



# **ETEROGENEITA' INTER/INTRATUMORALE: IL RUOLO DELLA TIPIZZAZIONE ISTOLOGICA**

## **RCC OLIGOMETASTATICO**

*La necessità di un*

**Approccio Multidisciplinare**

**Sala "A. Barbiero"**

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Ospedale Pederzoli

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Dipartimento di Patologia e Sanità Pubblica

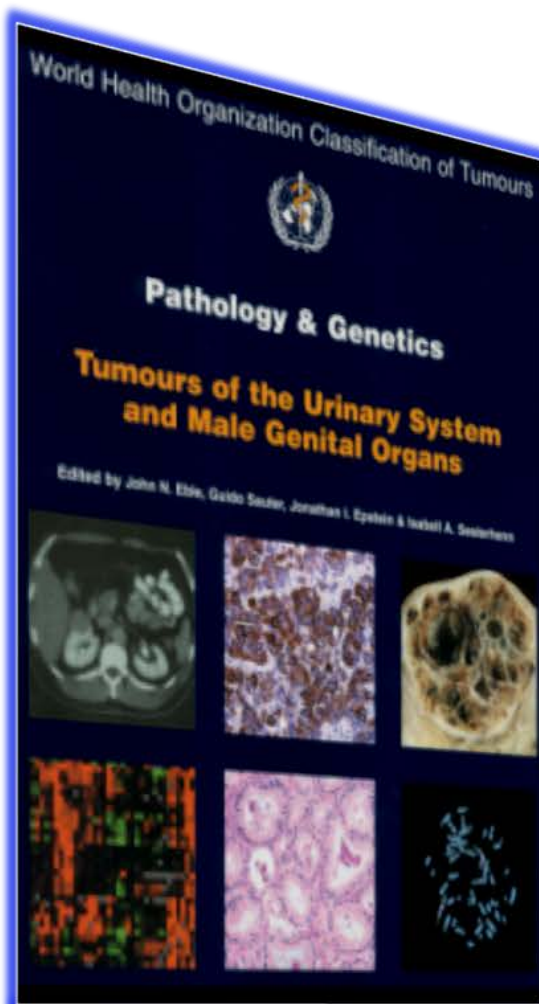
Università di Verona



PEDERZOLI

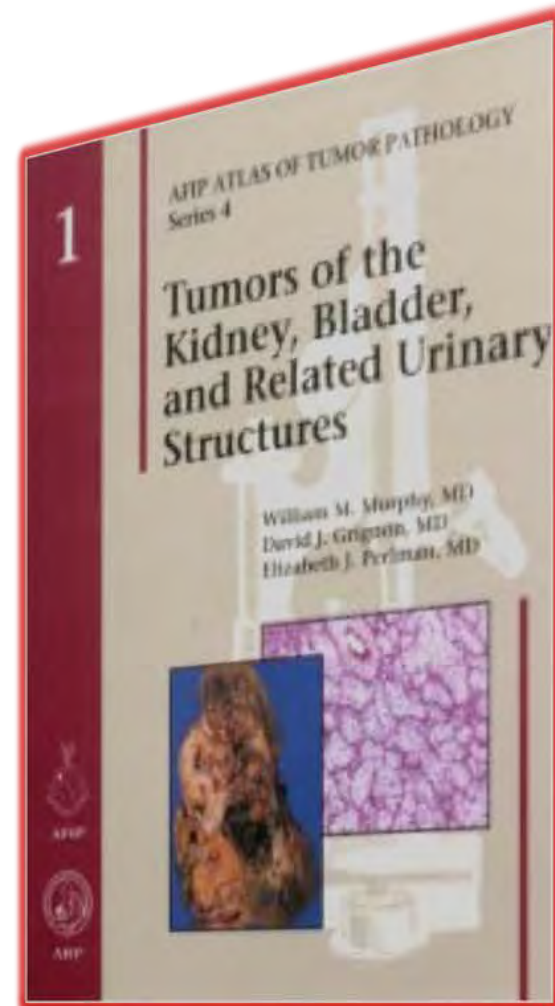


WHO 2004

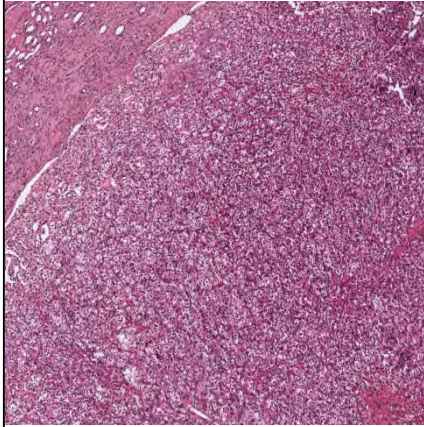


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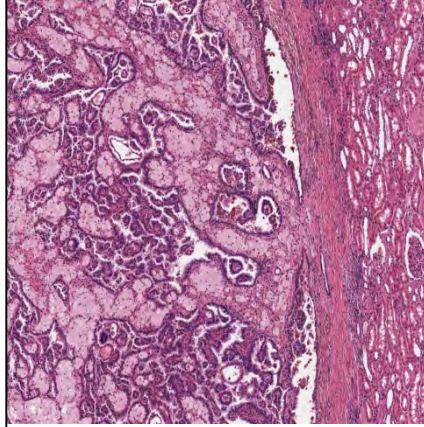
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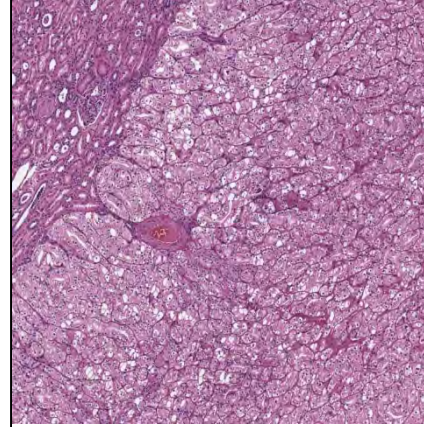
**Clear cell**



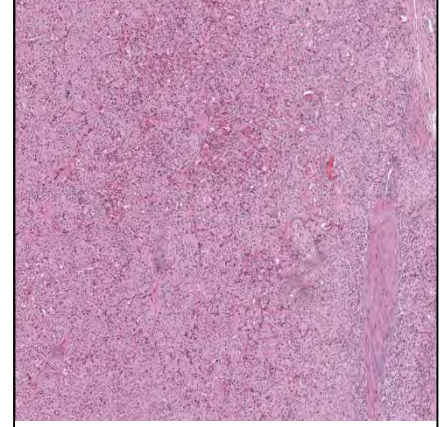
**Papillary**



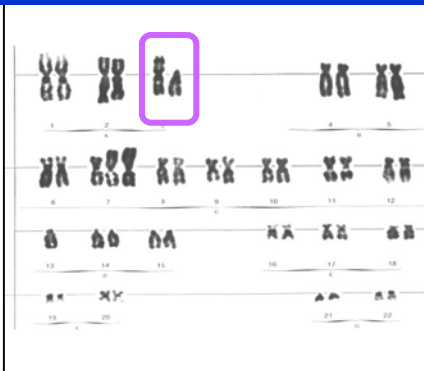
**Chromophobe**



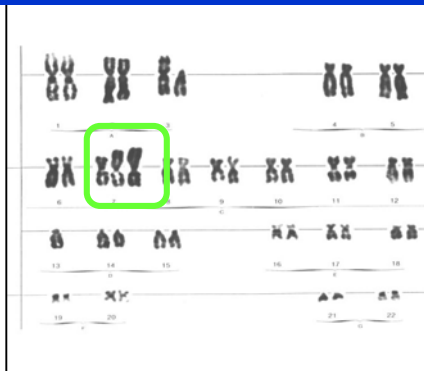
**Oncocytoma**



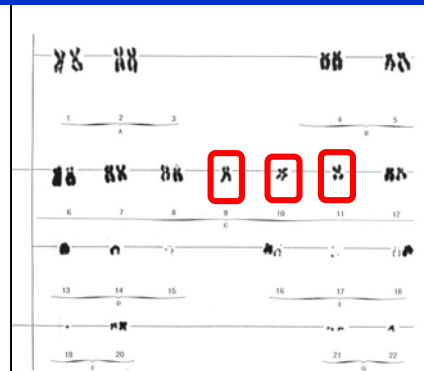
**CLASSIC CYTOGENETIC ANALYSIS**



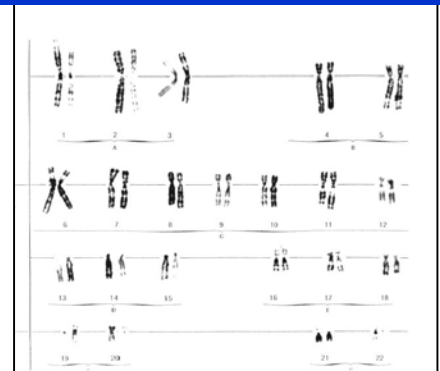
**3p deletion**



**7 and 17 trisomies**



**Multiple monosomies**



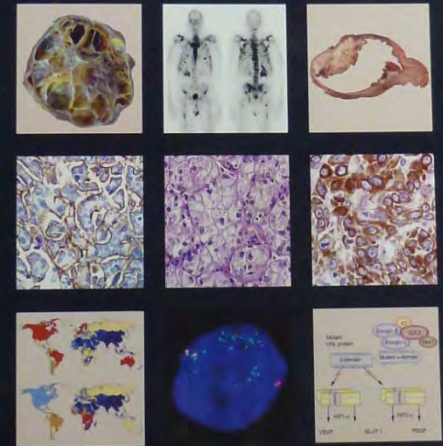
**Normal**

# WHO (2015) BLUE BOOK COMMITTEE



## WHO Classification of Tumours of the Urinary System and Male Genital Organs

Edited by Holger Moch, Peter A. Humphrey, Thomas M. Ulbright, Victor E. Reuter



# WHO 2016

## Renal cell tumours

Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1
Papillary renal cell carcinoma	8255/1
<u>Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma</u>	8311/3*
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3
<u>MiT Family translocation carcinomas</u>	8311/3
<u>Succinate dehydrogenase (SDH)-deficient renal carcinoma</u>	8312/3
Mucinous tubular and spindle cell carcinoma	8480/3
<u>Tubulocystic renal cell carcinoma</u>	8316/3
<u>Acquired cystic disease associated renal cell carcinoma</u>	8316/3
<u>Clear cell papillary renal cell carcinoma</u>	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0

## Metanephric tumours

Metanephric adenoma	8325/0
Metanephric adenofibroma	9013/0
Metanephric stromal tumour	8935/1

## Nephroblastic tumours

Nephrogenic rests	
Nephroblastoma	8960/3
Cystic partially differentiated nephroblastoma	8959/1
Paediatric cystic nephroma	8959/0

## Mesenchymal tumours

### *Mesenchymal tumours occurring mainly in children*

Clear cell sarcoma	8964/3
Rhabdoid tumour	8963/3

Congenital mesoblastic nephroma	8960/1
Ossifying renal tumour of infants	8967/0

### *Mesenchymal tumours occurring mainly in adults*

Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Rhabdomyosarcoma	8900/3
Osteosarcoma	9180/3
Synovial sarcoma	9040/3
Ewing sarcoma / Peripheral neuroectodermal tumour	9260/3
Angiomyolipoma	8860/0
Epithelioid angiomyolipoma	8860/1
Leiomyoma	8890/0
Haemangioma	9120/0
Lymphangioma	9170/0
Haemangioblastoma	9161/1
Juxtaglomerular cell tumour	8361/0
Renomedullary interstitial cell tumour	8966/0
Schwannoma	9560/0
Solitary fibrous tumour	8815/1

## Mixed epithelial and mesenchymal tumours

Cystic nephroma	8959/0
Mixed epithelial and stromal tumour	8959/0

## Neuroendocrine tumours

Well-differentiated neuroendocrine tumour	8240/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Paraganglioma	8693/1
Phaeochromocytoma	8700/0

## Miscellaneous tumours

Renal haematopoietic neoplasms	
Germ cell tumours	

## Metastatic tumours

# Clear cell papillary RCC

## New entity with indolent behaviour

**NUMBER OF CASES: 480 (FREQUENCY: 2,3%)**

CASES IN END STAGE RENAL DISEASE

CASES NOT IN END STAGE RENAL DISEASE

**MEAN AGE: 57**

**M/F: 1.4/1**

**MULTIFOCALITY: 18 CASES**

5 CASES IN END STAGE RENAL DISEASE

**TUMOR DIMENSION: 2,5 cm**

CASES IN END STAGE RENAL DISEASE: 2,5 cm

CASES NOT IN END STAGE RENAL DISEASE: 3,4 cm

**GRADING**

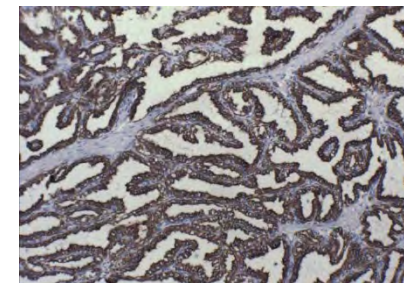
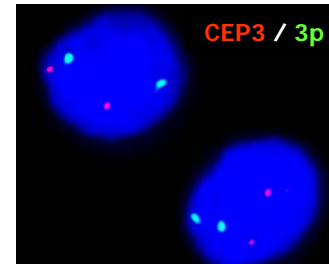
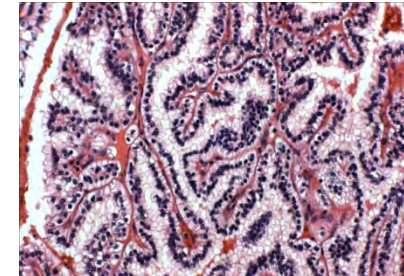
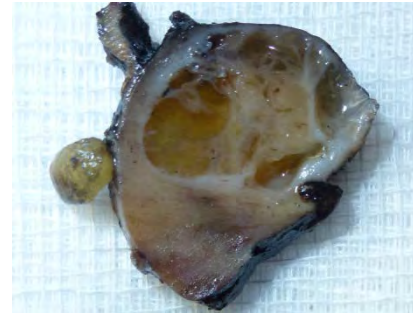
ALL TUMORS G1-G2

**PATHOLOGIC STAGE: pT1**

ALL TUMORS pT1a EXCEPT 3 CASES pT1b

**FOLLOW-UP (1-85 month)**

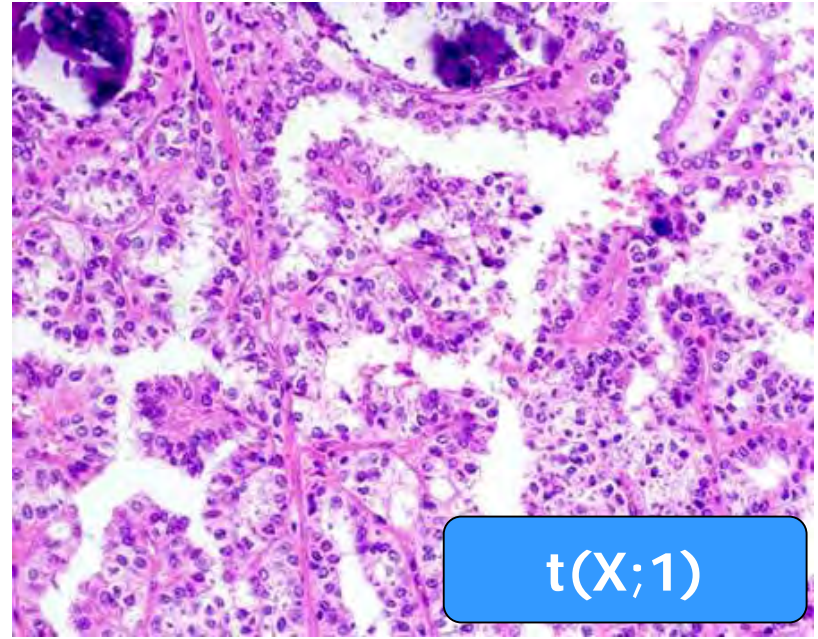
ALL CASES WITHOUT EVIDENCE  
OF RECURRENCES



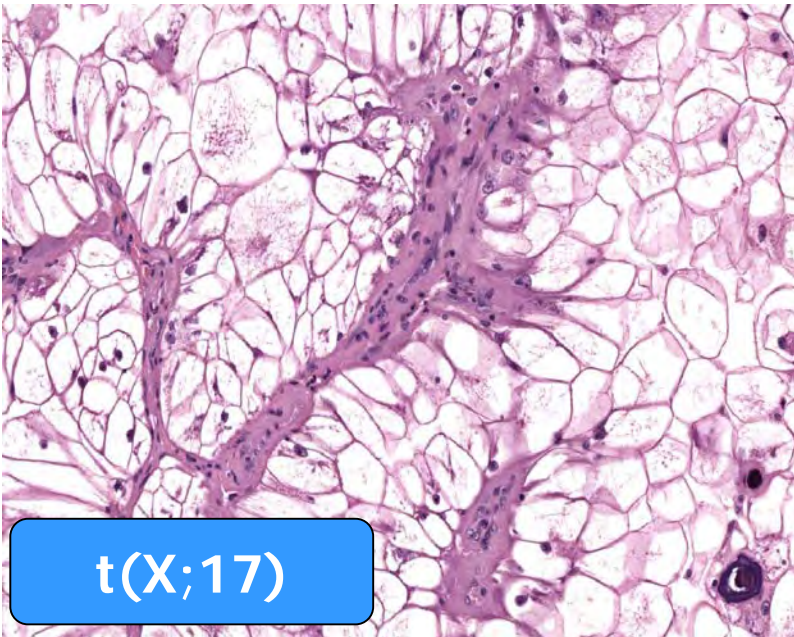
*CCPRCC represent:*

- 2.3% of all renal cell tumors
- 50% of all low malignant RCC
- 100%  $\leq 4$  cm in diameter

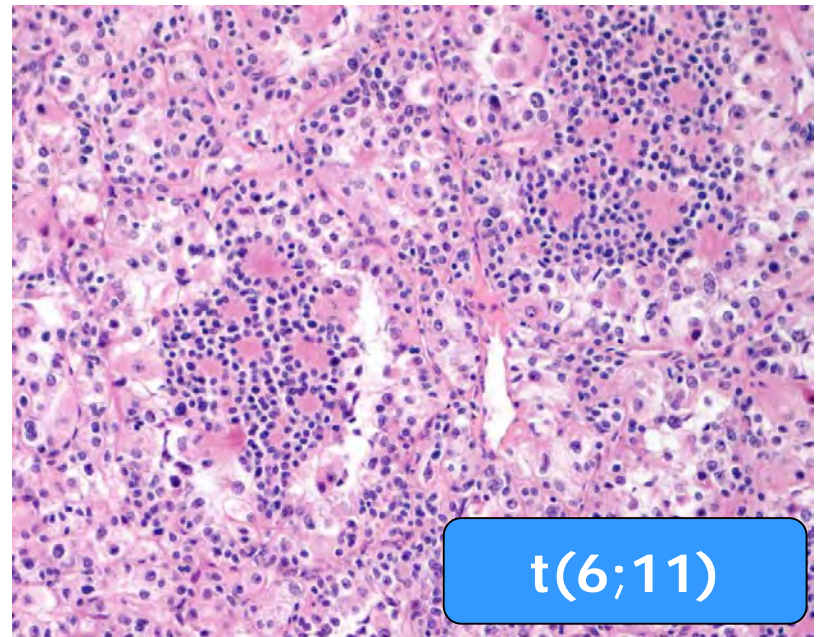
# MiTF/TFE family renal translocation carcinomas



t(X;1)



t(X;17)



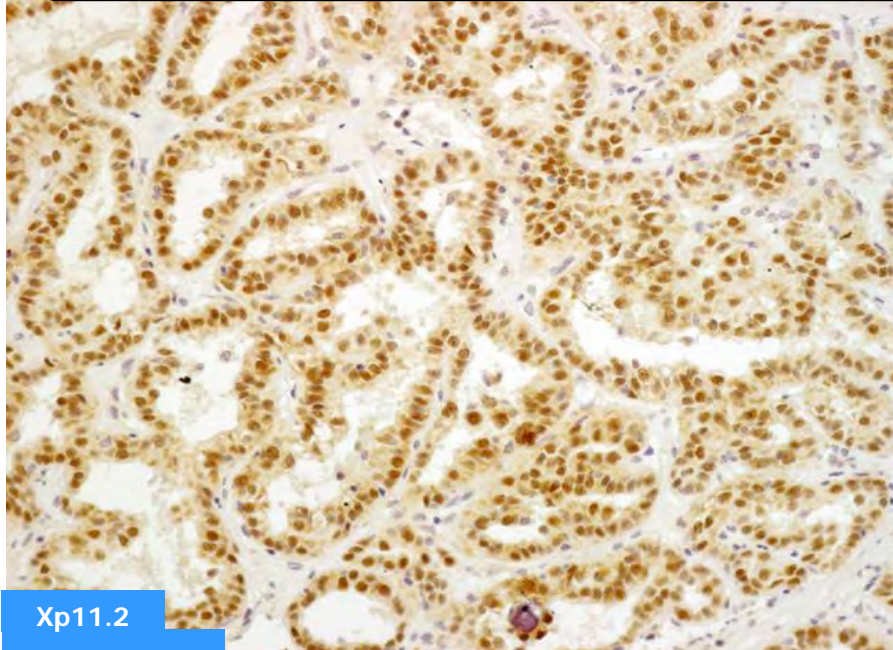
t(6;11)

# Translocation RCC

<b>Fusion</b>	<b>Translocation</b>
<b><i>ASPL-TFE3</i></b>	t(X;17)(p11.2;q25)
<b><i>PRCC-TFE3</i></b>	t(X;1)(p11.2;q21)
<b><i>PSF-TFE3</i></b>	t(X;1)(p11.2;p34)
<b><i>NonO-TFE3</i></b>	inv(X)(p11.2;q12)
<b><i>CLTC-TFE3</i></b>	t(X;17)(p11.2;q23)
<b><i>?-TFE3</i></b>	t(X;3)(p11.2;q23)
<b><i>Alpha-TFEB</i></b>	t(6;11)(p21;q12)

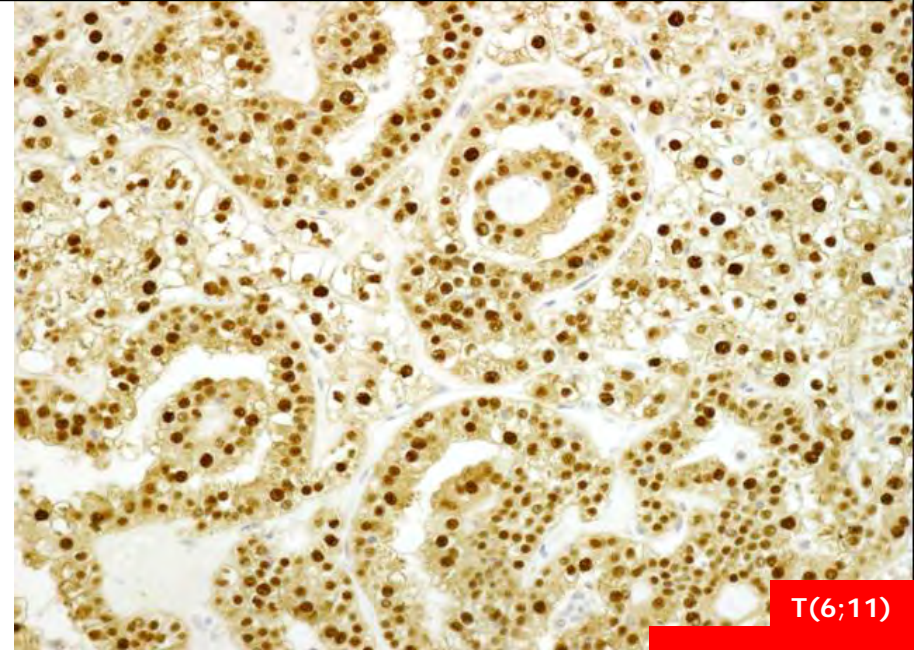


# Translocation carcinomas



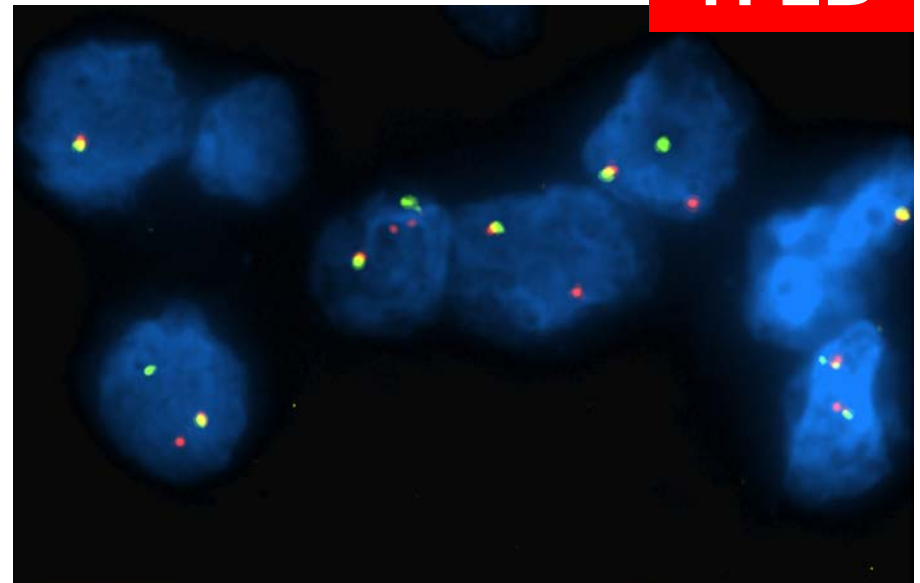
Xp11.2

**TFE3**



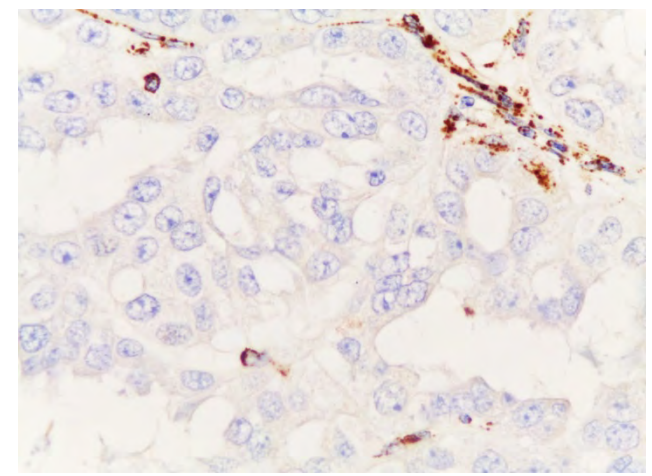
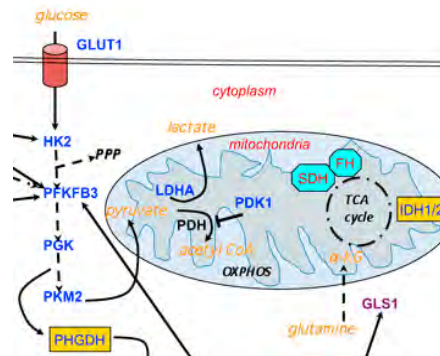
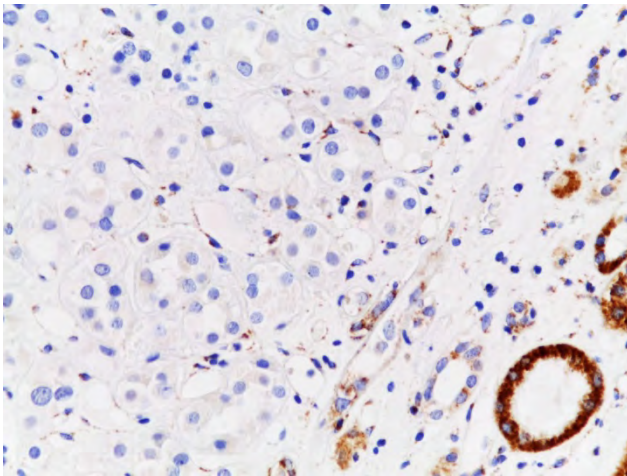
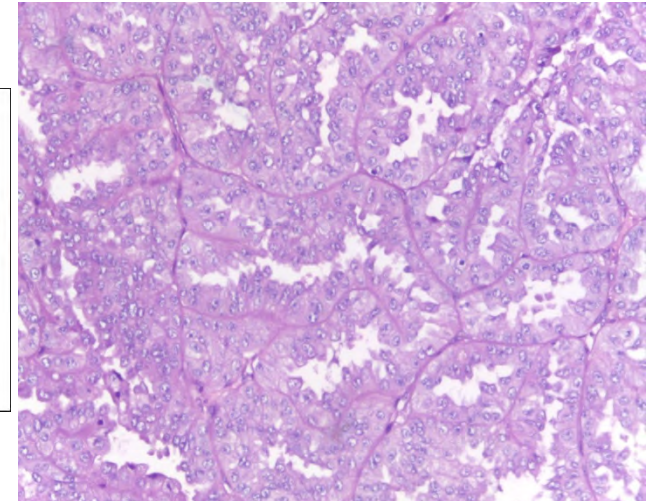
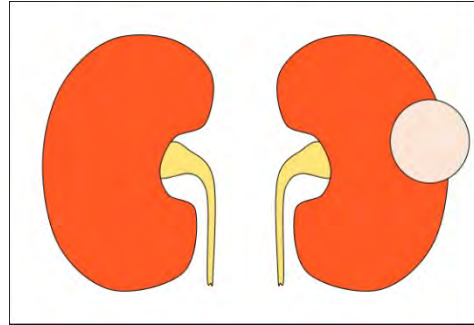
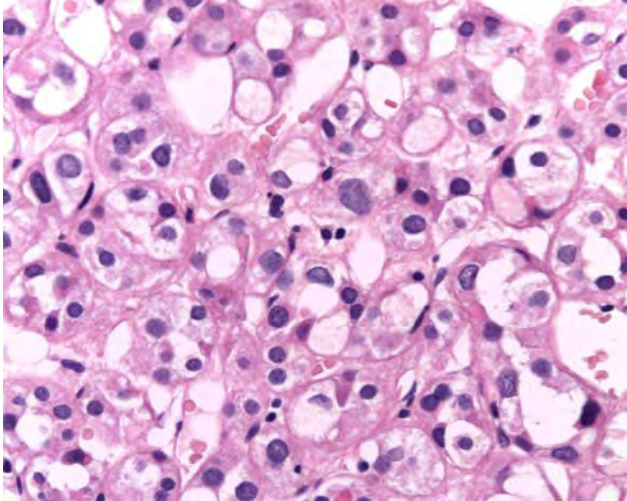
T(6;11)

**TFEB**



# Hereditary renal cancers

## Single Tumour



Succinate dehydrogenase-

HLRCC-associated Renal cell Carcinoma

# WHO 2016

## Renal cell tumours

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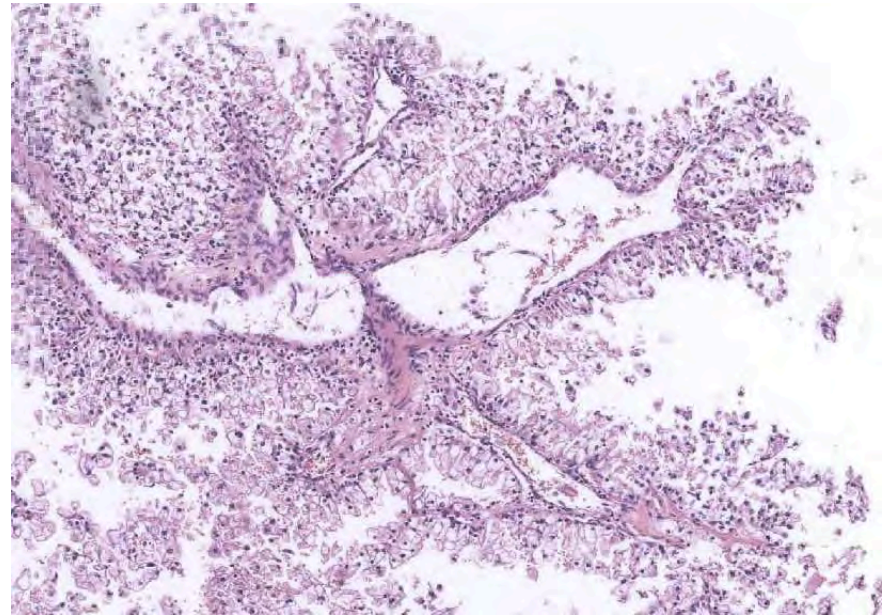
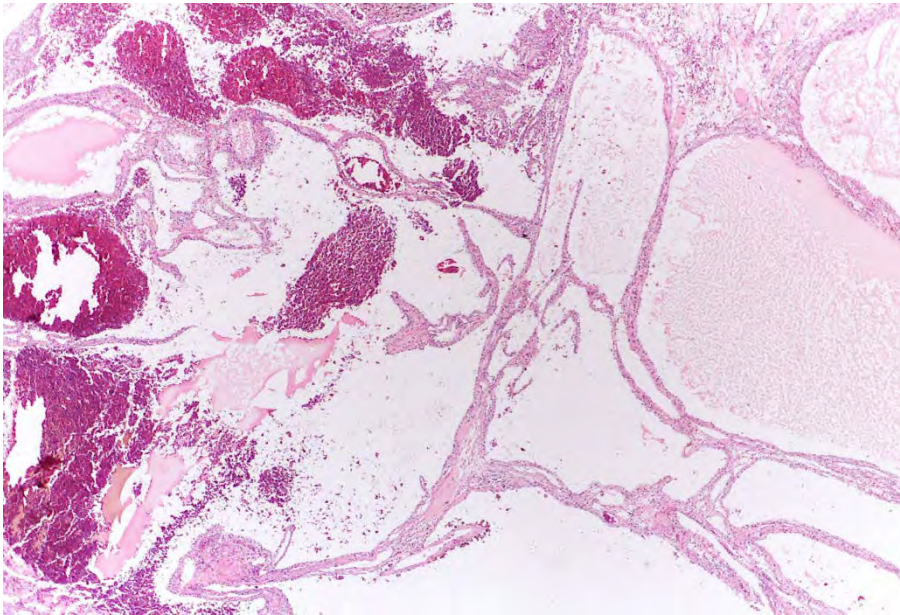
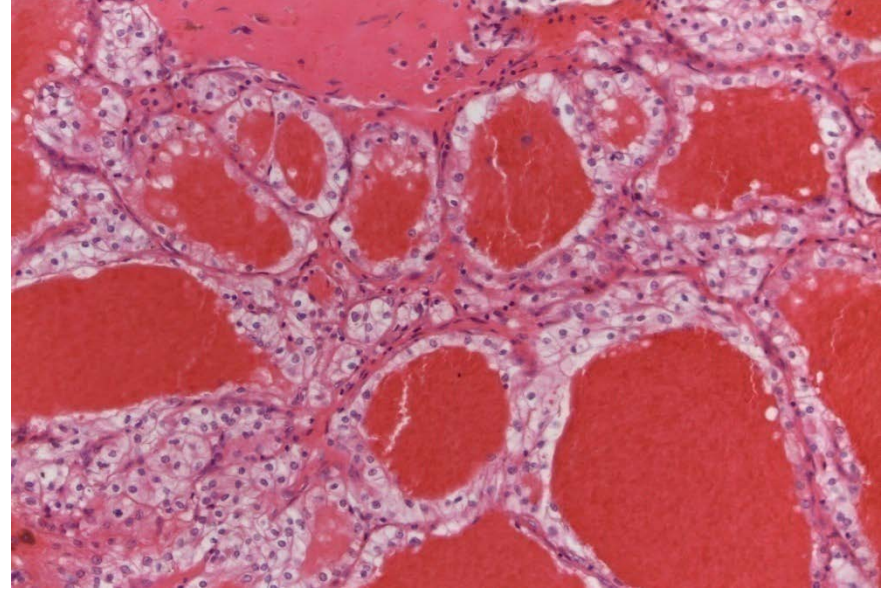
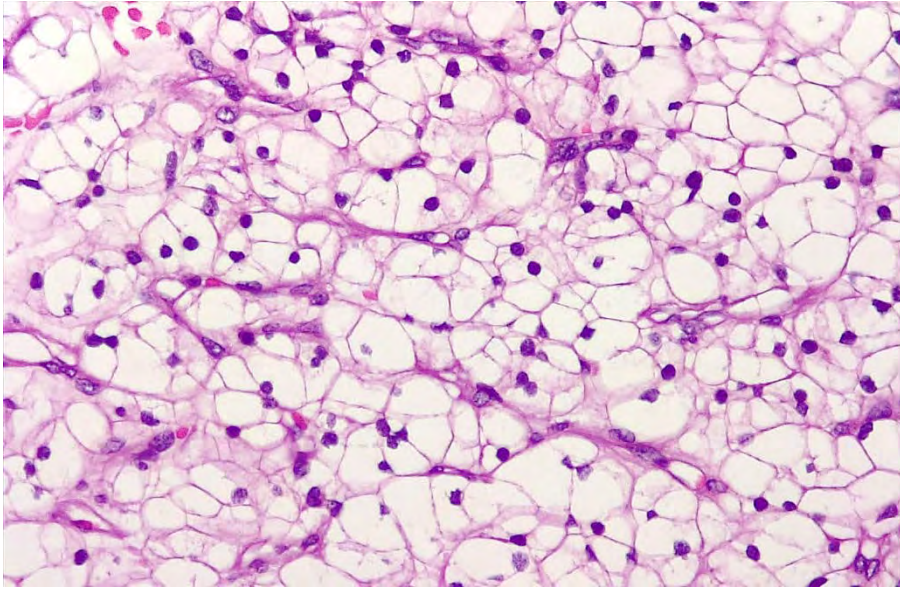
**90%**  
**Dei carcinomi renali metastatici**

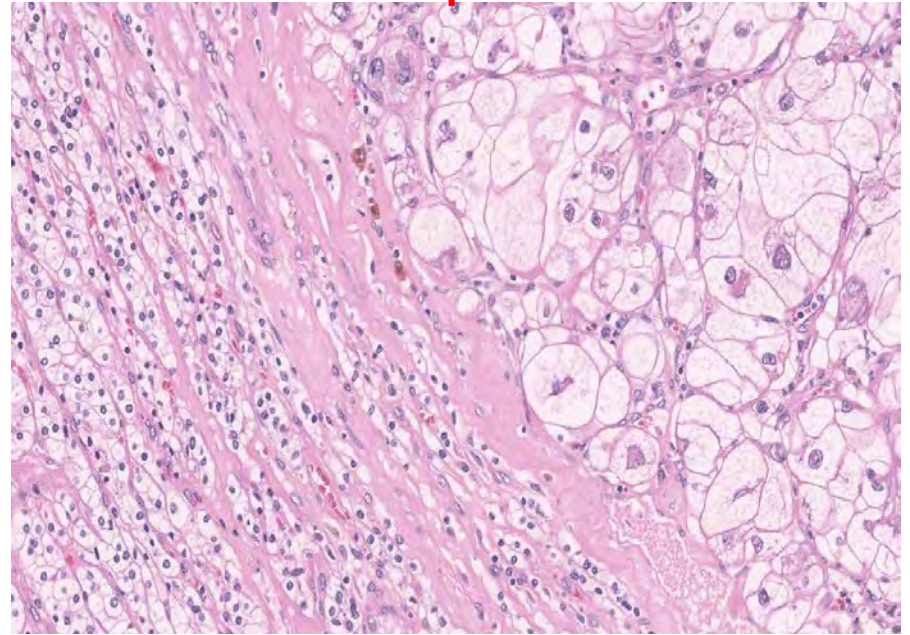
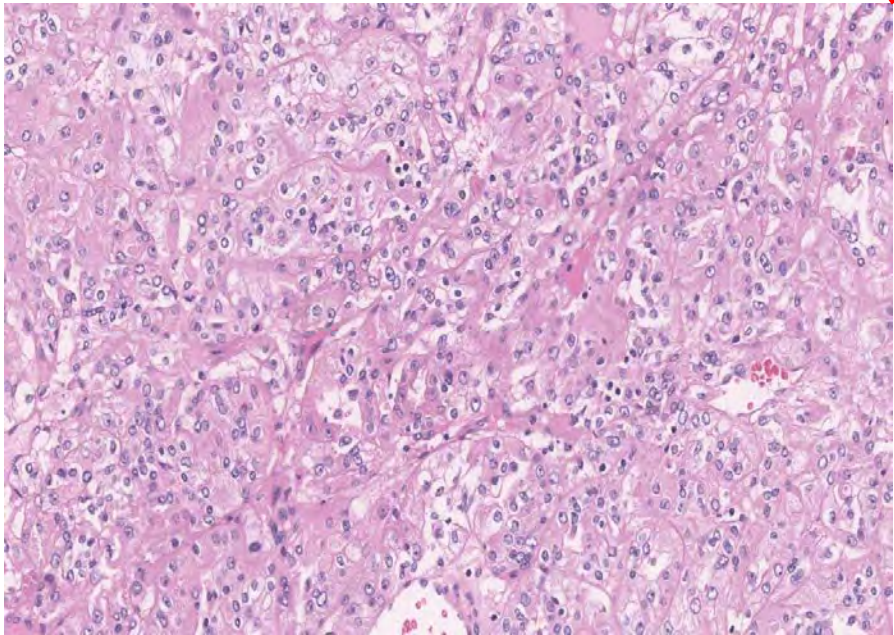
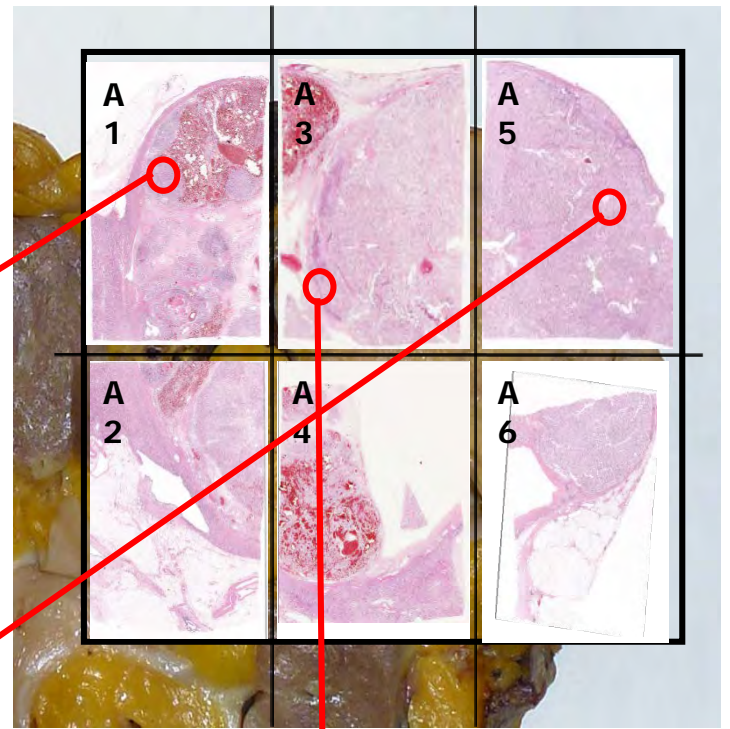
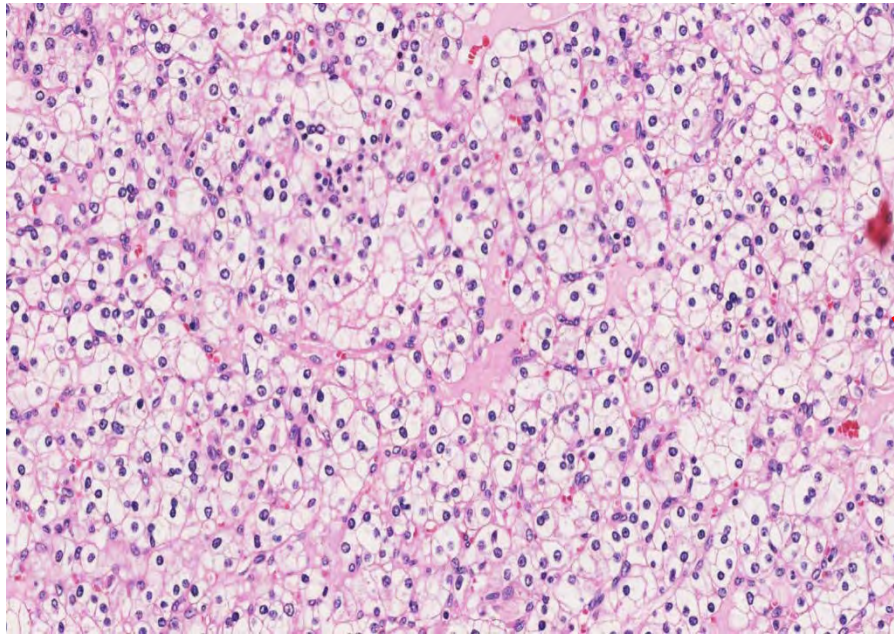
**10%**  
**Dei carcinomi renali metastatici**

# Clear cell renal cell carcinoma



# Clear cell renal cell carcinoma





# Grading of Clear Cell Renal Cell Carcinoma Should be Based on Nucleolar Prominence

*Brett Delahunt, MD, FRCPA, FRCPath,\* † Dianne Sika-Paotonu, MBiomedSc, †  
Peter B. Bethwaite, PhD, FRCPA,\* Thomas William Jordan, PhD,\* † Cristina Magi-Galluzzi, MD, ‡  
Ming Zhou, MD, ‡ Hemamali Samaratunga, FRCPA, § and John R. Srigley, MD, FRCPC ||*

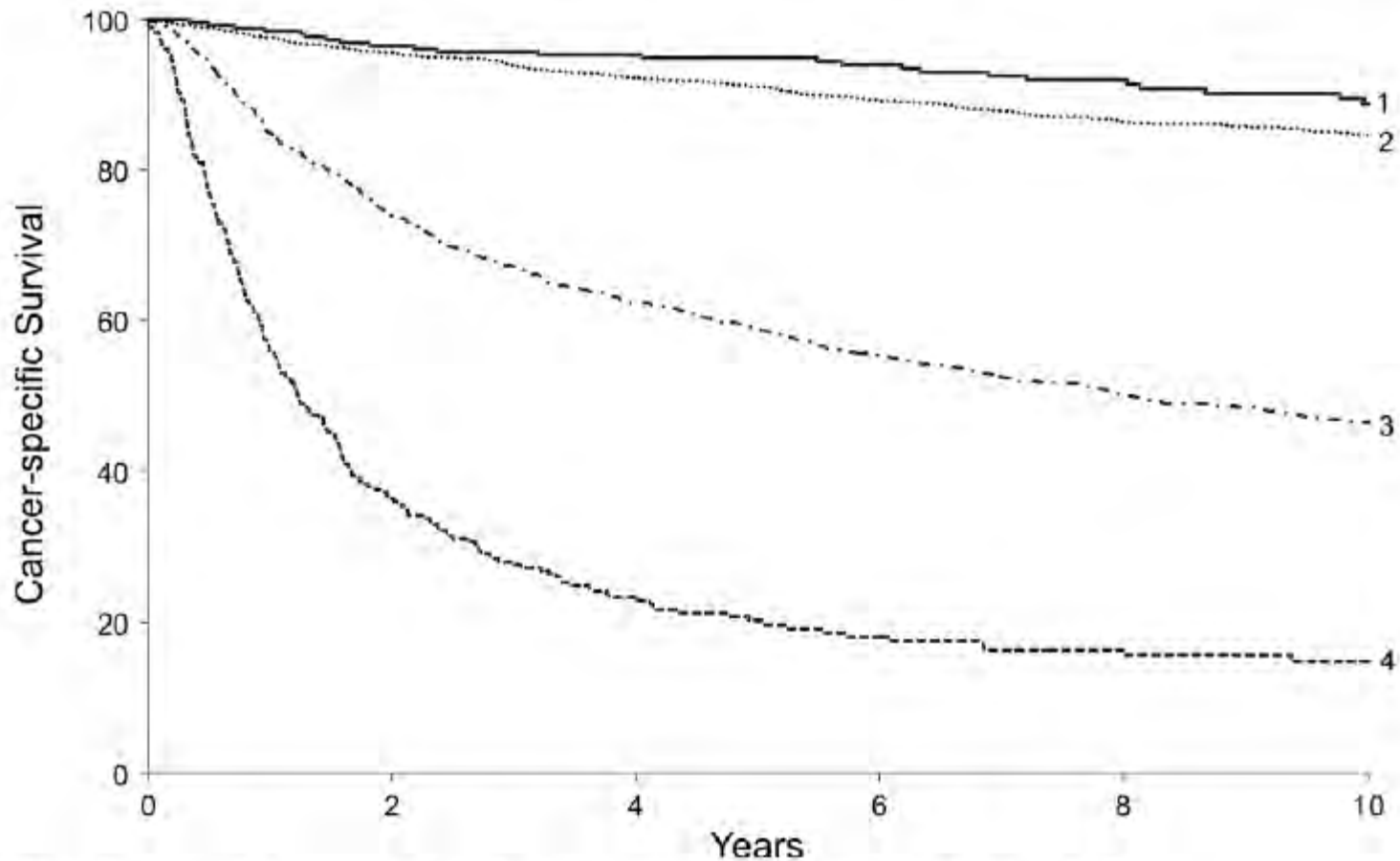
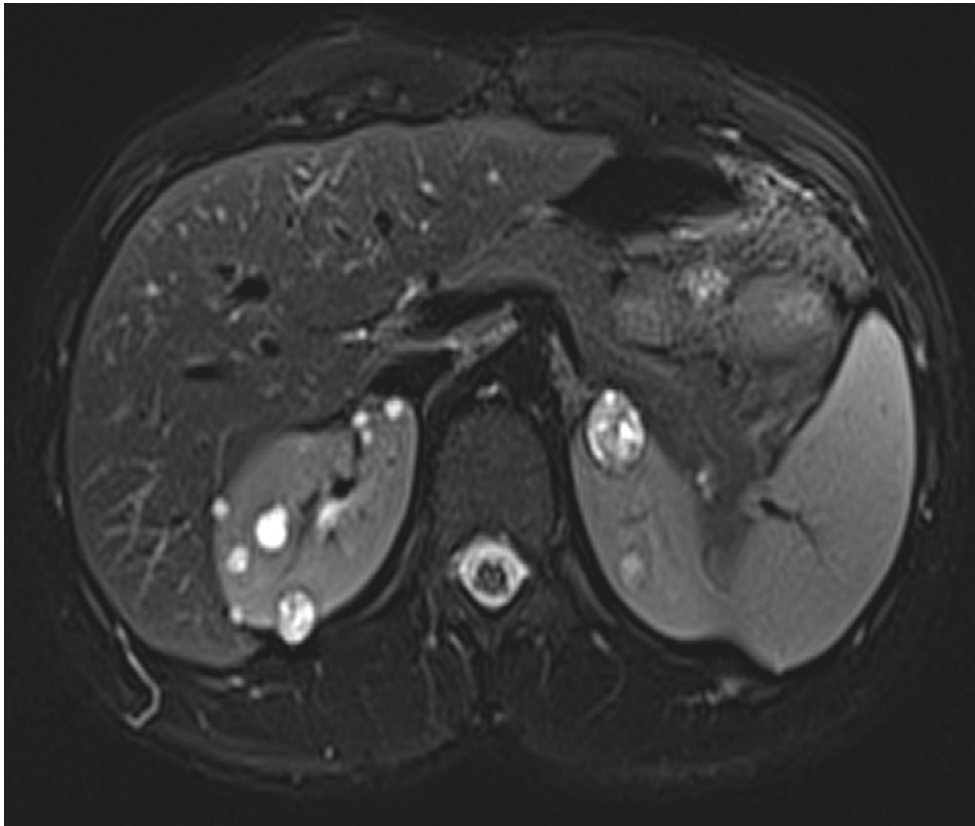


FIGURE 3. Cancer-specific survival by the ISUP grading system for 3017 patients with clear cell RCC.

# Clear cell renal cell carcinoma

20 years old, male

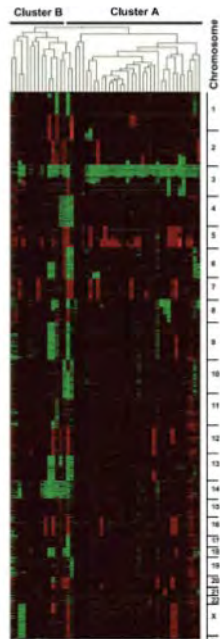
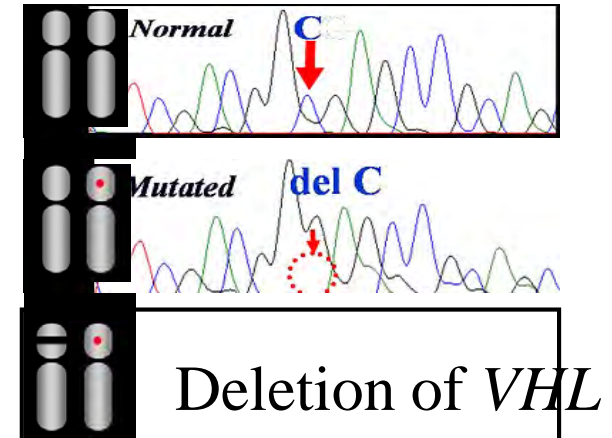
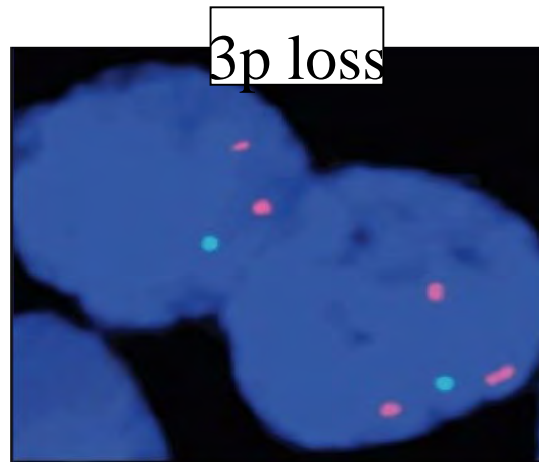


Type	Clinical Characteristics
1	Retinal hemangioblastomas CNS hemangioblastomas Renal cell cancers Pancreatic neoplasms and cysts
2A	Pheochromocytomas Retinal hemangioblastomas CNS hemangioblastomas
2B	Pheochromocytomas Retinal hemangioblastomas CNS hemangioblastomas Renal cell cancers Pancreatic neoplasms and cysts
2C	Pheochromocytomas only

## VHL Syndrome



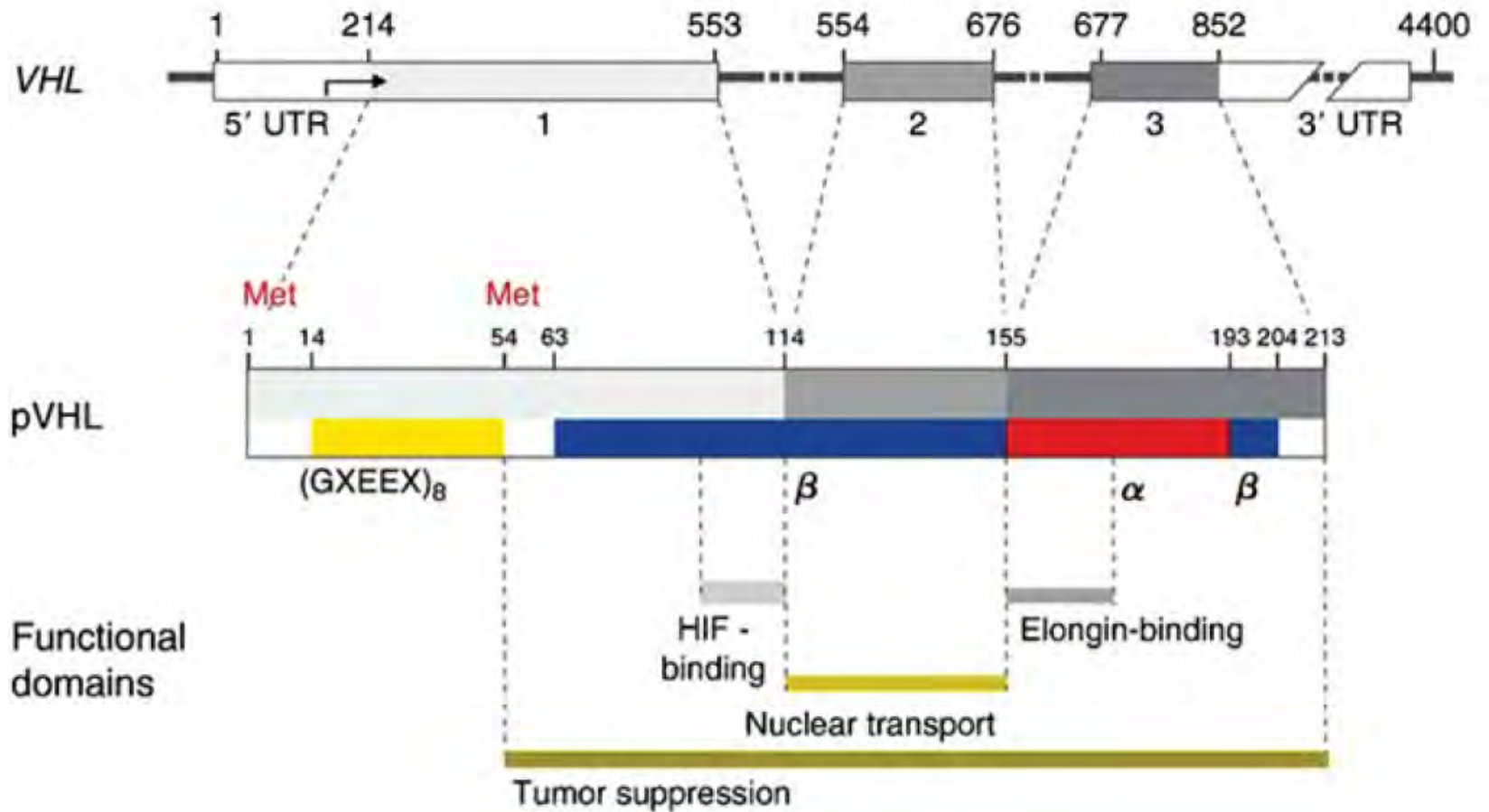
# Clear cell renal cell carcinoma



**BOTH CLUSTERS** Loss of chromosome 3p and gain of 5q and 7

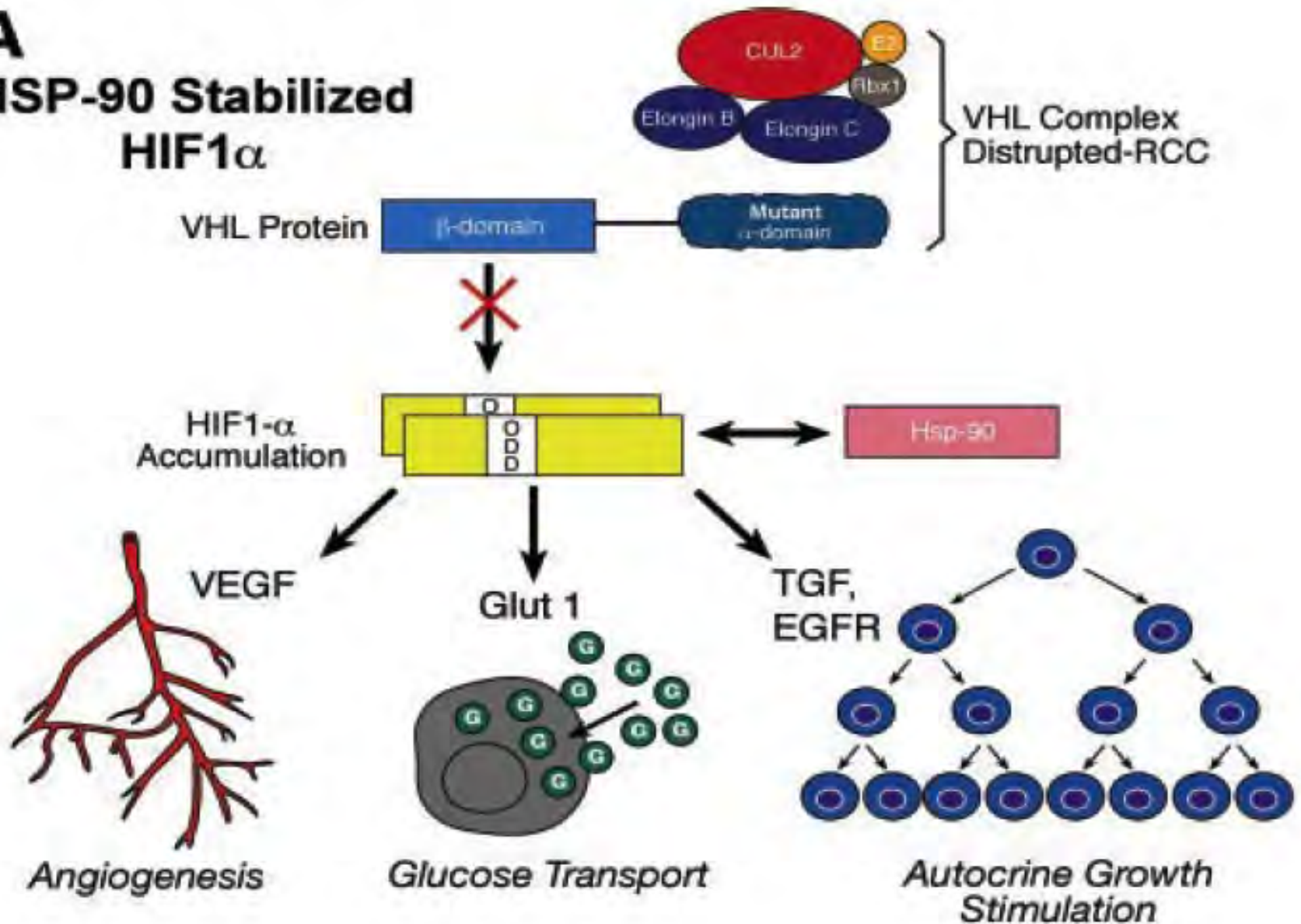
**CLUSTER A** Loss of 1p, 4, 9,13q, and14q

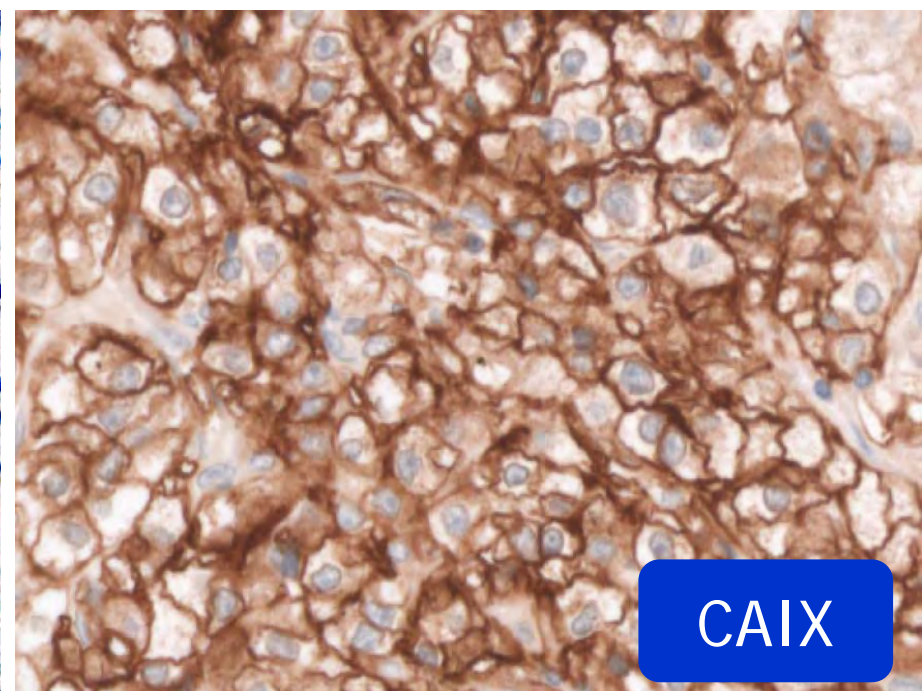
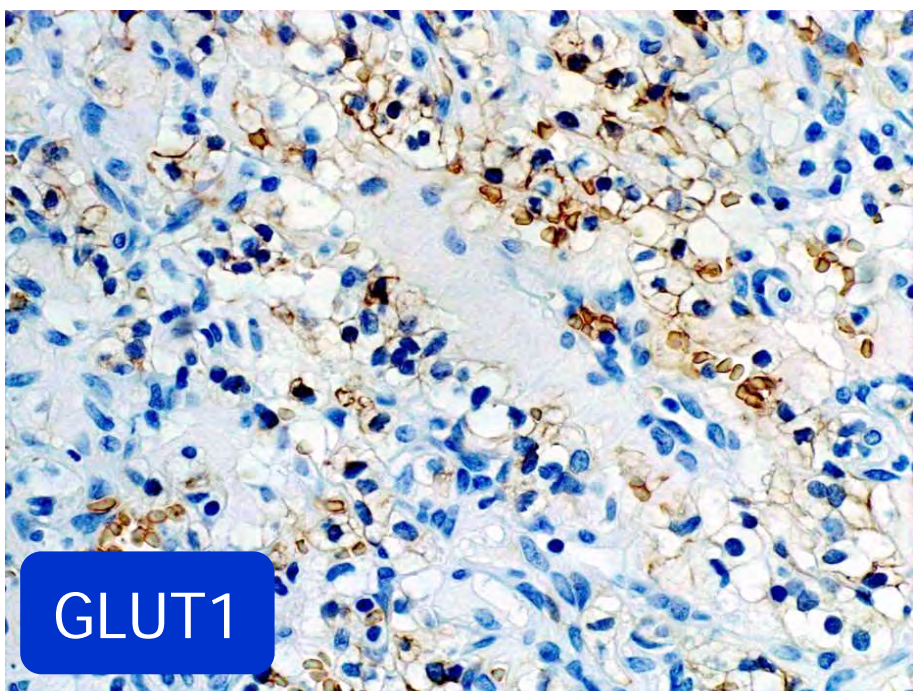
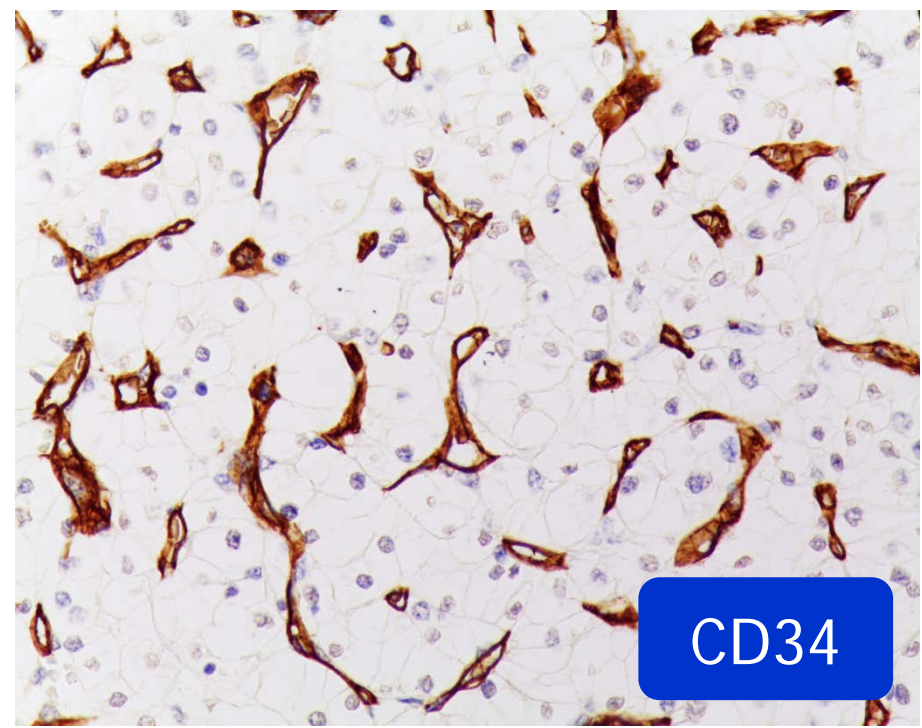
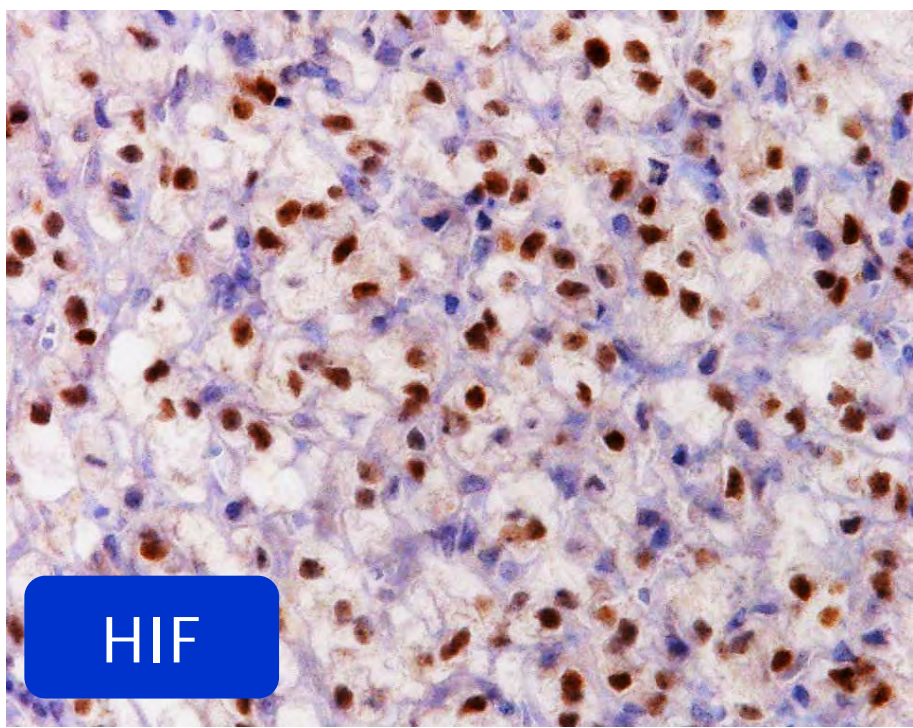
**CLUSTER B** High number of methylated CpGislands

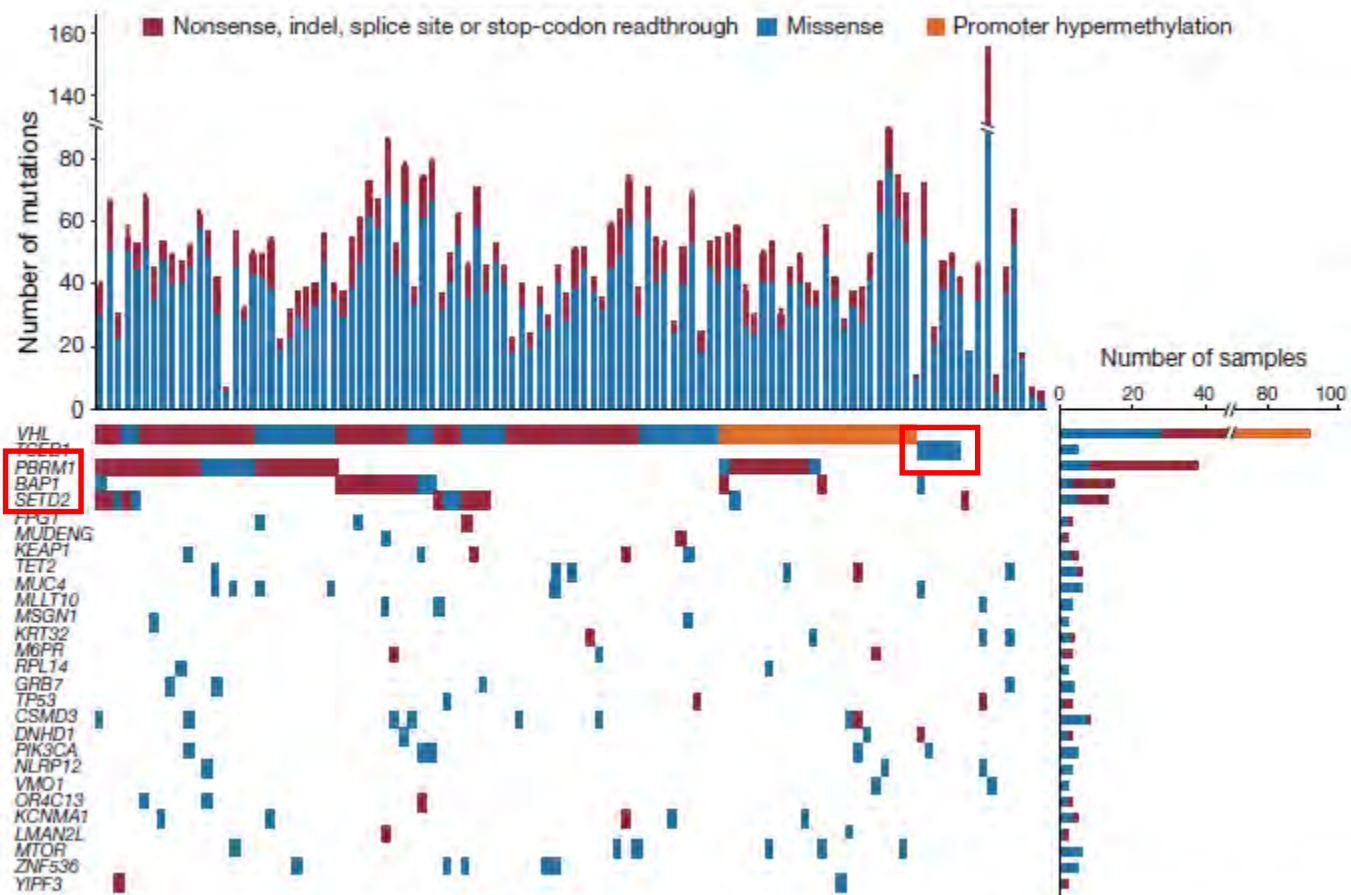


# A

## HSP-90 Stabilized HIF1 $\alpha$

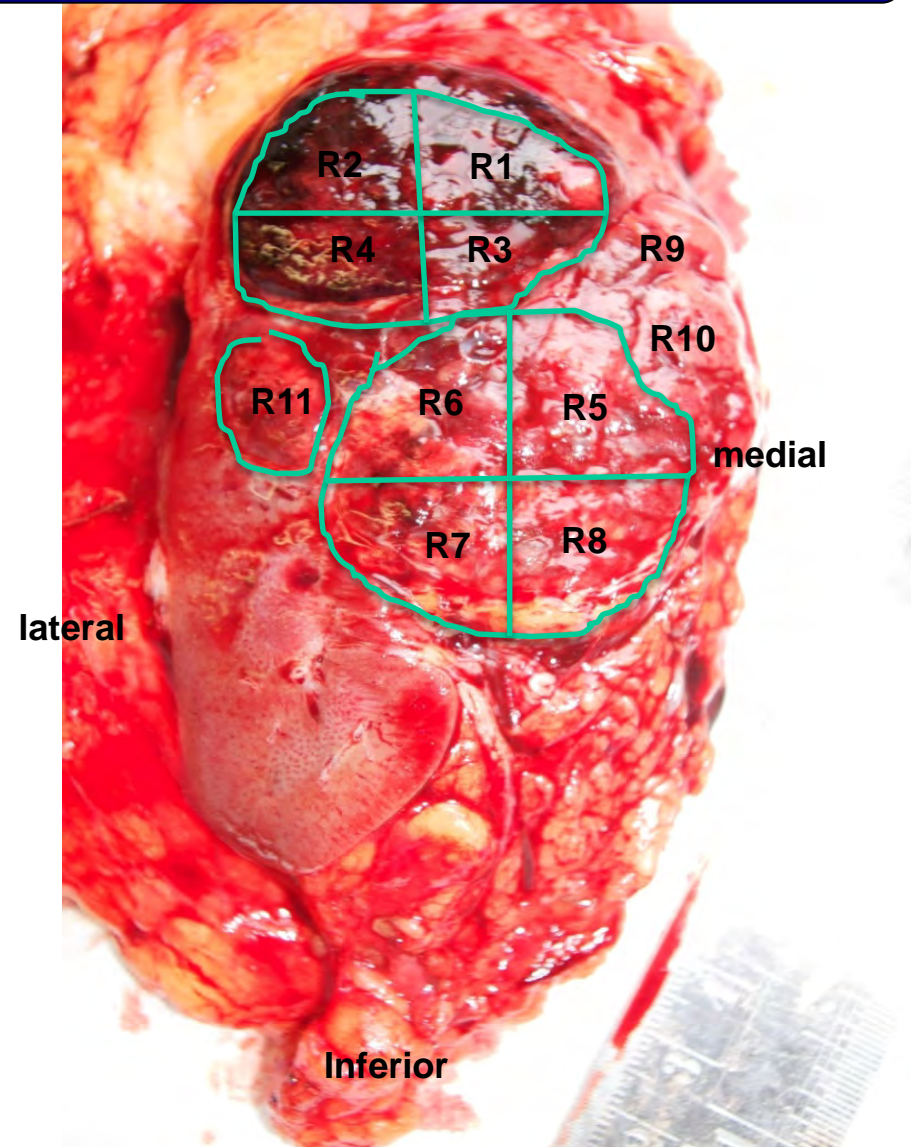
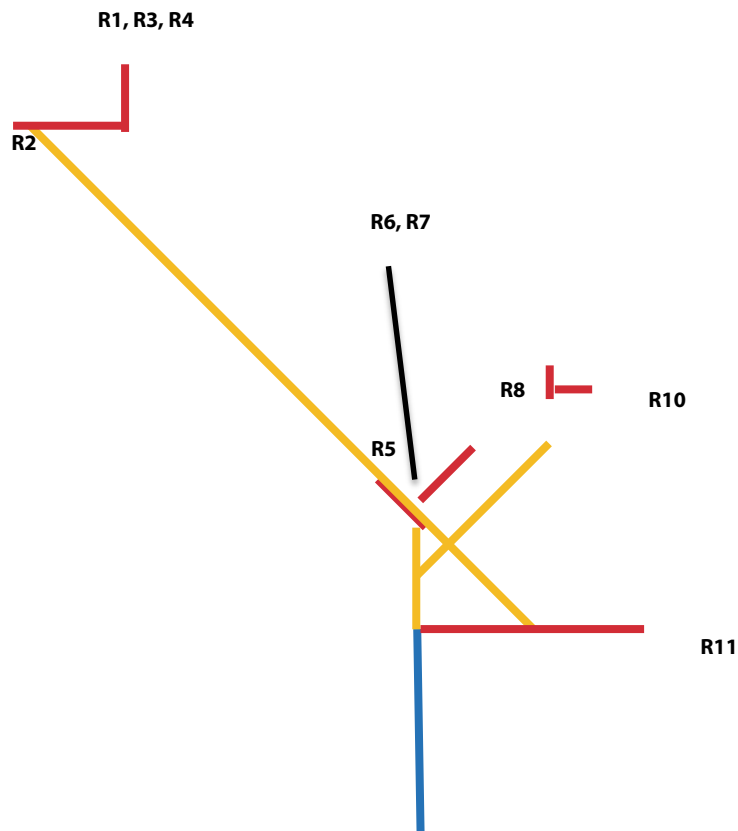




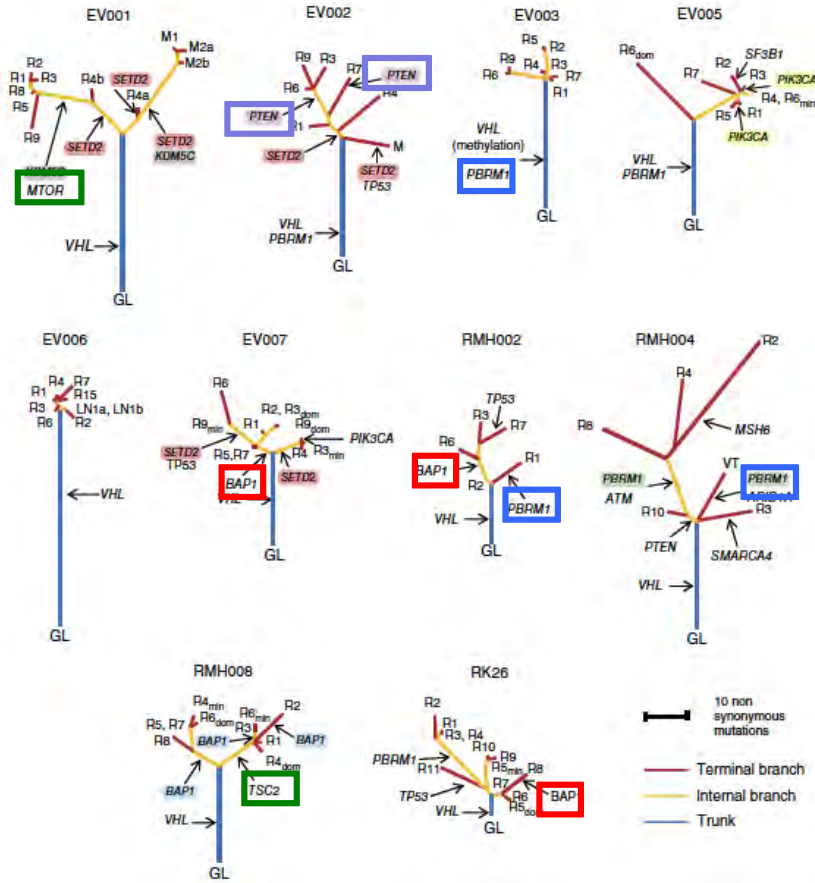


**Figure 3** Significantly mutated genes and pathways for 106 ccRCC specimens. The number of somatic mutations in each case (top) and the number of cases that had alterations in significantly mutated genes (bottom right) are shown in a bar plot.

# Branched Evolution and intratumoral heterogeneity in ccRCC



# Branched Evolution and intratumoral heterogeneity in ccRCC



67% of mutations are not shared by all regions

Single region sampling "misses" many mutations

High risk group

Low risk group

Therapeutic target

Convergent evolution

# Conclusioni

Il carcinoma renale rappresenta un gruppo eterogeneo di tumori (18 diversi istotipi nella WHO 2016), con caratteristiche biologiche e comportamento clinico distinti

La maggior parte carcinomi renali a cellule chiare presenta eterogeneità intratumorale, sia morfologica che genetica, ponendo problemi sia nella valutazione della neoplasia primitiva che nelle sue eventuali metastasi