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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

Disease	Gene	Disease Phenotype
Familial adenomatous polyposis	*APC*	Colonic polyposis
Polyposis	*MUTYH*	Colonic polyposis (recessive inheritance)
Gardner's syndrome	*APC*	Colonic polyposis in association with extra-colonic lesions
Oldfield's syndrome	*APC*	Colonic polyposis with sebaceous cysts.
Turcot syndrome*	*APC*	Malignant tumours of the CNS in association with polyposis
Familial Infiltrative	*APC*	Desmoid disease fibromatosis
Polyposis	AXIN	Polyposis and dental abnormalities

Syndromes with pre-existing hamartomatous polyps

Disease	Gene	Disease Phenotype
Peutz-Jeghers syndrome	STK11/LKB1	Abnormal pigmentation on lips and buccal mucosa
Ruvalcaba-Myhre-Smith syndrome (Bannayan-Riley-Ruvalcaba Syndrome) Cowden's syndrome	PTEN*	Macrocephaly, pigmented macules on penis
Juvenile polyposis	SMAD4	cystic hamartomatous polyps

Genetic Predispositions to Colorectal Cancer

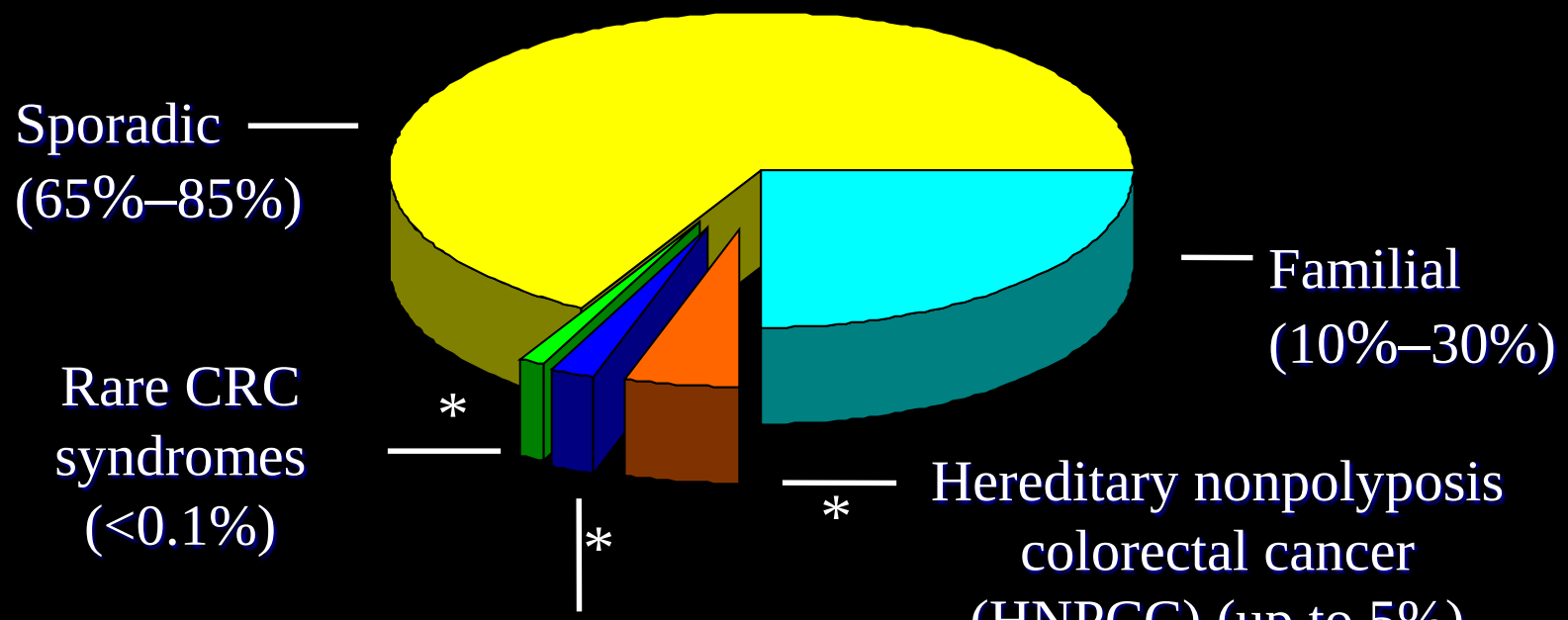
Syndromes without pre-existing polyposis:

Disease	Gene	Disease phenotype
Lynch Syndrome	MSH2 MLH1 PMS2 MSH6 EXO1(?) EPCAM…	few, if any polyps, CRC tends to be site specific (in women also endometrial cancer
Muir-Torre syndrome	MSH2 MLH1	HNPCC plus dermatological lesions and laryngeal cancer
Turcot's Syndrome	MSH2 MLH1	CRC plus CNS lesions

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

Hereditary Nonpolyposis Colorectal cancer (HNPCC)

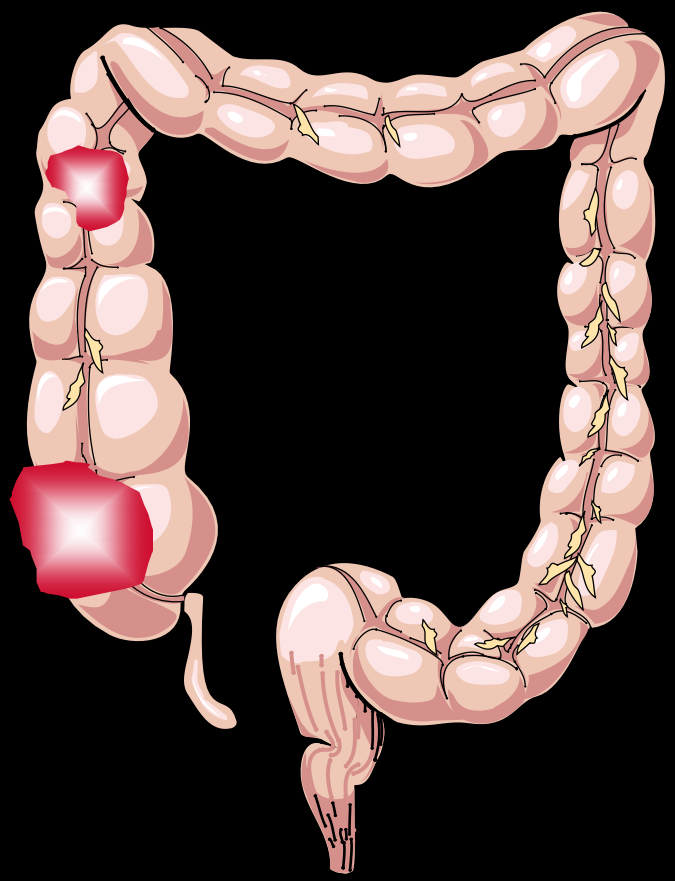
Definition: **HNPCC is defined by a set of clinical criteria**

Lynch Syndrome refers to HNPCC with DNA mismatch repair gene mutations

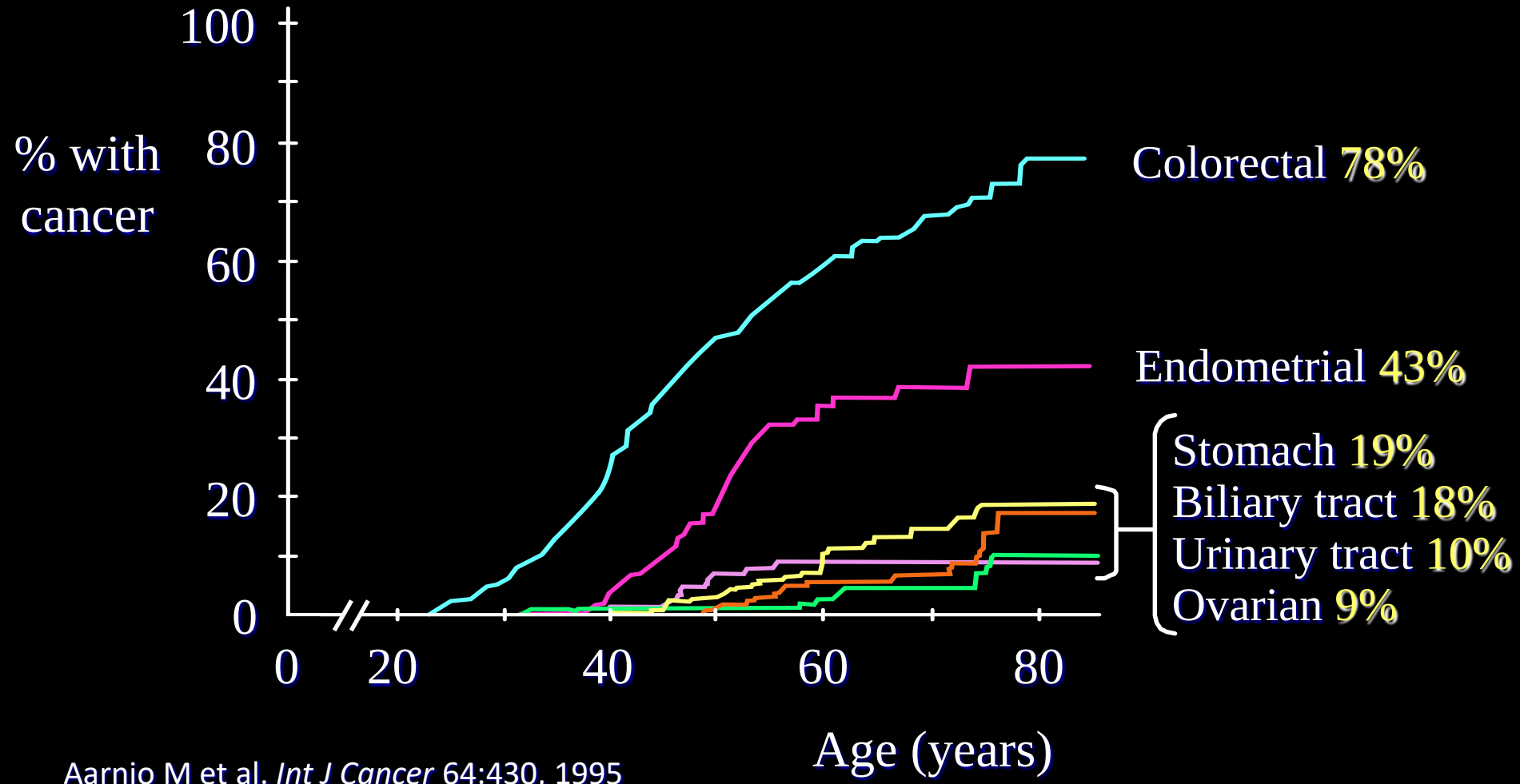
1. **Amsterdam Criteria**
2. **Bethesda Criteria**
3. **Modified Bethesda Criteria**
4. **Amsterdam II Criteria**

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

HNPCC

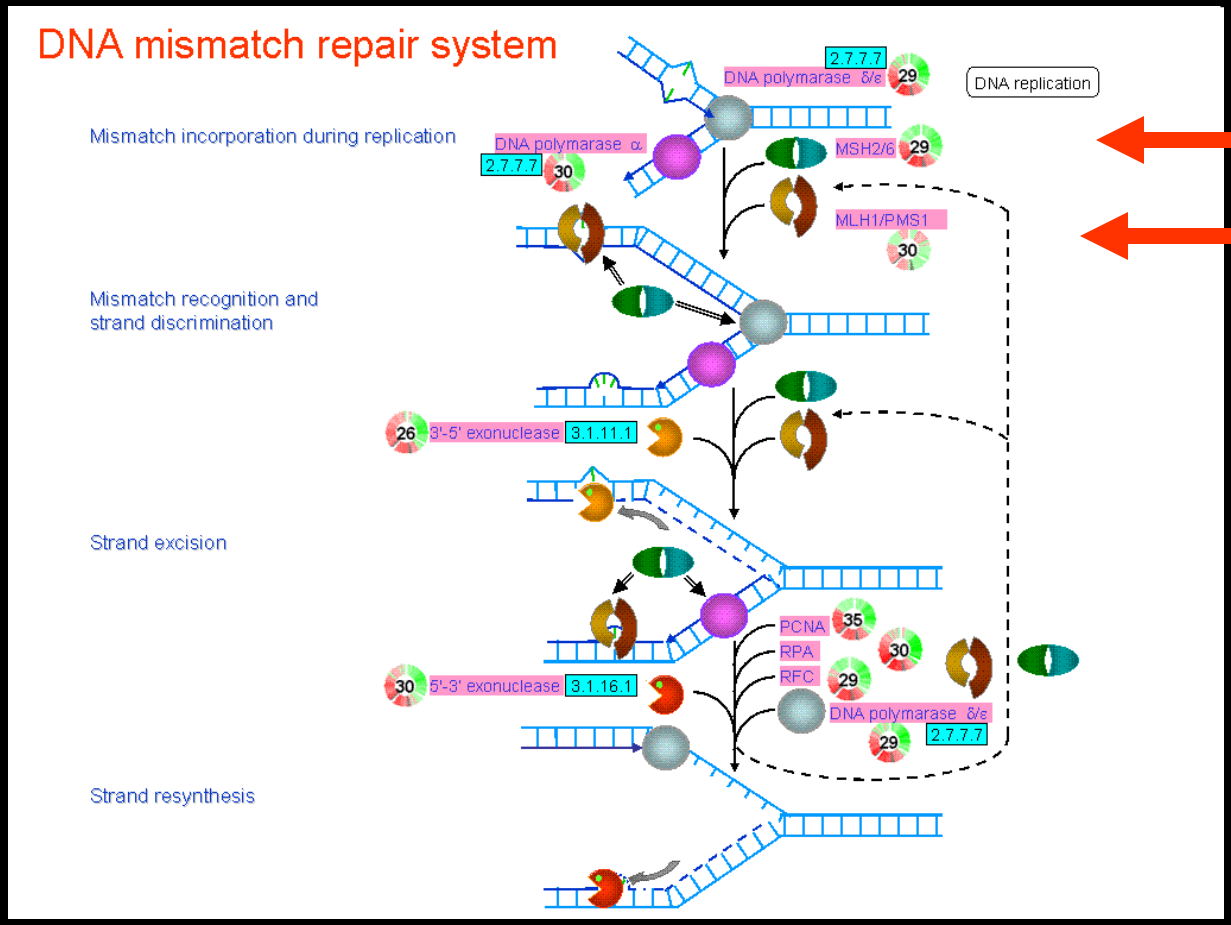
- **Rare autosomal dominant predisposition to CRC**
- **Frequency ~ 1:2,000 to ~ 1:4,000**
  (often reported to account for 5% of all CRCs)
- **The Danish CRC statistics suggest 1.7% of all CRCs**
  rising to 14.7% of patients <50 years of age
- **>80% penetrance by 75 years OR is it?**

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



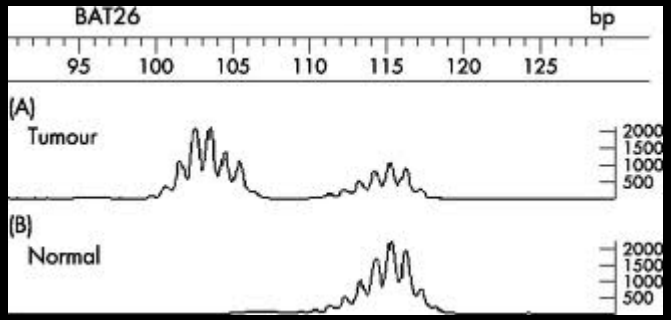
MSH/MSH6

MLH1/PMS2*

At least 22 genes involved in DNA mismatch repair

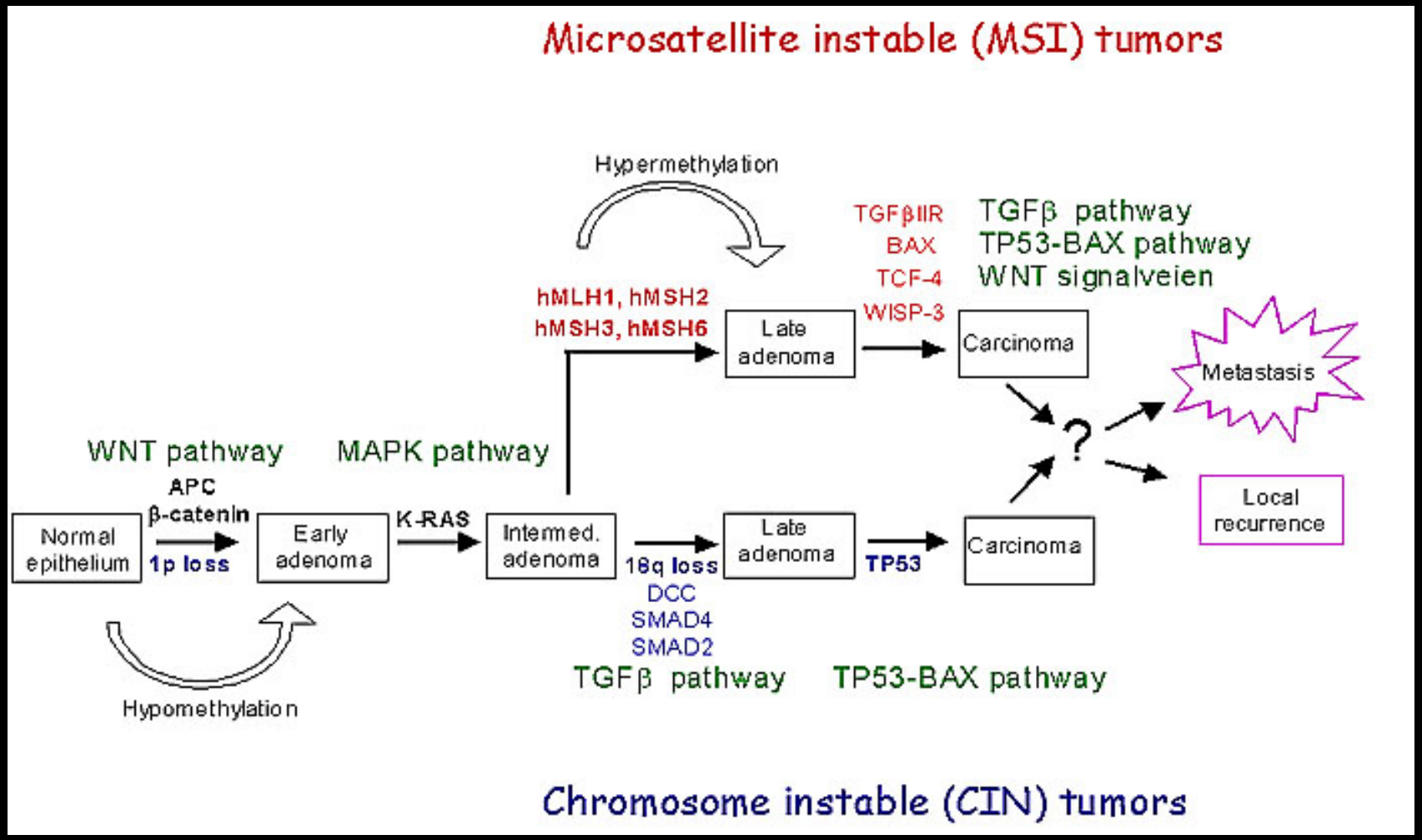
Tumour Specificity: Microsatellite Instability

- 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 <u>immediately</u> apparent genotype/phenotype correlation, DNA MMR is a house-keeping process.


Microsatellite instable (MSI) tumors
Hypermethylation
TGFβIIR
BAX
TCF-4
WISP-3
TGFβ pathway
TP53-BAX pathway
WNT signalveien
hMLH1, hMSH2
hMSH3, hMSH6
Late adenoma
Carcinoma
Metastasis
?
WNT pathway
MAPK pathway
APC
β-catenin
1p loss
Normal epithelium
Early adenoma
K-RAS
Interned. adenoma
18q loss
DCC
SMAD4
SMAD2
Late adenoma
TP53
Carcinoma
Local recurrence
TGFβ pathway
TP53-BAX pathway
Hypomethylation
Chromosome instable (CIN) tumors

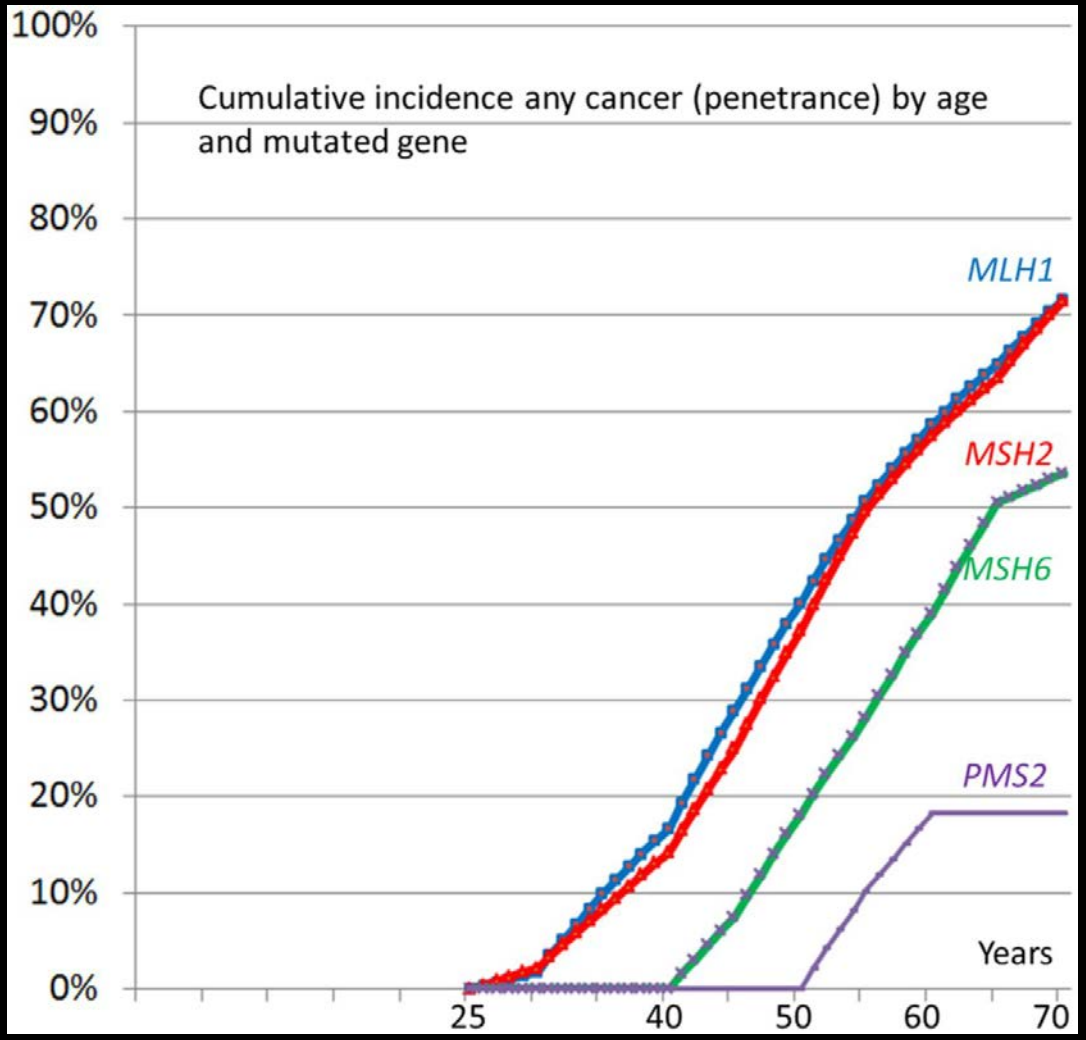
Genetic basis ctd.

- **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??**

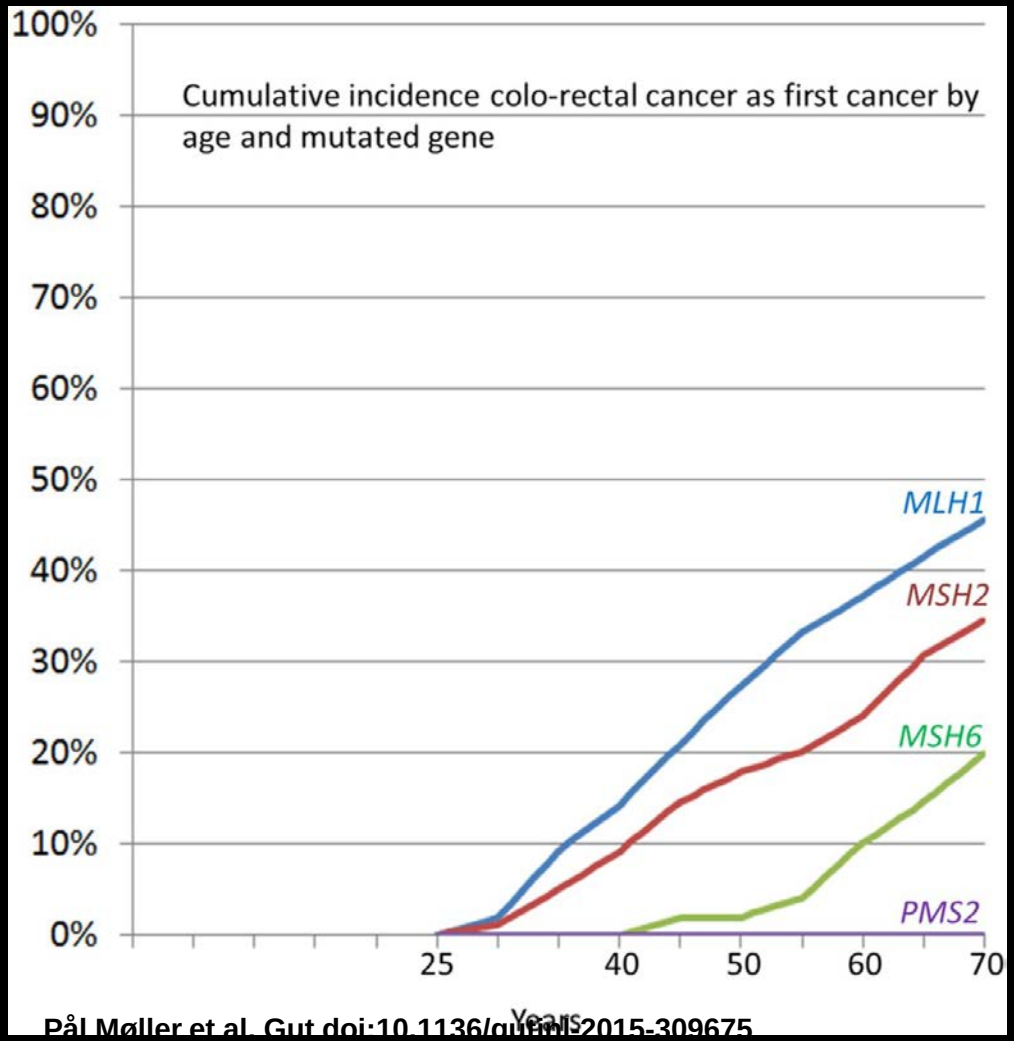
- **A considerable proportion of families are not accounted for by these genes – known as HNPCC.**

Calculated cumulative incidences by age and mutated gene for any cancer.



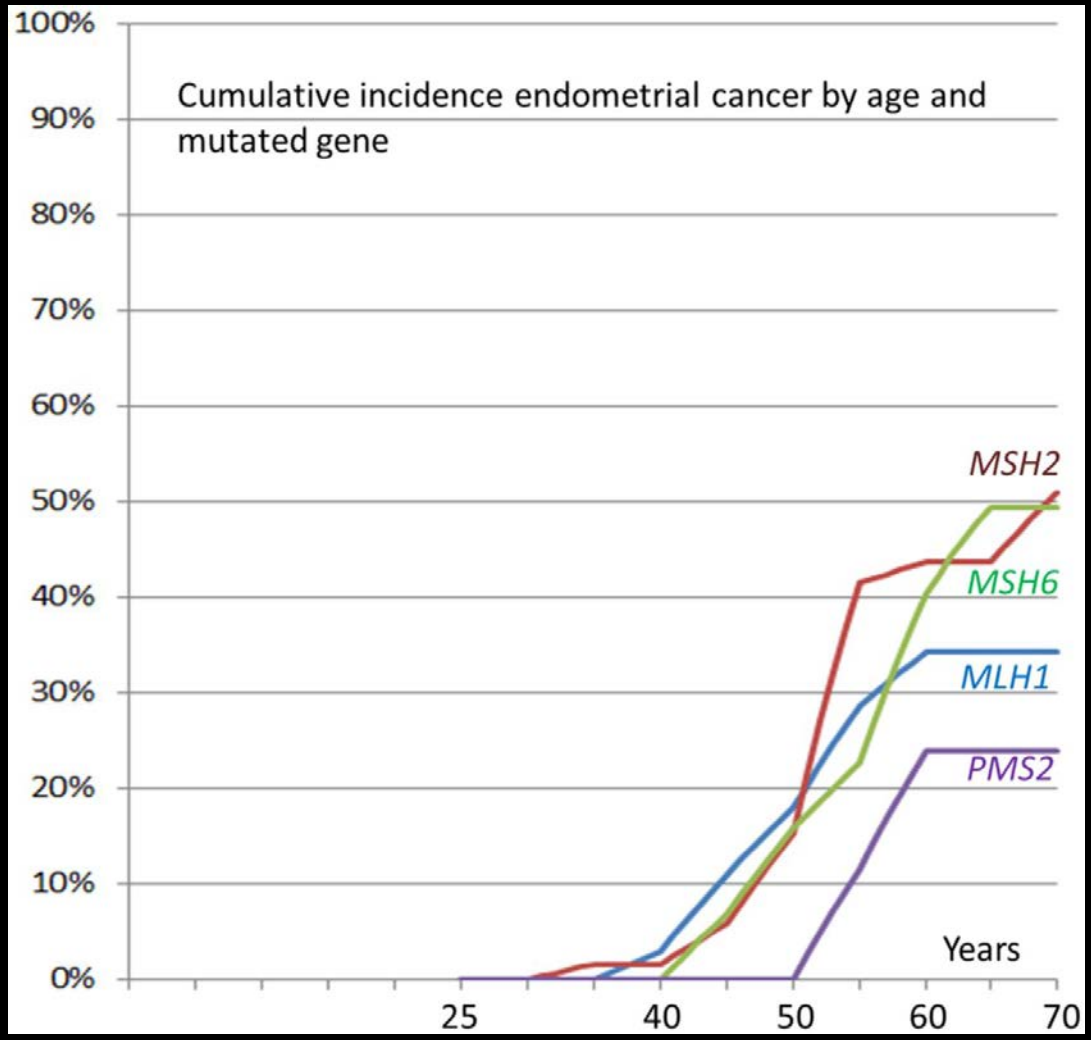
GUT

Calculated cumulative incidences by age and mutated gene for colorectal cancer (CRC) as the first cancer.



Pål Møller et al. Gut doi:10.1136/gutjnl-2015-309675

Calculated cumulative incidences by age and mutated gene for endometrial cancer as the first cancer by gene.



GUT

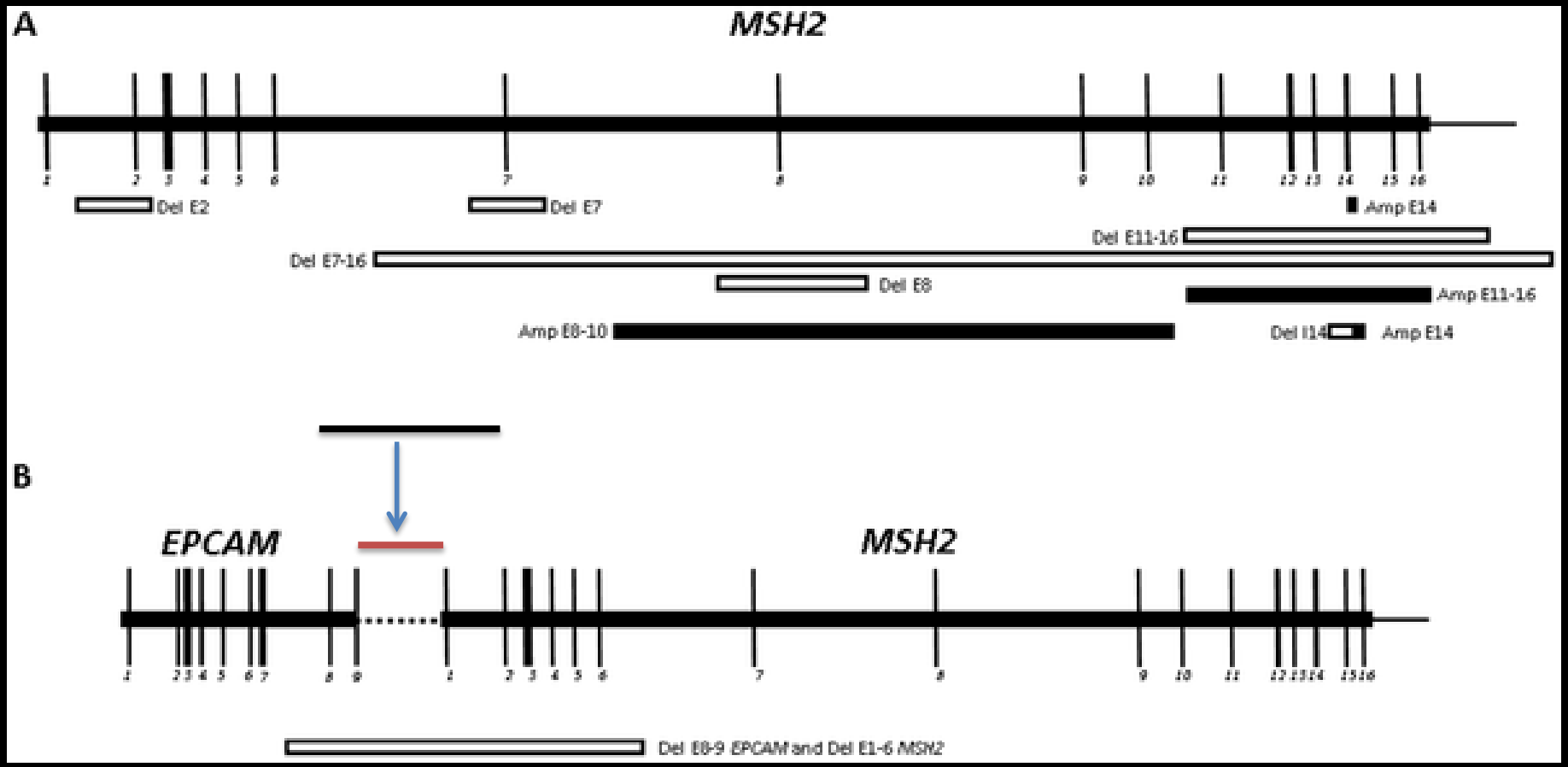
EPCAM – Not a gene linked to LS *per se*

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.



Romero A, Garre P, Valentin O, Sanz J, Pérez-Segura P, et al. (2013) Frequency and Variability of Genomic Rearrangements on MSH2 in Spanish Lynch Syndrome Families. PLOS ONE 8(9): e72195. https://doi.org/10.1371/journal.pone.0072195
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

Mutation Positive Patients

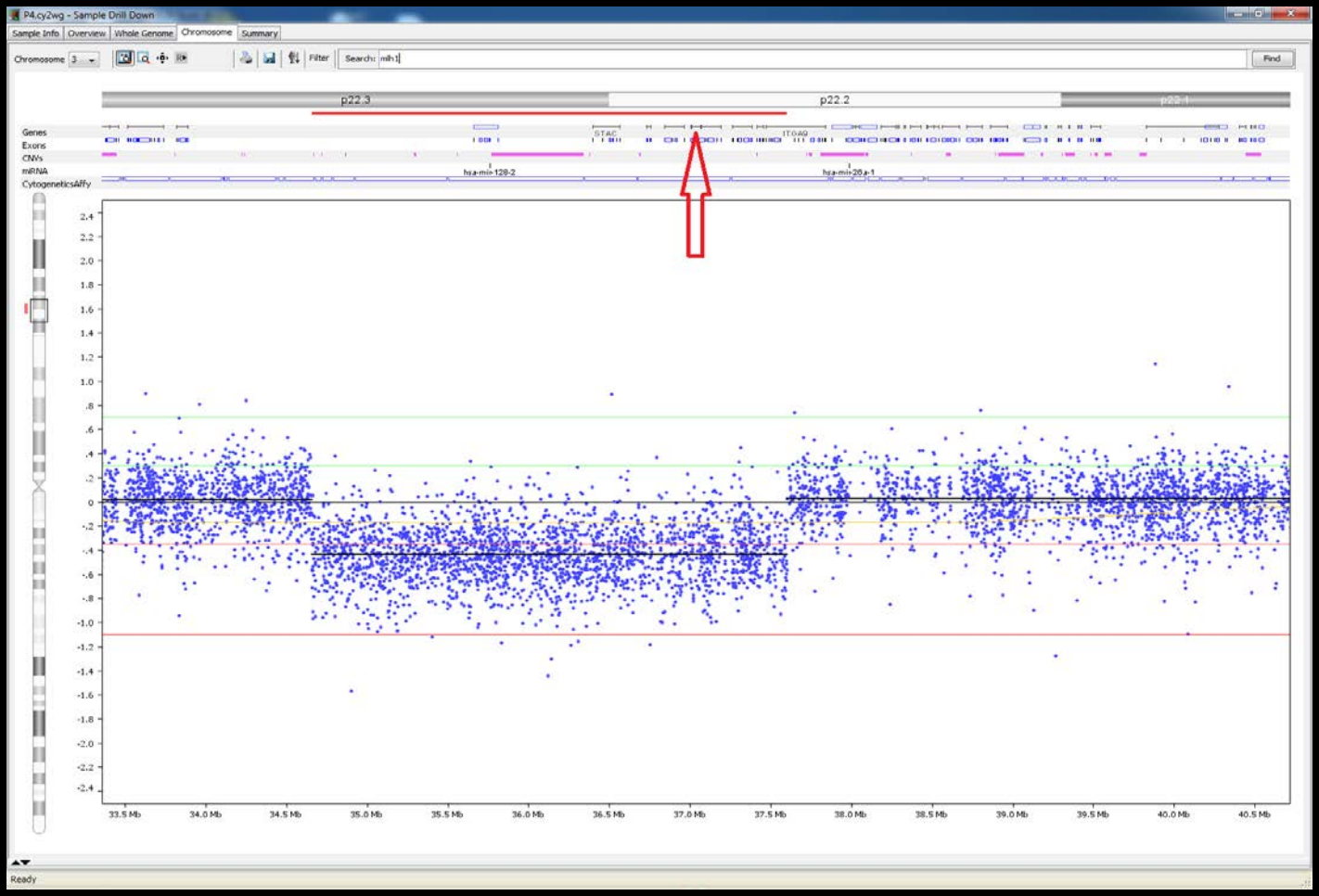
Identifying key modifying genes associated with Lynch Syndrome and the risk of early onset CRCs.

Mutation Negative Patients

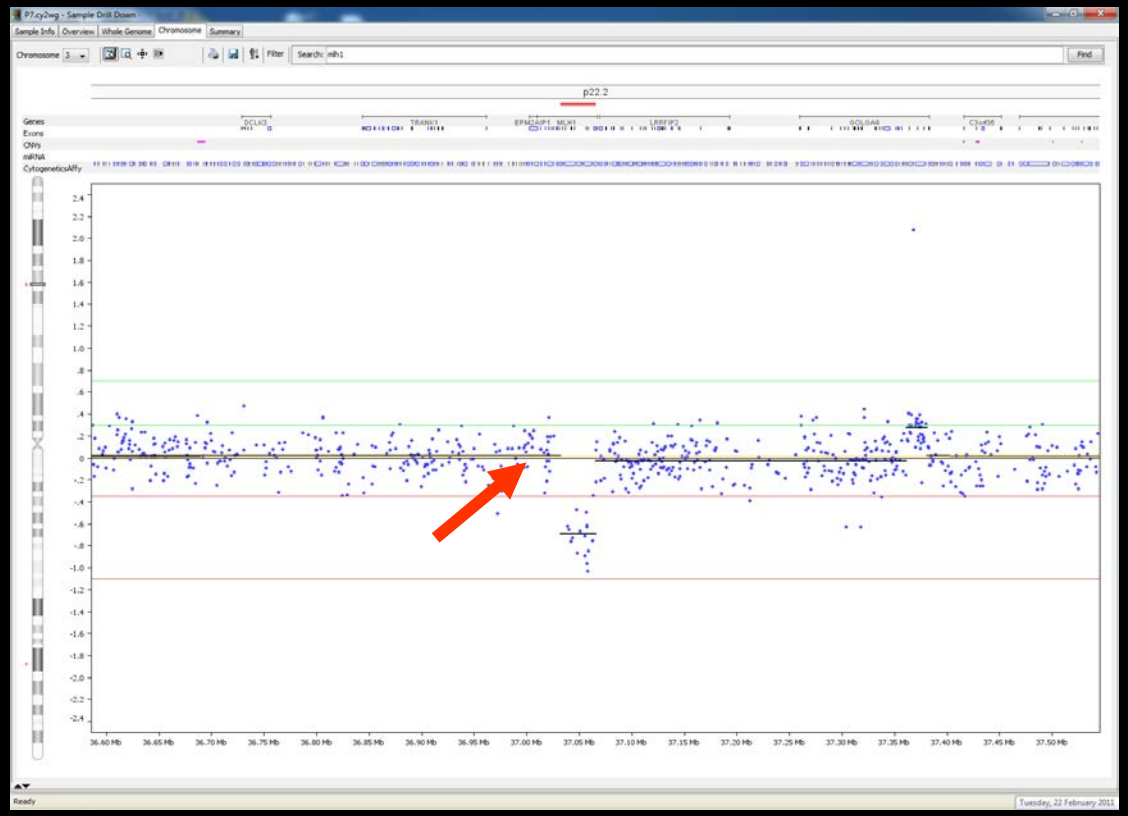
Undertaking a genome wide analysis on HNPCC patients

CNV analysis on known deletion carriers:

MLH1 Whole Gene Deletion:

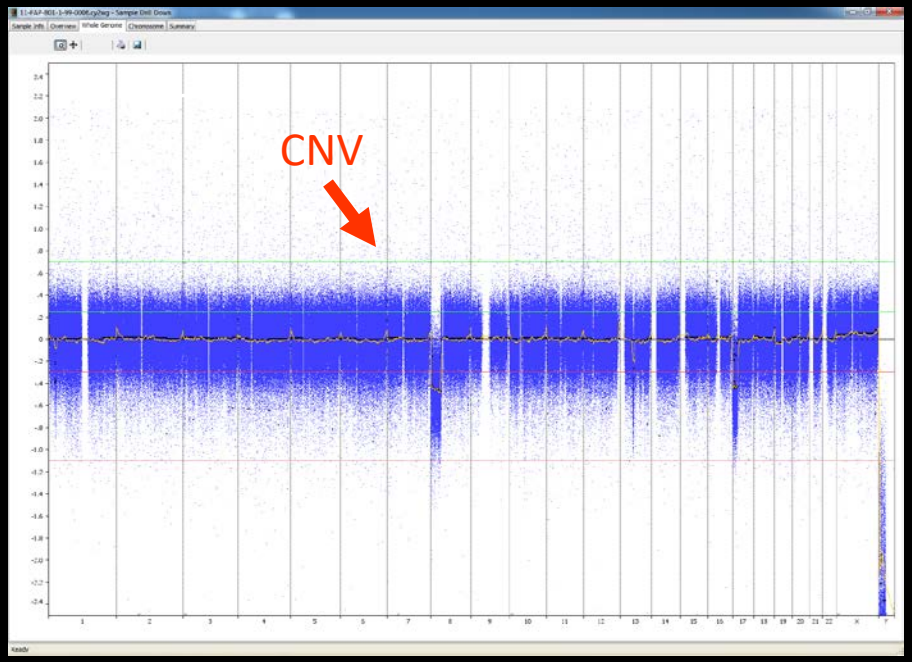


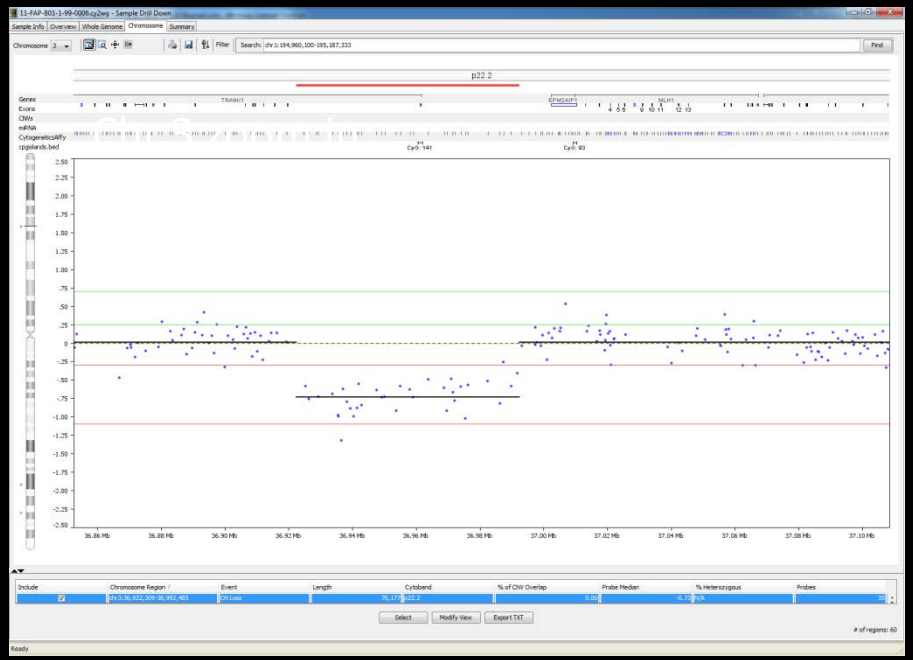
Smaller deletions detected by CNV analysis: MLH1 Exons 9-15 Deletion



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

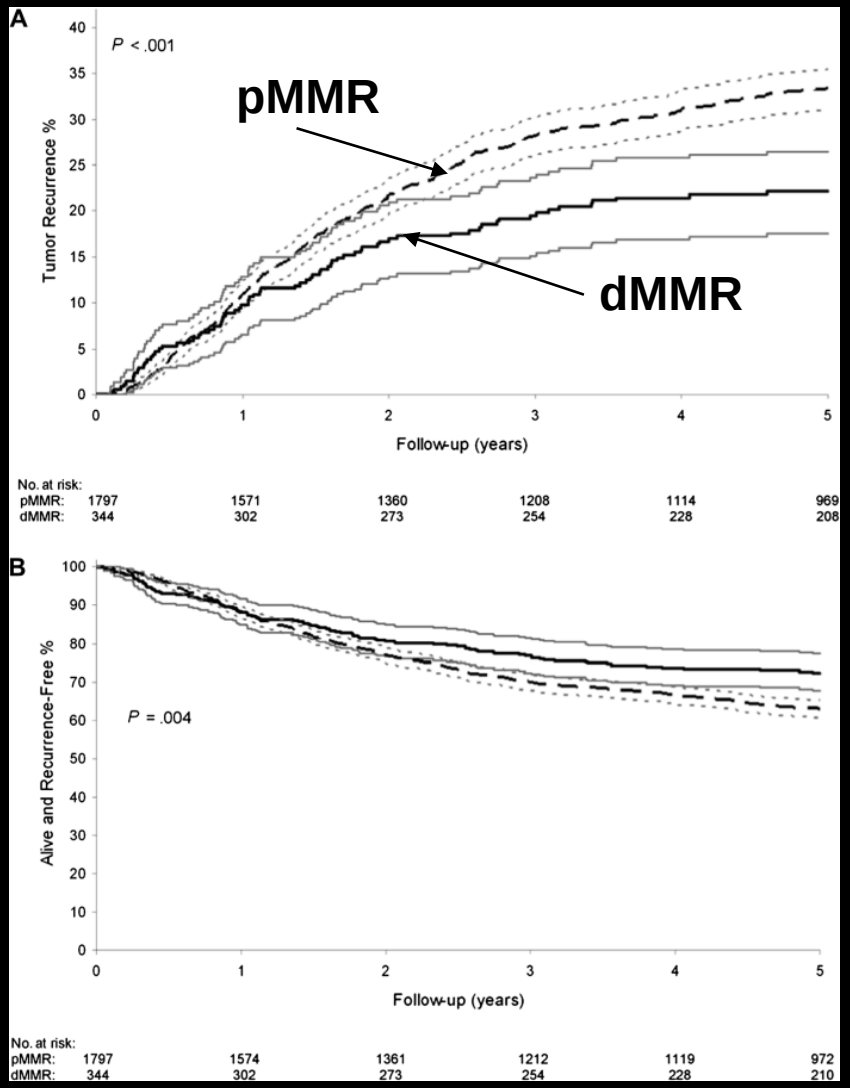
- 85% associated with chromosomal instability (CIMP)
- 15% associated with DNA microsatellite instability (MSI)
- Outcomes may be different between MSI associated tumours and CIMP tumours
- <10% of MSI tumours linked to LS

- WHY IS THIS IMPORTANT?

Stage II and II colon cancer recurrence and survival.

A. Recurrence

B. Disease free survival rates



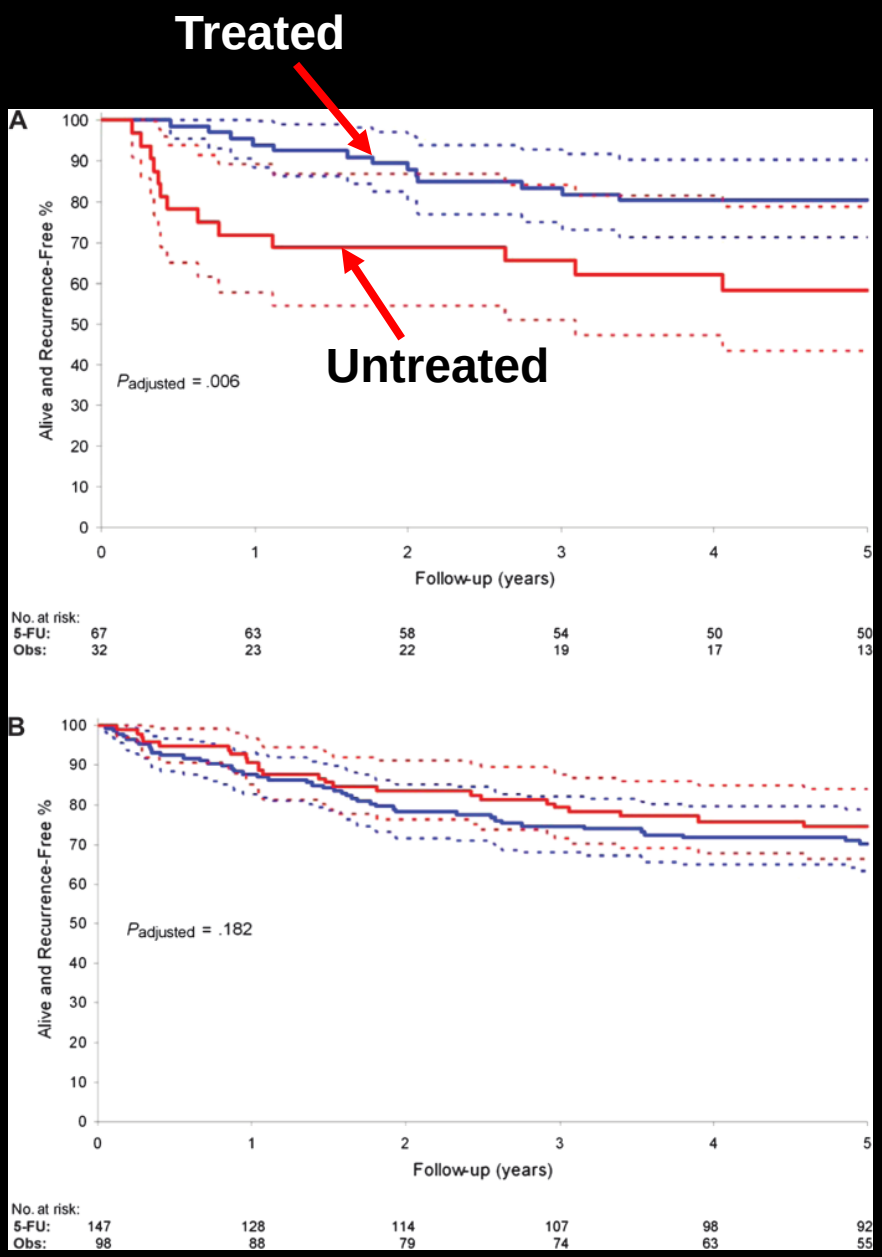
Sinicrope et al. JNCI 2011

Germline vs sporadic

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

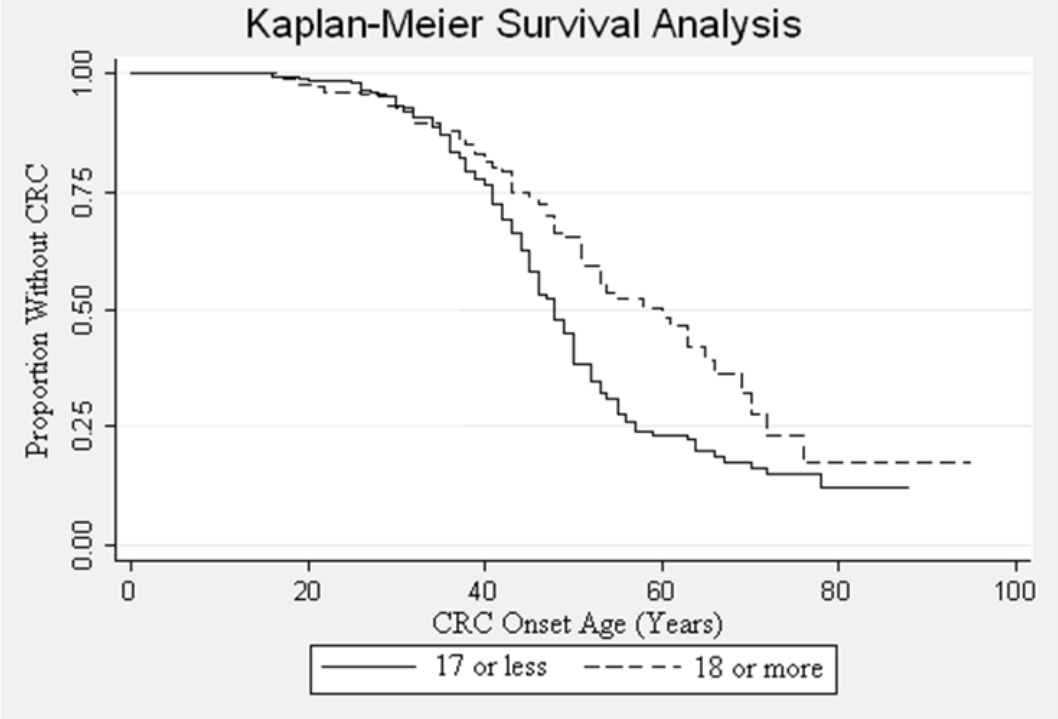
The Case For IGF1

- 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

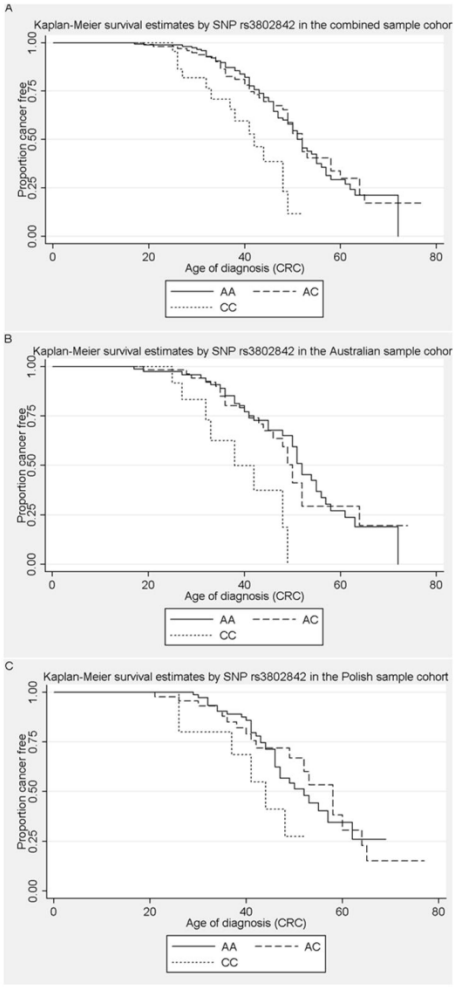
IGF1 Repeat polymorphism and cancer risk in HNPCC



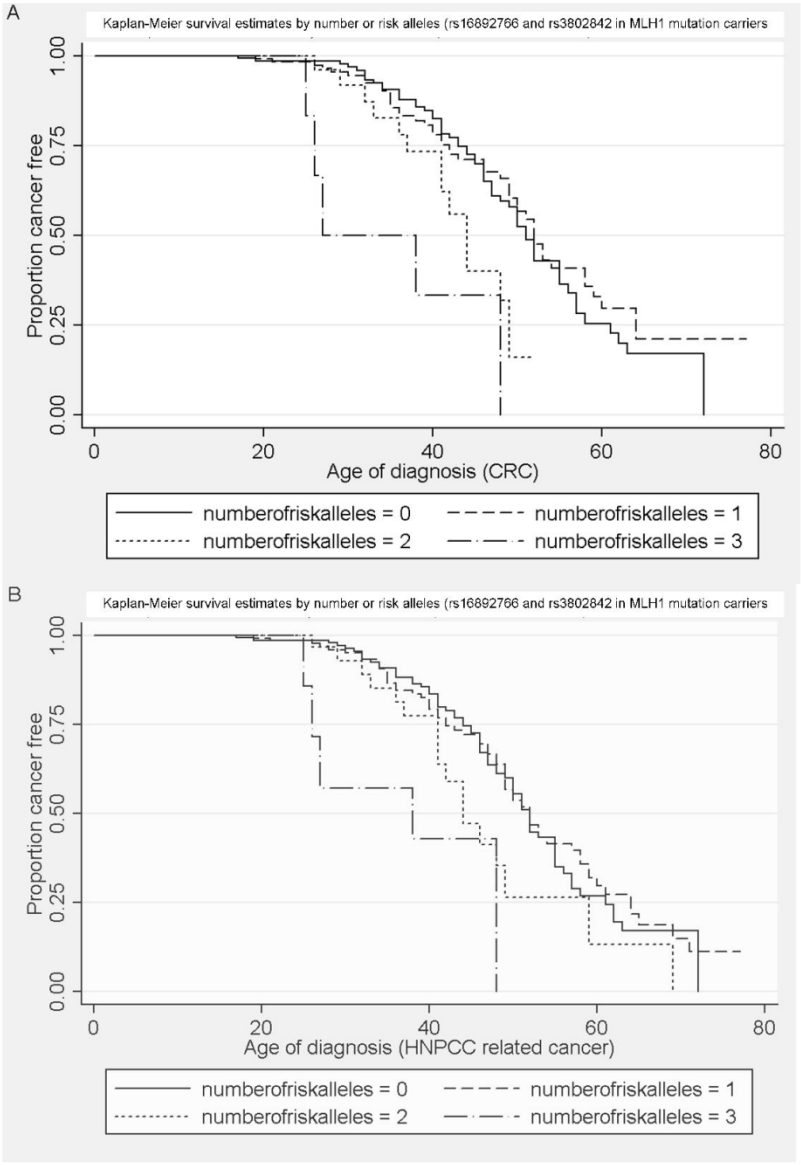
Genome wide association studies have revealed numerous genetic risk factors, all with small effect sizes

Are any of the new CRC susceptibility loci act as modifier genes in HNPCC

8q23.3	***rs16892766***
8q24.21	rs6983267
8q24	rs7014346
11q23.1	***rs3802842***
10p14	rs10795668
15q13.3	rs4779584
15q13.3	rs10318
18q21	rs4464148
1821.1	rs4939827



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