Inheritance and Genetic Testing for Colon Cancer

Randall W. Burt, M.D.,
Huntsman Cancer Institute at the University of Utah
Salt Lake City, Utah
Genetic Testing for GI Cancer Susceptibility

- Description of syndromes
- Genetic testing approach
- New developments for common familial colon cancer risk
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAP</td>
<td>APC, MYH (rare)</td>
</tr>
<tr>
<td>HNPCC</td>
<td>MLH1, MSH2, MSH6, PMS2 (rare)</td>
</tr>
<tr>
<td>Peutz-Jegher</td>
<td>STK11</td>
</tr>
<tr>
<td>Juvenile Polypososis</td>
<td>SMAD, BMPR1A</td>
</tr>
<tr>
<td>Cowden Syndrome</td>
<td>PTEN</td>
</tr>
</tbody>
</table>
Colon Cancer Risk in the Inherited Syndromes

- FAP
- HNPCC
- PJ
- JP
- CS
FAP

• About 1 in 10,000 births

• Autosomal dominantly inherited

• 100’s to 1000’s of colonic adenomatous polyps

• Average age of polyp occurrence, 16 years
Early FAP
FAP, Colon Cancer

• Near 100% risk
• Average age of diagnosis 39 yrs
• 7% have colon cancer by age 21
• 93% have colon cancer by age 50
FAP, Extra-Colonic Cancers

Life-time Risk(%)
FAP, Gene Discovery

- Disease description, Bussey, Gardner
- Search for the gene, Bodmer, White
- Lem Herrera at Roswell Park
- Adenomatous polyposis coli gene
The APC Tumor Suppressor Gene

Codon 1309
APC Gene Mutations Lead to 80% of all Colon Cancers

APC gene

Inherited mutation

Acquired mutation
Attenuated FAP

- Average of 30 adenomas
- Neoplasm occurrence delayed by about 10 years
- Adenomas more proximal
- Lifetime CRC risk 50-80%

Kundsen AL, Fam Cancer 2003; 2:43-55
MYH Gene

Accomplishes Oxidative Damage Repair

- Autosomal recessive
- Present in 6-10% of APC negative FAP patients with a moderate phenotype

HNPCC

- Few adenomas
- 80% CRC risk, mean 44 yrs
- More proximal colonic
- Frequent synchronous and metachronous CRC
HNPCC, Extra-Colonic Cancers

Life-time Risk (%)

Edometrial: 40
Ovarian: 10
Gastric: 25
Urinary tract: 15
Renal cell: 5
Biliary: 20
CNS: 5
Small Bowel: 10
Genes That Give Rise to HNPCC

HNPCC is associated with germline mutations in any one of five mismatch repair genes:

- **MSH2** on Chr 2
- **MSH6** on Chr 2
- **MLH1** on Chr 3
- **PMS1** on Chr 2
- **PMS2** on Chr 7
MMR Gene Mutations Lead to 15% of all Colon Cancers

MMR genes

- Inherited mutation
- Acquired mutation
Amsterdam II Criteria

CRC or other HNPCC cancers

- 3 relatives with cancer, 2 FDR of the third
- 2 generations affected
- 1 diagnosis <50 years of age

Vasen HF, Gastro 1999; 116:1453-6
Revised Bethesda Guidelines: When to do MSI or IHC tests on the tumor?

- CRC <50 years
- Person with 2 HNPCC tumors
- CRC with MSI histology (signet ring, etc)
- 2 FDR with HNPCC tumors, one < 50 years
- CRC in 2 or more FDR or SDR of person with an HNPCC tumor, any age

When to Suspect HNPCC

- Two relatives with colon cancer
- Colon cancer diagnosed under age 50 years
Genetic Testing for HNPCC

Amsterdam II Criteria

Revised Bethesda

MSI/IHC on tumor

Genetic Testing

Fraction of Cases to be tested for HNPCC

- Sporadic
- Any Familial Risk
- High Familial Risk, 10% to 15% of cases -- test these
- Hamartomatous Polyposis
- FAP
- HNPCC 1% to 3%
Peutz-Jeghers Syndrome

- 1 in 200,000 persons
- Peri-oral melanin pigment
- PJ polyps throughout GI tract
- Cancer risk 93% by age 65
PJS, Non-GI Cancers

Breast
Ovary
Lung
Cervix
Uterus
Testes

Life-time risk (%)
Juvenile Polyposis

- >10 juvenile polyps
- 1 in 100,000
- Up to 50% CRC risk
Cowden Syndrome

- 1 in 200,000
- Juvenile polyps throughout GI tract
- Tricholemmomas
- 17% CRC risk
- Extra-GI cancers:
  - Thyroid, 3% to 10%
  - Breast 25% to 50%
  - Uterine and ovarian, increased
Genetic Testing in the Inherited Syndromes

- Test person known to have the syndrome, usually by DNA sequencing
- Mutation not found: screen all relatives
- Mutation found:
  - Test relatives with mutation specific testing
  - Accuracy near 100%
Summary: Genetic Counseling and Informed Consent

- Medical issues
- Genetic issues
- Psychological issues
- Social/economic issues
- Children’s rights
Success of Finding Mutation in Initial Case

- FAP: 90%
- HNPCC: 50% to 70%
- Peutz-Jeghers: 50%
- Juvenile Polyposis: 50%
- Cowden syndrome: 90%
When to use Genetic Testing

1. When an inherited syndrome is suspected:

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAP</td>
<td>&gt; 10 to 20 adenomas</td>
</tr>
<tr>
<td>HNPCC</td>
<td>Amster/Beth criteria</td>
</tr>
<tr>
<td>PJ</td>
<td>PJ Polyps, pigment</td>
</tr>
<tr>
<td>JP</td>
<td>&gt;10 JP’s</td>
</tr>
<tr>
<td>CS</td>
<td>Trichelelemmoma</td>
</tr>
</tbody>
</table>

2. In relatives of a person with a genetic diagnosis=mutation specific testing
Inherited Colon Cancer

- **Sporadic cases**

- **HNPCC**, 1%-3%
- **HNPCC, 1%-3%**
- **FAP, <1%**
- Hamartomatous polyposis, <1%
- **Other inherited cases, 32%**

LOI of IGF2

- Present in colonic mucosa of 30% of CRC patients and 10% of healthy persons
- LOI of IGF2 in peripheral lymphocytes:
  - Patients with adenomas, OR=3.5 (1.1-11.4)
  - Patients with CRC, OR=21.7 (3.5-154)
  - Patients with Fm Hx CRC, OR=5.2 (1.7-17.0)

MYH Gene

Accomplishes Oxidative Damage Repair

Present in 1/3\textsuperscript{rd} of patients with >15 colonic adenomatous polyps but not FAP

## Moderate Susceptibility Markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Trait</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTHFR (Folate reductase)</td>
<td>Folate, B12, B6, Etoh</td>
</tr>
<tr>
<td>Microsomal epoxide hydrolase</td>
<td>Smoking, cooked meat</td>
</tr>
<tr>
<td>NAT2</td>
<td>Smoking</td>
</tr>
<tr>
<td>Thymidylate synthase</td>
<td>Folate inverse relation</td>
</tr>
<tr>
<td>?mild mutations of APC, MMR genes</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- Genetic testing now available for syndromes
  - Test possible syndrome cases
  - Test in families once mutation identified
- 10% to 15% of colon cancer cases need to be considered for genetic testing
- Genetic testing may soon be available for more common colon cancer susceptibility