Renal tumours
WHO 4

- MAJOR PARADIGM SHIFT IN EARLY 1990S IN UNDERSTANDING RENAL CANCER

The impact of genetics on the classification of renal carcinoma

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Molecular differential pathology of renal cell tumours

G. KOVACS

THE HEIDELBERG CLASSIFICATION OF RENAL CELL TUMOURS

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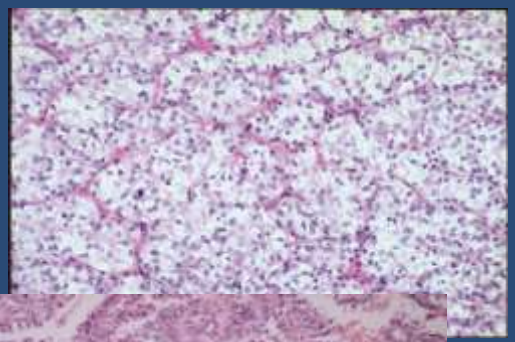
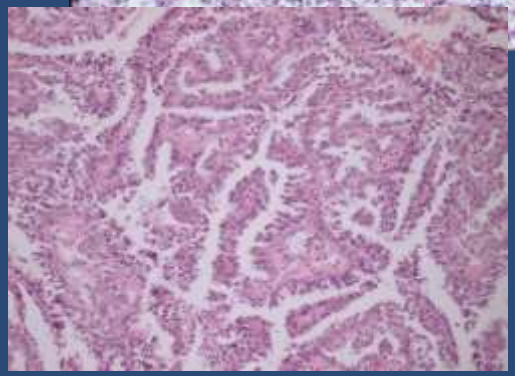
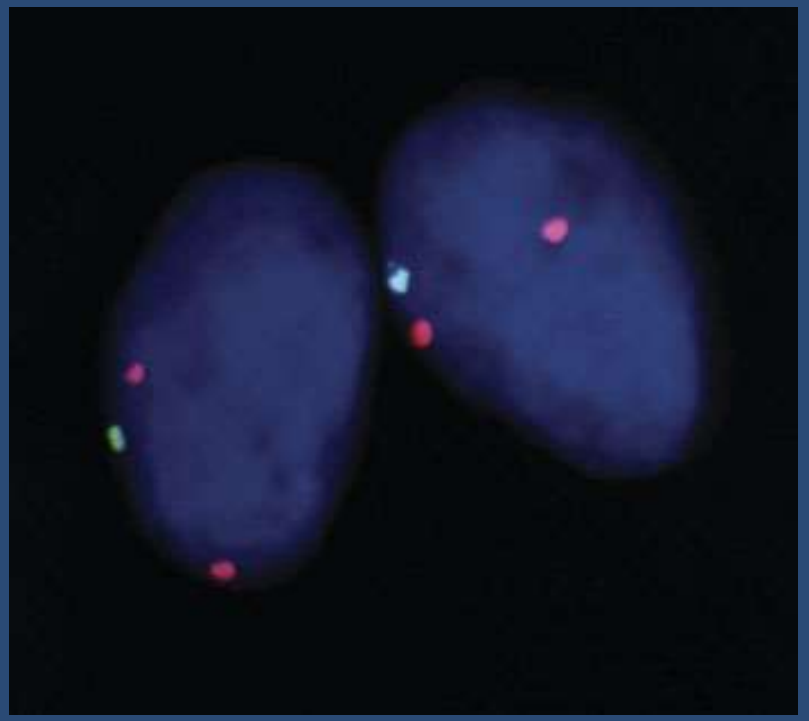




A CLASSIFICATION …BASED ON UNDERSTANDING THE GENETIC ABNORMALITIES INVOLVED WILL BE ROBUST IN TERMS OF BIOLOGY, CLINICAL BEHAVIOUR AND RESPONSE TO THERAPY

GENETIC ALTERATION IN RCC CORRELATES STRONGLY WITH MORPHOLOGY

HISTOPATHOLOGY	3p LOSS		VHL MUTATION	
	Y	N	Y	N
CLEAR CELL	25	8	18	25
PAPILLARY	1	7	0	8
ONCOCYTOMA	2	3	0	5
CHROMOPHOBE	0	3	0	3

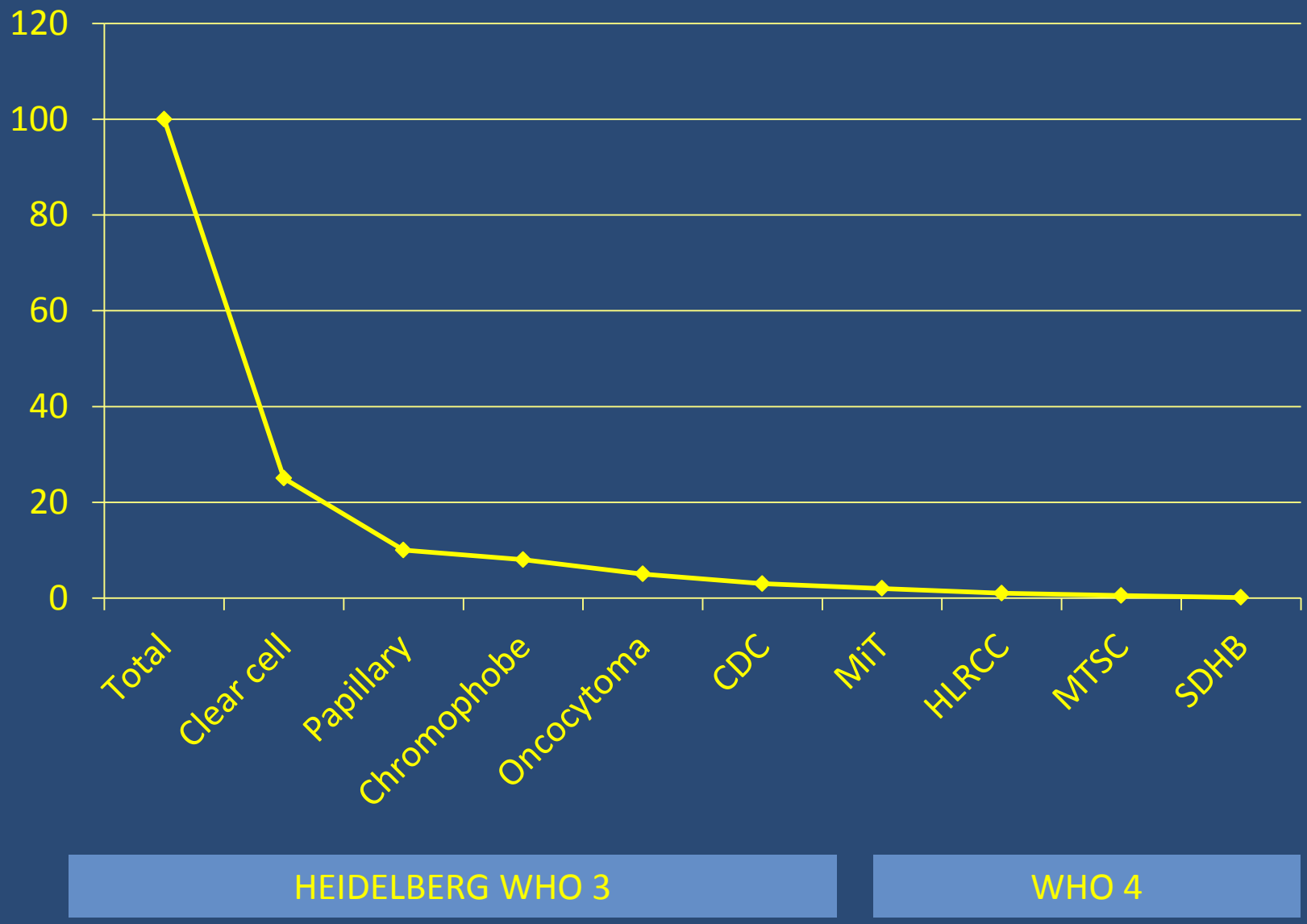


FOSTER ET AL 1994 Somatic mutations of the von Hippel - Lindau disease tumour suppressor gene in non-familial clear cell renal carcinoma

TUMOUR HISTOLOGY MATTERS BECAUSE IT REVEALS THE UNDERLYING GENETICS

WHO v4

- Clear cell renal cell carcinoma VHL and 3p-
  - Multilocular clear cell renal cell neoplasm of low malignant potential
- Papillary renal cell carcinoma c-met and chr 7+; Fumarate hydratase
- Chromophobe renal cell carcinoma Multiple chromosome loss
  - Hybrid oncocytic chromophobe tumour Folliculin
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma IN1 and sickle cell
- MiT family translocation renal cell carcinoma
  - Xp11 translocation renal cell carcinoma
  - t(6;11) renal cell carcinoma
- Carcinoma associated with neuroblastoma
- Mucinous tubular and spindle cell carcinoma Multiple chromosomal losses
- Tubulocystic renal cell carcinoma Fumarate hydratase
- Acquired cystic disease associated renal cell carcinoma
- Clear cell papillary (tubulopapillary) renal cell carcinoma
- Hereditary leiomyomatosis associated renal cell carcinoma Fumarate hydratase
- SDHB associated RCC SDHB
- RCC with monosomy 8 Monosomy * TCEB1
- ALK associated RCC ALK translocation or amplification
- Thyroid follicle like RCC
- Renal cell carcinoma, unclassified

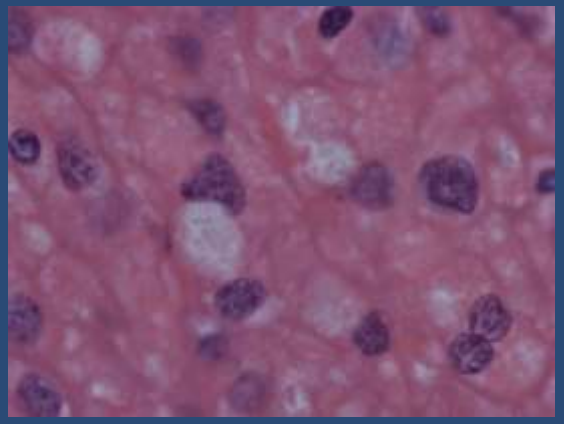


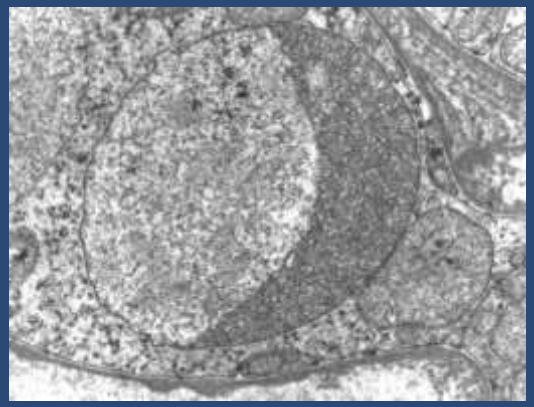
HEIDELBERG WHO 3

WHO 4

INHERITED RCC

- VHL
- FAMILIAL PAPILLARY RCC
- BIRT HOGG DUBE SYNDROME
- TUBEROUS SCLEROSIS
- HLRCC
- SDHB
- NON-SYNDROMIC FAMILIAL RCC





WHO CLASSIFICATION PROCESS

ISUP CONSENSUS – REPORT – CONSULTATION – WHO REPORT - 2016

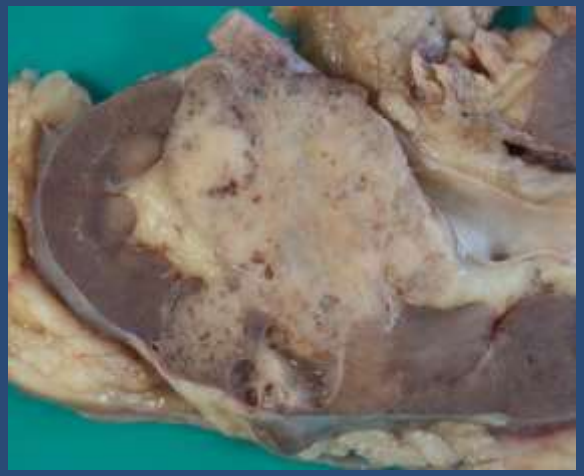
CONSOLIDATING DIAGNOSTIC CRITERIA

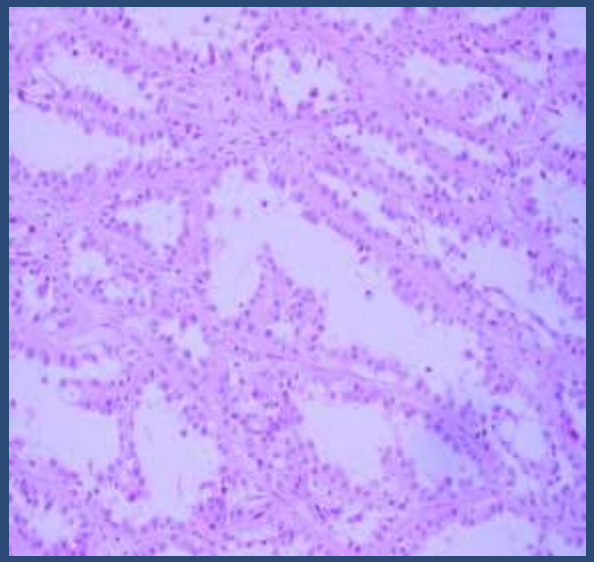
- PAPILLARY RCC
  - TYPE 1, TYPE 2, MIXED – ALSO GRADE
- COLLECTING DUCT CARCINOMA
  - Medullary involvement
  - Predominant tubular morphology
  - Desmoplastic stromal reaction
  - Cytologically high grade
  - Infiltrative growth pattern
  - Absence of other RCC subtypes or urothelial carcinoma

New entities

- Consensus sought for renal tumours described since 2004 (2002) (or renamed)
- Entities presented
- Discussion
- Voting
- Accepted, rejected, emerging

TUBULOCYSTIC CARCINOMA OF KIDNEY





WELL CIRCUMSCRIBED

TUBULAR OR MICROCYSTIC

SINGLE LAYERED CUBOIDAL EPITHELIUM

MILD NUCLEAR PLEOMORPHISM

AGGRESSIVE TUBULOCYSTIC RCC

- AGGRESSIVE TUBULOCYSTIC
- MORPHOLOGY OF FOCAL CDC LIKE
- YOUNG PATIENT

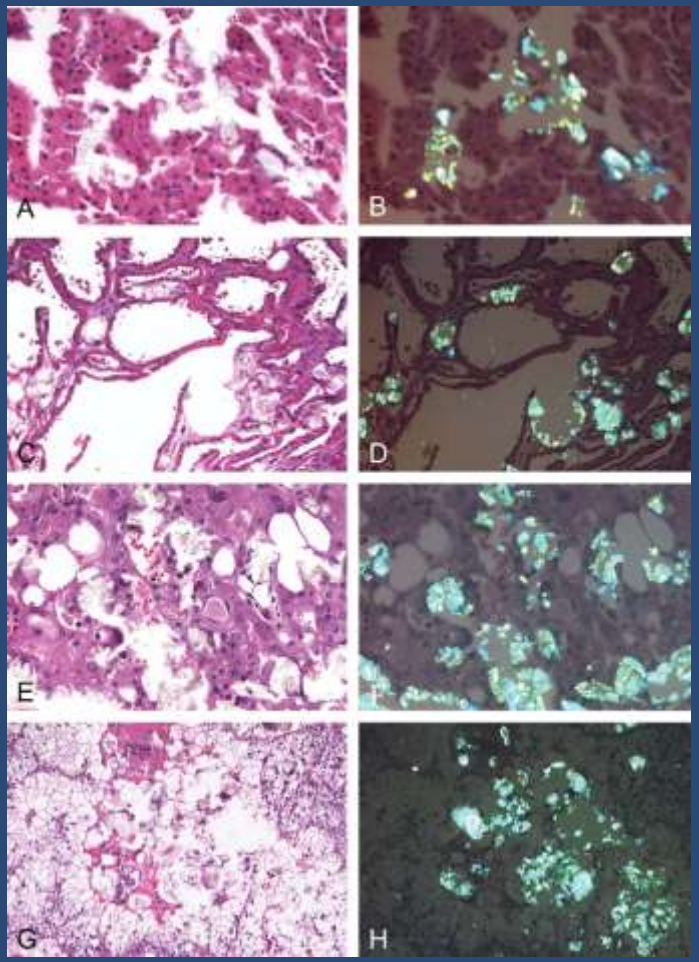
- **THINK HLRCC**

ESRD ASSOCIATED RCC

- 30 YEAR HISTORY OF RCC IN ESRD
- PREVIOUSLY CONSIDERED TO BE MOSTLY PAPILLARY
- NOW AT LEAST TWO NEW TYPES OF RCC RECOGNISED IN THIS CLINICOPATHOLOGICAL CONTEXT
  - ACKD ASSOCIATED RCC
  - CLEAR CELL PAPILLARY RCC IN ESRD
- 60% OF RCC IN ESRD

- **Atypical cyst or cyst with (atypical) epithelial proliferation**

OXALATE AND ACKD RCC

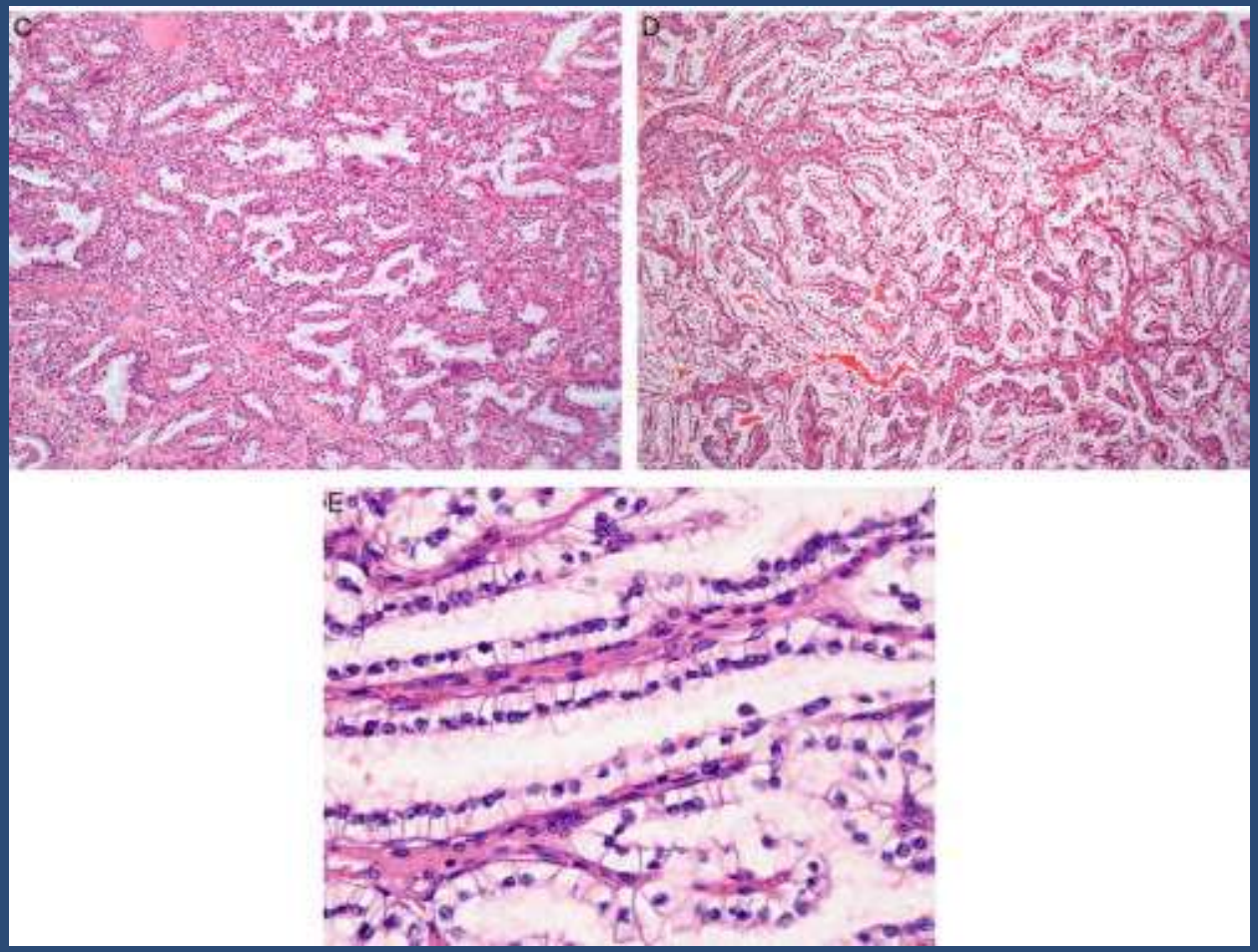


- OFTEN ENCAPSULATED
- OFTEN ARISING FROM CYST
- SOLID TUBULO-ACINAR MORE OFTEN THAN PAPILLARY ARCHITECTURE
- FINE LUMINAL SPACES
- CALCIFICATION & PSAMMOMA BODIES
- LARGE CELL WITH EOSINOPHILIC CYTOPLASM
- ONLY OCCASIONALLY CLEAR CELL

SULE et al 2005

CLEAR CELL PAPILLARY RCC

- ACKD OR NON-CYSTIC ESRD
- TUBULO-PAPILLARY ARCHITECTURE
- MAY BE CYSTIC
- CLEAR CELL CYTOLOGY
- SUBNUCLEAR CLEAR CYTOPLASM
  - MIMICKING SECRETORY ENDOMETRIUM
- AMACR – BUT CK7 +



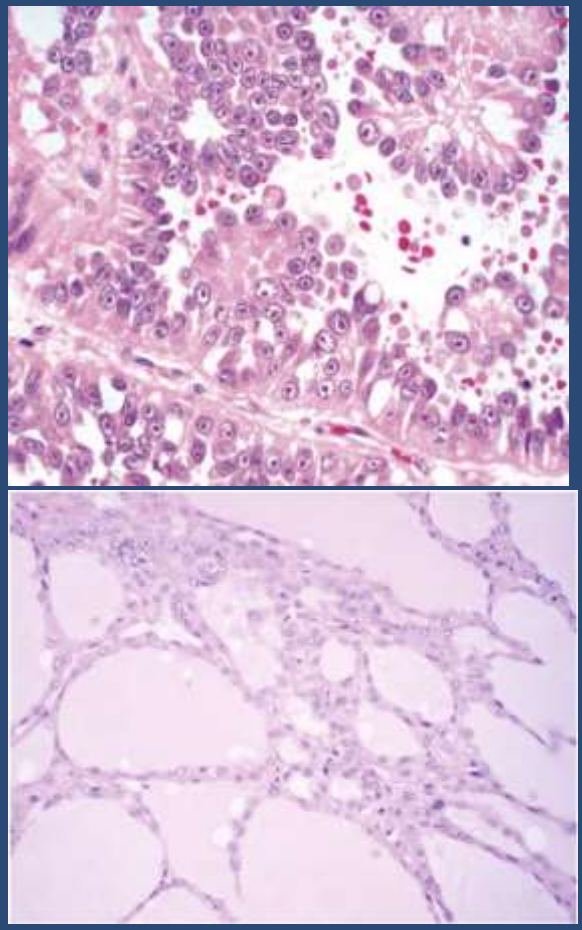
Aydin et al Am J Surg Path 2010

CLEAR CELL PAPILLARY RCC

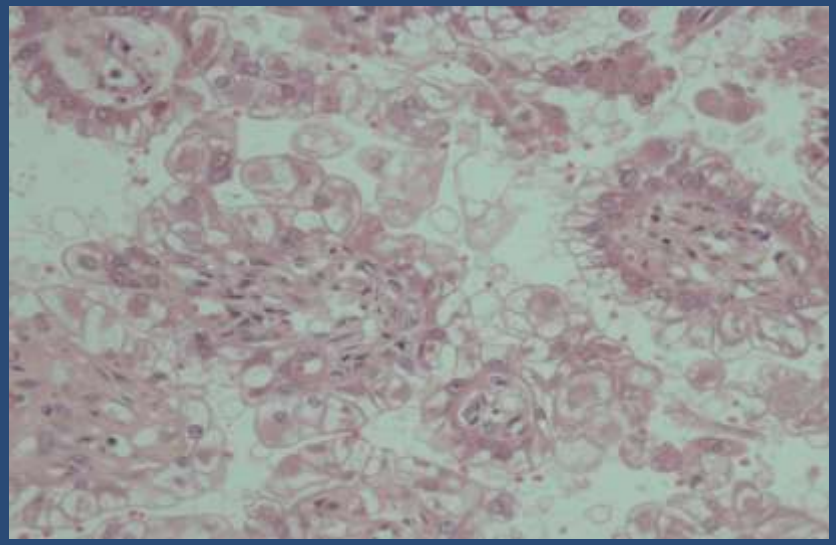
- NO VHL MUTATION NOR 3P LOSS
- NO TRISOMIES OF 7 AND 17
- POSITIVE CK7, HIF1a, CaIX
- NEGATIVE CD10, AMACR, TFE3

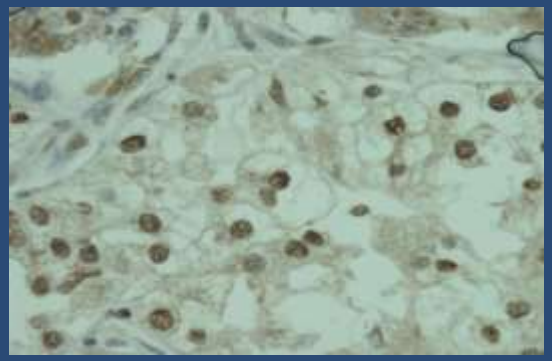
FUMARATE HYDRATASE AND RCC

- FIRST REPORT TYPE 2 PAPILLARY
- SECOND REPORT LOW GRADE CDC (TUBULOCYSTIC)
- SUBSEQUENT REPORTS ARCHITECTURE MAY BE TUBULAR, PAPILLARY TUBULOCYSTIC OR MIXED
- **MUTATION MUST BE DEMONSTRATED**



TRANSLOCATION ASSOCIATED RCC

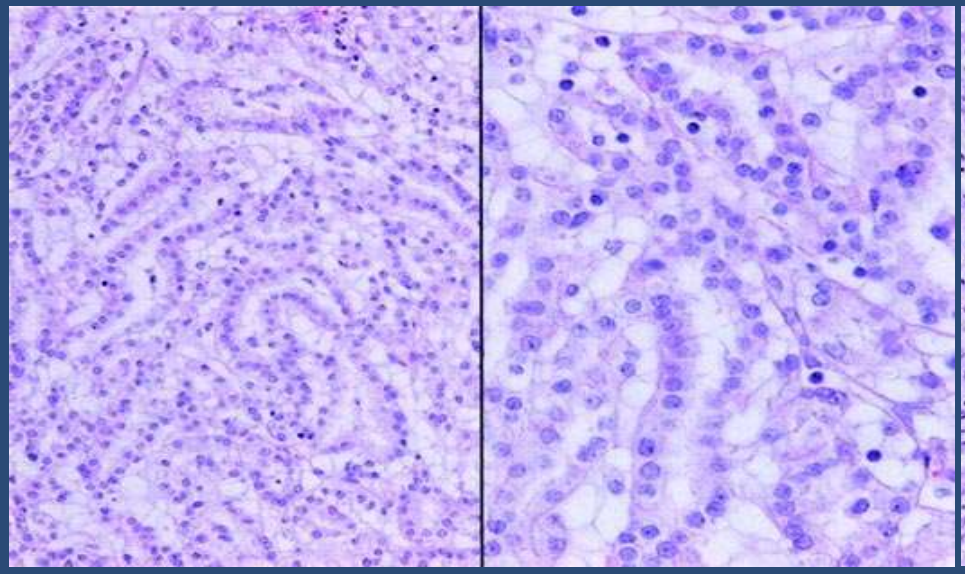




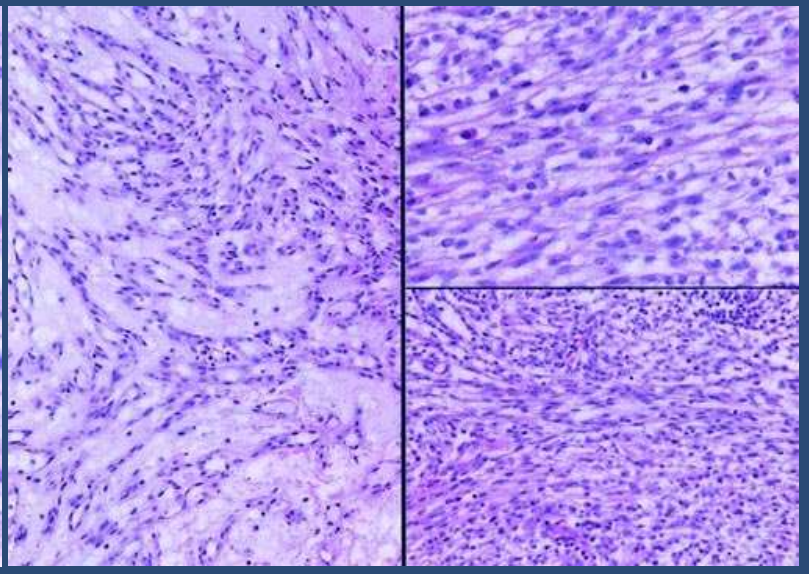
- YOUNGER PATIENTS
- MIXED CLEAR CELL AND PAPILLARY
- VOLUMINOUS CYTOPLASM
- PSAMMOMA BODIES
- TFE3, rarely B or C in nucleus

TO BE RENAMED **MiT family translocation renal cell carcinoma**

MUCINOUS TUBULAR AND SPINDLE CELL RENAL CARCINOMA



TUBULAR COMPONENT



SPINDLE CELL COMPONENT

ACCEPTED

- TUBULOCYSTIC RCC
- ESRD ASSOCIATED RCC
- CLEAR CELL PAPILLARY RCC
- HLRCC RENAL TUMOUR
- MiT FAMILY TRANSLOCATION RCC
- MUCINOUS TUBULAR AND SPINDLE CELL CARCINOMA

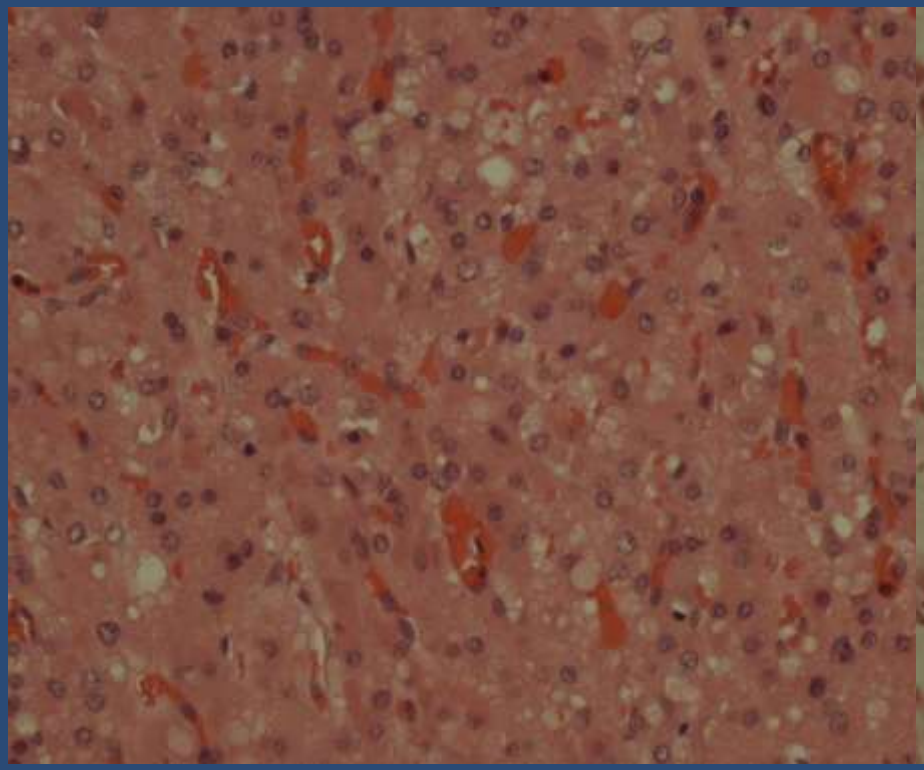
Emerging

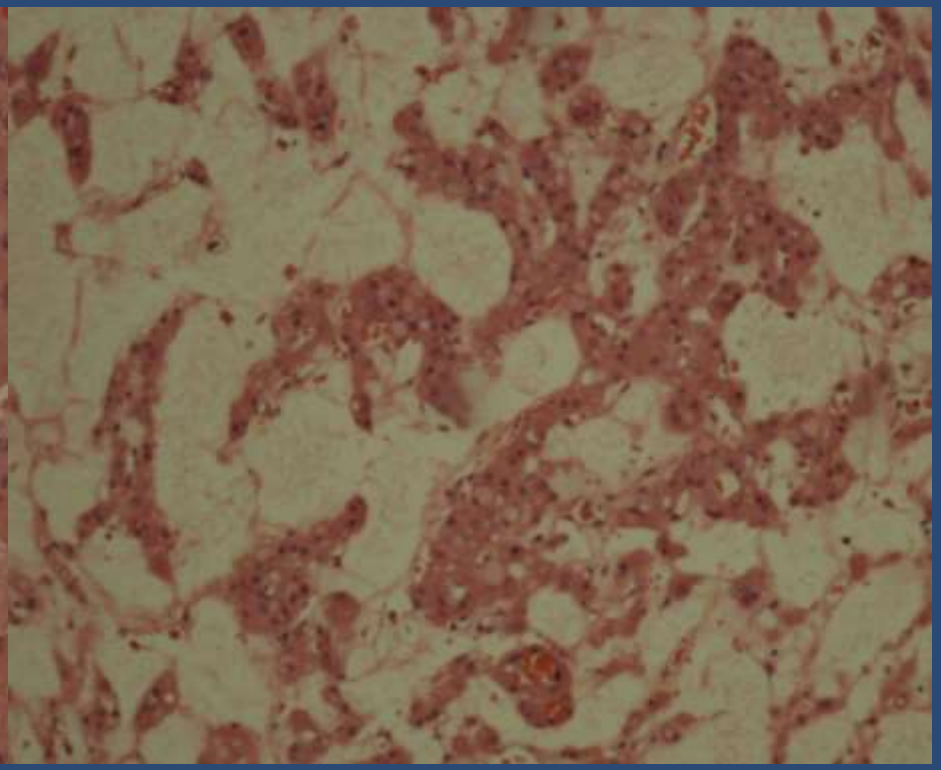
- SDH associated RCC
- ALK positive RCC
- Thyroid follicle like RCC

SDH MUTATION

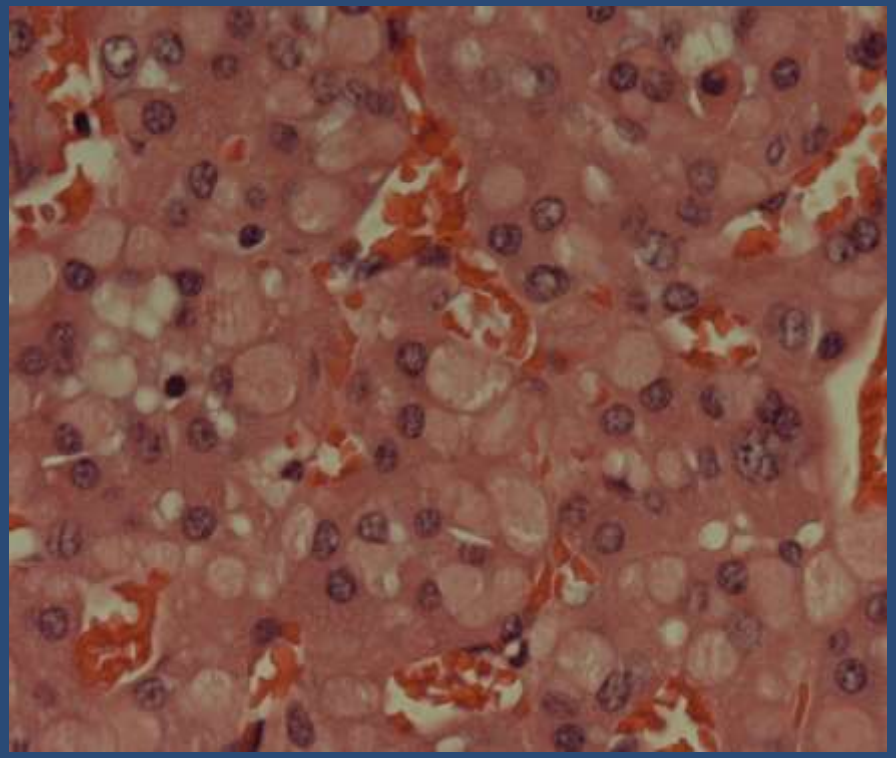
- RCC
  - OFTEN <30 YRS
  - POSSIBLE FEMALE PREPONDERANCE
  - OUTCOME UNDEFINED
  - CHARACTERISTIC MORPHOLOGY
  - SDHB IMMUNOCYTOCHEMISTRY
  - HEAD AND NECK PARAGANGLIOMA
  - PHAEOCHROMOCYTOMA

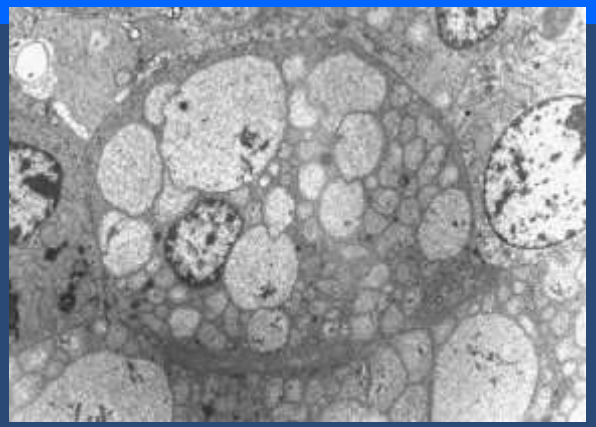
SDH HISTOLOGY

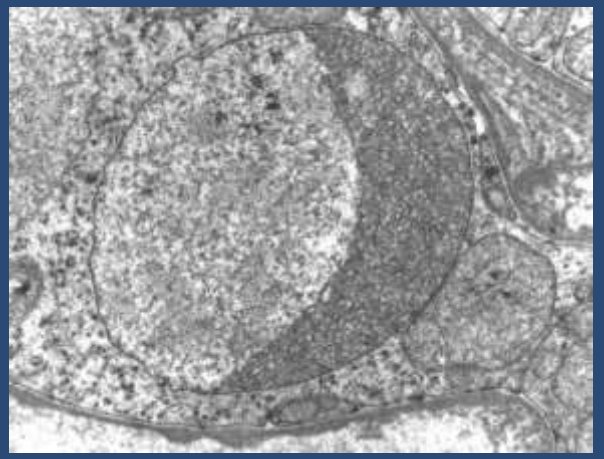




MITOCHONDRIAL MORPHOLOGY



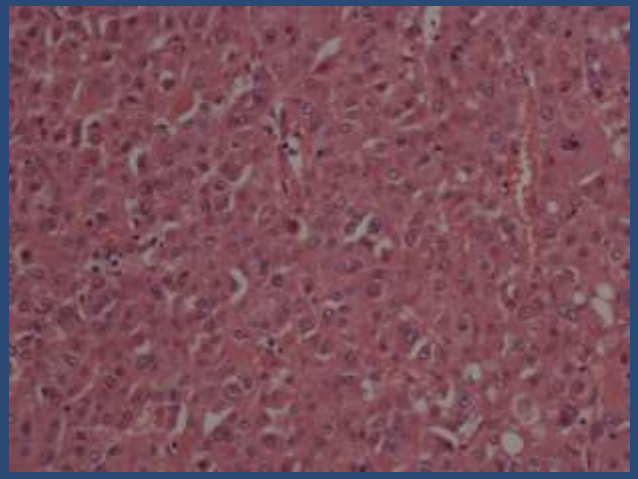


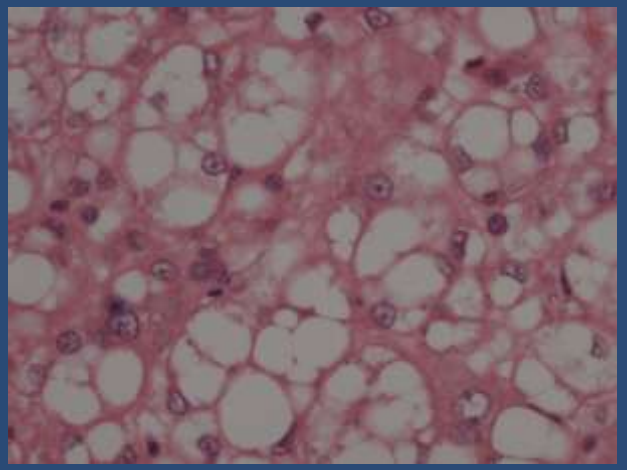


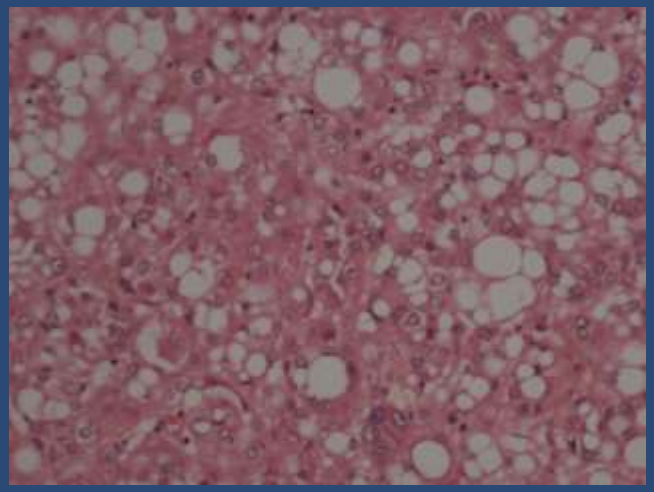
ALK 1 translocation RCC

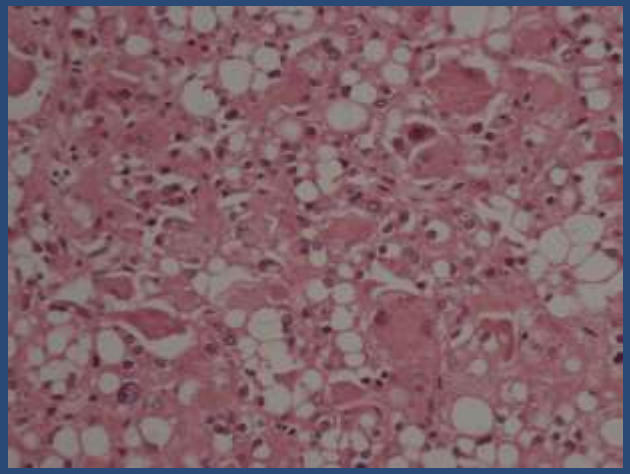
- Rare only four cases in literature
- May be associated with sickle cell trait
- Some indicative morphological features
- ALK1 positive immunocytochemistry
- t2:?? Translocation
  - Vin; EML4; TPM3; Copy number

Alk associated RCC





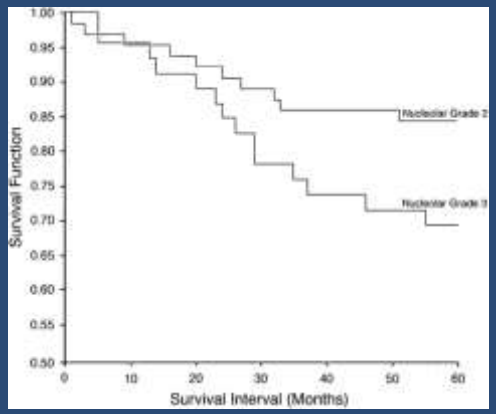




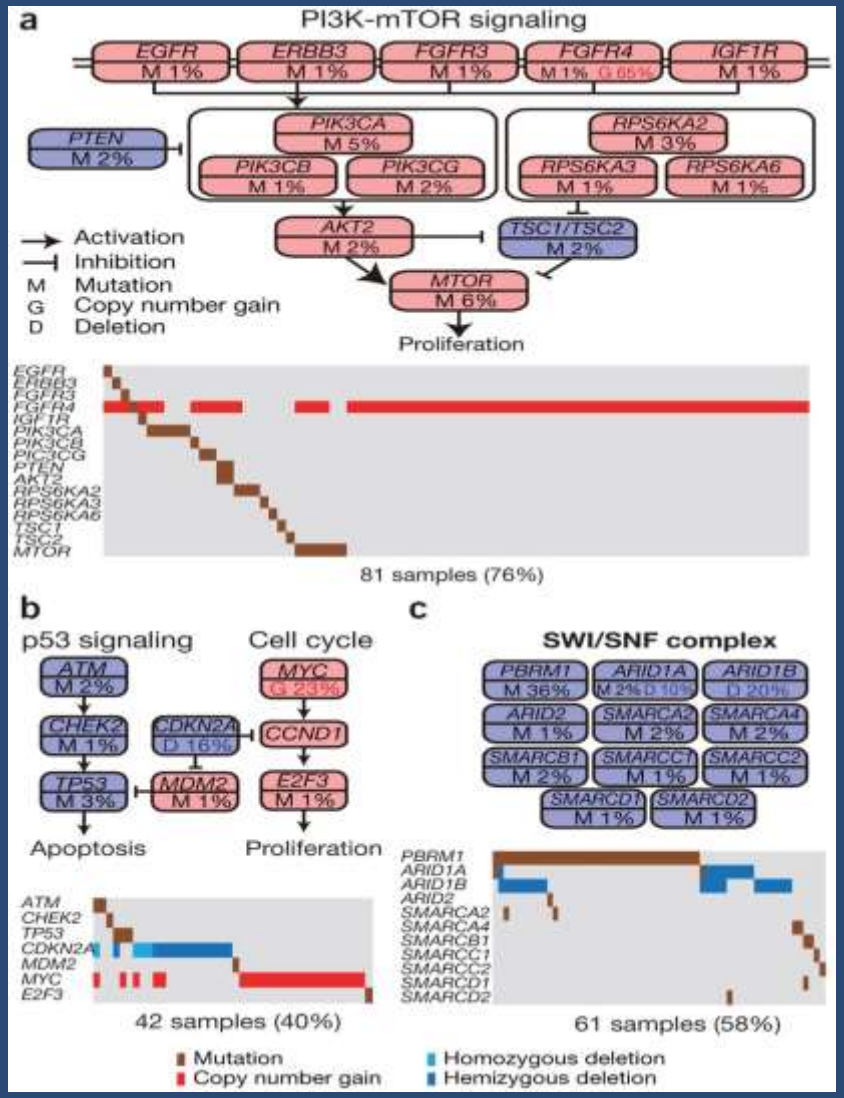
TUMOUR GRADE PREDICTS BIOLOGY
ISUP NUCLEOLAR GRADE

- Not applicable
- Grade X - Cannot be assessed
- Grade 1 - Nucleoli inconspicuous or absent at high power magnification
- Grade 2 - Nucleoli evident at high power magnification
- Grade 3 - Nucleoli large and prominent at low power magnification
- Grade 4 - Nuclei bizarre and/or multilobated, sarcomatoid or rhabdoid morphology

- Grade should be assigned according to the worst grade regardless of extent.
- This system has been validated for clear cell and papillary renal cell carcinoma. It has not been validated for chromophobe and other types of renal cell carcinoma.



HOW DOES IT REFLECT GENETICS?



CAN WE DEFINE TREATMENT PATHWAYS BY IDENTIFICATION OF DRIVER MUTATIONS?

DOES TUMOUR EVOLUTION CONFOUND THAT AIM?

SATO ET AL Nat Genet. Aug;45:860-7 (2013)

RENAL CELL CARCINOMA
WHAT REALLY MATTERS?