Hereditary Colonic Polyposis Syndromes

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Park City Pathology Course 2015
Disclosure

- Honorarium ad hoc consulting for Invitae
Colorectal Cancer

- Sporadic (70%)
- Familial (25%)
- Lynch (2-4%)
- FAP-MAP (< 1%)
- Hamartomatous/other polyposis syndromes (< 1%)
Familial CRC

- 626 CRCs < age 56 and family history of CRC
- MLH1, MSH2, MSH6, PMS2, APC, MUTYH, SMAD4, BMPR1A, POLE, POLD1
- 17% to 28% of familial CRCs were found to have a genetic diagnosis
Syndromes Associated With CRC

- Lynch syndrome (LS)
- Familial adenomatous polyposis (FAP)
- MUTYH-associated polyposis (MAP)
- Serrated polyposis syndrome (SPS)
- Li-Fraumeni syndrome (LFS)
- Peutz-Jeghers syndrome (PJS)
- Juvenile polyposis syndrome (JPS)
- Cowden syndrome (CS)
- Constitutional mismatch repair deficiency (CMMRD) syndrome
- POLE and POLD1 (CRC and adenoma predisposition)
- GREM1 (Hereditary mixed polyposis (HMP) syndrome)
- adenomatous polyps
- Pediatric cancer syndrome with increase risk of CRC
- Hamartomatous polyps
- Not really a syndrome: serrated polyps and adenomas
- Rare syndromes/Genes associated with CRC
## Syndromes/Genes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAP/AFAP</td>
<td><em>APC</em></td>
</tr>
<tr>
<td>MAP</td>
<td>Biallelic <em>MUTYH</em></td>
</tr>
<tr>
<td>CMMRD</td>
<td>Biallelic <em>MLH1, MSH2, MSH6, PMS2, EPCAM</em></td>
</tr>
<tr>
<td>PJS</td>
<td><em>STK11</em></td>
</tr>
<tr>
<td>JPS</td>
<td><em>SMAD4, BMPR1A</em></td>
</tr>
<tr>
<td>CS</td>
<td><em>PTEN</em></td>
</tr>
<tr>
<td>HMP</td>
<td><em>GREM1</em></td>
</tr>
<tr>
<td>?</td>
<td><em>POLE, POLD1</em></td>
</tr>
<tr>
<td>SPS</td>
<td>?</td>
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</tbody>
</table>
Inherited Syndromes and CRC Risk
Familial Adenomatous Polyposis (FAP)

- 100’s to 1000’s of colonic adenomatous polyps
- Penetrance for colorectal adenomas > 90% by age 40
- ~100% risk for CRC in untreated cases
- Risk of extra-colonic cancer
FAP: Genetics

• Incidence: ~1 in 10,000 births
• Genetics
  – Autosomal dominant
  – Gene: APC (5q)
  – ~ 25% of patients have negative family history
  – Genotype/phenotype correlations
FAP: Age and Development of Adenomas and CRC

- % of patients with neoplasia

Bussey HJR. Familial Polyposis Coli, 1975

ASCO
Other Polyps

- **Small bowel polyps (adenomas)**
  - Typically occur in the duodenum and ampulla
  - Occur in approximately 60-80%
  - Approximately 4-12% risk for duodenal/ampullary malignancy
  - Spigelman staging criteria used to predict degree of dysplasia and how frequently to screen

- **Gastric polyps (mainly fundic gland polyps)**
  - ~90% will have fundic gland polyps
  - Low risk of gastric malignancy but still increased compared to general population
FAP: Extra-Colonic Cancers

Lifetime Risk (%)

- Peri-ampullary
- Pancreatic
- Thyroid
- Gastric
- CNS
- Hepatoblastoma
FAP: Hepatoblastoma Risk

• General Population
  – 1% of all pediatric cancers
  – 0.5 - 1.5 diagnosis per 1 million children (younger than 15 years)

• FAP
  – 0.7 to 1.6% in children under age 5

FAP Variants

- **Gardner syndrome**
  - FAP with extra-intestinal growths

- **Turcot syndrome**
  - FAP and brain tumor (medulloblastoma)
  - 2/3 of Turcot have *APC* mutations

- **Attenuated FAP**
  - < 100 polyps and older age of CRC onset ~50’s
Gardner Syndrome

- Desmoid tumors
- Osteomas
- Supernumerary teeth
- CHRPE
- Soft tissue skin tumors
Desmoid Tumor
CHRPE

Attenuated FAP (AFAP)

- Average 30 colonic polyps (may be more than 100, but typically at later ages), more proximal in location
- CRC ~70% lifetime risk
- Later onset (CRC ~age 50)
- Fundic gland polyps and duodenal adenomas: similar presentation as classic FAP
FAP: Colorectal Management

- Annual colonoscopy
  - Start at age 10 to 12 years for FAP
  - 18-20 for AFAP
- Prophylactic colectomy in all FAP and in some AFAP cases
- Subsequent surveillance for rectal, pouch, and extracolonic tumors
MUTYH Associated Polyposis (MAP)

- Similar to AFAP phenotype
- 15 - 100 adenomas, can be > 100
- Multiple serrated polyps may occur
- Older age of CRC onset (~50’s)
- Autosomal recessive!
• *MUTYH (MYH)* gene-accomplishes oxidative damage repair

• Part of base excision repair pathway

• Two common mutations in Caucasian population (Y165C and G382D)
Reviewed 276 MAP cases

- Seventy-seven (28%) had at least 1 extra-intestinal tumor
- Compared to the general population, the incidence of extraintestinal malignancies was almost doubled in MAP patients (SIR: 1.9; 95% CI: 1.4 –2.5) and lifetime risk was 38% (95% CI: 23%–52%)
- No osteomas or desmoids

Of 150 patients who underwent EGD

- 17 (11%) had gastric lesions
- 26 (17%) had duodenal polyposis
- Cumulative lifetime risk was 4% for duodenal cancer
Genetic Testing: APC and MUTYH

- Colonic adenomas: ≥ 20 or fewer (>10) if young
  - APC and MUTYH
- Genetic diagnosis
  - adenomas = % APC mutation
  - other types of polyps = % APC mutation
  - > 500 adenomas = % MUTYH
  - Fundic gland polyposis = % APC mutation
  - Family history of colonic polyps: =
    - % APC if in parent or child
    - % MUTYH if in siblings only
Early Onset CRC w/o Polyposis

- Early onset CRC with few adenomas and normal tumor testing
  - Limited data to support APC, MUTYH, or p53

- 89 Dutch patients with CRC < 40 (or meeting other BGs) and MSS/MSI-low tumors
  - MUTYH (common mutations) no mutations found

Peutz-Jeghers Syndrome (PJS)

- Autosomal dominant
- 1 in 200,000 live births
- Peri-oral melanin pigment >95% of cases
- Characteristic polyps throughout GI tract
  - Occur more commonly in small bowel
- Commonly presents with intussusception in childhood
- Gene: STK11
PJS

• Tumor risks
  – Colorectal cancer (39%)
  – Esophageal (0.5%)
  – Small bowel (13%)
  – Gastric (29%)
  – Pancreatic (36%)
  – Sex cord tumors with annular tubules (SCTAT) (21%)
  – Breast cancer (54%)
  – Adenoma malignum of the cervix (10%)
  – Sertoli cell tumors of the testes (9%)

Cancer risks sited are cumulative risks from age 15-64

Giardiello FM et al. 2000
PJS, GI Cancers

Lifetime risk (%)

- Colon: 40%
- Pancreas: 35%
- Stomach: 25%
- Small Intestine: 15%
- Esophagus: 0%
PJS, Non-GI Cancers

![Bar graph showing lifetime risk (%) for non-GI cancers. The highest risk is for breast cancer, followed by ovary, lung, cervix, uterus, and testes.]
PJS: Diagnostic Criteria

Proband meets both criteria

- Two or more histologically confirmed PJS-type hamartomatous polyps
- Any number of PJS-type polyps detected in one individual who has a family history of PJS in a close relative(s)
- Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in a close relative(s)
- Any number of PJS-type polyps in an individual who also has characteristic mucocutaneous pigmentation

Juvenile Polyposis Syndrome

- Juvenile polyps mainly in the colon
  - Anemia and obstruction due to size and number of polyps
- Characteristic cancers: colon (~40%) and gastric (20%, mainly in individuals with gastric polyps)
- Other cancers may occur
- Symptomatic presentations
  - <30 years, benign complications
  - >30 malignant complications
- Multiple congenital anomalies in some individuals (cardiovascular, urogenital or CNS abnormalities)
JPS: Genetics

- Incidence: ~1 in 100,000
- Genetics
  - Autosomal dominant
    - SMAD4 (18q21) ~20-25%
    - BMPR1A (10q22-23) ~20-25%
JPS/Hereditary Hemorrhagic Telangiectasia (HHT)

- ~15%-22% of individuals with SMAD4 mutations will have the combined JPS/HHT syndrome.
- Individuals with the combined JPS/HHT syndrome have variable findings of juvenile polyposis and some of the following:
  - epistaxis
  - mucocutaneous telangiectases
  - arteriovenous malformations (AVMs): pulmonary, hepatic AVMs, cerebral, and GI
  - intracranial bleeding
- Findings of HHT may manifest in early childhood.
Juvenile Polyposis

Diagnostic Criteria

Any one of the following:

- More than five juvenile polyps of the colorectum
- Multiple juvenile polyps of the upper and lower GI tract
- Any number of juvenile polyps and a family history of juvenile polyps
Cowden Syndrome
PTEN Hamartoma Tumor Syndrome

- Characteristic skin findings and macrocephaly
- Colon cancer risk 9-16%
- Extra-colonic cancers:
  - Thyroid: 3-10% lifetime risk (Tan et al. = 35.2%)
  - Endometrial: slightly increased over average (Tan et al. = 28.2%)
  - Urinary tract/kidney slightly increased: (Tan et al. = 33.6%)
  - Melanoma = not previously a recognized component of Cowden syndrome (Tan et al. = 6% risk)

Cowden Syndrome

- Hamartomatous polyps throughout GI tract
  - Hamartomas are the most common histologic type, occurring in up to 29% in one study
- Colon polyps
  - Juvenile polyps, ganglioneuromas, adenomas, inflammatory polyps, hyperplastic polyps, sessile serrated polyps
  - Less commonly leiomyomas, lipomas and lymphoid polyps
- Hamartomatous polyps in the stomach, duodenum and small bowel
- Diffuse esophageal glycogenic acanthosis
Serrated Polyposis Syndrome (Hyperplastic polyposis)

- Increased risk of CRC, magnitude unknown
- Serrated polyps: sessile serrated polyp (sessile serrated adenoma), hyperplastic polyp, traditional serrated adenoma
- No known genetic cause
  - Some cases with MAP will meet criteria for SPS, although they usually have more adenomas than serrated polyps. Patients with Cowden syndrome may also technically meet criteria
- Family history of CRC is common, although these typically occur at older ages
- The risk of CRC for family members is unknown
- No proven extra-colonic features, though some studies suggest there is an increased risk
Serrated Polyposis

- WHO Diagnostic criteria, any one of the following:
  - > 20 serrated polyps distributed throughout colon
  - ≥ 5 serrated polyps proximal to the sigmoid colon, 2 of which are greater than 10 mm
  - ≥ 1 serrated polyps occurring proximal to the sigmoid colon in an individual who has at least one first-degree relative with serrated polyposis
Constitutional MMR deficiency (CMMRD) syndrome

- Autosomal recessive, biallelic MMR
- Childhood onset, sometimes infancy
- Characteristic features:
  - Hematologic malignancies
  - Brain tumors
  - Lynch syndrome tumors (colon, uterine, small bowel, etc)
  - Signs of NF1
    - Café au lait spots, skin-fold freckling, Lisch nodules and neurofibromas
CMMRD Cancers

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>n=14/32</th>
<th>n=10/29</th>
<th>n=21/85</th>
</tr>
</thead>
<tbody>
<tr>
<td>hematological</td>
<td>7</td>
<td>9</td>
<td>2.5</td>
</tr>
<tr>
<td>brain</td>
<td>7</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>LS-associated</td>
<td>16</td>
<td>19</td>
<td>14.5</td>
</tr>
<tr>
<td>mean age (y) at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- MLH1/MSH2
- MSH6
- PMS2

*(p=0.01) |

*(p=0.04) |
CMMRD Non-Malignant Tumors

Premalignancies and non-malignant tumours in 146 CMMRD patients

<table>
<thead>
<tr>
<th>Type of neoplasia</th>
<th>Number of patients</th>
<th>Median age at first diagnosis in years</th>
<th>Age range at first diagnosis in years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomas/polyps of colon and rectum</td>
<td>52</td>
<td>14</td>
<td>6–46</td>
</tr>
<tr>
<td>Duodenal adenomas/polyps</td>
<td>8</td>
<td>14</td>
<td>10–32</td>
</tr>
<tr>
<td>Gastric polyps</td>
<td>1</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>Hepatic adenomas</td>
<td>3</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>Neurofibromas</td>
<td>7</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>Optic glioma</td>
<td>1</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Pilomatrixomas (epithelioma of Malherbe)</td>
<td>2</td>
<td>2 years 8 months</td>
<td>–</td>
</tr>
<tr>
<td>Polyps of vocal cord</td>
<td>1</td>
<td>in infancy</td>
<td>–</td>
</tr>
</tbody>
</table>

NF Features

Figure 3  Signs of NF1 in the index patient of family 2. (a–c) CALS in the right inguinal region, right upper arm, and dorsum, respectively. (d) Freckling in the right axilla.
Case 1

- 35 yo male presents with hematochezia
- Colonoscopy reveals obstructing descending colon mass, scope not completed
- Biopsy reveals invasive moderately differentiated adenocarcinoma. No mention of polyps
- Subtotal colectomy was performed
- Referred to genetics
Case 1 Continued

- No family history of cancer or polyps
- Proband reports no personal history of polyps (surgical report not available during visit)
- MSI and IHC performed revealed
  - MSI-high
  - IHC (absent MLH1 and PMS2, normal MSH2 and MSH6)
- Differentials
  - Lynch syndrome
  - Sporadic colon cancer
  - Others?
Case 1 Continued

• Genetic testing of MLH1 and PMS2 revealed no mutation
• Promoter MLH1 hypermethylation testing was positive
• Confused yet???
• Surgical path report has one line out of four or five pages that reads: numerous polyps in surgical specimen, sessile serrated polyps
• Follow up completion colonoscopy reveals > 20 sessile serrated and/or hyperplastic polyps
Case 1 Conclusions

- Diagnosis: serrated polyposis syndrome
- Take home points:
  - SPS is associated with hypermethylation of MLH1 which is also seen in sporadic CRCs
  - Important to look at all/most colonoscopy and pathology records to determine appropriate differential diagnoses
Case 2

- 53 year old male referred for Gardner syndrome originally diagnosed in his 20s
- Colonic and gastric polyposis: polyp types not known
- Small bowel polyp/s: adenomas
- Astrocytoma age 45
- APC/MUTYH negative
- Differentials
  - Mosaicism
  - Missed mutation
  - Other syndrome
Case 2 Conclusions

• Panel genetic testing
  – SMAD4 deleterious mutation confirming JPS

• Take home points:
  – JPS may be misdiagnosed as FAP
  – Important to look at all/most colonoscopy and pathology records to determine appropriate differential diagnoses
  – Genetic testing is key in confirming diagnosis
Case 3

- 30 year old male presented to genetics with a recent diagnosis of descending colon cancer with > 20 adenomatous colon polyps
- Past history included
  - Colon cancer at 13 yo with subtotal colectomy (no records available)
  - Glioblastoma diagnosed at age 26
- Family history non-contributory
- Café au lait macules and axillary freckling
- Diagnosis?
Case 3 Continued

- Uninsured: Proceeded with panel genetic test because tumor testing was not an option
- MSI-high colon cancer
- MSI-stable brain tumor
- IHC
  - Absent PMS2 in colon cancer and normal tissue
  - Normal MLH1 and MSH2
  - Absent MSH6 in colon cancer, but present in normal tissue
Case 3 Conclusions

- Diagnosis:
  - Constitutional mismatch repair deficiency syndrome
- May present with colonic polyposis and look similar to other polyposis conditions
- Exceptionally young age of Lynch syndrome cancers
  - Childhood onset CRCs: CMMRD, LFS, others?
- Signs of NF1 are key
- IHC may be uninformative
Patterns or Something Unusual
# Hereditary CRC Syndromes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Phenotype</th>
<th>Lifetime CRC Risk</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Familial adenomatous polyposis, attenuated familial adenomatous polyposis</td>
<td>&gt;100 adenomas 10-100 adenomas</td>
<td>100% 80%</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>MYH</td>
<td>MYH Associated Polyposis</td>
<td>10-100s adenomas</td>
<td>~80%</td>
<td>1 in 40,000 to 1 in 20,000</td>
</tr>
<tr>
<td>POLE</td>
<td>Polymerase Proofreading Polyposis</td>
<td>&gt;5 adenomas, young onset colorectal cancer</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>POLD1</td>
<td>Polymerase Proofreading Polyposis</td>
<td>&gt;5 adenomas, young onset colorectal cancer</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>GREM1</td>
<td>Hereditary Mixed Polyposis</td>
<td>Multiple adenomas, hamartomas and serrated polyps Ashkenazi Jewish ancestry</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>MLH1</td>
<td>Lynch Syndrome</td>
<td>CRC, EC, other tumors, MSI</td>
<td>48-56%</td>
<td>1 in 400</td>
</tr>
<tr>
<td>MSH2</td>
<td>Lynch Syndrome</td>
<td>CRC, EC, other tumors, MSI</td>
<td>48-56%</td>
<td>1 in 400</td>
</tr>
<tr>
<td>MSH6</td>
<td>Lynch Syndrome</td>
<td>CRC, EC, other tumors, MSI</td>
<td>9-23%</td>
<td>1 in 400</td>
</tr>
<tr>
<td>PMS2</td>
<td>Lynch Syndrome</td>
<td>CRC, EC, other tumors, MSI</td>
<td>15-20%</td>
<td>1 in 400</td>
</tr>
<tr>
<td>EPCAM</td>
<td>Lynch syndrome</td>
<td>CRC, EC, other tumors, MSI</td>
<td>75%</td>
<td>1 in 400</td>
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<tr>
<td>SMAD4</td>
<td>Juvenile polyposis syndrome</td>
<td>≥5 juvenile polyps</td>
<td>9-50%</td>
<td>1 in 100,000 to 1 in 160,000</td>
</tr>
<tr>
<td>BMPRIA</td>
<td>Juvenile polyposis syndrome</td>
<td>≥5 juvenile polyps</td>
<td>9-50%</td>
<td>1 in 100,000 to 1 in 160,000</td>
</tr>
<tr>
<td>STK11</td>
<td>Peutz-Jehger's syndrome</td>
<td>P-J polyp/muco-cutaneous pigmentation, family history</td>
<td>36%</td>
<td>1 in 250,000 to 1 in 280,000</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden syndrome</td>
<td>Macrocephaly, hamartomas, and cutaneous manifestations</td>
<td>9%</td>
<td>1 in 200,000</td>
</tr>
<tr>
<td>TP53</td>
<td>Li Fraumeni Syndrome</td>
<td>Early onset colorectal cancer</td>
<td>Unknown</td>
<td>1 in 5,000 to 1 in 20,000</td>
</tr>
<tr>
<td>CDH1</td>
<td>Hereditary diffuse gastric cancer</td>
<td>Signet ring cell colorectal cancer</td>
<td>Unknown</td>
<td>10 to 40 in 100,000</td>
</tr>
</tbody>
</table>

Courtesy Brandie Leach
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene (frequency mutation found)</th>
<th>CRC risk (mean age of diagnosis)</th>
<th>Polyp histology</th>
<th>Polyp distribution</th>
<th>Mean age of GI symptom onset</th>
<th>Other disease manifestations</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hereditary Polyposis syndromes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Familial adenomatous polyposis</strong>&lt;sup&gt;1&lt;/sup&gt; (FAP)</td>
<td>APC (70-90%)</td>
<td>100% (39 years), AFAP&lt;sup&gt;2&lt;/sup&gt; 69% (58 years)</td>
<td>Adenomatous, except stomach: fundic gland polyps</td>
<td>Stomach: 23%-100% Duodenum: 50%-90% Jejunum: 50% Ileum: 20% Colon: 100%</td>
<td>35.8 years, AFAP&lt;sup&gt;2&lt;/sup&gt; 52 years</td>
<td>Desmoid tumors, epidermoid cysts, fibromas, osteomas, CHRPE&lt;sup&gt;3&lt;/sup&gt;, adrenal adenomas, dental abnormalities, pilomatrixomas, nasal angiofibromas</td>
<td>Duodenal or periampullary: 3%-5%, rare pancreatic, biliary, thyroid, gastric, CNS&lt;sup&gt;4&lt;/sup&gt;, hepatoblastoma, small bowel</td>
<td></td>
</tr>
<tr>
<td><strong>MUTYH associated polyposis (MAP)</strong></td>
<td>MUTYH recessive inheritance (16% to 40% if 15-100 adenomas and 7.5% to 12.5% if &gt; 100 adenomas but not FAP)</td>
<td>93-fold increased risk (48 years)</td>
<td>Adenomatous, hyperplastic, sessile serrated</td>
<td>Stomach: 11% Duodenum: 17% Colon: usually</td>
<td>Not determined</td>
<td>Sebaceous gland adenomas and epitheliomas, lipomas, CHRPE&lt;sup&gt;3&lt;/sup&gt;, osteomas, desmoid tumors, epidermoid cysts, and pilomatrixomas</td>
<td>Duodenal 4%, sebaceous gland carcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>Serrated polyposis syndrome (SPS)</strong></td>
<td>?</td>
<td>Up to 50% or greater in some studies (63 years)</td>
<td>Hyperplastic, sessile serrated, traditional serrated adenomas, adenomatous</td>
<td>Colon</td>
<td>48 years</td>
<td>None</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td><strong>Peutz-Jeghers syndrome (FJS)</strong></td>
<td>STK11 (80% to 94%)</td>
<td>39% (46 years)</td>
<td>Peutz-Jeghers, Adenomatous</td>
<td>Stomach: 24% Small bowel: 96% Colon: 27% Rectum: 24%</td>
<td>22-26 years</td>
<td>Mucocutaneous melanin pigment spots</td>
<td>Pancreatic 36%, gastric 29%, small bowel 13%, breast 54%, ovarian 21%, uterine 9%, lung 15%, testes 9%, cervix 10%</td>
<td></td>
</tr>
<tr>
<td><strong>Juvenile polyposis syndrome (JPS)</strong></td>
<td>SMAD4, BMPR1A (up to 60%)</td>
<td>Up to 68% (34 years)</td>
<td>Juvenile, Adenomatous</td>
<td>Stomach: 14% Duodenum: 7% Small bowel: 7% Colon: 98%</td>
<td>18.5 years</td>
<td>Macrocephaly, hypertelorism, 20% congenital abnormalities in sporadic type</td>
<td>Stomach and duodenum combined up to 21%</td>
<td></td>
</tr>
<tr>
<td><strong>PTEN hamartoma tumor syndrome (PHTS)</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>PTEN (30% to 55%)</td>
<td>9% to 16%</td>
<td>Juvenile, adenomatous, lipomas, inflammatory, ganglioneuromas, lymphoid hyperplasia</td>
<td>Esophagus: 66% Stomach: 75% Duodenum: 37% Colon: 66%</td>
<td>Not determined</td>
<td>Macrocephaly, Lhermitte-Duclos disease, trichelemmomas, oral papillomas, cutaneous lipomas, macular pigmentation of the glans penis, autism spectrum disorder, esophageal glycogenic acanthosis, multinodular goiter, vascular anomalies</td>
<td>Breast 85%, thyroid 35%, kidney 34%, endometrium 28%, melanoma 6%</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>FAP, familial adenomatous polyposis, includes Gardner syndrome, 2/3rds of Turcot syndrome cases and AFAP

<sup>2</sup>AFAP, attenuated familial adenomatous polyposis

<sup>3</sup>CHRPE, congenital hypertrophy of the retinal pigment epithelium

<sup>4</sup>CNS, central nervous system

<sup>5</sup>Includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome and adult Lhermitte-Duclos disease
## Additional conditions that exhibit gastrointestinal polyposis

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
<th>Cause</th>
<th>Histology of polyps</th>
<th>GI areas affected</th>
<th>Other disease manifestations</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Syndromes where polyps contain neural elements</strong></td>
<td>Neurofibromatosis type I (NFI)</td>
<td>Mutations of NF1 gene, autosomal dominantly inherited</td>
<td>Neurofibromas and ganglioneuromas</td>
<td>Small bowel-&gt;stomach&gt;colon</td>
<td>Café-au-lait spots</td>
<td>Cutaneous neurofibromas</td>
<td>Ampullary carcinoid, phenochromocytoma, GISTS¹</td>
</tr>
<tr>
<td></td>
<td>Multiple endocrine neoplasia type IIb (MEN2B)</td>
<td>Mutation of RET proto-oncogene, autosomal dominantly inherited</td>
<td>ganglioneuromas</td>
<td>Lips to anus, but most common in colon and rectum</td>
<td>Pheochromocytoma, parathyroid adenoma</td>
<td>Medullary thyroid carcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>Syndromes of uncertain etiology</strong></td>
<td>Cronkhite-Canada syndrome</td>
<td>Possibly infectious</td>
<td>Juvenile polyps</td>
<td>Stomach to anus</td>
<td>Skin hyperpigmentation, hair loss, nail atrophy, hypogeusia</td>
<td>12% to 15% colon cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serrated polyposis</td>
<td>Possibly inherited</td>
<td>Serrated</td>
<td>Colon</td>
<td>None known</td>
<td>Colon cancer risk probably increased</td>
<td></td>
</tr>
<tr>
<td><strong>Conditions with inflammatory polyps</strong></td>
<td>Inflammatory bowel disease</td>
<td>Crohn’s disease and ulcerative colitis</td>
<td>Pseudopolyps</td>
<td>Colon</td>
<td>As in inflammatory bowel disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Devon polyposis</td>
<td>Inherited</td>
<td>Fibroid polyps</td>
<td>Ileum, stomach</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cap polyposis</td>
<td>Unknown, possibly internal prolapse</td>
<td>Similar to solitary rectal ulcer</td>
<td>Rectosigmoid</td>
<td>Rectal bleeding</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Polyposis conditions arising from lymphoid tissue</strong></td>
<td>Nodular lymphoid hyperplasia</td>
<td>Isolated-&gt;immuno-deficiency-&gt;lymphoma</td>
<td>Hyperplasia of lymphoid nodules</td>
<td>Small bowel, stomach, colon</td>
<td>Related to underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple lymphomatous polyposis</td>
<td>A type of mantle cell lymphoma</td>
<td>Multiple malignant lymphomatous polyps</td>
<td>Small bowel and colon &gt;stomach</td>
<td>None known</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immunoproliferative small intestinal disease (a MALT² lymphoma)</td>
<td>Most cases from Campylobacter jejuni infection</td>
<td>Plasma cell proliferation</td>
<td>Small bowel</td>
<td>Malabsorption, progression to lymphoplasmacytic and immunoblastic lymphoma if not treated in early stages</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous non-inherited polyposis conditions</strong></td>
<td>Leiomyomatosis</td>
<td>Not known</td>
<td>Leiomyoma</td>
<td>Colon, other</td>
<td>None known</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lipomatous polyposis</td>
<td>Not known</td>
<td>Lipoma</td>
<td>Colon, other</td>
<td>None known</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple lymphangiomas</td>
<td>Not known</td>
<td>Lymphangioma</td>
<td>Colon</td>
<td>None known</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumatosis cystoides intestinalis</td>
<td>Not known</td>
<td>Inflammatory and air spaces</td>
<td>Colon and other GI locations</td>
<td>None known</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹GISTS, gastrointestinal stromal tumors  
²MALT, mucosa-associated lymphoid-tissue
Questions

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