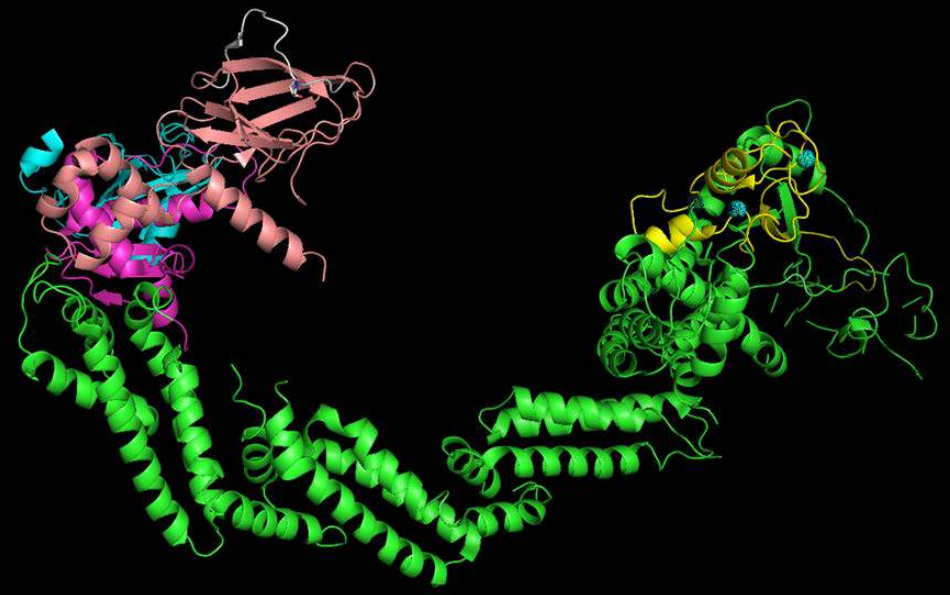
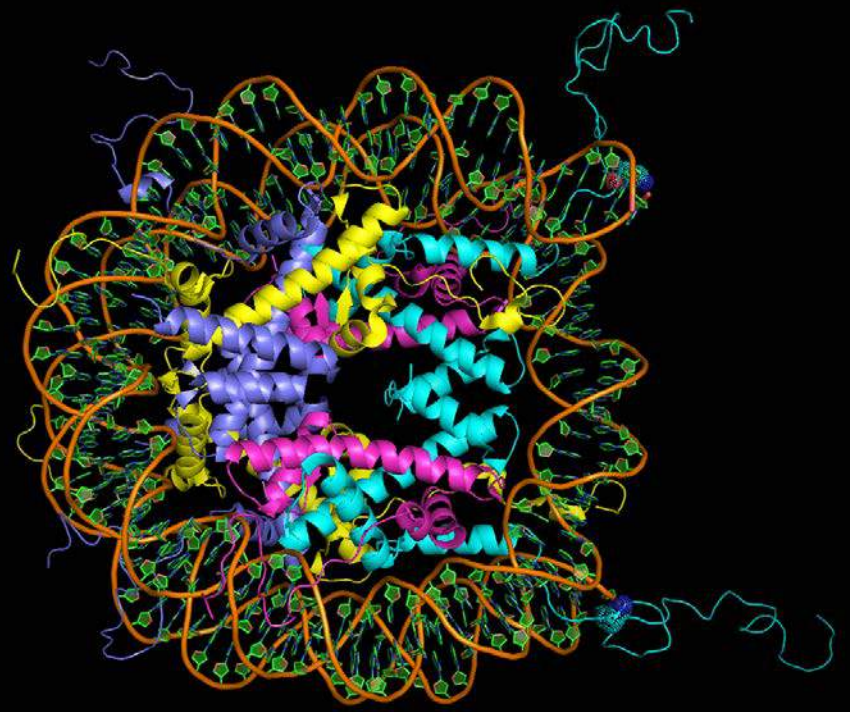
Renal Cell Cancer Genomes & Precision Medicine in 2017





Ravat Panvichian, MD
Ramathibodi Hospital

Topics

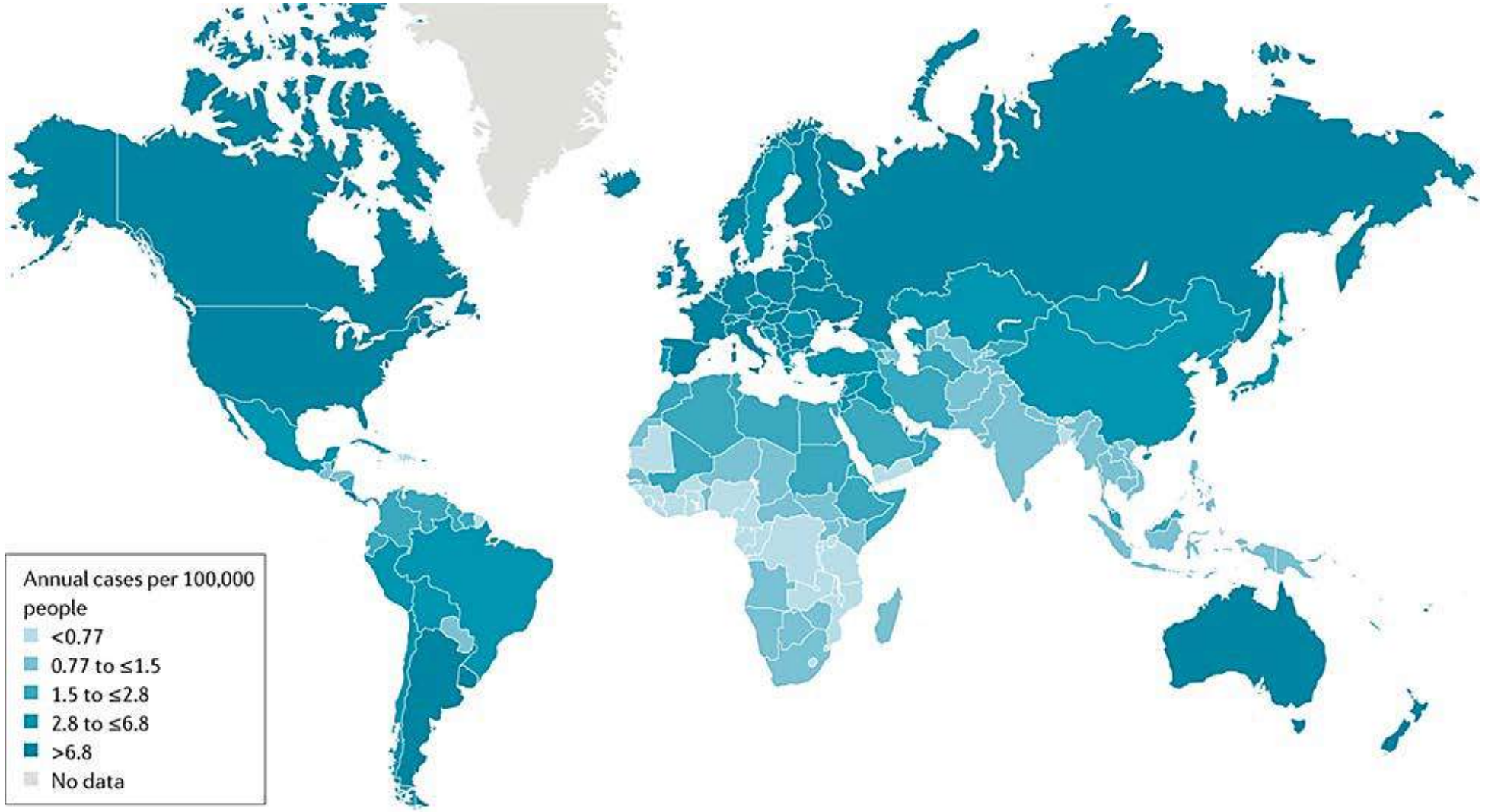
- RCC cancer genomes
- Precision Medicine of RCC in 2017

  (Targeting VEGFR kinase,

  PI3/AKT/mTOR pathways

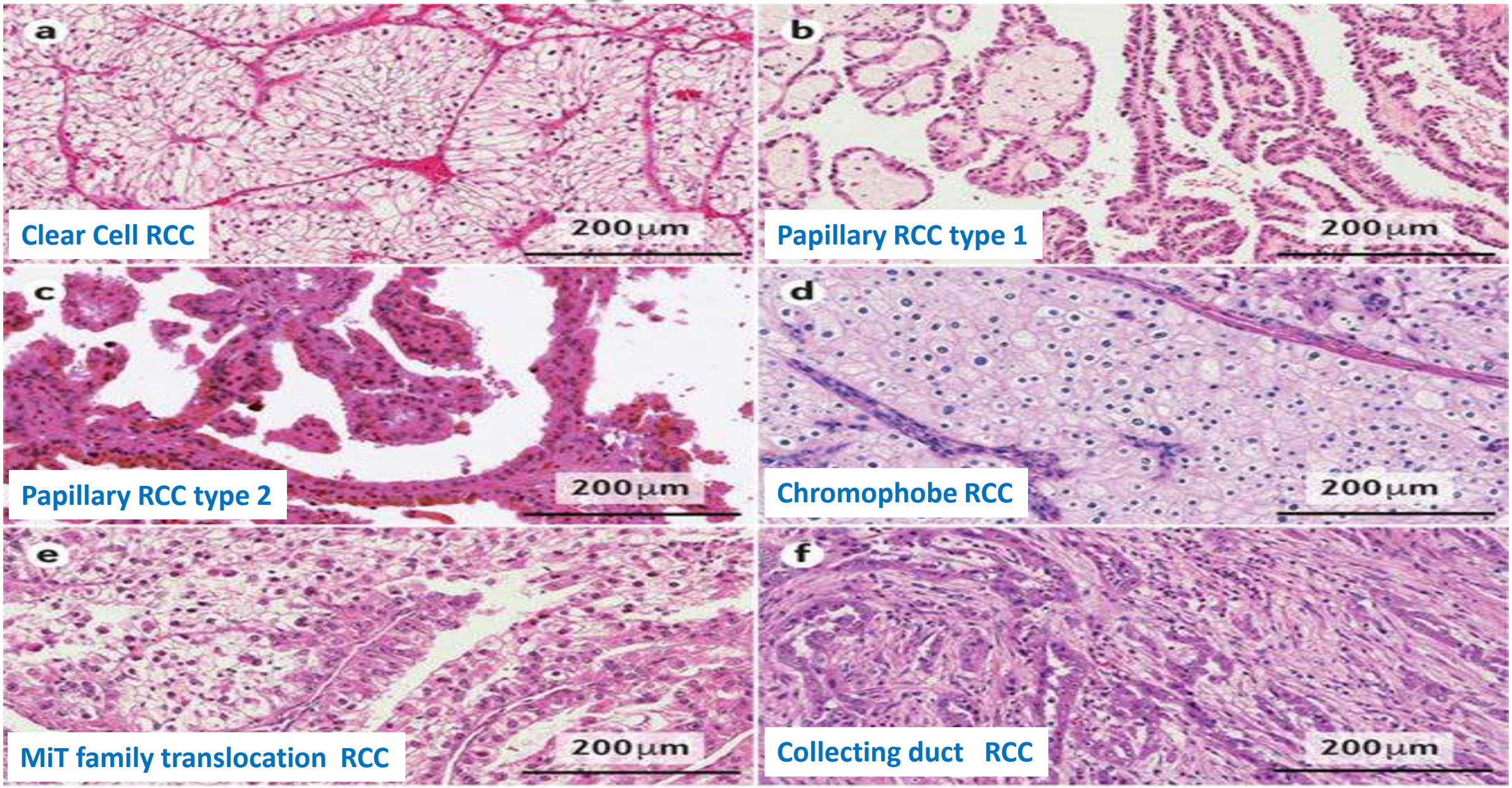
  & Immune Checkpoint inhibition)

Global kidney cancer incidence.



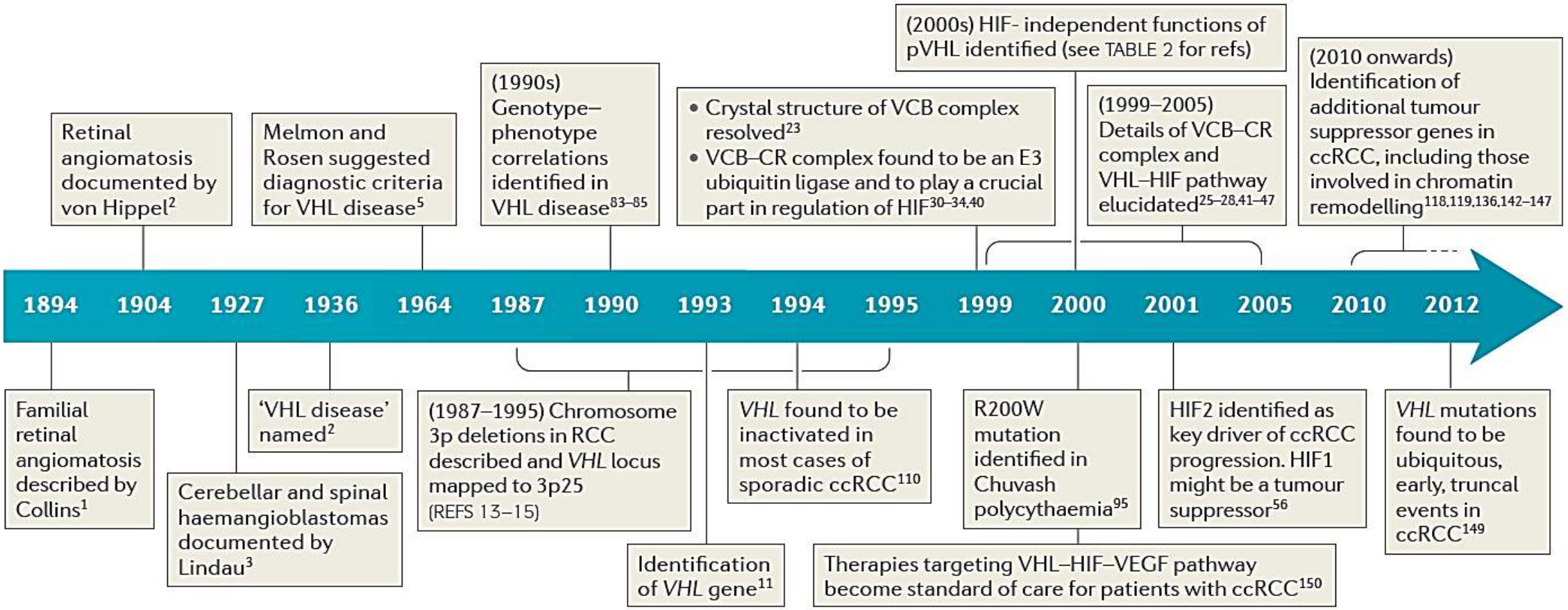
Ferlay, J., Soerjomataram, I., Ervik, M., GLOBOCAN 2012 v1.0
Cancer incidence and mortality worldwide 2013..

Distinct subtypes of renal cell carcinoma



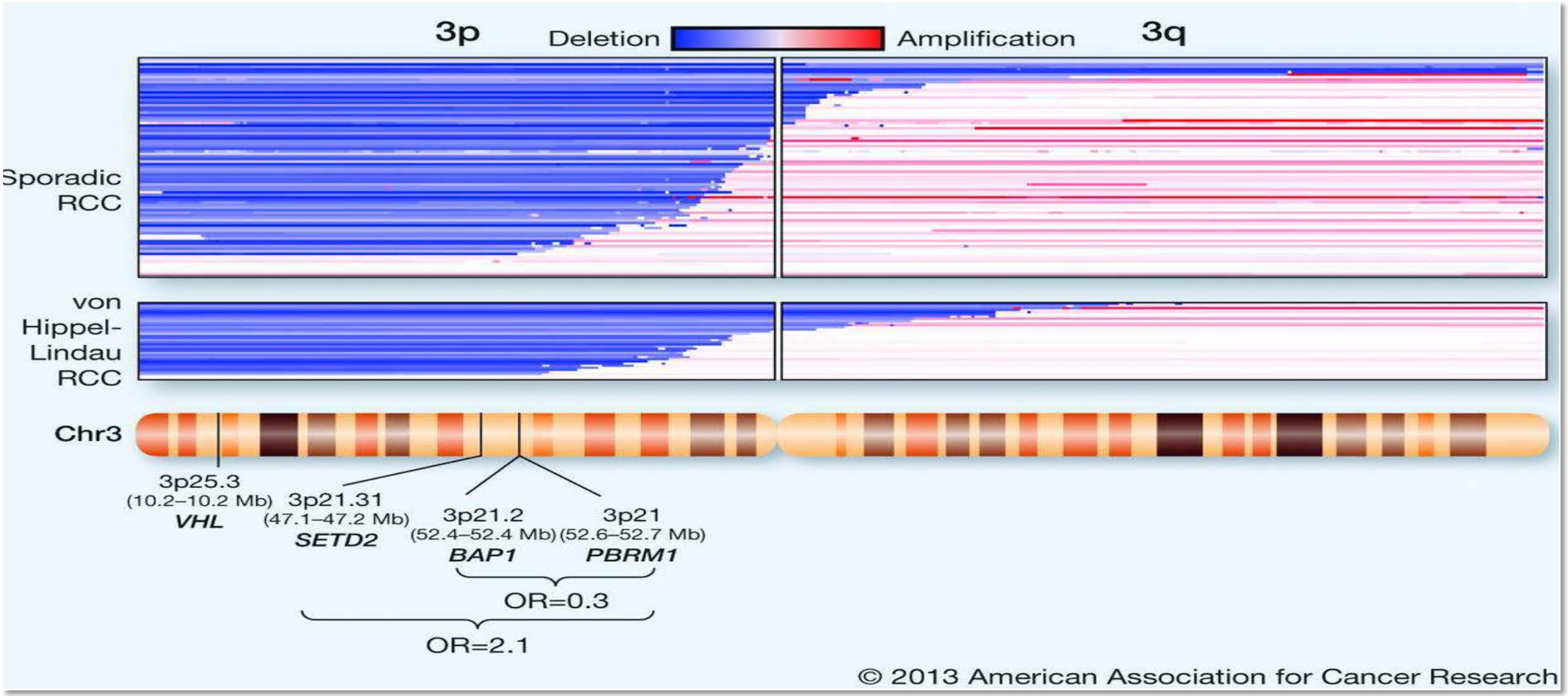
Hsieh, J. J. et al. Nat. Rev. Dis. Primers 2017; 3: 1-19

History of research on the von Hippel–Lindau (VHL) gene.



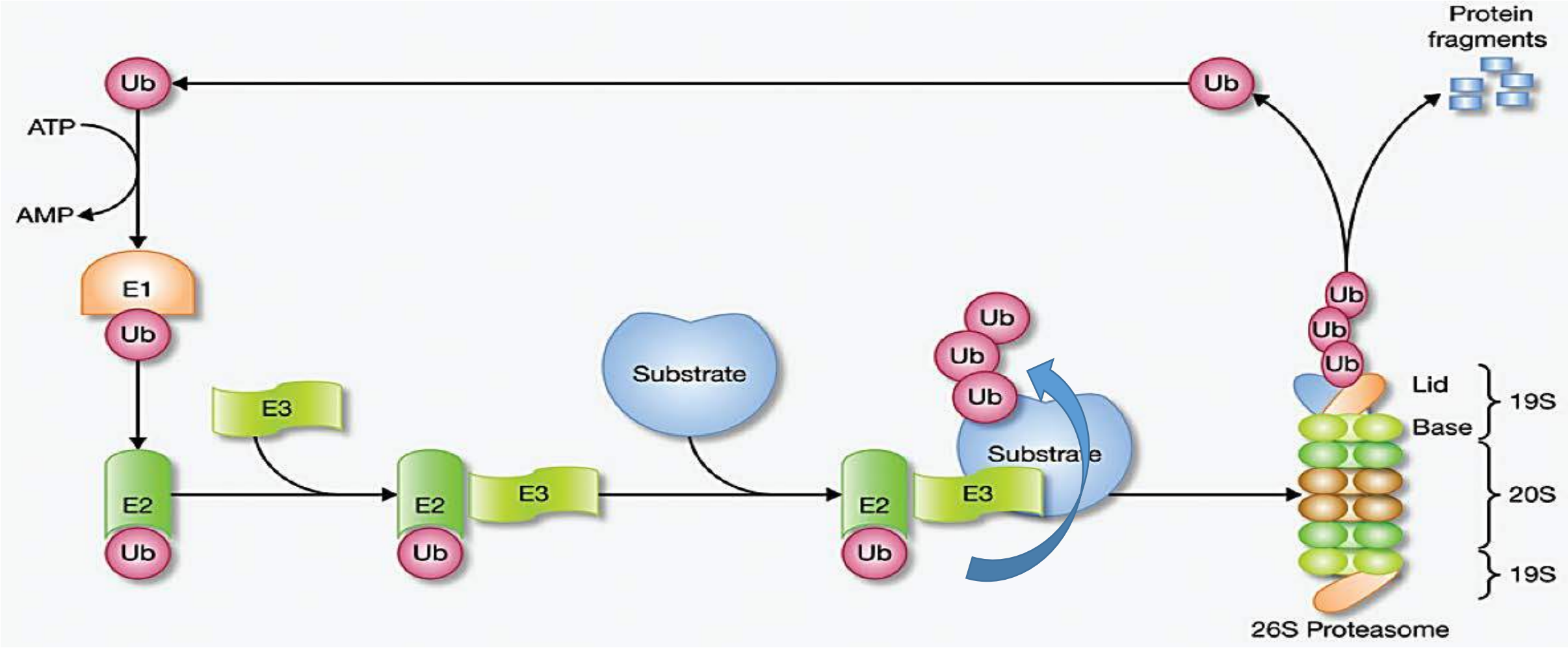
Gossage L., et al. Nature Reviews Cancer 2015; 15: 55-64

Schematic of chromosome 3 with the estimated position of VHL, SETD2, BAP1, and PBRM1 genes and corresponding DNA copy number alterations in sporadic and familial (von Hippel–Lindau syndrome) ccRCC.



Samuel Peña-Llopis et al. Cancer Res 2013;73:4173-4179

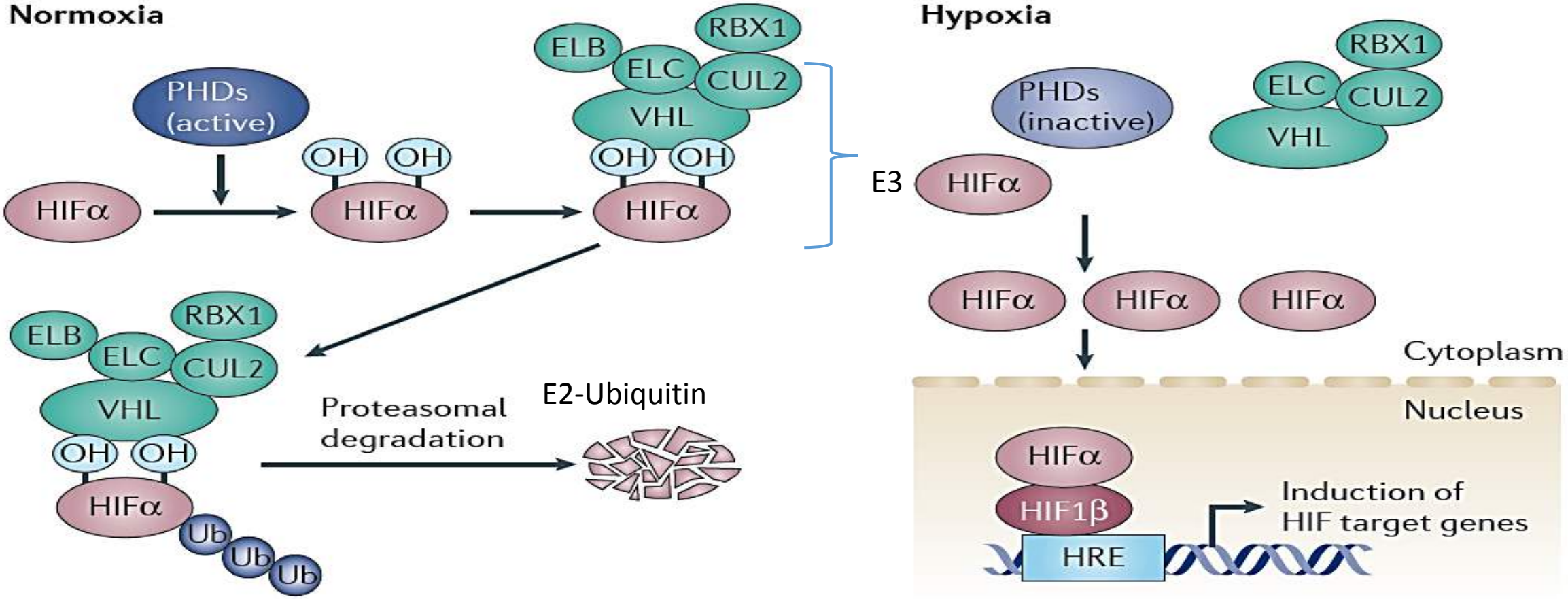
Ubiquitin-Proteasome System



E1, the ubiquitin-activating enzyme
E2, ubiquitin-conjugating enzyme
E3, ubiquitin ligase

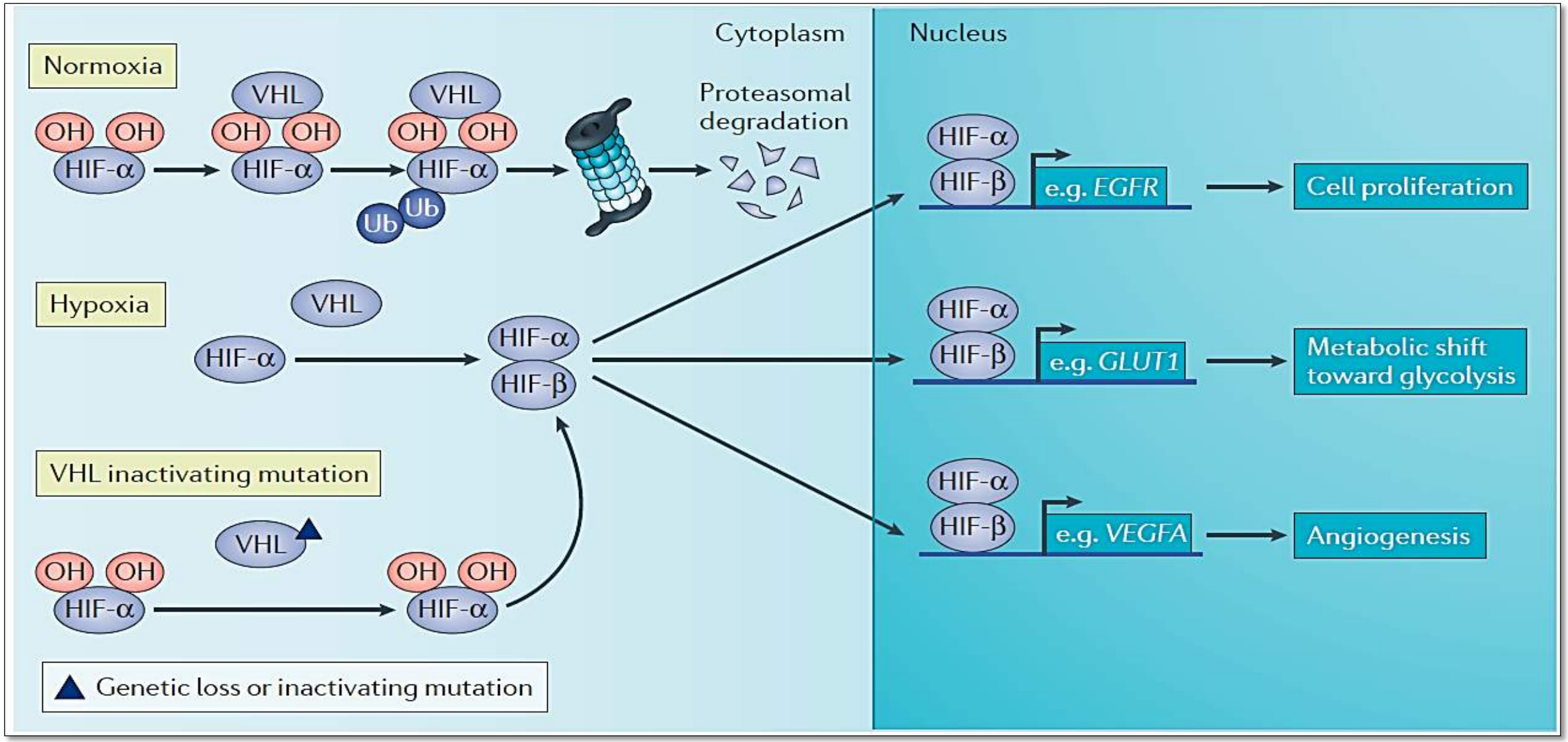
Nader Rahimi. Mol Cancer Ther 2012; 11(3); 538–48.

Oxygen-dependent hypoxia-inducible factor (HIF) regulation.



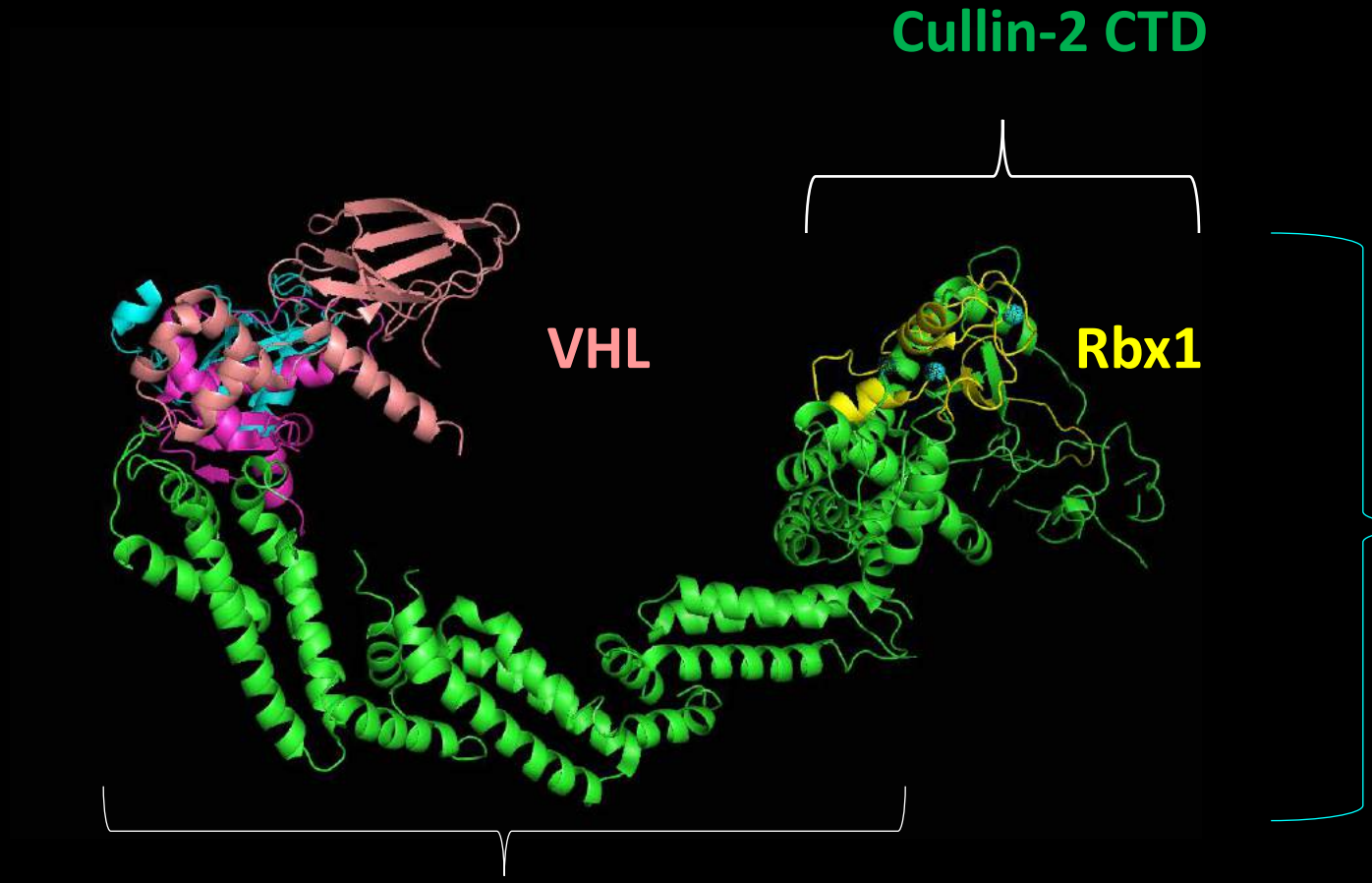
Gossage L., et al. Nature Reviews Cancer 2015; 15: 55-64

The VHL–HIF pathway in clear cell renal cell carcinoma (ccRCC)



Riazalhosseini, Y. & Lathrop, M. Nat. Rev. Nephrol 2016; 12: 655-666

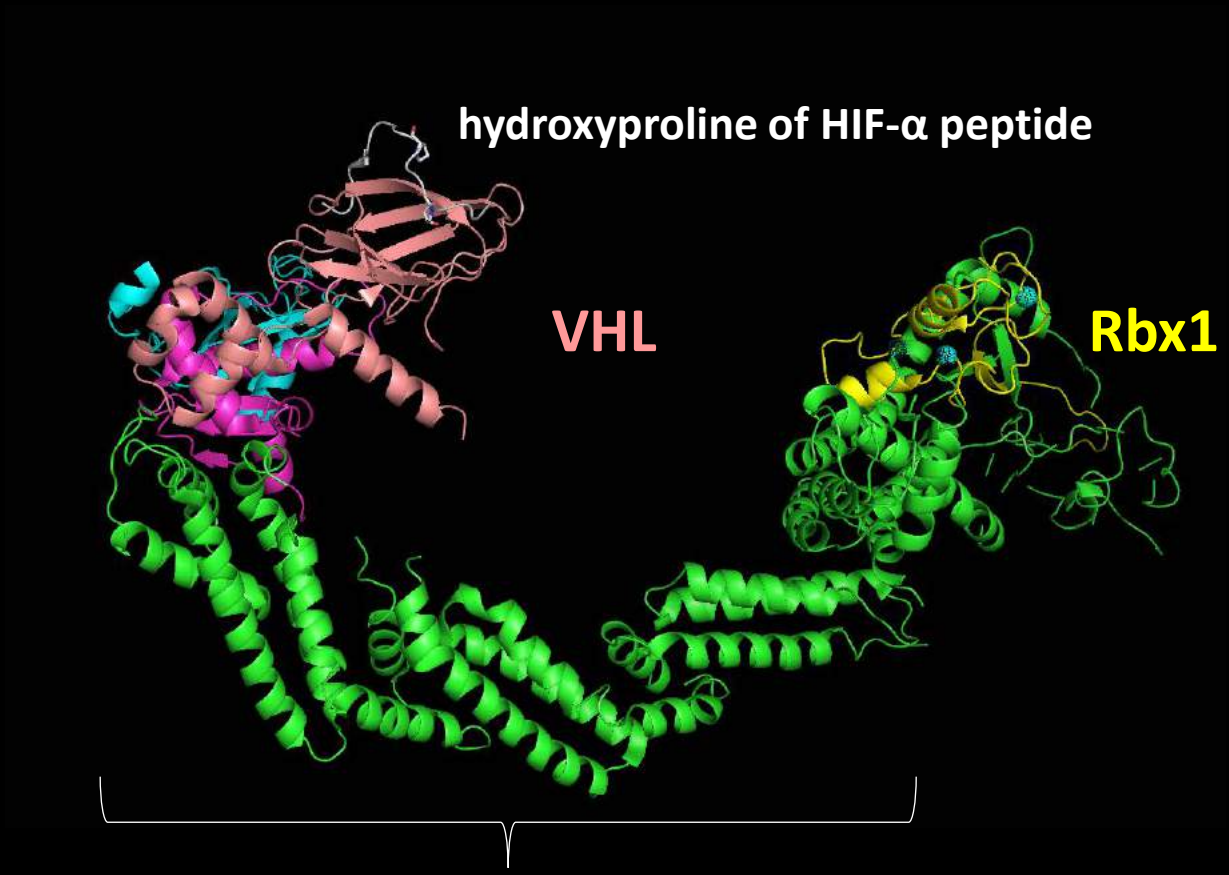
The VHL-EloginBC-Cul2 Ubiquitin Ligase Complex



PDB:5N4W align 1LQB

Hon WC, et al.Nature 2002; 417: 975-978
Cardote TAF, et al. Structure 2017; 25: 901-911

The VHL-EloginBC-Cul2 Ubiquitin Ligase Complex binds hydroxyproline of HIF-α peptide



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Hon WC, et al.Nature 2002; 417: 975-978
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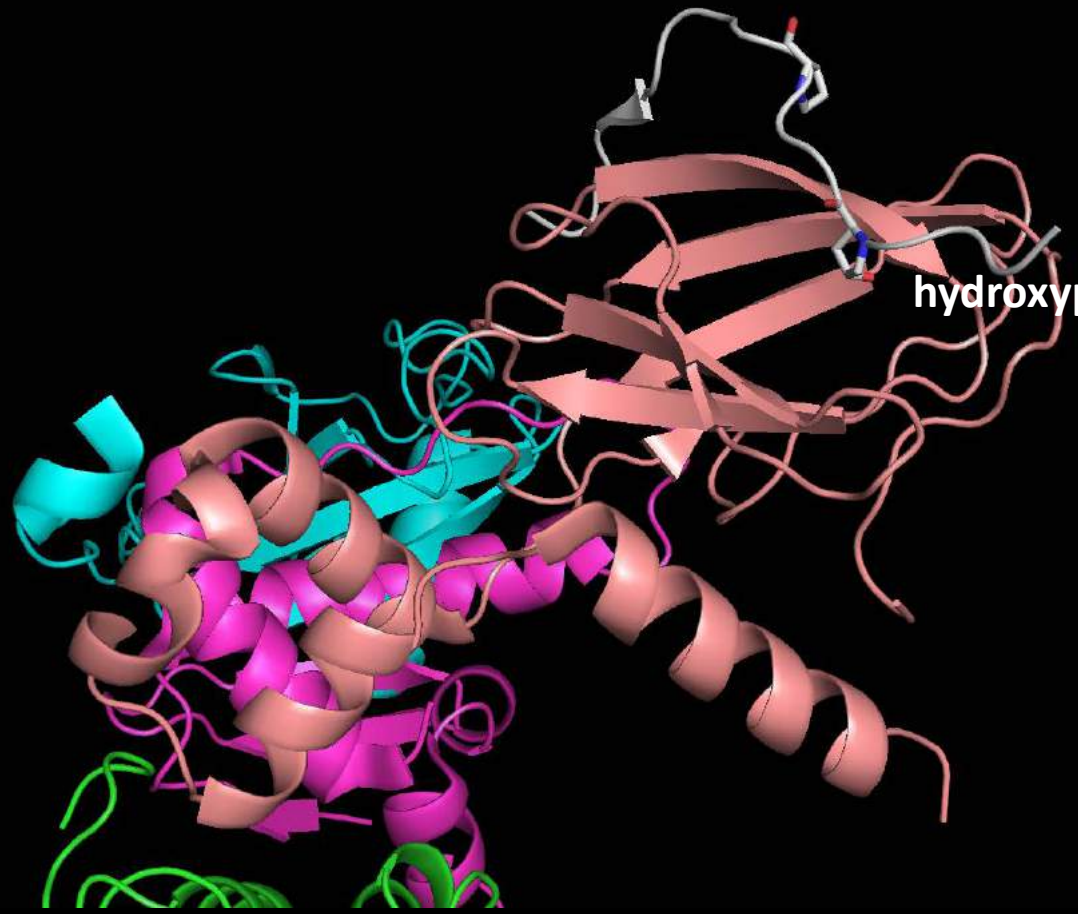
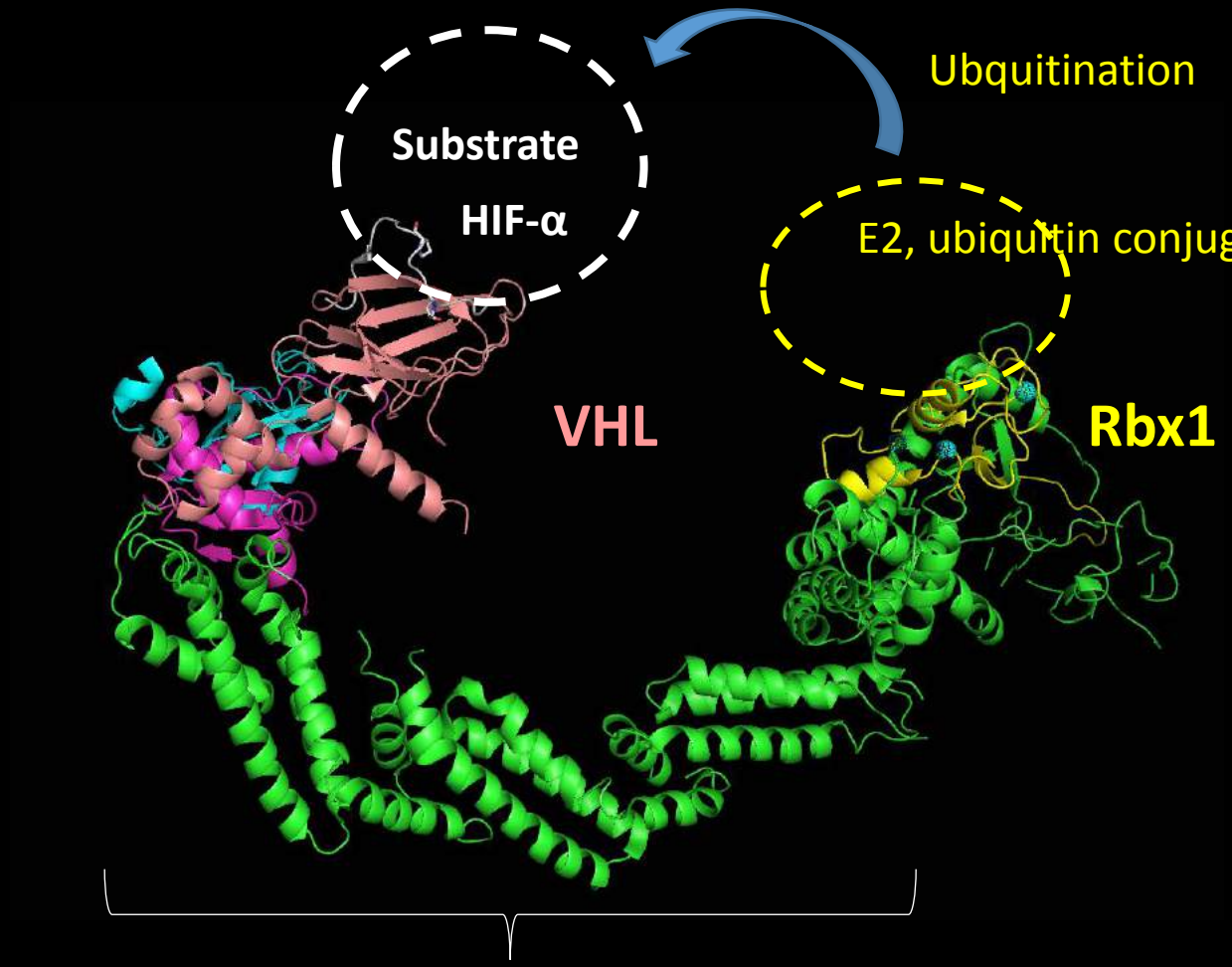


ElonginB
ElonginC

PDB:5N4W align 1LQB

Hon WC, et al.Nature 2002; 417: 975-978
Cardote TAF, et al. Structure 2017; 25: 901-911

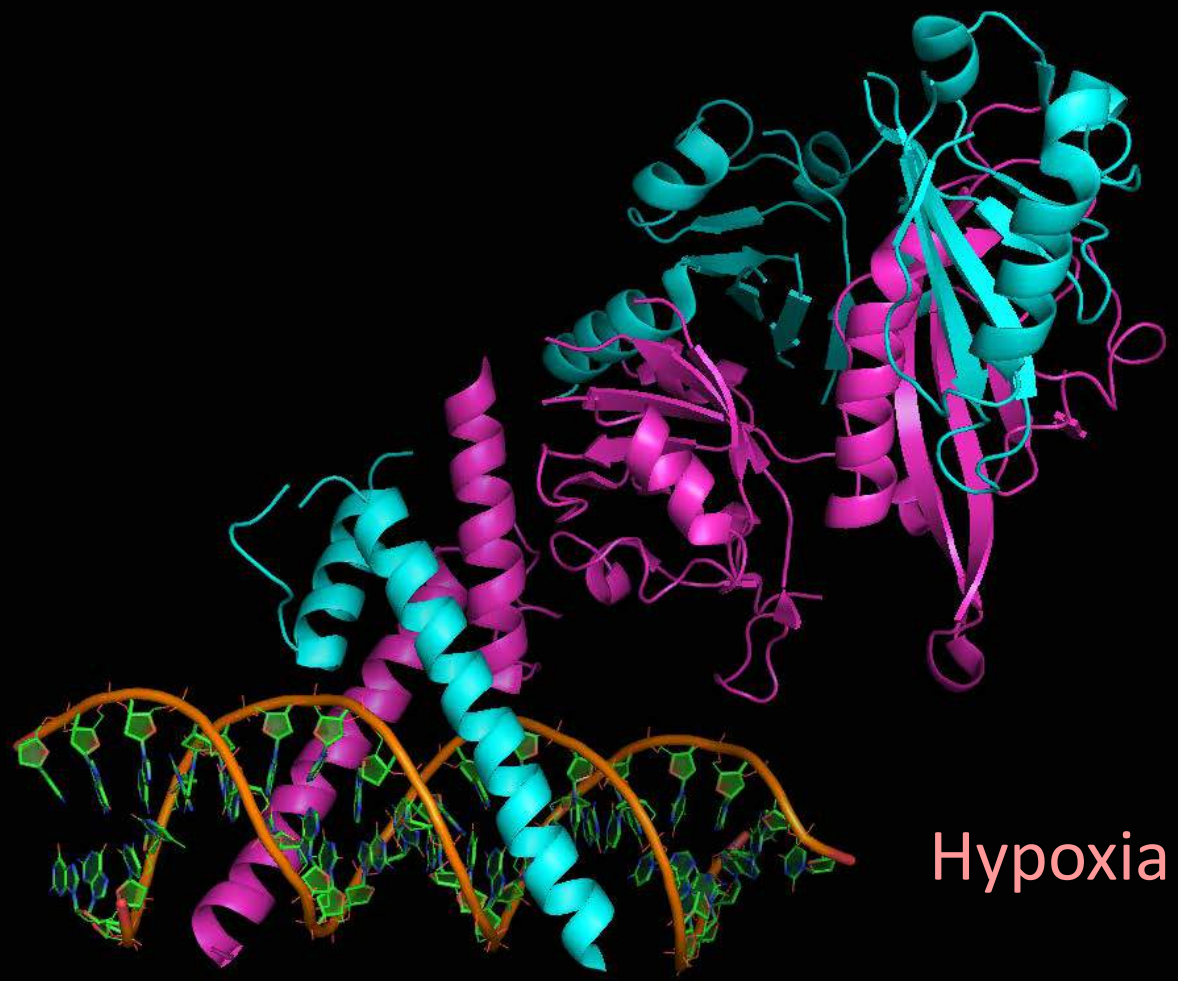
The VHL-EloginBC-Cul2 Ubiquitin Ligase Complex binds hydroxyproline of HIF-α peptide



PDB:5N4W align 1LQB

Hon WC, et al.Nature 2002; 417: 975-978
Cardote TAF, et al. Structure 2017; 25: 901-911

Heterodimeric HIF-1a: HIF-1β Complex with HRE DNA



HIF-1β

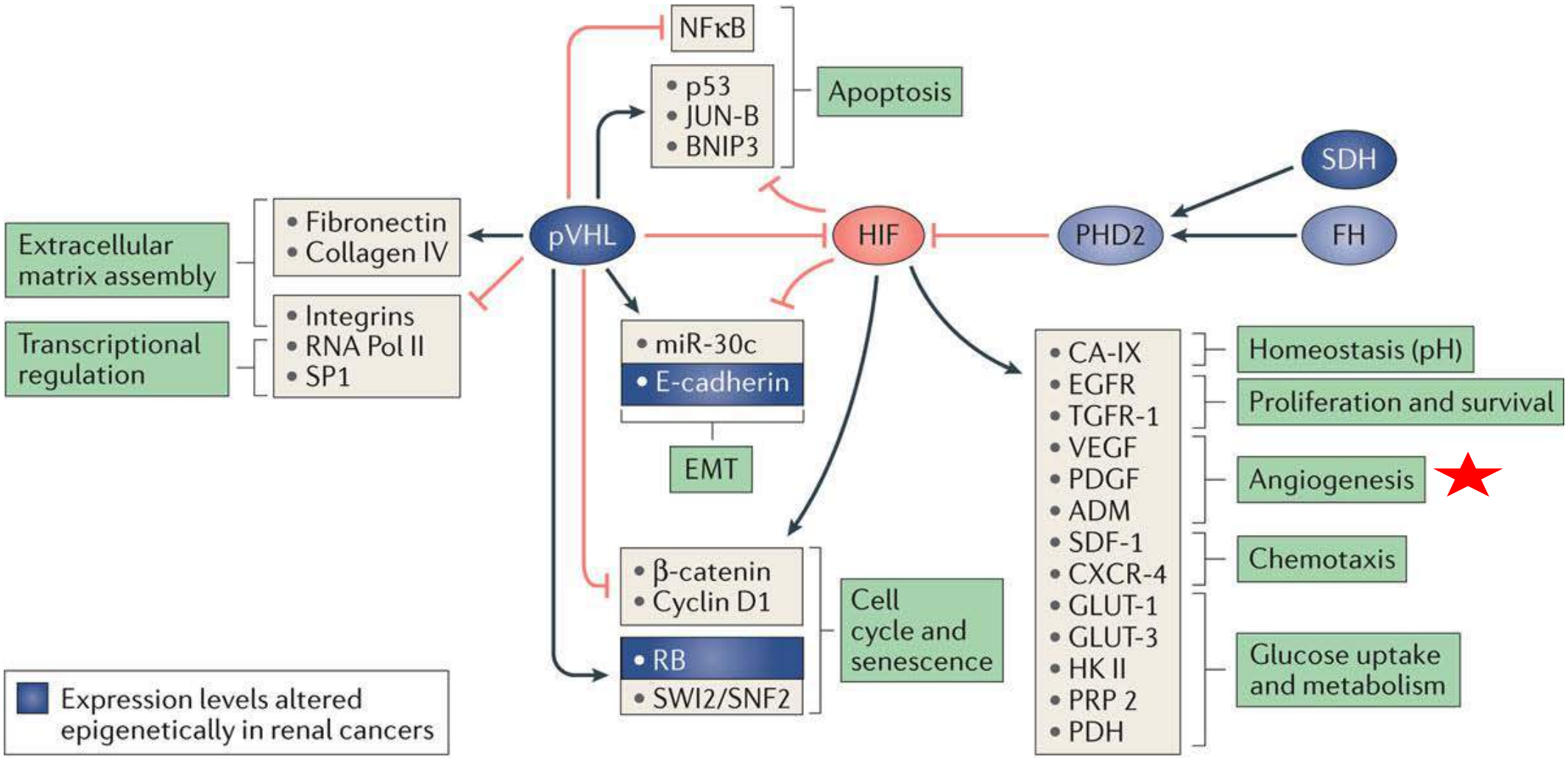
HIF-1α

Hypoxia response elements (HRE) DNA

PDB: 4ZPR

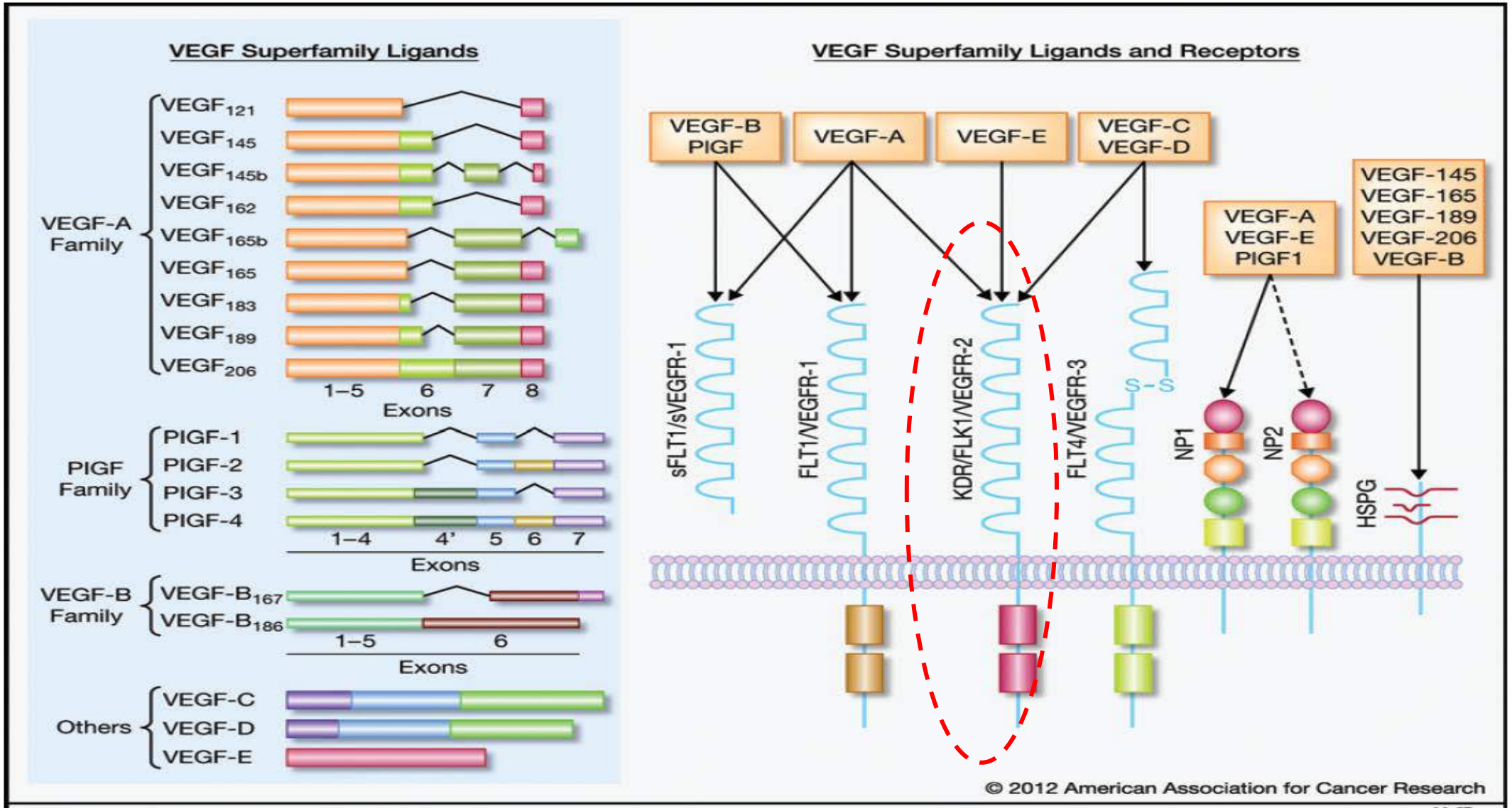
WU D. et al. Nature 2015: 524: 303-308

Involvement of pVHL in cellular physiology and RCC



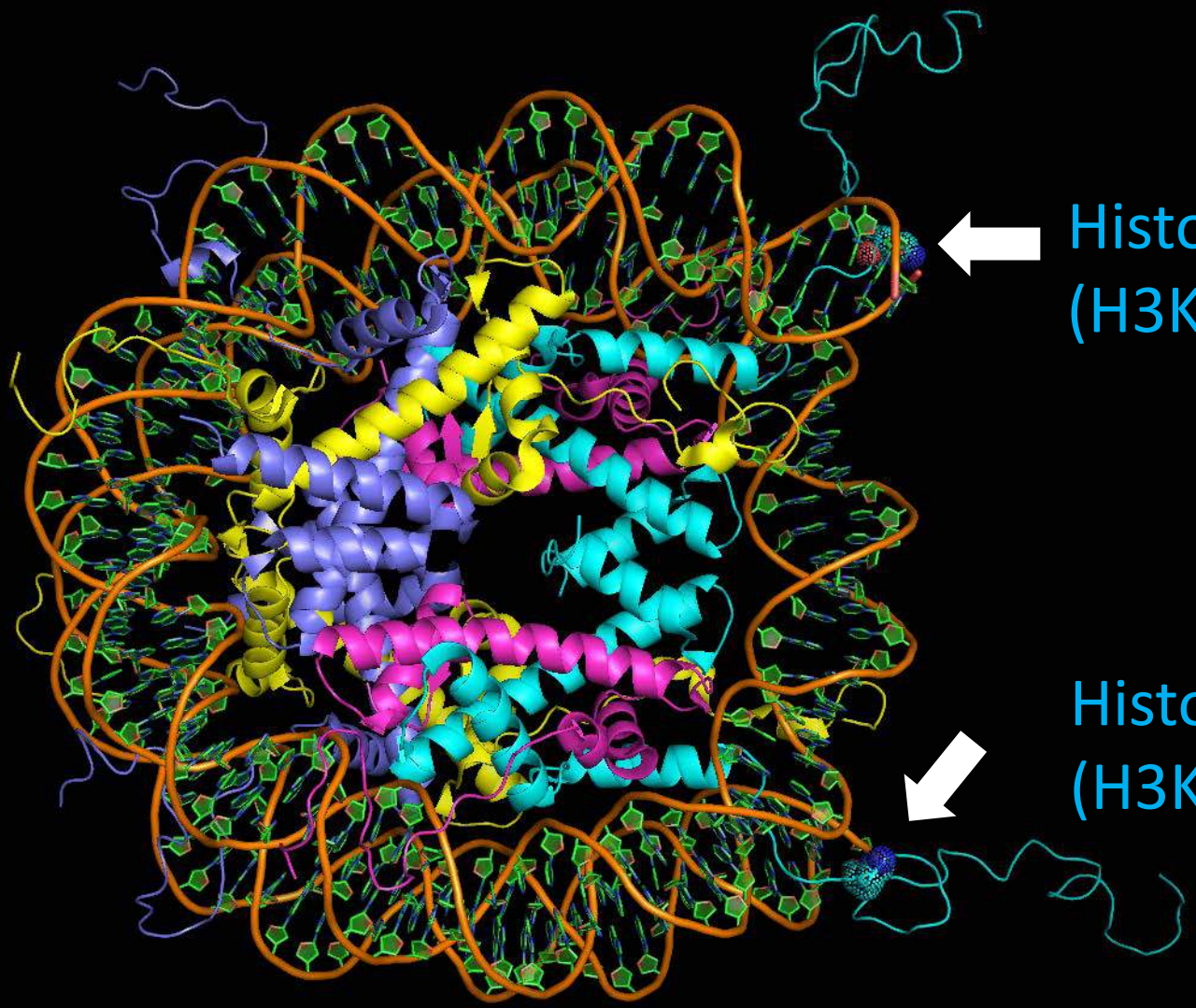
Morris, M. R. & Latif, F. Nature Reviews Nephrology 2017; 13: 47-60

VEGF superfamily ligands and receptors.



Nader Rahimi. Mol Cancer Ther 2012; 11(3); 538–48.

X-Ray Structure of the Nucleosome Core Particle at 1.9 A Resolution



Histone3Lysine36
(H3K36)

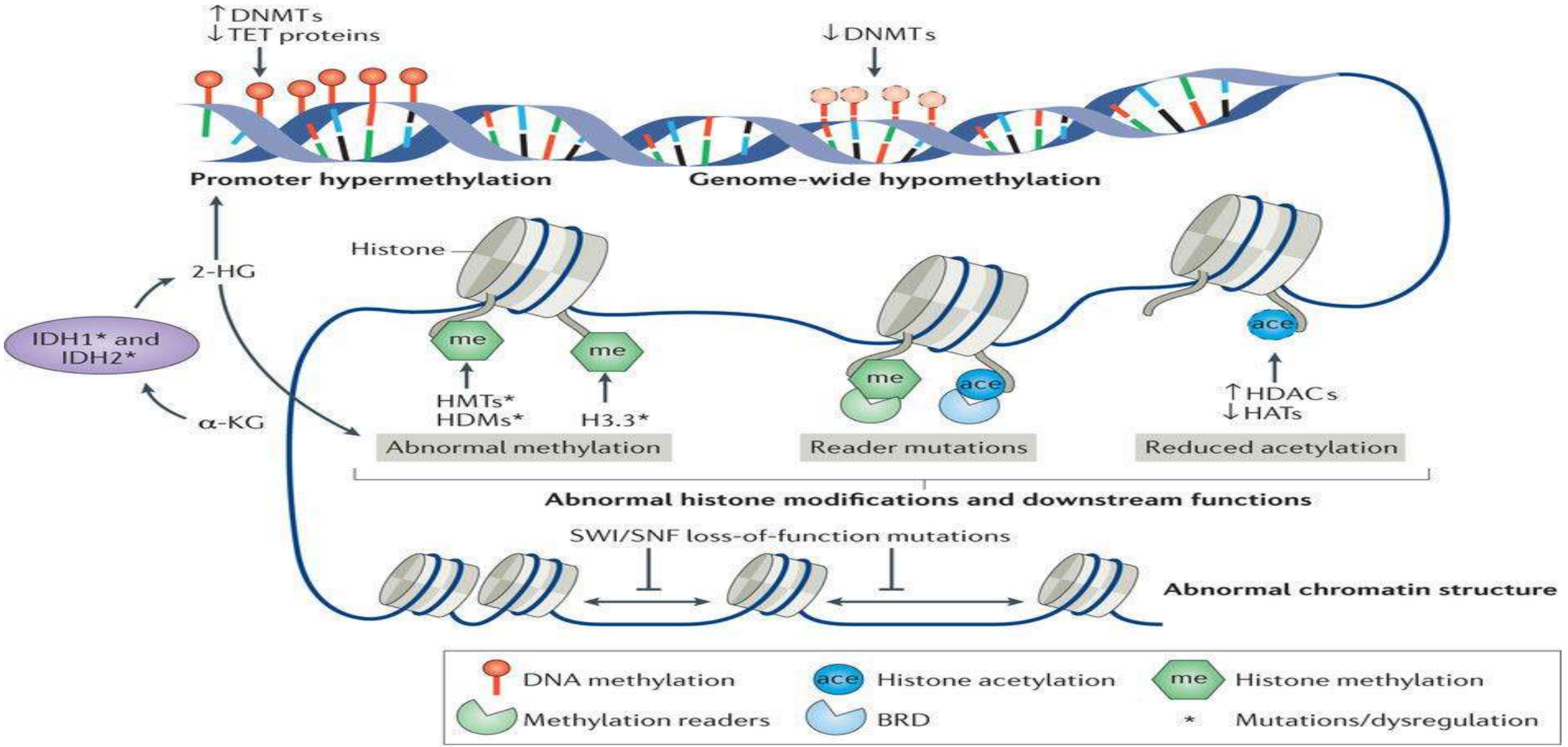
Histone3Lysine36
(H3K36)

Histone3
Histone4
Histone2A.1
Histone2B.2

PDB:1KX5

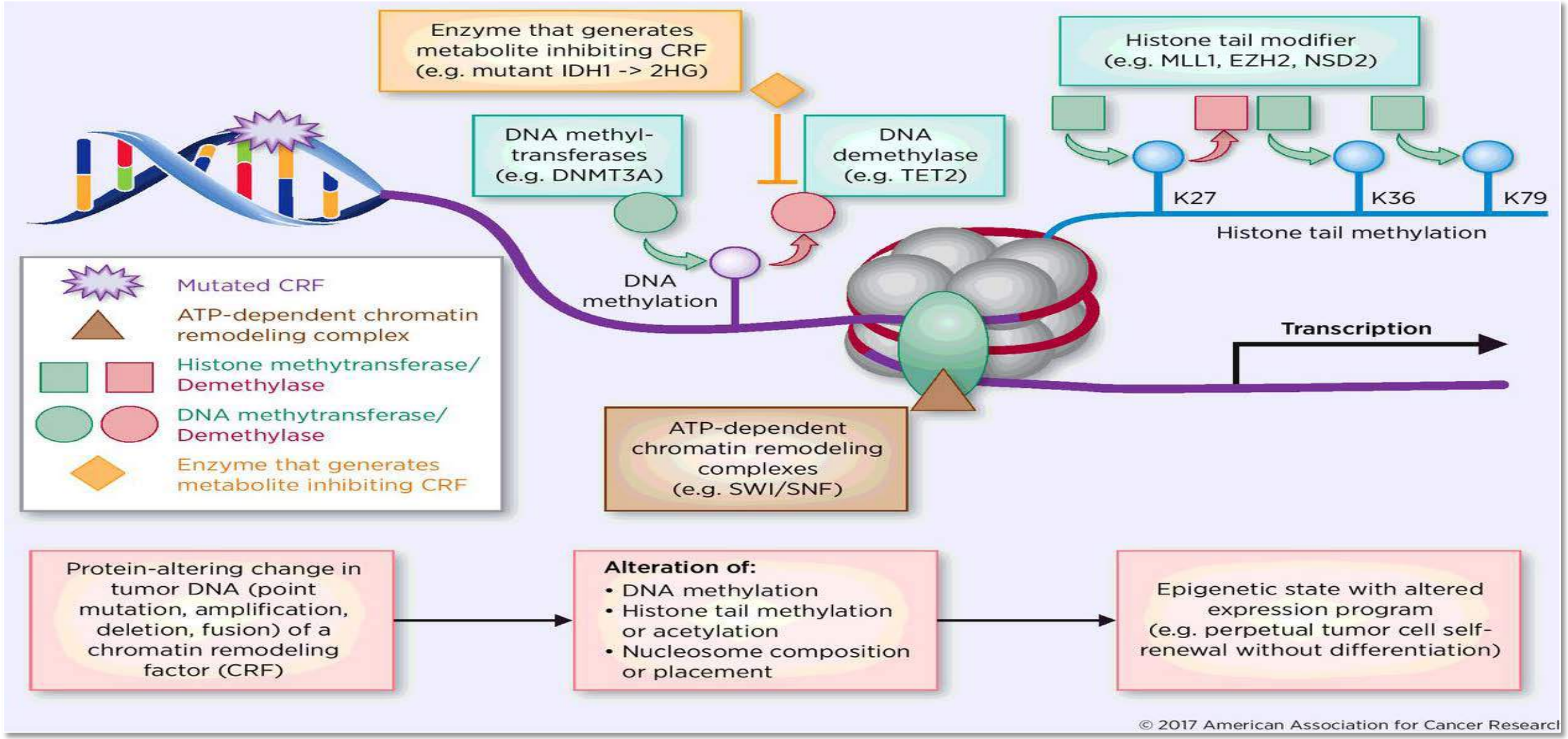
Davey CA, et al. J.Mol.Biol.2002; 319: 1097-1113

The landscape of epigenetic mutations in cancer



Sophia Xiao Pfister& Alan Ashworth. Nature Reviews Drug Discovery 2017;16:241–263

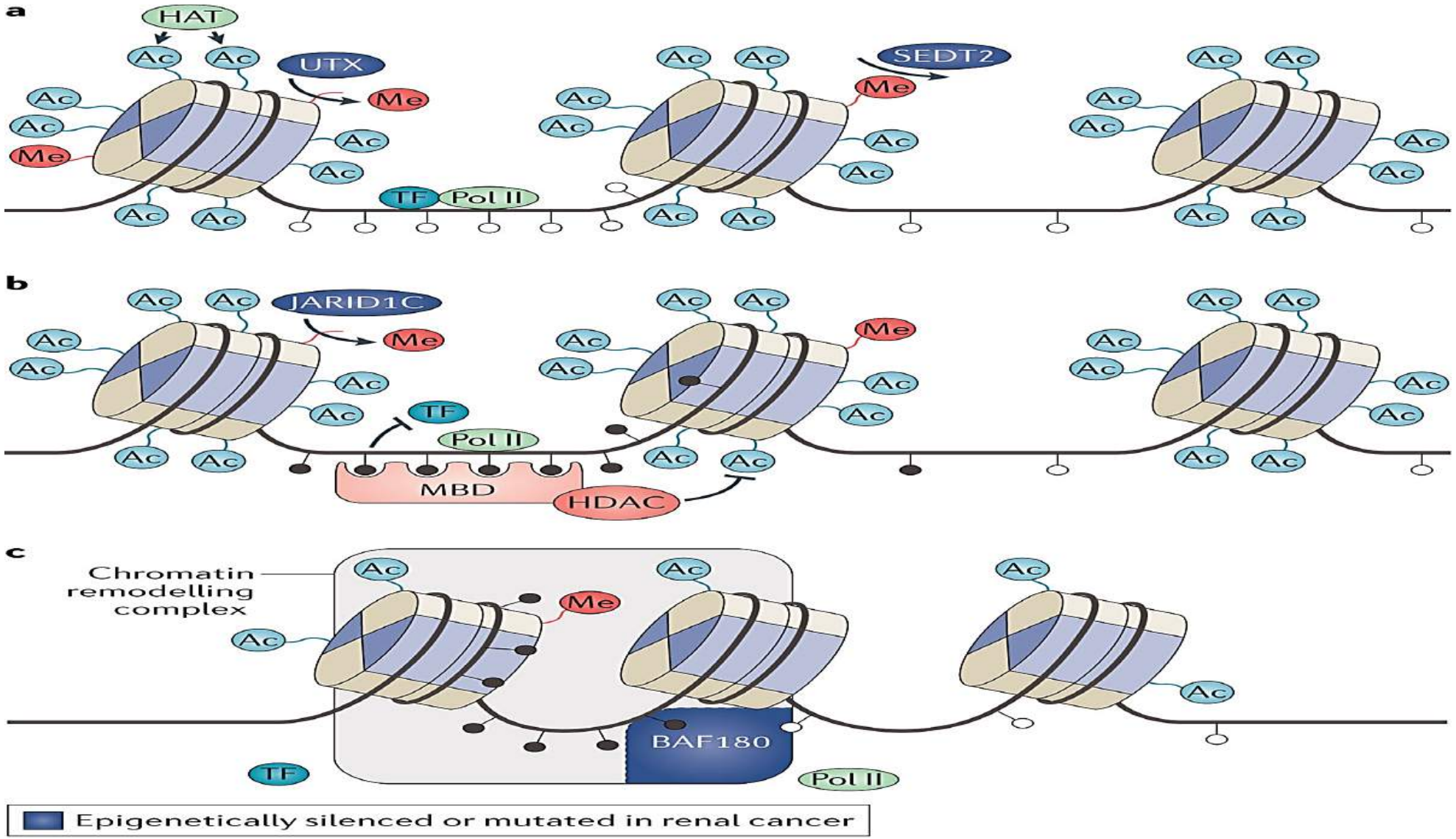
Schematic demonstrates how alterations in the coding DNA of CRFs result in tumor cell proliferation.



CRF: chromatin remodeling factor

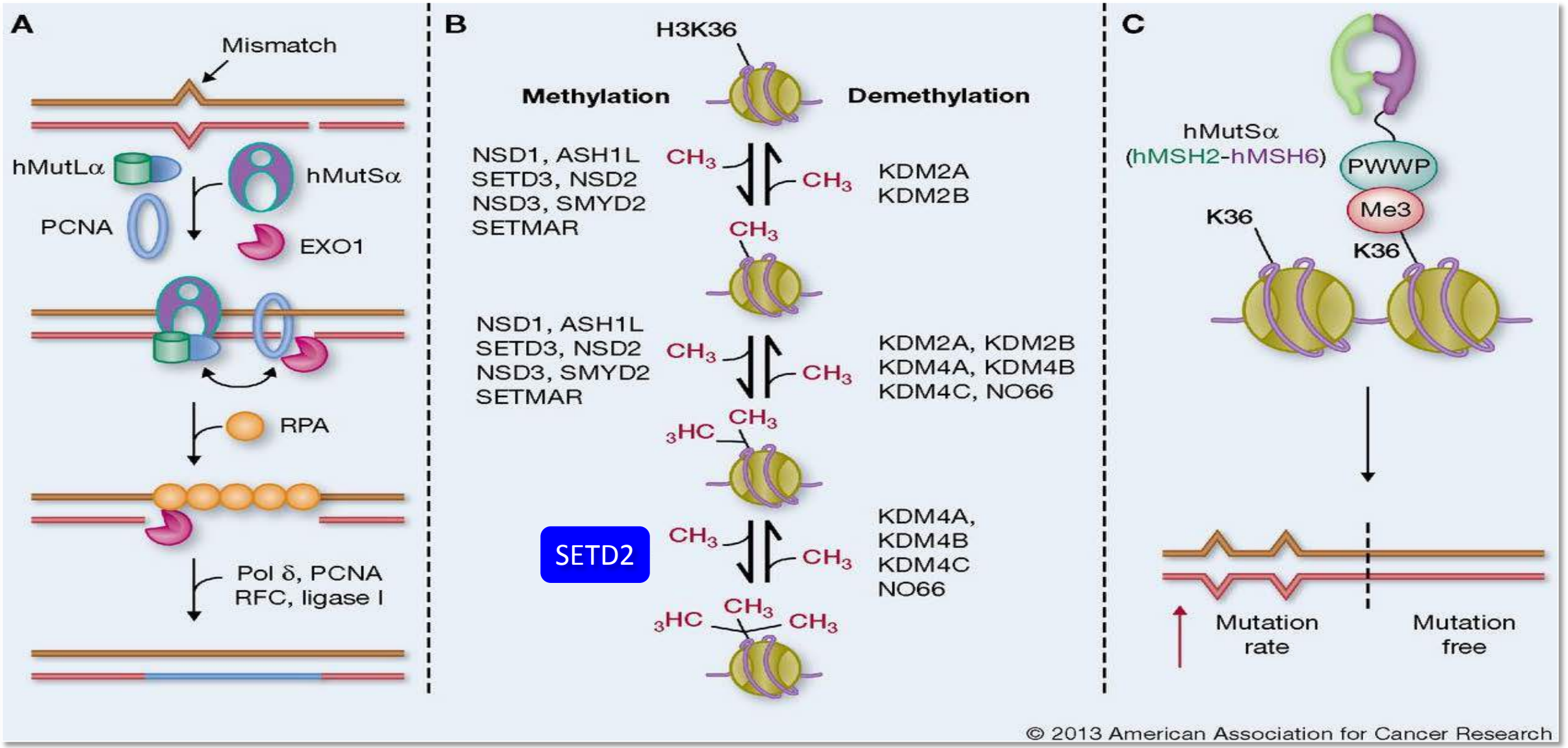
Carl Koschmann et al. Cancer Res 2017;77:227-233

Histone acetylation and methylation regulate gene expression



Morris, M. R. & Latif, F. Nature Reviews Nephrology 2017; 13: 47-60

Influence of H3K36me3 on MMR and genome stability.



Guo-Min Li Cancer Res 2013;73:6379-6383

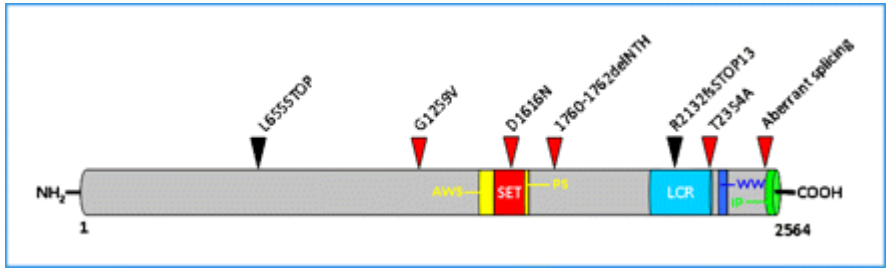
Functions of epigenetic regulators implicated in Cancer

Genes	Normal functions of gene product	Mutations that occur in cancer	Outcome of mutations
Histone methylation			
SETD2 (also known as HYPB)	H3K36 methyltransferase	Frequent inactivating mutations in ALL, gliomas, and renal, lung and breast cancers	• Global loss of H3K36me3 • DNA repair deficiency • DNA replication stress
Histone acetylation			
p300 (also known as EP300)	Histone acetyltransferase	• Truncating mutations in DLBCL, AML and cervical cancer • Fusion with MLL in serous endometrial tumours	Loss of acetyltransferase activity
CBP (also known as CREBBP)	Histone acetyltransferase	• Truncating and/or inactivating mutations in DLBCL, ALL, and lung and bladder cancers • Fusion with MLL gene in AML	Loss of acetyltransferase activity
Chromatin remodelling			
SNF5 (also known as SMARCB1, INI1 or BAF47)	Transcription co-activator subunit of the SWI/SNF complex	Biallelic inactivation in the majority of malignant rhabdoid tumours	Transcriptional silencing of tumour suppressor genes such as P16
ARID1A	DNA-binding domain-containing subunit of the SWI/SNF complex that confers functional specificity	Frequent inactivating mutations in various solid tumours (melanoma, ovarian, endometrioid, bladder, gastric, hepatocellular, and pancreatic tumours) and Burkitt lymphoma	Transcriptional silencing, DNA repair and replication deficiency
PBRM1 (also known as BAF180 or PB1)	Bromodomain-containing subunit of the SWI/SNF complex that targets chromatin	Frequent inactivating mutations in renal, hepatocellular, breast, gastric and pancreatic cancers	• Aberrant transcriptional regulation • Amplified HIF transcriptional signature • Increased cell growth in vivo
BRG1 (also known as SMARCA4)	Catalytic ATPase subunit of the SWI/SNF complex	Frequent inactivating mutations in medulloblastoma, Burkitt lymphoma, SCCOHT, and lung, pancreatic and renal cancers	Loss of cell cycle control by RB

Sophia Xiao Pfister& Alan Ashworth. Nature Reviews Drug Discovery 2017;16:241–263

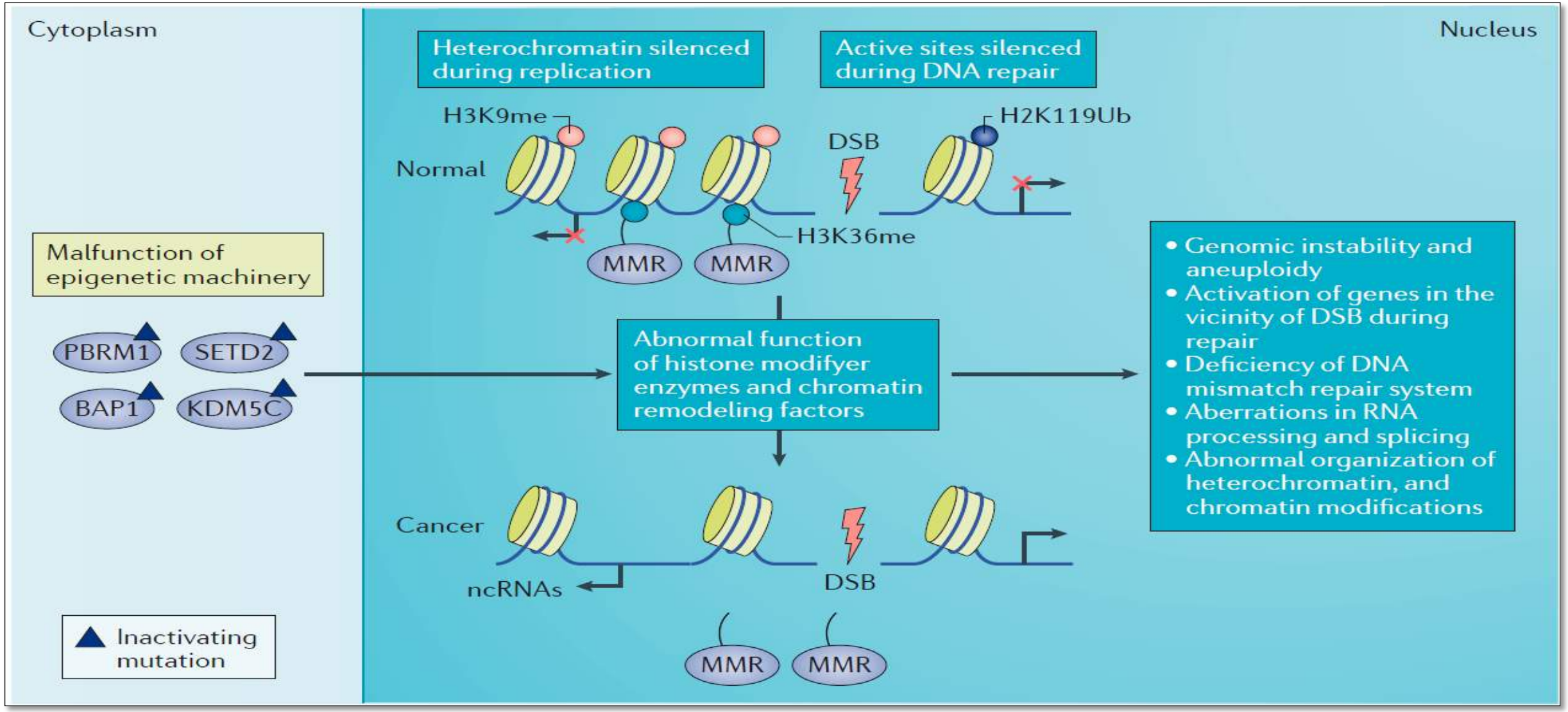
Histone Methyltransferase Gene SETD2 Is a Novel Tumor Suppressor Gene in Clear Cell Renal Cell Carcinoma

- **Sporadic clear cell renal cell carcinoma (cRCC)** is genetically characterized by the recurrent loss of the short arm of chromosome 3, with a hotspot for copy number loss in the 3p21 region.
- We applied a method called “gene identification by nonsense-mediated mRNA decay inhibition” to a panel of **10 cRCC cell lines with 3p21 copy number loss to identify biallelic inactivated genes located at 3p21.**
- This revealed inactivation of the histone methyltransferase gene **SETD2**, located on 3p21.31, **as a common event in cRCC cells.**
- SETD2 is nonredundantly responsible for trimethylation of the histone mark H3K36.
- Consistent with this function, we observed loss or a decrease of H3K36me3 in 7 out of the 10 cRCC cell lines.
- Identification of missense mutations in 2 out of 10 primary cRCC tumor samples added support to the involvement of loss of SETD2 function in the development of cRCC tumors.



Gerben Duns, et al. Cancer Res 2010; 70(11); 4287–91

Malfunction of the epigenetic machinery contributes to genomic instability and deficiency of the DNA repair system in clear cell renal cell carcinoma (ccRCC)



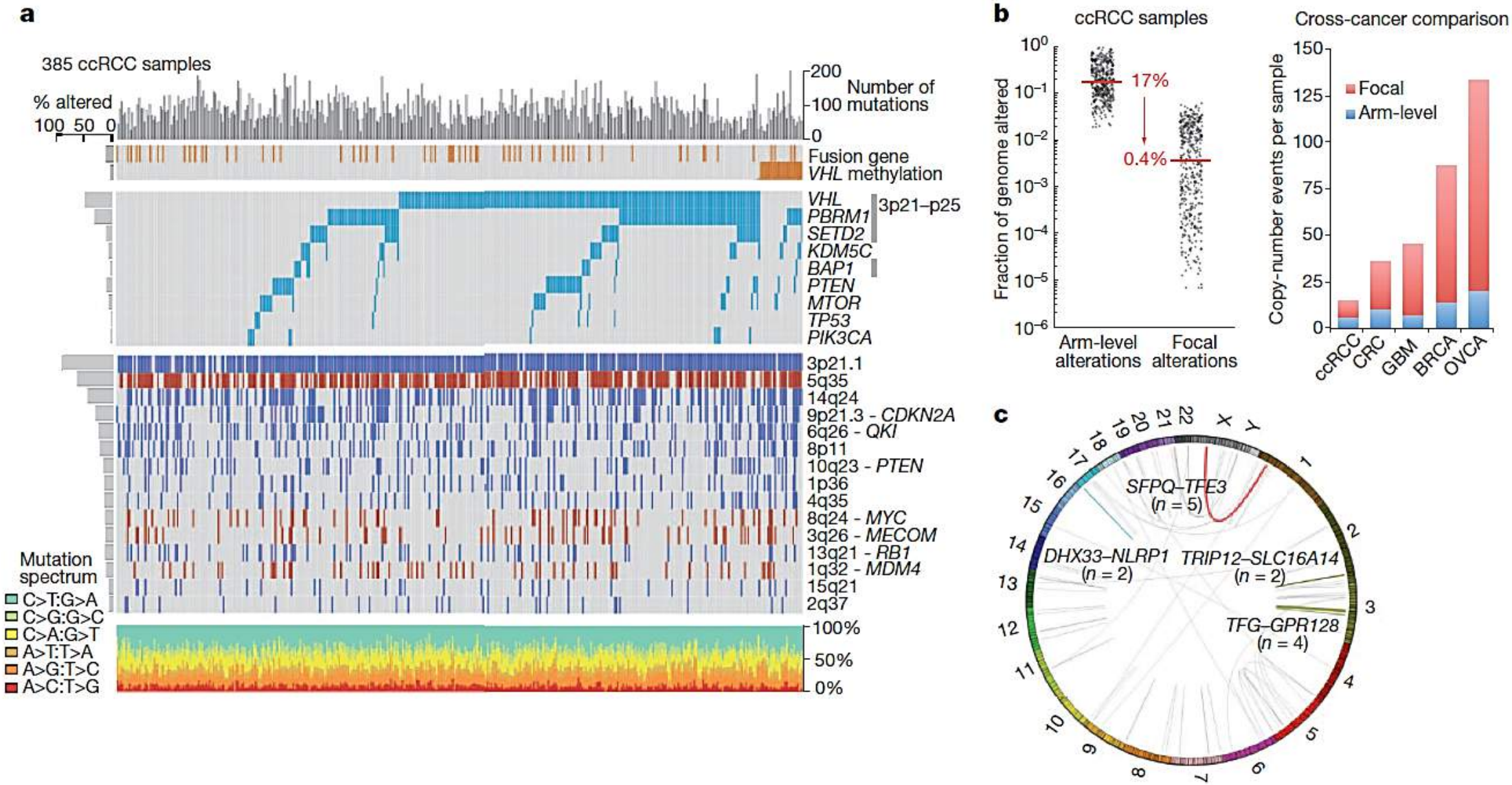
Riazalhosseini, Y. & Lathrop, M. Nat. Rev. Nephrol 2016; 12: 655-666

Comprehensive molecular characterization of clear cell renal cell carcinoma

- Genetic changes underlying clear cell renal cell carcinoma (ccRCC) include alterations in genes controlling cellular oxygen sensing (for example, VHL) and the maintenance of chromatin states (for example, PBRM1).
- We surveyed more than 400 tumours using different genomic platforms and identified 19 significantly mutated genes. **The PI(3)K/AKT pathway was recurrently mutated**, suggesting this pathway as a potential therapeutic target.
- Widespread DNA hypomethylation was associated with mutation of the H3K36 methyltransferase SETD2, and integrative analysis suggested that mutations involving the SWI/SNF chromatin remodelling complex (PBRM1, ARID1A, SMARCA4) could have far-reaching effects on other pathways.
- **Aggressive cancers demonstrated evidence of a metabolic shift**, involving downregulation of genes involved in the TCA cycle, decreased AMPK and PTEN protein levels, upregulation of the pentose phosphate pathway and the glutamine transporter genes, increased acetyl-CoA carboxylase protein, and altered promoter methylation of miR-21 (also known as MIR21) and GRB10.
- **Remodelling cellular metabolism thus constitutes a recurrent pattern in ccRCC that correlates with tumour stage and severity** and offers new views on the opportunities for disease treatment.

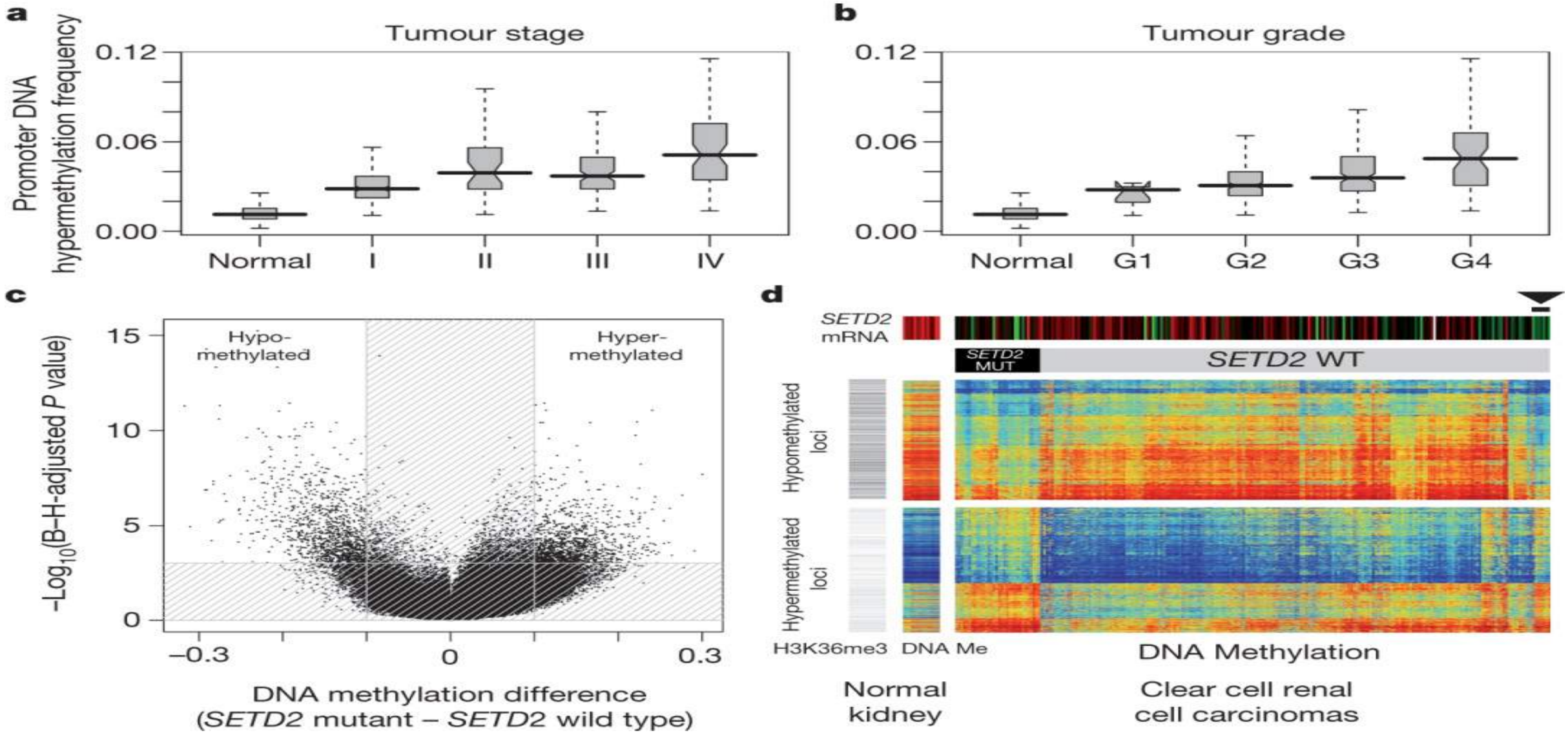
The Cancer Genome Atlas Research Network. Nature 2013; 499: 43-49

Somatic alterations in ccRCC.



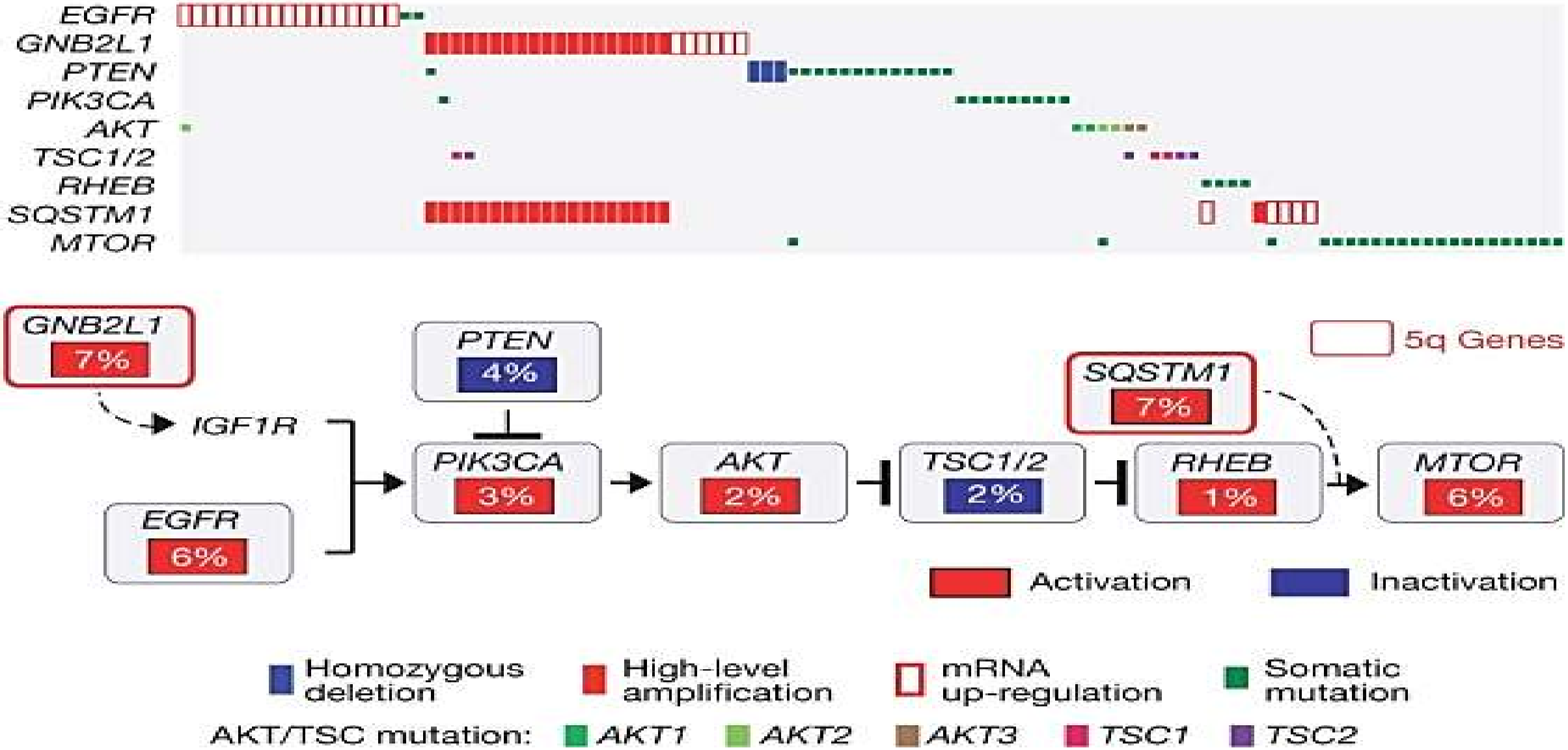
CJ Creighton et al. The Cancer Genome Atlas Research Network. Nature 2013; 499: 43-49

DNA methylation and ccRCC.



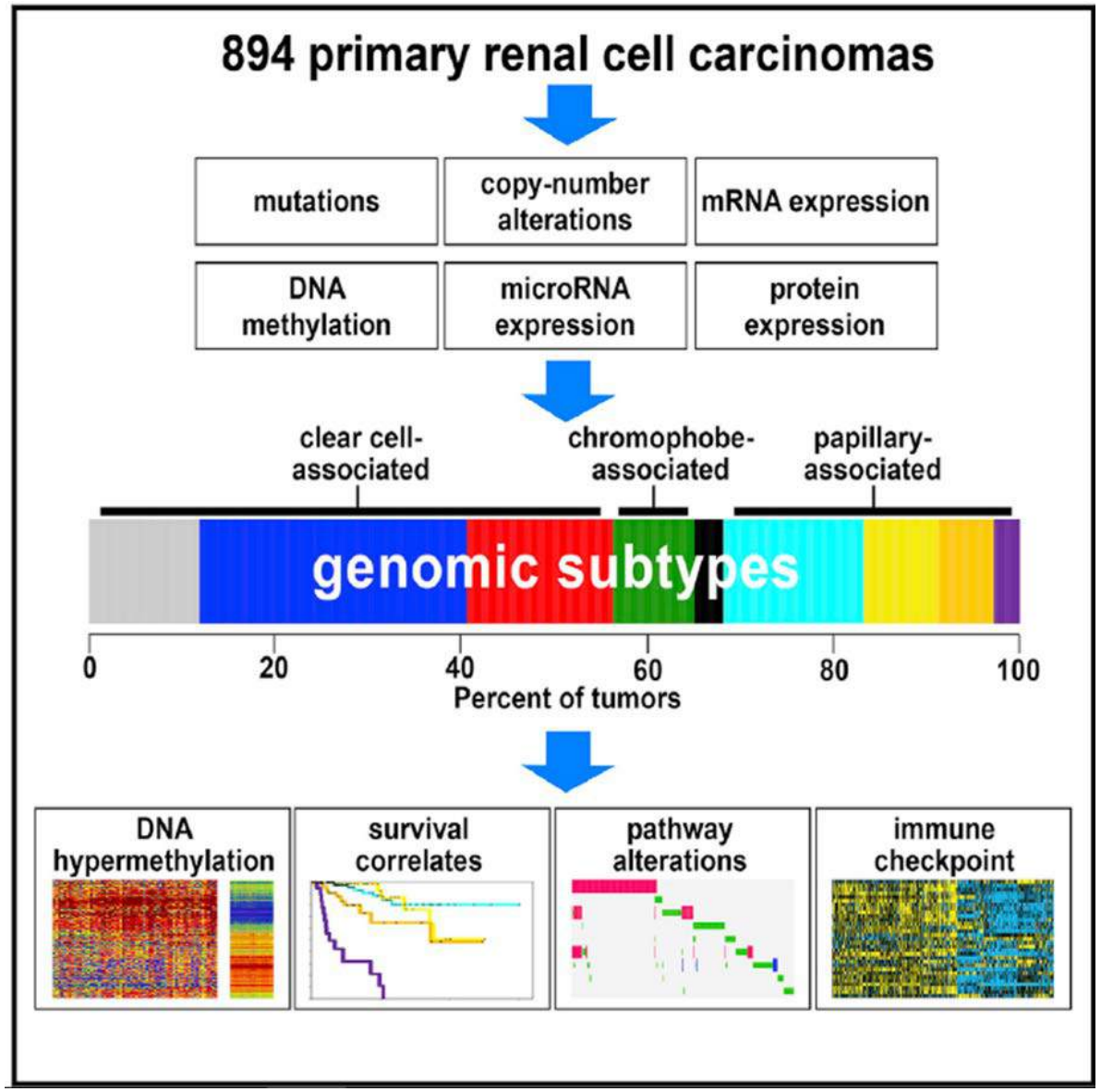
CJ Creighton et al. The Cancer Genome Atlas Research Network. Nature 2013; 499: 43-49

The PI(3)K/AKT/MTOR pathway (altered in ~28% of tumours)



CJ Creighton et al. The Cancer Genome Atlas Research Network. Nature 2013; 499: 43-49

Multilevel Genomics-Based Taxonomy of Renal Cell Carcinoma



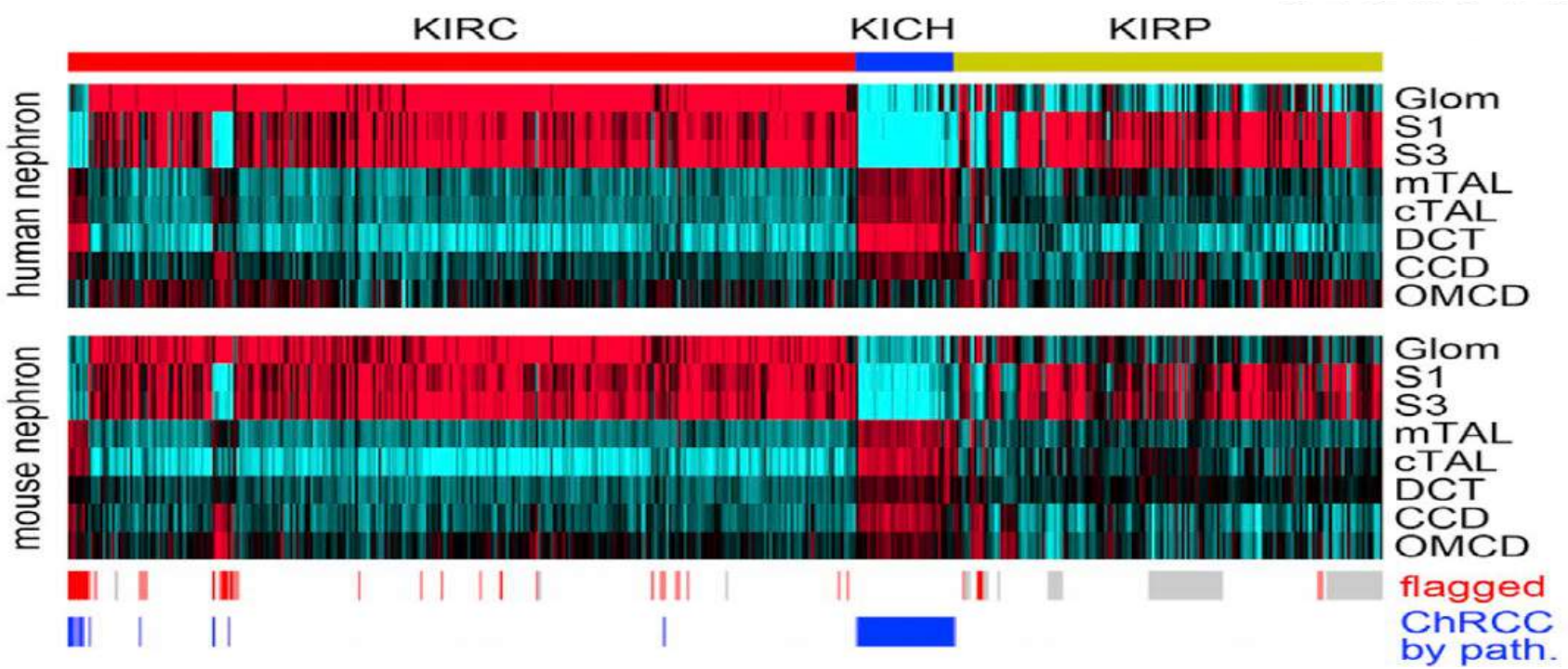
- Comprehensive molecular analysis of 894 primary renal cell carcinoma from TCGA cohort
- Nine subtypes defined by systematic analysis of five genomic data platforms
- Substantial molecular diversity represented within each major histologic type
- Presumed actionable alterations include PI3K and immune checkpoint pathways

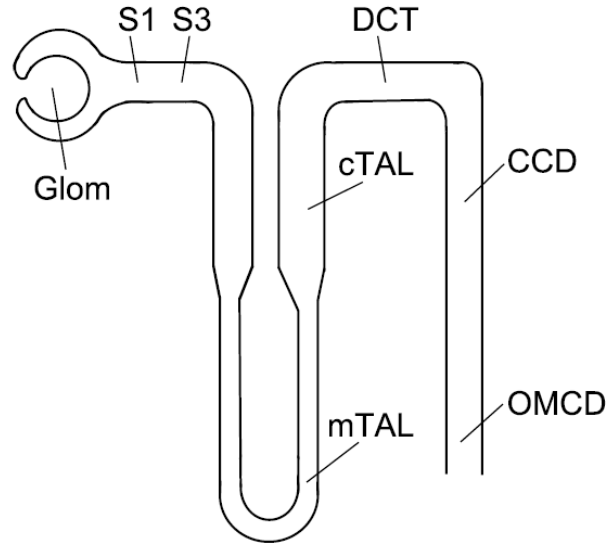
Chen et al., Cell Reports 2016; 14: 2476–2489

Many of the molecular differences among the clear cell, chromphobe, and papillary RCC types arise from their respective cells of origin

three different TCGA-sponsored projects:
‘‘KIRC,’’ = clear cell RCC project ;
‘‘KICH,’’ = chromophobe RCC project; and
‘‘KIRP,’’ = papillary RCC project

Expression profiles of RCCs
clear cell RCC ≅ the glomerulus and proximal nephron,
chromophobe RCC ≅ the distal nephron,
papillary RCC cases ≈ the proximal nephron

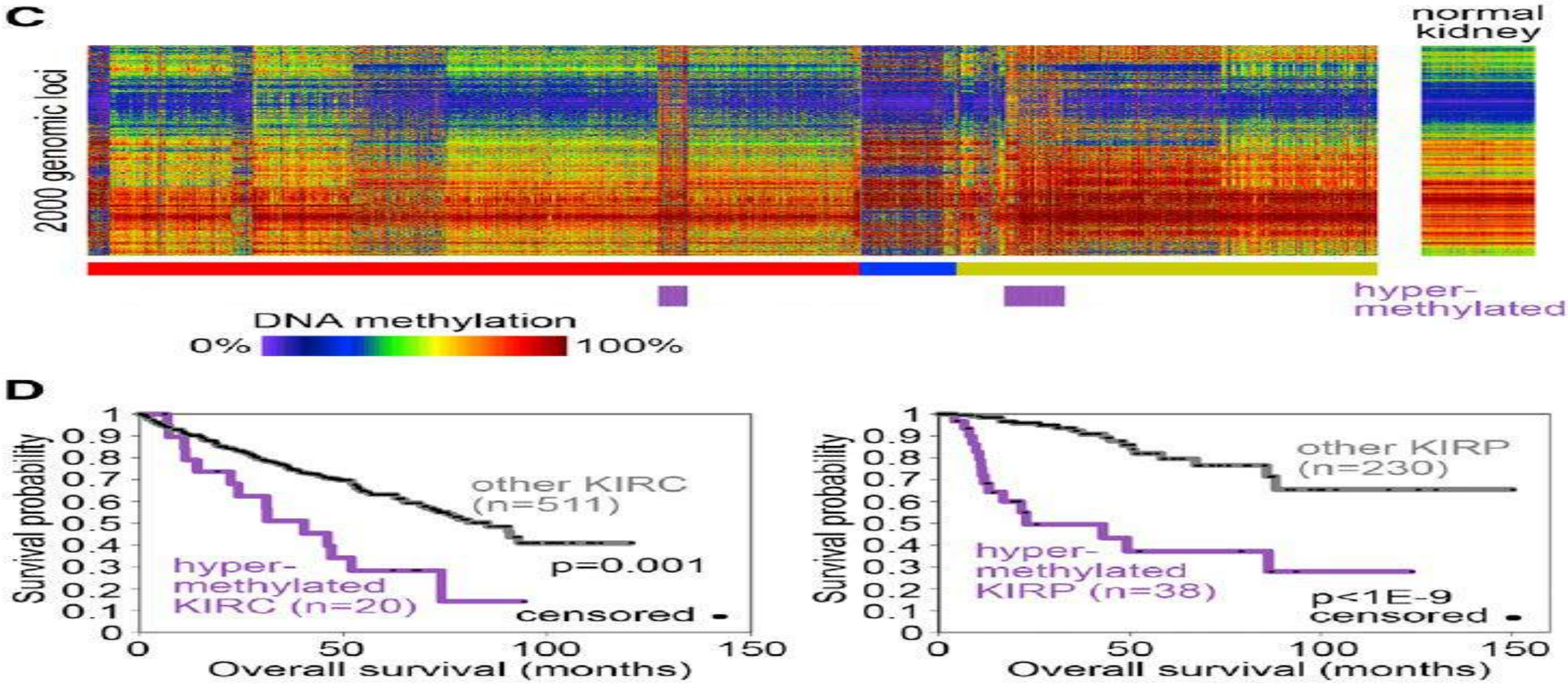




Chen et al. Cell Reports 2016; 14: 2476–2489

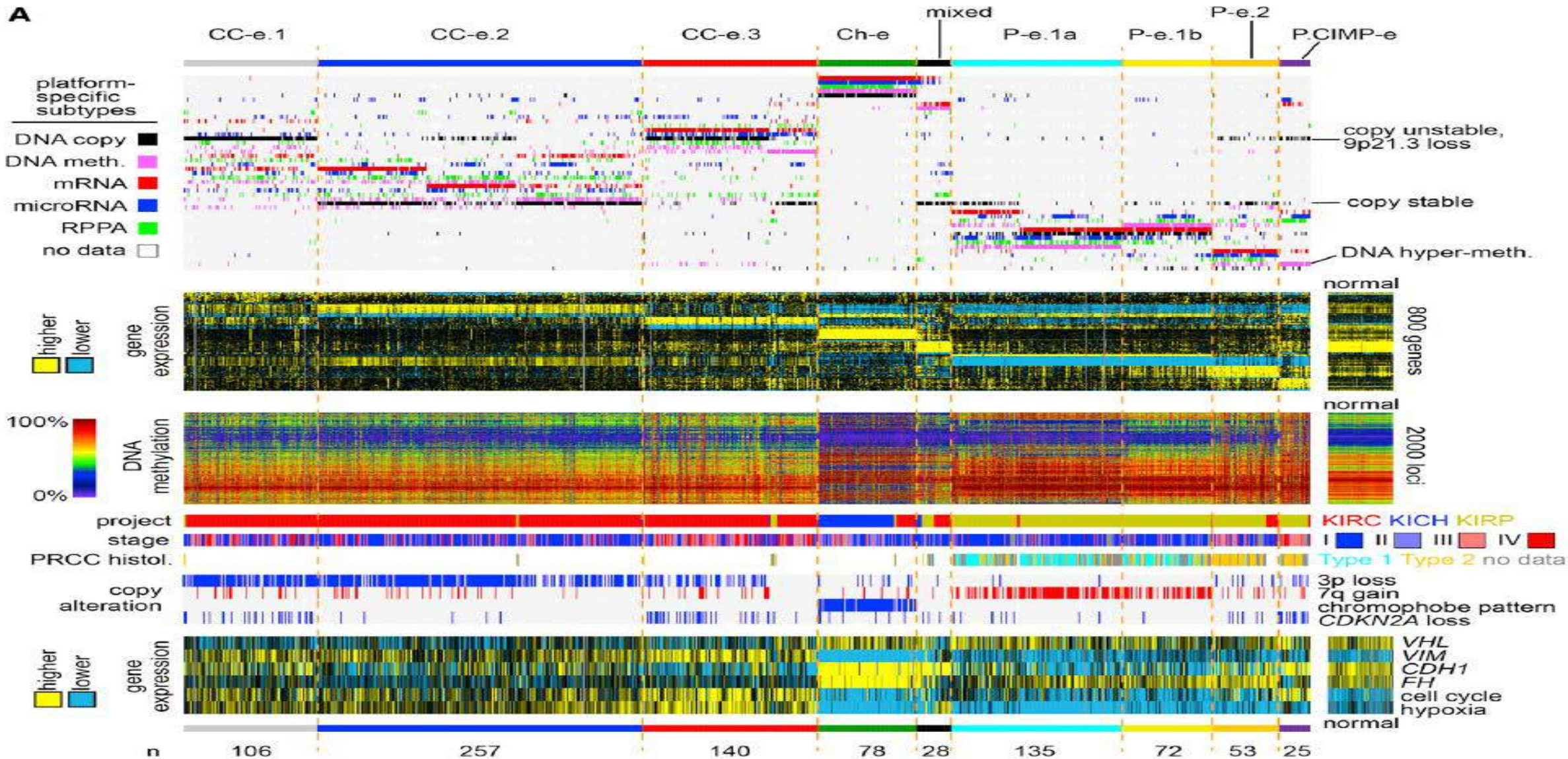
Davis et al. Cancer Cell 2014; 26: 319–330

Diverse DNA methylation patterns were evident both across and within the histology-based subgroups



Chen et al., Cell Reports 2016; 14: 2476–2489

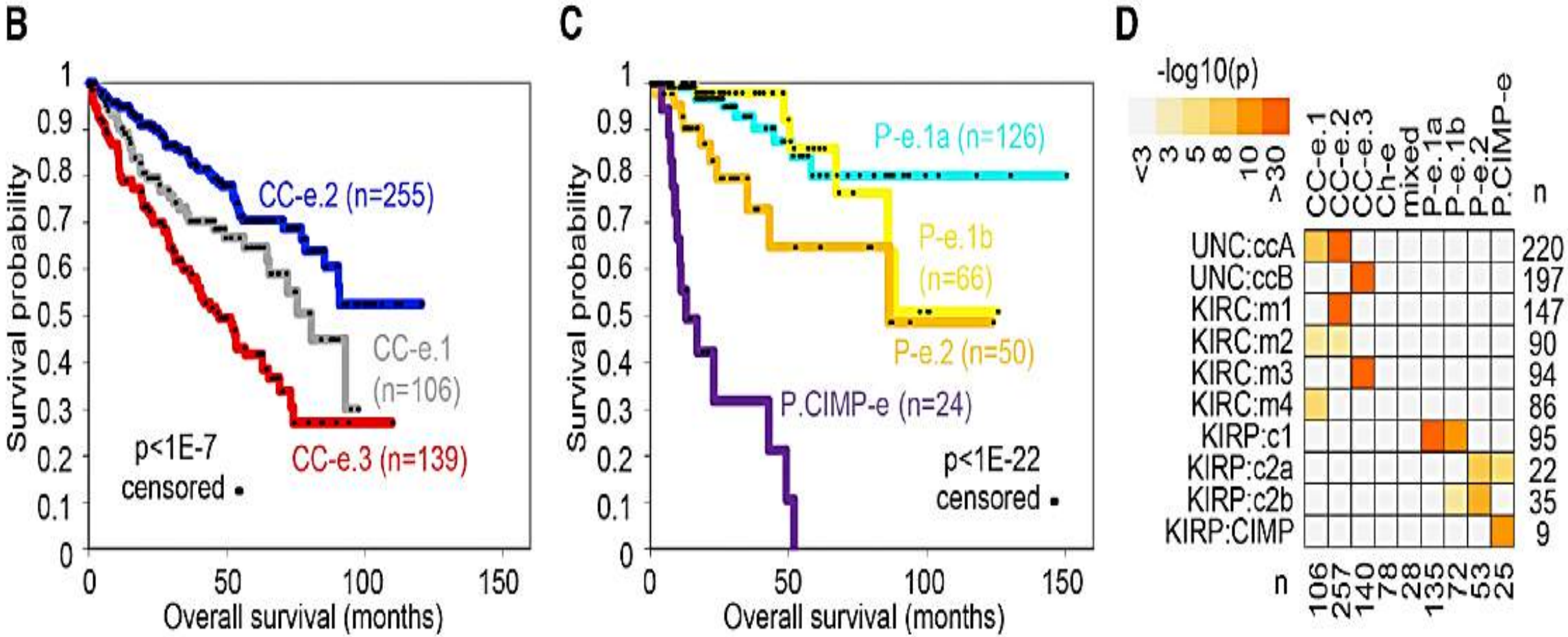
Multi-platform Analysis Uncovers Nine Major Genomic Subtypes of RCC



"e" signifying "enriched

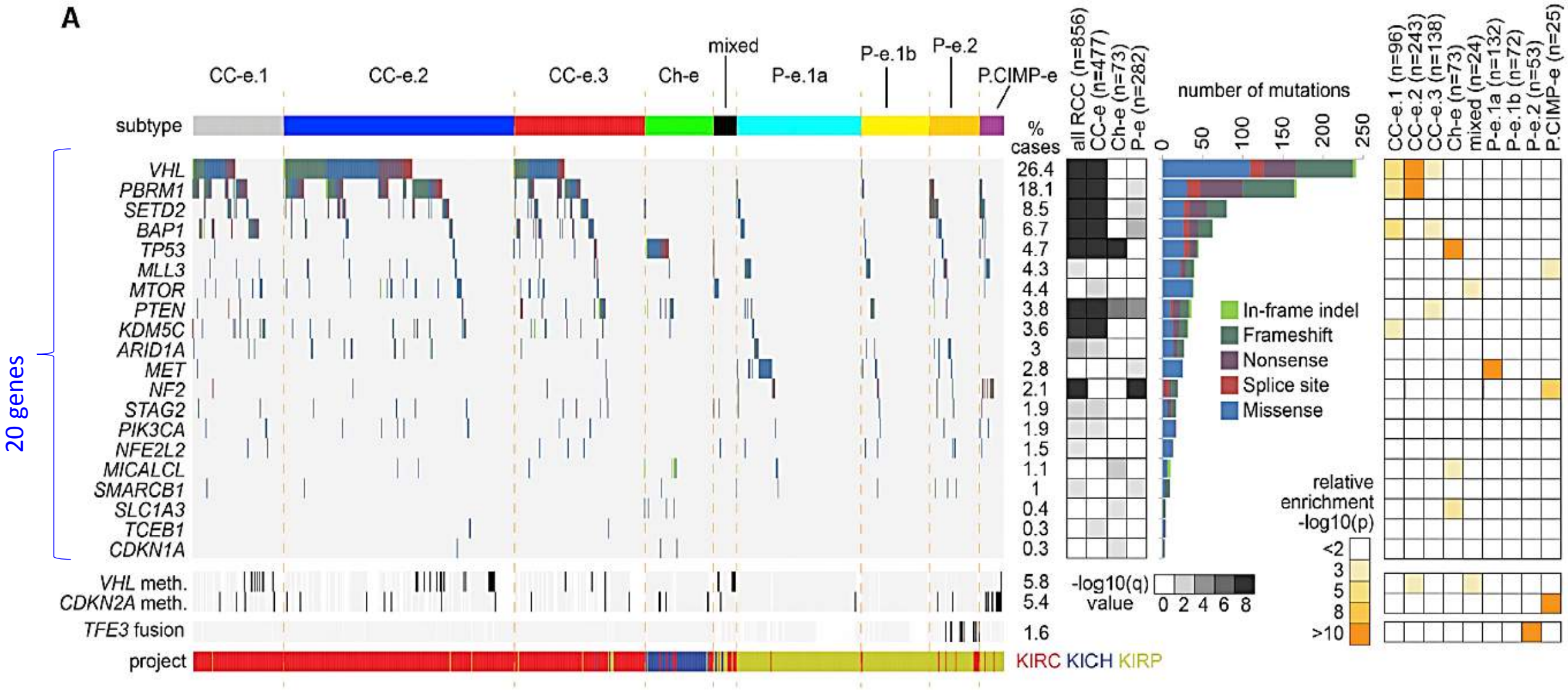
Chen et al., Cell Reports 2016; 14: 2476–2489

Multi-platform Analysis Uncovers Nine Major Genomic Subtypes of RCC



Chen et al., Cell Reports 2016; 14: 2476–2489

Somatic Mutations and Genomic Rearrangements across RCC Subtypes

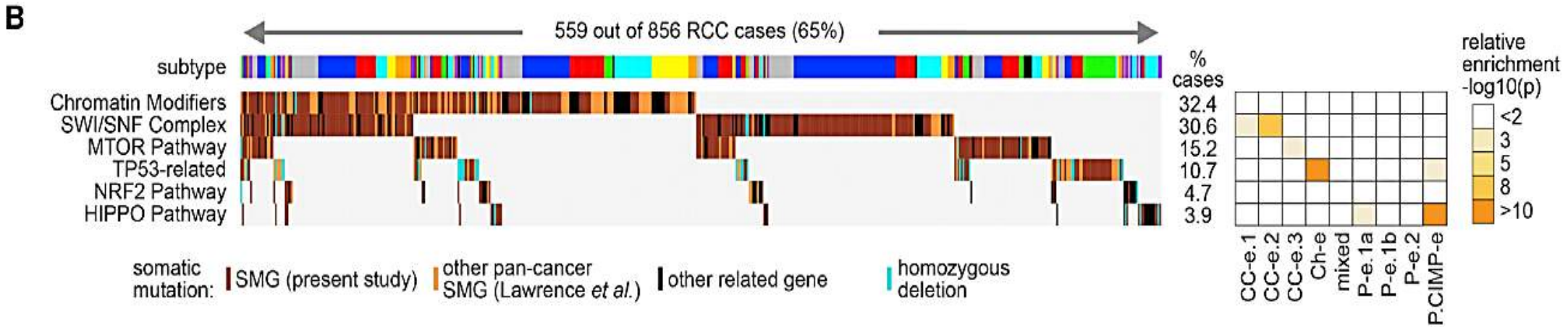


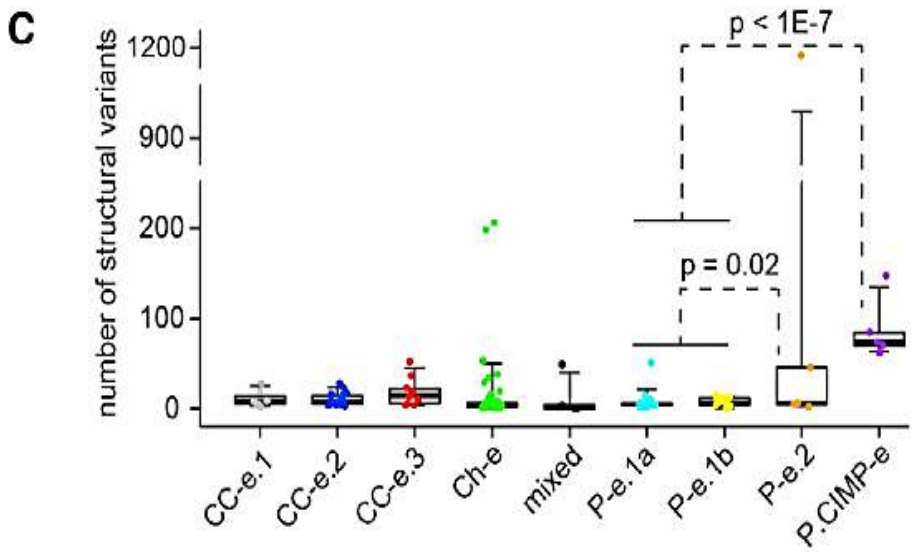
CDKN1A, cyclin dependent kinase inhibitor 1A; p21

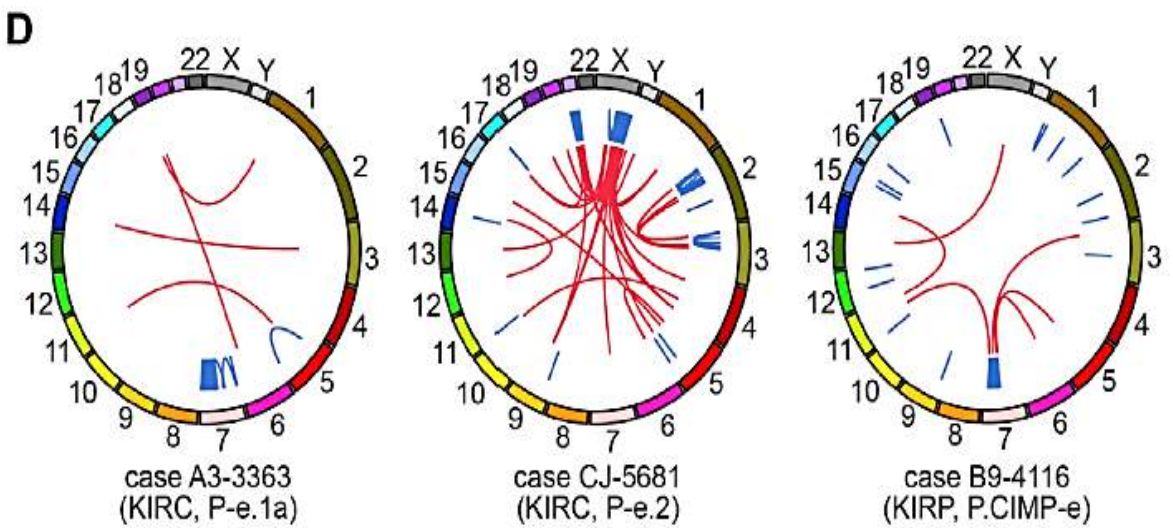
CDKN2A, cyclin dependent kinase inhibitor 2A; p16(INK4a) and the p14(ARF) proteins

Chen et al., Cell Reports 2016; 14: 2476–2489

Somatic Mutations and Genomic Rearrangements across RCC Subtypes

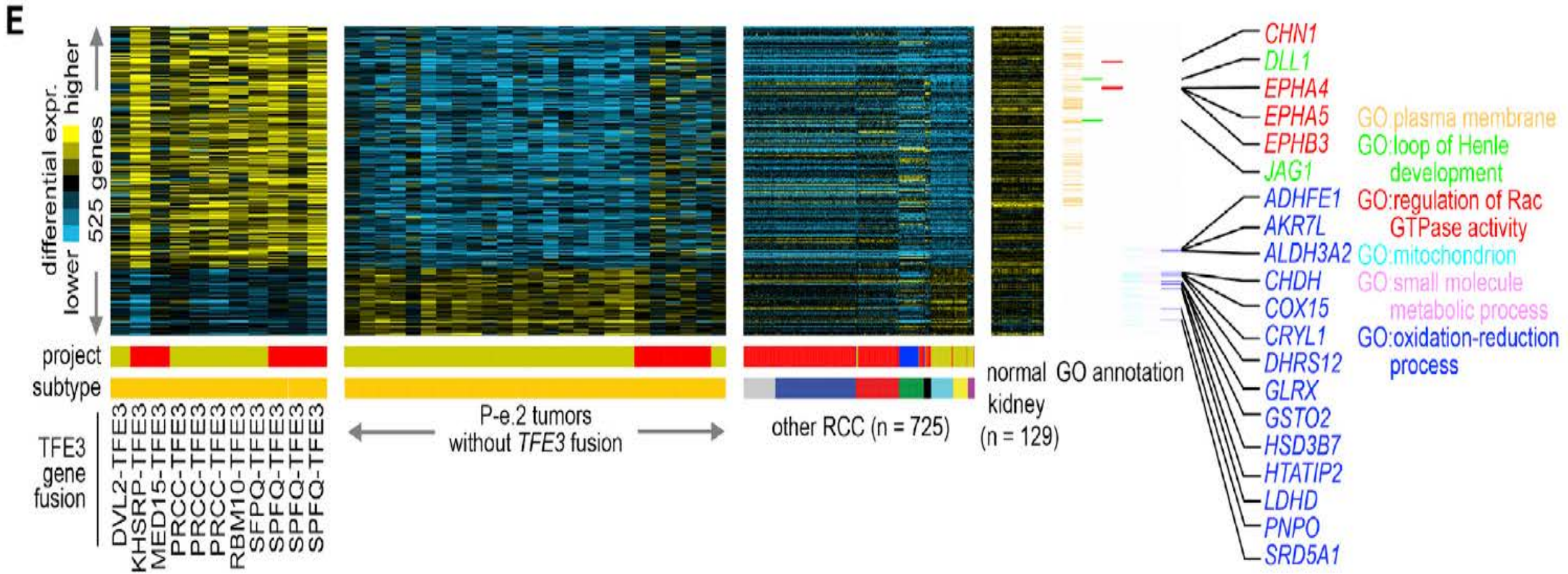






Chen et al., Cell Reports 2016; 14: 2476–2489

Global consequences of TFE3 fusion within P-e.2 subtype

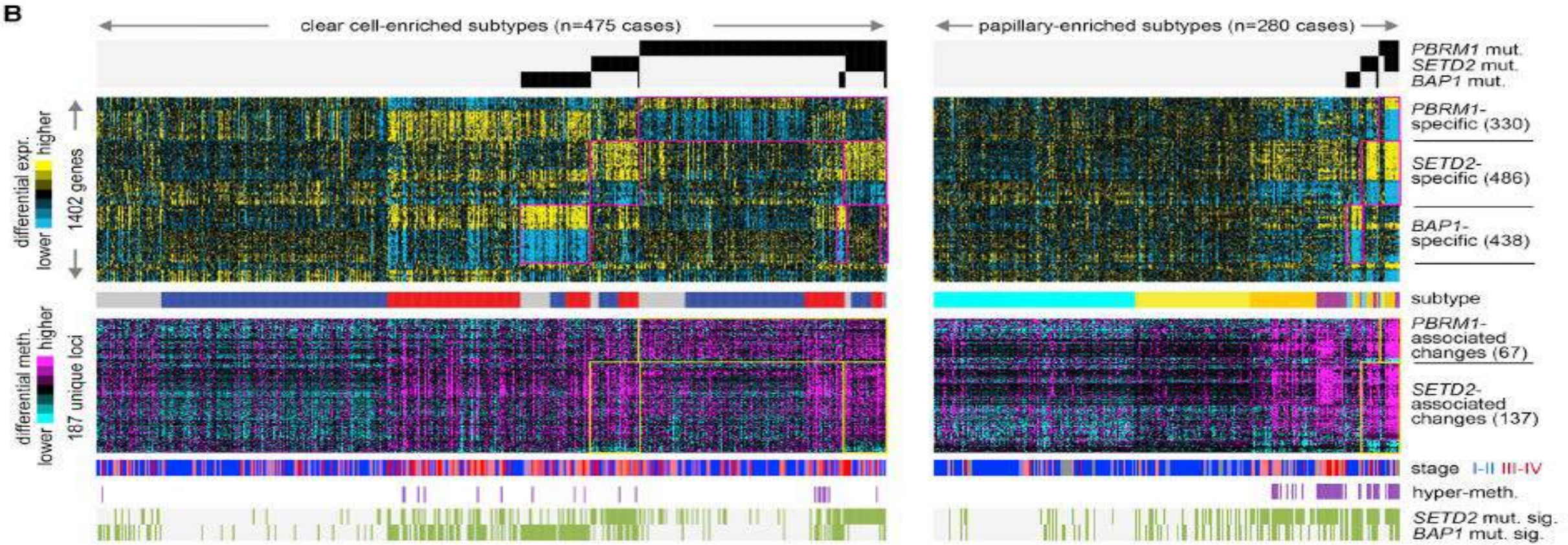


Chen et al., Cell Reports 2016; 14: 2476–2489

Chromatin Modifier Gene Mutations and Associated Molecular Alterations Common to Multiple RCC Subtypes

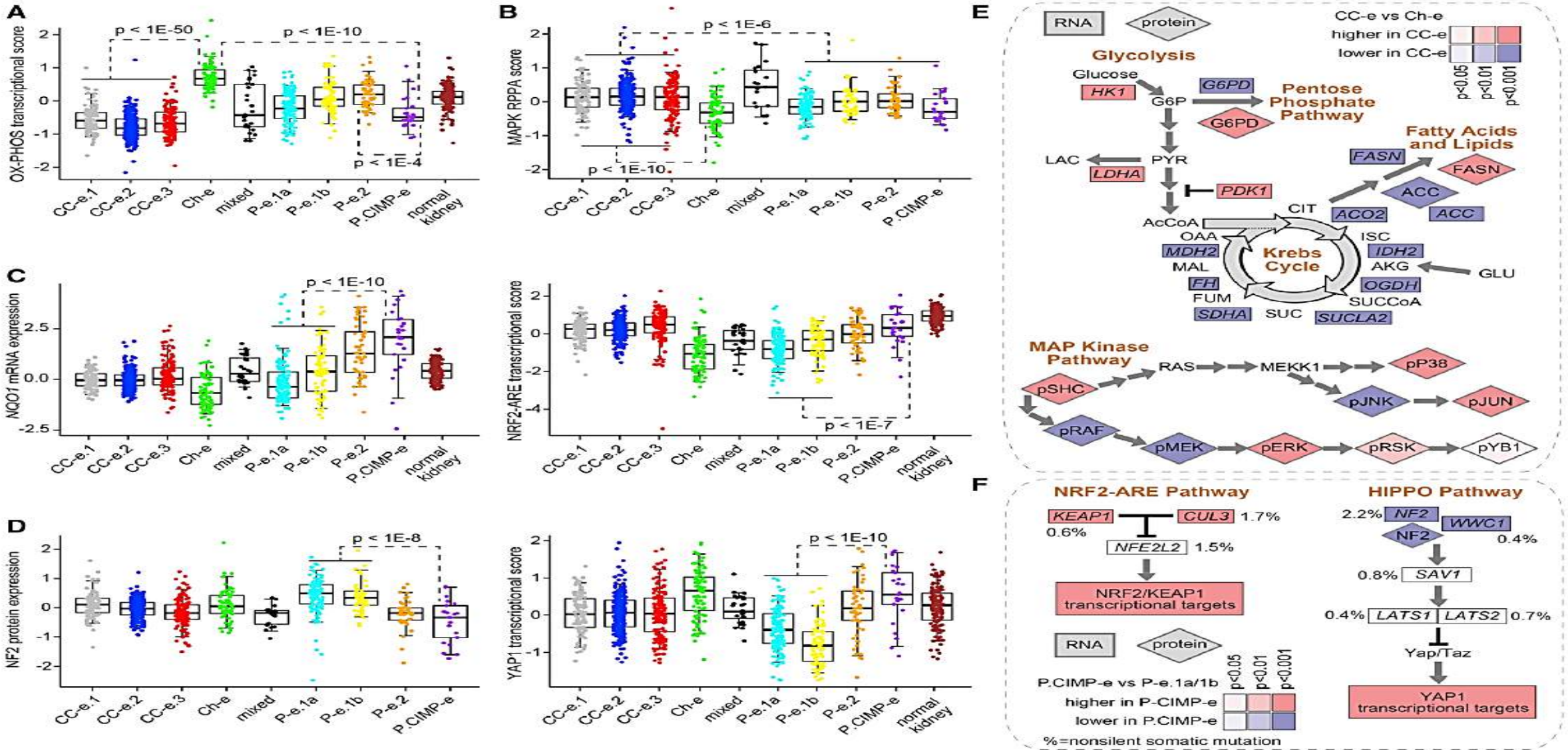
Chen et al., Cell Reports 2016; 14: 2476–2489

Chromatin Modifier Gene Mutations and Associated Molecular Alterations Common to Multiple RCC Subtypes



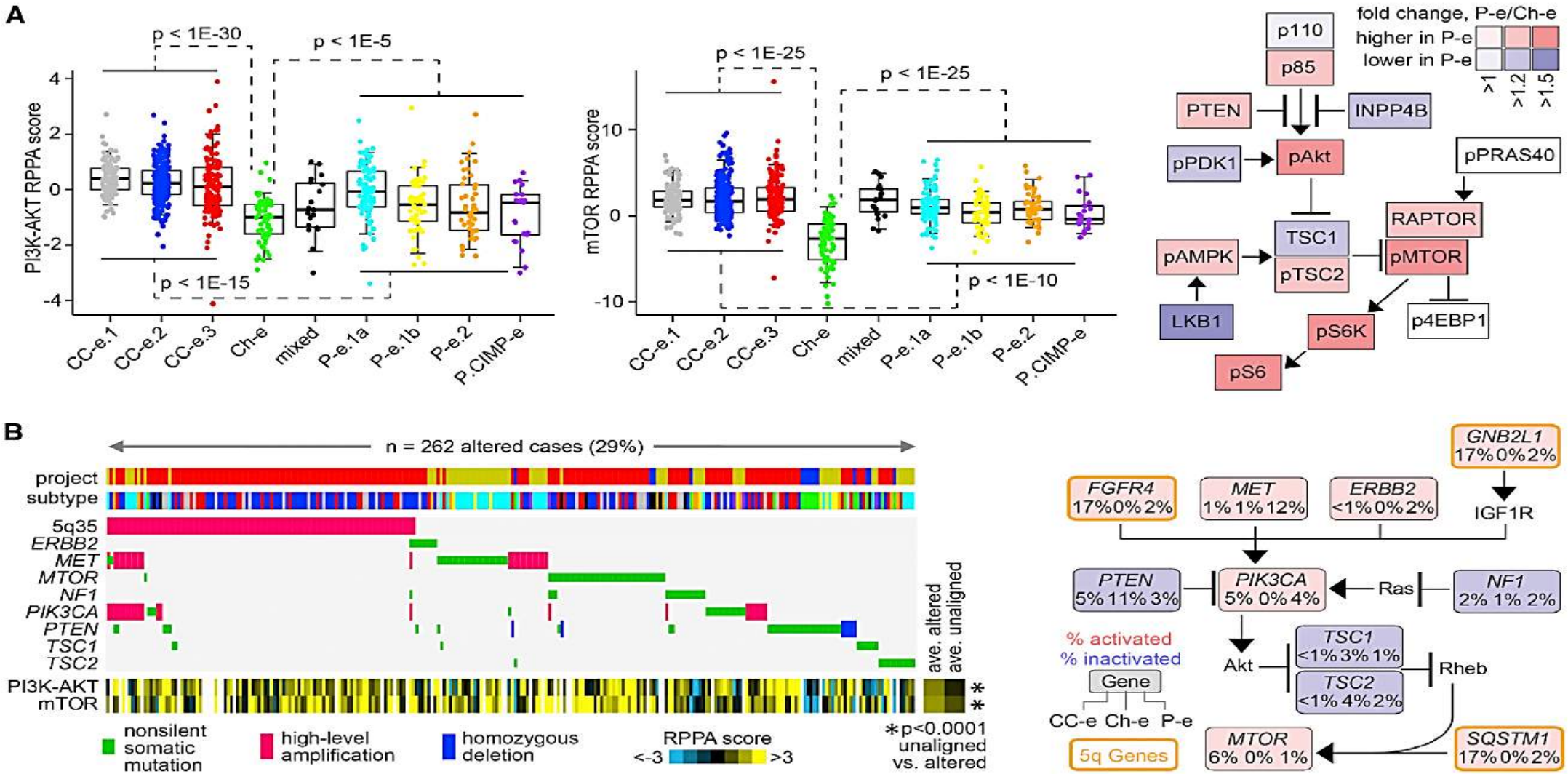
Chen et al., Cell Reports 2016; 14: 2476–2489

Differentially Active Pathways across RCC Genomic Subtypes



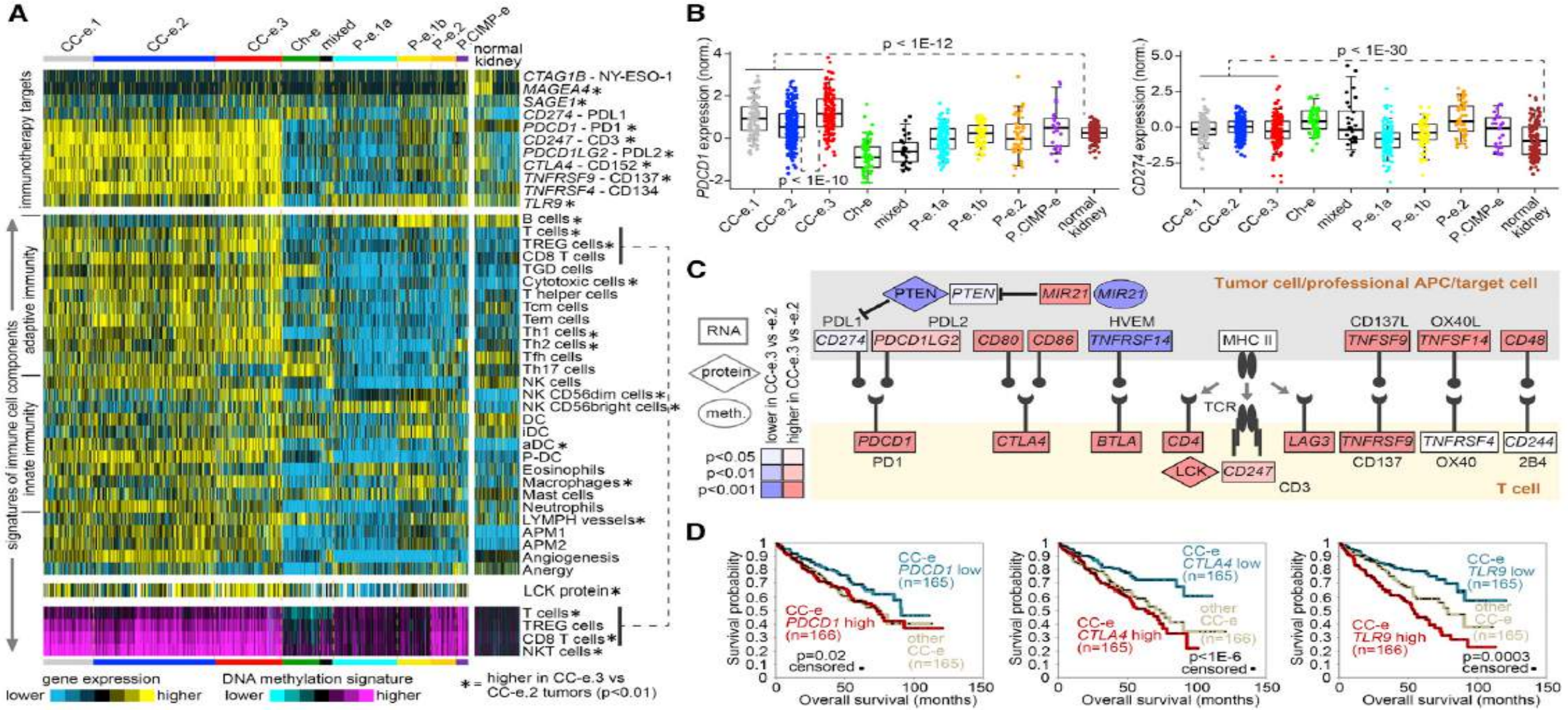
Chen et al., Cell Reports 2016; 14: 2476–2489

PI3K/AKT/mTOR Pathway-Related Alterations across RCC Genomic Subtypes



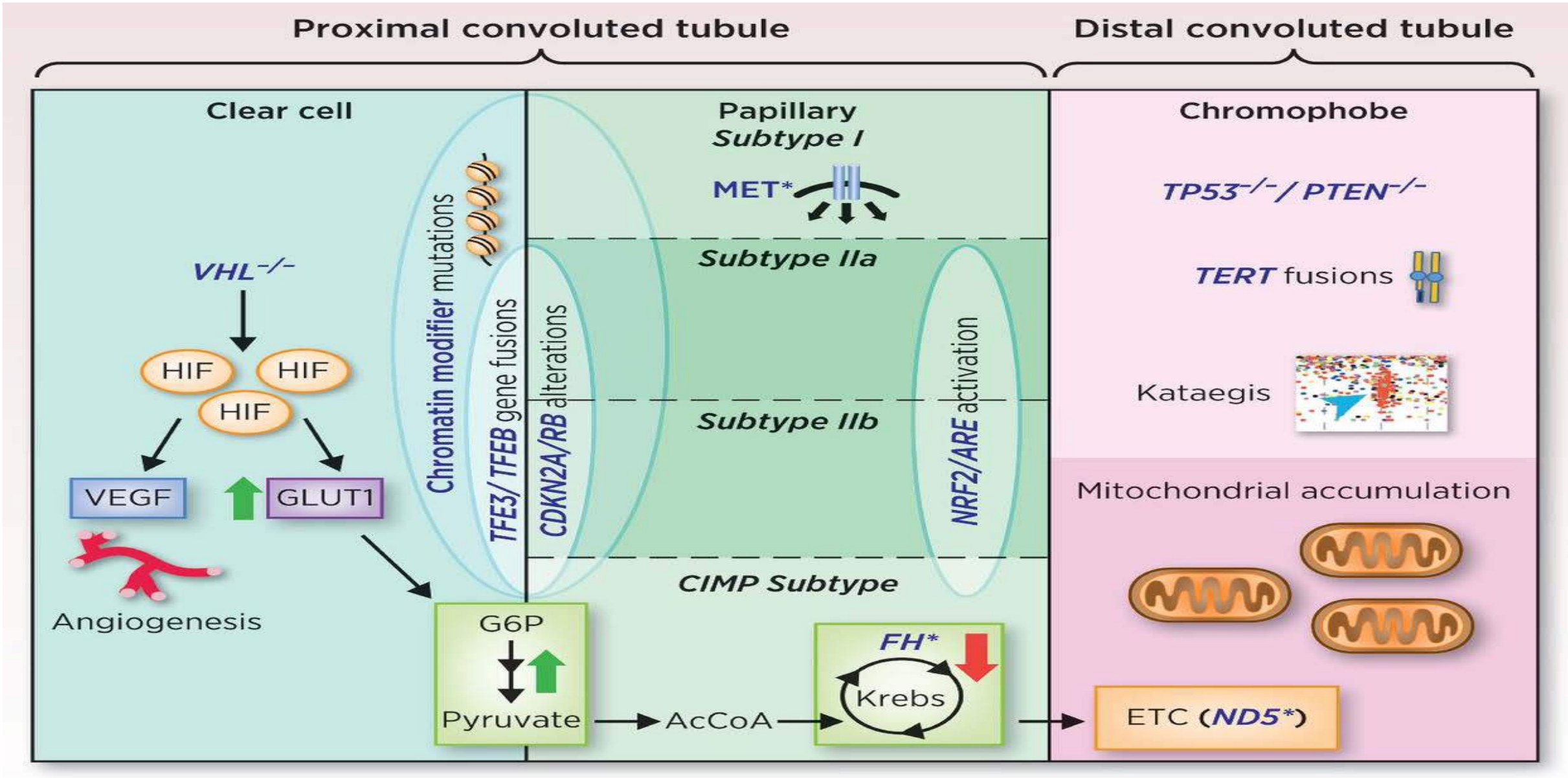
Chen et al., Cell Reports 2016; 14: 2476–2489

Immune-Checkpoint-Related Differences across RCC Genomic Subtypes



Chen et al., Cell Reports 2016; 14: 2476–2489

Molecular comparison of ccRCC, pRCC, and chRCC



Haake SM, et al. Mol Cancer Res 2016: 14(7); 589–98

Clinical and molecular distinctions among the pRCC moleculClinical and molecular distinctions among the pRCC molecular subtypesar subtypes

	pRCC-I	pRCC-IIa	pRCC-IIb	pRCC-IIc or CIMP
Survival	Good	Good	Intermediate	Poor
MET activation	++++	–	–	–
NRF2/ARE activation	–	+	+	+++
CDKN2A/RB alterations	–/+	++	++	+++
SETD2 mutation	–	–	++	–
SWI/SNF alteration	+	+	++	+
DNA hypermethylation	–	–	+	++++
FH mutation	–	–	–	++++

Haake SM, et al. Mol Cancer Res 2016: 14(7); 589–98

Hereditary syndromes associated with renal cell carcinoma

Syndrome (phenotype OMIM reference)	Gene (position)	Protein	Incidence of developing a kidney tumour (%)	Median age at diagnosis (years)	Other phenotypic features
Clear cell renal cell carcinoma*					
von Hippel–Lindau disease (193300)	VHL (3p25–26)	pVHL	25–45	40	• Haemangioblastoma • Pancreatic neuroendocrine tumours • Pheochromocytoma • Renal cysts • Pancreatic cysts • Ovary cystadenoma • Epididymal cystadenoma
BAP1 mutant disease (also known as tumour predisposition disease; 614327)	BAP1 (3p21)	BRCA-associated protein	No data	No data	• Breast cancer • Uveal melanoma • Mesothelioma • Other cutaneous melanocytic tumours
SDH-associated kidney cancer (185470, 602413, 602690 and 115310)	SDHB (1p36), SDHC (1q23) and SDHD (11q23)	Succinate dehydrogenase subunits B, C and D	5–15	30	• Paraganglioma • Carotid body tumours • Pheochromocytoma • Gastrointestinal stromal tumour
Papillary renal cell carcinoma					
Hereditary leiomyomatosis and renal cell cancer (150800)‡ (Main renal cancer type is papillary renal cell carcinoma type 2).	FH (1q43)	Fumarate hydratase	2–21	46	• Uterine leiomyosarcomas • Breast cancer • Bladder cancer • Cutaneous leiomyomas • Uterine leiomyomas
Hereditary papillary kidney cancer (605074)§ (Main renal cancer type is papillary renal cell carcinoma type 1.)	MET (7q31)	Hepatocyte growth factor receptor	No data	<60	No additional features

OMIM, Online Mendelian Inheritance in Man database.
*Familial clear cell kidney cancer with chromosome 3 translocation is another possible syndrome associated with clear cell renal cell carcinoma, but the genetic lesions and associated data are unknown.
‡Main renal cancer type is papillary renal cell carcinoma type 2.
§Main renal cancer type is papillary renal cell carcinoma type 1.

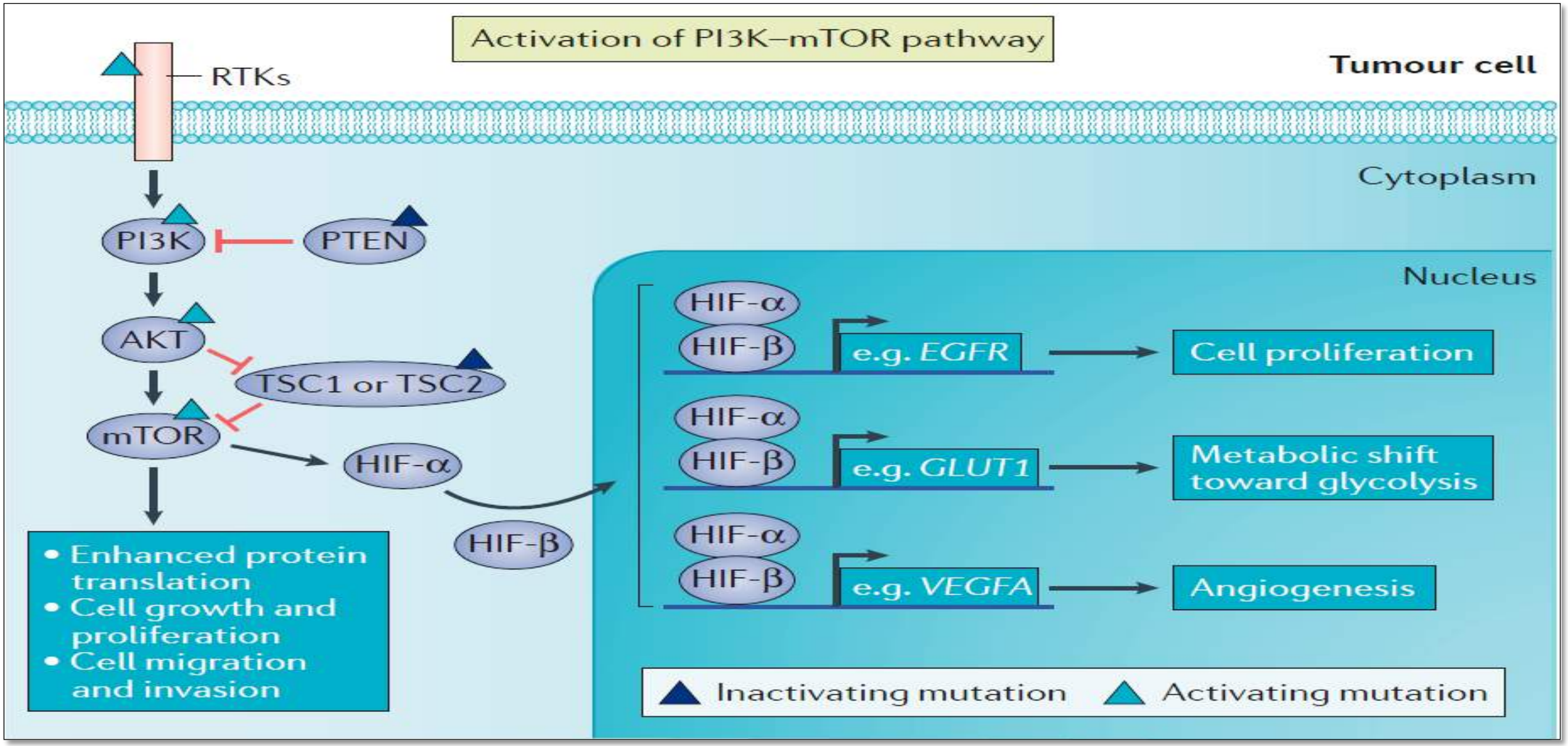
Hsieh, J. J. et al. Nat. Rev. Dis. Primers 2017; 3: 1-19

Hereditary syndromes associated with renal cell carcinoma

Syndrome (phenotype OMIM reference)	Gene (position)	Protein	Incidence of developing a kidney tumour (%)	Median age at diagnosis (years)	Other phenotypic feature
Multiple tumour types					
Birt–Hogg–Dubé syndrome (135150)|| (Main renal cancer types are hybrid tumours, oncocytomas, and chromophobe, papillary and clear cell renal cell carcinomas.)	FLCN (17p11.2)	Folliculin	34	50	• Fibrofolliculomas and trichodiscomas • Pulmonary cysts • Pneumothorax
Tuberous sclerosis complex (191100 and 191092)¶ (Main renal cancer types are angiomyolipomas, epithelioid angiomyolipomas, oncocytomas, and papillary and clear cell renal cell carcinomas; renal cysts also are common.)	TSC1 (9q34) and TSC2 (16p13)	Hamartin and tuberin	2–4	30	• Subependymal giant cell astrocytomas • Angiomyolipomas • Renal cysts • Facial angiofibroma • Ungual and periungual fibromas • Hypomelanotic macule • Forehead plaque • Cardiac rhabdomyomas • Connective tissue naevus
Cowden syndrome (also known as multiple hamartoma syndrome; 158350)# (Main renal cancer types are clear cell, papillary and chromophobe renal cell carcinomas)	PTEN (10q23)	Phosphatase and tensin homologue	34	40	• Breast cancer • Endometrial cancer • Thyroid cancer • Prostate cancer • Macrocephaly • Intestinal hamartomatous polyps • Benign skin tumours (multiple trichilemmomas, papillomatous papules and acral keratoses) • Dysplastic gangliocytoma of the cerebellum
Hyperparathyroidism jaw tumour syndrome (145001)** (Main renal cancer types are mixed tumours (epithelial and connective tissue), papillary renal cell carcinomas and nephroblastomas.)	HRPT2 (1q31)	Parafibromin	No data	No data	• Parathyroid carcinomas • Uterine carcinomas • Renal cysts and hamartomas • Hyperparathyroidism • Parathyroid gland tumours • Jaw fibromas

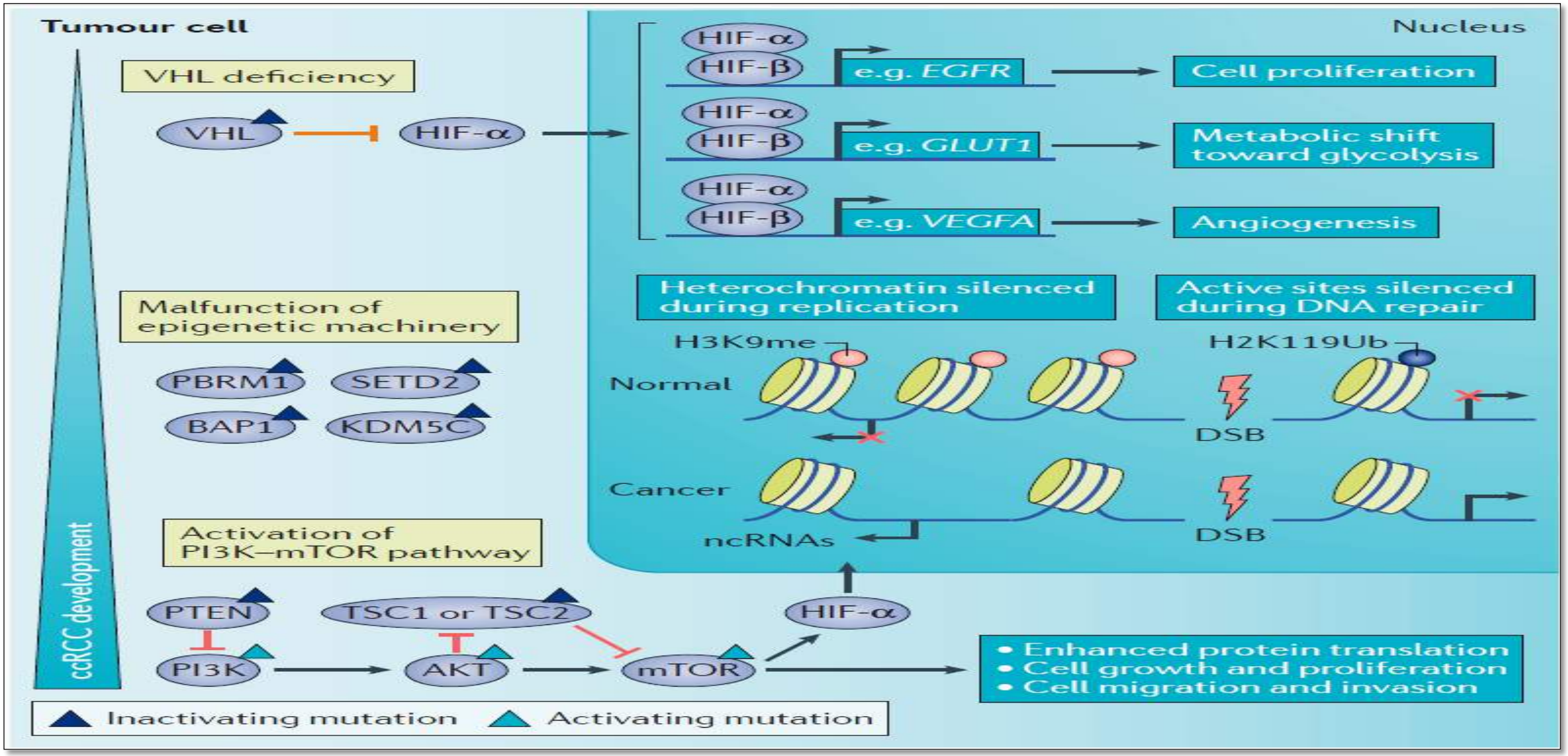
||Main renal cancer types are hybrid tumours, oncocytomas, and chromophobe, papillary and clear cell renal cell carcinomas.
¶Main renal cancer types are angiomyolipomas, epithelioid angiomyolipomas, oncocytomas, and papillary and clear cell renal cell carcinomas; renal cysts also are common.
#Main renal cancer types are clear cell, papillary and chromophobe renal cell carcinomas.
**Main renal cancer types are mixed tumours (epithelial and connective tissue), papillary renal cell carcinomas and nephroblastomas.

Activation of the PI3K–mTOR pathway in clear cell renal cell carcinoma (ccRCC)



Riazalhosseini, Y. & Lathrop, M. Nat. Rev. Nephrol 2016; 12: 655-666

Pathogenic pathways in clear cell renal cell carcinoma (ccRCC)



Riazalhosseini, Y. & Lathrop, M. Nat. Rev. Nephrol 2016; 12: 655-666

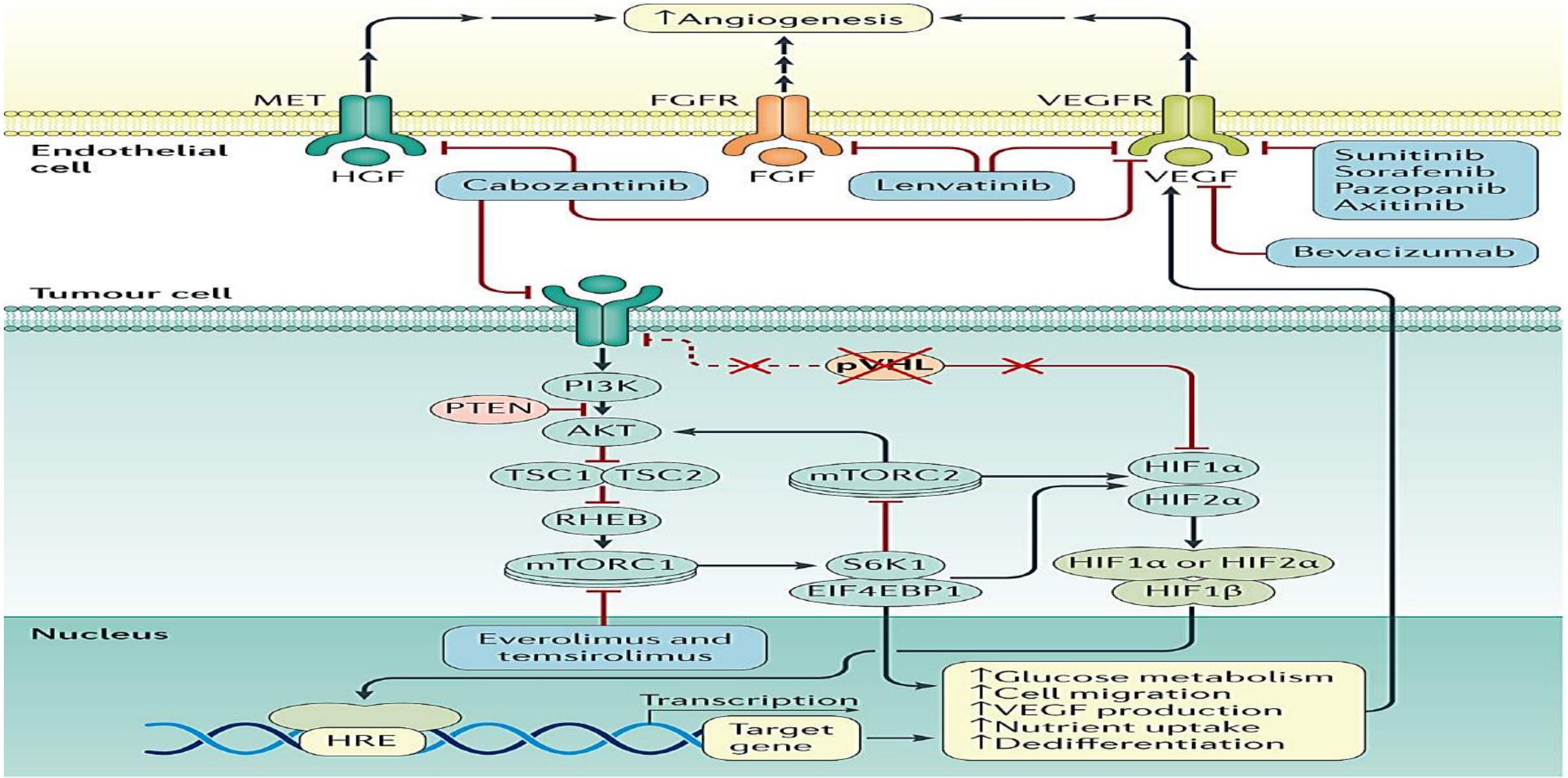
Recurrent somatic aberrations and therapeutic targets in RCC

Subtype	Affected genes or pathway	Characteristic chromosomal aberrations	Therapeutic targets (targeting agents used for RCC treatment)
ccRCC	VHL; PBRM1; SETD2; BAP1; PI3K–mTOR	Loss of 3p and 14q and gain of 5q	VEGFRs (sunitinib, pazopanib, axitinib); VEGFA (bevacizumab); mTOR (everolimus and temsirolimus)
Type I pRCC	MET	Gains of 7, 16 and 17	cMET (foretinib, cabozanitib)
Type II pRCC	ARF–NRE pathway		
chRCC	TP53; PTEN; electron transport chain complex I	Losses of 1, 2, 6, 10, 13 and 17	NA

ccRCC, clear cell RCC; chRCC, chromophobe RCC; NA, not available; pRCC, papillary RCC; RCC, renal cell carcinoma.

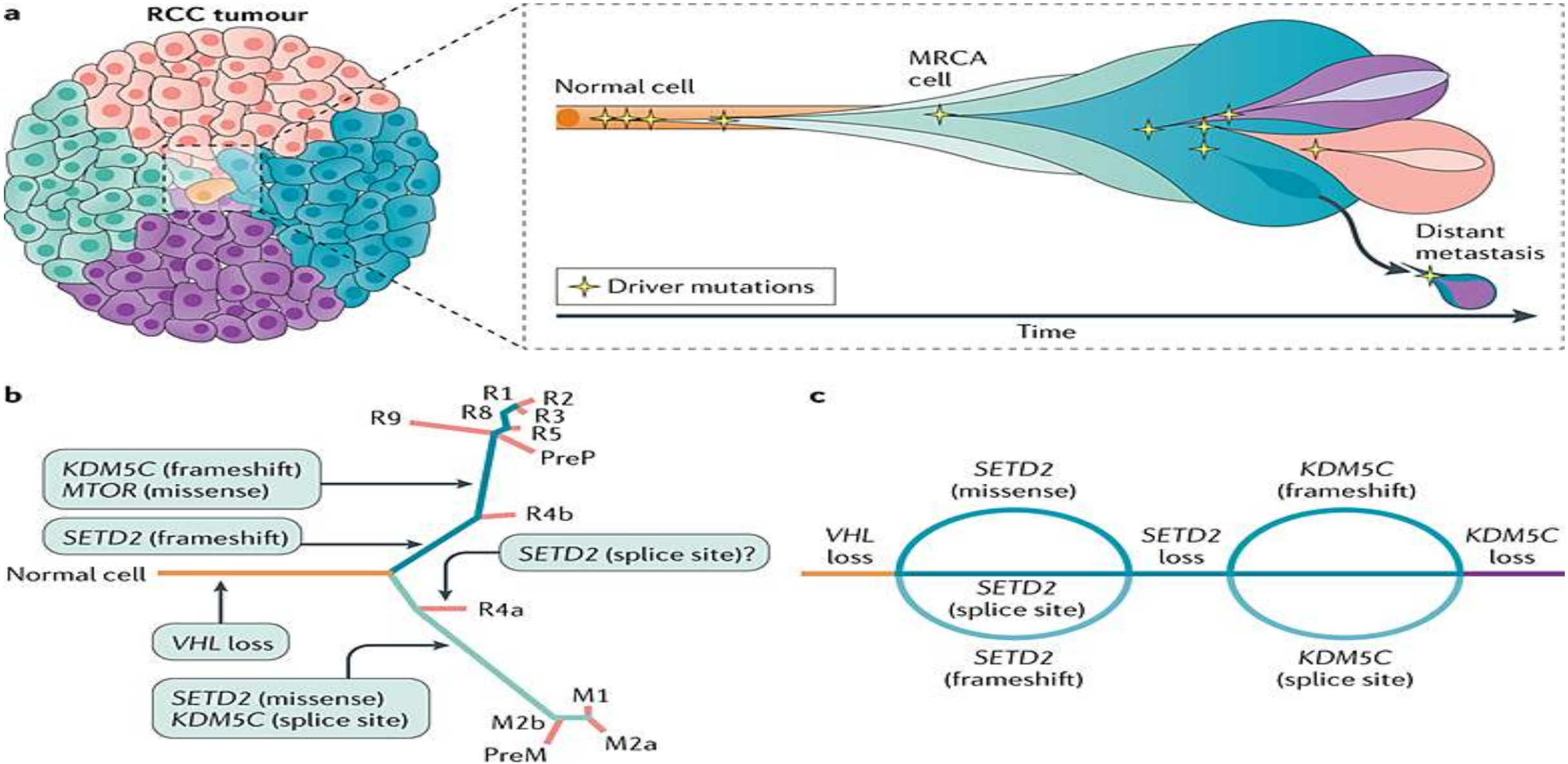
Riazalhosseini, Y. & Lathrop, M. Nat. Rev. Nephrol 2016; 12: 655-666

VHL inactivation in clear cell renal cell carcinoma and its implication in targeted therapy



Hsieh, J. J. et al. Nat. Rev. Dis. Primers 2017; 3: 1-19

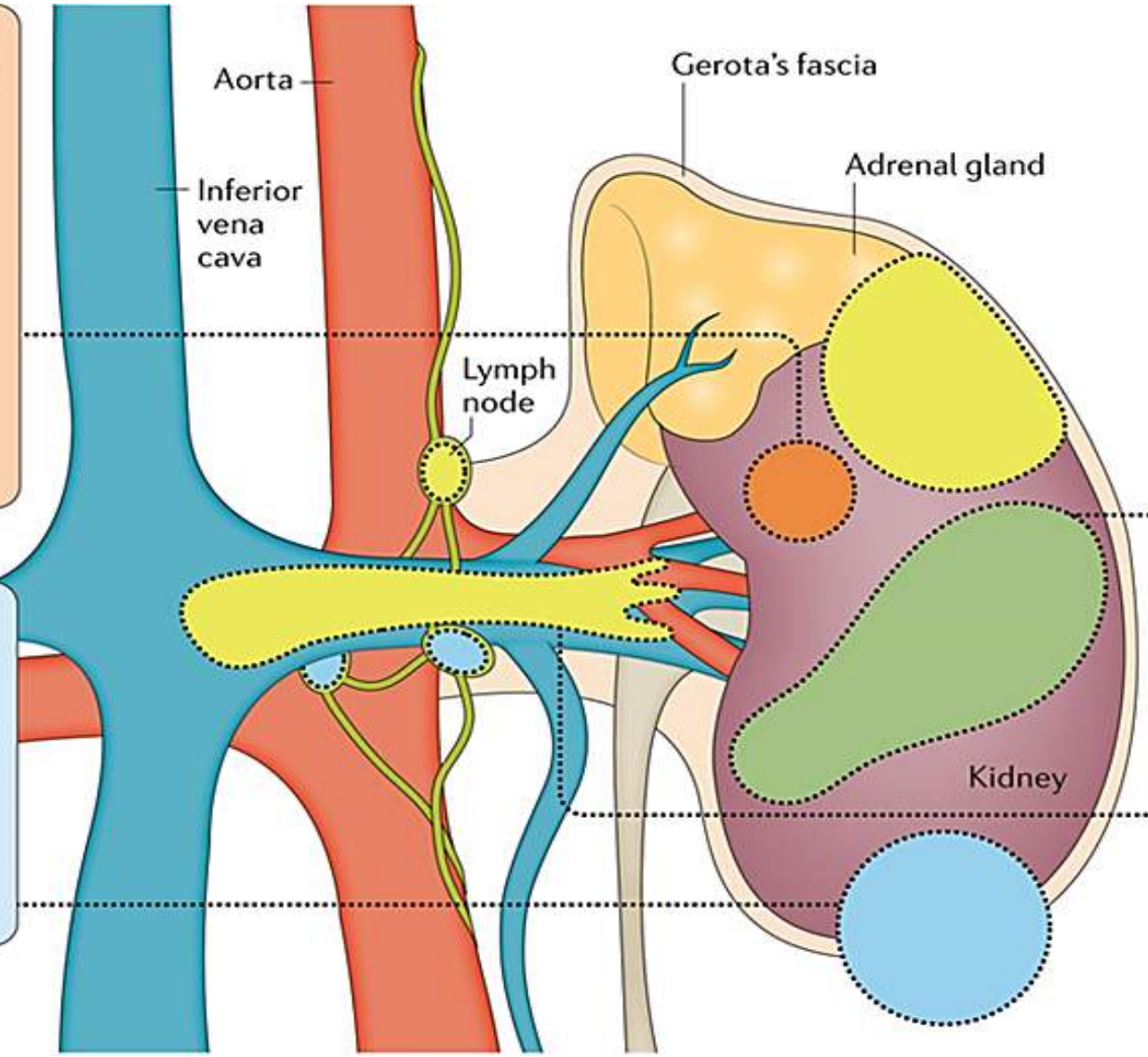
Cancer evolution and tumour heterogeneity in clear cell renal cell carcinoma.



MRCA cell, the most recent common ancestor (MRCA)

Hsieh, J. J. et al. Nat. Rev. Dis. Primers 2017; 3: 1-19

Stages of kidney cancer and recommended treatments.



Stage I
- Tumour <7 cm in the largest dimension
- Limited to the kidney
- 5-year survival rate of 95%

Management options
- Partial nephrectomy
- Radical nephrectomy
- If not technically feasible, active surveillance or ablative therapies in selected patients with small masses

Stage II
- Tumour >7 cm in the largest dimension
- Limited to the kidney
- 5-year survival rate of 88%

Management options
- Radical nephrectomy
- Partial nephrectomy in selected patients in whom the procedure is feasible

Stage III
- Tumour in the major veins or adrenal gland with an intact Gerota's fascia
- Or regional lymph nodes involved
- 5-year survival rate of 59%

Management options
- Radical nephrectomy plus adrenalectomy, tumour thrombus excision (if appropriate) and/or lymph node dissection
- Systemic treatment if inoperable, or owing to poor performance status

Stage IV
- Tumour beyond Gerota's fascia
- Distant metastases
- 5-year survival rate of 20%*

Management options
- Systemic treatment
- Elective cytoreductive nephrectomy

Hsieh, J. J. et al. Nat. Rev. Dis. Primers 2017; 3: 1-19

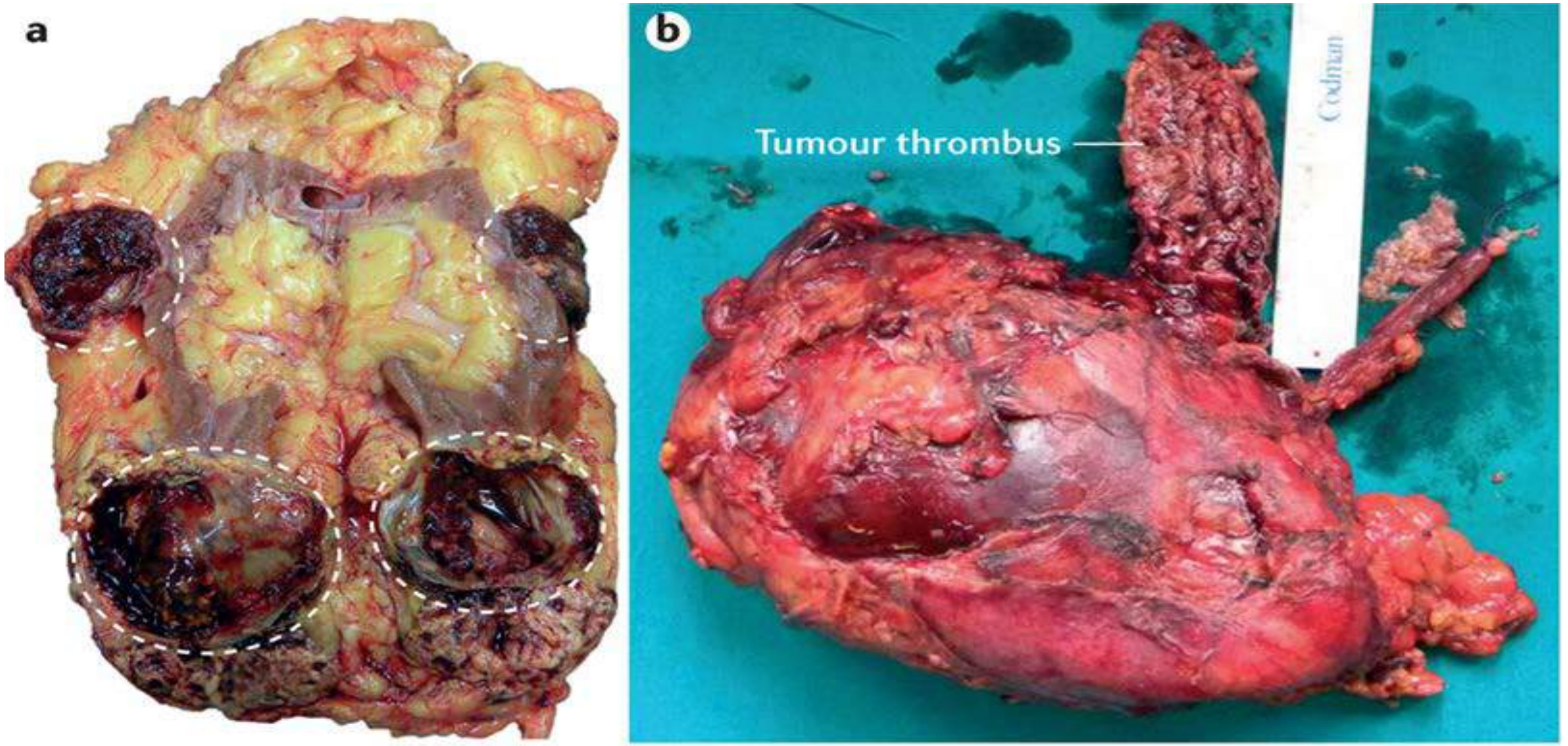
Nephrectomy scores to predict surgical complexity and outcomes

Nephrometry system	Parameters included	Outcomes prediction	External validation
R.E.N.A.L. nephrometry [25]	• Tumour size • Exophytic rate • Polar location • Renal sinus involvement • UCS involvement • Face location	• Blood loss • Warm ischaemia time • UCS lesion • Overall complications • Functional outcomes • Benign or malignant tumour • Tumour grade	Yes
PADUA classification [153]	• Tumour size • Exophytic rate • Polar location • Rim location • Renal sinus involvement • UCS involvement • Face location	• Blood loss • Both warm and cold ischaemia time • UCS lesion • Overall complications • Functional outcomes	Yes
Centrality Index [135]	• Tumour radius • Tumour depth (horizontal and vertical distances)	• Both warm and cold ischaemia time • Functional outcomes	Yes
Diameter-Axial-Polar system [136]	• Diameter • Axial distance • Polar distance	• Blood loss • Warm ischaemia time • Functional outcomes	No
Zonal NePhRO scoring system [137]	• Nearness to vital renal structures* • Physical zone • Tumour radius • Organization of the tumour	Perioperative complications	No
Arterial Based Complexity scoring system [138]	Size of the renal arterial branches that need to be dissected or transected to achieve complete excision of the renal tumour	• Both warm and cold ischaemia time • Urinary fistula	No

UCS, upper collecting system.
*Cortex, medulla and collecting system or renal sinus.

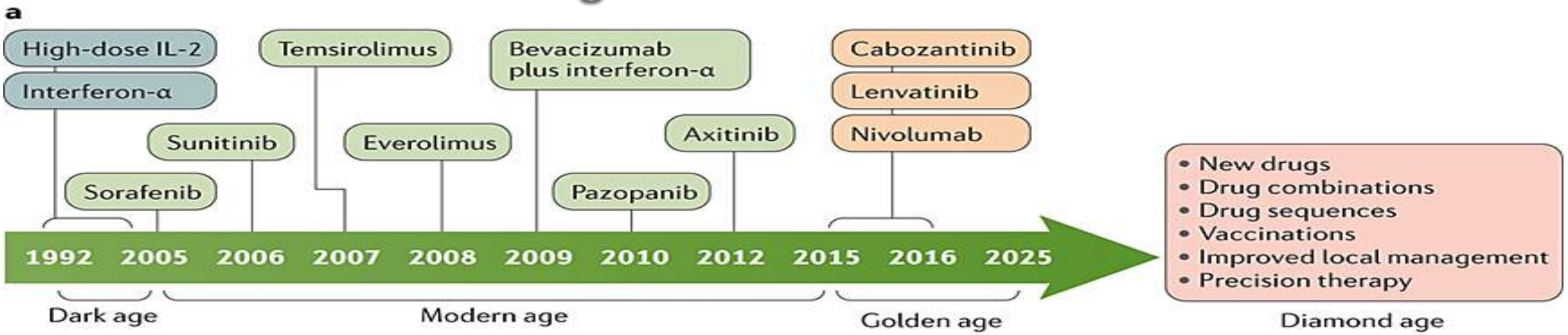
Hsieh, J. J. et al. Nat. Rev. Dis. Primers 2017; 3: 1-19

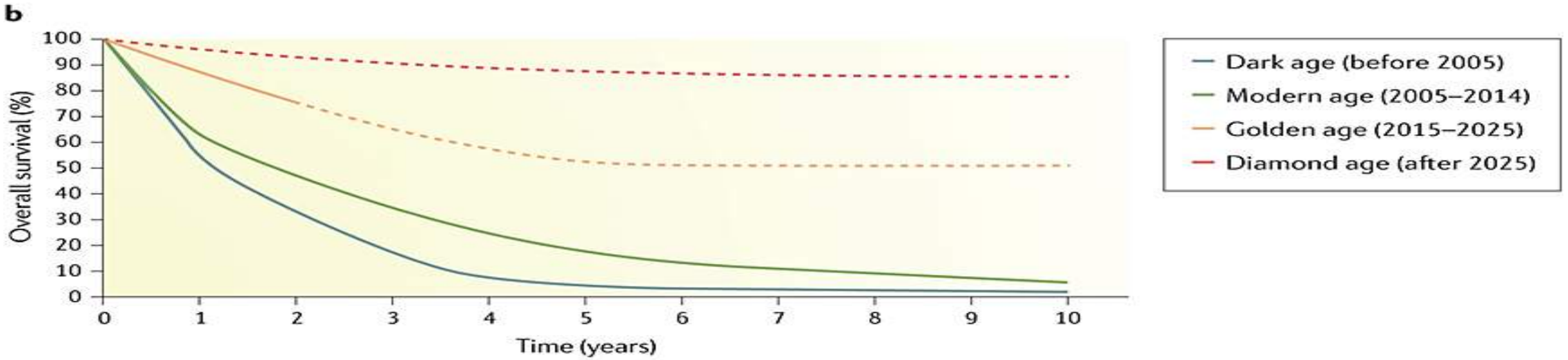
Indications for radical nephrectomy.



Hsieh, J. J. et al. Nat. Rev. Dis. Primers 2017; 3: 1-19

Therapeutic evolution and survival outcome of metastatic clear cell RCC through the four different eras





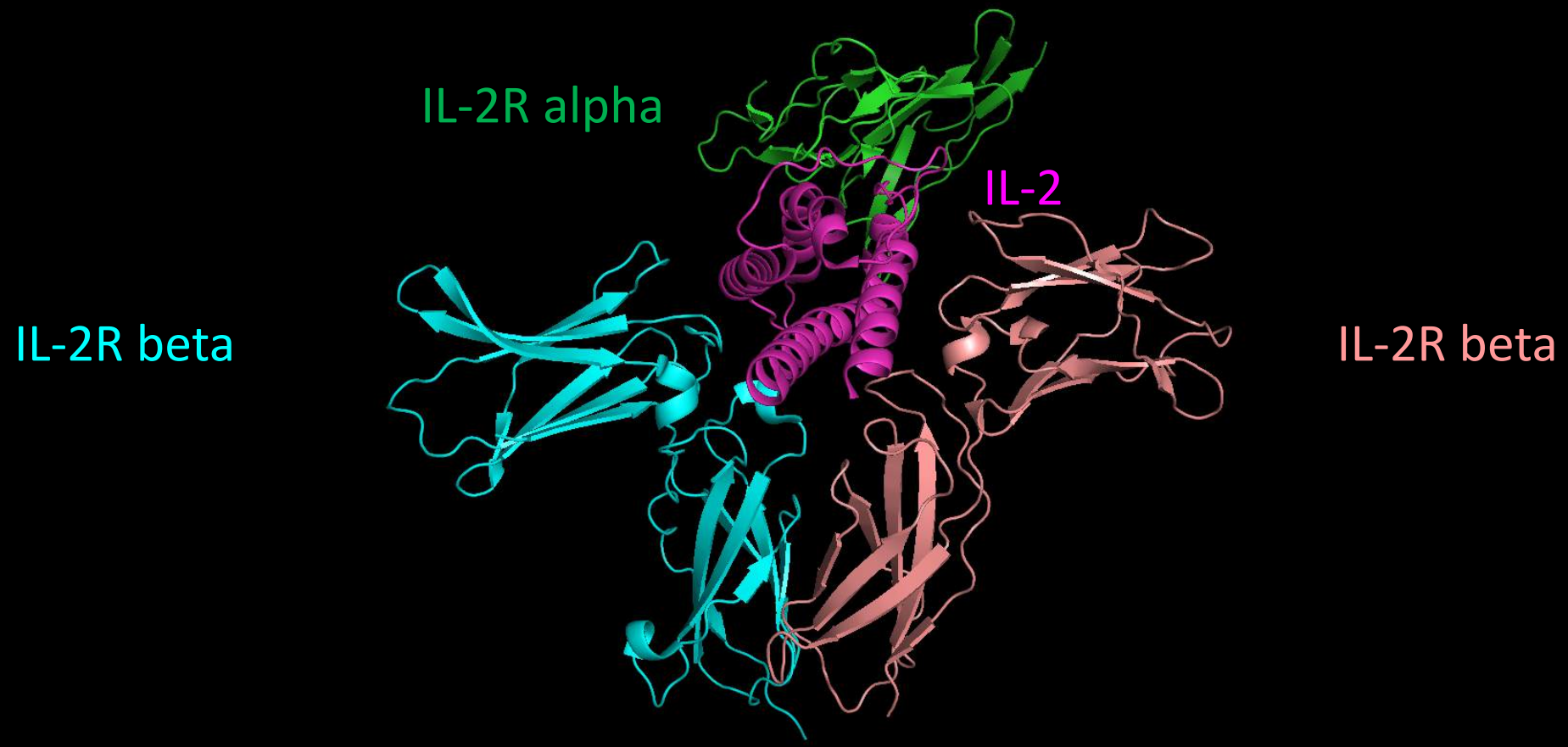
Hsieh, J. J. et al. Nat. Rev. Dis. Primers 2017; 3: 1-19

Limitations in the management of non-clear-cell RCC

- In fact, histological subtype is often unknown preoperatively.
- Limited data as a consequence of the exclusion in general of non-clear-cell histologies from registration trials of targeted agents over the past 10 years.
- Importantly, the tumours classed as nccRCC are fundamentally different; there is no reason to suppose that a therapy that is effective for papillary RCC would be effective for chromophobe or indeed any other subtype of kidney cancer.
- Nevertheless, **some trials** have been carried out and have broadly established **sunitinib** as a reasonable first-line option in nccRCC, although the efficacy is less than for clear cell renal carcinoma (ccRCC).
- Most patients with metastatic nccRCC are treated with targeted agents that are approved for ccRCC, with the data favouring vascular endothelial growth factor inhibitors over mechanistic target of rapamycin complex 1 inhibitors[22,204,205].
- Unfortunately, most patients with nccRCC succumb to their disease within 18 months despite systemic treatment[12,13,204,205,206], and currently, there is no evidence base for the treatment of nccRCC with immune checkpoint inhibitors.
- Encouragingly, a recent phase II trial reported **everolimus plus bevacizumab** as an effective combination in treating nccRCC in patients whose tumours display papillary features, achieving an overall response rate of 43% and a median progression-free survival of 12.9 months[194].
- Arguably, everolimus plus bevacizumab should be considered as the comparison arm in trials in rare RCC subtypes that show predominant papillary morphology (papillary RCC type I and type II and unclassified RCC with papillary features).
- Overall, the advances made are encouraging, but drug therapies that are tailored specifically to subtype remain an unmet need.
- Initiatives such as rarekidneycancer.org set up by experts and patient advocates are important steps to encourage rapid communication among patients with rare kidney cancer, doctors who specialize in nccRCC and trialists.

Hsieh, J. J. et al. Nat. Rev. Dis. Primers 2017; 3: 1-19

The human IL-2R signaling complex



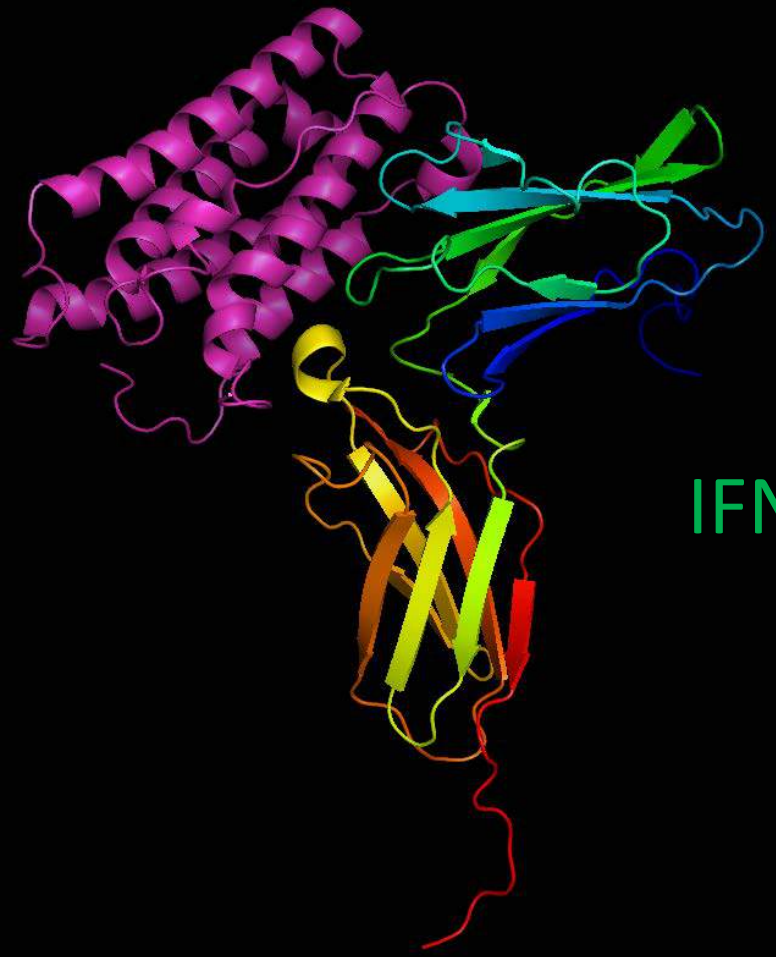
IL-2 is a cytokine that functions as a growth factor and central regulator in the immune system and mediates its effects through ligand-induced hetero-trimerization of the receptor subunits IL-2R alpha, IL-2R beta, and gamma (c)

PDB: 2ERJ

Stauber D.J.,et al. Proc.Natl.Acad.Sci.Usa 2006; 103: 2793

Model of the Human Interferon alpha-2 and Type I Interferon Receptor Complex

IFN-α



IFN receptor

PDB: 2HYM

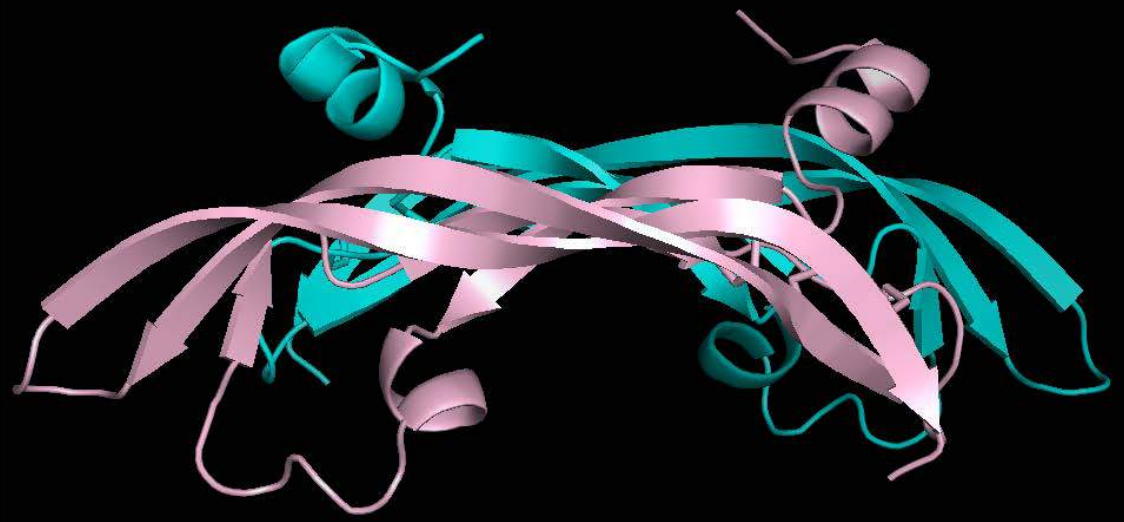
Quadt-Akabayov SR, et al. Protein Sci. 2006 Nov;15(11):2656-68

VEGF-A dimer

PDB: 3V2A

Brosso MS, et al. Blood 2012; 119: 1781-1788

VEGF-A dimer



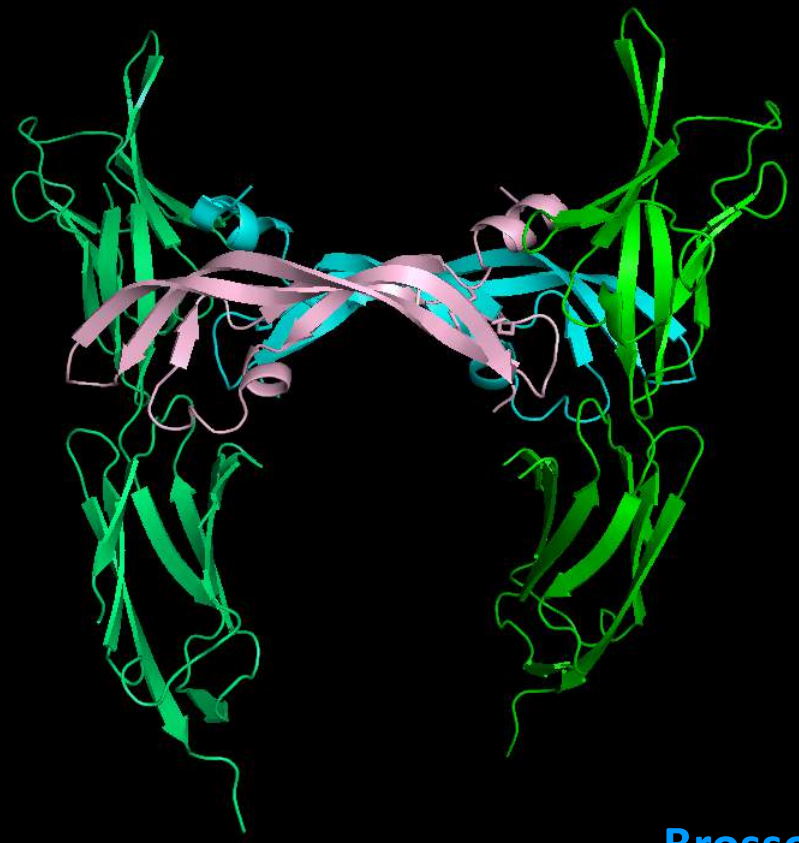
PDB: 3V2A

Brosso MS, et al. Blood 2012; 119: 1781-1788

VEGF-A binding VEGFR-2 domain 2,3

VEFR-D2

VEFR-D3



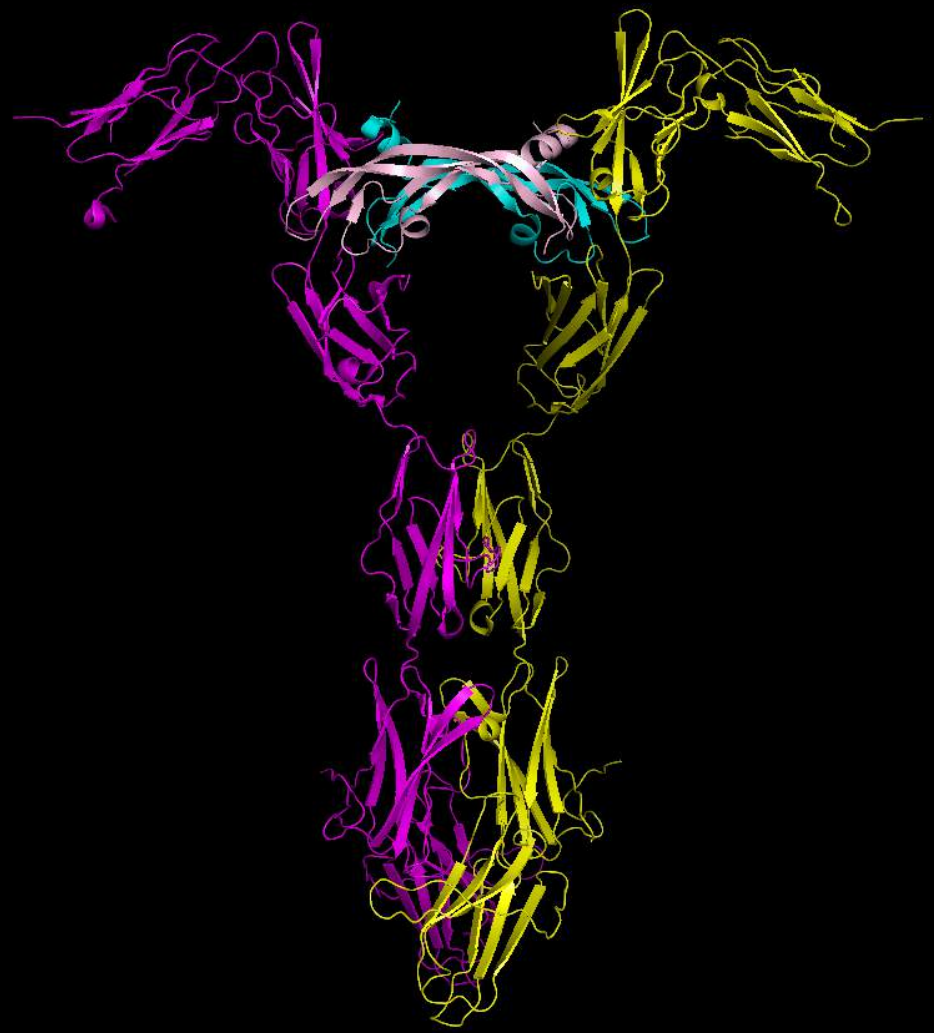
VEFR-D2

VEFR-D3

PDB: 3V2A

Brosso MS, et al. Blood 2012; 119: 1781-1788

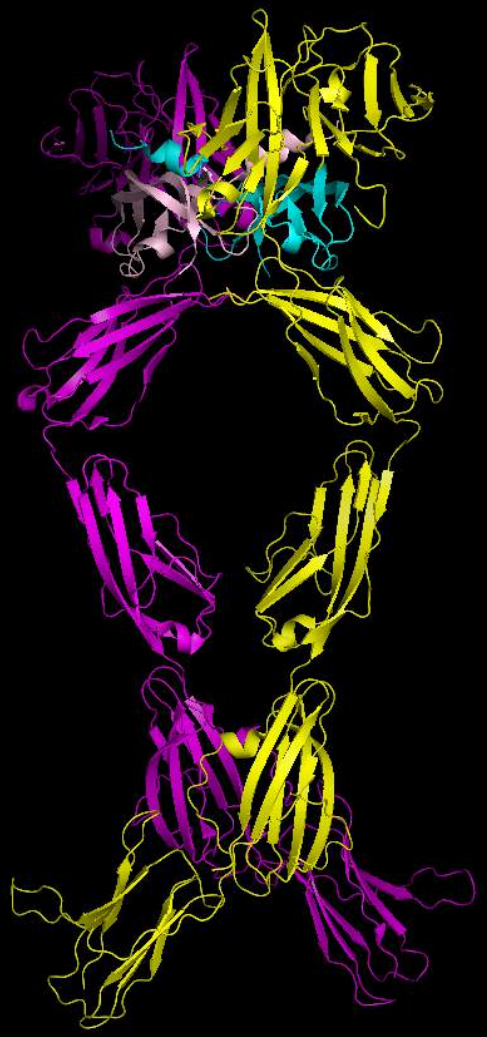
VEGF-A binding VEGFR-1 domain 1-6



PDB: 5T89

Markovic-Mueller, S., et al. Structure 2017; 25: 341-352

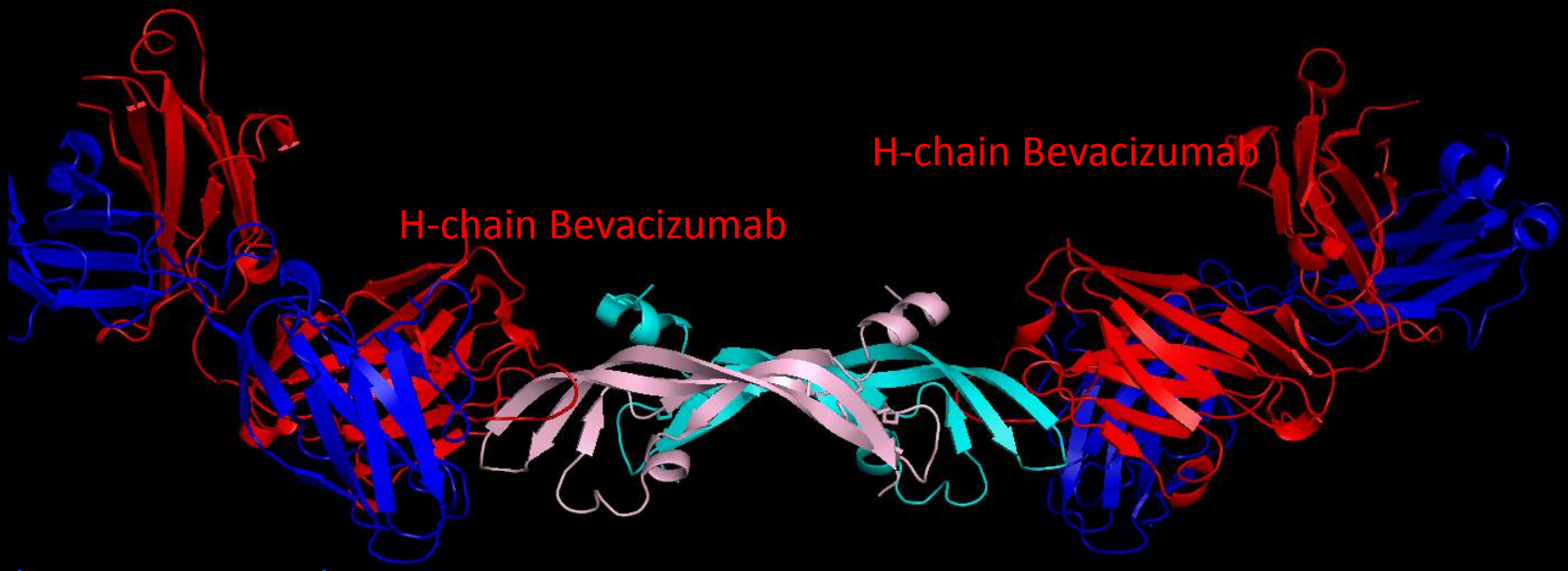
VEGF-A binding VEGFR-1 domain 1-6



PDB: 5T89

Markovic-Mueller, S., et al. Structure 2017; 25: 341-352

The Fab fragment of Bevacizumab binding VEGF



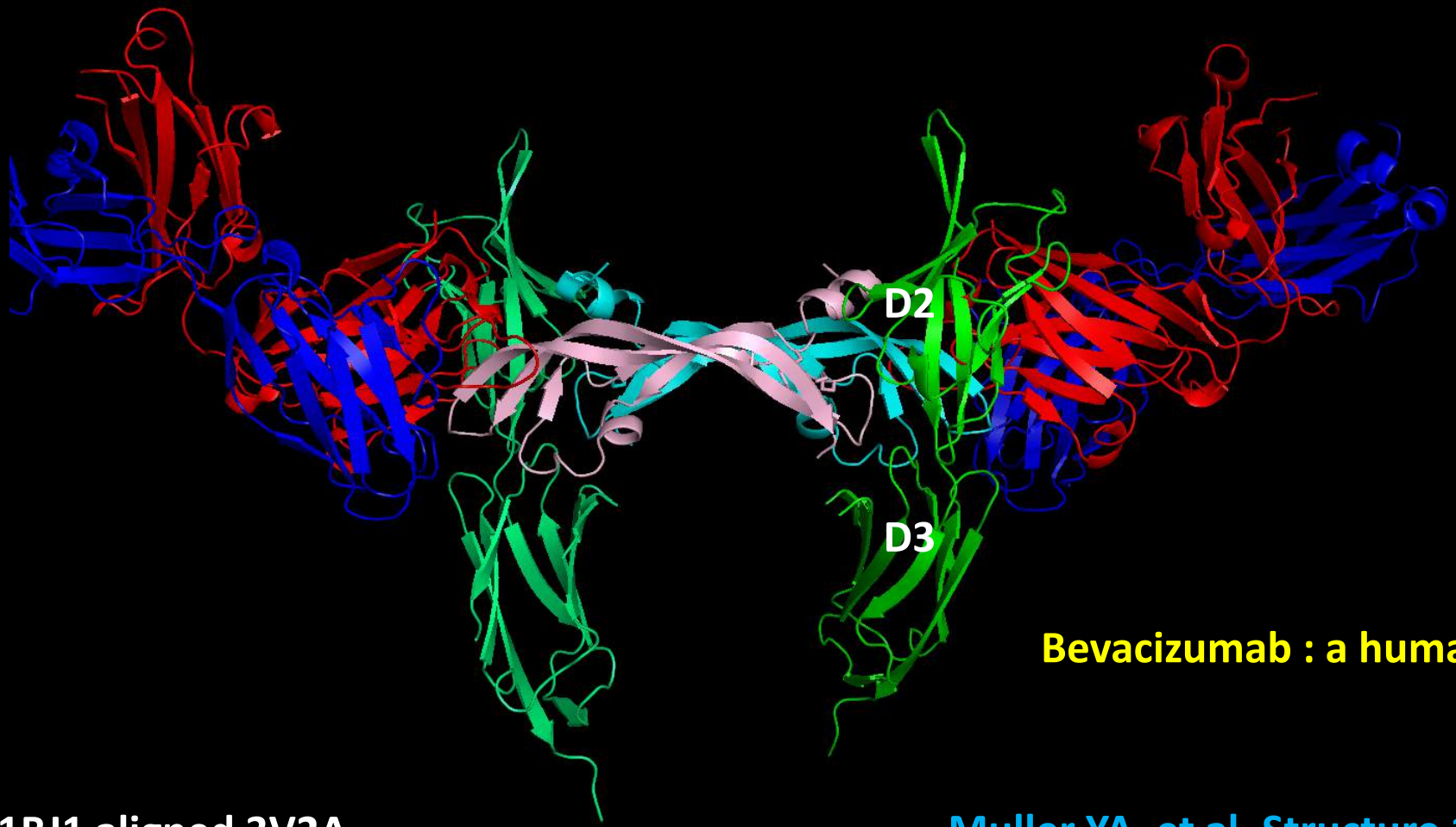
Bevacizumab : a humanized IgG1 mAb

Bevacizumab: A recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF).

PDB: 1BJ1

Muller YA, et al. Structure 1998; 6: 1153-1167

Bevacizumab interfering VEGF-VEGFR binding

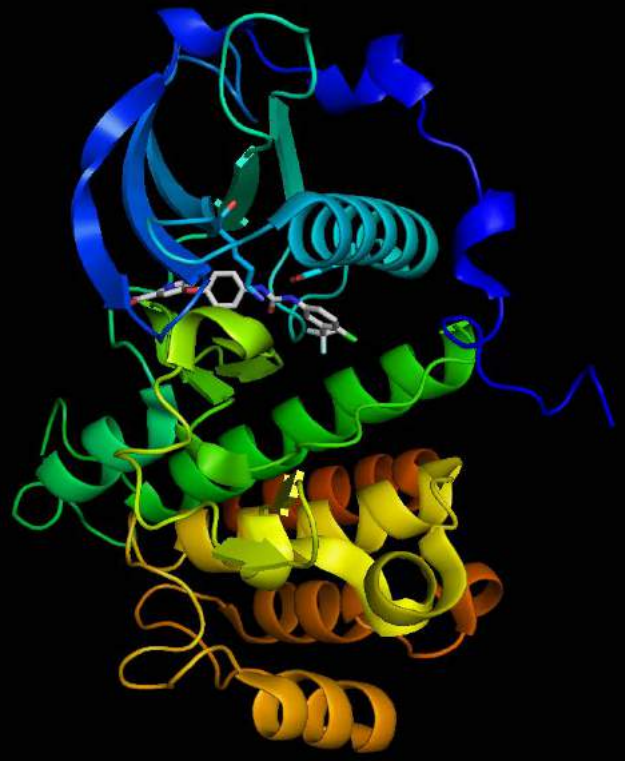


Bevacizumab : a humanized IgG1 mAb

PDB: 1BJ1 aligned 3V2A

Muller YA, et al. Structure 1998; 6: 1153-1167
Brosso MS, et al. Blood 2012; 119: 1781-1788

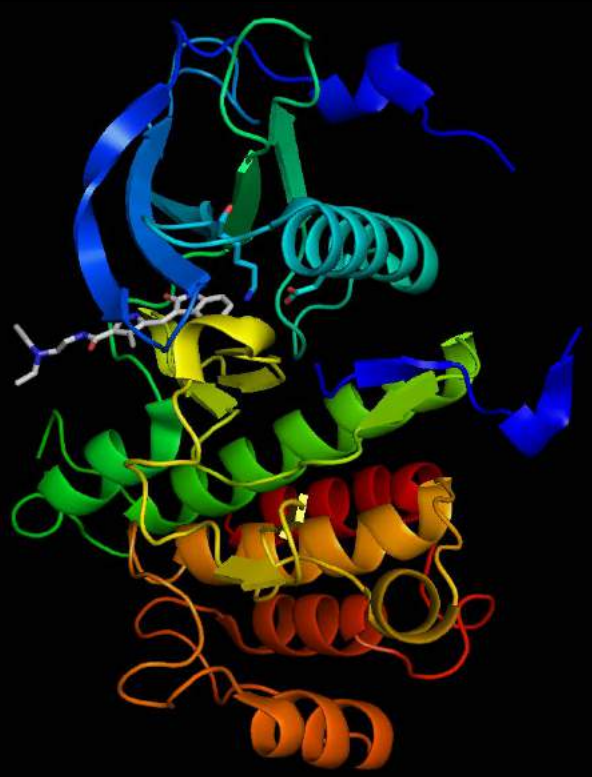
Sorafenib binding VEGFR2 (JM AND KD)



PDB: 4ASD

Michele McTigue et al. PNAS 2012;109:18281-18289

Sunitinib binding VEGFR2 (JM and KD)



Michele McTigue et al. PNAS 2012;109:18281-18289

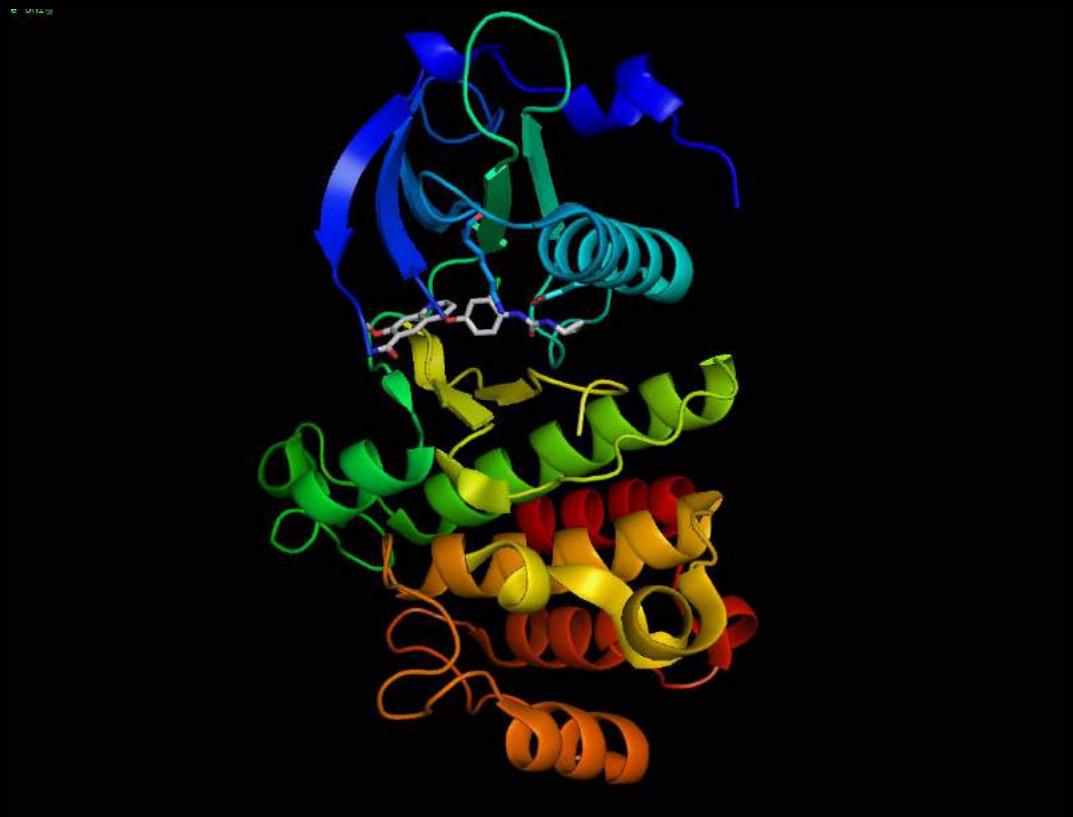
PDB: 4AGD

Axitinib binding VEGFR2 (JM and KD)

PDB: 4AGC

Michele McTigue et al. PNAS 2012;109:18281-18289

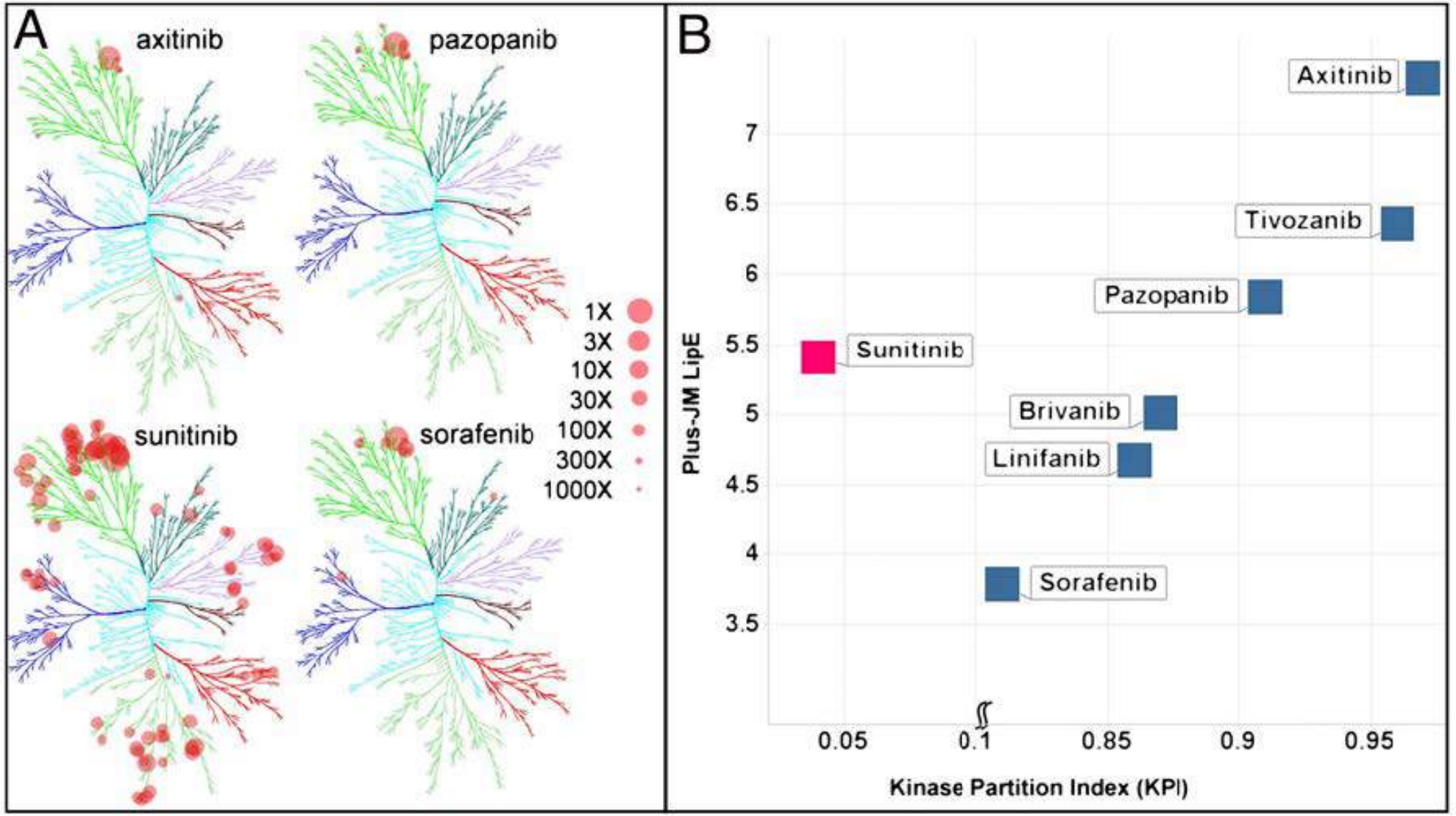
Lenvatinib binding VEGFR2



PDB: 3WZD

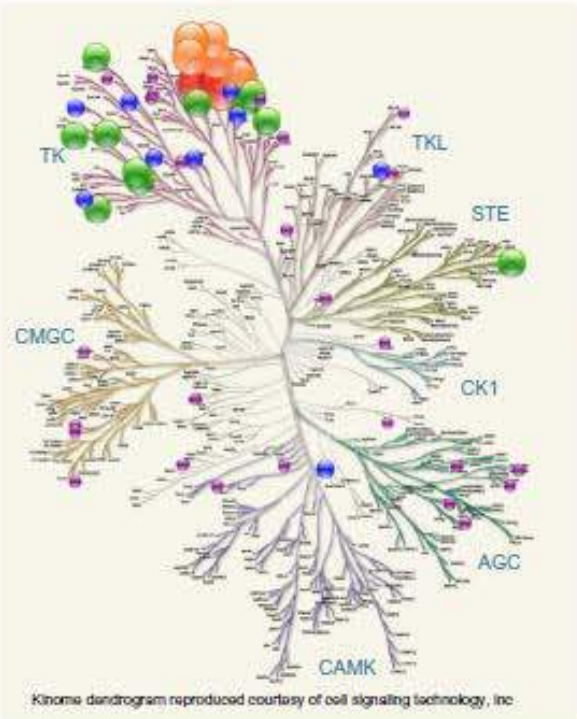
Okamoto, K., et al. ACS MED.CHEM.LETT.2015; 6: 89-94

Kinome selectivity tree of FDA-approved VEGFR TK drugs in RCC.

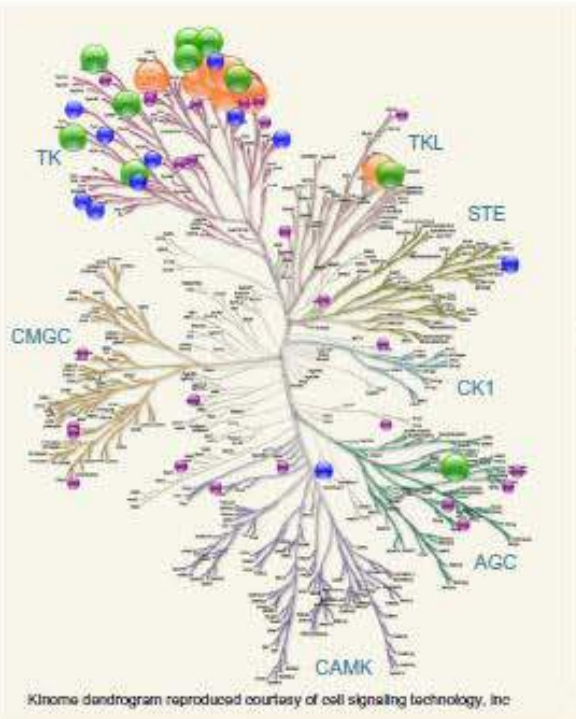


Michele McTigue et al. PNAS 2012;109:18281-18289

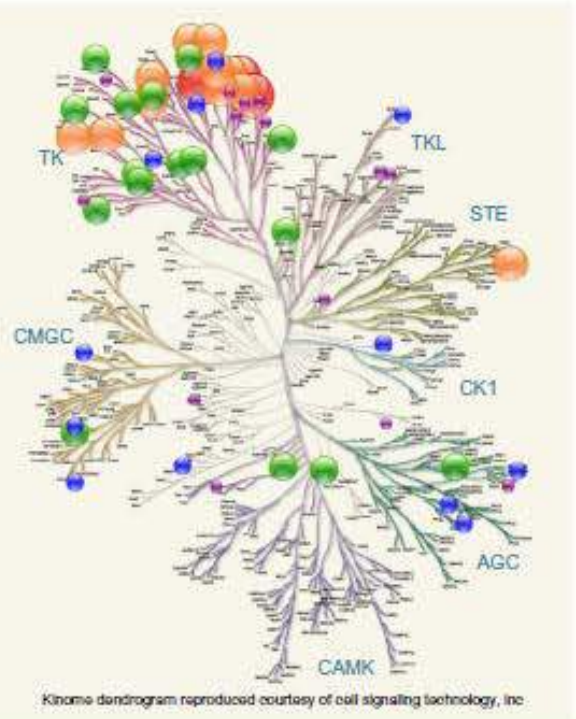
Lenvatinib



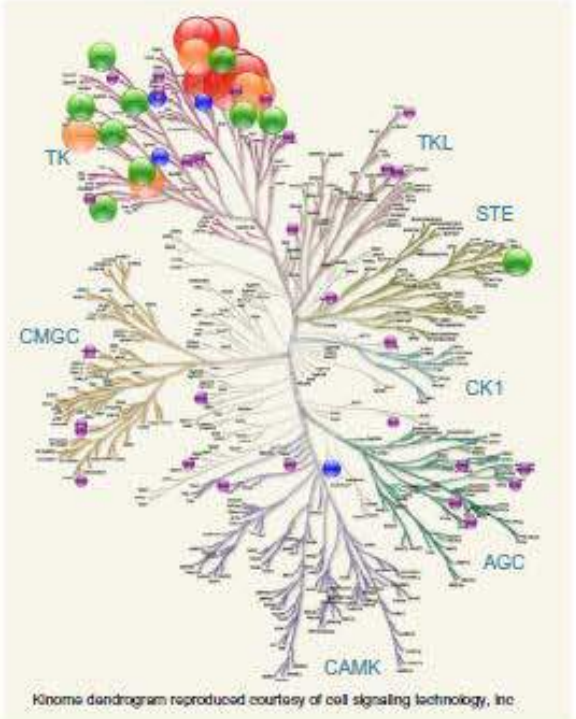
Sorafenib

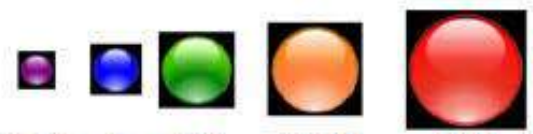


Sunitinib



Cediranib





IC50 (μM): >10 1 0.1 0.01 0.01<

Selected adverse events and quality of life of the approved agents

Drug	Adverse events	Improvement in quality of life?	Refs
Axitinib	Hypertension, diarrhoea, hypothyroidism and hand–foot syndrome	Yes versus sorafenib	157
Bevacizumab	Proteinuria, hypertension and bleeding	Not reported	160
Cabozantinib	Diarrhoea, hand–foot syndrome, hypertension, nausea and hypothyroidism	Not reported	159
Everolimus	Stomatitis, hypercholesterolaemia, hyperglycaemia and pneumonitis	No versus placebo	209
Nivolumab	Colitis, pneumonitis and endocrinopathies	Yes versus everolimus	165
Pazopanib	Diarrhoea, hypertension, liver function test abnormalities and hand–foot syndrome	• No versus placebo • Yes versus sunitinib	156
Sorafenib	Hypertension, diarrhoea, hand–foot syndrome and rash	Yes versus placebo	154
Sunitinib	Diarrhoea, hand–foot syndrome, mucositis and hypertension	Yes versus interferon-α	155
Temsirolimus	Stomatitis, hyperglycaemia, hypercholesterolaemia and oedema	Yes versus interferon-α	210

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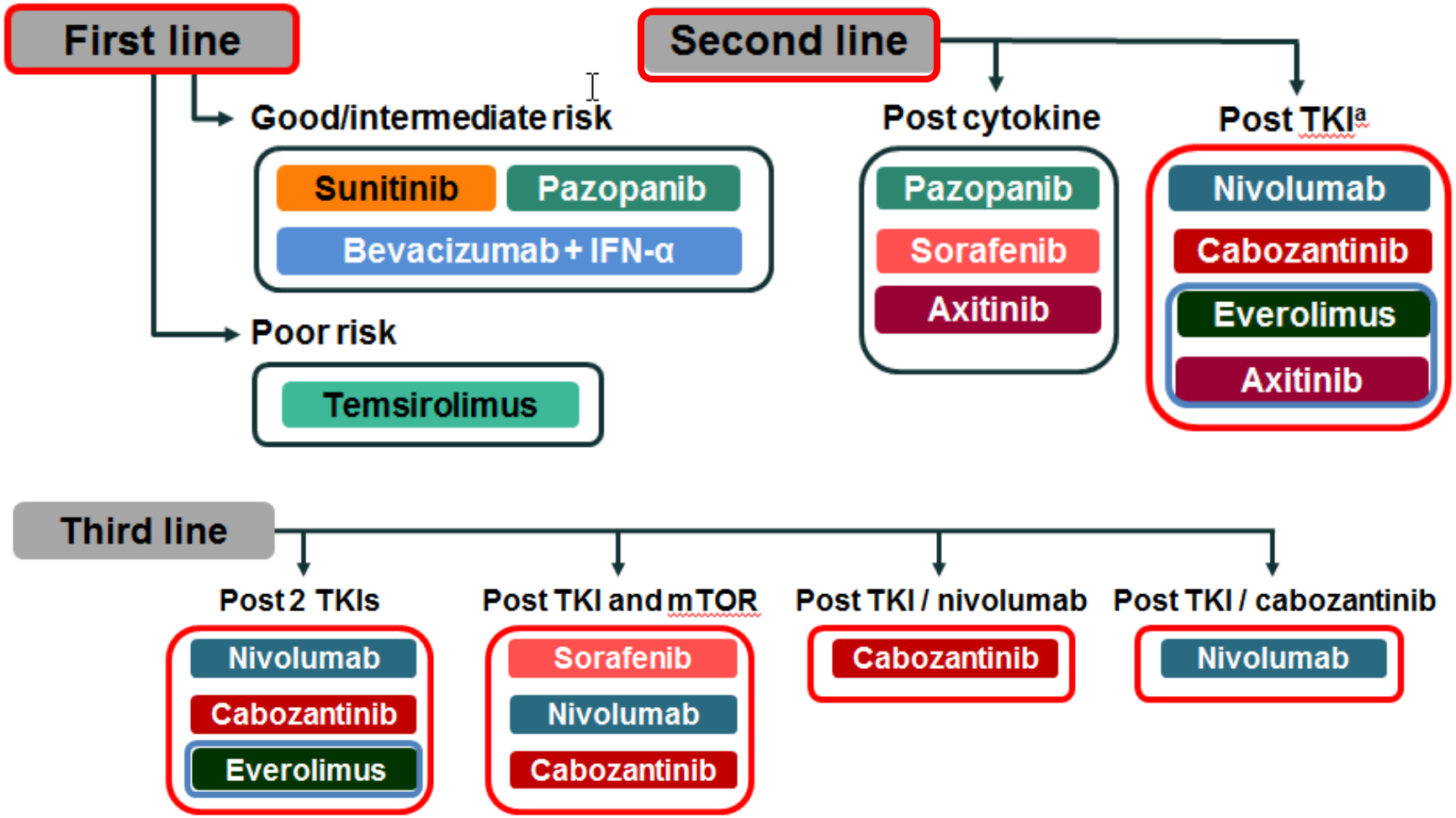
ESMO 2016 RCC Treatment Guidelines



Escudier *et al. Ann Oncol* 2016;27(Suppl 5):v58–v68

Algorithm for systemic treatment in mRCC

Histology and setting	Risk Group	Standard	Option	Ongoing Phase III Clinical Study
Clear cell 1st line	Good or intermediate risk	Sunitinib*	High-dose IL2	Axitinib+Pembrolizumab
		Bevacizumab + IFN-α*	Sorafenib	Axitinib+Avelumab
		Pazopanib*	Bevacizumab + low-dose IFNα	Cabozantinib + Nivo/ipi
	Poor prognosis	Temsirolimus	Sunitinib	Lenvatinib + Pembrolizumab
			Sorafenib	Lenvatinib+everolimus
			Pazopanib	Atezolizumab (adjuvant therapy)
Clear cell 2nd line	Post cytokines	Sorafenib	Sunitinib	
		Pazopanib		
		Axitinib		
	Post TKIs	Nivolumab	Axitinib	
		Cabozantinib	Everolimus	
			Sorafenib	

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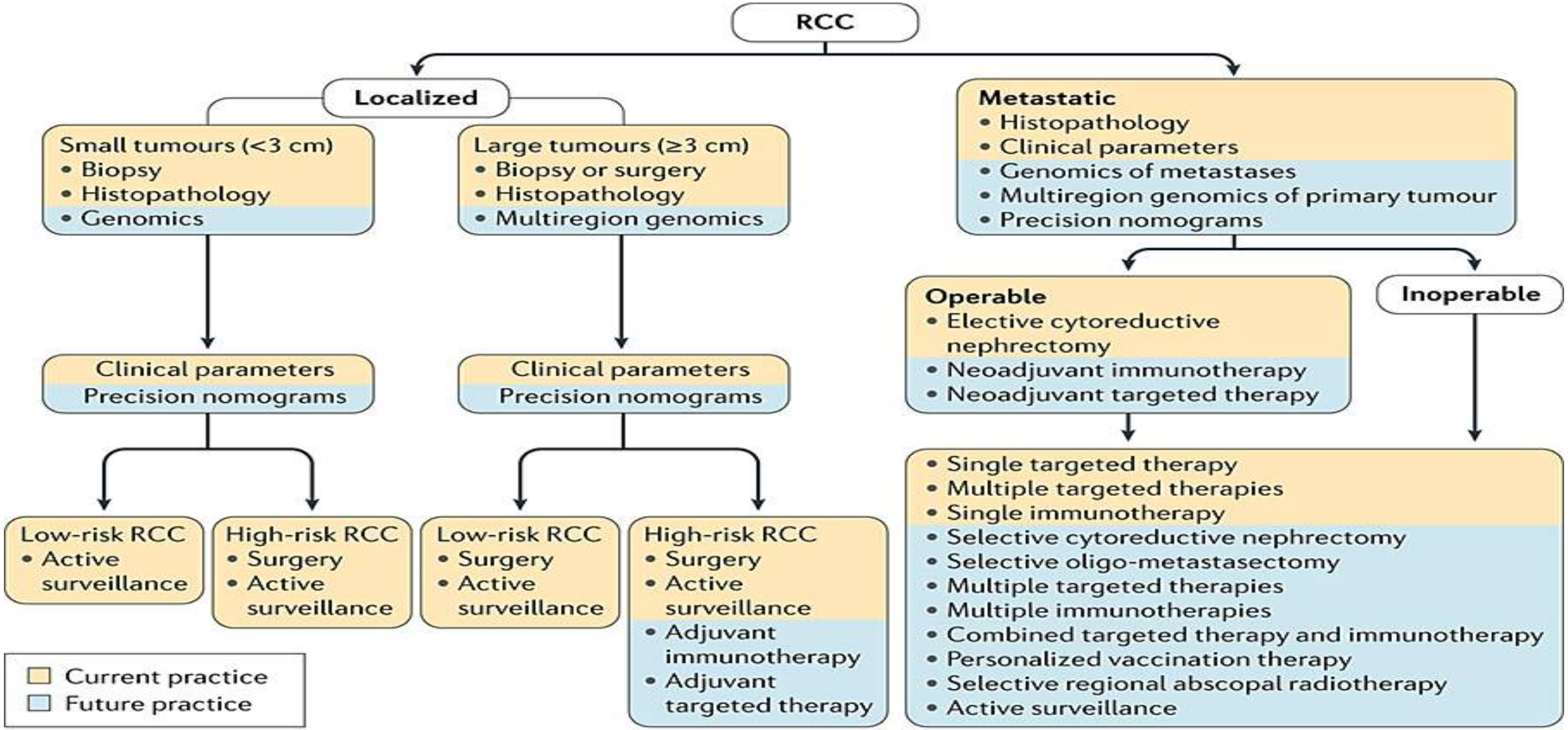
Algorithm for systemic treatment in mRCC

Histology and setting	Risk Group	Standard	Option	Ongoing Phase III Clinical Study
Clear cell 3rd line	Post 2 TKIs	Nivolumab	Everolimus	
		Cabozantinib		
	Post TKI and mTOR	Sorafenib	Other TKI	
		Nivolumab	Rechallenge	
		Cabozantinib		
	Post TKI/nivolumab	Cabozantinib	Axitinib	
			Everolimus	
	Post TKI/ Carbozantinib	Nivolumab	Everolimus	
			Axitinib	
Non clear cell histology		Sunitinib	Temsirolimus	
			Sorafenib	
			Pazopanib	
			Everolimus	

Escudier *et al. Ann Oncol* 2016;27(Suppl 5):v58–v68

Treatment algorithms for renal cell carcinoma



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