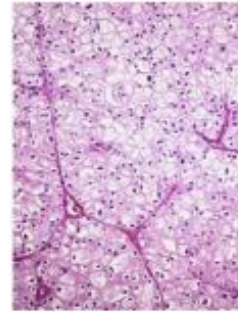
Human Renal Epithelial Neoplasms



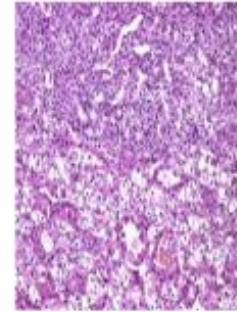
Clear Cell
VHL



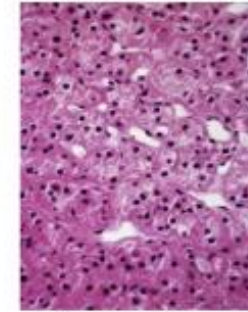
Papillary Type 1
Met



Chromophobe

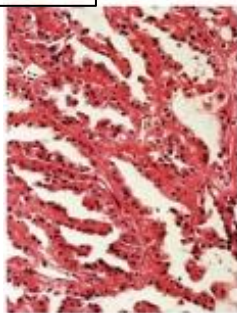


Hybrid

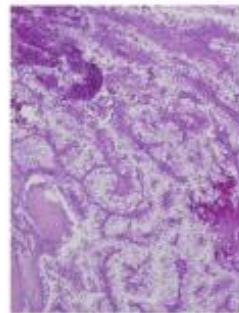


Oncocytoma

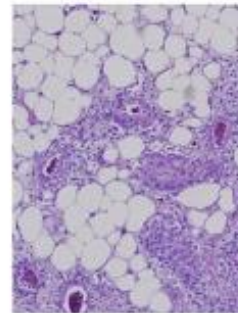
FLCN



Papillary Type 2
FH



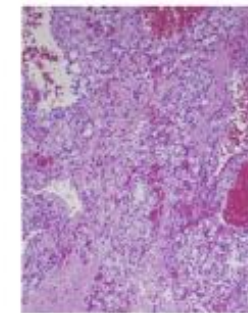
TFE3
TFE3, TFEB, MITF



Angiomyolipoma
TSC1, TSC2



Oncocytic
SDHB, SDHC, SDHD



Clear/Chromophobe
PTEN

*BAP1 germline
ccRCC*

PCR exon-resequencing ccRCC study

101 ccRCC cases

(96 clinical samples + 5 matched pair cell lines)

Screen the coding exons of 3,544 genes

(750 Mb total)

Copy number and expression

Follow-up series of 311 clear cell carcinoma clinical samples
with matching normals

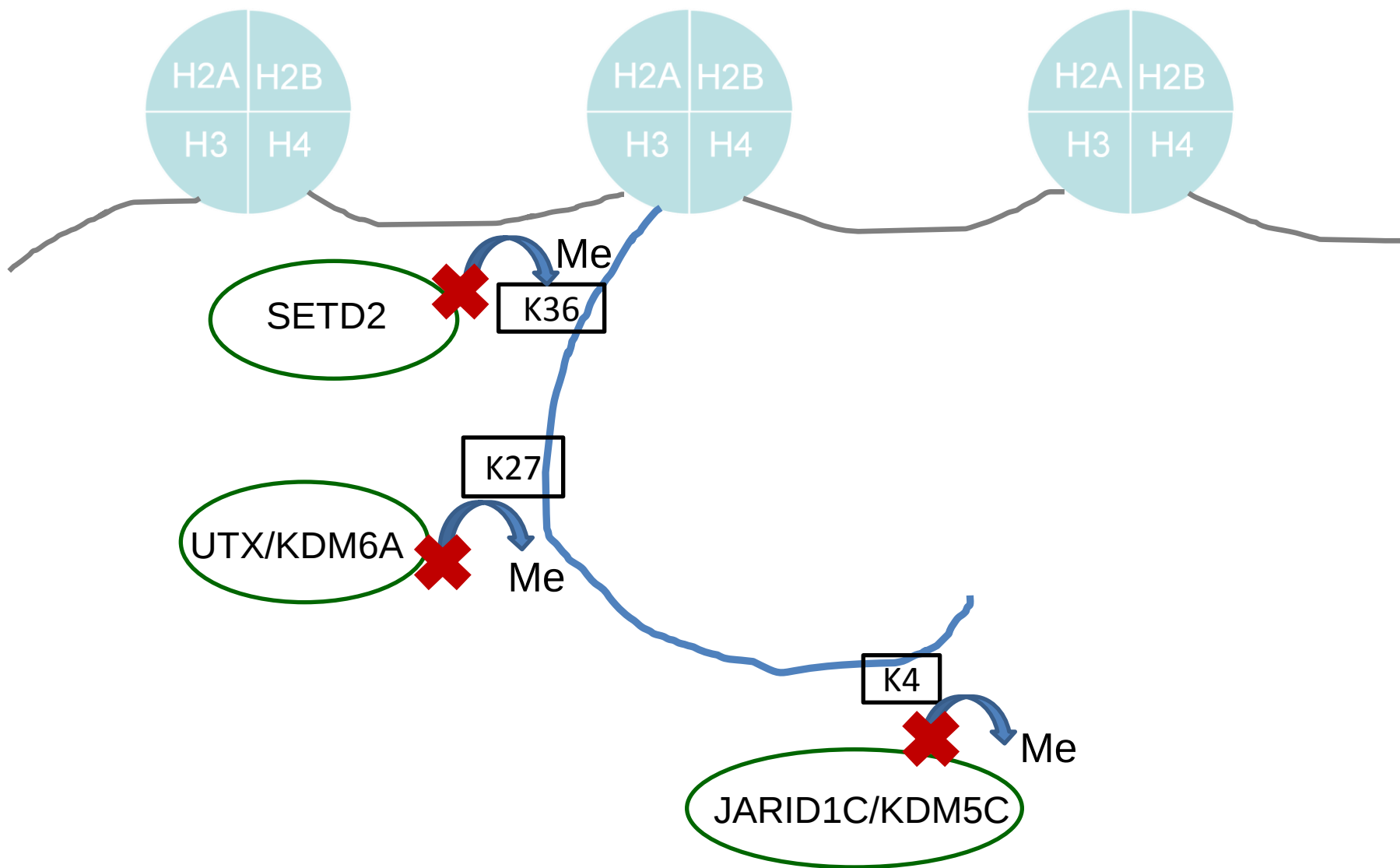
Four/five significantly mutated genes in ccRCC are histone methylase/demethylases

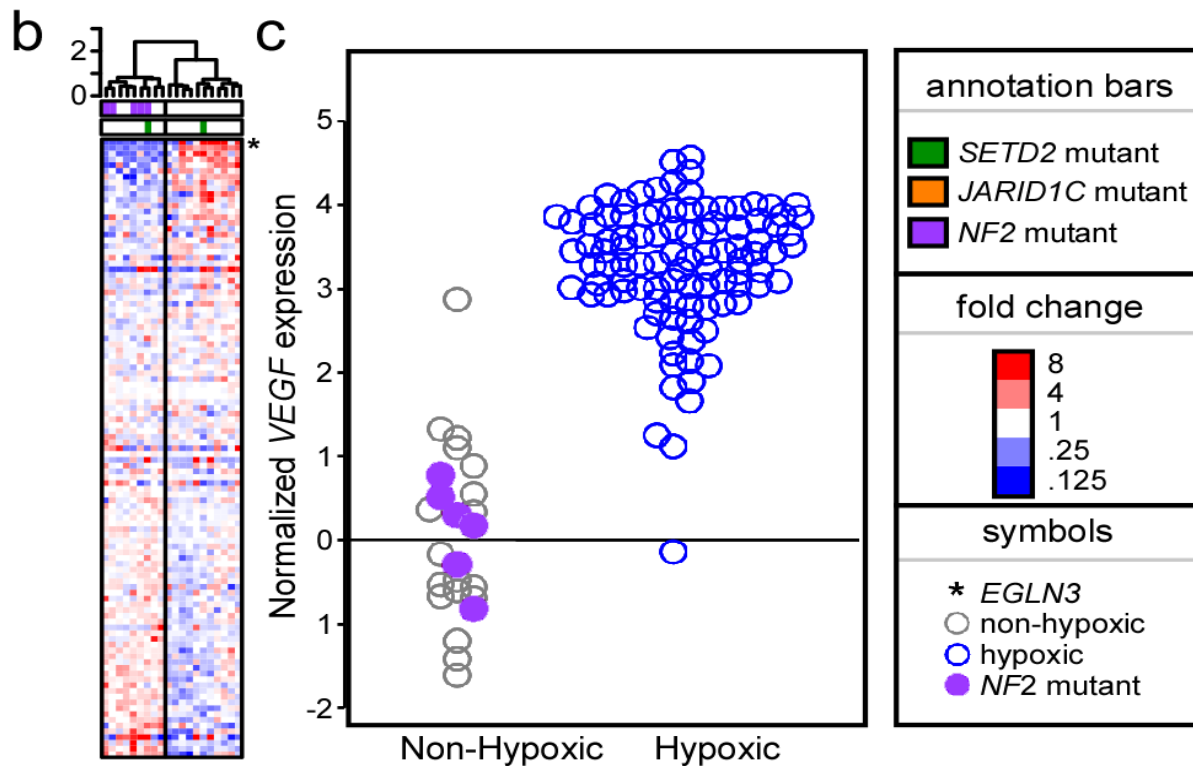
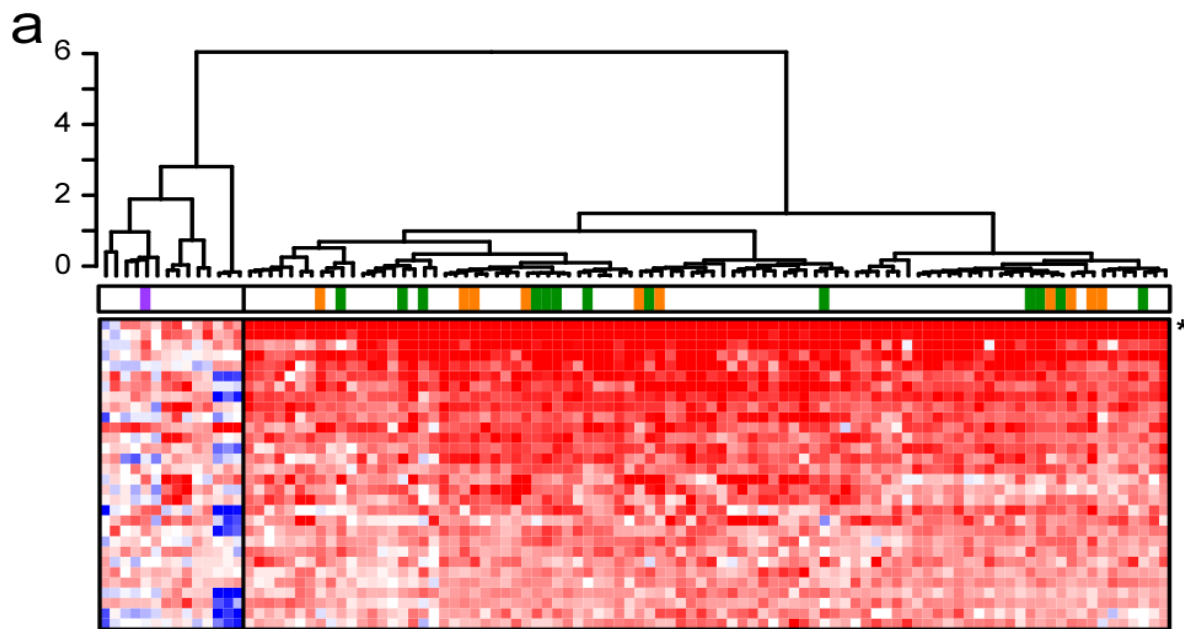
UTX(KDM6A) – H3K27 demethylase and MLL2/3 complex in H3K4 methylation
12/407 cases mutated (12/12 truncating)

SETD2 – H3K36 methyltransferase
15/407 cases mutated (12/15 truncating)

JARID1C – H3K4 demethylase
14/407 cases mutated (12/14 truncating)

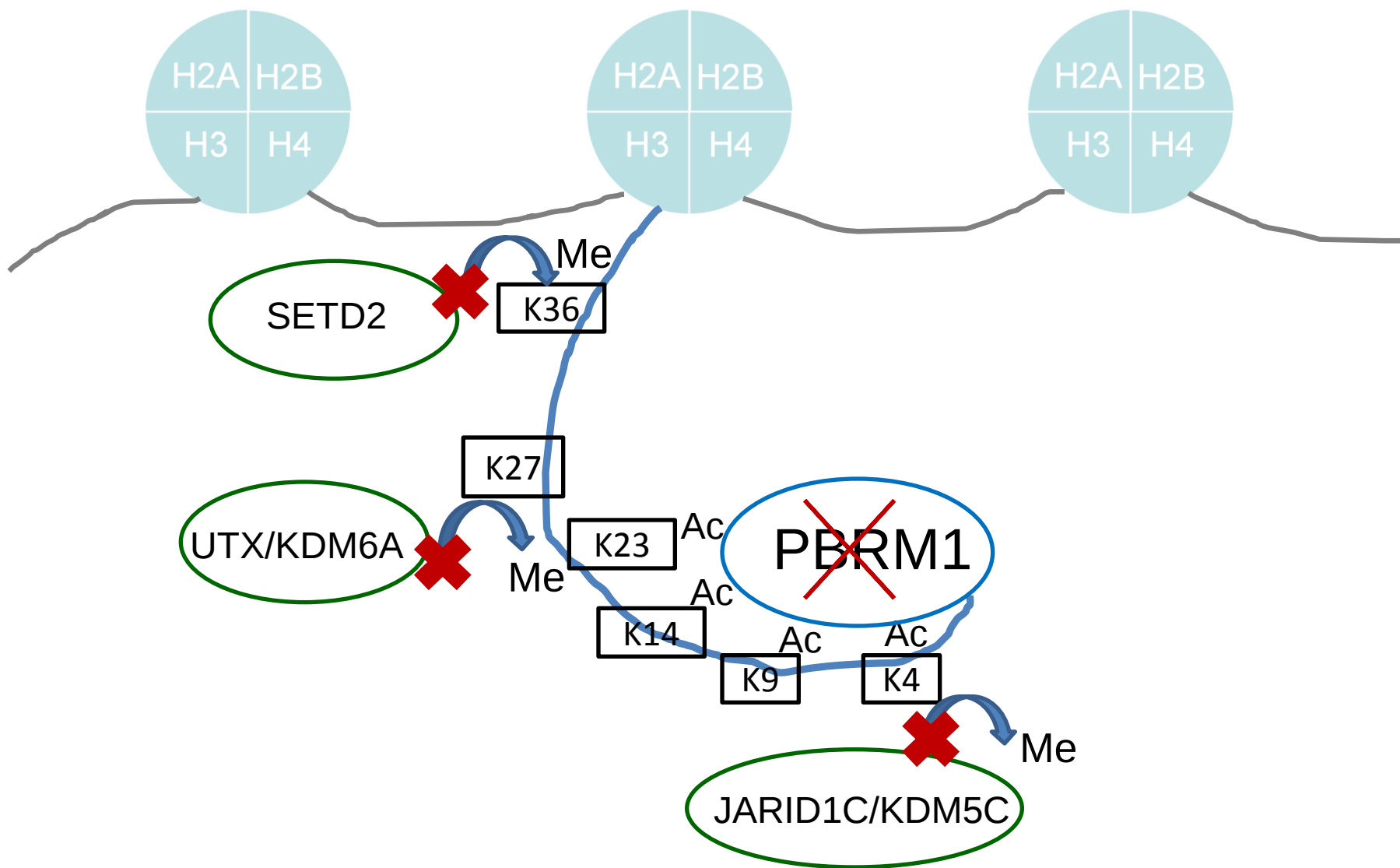
MLL2 – H3K4 methyltransferase
17/407 (including a silent, 6 truncating, 5 missense)



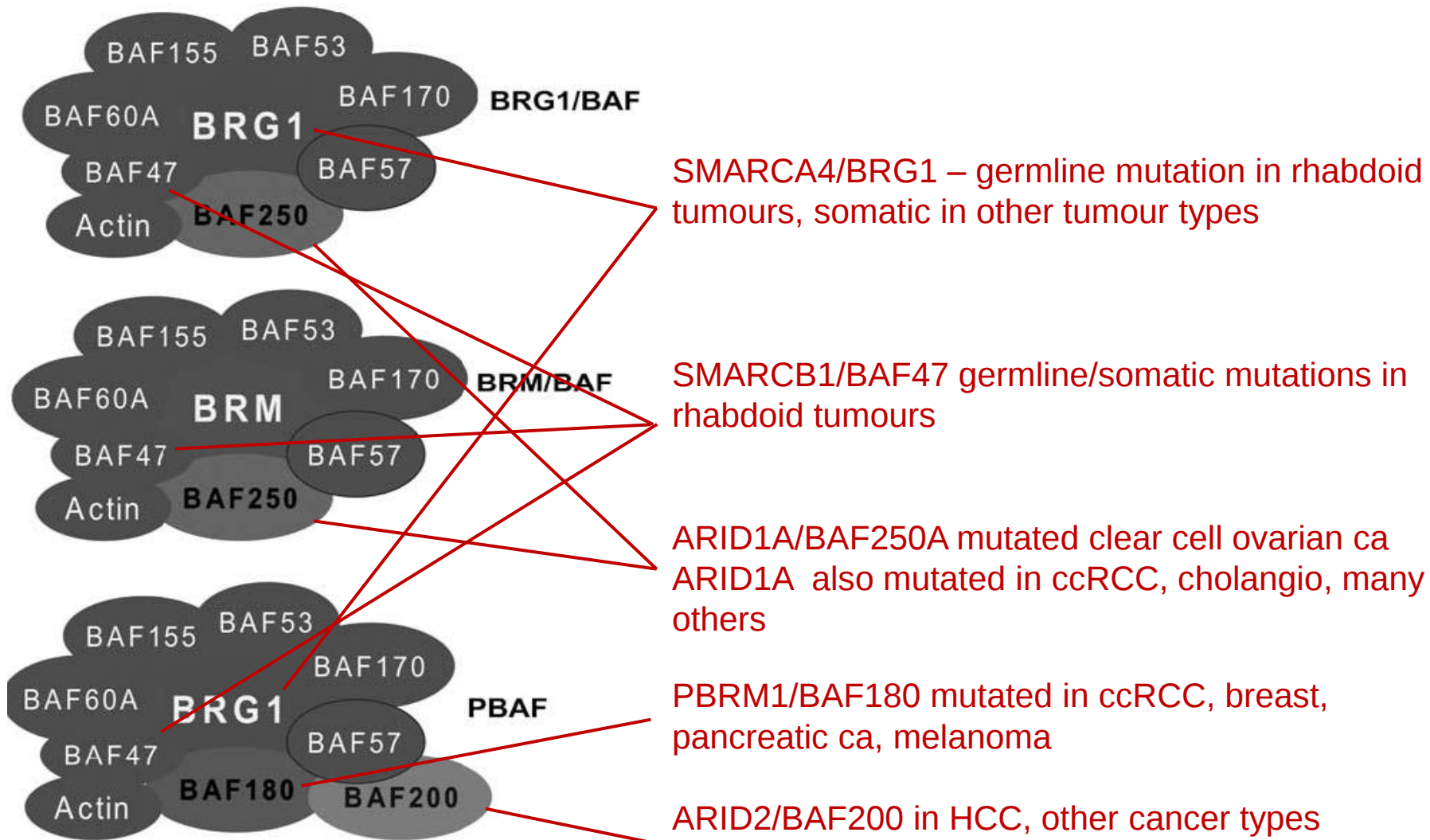


Somatic genetic heterogeneity in ccRCC

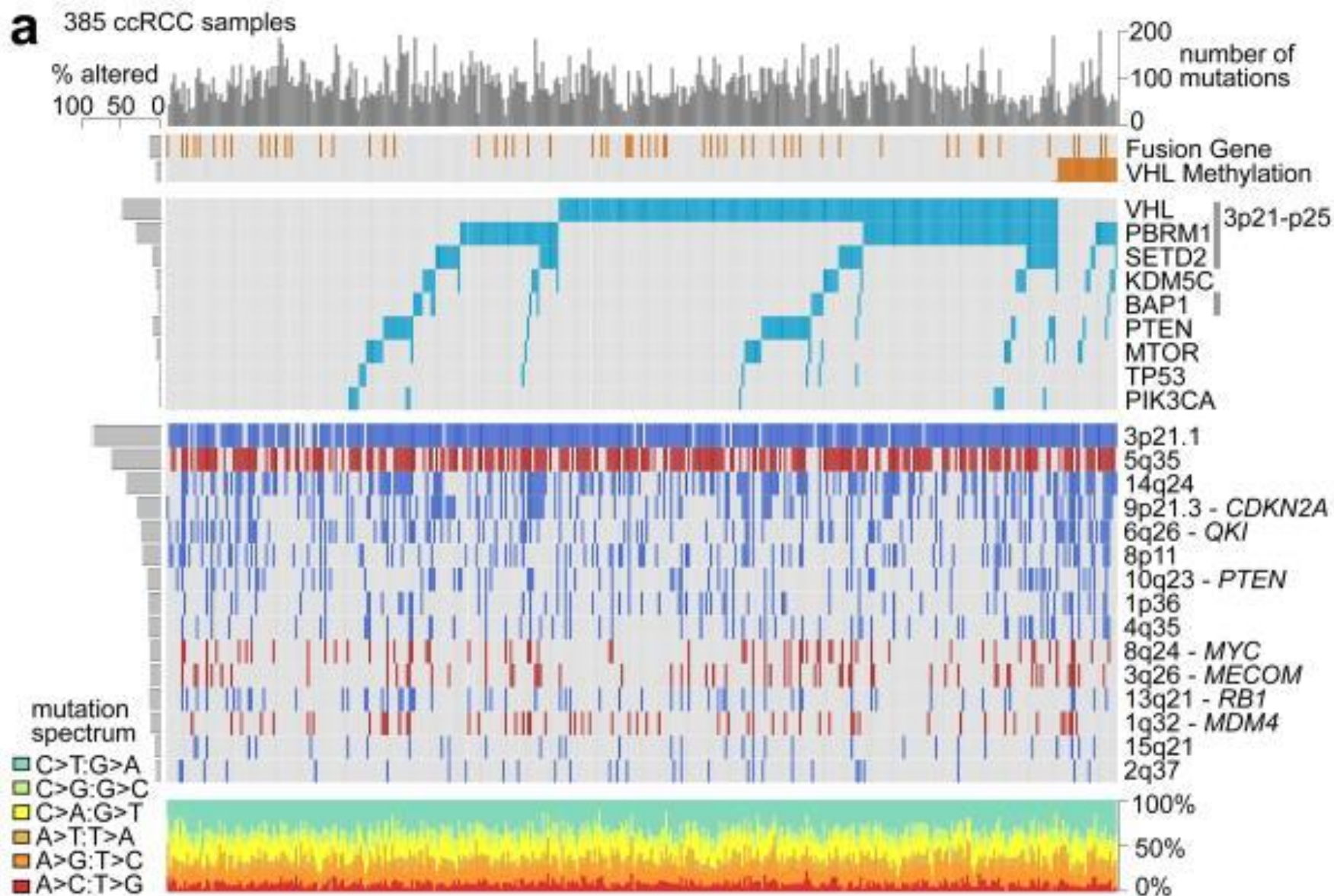
NF2 is mutated in non-VHL ccRCC



SWI/SNF complex components in cancer



TCGA ccRCC

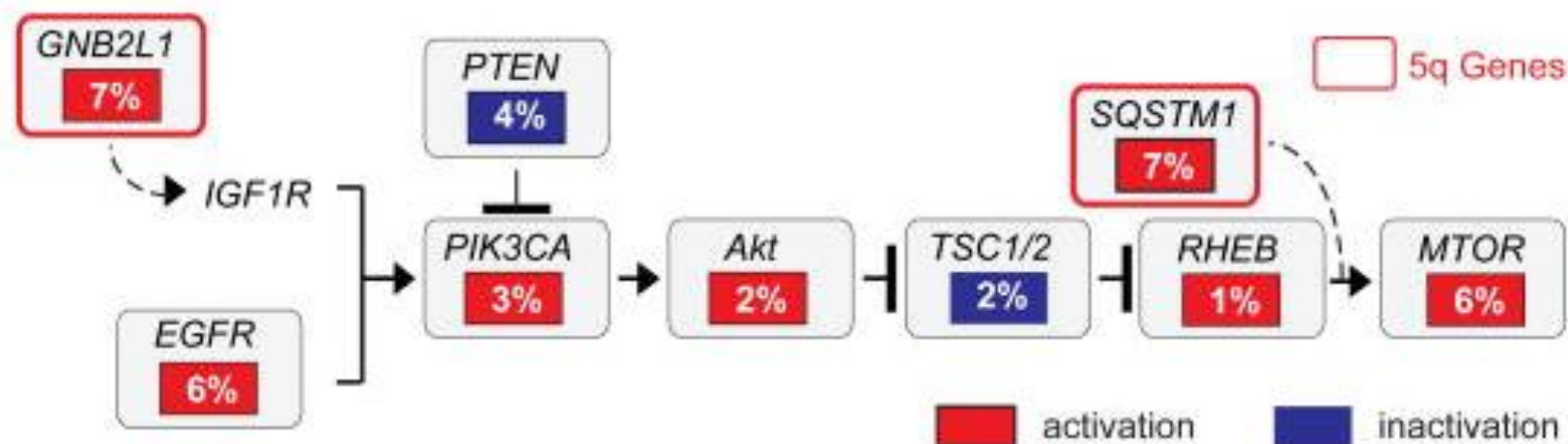
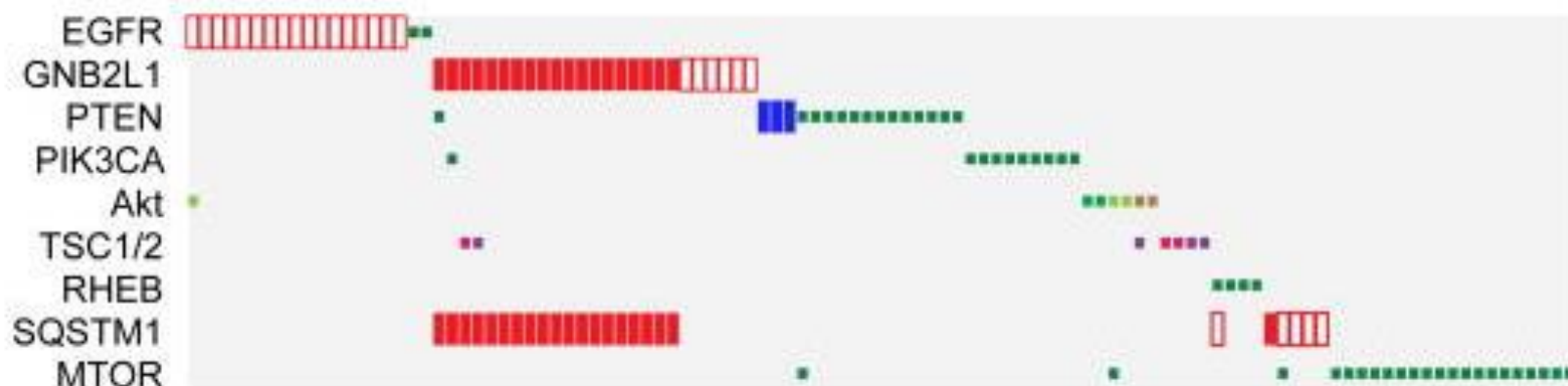


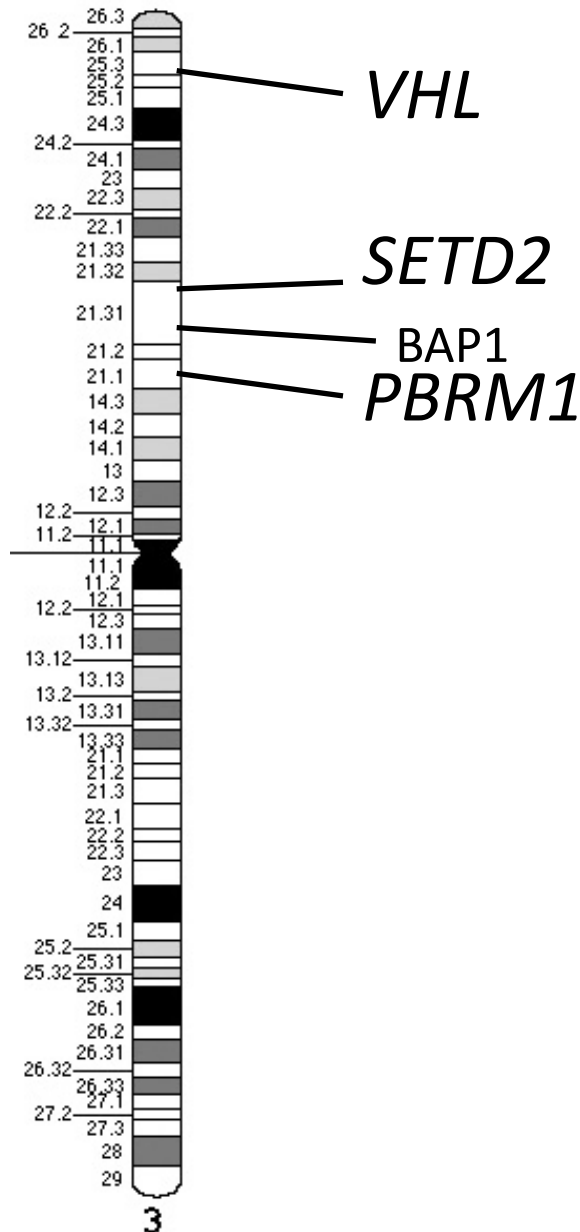
b

■ homozygous deletion ■ high-level amplification □ mRNA up-regulation ■ somatic mutation

Akt/Tsc mutation: ■ AKT1 ■ AKT2 ■ AKT3 ■ TSC1 ■ TSC2

PI3K pathway genes: 107 tumors altered (28% of core set samples)





36/38 PBRM1 mutant ccRCC have hypoxia signature

55/107 cases with a demonstrable* VHL mutation have a PBRM1 mutation

9/9 cases with a SETD2 mutation have mutation in either VHL or PBRM1

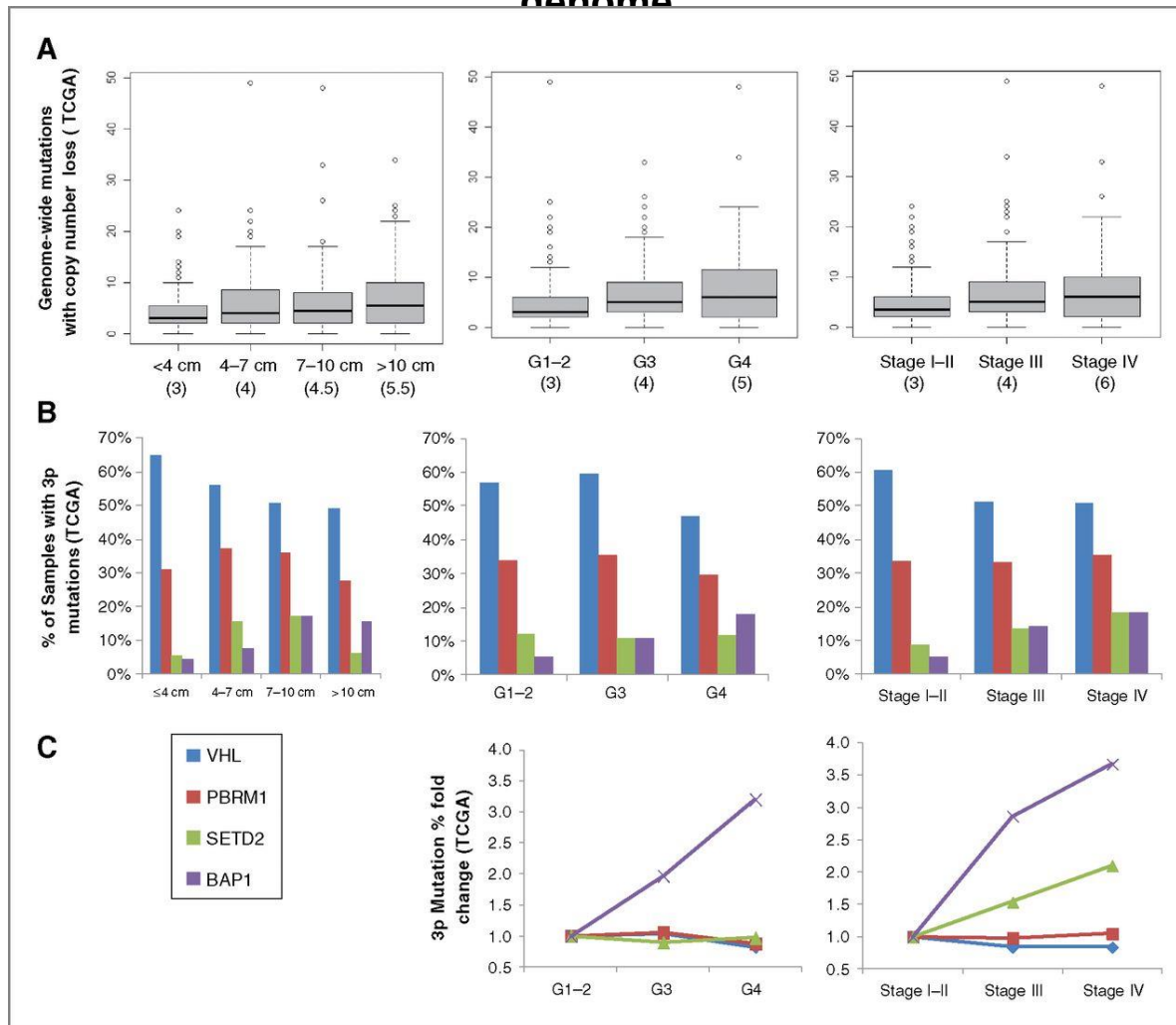
6/9 SETD2 mutant cases have a mutation in all three gene

4 tumour suppressor genes unmasked with only 5 hits as opposed to 8

3p LOH is most frequent marker in ccRCC

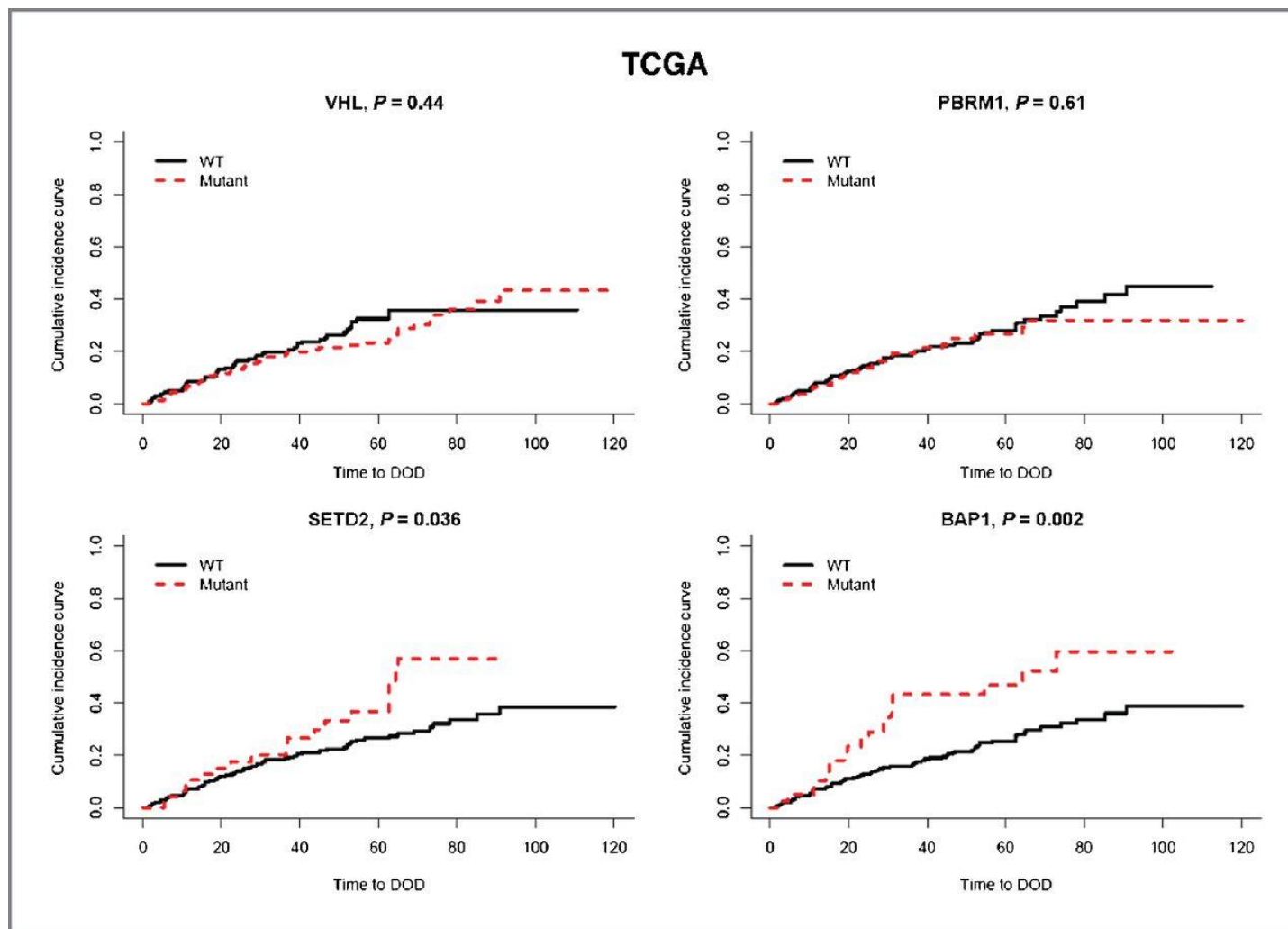
*point mutations only

A, box plots show the statistically significant incremental increase of purported TSGs as defined by mutations occurring in the setting of copy number loss across the ccRCC genome



Hakimi A A et al. Clin Cancer Res 2013;19:3259-3267

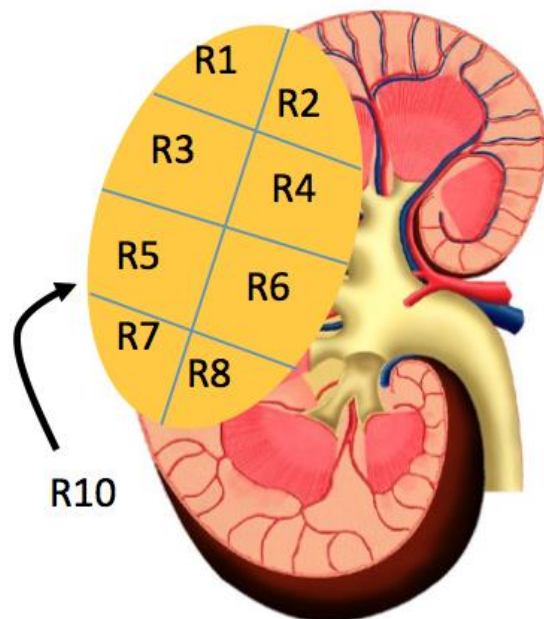
Competing risk cumulative incidence curves for the TCGA cohort (n = 421).



Hakimi A A et al. Clin Cancer Res 2013;19:3259-3267

Harvested regions:

Primary clear cell RCC



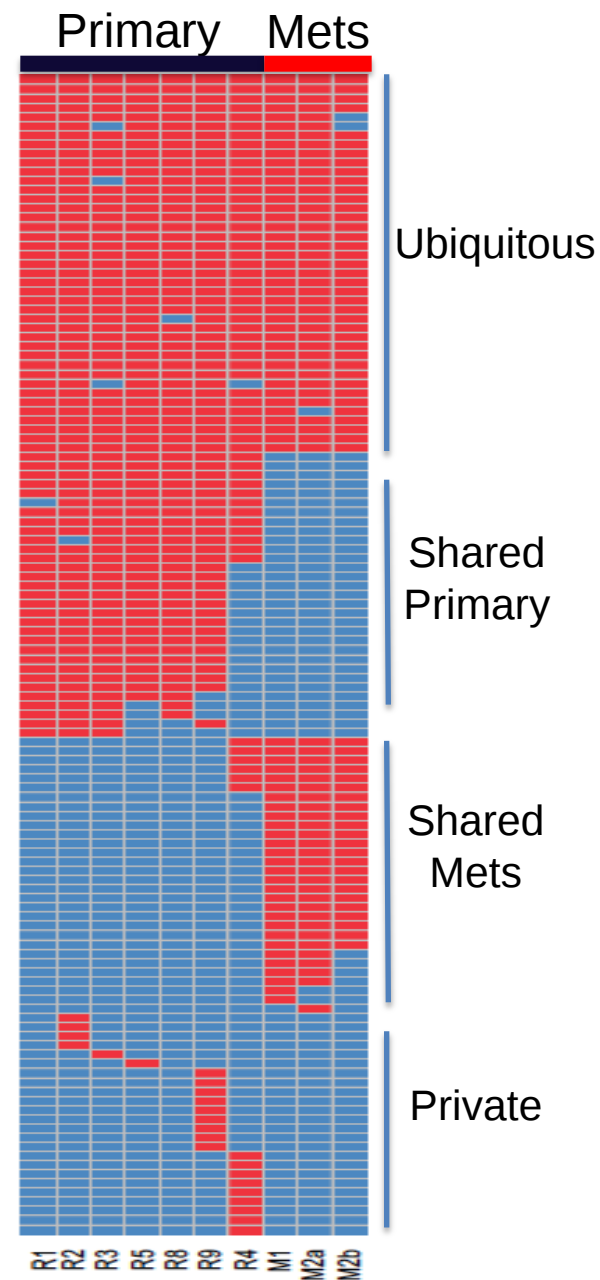
Chest wall metastasis

M2a,b

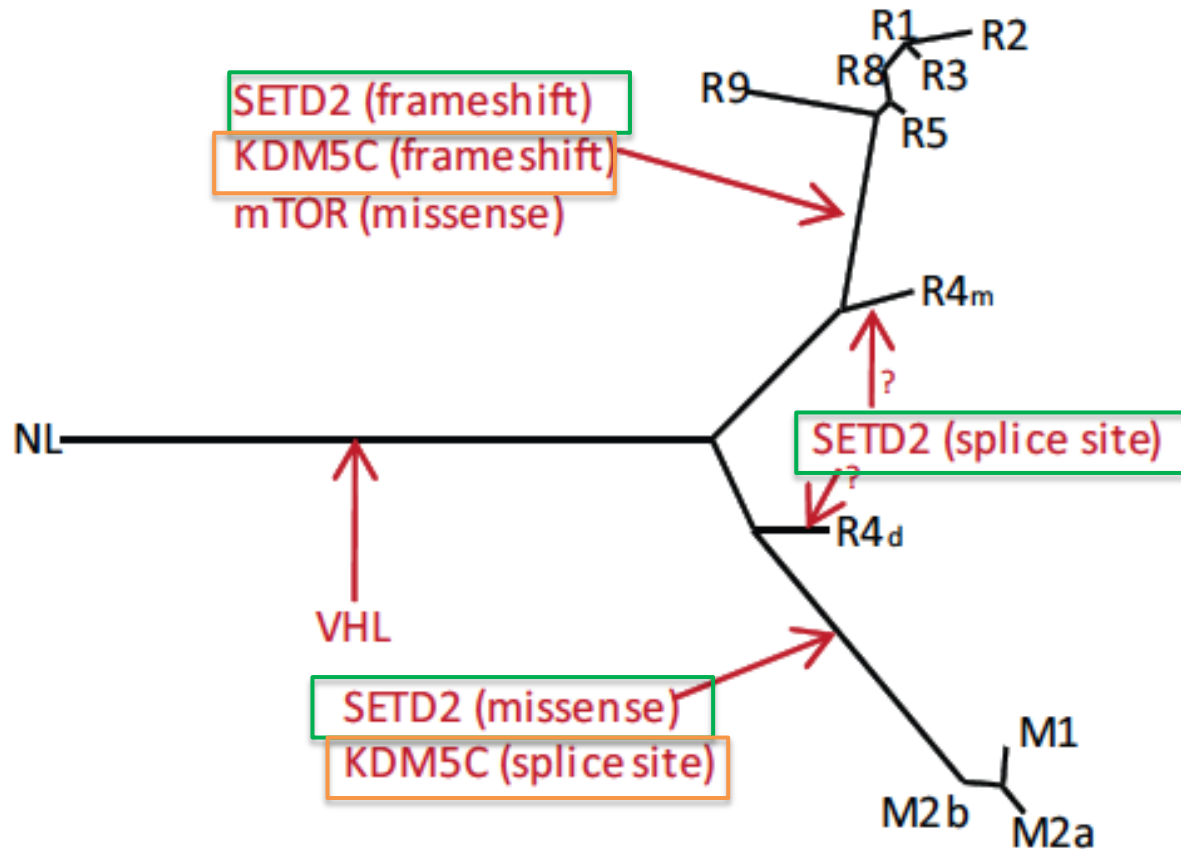
Perinephric metastasis

M1

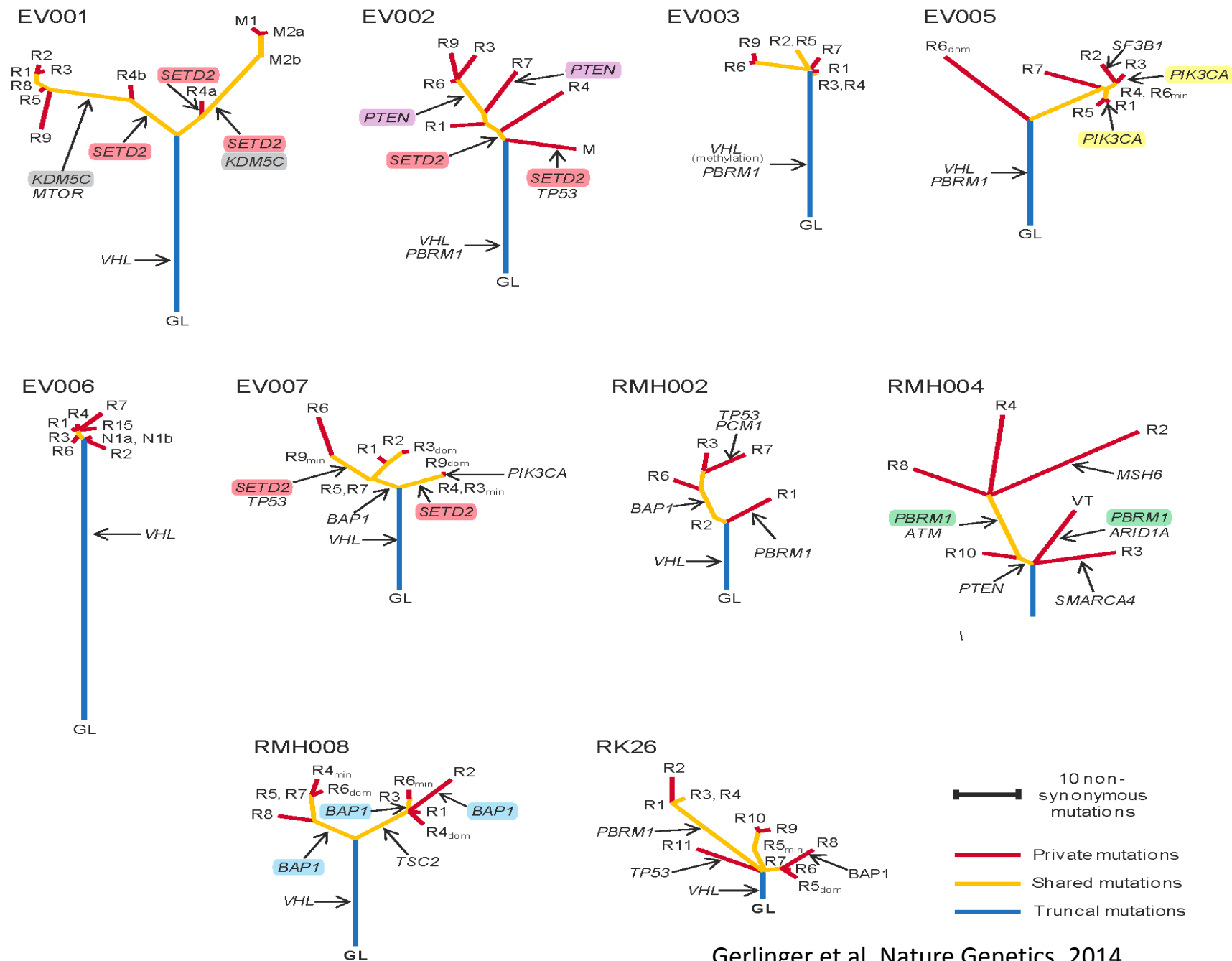
65% mutations from a single biopsy are heterogeneous – not shared by all parts of the tumour



Branched and convergent evolution

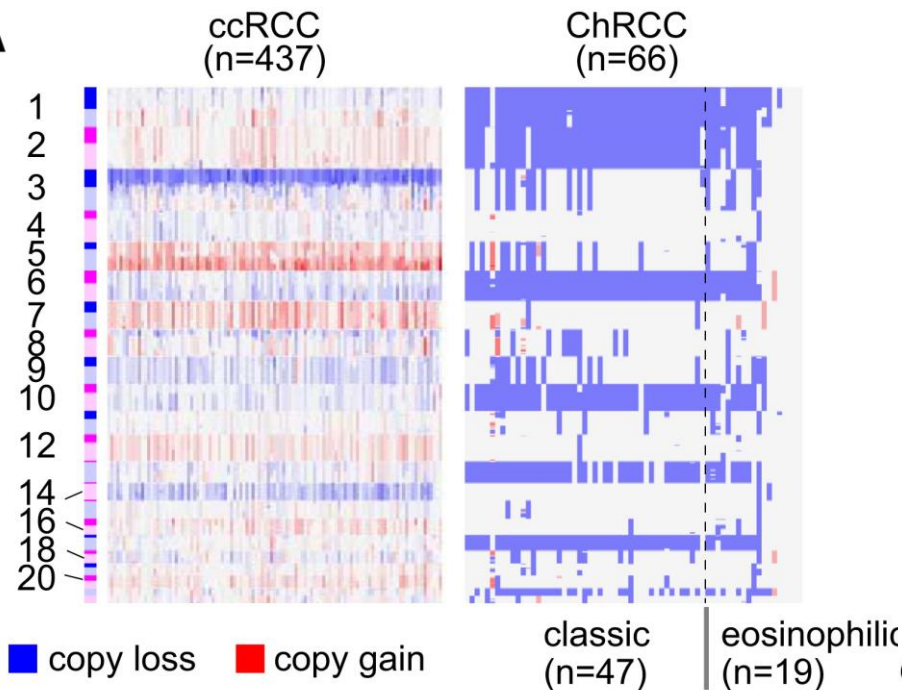


2 Histone modifying enzymes have 5 independent mutations across primary and metastasis

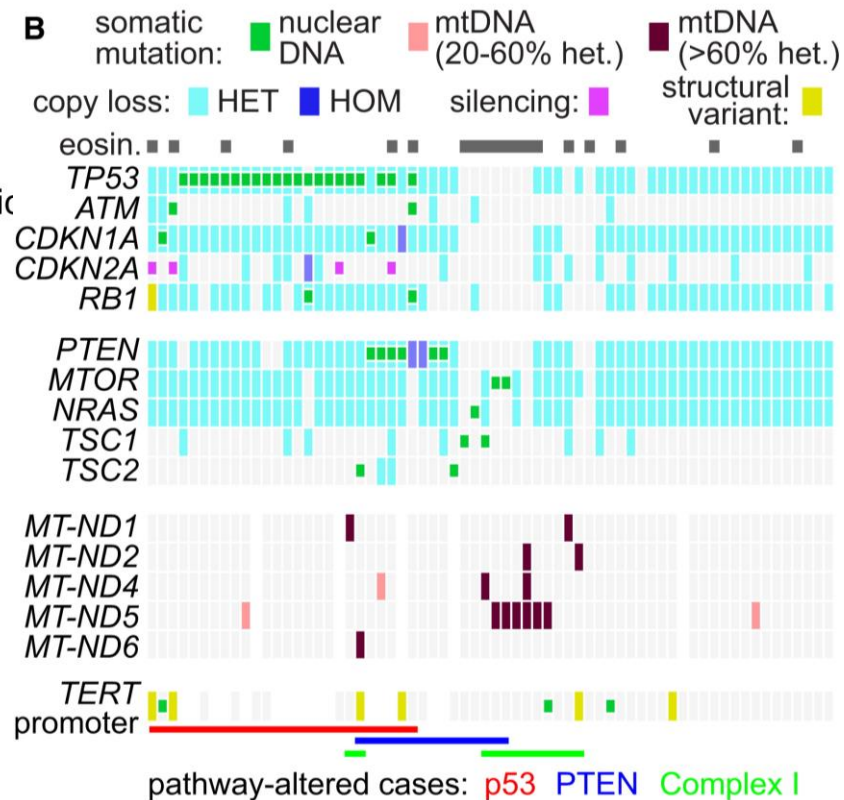


Chromophobe renal cell carcinoma

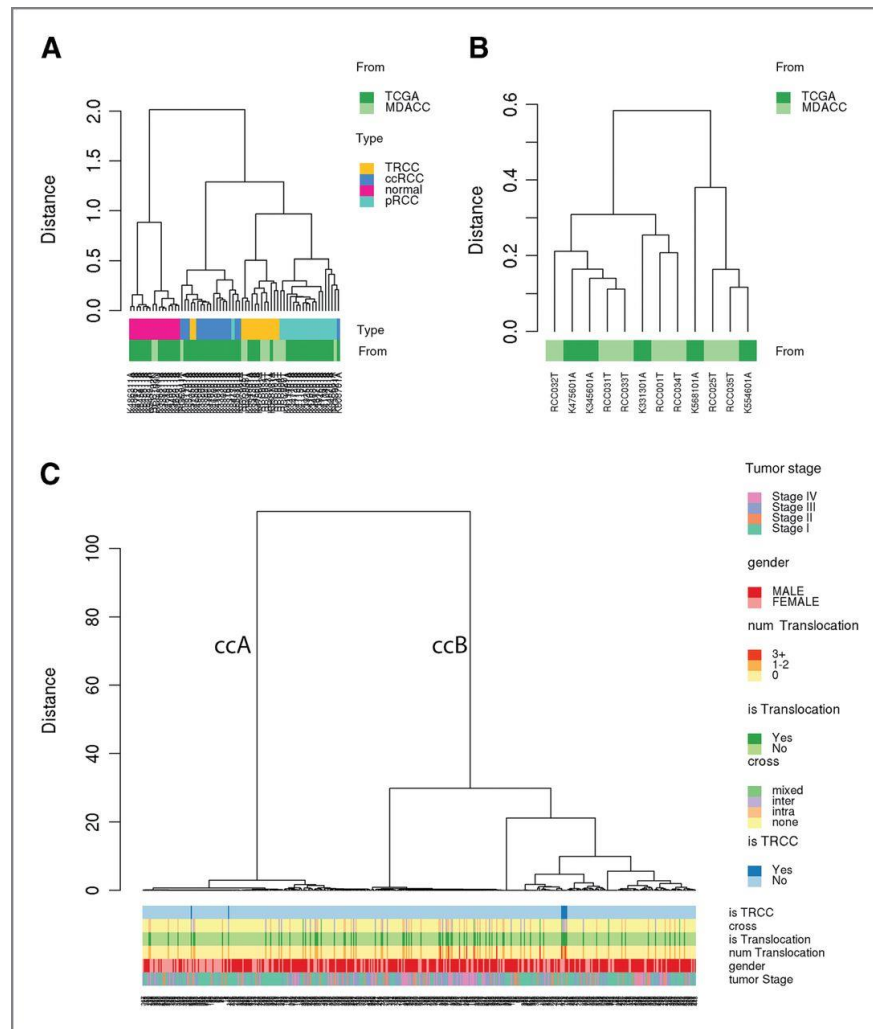
A



B



Translocation renal cell carcinoma (TRCC)



No VHL
No PBM1
No BAP1

Chromatin gene
mutations

unsupervised clustering of MITF/TFE TRCC, ccRCC, papillary RCC, and normal kidney tissue revealing that TRCC displays a unique transcriptomic profile as compared with normal kidney and other RCC types.

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CANCER RESEARCH UK



PREDICT
CONSORTIUM



The Institute
of Cancer Research

WTSI Cancer Genome Project

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