Inherited Predispositions to Bowel Cancer: Lynch Syndrome

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Definitions

• Hereditary Non Polyposis Colorectal Cancer (HNPCC) = families that fulfill a set of criteria (Amsterdam, Bethesda etc.)

• Lynch Syndrome (LS) = families where a DNA mismatch repair causative variant has been identified
## Genetic Predispositions to Colorectal Cancer

### Syndromes associated with polyposis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Disease Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
<td>Colonic polyposis</td>
</tr>
<tr>
<td>Polyposis</td>
<td>MUTYH</td>
<td>Colonic polyposis (recessive inheritance)</td>
</tr>
<tr>
<td>Gardner’s syndrome</td>
<td>APC</td>
<td>Colonic polyposis in association with extra-colonic lesions</td>
</tr>
<tr>
<td>Oldfield’s syndrome</td>
<td>APC</td>
<td>Colonic polyposis with sebaceous cysts.</td>
</tr>
<tr>
<td>Turcot syndrome*</td>
<td>APC</td>
<td>Malignant tumours of the CNS in association with polyposis</td>
</tr>
<tr>
<td>Familial Infiltrative</td>
<td>APC</td>
<td>Desmoid disease fibromatosis</td>
</tr>
<tr>
<td>Polyposis</td>
<td>AXIN</td>
<td>Polyposis and dental abnormalities</td>
</tr>
</tbody>
</table>
## Syndromes with pre-existing hamartomatous polyps

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Disease Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11/LKB1</td>
<td>Abnormal pigmentation on lips and buccal mucosa</td>
</tr>
<tr>
<td>Ruvalcaba-Myhre-Smith syndrome</td>
<td>PTEN*</td>
<td>Macrocephaly, pigmented macules on penis</td>
</tr>
<tr>
<td>(Bannayan-Riley-Ruvalcaba Syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cowden’s syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>SMAD4</td>
<td>Cystic hamartomatous polyps</td>
</tr>
</tbody>
</table>
# Genetic Predispositions to Colorectal Cancer

**Syndromes without pre-existing polyposis:**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Disease phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lynch Syndrome</strong></td>
<td>MSH2</td>
<td>few, if any polyps, CRC</td>
</tr>
<tr>
<td></td>
<td>MLH1</td>
<td>tends to be site specific (in women)</td>
</tr>
<tr>
<td></td>
<td>PMS2</td>
<td>also endometrial cancer</td>
</tr>
<tr>
<td></td>
<td>MSH6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EXO1(?)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EPCAM...</td>
<td></td>
</tr>
<tr>
<td><strong>Muir-Torre syndrome</strong></td>
<td>MSH2</td>
<td>HNPCC plus dermatological lesions and laryngeal cancer</td>
</tr>
<tr>
<td></td>
<td>MLH1</td>
<td></td>
</tr>
<tr>
<td><strong>Turcot’s Syndrome</strong></td>
<td>MSH2</td>
<td>CRC plus CNS lesions</td>
</tr>
<tr>
<td></td>
<td>MLH1</td>
<td></td>
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</tbody>
</table>
Lynch Syndrome

The most commonly inherited predisposition to colorectal cancer
Causes of CRC

Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996

Sporadic (65%–85%)

Familial (10%–30%)

Rare CRC syndromes (<0.1%)

Hereditary nonpolyposis colorectal cancer (HNPCC) (up to 5%)

Familial adenomatous polyposis (FAP) (<1%)

Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996
Hereditary Nonpolyposis Colorectal cancer (HNPCC)

Definition: HNPCC is defined by a set of clinical criteria.

Lynch Syndrome refers to HNPCC with DNA mismatch repair gene mutations.

1. Amsterdam Criteria
2. Bethesda Criteria
3. Modified Bethesda Criteria
4. Amsterdam II Criteria
Clinical Features of HNPCC

- Tumor site predominantly in proximal colon
- Extracolonic cancers:
  - Endometrial
  - Ovary
  - Stomach
  - urinary tract
  - small bowel
  - bile ducts
  - sebaceous skin tumour
  - Bladder
  - CNS (Turcot’s Syndrome)
  - Pancreatic
  - *Breast cancer?? The jury remains out*
Often Reported Cancer Risks in HNPCC

Aarnio M et al. *Int J Cancer* 64:430, 1995

% with cancer

Age (years)

- Colorectal 78%
- Endometrial 43%
- Stomach 19%
- Biliary tract 18%
- Urinary tract 10%
- Ovarian 9%

Aarnio M et al. *Int J Cancer* 64:430, 1995
HNPCC

• Rare autosomal dominant predisposition to CRC

• Frequency ~ 1:2,000 to ~ 1:4,000
  (often reported to account for 5% of all CRCs)

• The Danish CRC statistics suggest 1.7% of all CRCs
  rising to 14.7% of patients <50 years of age

• >80% penetrance by 75 years OR is it?
More recent cancer risk estimates

- Genotype restricted likelihood methods suggest:
  - CRC penetrance 45% by 70 y.o.a.
  - Endo Ca penetrance 14% by 70 y.o.a.

Implying a proportion LS patients are missed
DNA Mismatch Repair
Genetic basis of Lynch Syndrome

At least 22 genes involved in DNA mismatch repair

- MSH/MSH6
- MLH1/PMS2*
Tumour Specificity: Microsatellite Instability

- Tumour specific phenotype of mono-, di- & tri-nucleotide repeat instability

- 4 genes identified, MSH2, MLH1, MSH6 & PMS2 all involved in DNA Mismatch Repair. EPCAM also implicated in LS*

- No immediately apparent genotype/phenotype correlation, DNA MMR is a house-keeping process.
Microsatellite instable (MSI) tumors

WNT pathway

Normal epithelium
Normal epithelium

MAPK pathway

β-catenin
 apo-adenoma
 apo-adenoma

1p loss
18q loss

1p loss

K-RAS

Intemed. adenoma

hMLH1, hMSH2

hMLH3, hMSH6

Hypermethylation

TGFβ pathway

TGFB1R
BAX
TCF-4

WISP-3

Late adenoma

Carcinoma

Carcinoma

TP53-BAX pathway

TP53

Carcinoma

Chromosome instable (CIN) tumors

Metastasis

Local recurrence

Hypomethylation

?
Genetic basis ctd.

• MSH2 and MLH1 account for ~ 90% of all LS families
  – EPCAM “loss” results in a functional loss of MSH2*
  – Rare inherited “epimutations”

• Two additional MMR genes (MSH6, PMS2) account for a further ~ 5% of all LS families.
  • DO THEY CONFER AN IDENTICAL PHENOTYPE??

• A considerable proportion of families are not accounted for by these genes – known as HNPCC.
Calculated cumulative incidences by age and mutated gene for any cancer.
Calculated cumulative incidences by age and mutated gene for colorectal cancer (CRC) as the first cancer.
Calculated cumulative incidences by age and mutated gene for endometrial cancer as the first cancer by gene.
EPCAM – Not a gene linked to LS *per se*

EPCAM is associated with:

Congenital tufting enteropathy (CTE)

A rare recessively inherited intractable diarrhea of infancy characterized by villous atrophy and absence of inflammation, with intestinal epithelial cell dysplasia manifesting as focal epithelial tufts in the duodenum and jejunum.
MSH2 LGRs in Lynch syndrome patients.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0072195
EPCAM & MSH2

• Loss of the 3’ end of EPCAM & the 5’ end of MSH2 (promoter region) → read through that silences MSH2.

• Not necessary to include the 3’ end of EPCAM, as long as the promoter region of MSH2 is included
Identifying key modifying genes associated with Lynch Syndrome and the risk of early onset CRCs.

Mutation Positive Patients

Mutation Negative Patients

Undertaking a genome wide analysis on HNPCC patients
CNV analysis on known deletion carriers: MLH1 Whole Gene Deletion:
Smaller deletions detected by CNV analysis: MLH1 Exons 9-15 Deletion
CNV analysis: some results that await verification

• Some curious results:
• Large deletion upstream of MLH1...
Other factors affecting disease probability in Lynch Syndrome

- Environmental
- Genetic
- Environmental & Genetic
Sporadic CRC

- 85% associated with chromosomal instability (CIMP)
- 15% associated with DNA microsatellite instability (MSI)
- Outcomes may be different between MSI associated tumours and CIMP tumours
- <10% of MSI tumours linked to LS

WHY IS THIS IMPORTANT?
Stage II and II colon cancer recurrence and survival.
A. Recurrence
B. Disease free survival rates

Sinicrope et al. JNCI 2011
Effect of 5-FU adjuvant therapy on disease free survival

A. Effect of 5-FU on DFS in CRC patients with suspected germ-line changes in DNA MMR genes

B. Effect of 5-FU-based therapy on DFS with sporadic colon cancer (MMR deficient).

Sinicrope et al. JNCI 2011
Modifier Genes and Disease Risk
Modifier genes in Lynch Syndrome

• Patients with the same mutation present with different disease (e.g. CRC or Endo Ca)
• Patients with the same mutation develop disease at very different ages
• Families with the same mutation have different disease characteristics
Modifier Genes and Their Influence on HNPCC

- Variable ages of disease onset for unrelated patients with the same mutation
- Variable ages of disease onset for family members
- Differences in disease presentation in patients with the same mutation
The Case For IGF1

- IGF1 important in cell proliferation, differentiation and apoptosis.
- Essential for mammalian growth and development
- Elevated levels associated cellular transformation, tumour growth and metastasis
- Environmental and physiological factors result in fluctuations of IGF1 levels
- Genetic factors are also associated with differing IGF1 levels
The Case For IGF1

- Cytosine-Adenine repeat polymorphism located 969 base pairs 5’ of the initiation codon
- The length of the repeat influences transcription by affecting promoter activity
- Most common CA repeat length in the Caucasian population is 18
IGF1 Repeat polymorphism and cancer risk in HNPCC

Kaplan-Meier Survival Analysis

Proportion Without CRC

CRC Onset Age (Years)

17 or less
18 or more
Genome wide association studies have revealed numerous genetic risk factors, all with small effect sizes.
Are any of the new CRC susceptibility loci act as modifier genes in HNPCC

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>8q23.3</td>
<td>rs16892766</td>
</tr>
<tr>
<td>8q24.21</td>
<td>rs6983267</td>
</tr>
<tr>
<td>8q24</td>
<td>rs7014346</td>
</tr>
<tr>
<td>11q23.1</td>
<td>rs3802842</td>
</tr>
<tr>
<td>10p14</td>
<td>rs10795668</td>
</tr>
<tr>
<td>15q13.3</td>
<td>rs4779584</td>
</tr>
<tr>
<td>15q13.3</td>
<td>rs10318</td>
</tr>
<tr>
<td>18q21</td>
<td>rs4464148</td>
</tr>
<tr>
<td>18q21.1</td>
<td>rs4939827</td>
</tr>
</tbody>
</table>
Variant alleles of rs3802842 located on Ch 11 are associated with earlier age of CRC onset.
Increasing numbers of risk alleles appears to correlate with earlier disease onset.
Summary of Lynch Syndrome

- Due to mutations in DNA mismatch repair genes
- Highly variable disease penetrance
- Tumour specific signature (hypermutable)
- Modifier genes appear to play a role in disease expression
Summary

- HNPCC an important genetic predisposition to epithelial malignancies
- 4 genes associated with Lynch Syndrome
- Gene mutations take on many guises
- Modifier genes modulate disease expression
- Important in understanding events underlying a significant proportion of “sporadic” CRC