Family history of bowel cancer

- D Gareth Evans
- Christie and St Mary’s Hospital
  Manchester UK

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CANCER

• All cancer is genetic
• Some cancer has an inherited element
• A few cancers are caused by single genes
Knudsen’s Two hit Hypotheses in CRC
FAMILIAL COLON CANCER

Associated with adenomas

Multiple polyps
- Familial adenomatous polyposis coli \((\text{APC, MYH})\)
- Turcot’s syndrome \((\text{MSH2, MLH, MSH6, PMS2})\)

Few polyps
- Hereditary site specific colon cancer \((\text{MSH2, MLH, MSH6, PMS2})\)
- Cancer family syndrome \((\text{MSH2, MLH, MSH6, PMS2})\)
- Muir-Torre syndrome \((\text{MSH2, MLH, MSH6, PMS2})\)
FAMILIAL COLON CANCER

Associated with Hamartomas

Peutz-Jeghers syndrome *(STK11)*
Juvenile polyposis *(SMAD4, BMPR1A)*
Ruvalcaba-Myhre-Smith syndrome *(PTEN)*
Intestinal ganglioneuromatosis *(MEN. NF1)*
Mixed Polyposis *(GREM1)*
Familial adenomatous polyposis
polyposis coli

Autosomal dominant

Adenomatous polyps develop in second and third decades.
Carcinoma in third and fourth.

**SCREENING:** sigmoidoscopy\colonoscopy annual from 12yrs.
ophthalmology – CHRPE.
dental x–rays – osteomas.
genetic – DNA probes on chromosome 5.

**Treatment:** colectomy often in teenage years.
continue to need examination of rectal stump.
Also upper G.I. endoscopy.

Other tumours: HEPATOBLASTOMA, GLIOMAS, THYROID
Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
FAP Screening

1. Colonoscopy/sigmoidoscopy 1–2 yearly
2. Ophthalmology CHRPE (approx 60%)
3. Oral features (OPG +ve in 80%)
4. Skin (epidermal cysts common)
5. DNA Linkage/mutation studies
FAP

- APC gene
- Chromosome 5q21 (linkage 1986, cloned 1990)
- 15 exons - 77% of the gene in exon 15
- germline mutations result in FAP
- somatic mutations found in >70% of sporadic tumours
FAP
DNA studies

1. **Linkage** – need >1 affected person for predictive test.
   a) 90–99% certainty with extragenic markers (227, YN5.48)
   b) 99.5% certainty with CA repeat – very informative.
   c) 99.9% certainty with intragenic markers (Rsa1, Ssp1)

2. **Mutation work** only one affected person required.
   If the mutation is found (approx in 80%+) 100% CERTAINTY.
FAMILIAL ADENOMATOUS POLYPOSIS

Tumours associated with FAP

Desmoid tumours
Hepatoblastoma
Adrenal adenomas/adenocarcinomas
Papillary carcinoma of the thyroid
CNS tumours
FAP

Genotype/phenotype correlations

Attenuated phenotype with 5’ and 3’ mutations
Severe polyp phenotype with common 5bp deletion
Absence of CHRPE in mutations 5’ of exon 9
Desmoid disease and no CHRPE 3’ of codon 1444
Davies et al AJHG 1995; Scott et al Hum Mol Genet 1996
FAP

Genotype/phenotype correlations

Tailoring surgery to mutation

5’ and 3’ mutations IRA with possible pouch later
Ileal pouch as initial option if severe polyp phenotype
Ileal pouch with 5bp deletion and mutations 1250-1444
3’ of codon 1444 delay surgery to avoid desmoid

Age of detection of polyps (presymptomatic) in 143 FAP patients in Manchester Registry
Presymptomatic screening

- 9 patients initial endoscopy >30 yrs clear
- 9 patients only 1-3 polyps at initial screen
- 15-20% would be erroneously cleared at 30
- Our population contains large number of exon 4 and post 1450 mutations (beware!)
- ?whether rigid sigmoidoscopy + dye better
- Exon 4: predominant right sided disease
### Incidence and prevalence

<table>
<thead>
<tr>
<th></th>
<th>Birth incidence</th>
<th>Number living</th>
<th>Prevalence</th>
<th>Mutation identified</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NF1</strong></td>
<td>1 in 2,712</td>
<td>899</td>
<td>1 in 4,560</td>
<td>-</td>
</tr>
<tr>
<td><strong>FAP</strong></td>
<td>1 in 8,619</td>
<td>274*</td>
<td>1 in 14,963</td>
<td>222/283* (78%)</td>
</tr>
<tr>
<td><strong>Gorlin</strong></td>
<td>1 in 18,976</td>
<td>133</td>
<td>1 in 30,827</td>
<td>64/128 (50%)</td>
</tr>
<tr>
<td><strong>NF2</strong></td>
<td>1 in 33,000</td>
<td>70</td>
<td>1 in 58,461</td>
<td>56/70 (83%)</td>
</tr>
<tr>
<td><strong>VHL</strong></td>
<td>1 in 42,987</td>
<td>45</td>
<td>1 in 91,111</td>
<td>39/43 (91%)</td>
</tr>
</tbody>
</table>

* 6 living patients with MYH polyposis
Results: pre- and post-genetic register
Kaplan-Meier curve demonstrating probability of onset of polyposis according to mutation group

- Unknown mutation phenotype
- Mild early phenotype
- Classical phenotype
- Severe phenotype
- Mild desmoid phenotype
- Unknown mutation censored
- Mild early censored
- Classical censored
- Severe censored
- Mild desmoid censored

Probability of onset of polyposis vs. Time till onset of polyposis (years)
Kaplan-Meier curve demonstrating the cumulative survival according to genotype group

- Cumulative Survival vs Survival time (years)
FAP
Myths

1. Colonoscopy/sigmoidoscopy will detect all patients by 30 yrs
   i) At least 10% of FAP patients have no polyps at 30

2. Colorectal cancer 100% lifetime risk
   i) even unscreened non penetrant patients do occur
   1 & 2 wrong due to attenuated families, but classical cases occur

3. Accounts for 0.5-1% of colorectal cancer
   i) even if all 1 in 10,000 get CRC 1 in 25-30 of population get it (<0.25%)
   ii) No patients in series of 1400 CRC patients 1980-2000 (<0.1%)
   iii) Estimates from Scotland suggest 0.07%

4. The oldest that Gardner syndrome and polyposis were different
FAP
Myths

All FAP is due to dominant APC

- MYH1 excision repair gene now found as recessive cause
- Homozygous/hz mutations account for cases of multiple adenomas
- >20 cases with >100 adenomas have been shown to have AR MYH
- Up to 25% of families with non AD FAP have MYH disease

### COLON CANCER

<table>
<thead>
<tr>
<th>Affected relative</th>
<th>Lifetime risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>One 1st degree</td>
<td>1 in 17</td>
</tr>
<tr>
<td>One 1st degree &lt; 45</td>
<td>1 in 10</td>
</tr>
<tr>
<td>One 1st and one 2nd degree</td>
<td>1 in 12</td>
</tr>
<tr>
<td>Both parents</td>
<td>1 in 8.5</td>
</tr>
<tr>
<td>Two 1st degree</td>
<td>1 in 6</td>
</tr>
<tr>
<td>Three 1st degree</td>
<td>1 in 2</td>
</tr>
</tbody>
</table>

- Adapted from Murday (1990)
Colorectal Cancer Mechanism

• Mutator phenotype 12-13%
• Chromosomal instability phenotype 87%
LYNCH CANCER FAMILY SYNDROMES
(hereditary non polyposis colon cancer type 1 & 2)
Autosomal dominant, high penetration.

TYPE 1: Site specific colon cancer.
proximal prediliction.
onset 40-60 yrs.

Improved survival to stage matched controls.
Lynch type 1
Lynch type 2
The Lynch Amsterdam criteria include:

- 3 cases with colorectal cancer
- All 1st degree relatives of one
- Occur in at least 2 generations
- One case under 50 years
- All histologically proven
Lynch Modified Amsterdam criteria

- 3 cases with colorectal, TCC, endometrial, small bowel or biliary cancer
- All 1st degree relatives of one
- Occur in at least 2 generations
- One case under 50 years
- All histologically proven
Lynch
Micro-satellite instability

• Tumours from LS families shown to have instability in microsatellite repeats
• First noticed while typing families (linkage)
• Only realised to be significant in retrospect
• Very useful pre-screen in families
Lynch
Mismatch repair genes

- hMSH2 located 2p16 accounts for 40% HNPCC
- hMLH1 located 3p21 accounts for 35% HNPCC
- PMS2 located 7p22 accounts for 8% HNPCC
- MSH6 accounts for about 15% HNPCC
Mismatch repair genes

G A A A A A C A T T A A G G G A A C A T G A C A T G
C T T T T T G T A A T T

G A A A A A C A T T A A G G G A A C A T G A C A T G
C T T T T T G T A A T T

MLH1

PMS2

MSH2

MSH6

G A A A A A C A T T A A G G G A A C A T G A C A T G
C T T T T T G T A A T T

C C C T T T G T A C T G T A C
Lynch Syndrome

Risks associated with mutations

Men:  Colorectal cancer  74% by 70 years

Women: Colorectal cancer  30% by 70 years
       Uterine cancer    42% by 70 years

From Dunlop et al, Hum Mol Genet 1997, 6:105-10
Colorectal/endometrial/ovarian cancer risk in LS mutation carriers

* Colorectal cancer risk 80% in men 40-60% in women

* Endometrial risk 60%, Ovarian risk 12%

* Gastric cancer risk 13%

* Other cancer risks <4% individually

Aarnio et al Int J Cancer 1999
Lynch
Mismatch repair genes

- Approximately 60% of Amsterdam families
- Higher levels in Modified Amsterdam
- 0.5-3% of colorectal cancer
- Population frequency 1 in 1-5,000
<table>
<thead>
<tr>
<th>Study ref</th>
<th>Country/age selection</th>
<th>Number of cases</th>
<th>MSH2</th>
<th>MLH1</th>
<th>MSH6</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinol</td>
<td>Spain all ages+~</td>
<td>1222</td>
<td>5</td>
<td>3</td>
<td>Not tested</td>
<td>8/1222 (0.66%)</td>
</tr>
<tr>
<td>Barnetson</td>
<td>Scotland &lt;55yrs</td>
<td>870</td>
<td>16 (1.8%)</td>
<td>15 (1.7%)</td>
<td>7 (0.8%)</td>
<td>38/870 (4.4%)</td>
</tr>
<tr>
<td>Evans</td>
<td>England All ages+</td>
<td>1800</td>
<td>2 (0.1%)</td>
<td>4 (0.2%)</td>
<td>Not tested</td>
<td>6/1800 (0.33%)</td>
</tr>
<tr>
<td>Southey</td>
<td>Australia &lt;45 yrs@</td>
<td>131</td>
<td>4 (3%)</td>
<td>9 (7%)</td>
<td>4 (3%)</td>
<td>17/131 (13%)</td>
</tr>
<tr>
<td>Salovaara</td>
<td>Finland All ages+</td>
<td>535</td>
<td>1</td>
<td>17</td>
<td>Not tested</td>
<td>18/535 (3.4%)</td>
</tr>
<tr>
<td>Ponz de Leon</td>
<td>Italy All ages*</td>
<td>1721</td>
<td>2</td>
<td>1</td>
<td>Not tested</td>
<td>3/1721 (0.02%)</td>
</tr>
<tr>
<td>Katballe</td>
<td>Denmark All ages*</td>
<td>1200</td>
<td>6</td>
<td>4</td>
<td>Not tested</td>
<td>10/1200 (0.8%)</td>
</tr>
<tr>
<td>Percesepe</td>
<td>Italy All ages#</td>
<td>336</td>
<td>1</td>
<td>0</td>
<td>Not tested</td>
<td>1/336 (0.3%)</td>
</tr>
<tr>
<td>Hampel</td>
<td>USA All ages@</td>
<td>1066</td>
<td>13</td>
<td>5</td>
<td>3</td>
<td>21/1066 (2%)</td>
</tr>
</tbody>
</table>
MLH1 loss

MSH2 loss
319 families with proven HNPCC mutation

- 142 MSH2
- 118 MLH1
- 42 MSH6
- 13 PMS2

Testing now offered in 319 families

- overall uptake high circa 50-60%
- 330 unaffected gene carriers already identified
Lynch
Mutation testing

- 234 families with proven HNPCC mutation
- 111 MSH2
- 94 MLH1
- 24 MSH6
- 5 PMS2
- Testing now offered in 234 families
- overall uptake high circa 70-80%
- 190 unaffected gene carriers already identified
Overall uptake 55% of FDRs

Uptake was significantly lower in males ($p = 0.012$) and individuals <25 years ($p < 0.001$). Mutation carriers were more likely to undergo colorectal screening than untested FDRs (97.2% vs 34.9%; $P \leq 0.0001$). Of 216, 63 (29.2%)
Uptake of Predictive Testing in FDRS by Gender (p=0.012)
Cumulative Risks of Extracolonic Cancers for Mutation Carriers

Barrow et al Clin Genet 2009
LS Cancer Risks Compared to Population Risk
Lynch Myths

• Original paper suggested 12-13% of CRC
• Most frequent cause of familial CRC
• Muir-Torre a separate disorder (MSH2)
• Breast cancer a prominent component
• Two types of Lynch syndrome
HNPCC heterogeneity

- No evidence to suggest a locus explanation for Lynch 1/2
- Genotype/phenotype correlations within genes awaited
- Current evidence would suggest HNPCC mismatch genes only 1-3% CRC
- Only small proportion of polyp rich families (<50) dt APC or HNPCC
POLE & POLD1

- MMR like patterns
- Polyp rich
- Only about 1-2% of LS negative families
- POLE very common in Endometrial
Juvenile Polyposis

types

• <5 polyps no family history (sporadic)
• Juvenile polyps throughout GI tract
• Any number of polyps with a family history
Juvenile Polyposis genes

- Main gene SMAD4 (MADH4)
- New locus BMPRIA (TGFB related)
- PTEN only affected if CS or BRR spectrum
- Still possible another gene exists
Peutz Jeghers hamartoma

- Mucocutaneous skin pigmentation (fades)
- Gastrointestinal polyposis
- Autosomal dominant inheritance
- Presentation with pain/bleeding
Peutz Jeghers

risks

- Repeated operations for intussusception
- GI Cancer risk increased (Gastric, jejunum)
- Malignancy in ovary/testis, cervix (adenoma malignum), breast
- 48% chance of cancer related death by 57 yrs (St Mark’s data)
Peutz Jeghers gene

- Main gene LKB1 (STK11)
- No other locus yet
Colorectal cancer screening in LS mutation carriers

* CRC incidence significantly reduced by colonoscopy
* Now firm evidence for a survival benefit
* Projected benefit could equate to 7-13.5 years extra life
* Proctocolectomy could equate to 15 years extra life
* Risk of dying WITH screening not markedly increased

Jarvinen et al Gastroenterology 1995; Jarvinen et al 2000
Colorectal cancer screening in LS mutation carriers

* Interval cancers occur within 3 years of “normal” colonoscopy

* Rapid progression from polyp to cancer

* Adenoma miss rate can be high

CRC cumulative incidence in screened LS
Moller et al. Gut 2015 - 1,942 LS carriers from 10 countries
Lynch + other Screening

Lynch syndrome
Lead time possibly 1-3 years. Require 1-2 yrly screening
Full colonoscopy required (70% cancers right sided)

Non Lynch
Lead time probably similar to general population 5-10 yrs
5 yearly screening probably sufficient
Is full colonoscopy required as most cancers left sided?
Proportion of familial Colorectal cancer 2015

- MLH1: 11%
- MSH2: 9%
- PMS2: 2%
- MSH6: 4%
- GWAS SNPs: 22%
- POLE/POLD: 1%
- other: 49%
- STK11: 1%
- SMAD4/BMPR1A: 1%
Familial Colorectal cancer
What remains to be found?

• Genes causing MOST familial CRC
• Any further hererogeneity in PJS and JP
• Other genes such as mixed polyposis
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