The Genetics of Colorectal Cancer

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Colorectal Cancer

• Second leading cause of cancer death
• 150,000 cases per year
• 57,000 deaths per year
• Medical treatment not curative
COLORECTAL CANCER

Sporadic

FAP

HNPCC

MAP

Familial
Hereditary Syndromes

• Hereditary nonpolyposis CRC (HNPCC)
• Familial adenomatous polyposis (FAP)
• Attenuated FAP
• MYH associated polyposis (MAP)
Hereditary Nonpolyposis Colorectal Cancer
Hereditary Nonpolyposis Colorectal Cancer

- Autosomal dominant disease
- Mismatch repair gene mutation
- Proximal location of colorectal cancer
- Early age of onset
- Multiple primary malignancies
- Other family cancer
Hereditary Nonpolyposis Colorectal Cancer

• Warthin-Lynch Syndrome

• Lynch Syndrome
Amsterdam Criteria

3 or more with CRC

2 generations

1 diagnosed age < 50 yrs
COLORECTAL CANCER

HNPCC
right sided

44 yo

Sporadic
left sided

64 yo
Cancer Risks in HNPCC

Screening At-Risk Members

- Colonoscopy q 1-2 years starting age 20-25, then annually after 40 yo

- GYN exams in women annually, biopsy of endometrium and transvaginal ultrasound

- Screening for gastric and urologic cancer
Screening: Genetic Testing

- Mutation of the mismatch repair genes
- hMSH2, hMLH1, hPMS2, hMSH6
HNPCC Results From Failure of Mismatch Repair Genes

Base pair mismatch

Normal DNA repair

Defective DNA repair (MMR+)

T C T A C
A G C T G

T C G A C
A G C T G

T C T A C
A G C T G

T C T A C
A G AT G
HNPCC GENETIC TESTING

**Germline**
- MSH2
- MLH1
- MSH6

**Somatic**
- Microsatellite Instability
- & Immunohistochemistry

Blood

Cancer
Microsatellite Instability (MSI)

Normal

Microsatellite instability

Addition of nucleotide repeats
Immunohistochemistry

- Stain tumor for gene proteins
- Pursue absent of proteins
Revised Bethesda Criteria

- CRC less than 50 yo
- CRC and HNPCC related cancer
- CRC Crohns like less than 60 yo
- CRC and 1º relative CRC less than 50 yo
- CRC and two 1º or 2º degree relatives with any HNPCC related tumor
Familial Adenomatous Polyposis
Familial Adenomatous Polyposis

- Autosomal dominant disease
- Mutation of APC gene
- Hundreds of adenomas in colorectum
- Presence/absence extracolonic lesions
- Colorectal cancer inevitable
Cause of FAP

- Mutation of APC gene (Adenomatous Polyposis Coli)
- Located chromosome 5q 21
- Discovered 1991
Clinical Course

Puberty - polyps appear
15 y.o. – onset of polyps
33 y.o. - symptoms appear
36 y.o. – age of diagnosis
39 y.o. – age of colorectal cancer dx
42 y.o. - death from colorectal cancer
Treatment

• Proctocolectomy/ ileostomy
• Proctocolectomy/ ileoanal pull through
• Colectomy/ ileorectal anastomosis
APC GENE

CLASSIC FAP

5' 3'

codons 0 158 1596 2843

RNA

PROTEIN

RNA
APC GENE

CLASSIC FAP

5' codons 0 158

3' codons 1596 2843

RNA

PROTEIN
Attenuated FAP

- 5’ and 3’ APC gene mutations
- 6% of FAP pedigrees
- Oligopolyposis (<100 adenomas),
- Polyps right-sided
- Heterogeneous phenotype
- Later CRC (51 vs 39 y.o.)
Screening

- At-risk persons (1st degree relatives)
- Sigmoidoscopy
  q yr starting age 12,
  q 2 yrs after age 25,
  q 3 yrs after age 35,
  average risk guidelines after age 50
Screening: APC Gene Testing

- Gene test for mutation of APC gene
- Start at-risk persons age 10-12
- Pretest genetic counseling/consent
- Test affected pedigree member first
APC Gene Testing - At Risk

APC mutation
APC Gene Test Result

• Positive - FAP- sigmoid. yearly
• Negative - No FAP- sigmoid. age 25
MYH Associated Polyposis (MAP)
MYH Associated Polyposis

- Discovered in 2003
- Caused by mutation in MYH gene
- Polyposis (> 100 polyps)
- Oligopolyposis (< 100 polyps)
- Autosomal recessive condition
MAP

• Polyposis (> 100 polyps) - <1%

• Oligopolyposis (5-100 polyps) - 4% to 33%
MYH Gene

- Base excision gene
- Two deleterious mutations
  - Y165C and G382D
- Prevents mutations in DNA
- Fixes damaged base pairs
- Damaged by oxidative stress
Oxidative Damage

\[
G=C \quad \rightarrow \quad G^*=C \quad \rightarrow \quad G^*=A \quad \rightarrow \quad T=A
\]
Oxidative Damage

\[ G=C \rightarrow G^*=C \]

MYH
Oxidative Damage

\[ G=C \rightarrow G^*=C \rightarrow G=C \]

MYH
MYH Gene

- Polyposis
- CRC risk (carrier)
- CRC risk (carrier)
- Normal risk
MYH Management

• Biallelic mutations- like FAP or AFAP

• Monoallelic mutation- colonoscopy at 40 yr q 10 yrs (q 5 yrs).
Summary

• HNPCC
  – colonoscopic screening
  – MSI/IHC testing, MMR gene testing
• FAP/AFAP
  – APC gene testing
  – sigmoid/colonoscopy screening
• MAP
  – MYH gene testing