Are we ready to predict who will get what kind of cancer?

Endocrine

JE Gosnell MD
Assoc Prof of Clinical Surgery

3/6/15

Genetics in endocrine disease

- Thyroid
  - Papillary, follicular and medullary thyroid cancer
  - Parathyroid
  - Hyperparathyroidism, cancer
  - Adrenal
  - Pheochromocytoma, paraganglioma
- Pancreas
  - PNET

Genetic markers:
- RET
- RET/PTC
- BRAF
- RAS
- HRTP2
- CASR
- SDH
- VHL
- NFI
- TP53
- IGF2 gene

Thyroid cancer

- Identified risk factors: family history and radiation exposure
- Historical factors: local symptoms in the neck (pain, hoarseness, dyspnea). Other endocrine disorders (!)
- Signs: fixed mass, adenopathy
- US characteristics
- Biopsy: cytology, gene expression
- Germline and Somatic mutations: RET, RET/PTC mutations

Nothing to disclose

3/6/15

3/7/2015
Ideal disease for genetic testing

- Diseases that are autosomal dominant with high penetrance
- Diseases for which there are prophylactic treatment when discovered early
- Diseases for which there is an accurate screening test

Prophylactic surgery


1) The genetic mutation causing the hereditary malignancy must have a very high penetrance and be expressed regardless of environmental factors;
2) There must be a highly reliable test to identify patients who have inherited the mutated gene;
3) The organ must be removed with minimal morbidity and virtually no mortality;
4) There must be a suitable replacement for the function of the removed organ; and
5) There must be a reliable method of determining over time that the patient has been cured by “prophylactic surgery”

Medullary thyroid cancer

- Specific genetic test-direct DNA analysis
- Essentially 100% of affected patients develop disease
- Age-related progression
- Genotype-phenotype correlation
- Prophylactic/preclinical surgery for cure

1959: Hazard, Hawk and Crile
“Medullary (solid) carcinoma of the Thyroid: clinico pathological entity”

(J Clin Endocrinol Metab;19:152-161)
Medullary thyroid cancer

1966: Descriptions of parafollicular C cells
Williams et al.

(*J Clin Pathology 1966;9:103-13*)

Calcitonin is a sensitive and specific tumor marker (purified by Copp and Cheney 1962, but only later attributed to C-cells)

1961: John H. Sipple, MD
American Pulmonologist
Johns Hopkins, Syracuse

The Association of Pheochromocytoma with Carcinoma of the Thyroid Gland

*J H. Sipple, M.D.*
Syracuse, New York

(www.whonamedit.com)

1965-6: ED Williams and DJ Pollock
first description of MEN 2b as a syndrome

(*J Path Bact;1966*)

1990s: AD, chromosome 10
1993: RET proto-oncogene

(Mulligan et al, 1993)
(Donis-Keller et al, 1993)

Up to 10% of apparent "sporadic" cases of MTC will be found to have RET mutation

Medullary thyroid cancer

1990s: RET proto-oncogene encodes for transmembrane tyrosine kinase

Importance of early diagnosis:

Wells et al.
192 patients
“aggressive screening with Pentagastrin-stimulated Calcitonin levels”

- correlation of Ct levels with LN involvement
- better prognosis when patients treated earlier, with disease confined to the thyroid

(Ann Surg 1982;95:595)

Surgical treatment of a disease based on a genetic test

Medullary thyroid cancer: 804 kindred

Figure 1 Family 1
Genotype-phenotype correlation

Prophylactic thyroidectomy in 22 pts in MEN-2a family (c804Y)

normal thyroid glands in 2 pts, no patients had metastases in central lymph nodes, pheochromocytoma in 1 pt

(Gosnell, ANZJS 2006)

MTC, CCH= 15 pts
CCH= 5 pts
HPT= 5 pts

Genetics in thyroid carcinogenesis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Tumor Histology</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET (point mutation)</td>
<td>MTC (hereditary)</td>
<td>Germinal: 75%</td>
<td>[1-3]</td>
</tr>
<tr>
<td></td>
<td>MTC (sporadic)</td>
<td>Sporadic: 5%</td>
<td>[4]</td>
</tr>
<tr>
<td>RET (translocation)</td>
<td>MTC</td>
<td>Radiation associated: 50-60%</td>
<td>[5, 6, 7, 8]</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>PTC</td>
<td>20-60%</td>
<td>[9, 9]</td>
</tr>
<tr>
<td></td>
<td>PTCGTC</td>
<td>10-15%</td>
<td>[10, 2]</td>
</tr>
<tr>
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<td>ATC</td>
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<td>PTC</td>
<td>Sporadic: 15%</td>
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<tr>
<td></td>
<td>PTCGTC</td>
<td>Radiation associated: 15%</td>
<td>[12, 3]</td>
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<tr>
<td></td>
<td>ATC</td>
<td>10-15%</td>
<td>[10, 2]</td>
</tr>
<tr>
<td>XPNPEM mutation</td>
<td>PTC</td>
<td>25-60%</td>
<td>[13, 4]</td>
</tr>
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<td>[10, 2]</td>
</tr>
<tr>
<td>XPNPEM management</td>
<td>PTC</td>
<td>Radiation associated: 5%</td>
<td>[14, 12]</td>
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<tr>
<td></td>
<td>ATC</td>
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</tr>
<tr>
<td>PTH-1 loss or point mutation</td>
<td>PTC</td>
<td>10-15%</td>
<td>[15, 4]</td>
</tr>
<tr>
<td></td>
<td>PTCGTC</td>
<td>10-15%</td>
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<td></td>
<td>ATC</td>
<td>10-15%</td>
<td>[10, 2]</td>
</tr>
<tr>
<td>FGF19 point mutation</td>
<td>PTC</td>
<td>10-15%</td>
<td>[15, 4]</td>
</tr>
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<td></td>
<td>ATC</td>
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<td>[10, 2]</td>
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</tbody>
</table>

The table gives a general range of the prevalence of these events reported in the available literature. However, the actual risk defined in certain studies is influenced by sample size, ascertainment and geographic factors, lifetime exposure to radiation, advanced age at onset, etc. Moreover, the actual risk of several more rare and incidental additional events, such as agenesis, mesodermic defects, external ocular defects, etc., may be present, and may not be associated with familial hyperparathyroidism. It is possible, in certain settings, that a higher rate of occurrence occurs in familial hyperparathyroidism.

Genetics of sporadic and familial hyperparathyroidism

<table>
<thead>
<tr>
<th>Parathyroid disorder</th>
<th>Gene(s) involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic parathyroid adenoma</td>
<td>Cyclin D1; MEN1 (somatic)</td>
</tr>
<tr>
<td>Sporadic parathyroid carcinoma</td>
<td>HRPT2 (somatic and germline)</td>
</tr>
<tr>
<td>MEN 1</td>
<td>MEN1 (germline)</td>
</tr>
<tr>
<td>MEN 2</td>
<td>RET (germline)</td>
</tr>
<tr>
<td>HPT-FT (jaw tumor syndrome)</td>
<td>HRPT2 (germline)</td>
</tr>
<tr>
<td>Familial hypercalcaemic hyperparathyroidia</td>
<td>CASR and unidentified genes</td>
</tr>
<tr>
<td>Neonatal severe hyperparathyroidism</td>
<td>CASR and unidentified genes</td>
</tr>
<tr>
<td>Familial isolated hyperparathyroidism</td>
<td>MEN1, HRPT2, CASR, unidentified genes</td>
</tr>
</tbody>
</table>

(Arnold and Lauter, 2010)
HRTP2 gene

- Encodes for parafibromin
- Acts as a tumor suppressor gene
- Associated with HPT-Jaw tumor syndrome (mutations in about 70%)
- Associated with sporadic and hereditary parathyroid cancer (75%)

Genetics of adrenal disease

Pheochromocytomas and extra-adrenal paragangliomas are tumors derived from the neural crest

- Pheochromocytoma
  - Tumor arising from chromaffin cells of the adrenal medulla (sympathetic)
  - Associated with MEN 2 syndromes

- Paraganglioma
  - Extra-adrenal tumors originating from either sympathetic or parasympathetic nervous system
  - Associated with paraganglioma syndromes

Both are associated with constellation of symptoms, including episodic tachycardia, diaphoresis and headaches

Genetics of pheochromocytoma and paraganglioma

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>PGL1/PCC</th>
<th>Bithoracic/PCC or multiple PGL</th>
<th>Bilateral chromaffin tumors</th>
<th>Malignant risk</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHL</td>
<td>PCC</td>
<td>40% bilateral</td>
<td>Non-malignant</td>
<td>&gt;5%</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>NF1</td>
<td>PCC</td>
<td>15% bilateral</td>
<td>Epinephrine</td>
<td>5%</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>SDHNL</td>
<td>PGL</td>
<td>Single</td>
<td>Mixed</td>
<td>Low</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>SDHAF2</td>
<td>PGL (lacrimal and nasal)</td>
<td>50% multiple</td>
<td>Unclear</td>
<td>Low</td>
<td>Paternal</td>
</tr>
<tr>
<td>SDHA</td>
<td>PGL</td>
<td>20% multiple</td>
<td>Non-pheochromine</td>
<td>14-87%</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>SDHB</td>
<td>PGL</td>
<td>20% multiple</td>
<td>Non-pheochromine</td>
<td>14-87%</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>SDHC</td>
<td>PGL</td>
<td>50% multiple</td>
<td>Non-pheochromine</td>
<td>&lt;15%</td>
<td>Paternal</td>
</tr>
</tbody>
</table>

Succinate dehydrogenase genes (SDH)

- Encode for mitochondrial complex enzyme
- Proposed as an oxygen sensor
- Mutation results in little or no enzyme activity
SDHB mutations

- Most common mutation in patients with pheochromocytomas and paragangliomas
- Over 150 mutations identified
- Associated risk of malignancy is 34-97% (the highest among the SDH mutations)
- Associated with renal cell carcinoma and Cowden’s disease

Carriers should undergo more aggressive surveillance and treatment

(Pagan RA et al. Gene Reviews)

Conclusions

- There have been tremendous advancements in our understanding of the genetic causes of endocrine disease
- MTC a prototype disease for genetic testing and early treatment. Genetic testing should be offered to most if not all patients with even apparent sporadic MTC
- Parathyroid carcinoma is associated with mutations in the HRPT2 gene; genetic counselling and testing should be offered
- Pheochromocytomas and paragangliomas may be associated with mutations in the SDH genes; genetic testing should be offered.
- Identified mutations allow tailored approach to individual patients AND allow us to better predict disease in other endocrine organs and presence of disease in gene+ kindred

Limitations

- Not very good at predicting de-novo mutations
- Genotype-phenotype correlation is imperfect
- Ethical landscape is changing

Thank you

Jessica E. Gosnell MD
Associate Professor of Clinical Surgery