Genetic Aspects of Inherited colorectal cancer (CRC)

New data New insights

DNA repair
2004 – Service for genetics of GI Cancer

**Oncology**
- Tamar Peretz
- A. Hubert
- L. Kadouri
- N. Halpern
- M. Plessier
- Tamar Hamburger

**Genetic**
- I. Lerer
- D. Abeliovich
- L. Ben Avi
- V. Meiner
- M. Sagi
- A. Eilat

**Pathology**
- E. Pikarsky
- H. Goldshmith
- E. Ben Avraham
- R. Porat

**Surgery**
- A. Nissan
- A. Pikarsky

**Gynecology**

**Gastroenterology**

Rabin Medical Center
TASMC
- K. Wimmer
- I. Tomlinson

* The Israeli Cancer Association
GI-Oncogenetic Service in Hadassah
GI-Oncogenetic Service in Hadassah

1782 Patients > 1338 Families

124 Lynch families
3 C-MMRD families
7 MYH families
1 HMPS
FAP, BMPR1A, STK11, P53
BRCA1 /BRCA2
GI-Oncogenetic Service in Hadassah
Dedicated service for Surveillance:

- **Healthy carriers**
  - special surveillance protocols; chemoprevention,
  - disease biomarkers

- **Affected patients**
  - personalized medicine

- High risk undiagnosed patients
  - Ongoing diagnostic efforts
Colon Cancer can be prevented
Early detection improves prognosis

<table>
<thead>
<tr>
<th>Stage at diagnosis</th>
<th>% of total cases</th>
<th>Treatment</th>
<th>Common treatment regimens</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td></td>
<td>Surgery*</td>
<td>-</td>
<td>Stage I-80%</td>
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<tr>
<td>Stage II continued to primary site</td>
<td>39%</td>
<td>Surgery + adjuvant treatment</td>
<td>FOLFOX/XELOX 5-FU/5-fluorouracil</td>
<td>Stage II-80%</td>
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<tr>
<td>Stage III Spread to regional lymph nodes</td>
<td>37%</td>
<td>Systemic treatment - Neoadjuvant therapy - Liver confined metastases - maybe suitable for surgery</td>
<td>FOLFOX + Avastin FOLFIRI + Avastin</td>
<td>~65%</td>
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<tr>
<td>Stage IV Distant metastases</td>
<td>19%</td>
<td></td>
<td></td>
<td>~10% Operable liver metastases: 30-40%</td>
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</table>

Aspirin reduced risk for CRC - CAPP1, 2, 3...

Multitarget Stool DNA Testing for CRC DNA Screening (NEJM 3.2014)

Multistep process

Cancer Hub 3/2014
Inherited CRC

A relatively large number of monogenic syndromes associated with a high lifetime risk of CRC.

Normal epithelium  Adenoma  Carcinoma  Metastases
Genetic Aspects of Inherited colorectal cancer (CRC)

New data New insights
DNA repair
Variety of Syndromes and Genes

Lynch Syndrome
MSI in colon cancer
2004 - Inherited CRC

HNPCC
FAP (APC)

Rare Polyposis Syndromes
• Cowden's disease (PTEN)
• PJS (STK11)
• JPS (SMAD4, BMPR1A)

Adapted from Burt RW et al. Prevention and Early Detection of CRC. 1996
2014 - Inherited CRC

HNPCC - Lynch / Syndrome X
FAP (APC)
MAP (MutYH)
PPAP (POLE POLD1)

Rare Polyposis Syndromes
- Cowden's disease (PTEN)
- PJS (STK11)
- JPS (SMAD4, BMPR1A)
- HMPS

Adapted from Burt RW et al. Prevention and Early Detection of CRC. 1996
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Post-GWAS science:

GWAS have discovered over 100 haplotype-tagging SNPs that are associated with cancer risk.

Accumulation of functional evidence
Next-Generation Sequencing (NGS) ERA:

Analyze entire human genome in a clinically useful time frame

Faster & cheaper generation of data, increased accuracy
Sufficient for clinical application

NGS does not cover variety of complex genetic aberrations:
CNVs, structural changes, epigenomic changes

post-sequencing analysis
Bioinformatics
### COLOSEQ NGS PANEL (UW)

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Hereditary mixed polyposis syndrome


- 2 Ashkenazi kindreds with HMPS
- Autosomal Dominant
- multiple types of colorectal polyps, with CRC.

- Linkage analysis - A shared haplotype on chromosome 15q13.3
- Sequencing the coding regions - no novel pathogenic changes

- search for CNV in the region - a heterozygous duplication of 40kb on chr 15 at the 3’ end of the SCG5 gene

An Ashkenazi founder mutation

↑ GREM1 expression in colon epithelium → BMP pathway activity
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**MUTYH-associated polyposis (MAP)**

MUTYH - a post-replicative DNA glycosylase

Base excision repair (BER) repairs the majority of endogenous DNA damages (deaminations, depurinations, alkylations & oxidative damages)

A signature of a defect in MUTYH is high proportion of GC→TA transversions in tumor target genes

**APC & KRAS**
**MUTYH-associated polyposis (MAP)**
Autosomal recessive CRC

- 2002 - Germline bi-allelic mutations in *MYH* predispose to multiple adenoma or polyposis coli.

- Phenotype is similar to attenuated FAP
gene therapy

would you say you had a dominant or recessive character
Germline and somatic POLE & POLD1 mutations define a new class of hypermutated CRC & EC
Sarah Briggs & Ian Tomlinson, J Pathol 2013

Polymerase proofreading-associated polyposis (PPAP).

A combination of whole-genome sequencing, linkage analysis, and studies of LOH

Exonuclease domain (EDM) improves replication fidelity approximately 100-fold.

Germline EDM mutations confer a high risk of multiple adenomas and CRC. POLD1 mutations also predispose to Endometrial cancer.

Ultramutated microsatellite-stable, cancer (> a million base substitutions/ tumor)

Dominant inheritance
Variable phenotype
The features of tumor mutations can indicate an inherited condition

PPAP - ultramutated microsatellite-stable (mss) cancer

MAP – Exess of transvertions in tumor

Lynch (MMR) - microsatellite-unstable (MSI), wtBRAF tumors

Sporadic MSI  - microsatellite-unstable (MSI), mBRAF tumors

HMPS – over expression of GREM1
Genetic Aspects of Inherited colorectal cancer (CRC)

New data New insights

DNA repair

New data & perspective
Variety of Syndromes and Genes
Lynch Syndrome
MSI tumors
100 years for Lynch Syndrome

- 1913 - Warthin’s report on “Cancer Family Syndrome”
- 1960 – Henry Lynch re-identifying the syndrome

1993 – The genetics behind
100 years for Lynch Syndrome

- 1913 - Warthin’s report on “Cancer Family Syndrome”
- 1960 – Henry Lynch re-identifying the syndrome

1:1000

18,800,000 carriers worldwide

61,700 newly diagnosed Lynch related CRC worldwide


LS is seriously under-diagnosed.

<5 % of high risk patients received LS testing

*Cross et al, Genet Med. 2013
Lynch Syndrome in Israel

Incidence?

3 founder mutations among Ashkenazi

1 founder mutation among Jews from Georgia

3 recurrent mutations among Jews from Afghanistan, Iran, Ethiopia

Co-occurrence of BRCA and Lynch

* Bias!
Cancer Risks in Carriers by 70y Compared to the General Population

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General population risk</th>
<th>Lynch Risks</th>
<th>Mean Age of Onset</th>
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<td>Colon</td>
<td>5.5%</td>
<td>80%</td>
<td>44 years</td>
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<td>Endometrium</td>
<td>1.5-2.7%</td>
<td>&lt;60%</td>
<td>46 years</td>
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<td>Stomach</td>
<td>&lt;1%</td>
<td>11-19%</td>
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<td>Ovary</td>
<td>1-1.6%</td>
<td>9-12%</td>
<td>42.5 years</td>
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<td>Hepatobiliary tract</td>
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<td>Urinary tract</td>
<td>&lt;1%</td>
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<td>Small bowel</td>
<td>&lt;1%</td>
<td>1-4%</td>
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<tr>
<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1-3%</td>
<td>~50 years</td>
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Benefit of Surveillance
(Jervinen 1995, 2000)

2-3y surveillance intervals
A 63% reduction in the incidence of CRC
A 65% reduction in overall mortality

Gastroenterology. 2010 (Vasen et. al)

A cumulative risk of 6% after 10-years.

Risk for advanced cancer was 0.6% after 10-years

Screening for MMR is cost-effectiveness
Cancer Prev Res (Phila). 2011 (Vasen et. al)
Colon Cancer can be prevented
Cancer Risks in Carriers by 70y Compared to the General Population

Extracolonic cancer: Gene dependent – MSH6>MSH2>MLH1

Tissue selectivity?
Modifier genes?
Target genes?
Environment?
Epigenetic?
1993 - MMR- Mutation Mismatch Repair

MMR proteins recognize and repair base pair mismatches that occur during DNA replication - “DNA caretakers”

MMR-work in pairs

- MSH2
- MSH6
- MLH1
- PMS2
Microsatellite instability (MSI)

MMR Loss → IDLs → Microsatellite instability → Genes with microsatellites in coding regions are at 'risk' → Target genes:

- TGFBRII (PolyA 10)
- BAX (G8)
- IGFRIIR (G8)
- MSH3 (A)8
- MSH6
- TCF4
Carrier

Two sets of functional brakes, able to stop the car.

LOH

One set of functional brakes, able to stop the car.

No sets of functional brakes, unable to stop the car.
Tumor Testing – Surrogate Biomarker

[Diagram showing genomic DNA analysis]

**Cancer Hub 3/2014**
Mechanisms for LOH?

- Two sets of functional brakes, able to stop the car.
- One set of functional brakes, able to stop the car.
- No sets of functional brakes, unable to stop the car.

Intervention
The role of epigenetics in Lynch syndrome

no pathogenic mutation is identifiable in 33% of cases with LS.

Primary epimutation of MLH1 shows non-Mendelian inheritance patterns varying from: apparent heritability to the reversion of the methylated allele

Primary epimutation on *MLH1*
The role of epigenetics in Lynch

- MSH2 50%
- MLH1 30-40%
- PMS2 <5%
- MSH6 <10%
- EPCAM 1-3%

Tissue without EPCAM expression
- EPCAM
- MSH2

Tissue with EPCAM expression
- EPCAM
- MSH2

Cancer Hub 3/2014
CMMR-D

Autosomal recessive LS

Carrier of c.686_687delCT mutation in PMS2

Microsatellite instability (MSI)

Inactivation of the MMR system

Either by:

1. MMR gene mutations - Inherited (1/3)
2. Hypermethylation of MLH1 promoter - Sporadic (2/3)

Cancer Hub 3/2014
The Genomic Pathogenesis of Colorectal Cancer

Normal epithelium → Adenoma → Carcinoma → Metastases

- APC, K-ras 12p, DCC 18q, p53 17p, ...
- hMLH1, hMSH2, TGF-βRII, Bax, TCF4, ACVRII, Caspase 5, ...

CIN 85%

MSI 15%
MSI cancers are relatively insensitive to 5-fluorouracil

In vivo:

- Prognostic - those with tumors displaying MSI-H had a better five-year rate of overall survival.

- Predictive - There was no benefit of adjuvant chemotherapy in the group with MSI-H.

Targeted therapies based on molecular alterations in MSI+ CRC
Yamamoto et al. World J Gastroenterol 2012
Cancer Hub 3/2014
Thank you