Genetic Syndromes in Thyroid Cancer: Thyroid, Parathyroid, and Adrenal Themes

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Banner-University of Arizona Medical Center
University of Arizona – Phoenix Medical School
No conflicts of interest or financial relationships to disclose
Objectives

1. Describe the components of the consultation process for genetic syndrome evaluation and genetic testing

2. Review genetic syndromes which include thyroid cancer, both differentiated and medullary thyroid cancers

3. Understand the role of clinicians such as endocrinologists and surgeons in the evaluation of genetic syndromes
Genetics Consultation Process

- Alertness and recognition by clinician
- Genetic Counselor (CGC)/Medical Genetics (MD)
- Referral for consultation
  - 1-2 hour clinical assessment, including pedigree
  - Consent & sample collection
  - Follow-up and interpretation of results
- Commercial Testing Labs for Germline Mutation
Genetics Consultation “Fun Facts”

• Germline genetic testing: blood (lymphocytes), saliva (mucosal epithelium)

• Costs billed to insurance:
  $300-700 evaluation by CGC/MD
  $1500 commercial mutation testing
  differs by lab, insurer
  limit out-of-pocket to $100-250 (Invitae, Color)
Genetics Consultation “Fun Facts”

• Rarely test for a single gene (maybe RET)
• Panels with clinical association (max 42 gene)
• “Broad” panels when no target: 57-gene, 30-gene
• Turn-around time: 2-3 weeks usual, 5-12 days “stat”
• Re-requisitioning possible at no additional cost with some companies
Genetics Consultation “Fun Facts”

- ACMG (American College of Medical Genetics & Genomics)
- NSGC (National Society of Genetic Counselors)
- NCCN
- Endocrine-related professional society guidelines
- While breast cancer, pediatric congenital and metabolic disorders have specified guidelines, none exist exclusively for “endocrine” or “thyroid cancer” genetic testing
Why is JAX providing clinician training in genetic risk assessment?
Clinical Testing 2016: “Genetic Testing is a Quite Complicated Endeavor”

Testing is easily accessible for patients at risk but collaboration with a cancer genetic expert is important to guide testing strategy.

Baseline search for SDHB identifies >100 genes.
Genetics Consultation at BUMCP

Justin Gasparini, CGC
Marsha Grenger, Coordinator
Radiation Oncology @ 1111 E McDowell Rd
Phoenix, AZ 85006
(P) 602 839 6385
(F) 602 839 6000
Genetics Consultation Expertise

- Knowledge
- Family Pedigree
- Selection of Gene Panels & Commercial Labs
- Informed Consent
- Insurance Paperwork
- Follow-up and interpretation of results
- Time
Hereditary Cancer Syndromes

- Hereditary Breast & Ovarian Cancer Syndrome
- Hereditary Non-polyposis Colorectal Cancer Syndrome (Lynch Syndrome)
- Familial Adenomatous Polyposis (FAP)
- Cowden Syndrome (PHTS)
- Li-Fraumeni Syndrome
- Von Hippel-Lindau Disease
- Multiple Endocrine Neoplasias
## Hereditary Endocrine Syndromes

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<tr>
<th>Tumor Site</th>
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Hereditary Syndromes: *Thyroid Cancer*

- Hereditary Breast & Ovarian Cancer Syndrome
- *Hereditary Non-polyposis Colorectal Cancer Syndrome (Lynch Syndrome)*
- *Familial Adenomatous Polyposis (FAP)*
- *Cowden Syndrome*
- *Li-Fraumeni Syndrome*
- Von Hippel-Lindau Disease
- *Multiple Endocrine Neoplasias*
# Hereditary Thyroid Cancers, Syndromes & Associated Genes

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<td>Li-Fraumeni</td>
<td>TP53</td>
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Hereditary Medullary Thyroid Cancers

- MEN 2A, familial (FMTC), MEN 2B
- RET oncogene encodes tyrosine kinase receptor protein (chromosome 10)
- **Must test** all patients with MTC for RET
- **Must test** all kindred of RET+ patients
- Genotype-phenotype correlations
- FDA-approved targeted therapy: Vandetanib, Cabozantinib

Genotype–phenotype characterizations for specific RET codon mutations and associated risk level

codon 768
ATA risk level A
FMTC
MEN 2A
MTC most cases
Parathyroid rare
Pheo rare

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<th>Codon</th>
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ATA guidelines Kloos et al Thyroid 2009, Metzger et al Curr Opin Oncol 2014, ORION © 2013
Your Patient: “Alertness & Recognition”

A 65 year old man with right thyroid nodule incidentally detected by palpation on exam. No prior personal or family endocrine disease.
# Cytology Report

**Diagnosis**
*Right Thyroid: Atypia of undetermined significance (Bethesda Category III).*

**Microscopic Description:** The Papanicolaou stained ThinPrep slide shows a population of polygonal to spindly cells with round to ovoid to elongated nuclei, inconspicuous nucleoli and moderate eccentric granular cytoplasm. Binucleation and multinucleation noted. The cells are seen dispersed singly and in loose aggregates in a hemorrhagic background. The histopathologic sections of the aspirated material (cell block) show rare similar cells. Calcitonin and chromogranin are non-contributory due to scant cellularity/high background staining.

**Gross Description:** Received in cytolyt are 30 ml of dark clear fluid for cellular enhancement and cell block preparation, designated 1A. Received is a 1.5 ml molecular ThyroSeq tube. rm

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**PHOTOMICROGRAPH**

**Specimen 1: Right Thyroid**
Spindled cells with eccentric granular cytoplasm.

**Specimen 1: Right Thyroid**
Binucleation.
Your Patient: “Alertness & Recognition”

FINAL DIAGNOSIS:
THYROID, RIGHT, FINE NEEDLE ASPIRATE, OSS F16NY1-0220020/C16NY1-0215521, 10/28/2016, FROM CBLPATH, INC., MOLECULAR & GENOMIC PATHOLOGY LABORATORY TESTING:

Next Generation Sequencing Panel for Thyroid Cancer (ThyroSeq v2)

RESULTS:

A. HRAS mutation POSITIVE (p.Q61K, c.181C>A), see INTERPRETATION below.
B. Strong expression of the Calcitonin gene IDENTIFIED indicating medullary thyroid carcinoma profile.

INTERPRETATION:
HRAS mutation and strong overexpression of the Calcitonin gene were identified in this sample, which is diagnostic for medullary thyroid carcinoma (MTC). RAS mutations are found in sporadic MTC and MTC patients with RAS mutations have an intermediate risk for aggressive cancer. Correlation with cytological, imaging, and other clinical and laboratory data is recommended.

Calcitonin 7,568 pg/ml and CEA 179 ng/ml.

Surgical Histology:
4 cm right MTC, 0.7 cm left

Post-op calcitonin undetectable

RET mutation negative
Familial Non-Medullary Thyroid Cancers (FNMTTC)

- Well-differentiated thyroid cancer present in 2 or more 1st degree relatives
- No ‘syndromic’ or environmental risks
- 3-10% of all well-differentiated cancers will be FNMTTC
- 20% of screened family members will be diagnosed with thyroid cancer
- More aggressive variant
Familial Non-Medullary Thyroid Cancers (FNMTTC)

Screening offered to all 1st-degree family members, even without palpable disease. In this setting, nodules >5 mm warrant FNA.

Exact timing for screening is debatable: at age 10 years....at age 20 years.... ....10 years earlier than youngest age of diagnosis in the family.

Your Patient

A 30 year old woman has had two prior benign FNA’s. At recent visit home, her mom advised her to follow-up again because her “goiter” looks bigger. Both mom and dad have been treated for PTC. Ultrasound is shown.
Dear Dr. Milas,

Thank you for your interest in the familial thyroid cancer study at the National Cancer Institute. I have listed a few documents we will need from your affected family members in order to determine their eligibility for our study. If interested, they may fax or mail these records to the address and fax # listed below.

In order to qualify for the study, we will need at least two first degree relatives in the family who have or have had thyroid cancer to participate. In addition to the two affected family members, unaffected first degree family members may also participate (especially those interested in routine screening for thyroid cancer).

Roxanne Merkel, RN, BSN
Research Nurse Specialist
Endocrine Oncology Branch
National Cancer Institute
Center for Cancer Research
National Institutes of Health
10 Center Drive bldg 10, Room 5B40
Bethesda, Maryland 20892

Office: (301) 402-4395
Fax: (301) 451-5580
Roxanne.merkel@nih.gov
**FNMTMC**: Several candidate chromosomal loci (1q21, 6q22, 8p23.1-p22, and 8q24) and susceptibility genes (*SRGAP1*, *NKX2-1*, and *FOXE1*), suggesting that it is a polygenic familial cancer syndrome.

Kebebew et al: ATA 2015
Results of Screening in Familial Non-Medullary Thyroid Cancer.


Abstract

**BACKGROUND:** Although a family history of thyroid cancer is one of the main risk factors for thyroid cancer, the benefit of screening individuals with a family history of thyroid cancer is not known.

**METHODS:** A prospective cohort study was performed with yearly screening using neck ultrasound and fine-needle aspiration biopsy of thyroid nodule(s) >0.5 cm in at-risk individuals whose relatives were diagnosed with familial non-medullary thyroid cancer (FNMT). The eligibility criteria were the presence of thyroid cancer in two or more first-degree relatives and being older than seven years of age. Twenty-five kindred were enrolled in the study (12 families with two members affected, and 13 with three or more members affected at enrollment).

**RESULTS:** Thyroid cancer was detected by screening in 4.6% (2/43) of at-risk individuals from families with two members affected, and in 22.7% (15/66) of at-risk members from families with three or more patients affected (p = 0.01). FNMT detected by screening was characterized by a smaller tumor size (0.7 ± 0.5 cm vs. 1.5 ± 1.1 cm; p = 0.006), a lower rate of central neck lymph node metastases (17.6% vs. 51.1%; p = 0.02), less extensive surgery (hemithyroidectomy 23.5% vs. 0%; p = 0.002), and a lower rate of radioactive iodine therapy (23.5% vs. 79%; p < 0.001) compared to those affected at enrollment.

**CONCLUSIONS:** Screening of at-risk family members resulted in earlier detection of low-risk FNMT and was associated with a less aggressive initial treatment. Screening with thyroid ultrasound should be considered in kindred with three or more family members affected by FNMT. Since active screening might be associated with the risk of overtreatment, it should be implemented with caution, specifically in elderly individuals.
Familial Adenomatous Polyposis

- 3-11% rate of PTC among FAP patients
- Screening thyroid ultrasound
- Screening colonoscopy
- Optimal monitoring protocol for annual thyroid evaluation in FAP to be defined

Cribriform-Morular Variant of Papillary Thyroid Cancer

First named in 1994
More common in women
44% associated with FAP
Thyroid Cancer and FAP Genotype / Phenotype

Thyroid Cancer

CHRPE

Desmoids

Polyposis

Exon

Codon

Your Patient: 59 year old woman referred for primary hyperparathyroidism

- Incidental hypercalcemia on labs
- Fatigue and kidney stones
- No known thyroid disease
- History: uterine cancer
- Family history: hypothyroidism
- Physical examination without palpable neck mass or thyromegaly
Your Patient: 59 year old woman referred for primary hyperparathyroidism
55 year old man
PTC
Rx with 50,000U
Ergocalciferol
Calcium 13
iPTH <10
1,25 Vit D 98

PTHrp 78
(ref range 14-27 pg/ml)
Cowden Syndrome (CS)

- Characterized by benign hamartomas
- Increased risk of malignant transformation
- Dominantly inherited germline mutation
  - tumor suppressor *PTEN*
  - *PTEN* mut+ is ultimate diagnostic confirmation

Breast
Thyroid
Kidney
Intestine
Endometrium
PTEN Hamartoma Tumor Syndrome (PHTS)

BRRS
Bannayan-Riley-Ruvalcaba Syndrome

CS
Cowden syndrome

PS
Proteus & Proteus-like syndrome
PTEN: “Phosphatase and Tensin Homolog”
tumor suppressor gene on chromosome 10
PTEN
SDH (B-D)
KLLN
(RASAL1)

Charis Eng MD, PhD
Genomic Medicine Institute
Cleveland Clinic

## International Cowden Consortium (ICC) Operational Criteria for Diagnosis

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<th>Major</th>
<th>Minor</th>
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<td>Breast cancer</td>
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<td>Acral keratoses</td>
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<td>Renal cell carcinoma</td>
</tr>
</tbody>
</table>

*PTEN mut+* have AV malformations

**International Cowden Consortium (ICC) Operational Criteria for Diagnosis**

<table>
<thead>
<tr>
<th>Pathognomonic</th>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous lesions</td>
<td>Breast cancer</td>
<td>Fibrocystic breast disease</td>
</tr>
<tr>
<td>Trichilemmomas</td>
<td>Endometrial cancer</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>Acral keratoses</td>
<td>Thyroid cancer</td>
<td>Benign thyroid lesions</td>
</tr>
<tr>
<td>Papillomas</td>
<td>Macrocephaly</td>
<td>GI hamartomas</td>
</tr>
<tr>
<td>Mucosal lesions</td>
<td></td>
<td>Lipomas</td>
</tr>
<tr>
<td>Adult Lhermitte-Duclos disease</td>
<td></td>
<td>Fibromas</td>
</tr>
<tr>
<td><strong>2 Major but one must be macrocephaly or LDD</strong></td>
<td></td>
<td>GU tumors or malformation</td>
</tr>
<tr>
<td><strong>1 Major + 3 Minor</strong></td>
<td></td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td><strong>4 Minor</strong></td>
<td></td>
<td>Uterine fibroids</td>
</tr>
</tbody>
</table>
Cowden’s Disease
A Possible New Symptom Complex with Multiple System Involvement
Kenneth M. Lloyd, II, M.D., and Macey Dennis, M.D.
Youngstown, Ohio

In recent years an accelerated interest has been directed toward a better understanding of the rare, familial, developmental diseases. The purpose of this communication is to define an unusual symptom complex which previously has not been described. Because of the multiplicity of findings, and the ill-defined classification for this disease, it shall be referred to as “Cowden’s disease,” the family name of the propositus. The clinical findings include: an adenoid facies; hypoplasia of the mandible and maxilla; a high-arch palate; hypoplasia of the soft palate and uvula; microstomia; papillomatosis of the lips and oral pharynx; scrotal tongue; multiple thyroid adenomas; bilateral virginal hypertrophy of the breasts with advanced fibrocystic disease and early malignant degeneration; pectus excavatum; scoliosis; space-occupying lesions in the liver and bone; abnormalities of the central nervous system; and a history of forme fruste of the syndrome in other members of the family.

Case Report

A 20-year-old female was admitted to the Youngstown Hospital Association on March 14, 1962, because of a lesion on her right breast.

The patient had enjoyed good health until 2 months prior to admission when she developed a small, draining, ulcerative area on the inferior lateral surface of the right breast following minor trauma. This failed to heal in the subsequent months.

The patient had had difficulty with her breasts since her menarche at the age of 12 years, when the breasts had rapidly and progressively enlarged to an abnormal degree with the development of multiple, occasionally tender nodules of varying size. The skin overlying the breasts became increasingly discolored with frequent ulceration and drainage. Healing of these ulcerations was always retarded, but usually complete within a few weeks. A biopsy of a nodule in the left breast was done at the age of 16, and it was reported as showing fibrocystic disease of the breast. Bilateral simple mastectomy was recommended at the time but was refused. Hormone therapy was of no therapeutically beneficial and was discontinued 2 years prior to the present admission.

Past History

The patient had had her thymus irradiated at the age of 2. She had had all her teeth extracted at the age of 16 because of advanced decay and malocclusion.

Family History

The patient’s mother, age 55, has a large goiter and a marked emotional stutter. A sister, who died accidentally at the age of 20, had a high-arched palate, difficulty with articulation, a pectus excavatum, a large thyroid tumor, mild mental retardation, and numerous small skin tumors of an unknown nature. Her remaining sibling, a 24-year-old female, appears to be normal with none of the physical characteristics of her sisters. Two maternal aunts died of carcinoma of the breast. One maternal aunt died in a state mental institution at the age of 35 of post-encephalitic parkinsonism. She was described as having had

Received September 28, 1962: accepted for publication October 3, 1962.
From the Department of Medicine, Youngstown Hospital Association, Youngstown, Ohio.
Requests for reprints should be addressed to Kenneth M. Lloyd, II, M.D., Henry Ford Hospital, Box 166, Detroit 2, Michigan.
Trichilemmoma
Papillomas
Acral keratoses
Macrocephaly

Men: 58.0 cm
Women: 57.3 cm

Occipitofrontal circumference >2 standard deviations over the population mean

97.5th percentile
“The Eye Cannot See What The Mind Does Not Know”

Phillip Zaret, M.D.
Risk Calculator for Estimating a Patient’s Risk for PTEN Mutation

Welcome to the Cleveland Clinic risk assessment tool for estimation of a person’s risk of having a PTEN mutation. Clinical syndromes often associated with this gene mutation include Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS). This tool was designed for use by healthcare professionals. If you are not a healthcare professional, you are encouraged to discuss the results with your doctor or a genetics healthcare provider. Detailed information on the Cleveland Clinic adult score and pediatric criteria is available.

Tan et al Am J Hum Gen 2011
Should patients with Cowden syndrome undergo prophylactic thyroidectomy?

Mira Milas, MD, Jessica Mester, MS, CGC, Rosemarie Metzger, MD, MPH, Joyce Shin, MD, Jamie Mitchell, MD, Eren Berber, MD, Allan E. Siperstein, MD, and Charis Eng, MD, PhD, Portland, OR, and Cleveland, OH

(Surgery 2012;152:1201-10.)

**DIAGNOSES**

Age range 4-51 yrs (median 16 yrs)

- **Goiter** 56%
- **Thyroiditis or Both** 31%
- **Normal** 13%
- **Thyroid Cancer**

In *all* patients ≥ 13 yrs old
Of CS-associated cancers, thyroid cancer has the earliest onset and 2nd highest lifetime risk (35%).

Tan et al Clin Cancer Res 2012; study population was PTEN mut+
Clinical Implications for Germline \textit{PTEN} Spectrum Disorders

Joanne Ngeow, MBBS, MRCP, MPH\textsuperscript{a,b}, Kaitlin Sesock, MSc\textsuperscript{b,c,d}, Charis Eng, MD, PhD\textsuperscript{b,c,d,e,f,*}

Table 2
Cancer risks and screening recommendations for \textit{PTEN} hamartoma tumor syndrome

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk (%)</th>
<th>Lifetime Risk with \textit{PTEN} Hamartoma Tumor Syndrome (%)</th>
<th>Age at Presentation</th>
<th>Screening Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>12</td>
<td>\sim 85</td>
<td>40s</td>
<td>Starting at age 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Annual mammogram</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Consider MRI for patients with dense breasts</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td>35</td>
<td>30s–40s</td>
<td>Baseline ultrasound</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>examination at diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Annual ultrasound and clinical examination</td>
</tr>
<tr>
<td>Endometrial</td>
<td>2.6</td>
<td>28</td>
<td>40s–50s</td>
<td>Starting at age 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Annual endometrial biopsy or transvaginal ultrasound examination</td>
</tr>
<tr>
<td>Renal cell</td>
<td>1.6</td>
<td>34</td>
<td>50s</td>
<td>Starting at age 40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Renal imaging every 2 y</td>
</tr>
<tr>
<td>Colon</td>
<td>5</td>
<td>9</td>
<td>40s</td>
<td>Starting at age 40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Colonoscopy every 2 y</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2</td>
<td>6</td>
<td>40s</td>
<td>Annual dermatologic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>examination</td>
</tr>
</tbody>
</table>

Clinical Evaluation of your Patient

Relevant, thorough, and thoughtful history and examination

http://www.lerner.ccf.org/gmi/ccscore/

Risk Calculator for Estimating a Patient’s Risk for PTEN Mutation
Cowden Syndrome: Summary

- Higher than anticipated prevalence
- Screening for Cowden Syndrome is not difficult or invasive (“dot phrase” in Epic and measure head circumference)
- Pattern recognition is key
- Implications of Screening
  - Thoughtful patient counseling
  - Early genetics referral
  - Cancer preventative care
  - Ongoing surveillance
The Genomic Medicine Paradigm Shift

MIRA MILAS, MD*
Department of Surgery, Division of Surgical Oncology, Oregon Health and Science University (OHSU), Portland, Oregon

Genomic medicine is here to stay. The timeline it took to get here is quite impressive, when viewed in broad milestones of accomplishments, from discovery of the DNA double helix in the 1950s, recognition of hereditary cancer syndromes in the 1960s, basic molecular biology techniques to study DNA and RNA in the 1970s and 1980s, the Human Genome Project that spanned 1990–2003, and, in the last decade, to genomic profiling of cancer [1,2]. The extraordinary research of this last decade was translated into effective new clinical therapies more rapidly than ever before, especially in the field of oncology. In 2014, the paradigm shift thus refers to the adaptation that will be required of clinical medicine to usher in the future, when thinking about and taking care of a patient becomes inseparable from genetic information.

We are at that threshold now, and cancer is a great case in point. Both in scientific and lay venues, phrases that try to capture the new language of the paradigm shift abound: “cancer is a disease of the genome” [3], “personalized care,” “individual cancer profile,” “actionable molecular cytology” [4], “precision cancer treatment” [5], and the “advent of precision medicine” [6]. In many ways, “personalized care” in its fundamental meaning takes place at every physician–patient encounter. It is a person, not his or her disease or genome, sitting management and perspectives for future therapies. The content was intended to be comprehensive, relevant, and innovative. Thus, for example, the first section addresses the infrastructure needed to build a personalized medicine program in cancer care, the communication that can facilitate a cancer patient’s understanding and acceptance of what is and what is not possible with genomic medicine, and ethical principles that help surgical oncologists navigate decisions based on genetic data. None of these topics receive enough attention either in published literature or as part of professional society meetings. All are meaningful if personalized, genomic-based medical practice is truly to thrive in the next phase of healthcare evolution nationally and worldwide.

In oncology, it is also clear that genomic medicine stands to impact practice in three specific ways: facilitating more precise diagnosis; refining cancer prognosis and expected outcomes; and targeting therapeutics to be most effective at the level of an individual patient, instead of an individual malignancy. This issue of the Journal summarizes our current state of knowledge in these three areas and then elaborates on how personalized medical care has played out in some of the most commonly encountered fields of surgical oncology, such as endocrine surgery (thyroid cancer), breast oncology, colorectal cancer...
Inherited cancer syndromes and the thyroid: an update

Rosemarie Metzger and Mira Milas

Purpose of review
Knowledge related to hereditary thyroid cancer syndromes has expanded enormously. This review

ultrasound screening in these populations. It has also informed the appropriate extent of thyroid surgery and the circumstances in which prophylactic thyroidectomy is reasonable to consider as part of hereditary syndromes other than MEN2.

Summary
Recognition and early diagnosis of these syndromes allows for comprehensive medical care and may improve thyroid cancer-related outcomes. Ultrasound-based screening programs to detect thyroid disease are advised for patients and family members with hereditary cancer syndromes.

Keywords
Cowden syndrome, familial adenomatous polyposis, familial nonmedullary thyroid cancer, medullary thyroid cancer, multiple endocrine neoplasia

Rose: “Dr. Milas, I’ve invented a new screening tool for you!”
Mira: “I’m very interested to hear about it, Dr. Metzger”
Rose: “We just ask the patient……were you born?….and if they say, yes….we advise referral to genetics!”
Summary

1. **Consideration** of the presence of hereditary syndromes should be part of initial clinical visit. Must **screen** all MTC, pheo/paragangliomas.

2. **Genotype-phenotype risk stratification** by RET gene mutation and new medical therapies are available for patients with hereditary MTC.
Summary

3. Two or more first-degree relatives with papillary thyroid cancer raise question of familial and more aggressive thyroid cancer

3. Lifetime cancer risks, including for thyroid cancer, have been defined for individuals with PTEN gene mutations
Summary

5. **Ultrasound-based screening** for thyroid disease is part of evaluation of patients with FAP

Cowden Syndrome

*FNMT C if ≥3 family members*

*“Alertness and Recognition” that something is not quite usual*
Thank you
Supplementary material related to pheochromocytoma/paraganglioma
Paraganglioma
Pheochromocytoma

**Chemodectoma**

Extra-adrenal pheochromocytoma

Non-chromaffin paraganglioma

Glomus tumor

Carotid body tumor

**Chromaffinoma**

Para-aortic paraganglioma, etc....
Anatomic Location of Pheochromocytomas and Paragangliomas

Sympathetic paravertebral ganglia: thorax, abdomen, pelvis

Parasympathetic vagus, glossopharyngeal, skull base, “glomus tumors”

Nonfunctional
32 yr old man with VHL
Varied Presentations of Pheochromocytomas and Paragangliomas

- 40% Classical Triad: Headaches, Palpitations, Sweating
- 40% Incidental Finding
- 10% “Pheo Crisis”
- 10% Genetic Screening

NANETS Pancreas 2010
AAES 2015 www.endocrinediseases.org
DDX: Hereditary Pheochromocytomas and Paragangliomas (PC/PGL)

- Multiple Endocrine Neoplasia Type 2
- Von Hippel-Lindau Syndrome
- Hereditary Pheochromocytoma/Paraganglioma Syndrome
- Neurofibromatosis Type 1
- Carney Triad*(1977: PC/PGL, GIST, pulmonary chondroma/hamartoma)

*not the same as the endocrine Carney Complex with cardiac findings
True or False?

“Every patient diagnosed with pheochromocytoma or paraganglioma needs genetic evaluation”
Genetic Risk Assessment: Red Flags

• Young age of onset
• Bilateral or multifocal tumors
• Extra-adrenal tumors
• Malignant disease
• Positive family history

Genetic Risk Assessment:
~25% associated germline mutation

- Which genes? RET, VHL, SDH, NF1
- What pattern?

<table>
<thead>
<tr>
<th>Gene</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHL</td>
<td>9-11%</td>
</tr>
<tr>
<td>RET</td>
<td>5%</td>
</tr>
<tr>
<td>SDHB</td>
<td>4-5%</td>
</tr>
<tr>
<td>SDHD</td>
<td>4-5%</td>
</tr>
<tr>
<td>NF1</td>
<td>2%</td>
</tr>
</tbody>
</table>

Neumann et al. *NEJM* 2002; 346:1459
European Network for the Study of Adrenal Tumours (ENS@T)
Pheochromocytoma working group Gimenez-Roqueplo et al. *Clin Endocrinol* 2006; 65:699
## Mutation Risk Based on Age of Tumor Onset

<table>
<thead>
<tr>
<th></th>
<th>0-10y (n = 10)</th>
<th>11-20y (n = 47)</th>
<th>21-30y (n = 31)</th>
<th>31-40y (n = 44)</th>
<th>41-50y (n = 56)</th>
<th>&gt;50y (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VHL</strong></td>
<td>6 (60%)</td>
<td>17 (36%)</td>
<td>2 (6%)</td>
<td>3 (7%)</td>
<td>2 (4%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>RET</strong></td>
<td>-</td>
<td>-</td>
<td>4 (13%)</td>
<td>4 (9%)</td>
<td>5 (9%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>SDHD</strong></td>
<td>1 (10%)</td>
<td>2 (4%)</td>
<td>3 (10%)</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>SDHB</strong></td>
<td>-</td>
<td>5 (11%)</td>
<td>3 (10%)</td>
<td>2 (5%)</td>
<td>2 (4%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7 (70%)</td>
<td>24 (51%)</td>
<td>12 (39%)</td>
<td>12 (27%)</td>
<td>10 (18%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Tumor onset <20 years is associated with **VHL**

*Slide courtesy of T. Rich and E. Edelman*

Neumann et al. *NEJM* 2002; 346:1459
### Mutation Risk Based on Tumor Location

<table>
<thead>
<tr>
<th></th>
<th>VHL ($n = 30$)</th>
<th>RET ($n = 13$)</th>
<th>SDHD ($n = 11$)</th>
<th>SDHB ($n = 12$)</th>
<th>Hereditary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal</td>
<td>26</td>
<td>13</td>
<td>7</td>
<td>6</td>
<td>52/241 ($22%$)</td>
</tr>
<tr>
<td>Extra-adrenal</td>
<td>4 ($13%$)</td>
<td>-</td>
<td>4 ($36%$)</td>
<td>6 ($50%$)</td>
<td>14/30 ($47%$)</td>
</tr>
</tbody>
</table>

Extra-adrenal PGL is NOT associated with RET

*Slide courtesy of T. Rich and E. Edelman*
*Neumann et al. NEJM 2002; 346:1459*
## Mutation Risk Based on Focality

<table>
<thead>
<tr>
<th></th>
<th>VHL (n = 30)</th>
<th>RET (n = 13)</th>
<th>SDHD (n = 11)</th>
<th>SDHB (n = 12)</th>
<th>% Hereditary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unifocal</strong></td>
<td>18 (18%)</td>
<td>8 (38%)</td>
<td>7 (36%)</td>
<td>12 (40%)</td>
<td>45/245 (18%)</td>
</tr>
<tr>
<td><strong>Multifocal</strong></td>
<td>12 (40%)</td>
<td>5 (38%)</td>
<td>4 (36%)</td>
<td>-</td>
<td>21/26 (81%)</td>
</tr>
</tbody>
</table>

*SDHB has a low risk of multifocal tumors*

*Slide courtesy of T. Rich and E. Edelman*

Neumann et al. *NEJM* 2002; 346:1459
European Network Testing Protocol (Clin Endo 2006)

PC/Functional PGL

- Physical exam to r/o NF1
- Clinical features

- FamHx, “syndromic”
- Age < 35 yrs
- Extra-adrenal or multiple
- Both glands
- Cancer
- Sporadic

1st Tier testing

<table>
<thead>
<tr>
<th>RET/VHL/SDHB/SDHD</th>
<th>RET VHL</th>
<th>VHL SDHB SDHD</th>
<th>RET VHL</th>
<th>SDHB</th>
<th>VHL SDHB SDHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

2nd Tier testing

<table>
<thead>
<tr>
<th>SDHB SDHD</th>
<th>SDHB SDHD</th>
<th>VHL SDHD</th>
</tr>
</thead>
</table>

Cleveland Clinic
Genomic Medicine Institute