GENETICS IN ENDOCRINE ONCOLOGY
A PRACTICAL APPROACH
From Classical Syndromes to New Associations.

Tobias Else, MD,
Assistant Professor
Endocrine Oncology & Cancer Genetics Clinic
Comprehensive Clinical Care Center for von Hippel-Lindau disease
Metabolism, Endocrinology & Diabetes
Dept. of Internal Medicine
University of Michigan Health System
Objectives

• **Case-finding** of patients with hereditary predisposition to tumor development

• **Clinical approach** to cases with suspected or confirmed hereditary disease

• **Interpretation of genetic test results**

• **Follow-up surveillance** in patients with hereditary tumor predisposition
Overview

• Introduction
  • Genetics & syndromes overview

• Disease based approach
  • Genetic associations of different endocrine tumor syndromes

• Clinical cases
  • Clinical genetic & endocrine diagnostics
  • Clinical challenges

• Summary/Conclusion
Basics of a clinical genetic evaluation

- Personal history
- Family history
- Review of Systems
- Physical exam

→ Genetic testing
Features of familial cancer syndromes

Personal history/ROS/physical exam
- Metachronous/synchronous neoplasias
- Multiple primary tumors (particularly in paired organs), same syndrome spectrum
- Multiple rare tumors
- Prior known precursor lesion
- Tumor diagnosis at unusually young age
- Other congenital defects
- Cutaneous lesions commonly found in hereditary cancer susceptibility syndromes

Family History
- Unusual high number of family members affected with cancers
- Family history of the same tumors (or same tumor spectrum)
- Family history of other rare cancers
- Family history of known hereditary cancer susceptibility syndromes
Classical endocrine tumor syndromes

- Multiple Endocrine Neoplasia type 1
- Multiple Endocrine Neoplasia type 2
  - Familial medullary thyroid cancer (FMTC), MEN2A, MEN2B

‘New’ endocrine tumor syndromes

- Hereditary paraganglioma syndrome
- Primary hyperparathyroidism and jaw tumor syndrome

Hereditary tumor syndromes with endocrine tumor manifestations

- Von Hippel Lindau disease
- Neurofibromatosis type 1
- PTEN hamartomatous tumor syndrome (PHTS)/Cowden disease
- Familial adenomatous polyposis (FAP)
- Lynch syndrome
- DICER1 syndrome

Petr & Else, Semin Oncol 2016
Basics of germline genetic testing

Germline genetic testing
- Testing of germline DNA – usually obtained by blood draw
- Genetic make-up of an individual
  → Detects hereditary/inborn genetic changes

Tumor genetic testing (e.g. FoundationOne)
- Detects somatic changes specific to the tumor
- Genetic make-up of the tumor
  → Use for targeted therapy
What are genetic changes?

- **Chromosomal aberrations**
  - Additional, missing chromosomes, large translocations
  → karyotype, metaphase analysis

- **Larger deletions/duplications**
  - Deletions or duplications of larger areas
  → Chromosomal microarrays (CMA)

- **Small deletions/duplications**
  - 100-1000s of nucleotides
  → MLPA, CMA
  - Up to 100 nucleotides
  → MLPA, NGS, (Sanger)

- **Nucleotide changes**
  - Nucleotide insertions/deletions/duplications/mutations
  → Sanger sequencing, NGS
Library preparation

DNA fragmentation
(Capture) Adaptor binding Barcode binding

Sample 1
Sample 2
Sample 3

Pool

SEQUENCER

Output: FASTQ files

TTGGTATATCTAT
GGTTCTGTGCTCTCT
TTATCGAGCTTTAAAC

TTGGTCTCTCCACA
TTAGTGTACCTCTTT
CGGAGTTGATATTG

TTACGGAGTTTTTA
AGTTGTTGCCCCTTC
AAATCTCTGTAATG

Bioinformatics analysis
Demultiplex

Sequencing
Next Generation Sequencing (NGS)

**PRO**
- Ability to run multi-gene panel
- Calculate copy number changes

**CON**
- Might miss medium sized deletions
- Cheaper, but requires advanced technology
Why consider genetic testing?

• **Prevention/Screening** of diseases
  • Surveillance for associated tumors in proband/index patient and at-risk family members
  • Estimates are 2-4 additional individuals identified offset the costs of therapy for advanced tumors

• **Therapy/follow-up** of findings
  • Correct therapy/follow-up considering the underlying genetic condition
  • Can be considerably different
    • Observation for small RCC/pNET in VHL
    • Observation for small pNET in MEN1 rather than surgery

→ Genetic testing potentially alters care for the patient and family
→ That is what the insurances need to hear PRIOR to genetic testing
ACMG - guidelines

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD¹, Nazneen Aziz, PhD²,¹⁶, Sherri Bale, PhD³, David Bick, MD⁴, Soma Das, PhD⁵, Julie Gastier-Foster, PhD⁶,⁷,⁸, Wayne W. Grody, MD, PhD⁹,¹⁰,¹¹, Madhuri Hegde, PhD¹², Elaine Lyon, PhD¹³, Elaine Spector, PhD¹⁴, Karl Voelkerding, MD¹³ and Heidi L. Rehm, PhD¹⁵; on behalf of the ACMG Laboratory Quality Assurance Committee

3. Find x.

… not always as easy and obvious as you think!

Richards et al., Genet Med 2015
Evidence for or against pathogenicity
(pathogenic vs. benign)

• Type of mutation
• Genetic disease databases
• Databases of normal individuals (e.g. 1000 genomes, ExAC)
• Personal & family history
• Segregation with disease
• In vitro analysis
• In silico prediction
ACMG Classification spectrum

- Pathogenic = disease-causing
- Likely Pathogenic = likely disease-causing
- Likely benign = likely not disease-causing
- Benign = not disease-causing
- Variant of uncertain significance = don’t know!
Different labs – different opinions

… and none of the testing labs knows the full personal or family history

→ Work with a cancer geneticist
→ Rare syndromes/tumors – rare variants may sway towards clinical action
PHEOCHROMOCYTOMA
PARAGANGLIOMA (PCC/PGL)

Challenges in genetic testing and new phenotypes
CASE 1 - 21 year old male with paraganglioma

- New diagnosis HTN
- Elevated normetanephrine level (5fold), normal metanephrine level
- CT – large heterogeneous paraadrenal mass
- MIBG – positive with metastasis to skull & vertebrae

→ Surgery for primary mass
Dx - paraganglioma
PCC/PGL - Location

A Adrenal pheochromocytoma
B Extra-adrenal pheochromocytoma
C Head and neck paraganglioma

Fauci et al., Harrison’s Principles of Internal Medicine, 17th edition
GENETIC TESTING?
A Negative Family history?

- 4-generation pedigree

- **Non-contributory** is only a family history that has not been taken

- Family history can be negative:

  → *De novo* mutations (new in your patient – spontaneous mutations)
    - Varies from disease to disease → correlates with ‘reproductive fitness’ *VHL* 30%, *SDHx* <10%, unknown for *TMEM127, MAX*

  → **Non-paternity**
    - Maternity is a given – paternity is a chance!
    - Up to 10% non-paternity
    - Recent estimates ~1% that ‘Dad is not Dad’

  → **Incomplete penetrance**
    - Penetrance = patients with phenotype (e.g. tumor) AND gene mutation all mutation carriers
Genetic differential diagnosis

- Pheochromocytoma
- Paragnaglioma

- HPGL
  - SDHx
  - RCC, GIST, pituitary adenoma

- other
  - TMEM127, MAX
  - RCC

- HLRCC
  - FH
  - Leiomyomas, RCC, fibroids

- MEN2 FMTC
  - RET
  - pHPT, MTC

- NF1
  - NF1
  - Neurofibromas, Gliomas, MNST

- VHL
  - VHL
  - RCC, ELST, hemioblastomas, pNET

Petr & Else, Semin Oncol 2016
Multiple Endocrine Neoplasia type 2

- **RET proto-oncogene**
- **Type 2A**
  - Hyperparathyroidism (pHPT) (~25%)
  - Medullary thyroid carcinoma (MTC) (~90%)
  - Pheochromocytoma (~50%)
  - Cystein 630 & 634
- **Type 2B**
  - Marfanoid habitus
  - Mucosal neuromas
  - MTC (~100%)
  - Pheochromocytoma (~50%)
  - M918T

- Rare syndrome with germline **oncogenic mutation**
- **Elective thyroidectomy** – age 1 (MEN2B) or age 5 and older (MEN2A)
- **Annual Ca (pHPT), metanephrine levels (PCC) and calcitonin**
- PCC **always adrenal** localization & **metanephrine** producing
Von Hippel Lindau disease

- **Hemangioblastomas**
  - Retina
  - CNS (spine/cerebellum)

- **Endolymphatic sac tumor**

- **Pheochromocytoma**
  - Normetanephrine producing
  - Usually adrenal localization

- **Pancreatic neuroendocrine tumors**
  - Non-functional
  - Consider therapy >2cm

- **Renal cell cancer**
  - Therapy > 3cm

→ Brain/spine MRI (every 1-2 years)

→ Audiology exam

→ Abdominal MRI, plasma metanephrines (annual)

→ Work with the VHL-Alliance & associated centers
**SDHx-related hereditary paraganglioma syndrome**

- **Inheritance**
  - Autosomal dominant (*SDHA, SDHB, SDHC, SDHD, SDHAF2 [SDHx]*)
  - *SDHD* (imprinted gene) needs to be inherited from father in order to be pathogenic

- **Associated tumors & Penetrance**
  - Paragangliomas, 5-80%
  - Renal cell cancer, <5%
  - Pituitary tumors, <5%
  - Gastrointestinal stroma tumors (GIST), <5%
    - Children with GIST should be screened and tested

*Denes et al., JCEM 2014
Miettinen et al., Int J Biochem Cell Biol 2014*
**SDHx-related hereditary paraganglioma syndromes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Hormone</th>
<th>Localization</th>
<th>PCPGL risk</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SDHB</strong></td>
<td>NM</td>
<td>Abdominal, Head &amp; neck, less common thorax</td>
<td>~50-75%, likely lower</td>
<td>30% malignant</td>
</tr>
<tr>
<td><strong>SDHD</strong></td>
<td>None</td>
<td>Head &amp; neck, less common abdomen/thorax</td>
<td>~80%, likely lower</td>
<td>Needs to be paternally inherited to be disease causing</td>
</tr>
<tr>
<td><strong>SDHC</strong></td>
<td>None</td>
<td>Head &amp; neck, chest</td>
<td>Low</td>
<td>~60 patients described</td>
</tr>
<tr>
<td><strong>SDHA</strong></td>
<td>?</td>
<td>Abdominal, Head &amp; neck, thorax</td>
<td>unknown</td>
<td>Only very few patients described</td>
</tr>
<tr>
<td><strong>SDHAF2</strong></td>
<td>?</td>
<td>Head &amp; neck</td>
<td>unknown</td>
<td>Only few (4) families described, possible parent of origin effect</td>
</tr>
</tbody>
</table>

**Imaging** – cross sectional & most PCC/PGL will be Ga-DOTATATE positive
Surveillance for PCPGL

• Annual visits in Cancer Genetics Clinic
  • exam/history/review of systems

• Von Hippel-Lindau disease
  • Yearly plasma metanephrines and abdominal imaging
  • Refer to Comprehensive Clinical Care Center for VHL
    + brain & spine MRI, renal & pancreas imaging

• Multiple endocrine neoplasia type 2
  • Yearly plasma metanephrine levels
    + calcitonin & calcium

• Neurofibromatosis type 1
  • Clinical exam – low penetrance of PCPGL in NF1
Surveillance for *SDHx*-related hereditary PCC/PGL syndrome

- Every 2 years whole body MRIs
- Yearly metanephrines

**Concerns:**
- *False positives*
  - Overtreatment
- *Incidental findings*
  - Related/unrelated
- *Screening fatigue*
  - Dismissal of screening after years of no findings
  - Costs

→ **Definitely screen young women prior to pregnancy for active PCPGL**

→ Maternal mortality untreated 50% → treated 1%
→ Fetal mortality untreated ~70% → treated 1-17%

→ **Definitely screen for active PCPGL prior to any surgery or anesthesia**
GENETIC EVALUATION OF HYPERPARATHYRPOIDISM

A genetically neglected entity.
CASE 2

- 30 yo male with primary hyperparathyroidism
- SH: Resident at OSH
- PMH: **Low bone mineral density**, mild hypercalcemia, elevated PTH, high urine calcium
- 4-gland hyperplasia in pathology (3.5 gland removal)
Genetic differential diagnosis of pHPT

Primary hyperparathyroidism → MEN2 → RET → MTC, PCC

HPJT-syndrome → CDC73 → Uterine fibroids, osteomas

MEN1 → MEN1 → NET, pituitary

FHH → CASR → -------

other → (CDKN1B) → MEN1-like

→ Up to 10% of young (<45 years) have a hereditary predisposition

Petr & Else, Semin Oncol 2016
Akerstrom et al., Hormones & Cancer 2015
Multiple Endocrine Neoplasia type 1 - PPP

- **PPP (classical)**
  - Pituitary adenoma (20%)
    - Non-functional, prolactinoma
    - Cushing’s disease, acromegaly
  - pHPT (95%)
    - 4-gland hyperplasia
  - pNET (20-80%)
    - Non-functional, insulinoma, gastrinoma, VIPoma, glucagonoma
  - Duodenal gastrinoma
  - Adrenal adenoma
  - NET (lung, thymus)
  - Callagenoma, angiofibroma

- **Surveillance**
  - Endocrine exam, prolactin & other hormones (annual)
  - pituitary MRI (3-5 years)
  - Ca, PTH, 25OHVit D (annual)
  - Abdominal MRI/endoscopic US, gastrin levels (annual)
  - Review on abdominal MRI
  - Chest imaging (baseline & every 2-5 years)

*Thakker et al., JCEM 2012*
CASE 3

- 41 yo F with hypercalcemia, recently diagnosed after pregnancy. Referred to fellow’s clinic for hyperparathyroidism
- PMH: no kidney stones, no tumors, no surgeries
- Lab: Ca 11.4mg/dl (high), PTH 90pg/ml, PO4 2.6mg/dl

**Review of labs:**
- Ca since 2013 10.8-11.6mg/dl
- 24hr urine Ca 38mg (low), creatinine 30mg
  → calcium creatinine clearance 0.003 (<0.01)
CASE 4 – 18 years of hypercalcemia

• 52 yo M with pHPT presents for evaluation of possible genetic predisposition for pHPT.

• PMH/PSH:
  • Multiple episodes of kidney stones
  • 3x surgeries (1\textsuperscript{st} age 34), last with implant in forearm
  • Recurrent hyperparathyroidism, kidney stones & hypercalcemia

• → Finally in 2016 area of parathyroid tissue in forearm identified and normalization of calcium levels after removal
CDC73 – related disorder
Hyperparathyroidism – jaw tumor syndrome

- Ossifying fibromas – jaw tumors
  - (independent of pHPT)
  - ~30-40% of mutation carriers

- pHPT
  - 95% of mutation carriers (ascertainment bias)
  - Multiple adenomas
  - Risk for parathyroid cancer

- Uterine fibroids
- Kidney lesions
- Often large deletions (~35%)

- Surveillance
  - Jaw X-ray, physical exam
  - Ca (annual)
  - (US screening [kidney, uterus])

Jackson et al. GeneReviews, 2015
pHPT – genetic evaluation

- Consider genetic work-up / referral to Cancer Genetics for:
  - Age <35 (<45)
  - Male
  - > 1 gland involved
  - Multi-gland hyperplasia
  - Parathyroid cancer
  - Relapse after surgery
  - Positive family history
  - Other unusual tumors

Yes! I qualify for genetic testing!!
Surgery for pHPT – Know your Genetics!

Parathyroid adenoma
- Removal of adenoma only

Four gland hyperplasia
- Removal of 3.5 glands
- Explore for additional ectopic glands
- MEN1 – thymectomy
- Leave 0.5-1 gland in place or (autotransplant to forearm)

Parathyroid cancer
- Removal of as much diseased parathyroid tissue as possible
- Consider 3.5 gland removal and leave 0.5-1 parathyroid in place (or autotransplant)

→ Prevent early recurrence, avoid hypoparathyroidism
→ After surgery increased awareness for recurrence (neck, ectopic) or parathyromatosis
→ FHH – no surgery, benign disease!
ADRENAL CANCER (ACC) GENETICS

… beyond TP53 and Li-Fraumeni syndrome
A clinical approach to identify new associations
CASE 6 – Family history

55 yo F w/ a history of pheochromocytoma, now with adrenocortical carcinoma

Multiple neurofibromas, café au lait spots & Lisch nodules
CASE 6 - Neurofibromatosis

- The patient has clinical diagnosis of neurofibromatosis type 1 (NF1)
- NF1 does not need to be confirmed – it’s a clinical diagnosis
- ~4-7% of NF1 patients develop pheochromocytoma
  - (consider screening for NF1 patients with tachycardia or hypertension)

CASE II

Michel Bur, 47 years old, a resident of Ernsweiler bei Puttlingen in Lothringia, had suffered several years previously from a panophthalmitis of the right eye which had left the bulb completely shrunk. Otherwise, except for a childhood disease, supposedly miliaria, in his fifth to sixth year, he had always been well and able to follow his occupation as a day laborer. His intelligence did not seem exceptional, nor on the other hand below average. Since his disease he had commenced to stutter. Herr Bur had no history of rheumatic pains except for a painful tension in the neck, extending as far as the crown of the head, when he perspired heavily. He was especially prone to perspiring. He was unmarried, his parents were healthy,
The patient has clinical diagnosis of neurofibromatosis type 1 (NF1).

NF1 does not need to be confirmed – it’s a clinical diagnosis.

~4-7% of NF1 patients develop pheochromocytoma
  - (consider screening for NF1 patients with tachycardia or hypertension)

No need for further evaluation of pheochromocytoma associated syndromes (?)

NF1 does not classically predispose to adrenal cancer (?)
Genetic differential diagnosis ACC

Adrenocortical carcinoma

- MEN1
- FAP
- Lynch syndrome
- LFS
- BWS

MEN1

Petr & Else, Semin Oncol 2016
Genetic differential diagnosis ACC

- 50-80% of all kids with ACC have Li Fraumeni syndrome (TP53 mutation)

- Adults:
  - ~4% Li Fraumeni syndrome
  - ~4% Lynch syndrome
  - ~1% MEN1
  - ~1-4% other (e.g. Familial Adenomatous Polyposis, Carney Complex)

- Consider germline panel (definitely including TP53 – Chompret criteria for TP53 testing)
- Consider immunohistochemistry/MSI screening for Lynch syndrome (or germline testing) Confirmed NF1
Lynch syndrome & ACC

- Association of ACC – same proportion as in colon & uterine cancer
  → universal screening as in practice for colon cancer
- Lynch’s initial Family N: ascertained through a proband with ACC

*N Family.— The propositus (No. U-11770) was studied at the Omaha Veterans Administration Hospital where he expired at age 44 from adrenal cortical carcinoma. His medical history revealed that many of his immediate relatives had cancer and that they lived over a wide geographic area.

Lynch, Arch Int Med 1966
NEUROENDOCRINE TUMORS

... rarely index tumors ...
Neuroendocrine Tumors (NET)

- **Originate from APUD system**
  - Amine Precursor Uptake & Decarboxylation system – synthesis of various hormones

- **Foregut**
  - Ectopic hormone production
  - Gastrinoma
  - Pancreatic hormones (pNET)

- **Midgut**
  - Serotonin

- **Hindgut**
  - Non-functional
CASE 7

• 38 yo F with incidentally discovered liver metastasis and tumor in the ileum (primary)

• CT scan for abdominal discomfort
Genetic differential diagnosis NET

Neuroendocrine tumor

- NF1 → Neurofibromas, Gliomas, MNST
- VHL → RCC, ELST, hemgioblastomas, pheochromocytomas
- MEN1 → pHPT, pituitary adenomas

Petr & Else, Semin Oncol 2016
When to evaluate NET for a genetic association?

- **Most NET are sporadic and do not require genetic evaluation**
  - No association of midgut or hindgut NET with genetic syndromes

- **Multiple Endocrine Neoplasia type 1**
  - Personal or family history of hyperparathyroidism or pituitary tumor
  - **Always foregut**
  - Every gastrinoma (up to 25% are MEN1 positive))

- **Von Hippel Lindau disease**
  - Personal or family history of other VHL manifestations
  - **Always non-functional**
  - **Always in the pancreas** – never first manifestation

- **Neurofibromatosis type 1**
  - Somatostatinoma, other manifestations of NF1

- **Tuberous sclerosis**
CASE 7

- 38 yo F with incidentally discovered liver metastasis and tumor in the ileum (primary)

- CT scan for abdominal discomfort

- Tumor – ileum (midgut)
  - Biopsy liver – well differentiated, low grade neuroendocrine neoplasm

- No family history of any cancers

- No other manifestations of VHL, MEN1, TSC, NF1

→ No genetic testing recommended
THYROID CANCER

Medullary thyroid cancer – Differentiated thyroid cancer
Medullary Thyroid Cancer

~7% of MTC patients have germline \( RET \) mutations

Some \( RET \) mutations specifically increase risk for MTC \( \rightarrow \) Familial Medullary Thyroid Cancer (FMTC)

Regardless of mutation and family history – everybody with pathogenic \( RET \) mutation should be screened for phochromocytoma

Everybody with MTC should have screening for pheochromocytoma or genetic testing prior to surgery to prevent complications due to catecholamine release during surgery

\( \rightarrow \) 

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Table 4. Relationship of Common \( RET \) Mutations to Risk of Aggressive MTC in MEN2A and MEN2B, and to the Incidence of PHEO, HPHT, CLA, and HD in MEN2A

<table>
<thead>
<tr>
<th>RET mutation (^a)</th>
<th>Exon</th>
<th>MTC risk level (^b)</th>
<th>Incidence of PHEO (^c)</th>
<th>Incidence of HPHT (^c)</th>
<th>CLA (^d)</th>
<th>HD (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A898F</td>
<td>12</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>S891A</td>
<td>15</td>
<td>MOD</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>R912P</td>
<td>16</td>
<td>MOD</td>
<td>-</td>
<td>-</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>M918T</td>
<td>16</td>
<td>HST</td>
<td>+++</td>
<td>-</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

ATA guidelines, Wells et al, Thyroid 2015
DIFFERENTIATED THYROID CANCER (DTC)

Is a genetic evaluation warranted?
CASE 9 – differentiated thyroid cancer

- 20-year-old female with DTC
  - with lump in her neck, found incidentally by her primary care physician.
  - Thyroid US: Right lobe: nodule - 1.9x1.7x1.4cm, hypoechoic, left lobe: several nodules, sub-cm size.
  - FNA concerning for papillary thyroid cancer.
  - She underwent surgery, which revealed differentiated thyroid cancer. A surgeon refers her for a genetic evaluation.
While unusual young age is often a feature suggestive of genetic predisposition, thyroid cancer at age 20 is not ‘that unusual’

CASE 9 – family history

(maternal: German, Norwegian
paternal: Irish, German, Native American (N) AJ (N) Consanguinity

- 83 Colon 163 DM HTN
- 78 several had cancer: breast, colon, lung and head/neck
- 7 MI
- 6 Bronchus, Lung 162 dx 70s (+) tob
- 5 stroke
- 4 Dementia/Alzheimer's
- 3 84 HTN CAD
- 2 79 HTN glaucoma partial thyroidectomy
- 1 80 seizures blindness late in life
- 0 60 emphysema cirrhosis

62 heart problems
55 heart problems
Other lymphomas 202.0 30s dx 30s AIDS
Unspecified site 199 unknown primary poorly differentiated adenocarcinoma

- 45 Thyroid 193
- 23
- 20
- 32.30
- 23.21
- 26
- 24
- 24
- 11
- 15.13
- 16 severe autism

- 33 Autism spectrum disorder high functioning
- 26
Although thyroid cancer has an increased familial risk, a single gene mutation is rare.

Possibly contribution from predisposition to Hashimoto thyroiditis.
Genetic predisposition to DTC

- **Cowden disease/PTEN – hamartoma tumor syndrome (PHTS)**
  - Macrocephaly, acral keratosis, oral mucosal cobblestoning, history of breast/uterine cancer, autism spectrum disorder
  - Typically goiter with follicular thyroid cancer (although papillary common too)

- **CHEK2 – related cancer syndrome**
  - Risk increase for breast cancer, colon cancer & thyroid cancer (~2-5 fold)

- **DICER1 syndrome**
  - Macrocephaly, goiter, family or personal history of Sertoli-Leydig cell tumor, Pleuropulmonary blastoma
  - Typically goiter, rarely papillary thyroid cancer

- **Familial Adenomatous Polyposis (FAP)**
  - Colon polyps, colon cancer, osteomas, supernumerary teeth, retinal hyperpigmentation
  - Thyroid – cribriform-morula variant of papillary thyroid cancer
DTC - summary

- Papillary thyroid cancer often occurs in familial pattern
- Rarely single gene defect – possibly contribution from familial Hashimoto disease
- Differential diagnosis
  - Cowden Disease, CHEK2, DICER1, FAP
- Careful family history, personal history and review of records is helpful!
- Rare histological diagnosis/cancer can be ONLY indication for genetic testing
- FAP – negative family history?
  - Attenuated form does not produce full syndromic phenotype
  - New mutation - ~30% in FAP
SUMMARY & CONCLUSION

Genetic work-up is more than simply sending off ‘blood for sequencing’
Pheochromocytoma
Paragnaglioma

Medullary thyroid cancer

Neuroendocrine tumor

Differentiated thyroid cancer

Adrenocortical carcinoma

Goiter

CMV

HPGL

SDHx

RCC, GIST, pituitary adenoma

other

TMEM127, MAX

RCC

HLRCC

FH

Leiomyomas, RCC, fibroids

MEN2 FMTC

RET

pHPT

NF1

NF1

Neurofibro-mas. Gliomas, MNST

VHL

VHL

RCC, ELST, hemangioblastomas

MEN1

MEN1

pHPT

PHTS

PTEN

Breast ca, uterine ca, hamartomas

other

CHEK2

Breast ca

DICER1

DICER1

PPB, pituitary blastomas, cystic nephromas, SLCT

DICER1 syndrome

FAP

APC

Colon ca, duodenal ca, desmoid

MSH2, MSH6, MSH1, PMS2, EPC AM

Colon ca, uterine ca, pancreatic ca, ovarian ca

LFS

TP53

Breast ca, brain ca, lung ca, sarcoma, leukemia

Lynch syndrome

BWS

IGF2 locus

Wilms tumor, hepatoblastoma

BWS

IGF2 locus

Wilms tumor, hepatoblastoma

Petr & Else, Semin Oncol 2016
Genetic work-up requires

- A detailed **personal history, physical exam and review of systems**
  - Unusual tumors, multiple tumors, skin findings etc.
- **Family history** – at least 4 generations
  - A negative family history does **NOT** exclude genetic testing
- **Detailed review of laboratory, pathology and genetic testing**
  - Small details might change the differential diagnosis
- **Work with patient and family as a team**
  - In Cancer Genetics we do NOT see single patients but rather families
- **Make use of a multidisciplinary approach**
  - Endocrine Tumor Genetics requires
    - Radiology, pathology, dermatology, oncology, genetics, genetic counselors
THANK YOU FOR YOUR ATTENTION!