Endocrine and Hereditary Considerations in Neuroendocrine Tumors

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Conflicts of Interest

• Member of Consultant Advisory Board, EISAI Corporation
• Speakers Bureau EISAI Corporation
A Puzzle
Anatomical Distribution of Neuroendocrine Tumors

- **Pituitary gland**: Pituitary adenomas
- **Thyroid Gland**: Medullary Thyroid carcinomas
- **Parathyroid tumors** (adenomas) Thymus: ectopic parathyroid adenomas and mediastinal carcinoid tumors
- **Pulmonary Neuroendocrine tumors**: bronchus (bronchial adenomas and carcinoid)
- **Pulmonary carcinoid tumors**: typical carcinoid
  - (TC; low-grade);
  - atypical carcinoid (AC; intermediate-grade)
  - small-cell lung cancer (SCLC),
  - large cell neuroendocrine carcinomas of the lung (LCNEC)
- **Extrapulmonary small cell carcinomas** (ESCC or EPSCC)
Anatomical Distribution ...

- **Gastroenteropancreatic neuroendocrine tumors** (GEP-NET)
- **Foregut GEP-NET** (foregut tumors can conceptually encompasses not only NETs of the stomach and proximal duodenum, but also the pancreas, and even thymus, lung and bronchus)
  - Pancreatic endocrine tumors (if considered separately from foregut GEP-NET)
- **Midgut GEP-NET** (from distal half of 2nd part of the duodenum to the proximal two-thirds of the transverse colon)
  - appendix, including well differentiated NETs (benign); well differentiated NETs (uncertain malignant potential); well differentiated neuroendocrine carcinoma (with low malignant potential); mixed exocrine-neuroendocrine carcinoma (goblet cell carcinoma, also called adenocarcinoid and mucous adenocarcinoid)
- **Hindgut GEP-NET** Distal colon and Rectum
- **Liver and gallbladder**
- **Adrenal tumors: Pheochromocytomas**
- **Peripheral Nervous System: Paraganglionomas, Schwannomas and olfactory neuroblastomas**
- **Ovary and testis**
- **Prostate**
Common NeuroEndocrine Tumors

- Gastro-enteropancreatic NeuroEndocrine Tumor
- Carcinoid Tumors
- The incidence is 5.25 cases per 100,000 persons
- Prevalence may exceed 100,000 in the United States

Yao JC, Clinical Oncology 2008
Features of Neuroendocrine tumors

- Functioning or Non-functioning in terms of hormonal secretion
- Tissue immuno-reactivity for specific hormones does not always reflect secretory activity of the tumor cells.
- The great majority of NET may secrete neuroendocrine peptides, that is common among all of them, even if we consider them as non-functional, those peptides are the source of a biomarkers for both diagnosis and follow up.
- Receptors and genetic markers are acquiring a relevant role in the characterization of NET, both improving knowledge of biology and physiopathology of NET, as well as in developing specific strategies to establish an early diagnosis and targeted therapies,
- To adopt prophylactic strategies in familial forms, and to identify more efficacious targets for therapy
Hormonal Aspects of Neuroendocrine Tumors

- Hormone production in excess from a known endocrine organ:
  - Pituitary Adenoams (Prolactin, GH, ACTH, TSH, Alpha subunits glycoproteins, FSH and LH)
  - C- Cell Medullary thyroid carcinomas (Calcitonin and Calcitonin gene related peptide)
  - Parathyroid Hormone (PTH)
  - Pheochromocytoma (noradrenaline and adrenaline)
  - Pancreatic hormones (see next)

- Hormone production in excess in “non-endocrine” organ
  - Gastric Carcinoid (gastrin)
  - Carcinoid Tumors (see next)
  - Paraganglionomas: (Dopamine)
Hormone Secretion from Pancreatic Neuroendocrine Tumors

- Gastrinoma (gastrin)
- Insulinomas (Insulin, c-peptides, proinsulin)
- VIPoma (Vasoactive intestinal Polypeptide)
- Glucagonomas (Glucagon)
- Somatostatinomas (somatostatin)
- GRFoma (Growth hormone Releasing Factor)
- ACTHomas
- PPoma
- Non functioning 70%
Enterochromaffin Like Cells Secretion

FIGURE 287-5 Regulation of gastric acid secretion at the cellular level. ECL cell, enterochromaffin-like cell.
Hormonal Aspects of Carcinoid Syndrome

- Flushing
  - Erythematous: Sudden, diffuse erythematous flush affecting face, neck, and upper chest; short duration 1-5 minutes with palpitation, and warmth sensation, 20-70% of midgut carcinoid
  - Violaceous: similar, last longer, associated with facial telengectasia usually not felt by the patient; late stage of midgut carcinoid
  - Prolonged flushing: last several hours to several days, sometimes involves whole body, associated with profuse lacrimation, swelling of salivary gland, hypotension, and facial edema associated with malignant bronchial tumor
  - Bright red, patchy flush associated with histamine release, seen in chronic atrophic gastritis and EC-like cells
Flushings in Carcinoid Tumors
Precipitators of Flushing

– Spontaneous
– Mental stress
– Physical Stress
– Infection
– Alcohol
– Spicy food
– Catecholamine injection
– Calcium
– Pentagastrin
Mediators of Flushing

• It was believed to be due to Serotonin or serotonin metabolites
• There is a clear correlation between the onset and intensity of the release of tachykinins
• Blockage of tachykinins secretion by octreotide abolishes the flushing
• Histamine specially in bright red flushing in lung and gastric Eclomas
• Endothelium derived relaxing factors or Nitric Oxide release and vasodilation
• Kallikrein and bradykinins release during the flushing
Diarrhea in Carcinoid Syndromes

• Occurs in 30 to 80% of patients
• Associated always with cramping
• Release of serotonin, tachykinin, histamines, kallikrein and prostaglandin stimulates peristalsis, electromechanical activity and tone in intestine
• Secretory diarrhea with fluid and electrolytes imbalance
• Malabsorption results from secondary fibrosis usually present with carcinoid tumors, and bacterial overgrowth
Serotonin and Diarrhea

- Serotonin is the primary mediator of intestinal motility.
- Serotonin is believed to be responsible for the diarrhea in the carcinoid syndrome.
- Serotonin affects gut motility and induces secretion of intestinal fluid and electrolytes.
- Serotonin receptor antagonist such as ondansteron and ketanserin relieve the diarrhea to a certain degree.
Serotonin Signaling in the gut
D-D-D= Diarrhea, Dermatitis, Dementia

- Functioning carcinoid tumor cells indirectly depress endogenous niacin production by diverting tryptophan metabolism towards serotonin and away from niacin.
- Anorexia and diarrhea, reduce the availability of exogenous niacin.
- The decreased availability of endogenous and exogenous niacin eventually results in the depressed tissue niacin levels responsible for the development of pellagra.
Carcinoid Heart Disease

Clinical Characteristics

• Causes stenosis or regurgitation of valves of the right heart
• Substance inducing fibrosis released from metastatic liver directly to right heart, but degrades in lungs, unless the primary lesion is in the lungs
• Probably Somatostatin analogues decreased the rate of cardiac carcinoid from 70% to 10%.
Insulinomas

- Is a rare tumor (1/250,000), 90% is benign
- Can be a component of MEN1, then is usually multifocal
- Multiple hormone can be secreted from one tumor and the predominant one may drive the clinical presentation
- The hormonal secretion may vary over time
- Whipple Triad
- Causes post absorptive and post exercise hypoglycemia
- 5-10% malignant in MEN1
Clinical Manifestation of Insulinoma

- Diplopia, blurred vision, sweating, palpitation or weakness: 85%
- Confusion or behavioral changes: 80%
- Unconsciousness or amnesia: 53%
- Grand Mal Seizures: 12%, usually early morning seizures
Gastric Carcinoid

- Represent 1% of gastric tumor
- Divided in 3 distinct groups based on clinical histological characteristics
  - Type I is associated chronic atrophic gastritis type A in 80% of the cases and frequent Pernicious anemia
  - Type II is associated with Zollinger ellison syndrome in isolation or associated with MEN-1 in 60% of the cases
  - Type III Represent sporadic gastric carcinoids without hypergastrinemia and 50-60 developing metastasis
Clinical Presentation and Diagnosis of Zollinger- Ellisson Syndrome

- A triad of abdominal pain, heart burn and diarrhea are common presenting symptoms
- Is associated severe refractory peptic ulceration complicated by hemorrhage, perforation and strictures
- Diarrhea is results of severe hyperacidity degradation of pancreatic lipase and consequent fat malabsorption
Pancreatic NeuroEndocrine Tumor

- PNETs arise from Stem-like non-islet ductal progenitor Cells
- Association with the gene mutations of:
  - MEN1 (Representing MEN1 Syndrome)
  - VHL (representing Von Hippel Lindau)
  - NF1 (representing Neurofibromatosis 1)
  - TSC1/TSC2 (Tuberous Sclerosis)
  - More recent exome sequencing from sporadic PNET shows 44% incidence MEN1 mutation
  - 43% in DAXX/ATRX
  - 14% in mechanisitic target of rapamycin (mTOR)
Glucagonoma Syndrome

Necrolytic Migratory Erythema
Malignant in 75% of the case
**Table 9 Clinical features of the VIPoma syndrome (7)**

<table>
<thead>
<tr>
<th>Sign/symptom</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretary diarrhea</td>
<td>89-100</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>67-100</td>
</tr>
<tr>
<td>Weight loss</td>
<td>33-72</td>
</tr>
<tr>
<td>Dehydration</td>
<td>44-95</td>
</tr>
<tr>
<td>Hypochlorhydria</td>
<td>34-76</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>20-50</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>25-50</td>
</tr>
<tr>
<td>Flushing</td>
<td>13-28</td>
</tr>
<tr>
<td>Dilated, atonic gallbladder</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Other Hormonal Secretion of PNET

- Somatostatin with a Triad of Diabetes, Steatorrhea and cholelithisasis
- PTH causing Hypercalcemia
- GHRH causing ectopic Acromegaly
- ACTH causing Cushing’s syndrome
### WHO 2010 clinicopathologic Classification of NETs

<table>
<thead>
<tr>
<th>NET Grade 1</th>
<th>Mitotic count &lt;2 per 10 HPF and/or Ki-67 index ≤2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NET Grade 2</td>
<td>Mitotic count 2–20 per 10 HPF and/or Ki-67 index 3%-20%</td>
</tr>
<tr>
<td>NET Grade 3</td>
<td>Mitotic count &gt;20 per 10 HPF and/or Ki-67 index &gt;20%</td>
</tr>
<tr>
<td></td>
<td>Large Cell</td>
</tr>
<tr>
<td></td>
<td>Small cells</td>
</tr>
<tr>
<td>Mixed Endocrine – exocrine tumors</td>
<td></td>
</tr>
</tbody>
</table>
Common Biomarkers

**Type II**
Considered surrogate endpoint for the disease because a change indicates clinical benefit

**Type I**
Capture the effects of an intervention in accordance with the mechanism of the drug action, even though the mechanism may not be associated with clinical outcome

**Type 0**
Markers of the natural history of disease correlate longitudinally with known clinical indices (symptoms) over the full range of a disease state

**Change correlates with therapeutic intervention**

**Correlation observed between levels and symptoms**

**Biological media**
Tissue, blood, CSF, urine
Biomarkers of Diagnosis and Prognosis

• Chromogranin A levels, which represents a constitutive NeuroEndocrine secretory protein, is the most widely accepted biomarker.

• CgA was compared to a panel of biomarkers and proved to be the most accurate, with a specificity of 85.7% and sensitivity of 67.9%

• 60-80% of patients with NeuroEndocrine tumors have elevated CgA levels

• CgA levels correlate with disease burden and poor outcomes

• Measuring baseline and serial CgA levels may be used to predict clinical outcome and tumor response

Bajetta E, Cancer 1999, Chou WC JCO 2013
Current NET monoanalyte biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Type</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CgA</td>
<td>0−II</td>
<td>43−100%</td>
<td>10−96%</td>
<td>[39, 52−54, 89−91]</td>
</tr>
<tr>
<td>u5-HIAA</td>
<td>0−II</td>
<td>35%</td>
<td>up to 100%</td>
<td>[65]</td>
</tr>
<tr>
<td>Substance P</td>
<td>0</td>
<td>32%</td>
<td>85%</td>
<td>[67]</td>
</tr>
<tr>
<td>Pancreatic polypeptide</td>
<td>0</td>
<td>50−80%</td>
<td>no data</td>
<td>[92]</td>
</tr>
<tr>
<td>Pancreastatin</td>
<td>I</td>
<td>64%</td>
<td>58−100%</td>
<td>[53, 54, 91]</td>
</tr>
<tr>
<td>NSE</td>
<td>I</td>
<td>33%</td>
<td>up to 100%</td>
<td>[65]</td>
</tr>
<tr>
<td>NKA</td>
<td>I</td>
<td>88%</td>
<td>no data</td>
<td>[57]</td>
</tr>
<tr>
<td>CgB</td>
<td>I</td>
<td>99%</td>
<td>no data</td>
<td>[53]</td>
</tr>
<tr>
<td>ProGRP</td>
<td>I</td>
<td>99%</td>
<td>43%</td>
<td>[74]</td>
</tr>
<tr>
<td>NT-BNP</td>
<td>II</td>
<td>87%</td>
<td>80%</td>
<td>[71]</td>
</tr>
<tr>
<td>CTGF</td>
<td>II</td>
<td>88%</td>
<td>69%</td>
<td>[73]</td>
</tr>
</tbody>
</table>

u5-HIAA = Urinary 5-HIAA; ProGRP = progastrin-releasing peptide; NT-BNP = N-terminal brain natriuretic peptide.

1 Midgut NETs. 2 In carcinoid heart disease. 3 For right-ventricular dysfunction.
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Study design</th>
<th>Results</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHROMOGRANIN A</strong></td>
<td>Retrospective n=54 with advanced GEP-NETs</td>
<td>Baseline CgA: Elevated in 85%</td>
<td>Baseline and serial CgA may have utility to monitor outcomes during treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower baseline CgA (&lt;2 xULR): longer overall survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serial CgA: Smaller increases (&lt;15%); favorable</td>
<td></td>
</tr>
<tr>
<td><strong>Multi-transcript molecular signature</strong></td>
<td>PCR score in training (n=130), validation set (n=182) of blood samples in GEP-NETs</td>
<td>Treatment naïve (vs. treated): higher</td>
<td>Biomarker transcript panel very accurately identifies GEP-NETs, differentiates stable from progressive disease and exhibits potential to monitor treatment efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-treatment (vs. post-): reduced</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complete remission (vs. controls): not different</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Progressive disease (vs. stable): higher (all P significant)</td>
<td></td>
</tr>
</tbody>
</table>
## MOLECULAR BIOMARKERS

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Study design</th>
<th>Results</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>sVEGFR2</td>
<td>Prospective Phase II n=44 with metastatic NETs treated with pazopanib</td>
<td>After treatment: decreased (P&lt;0.001) Duration of Rx: decreased (P=0.004) Decreased sVEGFR2 &gt;20% (vs. &lt;20%): longer mean progression free survival (P=0.067)</td>
<td>SVEGFR2 has potential to monitor efficacy of treatment specifically with pazopanib and multi-kinase inhibitors</td>
</tr>
<tr>
<td><strong>p-mTOR</strong></td>
<td>Immunohistochem. on tumor samples n=69 with NETs</td>
<td><strong>p-mTOR:</strong> Expressed in 85% <strong>IGF1R:</strong> Expressed in 66% <strong>p-mTOR and IF1R:</strong> Both expressed in 16%</td>
<td>IGF1R and p-mTOR may have some utility in the identification of appropriate patients for trials with mTOR inhibitors</td>
</tr>
</tbody>
</table>
Utility of Current NET biomarkers

M. Duque, 2013 Pancreas
# Hereditary Forms of NET

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Frequency</th>
<th>Location/type genetic abnormality</th>
<th>Altered protein function(s)</th>
<th>Frequency PETs</th>
<th>Type PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Endocrine Neoplasia type 1 (MEN1) (Wermer’s syndrome)</td>
<td>Prevalence-1–10 per 100,000</td>
<td>11q13 (encodes 610 amino acid protein, menin)</td>
<td>Nuclear location; exact function unclear-interacts JunD, NFκB, SMAD signaling pathways. Effects cell cycle, growth, genomic stability, and apoptosis.</td>
<td>80–100% (microscopic) 20–80% (clinical)</td>
<td>Nonfunctional (NF)(microscopic)&gt;functional (20–80%)</td>
</tr>
<tr>
<td>Von Hippel-Lindau disease (VHL)</td>
<td>Prevalence-2–3 per 100,000</td>
<td>3p25 (encodes 232 amino acid protein, [pVHL])</td>
<td>Interacts elongins which act as transcriptional regulators that degrades HIF, regulates cell cycle, VEGF</td>
<td>10–17%</td>
<td>&gt;98% NF</td>
</tr>
<tr>
<td>Von Recklinghausen’s Disease (neurofibromatosis 1, NF-1)</td>
<td>Prevalence-1 per 4–5,000</td>
<td>17q11.2 (encodes 2485 amino acid protein neurofibromin)</td>
<td>Ras GTPase-activating activity, bind microtubules, modulates adenylate cyclase, mTor-regulates growth, cell cytoskeleton</td>
<td>Uncommon (0–10%)</td>
<td>Duodenal somatostatinomas, rare PETs</td>
</tr>
<tr>
<td>Tuberous sclerosis (Bourneville’s disease)</td>
<td>Prevalence-1 per 10,000</td>
<td>9q34 (TSC1) (encodes 1164 amino acid protein, hamartin) 16p13(TSC2) (encodes 1807 amino acid protein, tuberin)</td>
<td>Interact PI3K signaling pathway regulating GTPase, mTor which plays a key role in growth, energy regulation, response to hypoxia, nutrients</td>
<td>Uncommon</td>
<td>Rarely develop functional, NF PETs</td>
</tr>
</tbody>
</table>
The diagnostic criteria established during a consensus conference at the VII International Multiple Endocrine Neoplasia Workshop Gubbio, Italy 1999

Two or more of the following criteria in a single patient or in first, and/or second-degree relatives, may suggest the diagnosis of MEN1 and lead to a genetic analysis of the MEN1 gene.

1. Primary hyperparathyroidism with multiglandular hyperplasia and/or adenoma, or recurrent primary hyperparathyroidism
2. Duodenal and/or pancreatic endocrine tumors both functional (gastrinoma, insulinoma, glucagonoma) or non-functional or multisecreting tumors, as proven by immunohistochemistry
3. Gastric enterochromaffin – like tumors
4. Anterior pituitary adenoma both functional (growth-hormone-secreting tumors or acromegaly, prolactinoma) or non-functional proven by immunohistochemistry
5. Adrenocortical tumours, both functional and non-functional
6. Thymic and bronchial tube endocrine tumors (foregut carcinoid tumors)
Tumor Locations in MEN1

MEN1 (n=130)

- **Pituitary** (47%)
  - Prolactinoma (21%)
  - Nonfunctioning (11%)
  - ACTH (7%)
  - Growth hormone (3%)

- **Thyroid** (13%)
  - Follicular adenoma (8%)
  - Papillary adenoma (5%)

- **Parathyroid** (99%)

- **Skin** (60-90%)
  - Collagenoma (62%)
  - Angiofibroma (64%)
  - Lipoma (5%)
  - Melanoma (3%)

- **Thymic Carcinoid** (1%)

- **Bronchial/Lung Carcinoid** (8%)

- **Gastric Carcinoids** (7%)

- **Pancreatic endocrine tumor (PET)** (66%)
  - Nonfunctional (4%)
  - Insulinoma (12%)
  - Gastinoma (47%)
  - Other PETs (4%)

- **Adrenal** (16%)
  - Nonfunctional (11%)
  - Functional (5%)
### Characteristics of MEN1

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Oncogenes and their role in disease development</th>
<th>Phenotypes – clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN1 (Werner syndrome)</td>
<td>Menin – (tumor suppressor gene) controls the expression of inhibitors of the activity cyclin-dependent kinase p27Kipl and p181nk4c. The lack of menin activity results in down-regulation of p27Kipl and p181nk4c and leads to uncontrolled cell growth</td>
<td>primary hyperparathyroidism Zollinger–Ellison syndrome, insulinoma VIPoma pituitary tumors adrenocortical tumors thymic and/or bronchial tube endocrine tumors (foregut carcinoid tumors)</td>
</tr>
</tbody>
</table>
I. Menin gene (>9kb)[11q13]

II. Menin (610AAs)

III. Menin interacting proteins

III. A. Transcription regulation
- JunD
- NF-κB
- Pem
- Smad3
- CHES1
- mSin3A
- HDAC1

III. B. Genome stability
- RPA2
- FANCD2

III. C. Cell division
- NMHC II-A

III. D. Cell cycle control
- NM23H1
- ASK

Others:
- Transcription regulation: RunX2, Smad 1, 5, MLL histone methyl-transferase complex, ER-alpha, IGFBP-2 promoter, double-stranded DNA.
- Cell division: Vimentin, Glial fibrillary acidic protein (GFAP).
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<th>Oncogenes and their role in disease development</th>
<th>Phenotypes – clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN2 (2a, 2b)</td>
<td>1. RET-oncogene encodes a receptor tyrosine kinase with two alternative isoforms – RET 9, RET 51.</td>
<td>medullary thyroid carcinoma (MEN 2a and 2b) – 100%</td>
</tr>
<tr>
<td></td>
<td>2. RET protein is a subunit of complex that binds growth factors of the glial-cell-derived neurotrophin factor (GDNF).</td>
<td>phaeochromocytoma (MEN 2a and 2b) – 50%</td>
</tr>
<tr>
<td></td>
<td>3. Most MEN 2a mutations affect cysteine (634) in extracellular domain.</td>
<td>primary hyperparathyroidism (MEN 2a) – 25%</td>
</tr>
<tr>
<td></td>
<td>4. Most MEN 2b patients carry the M918T mutation in intracellular tyrosine kinase domain</td>
<td>neuromas of the tongue ganglioneuromas of the intestine and a marfanoid habitus (MEN 2b) – 95%</td>
</tr>
</tbody>
</table>
Ret Protoncogene Mutation

Under normal conditions, when GDNF binds to the receptor it produces a growth effect. When GDNF is removed, the signal stops. When the receptor is a mutant, it will constantly provide a signal for the cell to grow and divide, even in the absence of GDNF. Uncontrolled growth then produces...
## Features of MEN 2

<table>
<thead>
<tr>
<th>The Tumor</th>
<th>MEN2A</th>
<th>MEN2B</th>
<th>FMTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hyperplasia</td>
<td>10-35% [14, 15]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Medullary Thyroid Carcinoma</td>
<td>100%[16]</td>
<td>85%[16]</td>
<td>100%[16]</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>50%[17]</td>
<td>50% [17]</td>
<td>-</td>
</tr>
<tr>
<td>Mucosal Neuroma</td>
<td>-</td>
<td>100%[16]</td>
<td>-</td>
</tr>
<tr>
<td>Ganglioneuromatosis of GI tract</td>
<td></td>
<td>98%[17]</td>
<td></td>
</tr>
</tbody>
</table>
Medullary Thyroid Carcinomas, Clinical Aspects

- Can be a Painful nodule on palpation
- Diarrhea can be a presenting symptoms of medullary Thyroid Carcinomas
- Secrete calcitonin, Calcitonin gene related peptide and Carcinoembryonic antigen
- Calcitonin and CEA are markers of the tumor
- Calcitonin is the marker of presence of C-Cells
- Whereas CEA is representing the aggressiveness and growth of the tumor, Increasing CEA is worrisome
- Rarely Medullary thyroid cancer secretes ACTH, histamine and other NeuroEndocrine hormones
- Metastasis are in local and mediastinal lymph nodes, but milliary liver metastasis is classical and needs to be examined with intraoperative ultrasonography and biopsy
- Bone metastasis are highly vascular and can cause cord compression
- Vandetanib, Pazopanib and Sutinib are effective in controlling the disease progression
- Somatostatin analogues and Lanreotide is also helpful for control of the disease
- Any patient with Medullary thyroid carcinoma should be checked for RET protoncogene mutation and prior to surgery have metanephrine measured
<table>
<thead>
<tr>
<th>Affected Codon</th>
<th>Exon</th>
<th>Clinical syndrome</th>
<th>Percentage of all MEN-2 Mutation</th>
<th>Risk Category, ATA 2009</th>
<th>Consensus risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>609</td>
<td>10</td>
<td>MEN-2A/FMTC</td>
<td>0-1</td>
<td>B</td>
<td>High</td>
</tr>
<tr>
<td>611</td>
<td>10</td>
<td>MEN-2A/FMTC</td>
<td>2-3</td>
<td>B</td>
<td>High</td>
</tr>
<tr>
<td>618</td>
<td>10</td>
<td>MEN-2A/FMTC</td>
<td>3-5</td>
<td>B</td>
<td>High</td>
</tr>
<tr>
<td>620</td>
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<td>MEN-2A/FMTC</td>
<td>6-8</td>
<td>B</td>
<td>High</td>
</tr>
<tr>
<td>630</td>
<td>11</td>
<td>FMTC</td>
<td>&lt;0.1</td>
<td>B</td>
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</tr>
<tr>
<td>634</td>
<td>11</td>
<td>MEN-2A</td>
<td>80-90</td>
<td>C</td>
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</tr>
<tr>
<td>768</td>
<td>13</td>
<td>FMTC</td>
<td>0-1</td>
<td>C</td>
<td>Intermediate</td>
</tr>
<tr>
<td>790</td>
<td>13</td>
<td>MEN-2A/ FMTC</td>
<td>&lt;0.1</td>
<td>A</td>
<td>Intermediate</td>
</tr>
<tr>
<td>791</td>
<td>13</td>
<td>FMTC</td>
<td>&lt;0.1</td>
<td>A</td>
<td>Intermediate</td>
</tr>
<tr>
<td>804</td>
<td>14</td>
<td>FMTC(age of onset variable )</td>
<td>0-1</td>
<td>B</td>
<td>Intermediate</td>
</tr>
<tr>
<td>883</td>
<td>15</td>
<td>MEN-2B</td>
<td></td>
<td>D</td>
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</tr>
<tr>
<td>891</td>
<td>15</td>
<td>FMTC</td>
<td>0-1</td>
<td>A</td>
<td>Intermediate</td>
</tr>
<tr>
<td>918</td>
<td>16</td>
<td>MEN-2B</td>
<td>10-20</td>
<td>D</td>
<td>Highest</td>
</tr>
<tr>
<td>920</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Highest*</td>
</tr>
<tr>
<td>922</td>
<td></td>
<td>Sporadic/MEN-2B</td>
<td></td>
<td></td>
<td>Highest*</td>
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</tbody>
</table>
Genetic Testing for MEN2

- RET mutation is known in family
  - Obtain genetic test report from relative with mutation
    - Education, counseling and informed consent
      - Known mutation (single site) genetic testing
        - No mutation (true negative)
          - No additional evaluation for MEN2 needed
        - Mutation
          - MEN2 management indicated³
            - Recommend genetic testing to at-risk relatives
    - Mutation
      - MEN2 management indicated³
        - Risk uncertain; manage on a case-by-case basis
  - RET mutation is unknown in family
    - Education, counseling and informed consent
      - Testing for targeted exons³
        - No mutation
          - Patient unlikely to have hereditary MTC³
        - Variant of uncertain significance
          - Recommend genetic testing to at-risk relatives
**Other Hereditary form of Neuroendocrine tumor**

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Oncogenes and their role in disease development</th>
<th>Phenotypes – clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Hippel-Lindau</td>
<td>VHL – gene responsible for creating the full length protein pVHL30 regulating cell cycle control, mRNA stability and activity of hypoxia-inducible gene expression</td>
<td>haemangioblastomas of central nervous system and retinae clear cell renal carcinoma phaeochromocytoma pancreatic cystic and/or endocrine tumors</td>
</tr>
<tr>
<td>Neurofibromatosis type 1 (Recklinghausen disease)</td>
<td>NF1 (suppressor gene) responsible for the expression of neurofibromin. Neurofibromin is homologous of proteins activating GTP-ase-dependent p21 Ras. Its importance lies in the tumor suppressing by regulating the activation of the Ras-dependent signal</td>
<td>cafe au lait macules of skin neurofibromas auxiliary or inguinal freckling optic glioma retinal Lisch nodules</td>
</tr>
<tr>
<td>Paraganglionesoma</td>
<td>Succinate dehydrogenase Gene mutation Causing activation of hypoxemia induced Factor (HIF gene)causing angiogenesis</td>
<td>Paragnagllionomas of 95% benign and 5% malignant involving glomus tumor jugulare, and other form of paranganglionesoma</td>
</tr>
</tbody>
</table>
American Thyroid Association risk level and timing of prophylactic thyroidectomy in MEN2A

<table>
<thead>
<tr>
<th>ATA risk level</th>
<th>Age of prophylactic surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A (codons 768, 790, 791, 804, and 891)</td>
<td>Consider operative resection before age 5 years</td>
</tr>
<tr>
<td></td>
<td>May delay operative resection if: annual serum calcitonin AND annual neck ultrasound (no lesions &gt;5 mm and no concerning adenopathy AND Less aggressive family history AND Family preference)</td>
</tr>
<tr>
<td>Level B (codons 609, 611, 618, 620, and 630)</td>
<td>Consider operative resection before age 5 years</td>
</tr>
<tr>
<td></td>
<td>May delay operative resection if: annual serum calcitonin AND annual neck ultrasound (no lesions &gt;5 mm and no concerning adenopathy AND Less aggressive family history AND Family preference)</td>
</tr>
<tr>
<td>Level C (codon 634)</td>
<td>Before 5 years of age</td>
</tr>
</tbody>
</table>