Partnering with Geneticists in the Care of Your Patients with Familial Cancer Syndromes of the Head and Neck

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How Can Geneticists Help?

- Differential diagnosis of Familial Cancer Syndromes in families with multiple tumors
- Obtaining detailed family histories and explaining the role of gene testing
- Arranging appropriate and complete testing
- Explaining results to family and referring physicians
- Arranging for further management/surveillance
- Performing family outreach, counseling and testing to satisfy “Duty to Warn”

Family History

Is more than “Anyone else in the family have what you have?”

Is crucial for deciding if a syndrome is traveling in the family and formulating the differential diagnosis

Identifies who else is at risk in the family

Identifies the best person to test when your patient is an asymptomatic but “at-risk” family member

Discuss Three Conditions

Multiple Endocrine Neoplasia 2
Multiple Endocrine Neoplasia 1
Hereditary Paraganglioma
MEN2

MEN 2A
Medullary thyroid carcinoma 95%
Pheochromocytoma 50%
Parathyroid hyperplasia or adenoma 25-30%

MEN 2B
Medullary thyroid carcinoma 100%
Pheochromocytoma 50%
Parathyroid hyperplasia or adenoma rare
Mucosal neuromas of the lips and tongue
Ganglioneuromatosis of the gastrointestinal tract

Familial medullary thyroid carcinoma (FMTC)
Medullary thyroid carcinoma 100%

Genetics

Inheritance: Autosomal Dominant

Gene(s): RET gene is the only gene involved

RET is a receptor tyrosine kinase that is activated to phosphorylate proteins upon binding of growth factors to receptors on the outside of cells

Mutations are all amino acid changes (missense) in specific portions of the gene that cause a gain of function making the RET gene product is inappropriately active.
Genotype-Phenotype Correlation

MA, majority
MI, minority
R, rare

MEN2 - Utility of Gene Testing

Different specific genotypes are partially predictive of the clinical picture - Helps in the management of individual patient
Genotype allows testing and presymptomatic diagnosis and management of other family members.

MEN2: Who needs gene testing?

Every patient with clinical MEN2
Every patient with familial pheochromoctoma
Every patient under ~45y with nonfamilial pheochromoctoma
Every patient with bilateral pheochromoctoma
Every patient with MTC (yield of RET mutations ~7%)

MEN1

Parathyroid tumors 90%
Pituitary tumors: usually prolactinoma Common (10-16%)
Well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract
Gastrinoma – Zollinger-Ellison 40%
Insulinoma - 10%
Glucagonoma 2%
VIP-oma: 2%

>50% of MEN1 pancreatic tumors are NON-secreting
MEN1 (cont.)

10% Carcinoid: Usually bronchial/thymic and NOT mid or hindgut

20-40% Primary adrenocortical tumors: hypercortisolism or hyperaldosteronism

Non-endocrine tumors: facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas, and leiomyomas

Genetics

Inheritance: Autosomal Dominant

Gene(s): MEN1 plus a few others (rare)

>1300 MEN1 mutations are known that terminate the protein or cause loss of function. There is no genotype-phenotype correlation

1-4% of mutations are large deletions that are missed by standard sequencing

Prevalence: ~1/40,000

Polymerase Chain Reaction - PCR

Deletions or Duplications are missed by Sequencing
**MEN1 - Utility of Gene Testing**

- Identifying any mutation is partially predictive of the clinical picture - Helps in the management of individual patient

- Genotype allows testing and presymptomatic diagnosis and management of other family members.

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**MEN1 Who needs gene testing?**

- Individuals with at least one typical MEN1-type tumour and at least one of the following:
  1. a first-degree relative with a major endocrine tumor;
  2. an age of onset less than 30 yr; and/or
  3. multiple pancreatic tumors or multiglandular parathyroid hyperplasia

- Patients with familial primary hyperparathyroidism

- Patients with clinical picture of MEN1, familial or not

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**Hereditary Paraganglioma-Pheochromocytoma syndromes (HPGL/PCC)**

- Hereditary Paraganglioma-Pheochromocytoma syndromes (HPGL/PCC) are caused by mutations in four subunits of succinate dehydrogenase
  - SDHB (PGL4) - predisposes to abdominal, malignant PGL
  - SDHC (PGL3) - predisposes to head and neck PGL (rare)
  - SDHD (PGL1) - predisposes to head and neck PGL
  - SDH5 (PGL2) - predisposes to head and neck PGL (rare)
  - SDHA (PGL5) - rare

- Paraganglioma is also a component of
  - Von Hippel-Lindau syndrome (VHL)
  - Multiple Endocrine Neoplasia Type 2 (MEN2 – RET gene) –
Genetics

Inheritance: Autosomal Dominant

Gene(s): SDHB, SDHD, SDHC, SDH5, SDHA

Hundreds of mutations are known that terminate the protein or cause loss of function. Certain ethnic groups may have a few very frequent mutations.

There is no correlation between location or type of mutation in a gene and clinical picture.

There IS strong correlation between which gene is mutated (SDHB versus SDHD) and the relative frequency of head and neck versus extrasympathetic paragangliomas.

Prevalence: Similar to MEN2 but not really known

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Proportion of Hereditary PGL</th>
<th>Mutations</th>
<th>Frequency of mutation detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDHD</td>
<td>~50% Head and neck</td>
<td>Sequence variants</td>
<td>70-100%</td>
</tr>
<tr>
<td></td>
<td>~13% Extra-adrenal sympathetic PGL</td>
<td>Partial deletions</td>
<td>?</td>
</tr>
<tr>
<td>SDHB</td>
<td>20% Head and neck</td>
<td>Sequence variants</td>
<td>70-90%</td>
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<td></td>
<td>24% Extra-adrenal sympathetic PGL</td>
<td>Partial deletions</td>
<td>~10%</td>
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<tr>
<td>SDHC</td>
<td>4% Head and neck</td>
<td>Sequence variants</td>
<td>70-100%</td>
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<tr>
<td></td>
<td>Partial deletions</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>SDH5</td>
<td>Rare</td>
<td>Sequence variants</td>
<td>?</td>
</tr>
<tr>
<td>SDHA</td>
<td>Very Rare</td>
<td>Sequence variants</td>
<td>?</td>
</tr>
</tbody>
</table>

SDHD Shows Maternal Imprinting

- The maternal copy of SDHD is normally inactive.
- Mutation in SDHD will only be manifest in a child if it is inherited from the father.

SDHD Paraganglioma Syndrome with Maternal Imprinting
SDH gene mutations have also been reported to be associated with

- GIST (Carney-Stratakis dyad)
- clear cell RCC
- papillary thyroid carcinoma

PGL: Who should be tested?

- Prevalence of mutations (SDHB/C/D/5/A among apparently isolated paraganglioma cases is ~8%

- Highest mutation prevalence in individuals with
  - Multiple, including bilateral, tumors
  - Multifocal with multiple synchronous or metachronous tumors
  - Recurrent tumors
  - Early onset (i.e., age <40 years)
  - malignant sympathetic paraganglioma, esp., extra-adrenal
  - A family history of paraganglioma or other syndromic features

Testing issues

- About 70% of familial cases have a mutation in SDHB, SDHD (more common) or SDHC, SDH5 (rare) detectable by sequencing
- Sequencing identifies >70% of mutations in these genes
- Large deletions also exist and can be detected by other methods
- Variants of uncertain significance can be found

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Duty to Warn in Genetics

Tarasoff v. Regents of the University of California, a woman was killed by her stalker after he had confided his intention of killing her to his therapist. The court concluded that a physician or therapist has a duty to warn if:
- he or she has a special relationship with either the person who may cause the harm
- the person at risk is identifiable, and
- the harm is foreseeable and serious

Duty to Warn 2 (Florida)

In Pate v. Threlkel, a woman received treatment for medullary thyroid carcinoma. Three years later, her adult daughter was diagnosed with the same type of cancer. The daughter sued the doctor who had treated her mother, arguing that if she had known earlier about the genetic risk of thyroid cancer, she could have taken preventive action and her condition would have been avoided or detected at an earlier and curable stage.

The court agreed with her argument that the physician had a duty to warn of the risk to his patient’s children, but concluded that this duty was satisfied by warning the patient about the risk to her relatives.

Duty to Warn 3 (New Jersey)

In Safer v. Estate of Pack, a woman was diagnosed with colorectal cancer due to familial adenomatous polyposis. She sued the estate of the physician who treated her father for the same condition 30 years earlier, alleging a violation of duty on the part of this physician because he failed to warn her of her own health risks.

She argued that if she had known about her risk of having this condition, her cancer could have been detected at an early and curable stage through regular surveillance.

Safer v. Estate of Pack court found that the physician’s duty to warn may not be satisfied in all cases by informing the patient of the risk to his relatives. The court asserted that the physician must take reasonable steps to guarantee that immediate family members are warned.

Take Home Message:

Be on the Look-Out for Hereditary Cancer Syndromes

- Unusually early age at onset
- Multiple or bilateral tumors
- Recurrent independent primary tumors
- Kinds of tumors
- Family history - be thorough!
- Remember the DUTY TO WARN

Consider referring to the Cancer Risk Program when a patient and his family need counseling and testing