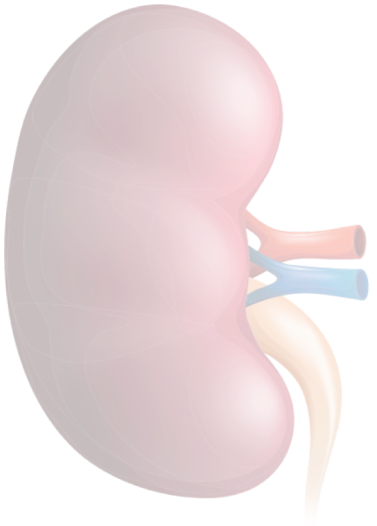
Genetic subtype of Renal cancer

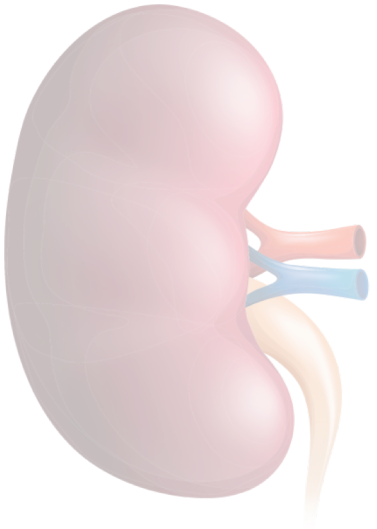
DURS Annual Meeting – May 4, 2018

Karina Rønlund
MD, Ph.D.
Department of Clinical Genetics
Vejle Hospital



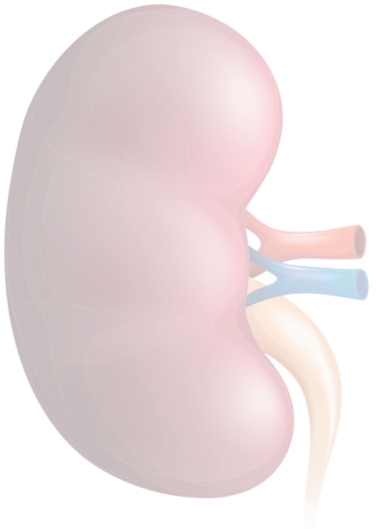
Genetic subtype of Renal cancer

- Introduction
- Renal Cancer Syndromes
- Genetic counseling



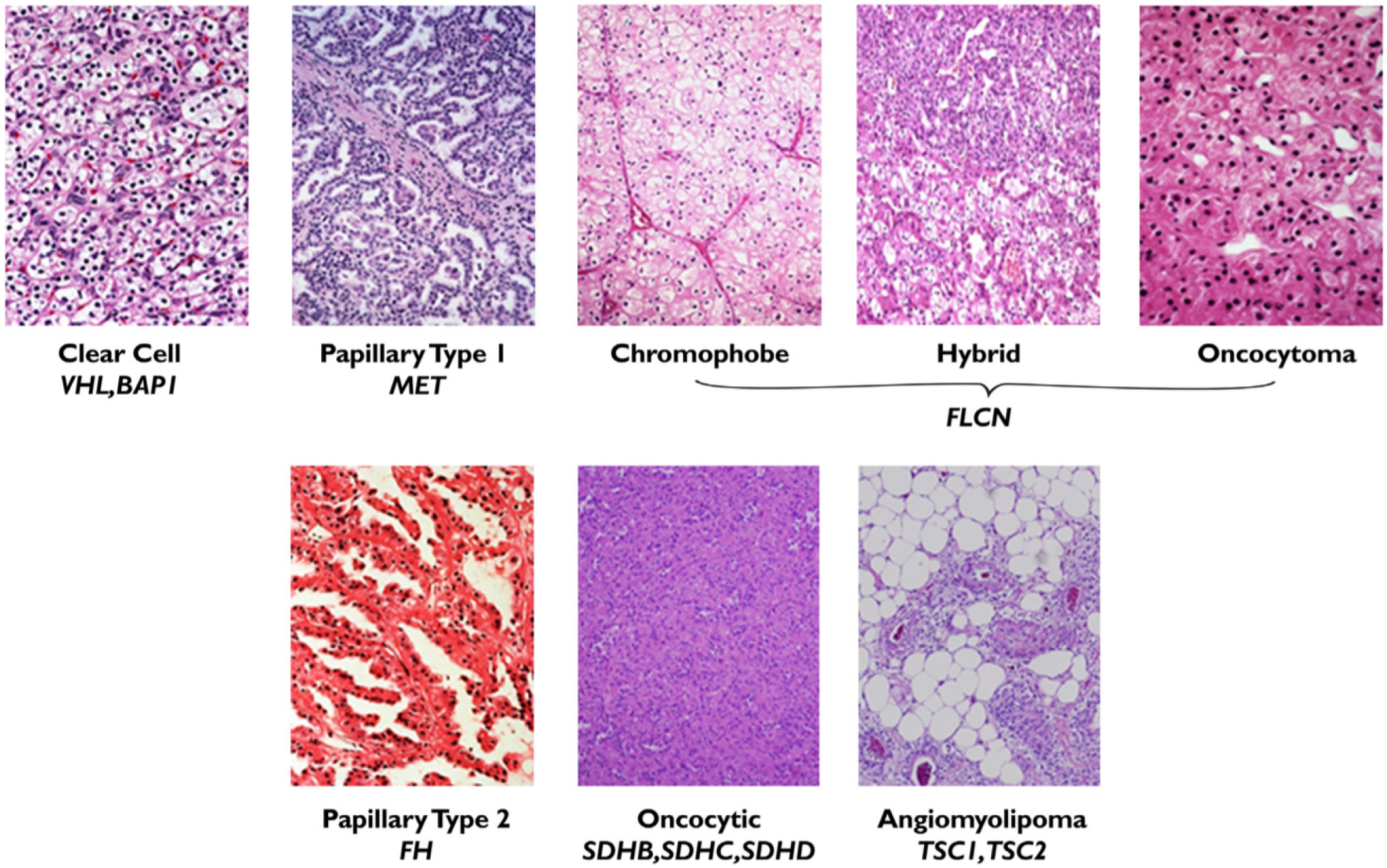
Genetic subtype of Renal cancer

- Hereditary renal cancer accounts for 3-5% of all renal cancer.
- Some inherited cancer susceptibility syndromes are associated with inherited risk of kidney cancer.
- Patients develop renal cancer at an earlier age.
- The lesions can be multifocal, bilateral and heterogeneous.



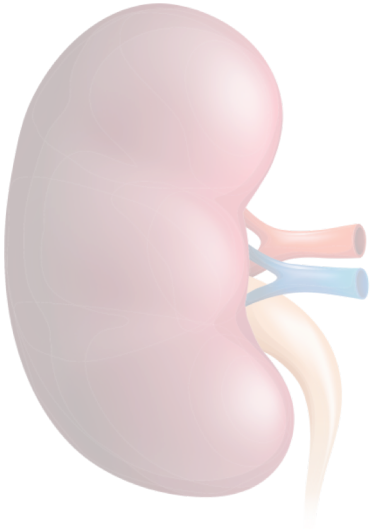
Genetic subtype of Renal cancer

- Arising from the renal tubular epithelial cells, renal cell carcinoma (RCC) accounts for more than 90% of primary kidney tumors in adults.



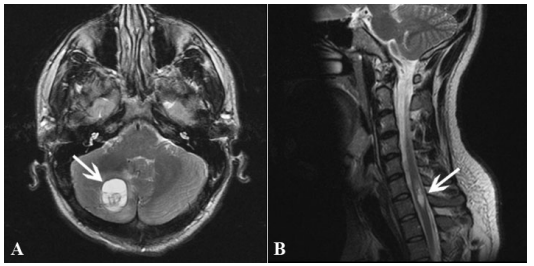
Genetic subtype of Renal cancer

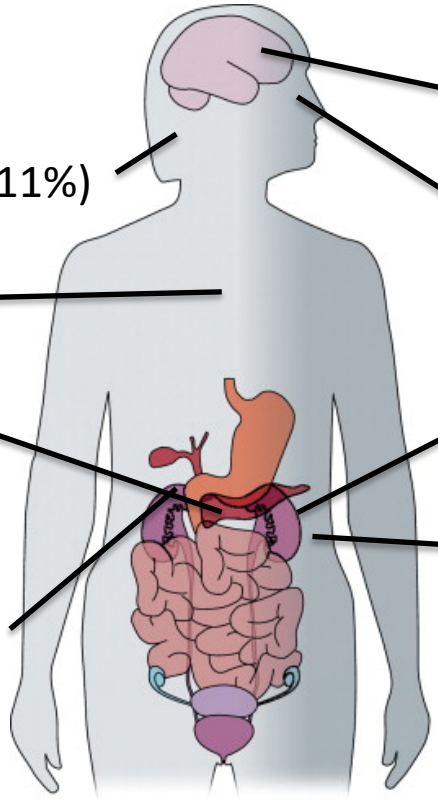
- Von Hippel-Lindau (VHL) syndrome
- Birt-Hogg-Dubé syndrom
- Hereditary papillary renal cancer
  - Hereditary papillary renal cell carcinoma (type 1 papillary)
  - Hereditary leiomyomatosis and renal cell cancer (type 2 papillary)
- Tuberous Sclerosis Complex
- Cowden syndrome
- *BAP1* Tumor Predisposition Syndrome
- Succinate dehydrogenase renal cell cancer
- Chromosome 3 translocations
- Familial renal cell cancer



Von Hippel-Lindau (VHL) syndrome

- Inherited in an autosomal dominant,
  - *VHL 3p25.3*
  - *20% de novo*





Endolymphatic sac tumors (11%)

Hemangioblastomas (27%)

Pancreatic cysts (21%)

Neuroendocrine tumors

Pheochromacytoma (16%)

Hemangioblastomas CNS (49%)

Hemangioblastomas retina (52%)

Clear cell renal cell carcinoma (30%)

Renal cysts (42%)

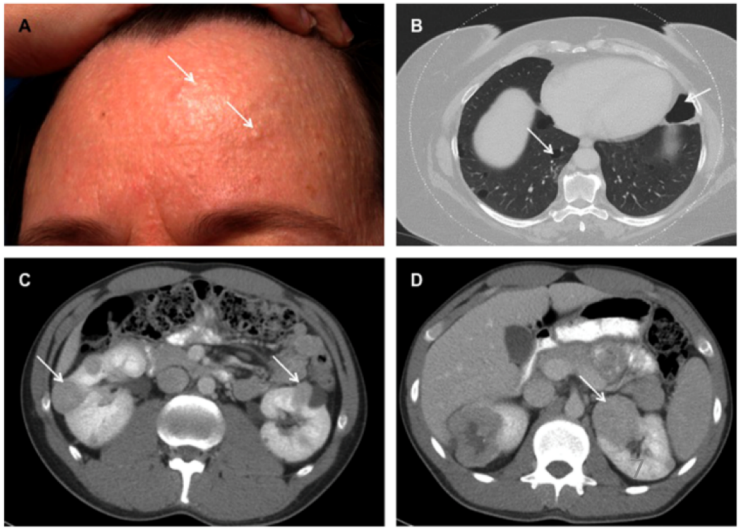
Birt-Hogg-Dubé syndrome (BHDS)

- Inherited in an autosomal dominant,
  - *FLCN 17p11.2*

- Cutaneous manifestations
  - Fibrofolliculomas, trichodisomas/angiofibromas, perifollicular fibromas and acrochordons.

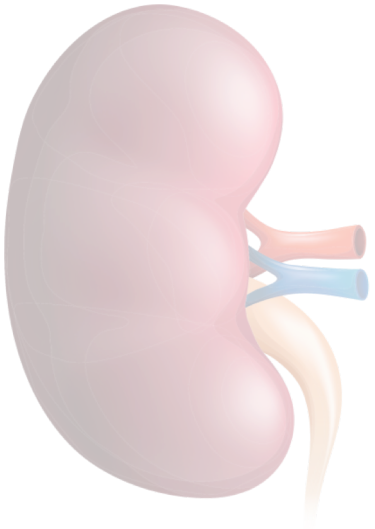
- Pulmonary cysts/history of pneumothorax

- Various types of renal tumors
  - Hybrid of oncocytoma and chromophobe histologic cell types (oncocytic hybrid tumor (67%)
  - Chromophobe renal cell carcinoma (23%)
  - Renal oncocytoma (3%) a benign tumor
  - Clear cell carcinoma
  - Papillary renal carcinoma
- Bilateral, multifocal and slow growing.
- Median age of diagnosis is 48 years (31-71 years)
- Sevenfold increased risk for renal tumors.



Genetic subtype of Renal cancer

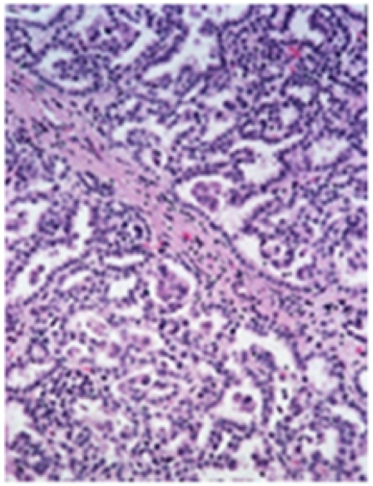
- Von Hippel-Lindau (VHL) syndrome
- Birt-Hogg-Dubé syndrom
- Hereditary papillary renal cancer
  - Hereditary papillary renal cell carcinoma (type 1 papillary)
  - Hereditary leiomyomatosis and renal cell cancer (type 2 papillary)
- Tuberous Sclerosis Complex
- Cowden syndrome
- *BAP1* Tumor Predisposition Syndrome
- Succinate dehydrogenase renal cell cancer
- Chromosome 3 translocations
- Familial renal cell cancer



Hereditary papillary renal cell carcinoma (type 1 papillary)

- Inherited in an autosomal dominant,
  - *MET 7q31*

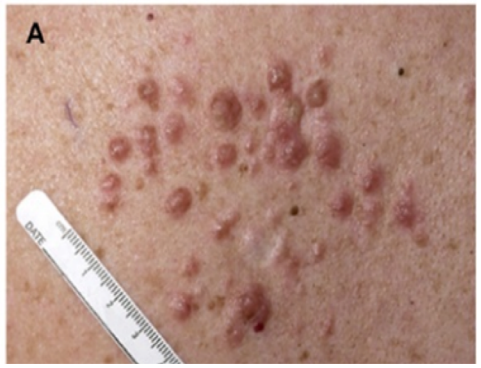
- Multifocal papillary renal cancer (type 1)
- Bilateral.
- Quite rare!
- Almost complete penetrance at age 80.
- Age of detection 50-70 years.

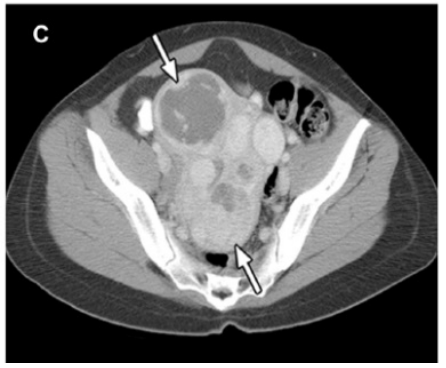


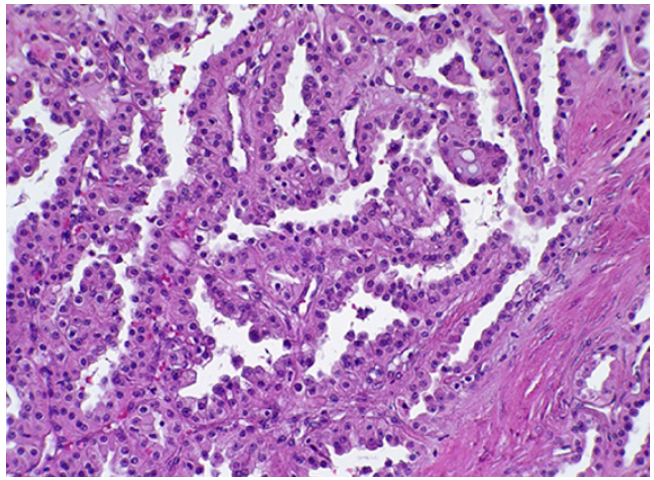
Papillary Type I
MET

Hereditary Leiomyomatosis and Renal Cell Cancer

- HLRCC
- Inherited in an autosomal dominant,
  - *FH 1q43*
- Cutaneous leiomyomata
- Uterine leiomyomata
- Solitary renal tumors type 2 papillary to tubulo-papillary to collecting duct carcinomas.
- Renal cell cancer occur in 10-16% of individuals with HLRCC, median age of detection is 44 years.

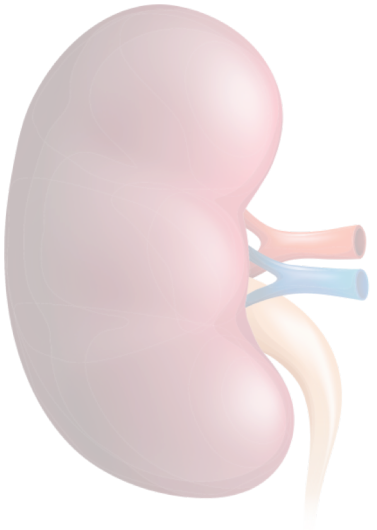




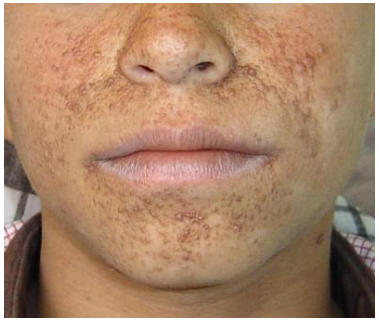


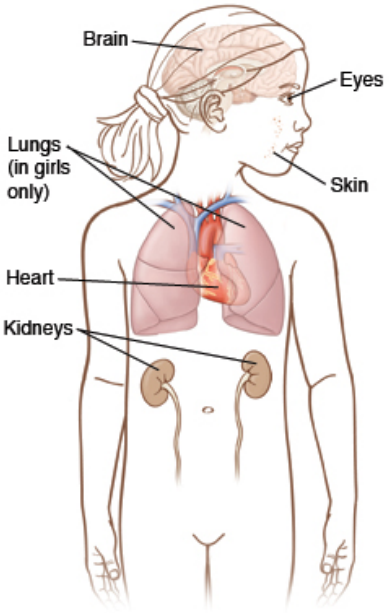
Genetic subtype of Renal cancer

- Von Hippel-Lindau (VHL) syndrome
- Birt-Hogg-Dubé syndrom
- Hereditary papillary renal cancer
  - Hereditary papillary renal cell carcinoma (type 1 papillary)
  - Hereditary leiomyomatosis and renal cell cancer (type 2 papillary)
- Tuberous Sclerosis Complex
- Cowden syndrome
- *BAP1* Tumor Predisposition Syndrome
- Succinate dehydrogenase renal cell cancer
- Chromosome 3 translocations
- Familial renal cell cancer



Tuberous Sclerosis Complex



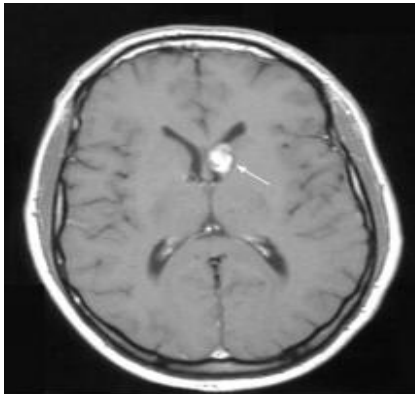


- Inherited in an autosomal dominant,
  - *TSC1 9q34.13(24%) &*
  - *TSC2 16p13.3(66%)*
  - *10% unknown*

- Kidney: 5 different renal lesions occur in TSC
  - Benign angiomyolipomas (70% of affected individuals)
  - Epithelial cysts (20%-30%)
  - Oncocytoma (benign adenomatous hamartoma < 1%
  - Malignant angiomyolipoma < 1%
  - Renal cell carcinoma < 3%

- Skin (hypomelanotic macules, facial angiofibromas, shagreen patches)

- Brain (cortical dysplasias 90%, subependymal nodules 80% and subependymal giant cell astrocytomas, seizures, intellectual disability)

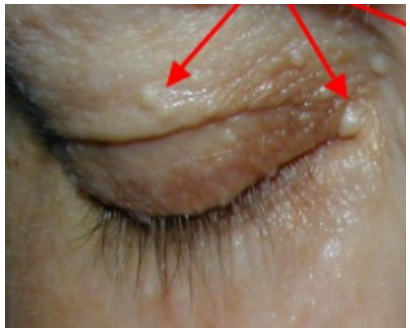


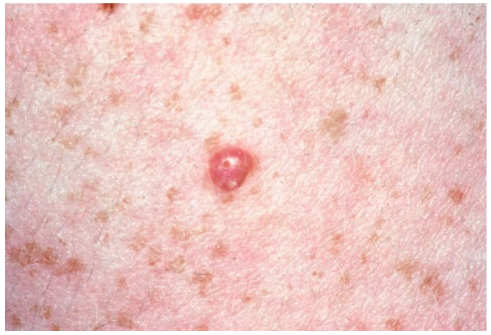
- Heart (rhabdomyomas, arrhythmias) 47-67%.

- Lungs (lymphangioleiomymatosis (LAM)) 10-80%.

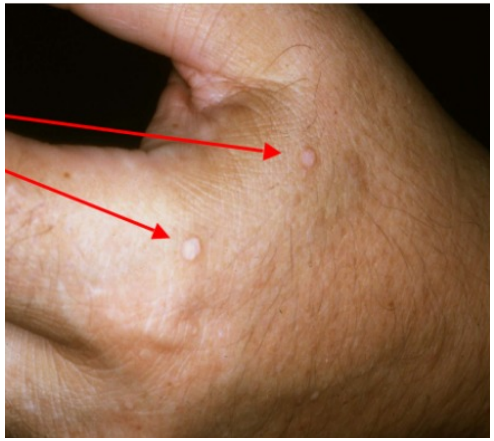
- CNS tumors are the leading cause of morbidity and mortality; renal disease is the second leading cause of early death.

Cowden syndrome



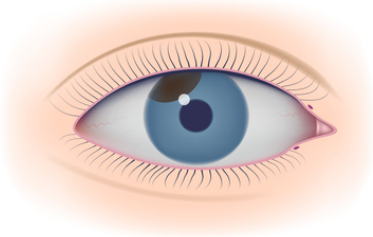


- *PTEN* hamartoma tumor syndrome (PHTS)
- Inherited in an autosomal dominant,
  - *PTEN 10q23.31*
- Mucocutaneous lesions:
  - Trichilemmomas, acral keratoses, papillomatous lesions and mucosal lesions
- Tumor risk:
  - 85% lifetime risk for female breast cancer
  - 35% lifetime risk for epithelial thyroid cancer, median onset 37 y
  - 35% lifetime risk for renal carcinoma - starting age at risk 40s
  - 28% lifetime risk for endometrial cancer
  - 9% lifetime risk for colorectal cancer
- The predominant histology is papillary renal cell carcinoma.

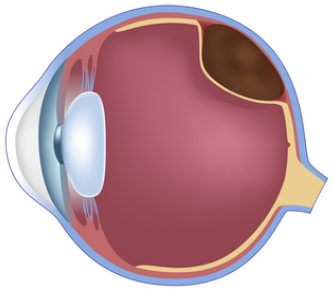


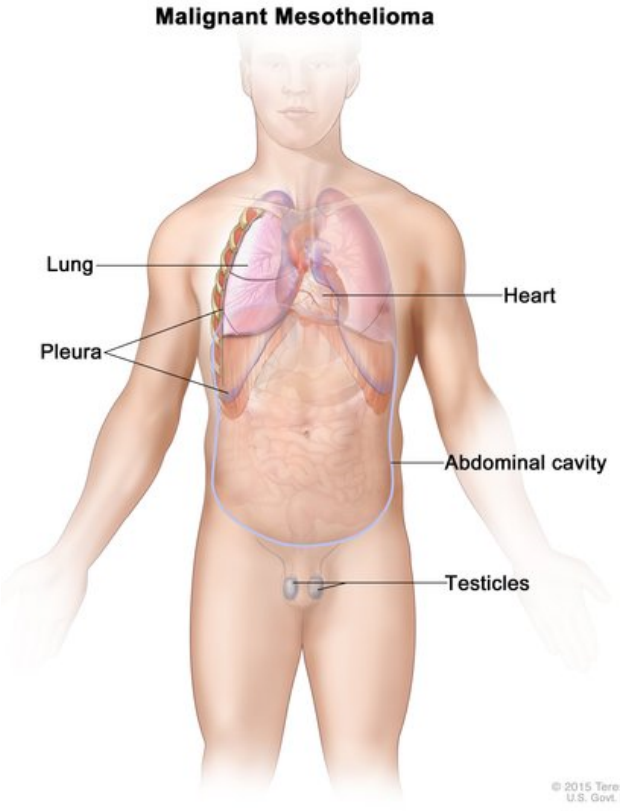
BAP1 Tumor Predisposition Syndrome

- Inherited in an autosomal dominant,
  - *BAP1 3p21.1*



- Atypical Spitz tumors
- Uveal melanoma
- Malignant mesothelioma
- Cutaneous melanoma
- Clear cell renal cell carcinoma
- Basal cell carcinoma



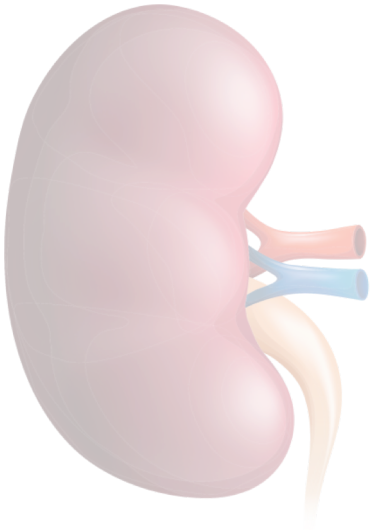


- Median age af ccRCC 47 years

- More than 70 families with the condition have been literature.

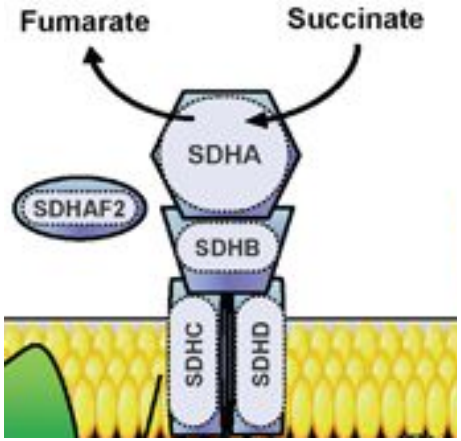
Genetic subtype of Renal cancer

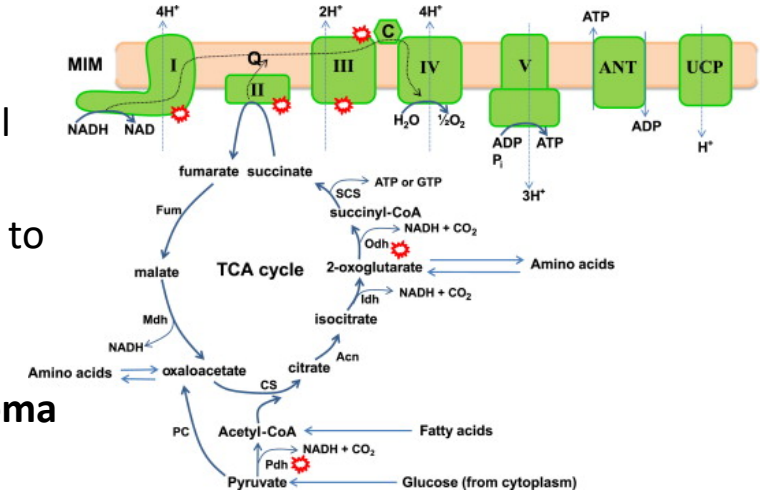
- Von Hippel-Lindau (VHL) syndrome
- Birt-Hogg-Dubé syndrom
- Hereditary papillary renal cancer
  - Hereditary papillary renal cell carcinoma (type 1 papillary)
  - Hereditary leiomyomatosis and renal cell cancer (type 2 papillary)
- Tuberous Sclerosis Complex
- Cowden syndrome
- *BAP1* Tumor Predisposition Syndrome
- Succinate dehydrogenase renal cell cancer
- Chromosome 3 translocations
- Familial renal cell cancer



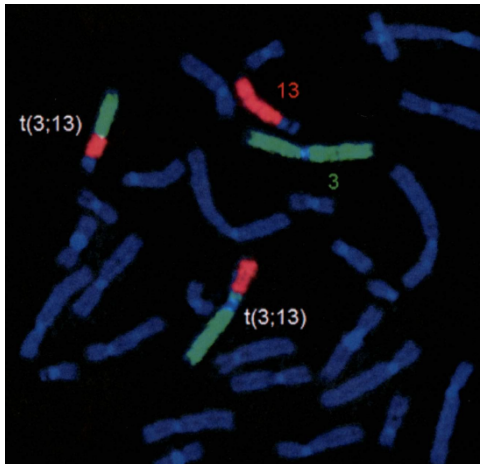
Succinate dehydrogenase renal cell cancer

- Hereditary Paraganglioma-Pheochromocytoma Syndromes
- The genes responsible encode the subunits of the mitochondrial enzyme succinate dehydrogenase (SDH).
- Inherited in an autosomal dominant,
  - *SDHB 1p36.13*
  - *SDHC 1q23.3*
  - *SDHD 11q23.1*
- Paragangliomas (tumors that arise from neuroendocrine tissues symmetrically distributed along the paravertebral axis from the base of the skull to the pelvis)
- Pheochromocytomas (paragangliomas that are confined to the adrenal medulla)
- **Renal clear cell carcinoma** and **papillary thyroid carcinoma**
- Median age af ccRCC 33- 47 years





Chromosome 3 translocations



Gene MITF

Analyse: **Kromosomanalyse på perifert blod**

Indikation: Abortus habitualis

Metode: G-Båndsanalyse (båndkvalitet:500-550)

Materiale: Blod - Postnatal prøve

RESULTAT

Karyotype: **46,XY,t(3;13)(p13;q21.1)**

BESKRIVELSE OG KONKLUSION

Der er ved standard kromosomundersøgelse i samtlige metafaser fundet at et stykke fra kromosom 3 og et stykke fra kromosom 13 har byttet plads. Dette resulterer i en tilsyneladende balanceret reciprok translokation og den abnorme hanlige karyotype:

46,XY,t(3;13)(p13;q21.1)

Translokationen er verificeret ved FISH analysen.

Translokationen giver sandsynligvis ingen symptomer for patienten selv, da den er balanceret.

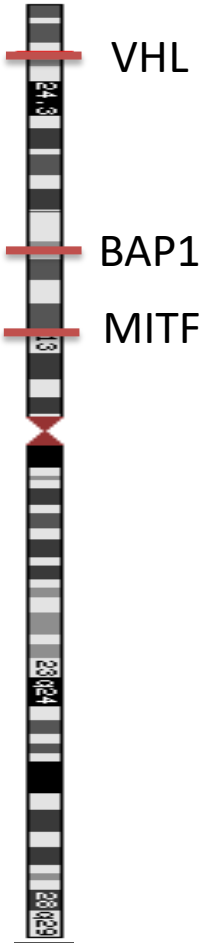
Ved graviditet er der øget risiko for at fosteret arver translokationen i ubalanceret form, hvilket kan resultere i abort, misdannelser og mental retardering.

Der bør tilbydes prænatal diagnostik i fremtidige graviditeter.

I er velkomne til at henvise patienten til genetisk rådgivning med henblik på familieudredning.

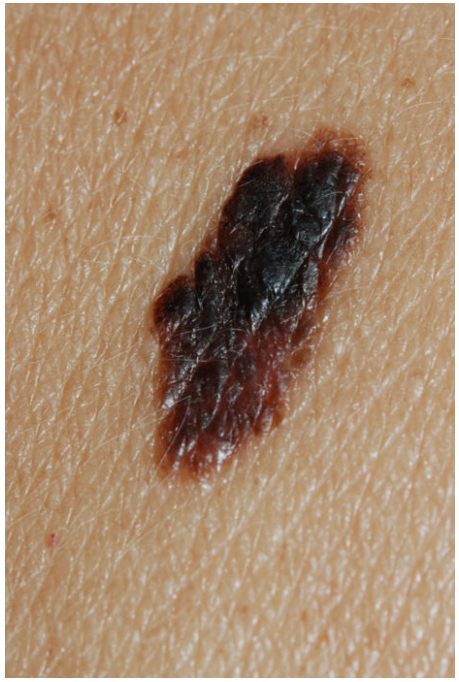
Med venlig hilsen
Zuzana Lohse
Læge

Med venlig hilsen
Thomas Dyrsø Jensen
Ledende overlæge, Ph.D.



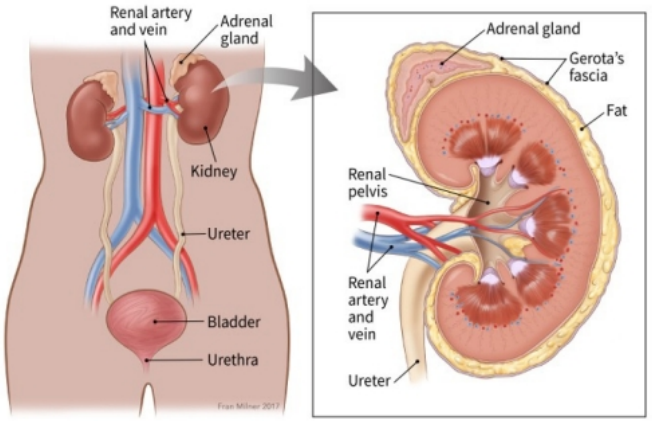
MITF-related melanoma and renal cell carcinoma predisposition syndrome

- Inherited in an autosomal dominant,
  - *MITF 3p13*
- A gain-of-function germline mutation in the MITF gene.
- Higher incidence of melanoma, multiple primary melanomas and increase in nevus number and size.
- It may also predispose to co-occurring melanoma and renal cell carcinoma and to pancreatic cancer.



Familial renal cell cancer

- Renal cell carcinoma in families were we do not have a detectable germeline mutation.
- Less than 20% of patients with features of nonsyndromic inherited RCC have a detectable mutation in a known familial RCC gene.
- CDKN2B



Germline Mutations in the *CDKN2B* Tumor Suppressor Gene Predispose to Renal Cell Carcinoma
Mariam Jafri et al. Published July 2015

Genetic subtype of Renal cancer

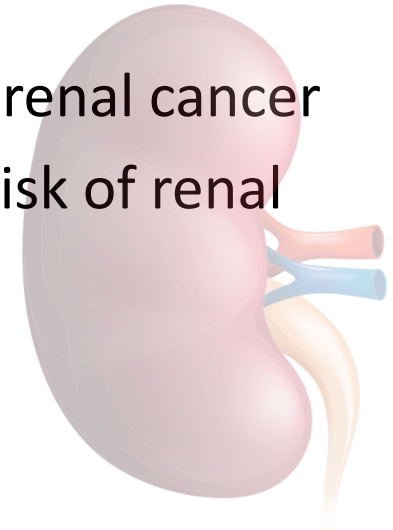
Inherited cancer susceptibility syndromes associated with an increased risk of renal cancer

Syndrome	Gene	Protein	Renal cancer type	Other cancers
BAP1 mutant disease	*BAP1*	BRCA associated protein	Clear cell	Melanomoa Uveal melanoma Mesothelioma
Birt-Hogg-Dubé syndrome	*FLCN*	folliculin	Oncocytic, chromophobe	---
Familial clear cell renal cancer with chromosome 3 translocation	Translocation chr 3		Clear cell	---
Hereditary Leiomyomatosis and Renal Cell Cancer	*FH*	fumarate hydratase	Papillary type 2	---
Hereditary papillary renal cancer	*MET*	c-MET	Papillary type 1	---
PTEN hamartoma syndrome	*PTEN*	PTEN	Clear cell	Breast cancer Thyroid cancer
SDH associated renal cancer	*SDHB* *SDHC* *SDHD*	succinate dehydrogenase subunits B, C, D	Clear cell, chromophobe, oncocytoma	Paraganglioma Pheochromocytoma
Tuberous Sclerosis Complex	*TSC1* *TSC2*	hamartin tuberin	Angiomyolipoma Epitheliod angiomyolipoma	Angiomyolipomas Subependymal giant cell astrocytomas
Von Hippel Lindau disease	*VHL*	pVHL	Clear cell	CNS - hemangioblastoma (brain, spine, retina) Adrenal - pheochromocytoma Inner ear - endolymphatic sac tumors Pancreas - neuroendocrine tumors

Hereditary Renal Cancer Syndromes
Naomi B. Haas et al. *Adv Chronic Kidney Dis*. 2014 January ; 21(1)

Genetic subtype of Renal cancer

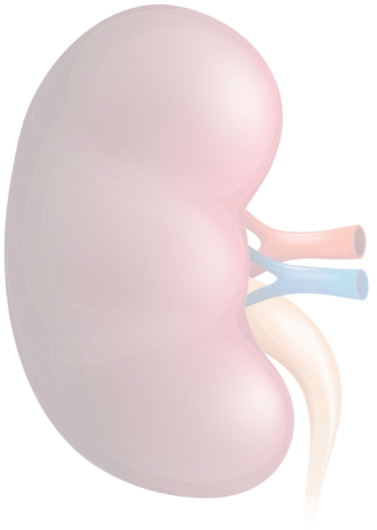
- Criteria for reference to genetic counseling:
  - Renal cancer before age 40
  - Bilateral and/or multifocal renal cancer before age 60
  - Renal cancer in 2 first-degree relatives
  - Known cancersyndrom with increased risk of renal cancer
  - Patogenic variant i a gen related to incresed risk of renal cancer



Genetic subtype of Renal cancer

Thank You For Attention!

Questions?



Vejle Sygehus
- en del af Sygehus Lillebælt

Region Syddanmark