1. Background

- PTEN-hamartoma tumor syndrome (PHTS) is the molecular diagnostic term describing patients with diverse syndromes, comprising a spectrum of lesions that affect
  - skin, mucous membranes, breast, thyroid gland, kidney, and gastrointestinal tract
Background

• Autosomal dominant disorder caused by a germline mutation in *PTEN* (phosphatase and tensin homolog, deleted on chromosome 10) (or *MMAC1*)
• *PTEN* is localized to chromosome 10q22-23
• It encodes a dual-specificity phosphatase which functions as a tumor suppressor

PTEN-Hamartoma Tumor Syndrome

• Cowden syndrome (CS) is part of the PHTS
• Bannayan–Riley–Ruvalcaba syndrome (BRRS)
• Proteus syndrome (PS)
• Proteus-like syndrome

Cowden syndrome

• CS has a reported incidence of 1 in 200,000
• However, it is likely that it is actually more common and that cases are overlooked because of the complex clinical criteria for CS
• Many of the manifestations of CS are common in the general population, and the finding that only about half of the patients with CS have a known family history

Cowden syndrome

• Cowden syndrome (CS), the principal PTEN-related disorder is characterized by multiple neoplasms and hamartomas, mucosal papillomatosis, and skin lesions
• CS was originally felt to be mainly a dermatological disease - until increased risks for breast and other tumors were established
Cowden syndrome

The major criteria include:
- Breast cancer
- Endometrial cancer
- Nonmedullary thyroid cancer
- Macrocephaly
- Multiple gastrointestinal hamartomas or ganglioneuromas

The major criteria also include mucocutaneous lesions:
- Trichilemmomas
- Multiple palmo-plantar keratosis
- Multifocal or extensive oral mucosal papillomatosis
- Multiple cutaneous facial papules
- Macular pigmentation of the glans penis

Cowden syndrome

Minor criteria
- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthosis (≥3)
- Lipomas (≥3)
- Mental retardation (ie, IQ ≤ 75)
- Renal cell carcinoma
- Testicular lipomatosis
- Thyroid cancer (papillary or follicular variant of papillary)
- Thyroid structural lesions (eg, adenoma, MAN, multinodular hyperplasia)
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

Gastrointestinal Manifestations
- Multiple gastrointestinal hamartomas or ganglioneuromas

Note: From Pilarski et al, 2013
Immunohistochemistry

- Assessment of PTEN expression provides additional support to the diagnosis of PHTS
- Somatic PTEN loss is rare in sporadic tumors
- Complete PTEN loss by IHC is strongly suggestive/diagnostic of PHTS or Cowden syndrome
  – PTEN genotyping confirms the diagnosis

Dysplastic Cerebellar Gangliocytoma in a Patient with Lhermitte–Duclos Disease

Many of the ganglion cells have lost PTEN expression
Thyroid Pathology

Thyroid pathologic findings in patients with PHTS that normally affect the follicular cells include
- Multinodular hyperplasia
- Multiple adenomatous nodules (MAN)
- Follicular adenoma
- Follicular carcinoma
- Papillary carcinoma

Thyroid Pathology

- Follicular carcinoma is an important feature in CS and BRRS
- According to the diagnostic criteria for CS, follicular carcinoma is a major criterion, and multinodular hyperplasia, adenomatous nodules, and follicular adenomas are minor criteria

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<tr>
<th>Thyroid Pathology</th>
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<tr>
<th>Age at diagnosis</th>
<th>Total Cases (20)</th>
<th>CD (14)</th>
<th>BRRS (6)</th>
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<tbody>
<tr>
<td></td>
<td>33.7 (9-76) y</td>
<td>41.7 (13-76) y</td>
<td>15 (9-23) y</td>
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<tr>
<td>Multiple Adenomatous Nodules</td>
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<td>Follicular Carcinoma</td>
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<td>Follicular Adenoma</td>
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<tr>
<td>Lymphocytic Thyroiditis</td>
<td>55% (11)</td>
<td>43 % (6)</td>
<td>83% (5)</td>
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<td>Papillary Thyroid Carcinoma</td>
<td>60% (12)</td>
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<tr>
<td>C-cell Hyperplasia</td>
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<td>83% (5)</td>
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<tr>
<td>Nodular Hyperplasia</td>
<td>25% (5)</td>
<td>28% (4)</td>
<td>17% (1)</td>
</tr>
</tbody>
</table>
Thyroid Pathology

- Multiple adenomatous nodules (MAN) are characteristic findings in these syndromes
- Gross: multiple firm yellow-tan well-circumscribed unencapsulated nodules
- These nodules are multicentric, bilateral
- Features similar to follicular adenomas
- The majority of carcinomas arise in a background of MAN
PTEN expression appears to be both sensitive and specific for Cowden syndrome

3. Genodermatosis

- The great majority (almost 100%) of affected CS individuals, by the third decade of life, develop the mucocutaneous stigmata lesions, as trichilemmomas, papillomatous papules, acral and plantar keratoses
- Facial lesions occur in the majority of patients
Genodermatosis: Major Diagnostic Criteria

Multiple mucocutaneous lesions (any of the following):
1. Multiple trichilemmomas ($\geq 3$, at least one biopsy proven)
2. Acral keratoses ($\geq 3$ palmoplantar keratotic pits and/or acral hyperkeratotic papules)
3. Mucocutaneous neuromas ($\geq 3$)
4. Oral papillomas (particularly on tongue and gingiva), multiple ($\geq 3$) OR biopsy proven OR dermatologist diagnosed

Mucocutaneous Neuromas

- More than half of CS patients develop mucocutaneous neuromas before age of 18 years
- At least three mucocutaneous neuromas present on the face or elsewhere on the body, with or without a skin biopsy, should count as a major diagnostic feature of CS/PHTS

Cowden syndrome

- Trichilemmomas and mucocutaneous papillomatous papules are one of the first signs of the disease
Trichilemmomas

- The most distinctive and peculiar facial features of CS consist of multiple small and keratotic papules concentrated around the orifices and are usually connected with hair follicles
- Multiple trichilemmomas are present in the central portion of the face, including the eyes, nose, mouth, and forehead

Trichilemmomas

- Is a hamartoma of the hair follicle infundibulum
- Most are sporadic
- Multiple are pathognomonic for Cowden syndrome

Trichilemmomas

- Trichilemmoma is a clinically significant sign of CS when seen in multiplicity (at least $\geq 3$), but at least one lesion should be biopsy-proven given the difficulty with clinical diagnosis
PTEN expression in trichilemmomas associated with Cowden syndrome

Oral papillomas
• Oral papillomas are a major criterion for diagnosis of CS
• Oral papillomas are usually present in the lips and can be found also in the tongue, buccal mucosa, and gingivae.
### Oral papillomas

- Some authors have reported CS families with 100% of patients developed oral papillomas by the second decade
- Diagnoses in these patients were characteristically based on dermatological features
- Oral papillomas are typically asymptomatic and thus can be distinguished from mucocutaneous neuromas in the same location

### 4. Conclusion

- A diagnosis of CS is important because it confers a significant risk for cancer
- Recognition of CS is important so that cancer screening and genetic counseling can be initiated

### 4. Conclusion

- Multiple syndromes are now known to be associated with characteristic skin neoplasms
- Early recognition of these skin lesions may help in an early diagnosis of the underlying malignancies that occur in CS patients

**Thank you! Questions?**