14.20-15.00 Inherited colon cancer and other inherited cancer predispositions

Dr Anne De Leener
Centre de Génétique Humaine
INHERITED COLORECTAL CANCER (CRC)

HNPCC: Hereditary non polyposis colorectal cancer
FAP: Familial Adenomatosis Polyposis
MAP: MYH associated Adenomatosis Polyposis

Colorectal cancer

- **Sporadic**
- **Familial**
- **HNPCC**
- **FAP**
- **MAP**

- **84%**
- **10%**
- **5%**
- **1%**

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Inherited colorectal cancer

- **Rare disease:** <10% of all the CRC
- **High risk:** cumulative risk of CRC:
  - 40 - 50% at 70 yo for Lynch and hamartomatous polyposis
  - 100% at 40 yo for FAP linked to APC
- **Need of medical care**
- **Possibility of predictive testing**

- "Polyposis"
- "Non polyposis"

- FAP
  - Attenuated polyposis
- Other polyposis
- LYNCH syndrome
Introduction to Lynch Syndrome: Terminology

MMR = *MisMatch Repair*

MMRD = *Mismatch Repair Deficient*

MLH1, MSH2, MSH6, PMS2, EPCAM = 5 main genes involved in the MMR process

RER phenotype (*Replication EError*) = mutator phenotype cause by MMRD

MSI-H cancer (*MicroSatellite Instability-High*) = cancer with RER mutator phenotype = MMRD cancer

MSS = *MicroSatellite Stable*
The mismatch repair (MMR) system

Replication errors cause mismatches on new DNA molecule. MMR system identifies and repairs misincorporated bases.

Functions of MMR system:

1°) Identify the mismatch
2°) Identify the strand to be corrected
3°) Remove the wrong sequence
4°) Synthesize a correct complementary strand
Introduction to LYNCH syndrome: MMR deficiency and et instability

Gene

Replication error: 1bp deletion (or insertion)

MMR-proficient

MMR-deficient

Reparation

No reparation = mutation

Tumor DNA

Corresponding normal DNA
How to study MMR function in the tumors

✓ Look for microsatellite instability

✓ Immunohistochemistry of MMR proteins
  - Simple
  - Specificity = Molecular biology
  - Sensitivity > Molecular biology
  - Other advantage: tells you which molecule is absent
Microsatellites instability (MSI): 15% of CRC

Selection of at least 5 monomorphic microsatellites: no variation in the population

FIG. 12

Number of unstable markers

Normal ou non MSI
Ou douteux

MSI-H
Immunohistochemistry of MMR proteins in CRCs

Tested protein: MLH1 MSH2 MSH6 PMS2

MSI-H CRCs → (One or more than one protein absent)

MSS CRCs → (All the MMR proteins are present)
Number of mutations accumulated: MSS vs MSI-H CRC

- median number of non-synonymous mutations per tumor with genome wide tools
- MSI-H tumors have by far the greatest numbers of mutations

B Vogelstein et al. Science 2013;339:1546-1558
Genotype-phenotype relationship in sporadic colorectal cancers

<table>
<thead>
<tr>
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<th>CIN or MSS CRC</th>
<th>MSI-H CRC</th>
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<tbody>
<tr>
<td>Frequency</td>
<td>85%</td>
<td>15%</td>
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<tr>
<td>Localization</td>
<td>70% after splenic angle</td>
<td>80% right-sided</td>
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<tr>
<td>Polyp dwell time</td>
<td>Adenoma → CRC ≈ 10 years and rarely</td>
<td>Adenoma → CRC very rapid (≈ 1 year)</td>
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<tr>
<td>Pathology (not rules but correlations)</td>
<td>Often well differentiated adenocarcinoma</td>
<td>Poor differentiated CRC with lymphoid infiltrate</td>
</tr>
<tr>
<td>Prognostic</td>
<td>reference</td>
<td>better</td>
</tr>
<tr>
<td>Risk factors</td>
<td>common</td>
<td>Tobacco, lack of estrogens</td>
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<td>First change on the way to CRC</td>
<td>Loss of APC function</td>
<td>Epigenetic loss of MLH1 function</td>
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<td>Genetic predisposition</td>
<td>FAP and MAP polyposes, type X HNPCC</td>
<td>Lynch syndrome</td>
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Sporadic MSI-H CRC: epigenetic MLH1 inactivation/Methylation

Hypermethylation of MLH1 = the mechanism of MMR loss of function for sporadic MSI-H CRCs

When considering a MLH1-negative CRC, 2 biological parameters are in favor of a sporadic disease

1. Hypermethylation of MLH1
2. Presence of BRAF V600E acquired mutation
A. HNPCC Genes & LYNCH Syndrome

3% of CRC (2% of endometrial cancers)
9% if before 50 yo
Genes: **MSH2 (40%), MLH1 (30%), MSH6, (PMS2 & EPCAM)**
MMR: mismatch repair genes

- Constitutional mutation in MMR gene
- Somatic mutation in a cell
- Somatic instability of repeated sequences
  - Microsatellites instability
  - Inactivation of the gene (TGF type II, BAX, etc)

Phenotype MSI

Cancer
LYNCH Syndrome

- 70-80% lifetime risk of CRC
- MLH1 – MSH2: highest risk (44 yo)
- 11-19% risk of intestinal type **gastric tumor** (higher in at risk population: Japan)

Woman:
- risk of **endometrial** cancer: 30-60% (46–62 y)
- Risk of ovarian cancer: 9-12% (42y), all types but not borderline tumor

Skin lesions: sebaceous carcinomas (Torre-Muir syndrome), keratoacanthomas, epithelioma

Other:
- **Bowel**, hepatobiliary, **urinary tract** (typically transitional carcinomas of the ureter and renal pelvis)
- Brain tumor (glioblastomas): Turcot syndrome
- Pancreas?

**Relative risk > 8**

**Effect of tobacco +++**
Cancer risks in Lynch syndrome, the AD predisposition to MMRD cancers

Lynch Syndrome-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract and brain tumors, sebaceous gland adenomas and keratoacanthomas, and carcinoma of the small bowel.
LYNCH syndrome criteria's

Old: Amsterdam I or II: bad sensibility and specificity. 40% of LYNCH families (mutation identified) do NOT present with the Amsterdam criteria's.

Bethesda revised:
Sensibility: ? 62-81%
Specificity : 95% for MSH2 and MLH1

Jerusalem criteria’s (2010):
Cancer before 70 yo

Table 2. Revised Bethesda Criteria

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<th>Tumours from individuals should be tested for MSI in the following situations:</th>
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<tbody>
<tr>
<td>• Colorectal cancer diagnosed in a patient less than 50 years of age</td>
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<tr>
<td>• Presence of synchronous or metachronous colorectal or other HNPCC-associated tumours, regardless of age</td>
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<tr>
<td>• Colorectal cancer with MSI-H histology diagnosed in a patient less than 60 years of age</td>
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<tr>
<td>• Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under the age of 50 years</td>
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<tr>
<td>• Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age</td>
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LYNCH Syndrome

Importance of the family history
Prediction program: PREMM, MMRpro, MMRpredict

### Recommendations

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<th>Recommendations</th>
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<tr>
<td>Family history should be evaluated using a validated prediction model (e.g. PREMM1,2,6) or the revised Bethesda criteria. Individuals considered at risk should be referred for genetic counseling. A first step may be the retrieval and immunohistochemical analysis of stored samples of family members after appropriate consent. This is possibly followed by germline mutation analysis of the referred individual.</td>
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<td>Investigation of all colorectal cancers by immunohistochemistry (IHC) of the four mismatch repair (MMR) proteins or by microsatellite instability (MSI) testing is recommended. In case of a positive family history (e.g. based on PREMM1,2,6) or other risk factors, both IHC and MSI should be performed if either MSI of IHC performed alone remains inconclusive.</td>
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<td>Immunohistochemistry and MSI tests should only be performed in laboratories that are ISO accredited for these tests.</td>
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<td>If the only reason for germline mutation analysis is a positive IHC for MLH1, germline mutation analysis should be accompanied by MLH1 promoter methylation or BRAF mutation analysis.</td>
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<td>Patients with a positive IHC or MSI result should be offered referral for genetic counseling, which may result in germline mutation analysis.</td>
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<td>In families with a known causal mutation, predictive testing should be offered to all relatives from the age of 13 onwards and after genetic counseling.</td>
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<td>In confirmed Lynch syndrome patients, yearly surveillance (including colonoscopy) is recommended. To maximally prevent the associated risk of endometrial and ovarian cancer, hysterectomy and bilateral oophorectomy is an option to be discussed with mutation carriers who have completed their families, especially after the age of 40 years. The option of surveillance for endometrial cancer should also be discussed with the patient; it should be mentioned that currently the benefit is unproven.</td>
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<tr>
<td>In families without identified causal mutation, the decision for surveillance should be based on the family or the personal history.</td>
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<td>Participation of patients in the FAPA registry is recommended and should be offered to patients concerned.</td>
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**MSI-H cancer treatment?**

Better prognosis
No response to 5FU
Lower interest of chemotherapy in stage II and III
New treatments: immunotherapy

**BACKGROUND**

Somatic mutations have the potential to encode “non-self” immunogenic antigens. We hypothesized that tumors with a large number of somatic mutations due to mismatch-repair defects may be susceptible to immune checkpoint blockade.
Case 1:

- Colon cancer
- Bladder cancer
- Endometrial cancer
- Breast cancer

Family tree:

- Gaston 32
- Germaine 78
- DCD <50
- K.SEIN >70

- Clarisse 63
- Joëlle 61
- Julie 58
- Serge 46
- Jean-François 58
- Nicole 54
- Xavier 52

- Simon 45
- Noémie 44
- 2

- Pierre
- Jules 29
- Jula 29
- Nathalie 25
- Marianne 21
MSH2 mutation found in the family: possibility of predictive testing

Colon cancer
Bladder cancer
Endometrial cancer
Breast cancer

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B. POLYPOSIS

About 95% of CRC arise from polyps

Hyperplastic

Adenoma

P juvenile

Peutz-Jeghers

Hamartomas

Lymphoma

Lipoma

Hamartomatous P

« Polyp »
Colorectal polyposis « genetically determined »

Adenomatous Polyposis

▪ Adenomatous polyposis Linked to APC
  *Familial Adenomatous Polyposis* (mutation APC)
  Classic and attenuated forms

▪ Adenomatous polyposis linked to MUTYH (bi allelic mut. MUTYH)
  *MYH-Associated Polyposis* (MAP)

▪ Adenomatous polyposis associated with axin (mutation axin 2)

▪ Adenomatous polyposis associated with POL (mutation POLE or POLD1)
Colorectal polyposis « genetically determined »

Hamartomatous polyposis

- Polyposis of Peutz-Jeghers (mutation \textit{STK11/LKB1}) -> see Dr Duhoux
- Juvenile polyposis (mutation \textit{SMAD4} or \textit{BMPR1A}), associated manifestations
- Cowden* (mutation \textit{PTEN}) -> see Dr Duhoux
- Ganglioneuromatosis*

* \textit{Not associated with an increase of RR of CRC}

Hyperplastic polyposis (gene?)
Familial Adenomatous Polyposis:
clear autosomal dominant transmission

Easy diagnostic in beginning of the seventies
Standard care of family → No death.
Responsible APC mutation discovered in 2011
Interest of testing: 1. Avoid colonoscopies
2. Avoid transmission

APC mutation p.Glu412X
FAP and the APC gene

Correlation genotype - phenotype

AFAP Codons 78-157
AFAP Codons 312-412
Polypose profuse Codons 1250-1464
AFAP Codons 1595-2843

CHRPE Codons 463-1387
T. desmoïdes Codons 1444-1578
Germline APC mutations and predisposition to CRC

✓ Incidence: 1/7000 to 1/14000
✓ 1% of CRC
✓ Genesis of adenomatous polyps shortened among people who carry a germline APC mutation
✓ Stochastic (=random) loss of the WT allele of APC in a colonic stem cell induces a selective advantage leading to the formation of an adenoma.
✓ Loss of the WT APC allele happens many times (10^7 crypts/colon) ⇒ hundreds or thousands of polyps
✓ at different evolutionary stages
✓ evolutionary potential to cancer identical to sporadic MSS polyps
Hundreds or thousands of polyps at different evolutionary stages.

Evolutionary potential to cancer identical to sporadic MSS polyps.
Germline APC mutations and predisposition to other tumors

APC loss-of-function mutations can participate to the development of other tumors that can also occur in FAP:

1. Malignant tumors: thyroid cancer (RR: 7.6), pancreas cancer (RR: 4.46), hepatoblastoma, medulloblastoma (Turcot Syndrome)

2. Benign tumors: adenomatous polyps of the upper digestive tract, desmoid tumors, osteomas, epidermoid cysts, benign hypertrophy of retina pigment epithelium

Skin lesions can occur very early, before CRC
Asymptomatic congenital hypertrophy of the pigmented epithelium of the retina
(inconstant but almost pathognomonic FAP lesion)

FAP with osteomas (Gardner syndrome)

- Bone deformation of the mandibular left angle

- Radiography → osteoma
Familial adenomatous polyposis (FAP)

**Recommendations**

It is preferable that first-degree family members of patients with classic adenomatous polyposis and a pathogenic APC (adenomatous polyposis coli) mutation are referred for genetic counseling at the age of 10-12 years. If a clinical picture characteristic of attenuated familial adenomatous polyposis (AFAP) is seen with multiple family members, this may take place at a later age (young adult age).

If a pathogenic APC mutation is found in the index patient, genetic testing is recommended as it may provide a decisive answer for all family members in relation to risk of the disorder. Children of mutation carriers have a 50% chance of the genetic predisposition to (A)FAP.

In the case of a person with MAP (biallelic MUTYH mutations), all brothers and sisters of this person should be referred for genetic evaluation given they have a 25% chance of a genetic predisposition. The a priori chance of MAP in a child of a patient with MAP is <1%, given the other parent has a small risk (± 2%) of being a carrier of a MUTYH mutation as well. To determine the risk for potential children of a patient with MAP, it is advised that MUTYH mutation testing is performed on the other parent. If the other parent is shown to be a mutation carrier, the children have a 50% chance of biallelic MUTYH mutations.

All patients under the age of 60 years with >10 adenomas cumulatively, should be referred for genetic counseling. Exceptionally, referral for genetic analysis should also be considered for young persons with <10 adenomas (high grade dysplasia). In persons ≥60 years of age with more than 10 adenomas cumulatively genetic testing should be considered in case of a positive family history of multiple adenomas.

Periodic endoscopic examination is recommended in the following patients:

- Patients with FAP, AFAP, MAP or ‘adenomatous polyposis of unknown origin.’
- Persons with a pathogenic APC mutation
- Persons with biallelic pathogenic MUTYH mutations
- Risk carriers: first-degree family members of patients with adenomatous polyposis where the disorder cannot be confirmed by mutation analysis because a pathogenic mutation has not been found in the index patient
- Risk carriers: first-degree family members of mutation carriers, who have not (yet) been tested themselves.

**Classic FAP:** in mutation carriers or risk carriers of classic FAP, yearly surveillance using sigmoidoscopy is recommended from the age of 10-12

**AFAP or MAP:** in mutation carriers or risk carriers of AFAP or MAP, surveillance using colonoscopy is recommended once a year or every two years from the age of 18.

Participation of patients in the FAPA registry is recommended and should be offered to patients concerned.

APC mutation carriers should be screened for extracolonic manifestations.
FAP: follow up
Child carrier of the germline mutation or from a suspected FAP family without mutation identified

► Annual Recto-sigmoidoscopy from 10-12 yo
► Coloscopy when polyps are detected
► Prophylactic surgery at de 15-25 yo
  • colectomy with ileorectal anastomosis, or
  • coloproctectomy with ileo-anal anastomosis and ileal
► Supervision of rectum or reservoir
► Supervision of the upper digestive tract
Adenomatous polyposis associated with MUTYH

**Prevalence**
- **30%** of « *APC* negatives » adenomatous polyposis with attenuated form (15< polyps <100)
- **10%** of « *APC* negatives » adenomatous polyposis with classical form (polyps >100)

**Molecular genetic**
- Bi allelic mutation of the *MYH* gene (*MUTYH*): recessive
- Gene involved in the Base Excision Repair system: accumulation of somatic mutations (transversions)

**Clinical characteristics?**
- Mostly attenuated polyposis (<100), colon and duodenum.
- Dermatological lesions (sebaceous adenomas) other?
MUTYH: follow up of the index case

- **CRC**: (Video) colonoscopy at 20, 25, 30 yo -> each 2 y
- **Duodenal**: surveillance: fibroscopy OGD idem
- Initial consultation in dermatology
MUTYH: follow up of the family

Indication of MUTYH analysis

Targeted analysis of the 2 mutations found in the index case

Targeted analysis of the 2 mutations found in the index case

Targeted analysis or complete analysis

No analysis

Medical follow up

Coloscopy > 40y each 5y

Coloscopy regarding test:
- Bialleic: idem IC
- Monoalleic: Colo / 5 y
- Ø MUT: Ø Coloscopy

Coloscopy regarding genotype
(Mono or bi-allelic)

No follow up
Conclusion: Two main genetic varieties of colorectal cancers (CRC)

**Standard MSS CRC: microsatellite stable**
- Carcinogenesis and clonal expansion starts with APC loss of function
- Slow evolution
- All MMR caretaker proteins expressed (→ sepias color of nuclei in IHC)
- Respond to 5FU

**MSI-H CRC: a very different disease**
- First phenotypic change on the way to carcinogenesis: loss of MMR caretaker function
- Very rapid evolution once clonal expansion has started
- ≥ 1 MMR protein lost in tumor cells nuclei (detected by IHC)
- Better prognosis
- No response to 5FU.
  ✓ Immunotherapy
Other inherited cancer predispositions:

**Breast:** see Dr Duhoux
Other inherited cancer predispositions

Kidney: genes involved in sporadic forms of kidney carcinomas. 2-3% inherited

- **VHL**: Von Hippel Lindau Disease
  - TSG
  - Clear cell

- **MET**: HPRC
  - Oncogene
  - Papillary type 1

- **FH**: Leiomyomatosis
  - TSG
  - Uterine
  - Cutaneous
  - Papillary type 2

- **FLCN**: Birt Hogg Dube
  - TSG
  - Cutaneous
  - Pneumothorax / Cyst
  - Various

Linehan et al., Semin Cancer Biol 2013
Other inherited cancer predispositions

**Kidney:**

**Von Hippel Lindau** (80% of inherited cases)
1st cause of hereditary renal and pheo. cancers
1/36000
Mutation in VHL gene (> 300), also in 75% of the sporadic cancers (somatic)
Hemangioblastoma (of the retina)

**Pheochromocytoma and PGL:**
See Dr Persu
Other inherited cancer predispositions

**Pancreas**: STK11, SPINK1, PRSS1, CDKN2A, BRCA2, MMR, BRCA1, APC

**Melanoma**: CDKN2A, CDK4, BAP1, MITF, MC1R

**Endocrine syndrome**: MEN1, MEN2 (RET)
Panel 26 genes multiplicom: interest in mixed investivation (ovary) but no CNV analysis

New diagnostic tools

Pancreatic cancer
Parathyroid cancer
Kidney cancer
Endometrial cancer
Colon cancer
Gastric cancer
FAM175A
ATM
PALB2
STK11
MEN1
PTEN
CDH1
MUTYH
CHEK2
BLM
XRCC2
EPCAM
MLH1
MSH6
PMS2
MSH2
General conclusion: Partners involved in the correct care for high risk subjects

Many doctors:
- General Pract.
- Gynecologist
- Radiologist
- Surgeon
- Oncologist…

Geneticists
- Oncogeneticist
- Molecular biologist

Prevention ⇒ Normal life with low risk
Thank you for your attention!

Anne.deleener@uclouvain.be