Objectives

- Diagnose mucous membrane signs of genetic disease more accurately
- Recognize benign findings that indicate an increased risk for systemic disease
- Obtain a targeted family history for genetic syndromes with mucosal features
HHT Diagnostic Criteria
3 or more confirms

- Nosebleeds (epistaxis). Spontaneous and recurrent; nighttime nosebleeds heightens concern
- Mucocutaneous telangiectases Multiple, at characteristic sites
- Visceral arteriovenous malformation (AVM)
- Family history. A first-degree relative with HHT


Transillumination of the fingers for vascular anomalies


Hereditary Hemorrhagic Telangiectasia

- Autosomal dominant, variable expressivity, no genotype/phenotype correlations
- At least 1:10,000 persons
- Location: lips, tongue, buccal mucosa, face, chest, fingers
  - Abnormal arterial connection; not contractile
- Vaginal telangiectasias have been described
  - Humphries JE, Obstet Gynecol;1993:81,865-6

HHT: Evaluation

- Medical history, exam
  - heart, lung, liver, neurologic
- CBC (anemia, polycythemia)
- Contrast echo, pulmonary artery pressure
- Head MRI with & without GAD
- Genetic consultation
  - ACVRL1, ENG, (SMAD4 with polyps), GDF2

Which associated skin change is most likely?

A) Striae
B) Mucosal neuromas
C) Syringomas
D) Basal cell nevi
E) Mucous cysts
Which associated skin change is most likely?
A) Striae
B) Mucosal neuromas
C) Syringomas
D) Basal cell nevi
E) Mucous cysts

Marfan syndrome
- Autosomal dominant, variable expressivity
- 1:5,000 persons
- 25% new (de novo) mutations
- Affects skeletal, ocular and cardiovascular systems
- Potentially fatal; may not be evident until adolescence

Marfan Syndrome
Skeletal abnormalities
- Long extremities
- Reduced arm-span to height; upper to lower segment ratios
- Pectus
- Scoliosis
- Pes planus

Marfan Syndrome
Facial Skeletal Features
- Down-slanting, deep eyes
- Malar hypoplasia
- Micro-, retrognathia
- High, arched palate
- Tooth crowding

Marfan Syndrome
Skeletal abnormalities
- Long extremities
- Reduced arm-span to height; upper to lower segment ratios
- Pectus
- Scoliosis
- Pes planus

Ghent Systemic Score
<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist and thumb sign</td>
<td>3</td>
<td>Protrusio acetabulae</td>
<td>2</td>
</tr>
<tr>
<td>Wrist or thumb sign</td>
<td>1</td>
<td>Reduced elbow extension</td>
<td>1</td>
</tr>
<tr>
<td>Pectus carinatum</td>
<td>2</td>
<td>Skin striae</td>
<td></td>
</tr>
<tr>
<td>Pectus excavatum or chest asymmetry</td>
<td>1</td>
<td>Reduced upper-to-lower segment ratios</td>
<td>1</td>
</tr>
<tr>
<td>Hindfoot deformity</td>
<td>2</td>
<td>Scoliosis</td>
<td>1</td>
</tr>
<tr>
<td>Pes Planus</td>
<td>1</td>
<td>Craniofacial features</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
<td>Myopia</td>
<td>1</td>
</tr>
<tr>
<td>Dural ectasia</td>
<td>2</td>
<td>Mitral Valve Prolapse</td>
<td>1</td>
</tr>
</tbody>
</table>

Marfan Syndrome
- Fibrillin-1 (FBN1) mutation
  - Extracellular matrix protein
  - Elastic fibrils of lens, aorta, skin
  - regulator of TGF-b (transforming growth factor beta) signaling
- Rarely, mutations in TGFBR1 and TGFBR2
  - type called “Loey’s-Dietz”
  - additional traits: bifid uvula, easy bruising or abnormal scars

Marfan Syndrome
- Fibrillin-1 (FBN1) mutation
  - Extracellular matrix protein
  - Elastic fibrils of lens, aorta, skin
  - regulator of TGF-b (transforming growth factor beta) signaling
- Rarely, mutations in TGFBR1 and TGFBR2
  - type called “Loey’s-Dietz”
  - additional traits: bifid uvula, easy bruising or abnormal scars
**Marfan: vascular abnormalities**

- Aortic dilatation
  - Z-score >= 2.0
- Dissection
- Mitral valve prolapse
- Arrhythmia

**Marfan syndrome**

- Prognosis by cardiovascular defects: common cause of death, aortic abnormalities in adults
- Advice: Minimize contact sports, Avoid isometric exercises, Valsalva maneuver.
- Long-term propranolol decreases myocardial contractility, risk of aortic dilatation. Losartan (ARBs) superior to beta-blockers.
- Prosthetic replacement of aneurysmal and valve heart defects, aortic root

---

**Hypermobility Syndromes**

<table>
<thead>
<tr>
<th>6 Types (After 1997)</th>
<th>Cell Type</th>
<th>Features</th>
<th>Inheritance</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>I, II</td>
<td>Extensible Skin, Joints, Scars, Bruising</td>
<td>AD, AR</td>
<td>Type V Collagen</td>
</tr>
<tr>
<td><strong>Hypermobility</strong></td>
<td>III</td>
<td>Joint Hypermobility, Pain, dislocations</td>
<td>AD</td>
<td>Unknown</td>
</tr>
<tr>
<td>Vascular</td>
<td>IV</td>
<td>Thin skin, GI or uterine rupture</td>
<td>AD</td>
<td>Type III Collagen</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>VI</td>
<td>Hypotonia, lax joints, eyes, scoliosis</td>
<td>AR</td>
<td>Lysyl hydroxylase</td>
</tr>
<tr>
<td>Arthrochalasia</td>
<td>Vlla, b</td>
<td>Severe joint mobility, soft dislocation</td>
<td>AD</td>
<td>Type I Collagen</td>
</tr>
<tr>
<td>Dermatosparaxis</td>
<td>Vllc</td>
<td>Severe skin fragility, extensibility</td>
<td>AR</td>
<td>Procollagen IVN-peptidase</td>
</tr>
</tbody>
</table>

---

**Beighton Scale**

**Ehlers-Danlos syndrome**


**Ehlers Danlos Syndrome**

“Gorlin sign”
4 The most likely causative mutation is which of the following?
A) RET
B) COL3A1
C) PTEN
D) COL7A1
E) ECM1

5 Which of following diagnoses should be considered?
A) Multiple mucosal neuromas
B) Myxoid neurofibromas
C) Syringomas
D) Basal cell nevi
E) Mucous cysts
Which of the following diagnoses should be considered?

A) Multiple mucosal neuromas
B) Myxoid neurofibromas
C) Syringomas
D) Basal cell nevi
E) Mucous cysts

**Multiple Endocrine Neoplasia Type 2B**
- Also called Mucosal Neuroma Syndrome
- Autosomal Dominant
- \textit{RET} is the only gene; testing detects 98%
- Oral mucosal neuromas may be first to present

**MEN 2B**
- Medullary Thyroid Cancer (MTC) in virtually all (100%)
  - Early thyroidectomy (< age1)
- Pheochromocytoma (50%)
- Gastrointestinal symptoms from hamartomas (ganglioneuromas)
- Hyperparathyroidism (30%)
**MEN2B**

**Oral Mucosal Neuromas**
- On tongue, pathognomonic for MTC
- "Blubbery" lips
- Oral findings benign

**Cowden syndrome**
- Macrocephaly
- "Overgrowth" syndrome

**PTEN Hamartoma**

**Cowden syndrome**
- Cancers of the thyroid (35%), breast (up to 67%), colon (9%), renal (35%), melanoma (5%) and endometrium (30%)
- Thyroid cancer: follicular or papillary, not medullary
- Numerous benign hamartomas

24-year-old; metastatic Medullary Thyroid Cancer

PET Scan
PTEN Hamartoma: Cowden Syndrome

Pathognomonic
- Adult Lhermitte-Duclos disease
- Mucocutaneous
  - Facial trichilemmomas
  - Acral keratoses
  - Papillomas

Major
- Breast cancer
- Thyroid cancer
- Macrocephaly
- Endometrial cancer

From Int J Neuroradiology official blog: Jan 12, 2013

What is Lhermitte–Duclos disease?
- Adult onset in Cowden
- Hamartomatous overgrowth of the cerebellum
- Gangliocytoma

PTEN Hamartoma: Cowden Syndrome Criteria
- Diagnostic Criteria updated every year by the National Comprehensive Cancer Network (NCCN)
- Operational diagnosis if:
  - 6 or more facial papules-at least 3 trichilemmoma
  - Cutaneous papules and oral papules
  - 6 or more palmo/plantar keratoses

PTEN Hamartoma

Cowden syndrome

Acral papules

PTEN Hamartoma

Facial Tricholemmomas

Banayan-Riley Ruvalcaba
- Allelic to Cowden (PTEN), autosomal dominant

Penile Hyperpigmented Macules
PTEN Hamartoma Syndrome

Surveillance
• Age < 18: annual thyroid ultrasound, skin check, physical exam
• Adults: annual thyroid ultrasound, dermatology exam, colonoscopy, renal imaging. For family cancer hx, begin screening 5-10 years prior to youngest diagnosis
• For women: mammogram, breast MRI, transvaginal ultrasound or endometrial biopsy

With digital pigment and anemia, risk of which cancer is increased?
A) Gastrointestinal
B) Lung
C) Esophageal
D) Skin
E) Breast

Peutz-Jeghers Syndrome

• STK11 mutation, autosomal dominant
• 94% with clinical diagnosis have mutation
• Association of gastrointestinal (P-J) polyps and mucocutaneous pigmentation
• Polyps most common in small intestine (jejenum > ileum > duodenum)
• Overall cancer relative risk up by 10%

Genetics Referral Indications
• Mucocutaneous Pigmentation and one or more P-J polyps
• Ovarian sex cord/ Sertoli cell tumor
• Adenoma malignum of the cervix
• Pancreatic or breast cancer


Risk of which cancer(s) is increased?
A) Gastrointestinal
B) Thyroid
C) Testicular
D) Pancreatic
E) Breast
Risk of which cancer(s) is increased?

A) Gastrointestinal  
B) Thyroid  
C) Testicular  
D) Pancreatic  
E) Breast

Carney syndrome: A Multiple Endocrine Neoplasia

- Embolic stroke secondary to cardiac myxomas
- Endocrine abnormalities: Cushing’s syndrome caused by PPNAD (pigmented nodular adrenocortical disease); 25%
- acromegaly due to growth hormone/ pituitary adenomas
- prolactinemia

Carney Complex
- Pale at birth
- Brown to black
  - "ink spot" lentigines
- Increased at puberty
- Face, lips, mucosa
- Inner or outer canthi, vaginal or penile mucosa

Primary Pigmented Nodular Adrenocortical Disease (PPNAD)
- causes Cushing syndrome
- 75% of females, 100% have PPNAD at autopsy

McCune-Albright

- "Coast of Maine" Café-au-Lait Macule
- Polyostotic Fibrous Dysplasia

Basal Cell Nevus syndrome

- Jaw Keratocysts
- Appear age 8 to 30’s; Benign, cause tooth loss, appear clinically after damage
I. **Autosomal Dominant Inheritance**

II. 

III. 

---

**Basal Cell Nevus Syndrome**

- Also Gorlin syndrome or Nevoid Basal Cell Carcinoma syndrome (NBCCS)
- Autosomal dominant; 1:30,000
- Patched (**PTCH1**) mutation on 9q22.3; also in sporadic BCC
- 20-30% *de novo* mutation
- Tumor suppressor

---

**Sonic Hedgehog**

- Acts as Tumor Suppressor
- PTCH1
- Smoothened
- Transcription Cascade

Patched1, when *not* bound with Sonic hedgehog, joins Smoothened to suppress transcription.

---

**Nevoid Basal Cell Carcinoma Syndrome (NBCCS)**

**Major Criteria**

- Falx calcification
- Jaw keratocysts
- Palm/ plantar pits
- > 5 BCC’s in a lifetime

**Minor Criteria**

- Medulloblastoma
- Pleural cysts
- Macrocephaly
- Vertebral or rib abnormalities
- Polydactyly
- Ovarian or Cardiac fibromas
- Eye anomalies

---

**In Summary....**

- Multiple similar benign growths suggest a single gene cancer predisposition might be present
- A pedigree is a visual tool to recognize a genetic disorder
- Certain benign pathology diagnoses warrant further consideration
  - *e.g.* Fibrofolliculoma, jaw keratocyst, multiple mucosal neuroma
Thank You!