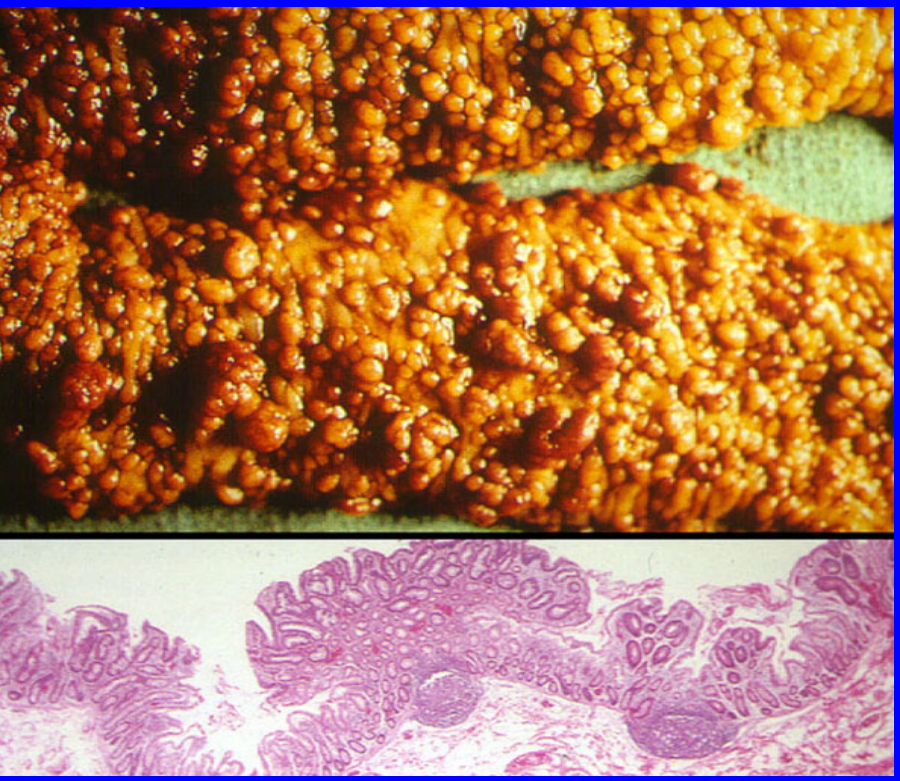
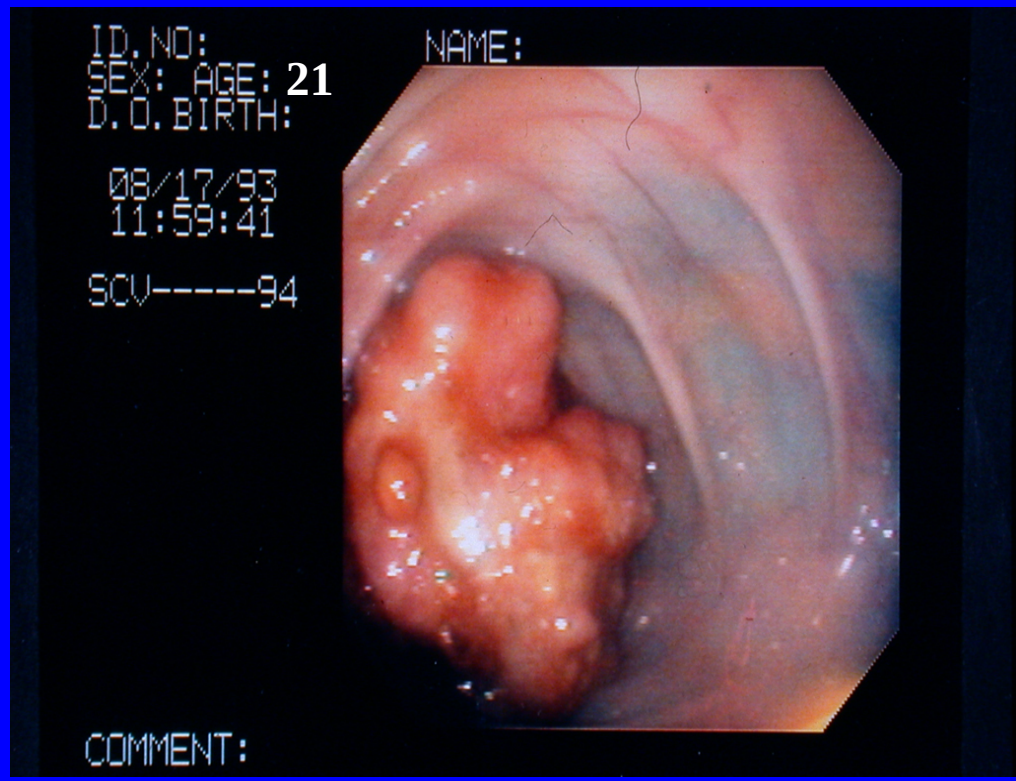
Genotypic/Phenotypic Spectrum of Hereditary Colorectal Cancer





Familial Adenomatous Polyposis

Hereditary Nonpolyposis Colorectal Cancer

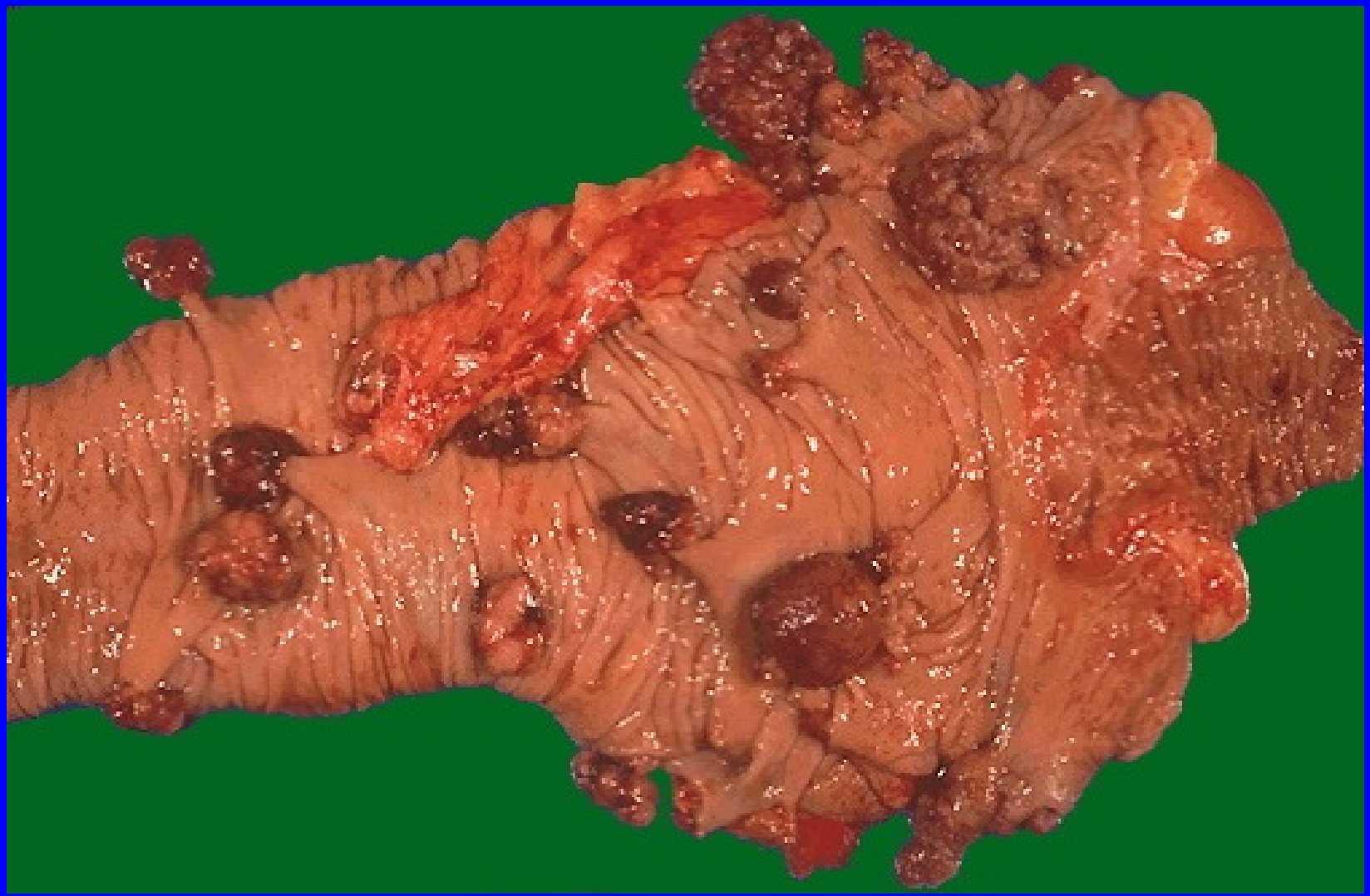
Autosomal Dominant
Chromosomal Instability

Autosomal Dominant
Microsatellite Instability

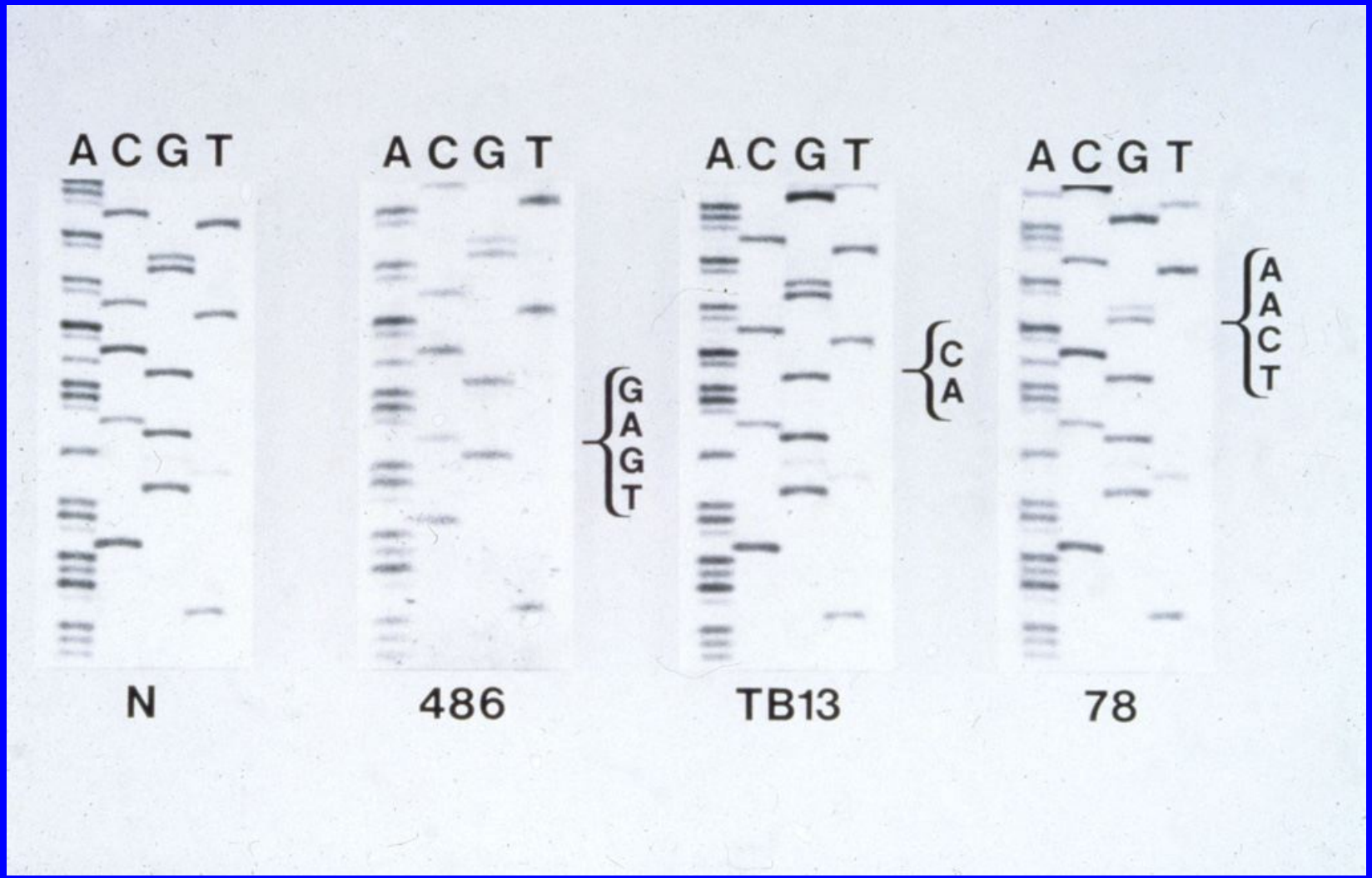
Germline APC Mutations

Germline MMR Mutations

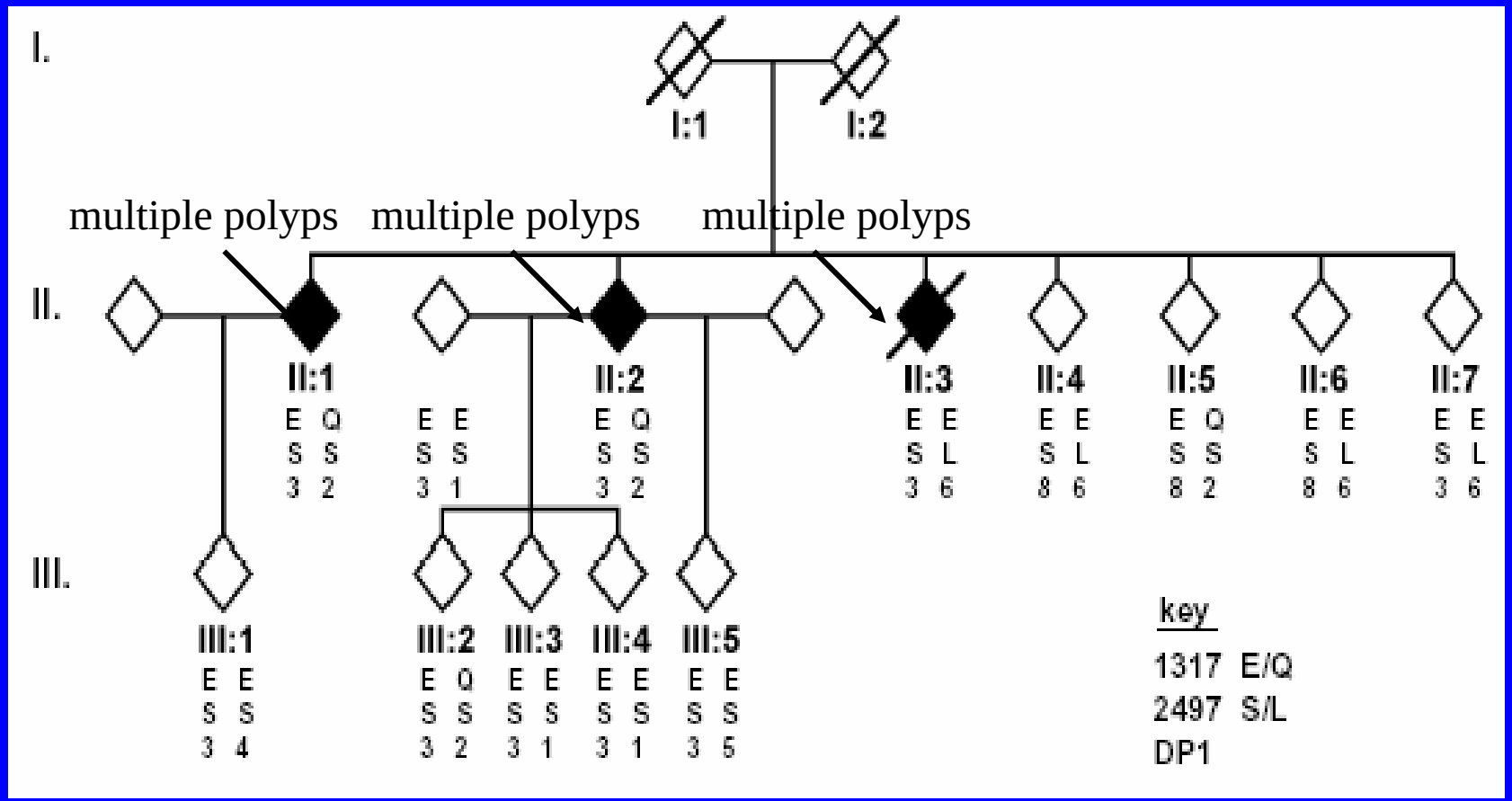
Attenuated Polyposis



APC Mutations in Colorectal Polyps and Cancers

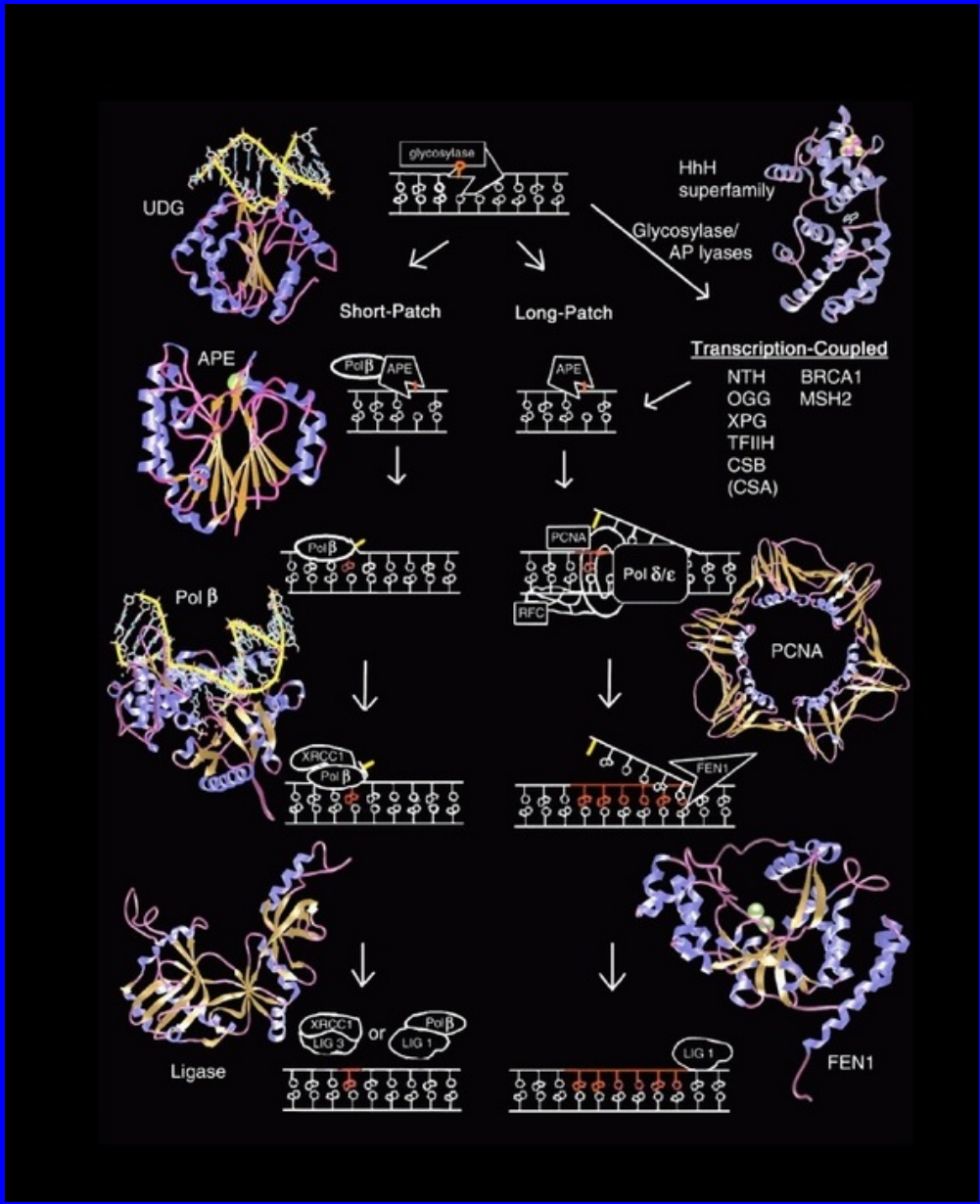


Family N - Autosomal Recessive Colorectal Cancer?



Polyps and Tumors in Family N had APC G ⟶ A Transversions (that's rare!)

Base Excision Repair



Two Functionally Important MYH Mutations

tyrosine

Exon 7 (codon 165) …GGGCTACTATT…

cysteine

Exon 7 (codon 165) …GGGCTGCTATT…

glycine

Exon 13 (codon 382) …ctcaGGTCTGC…

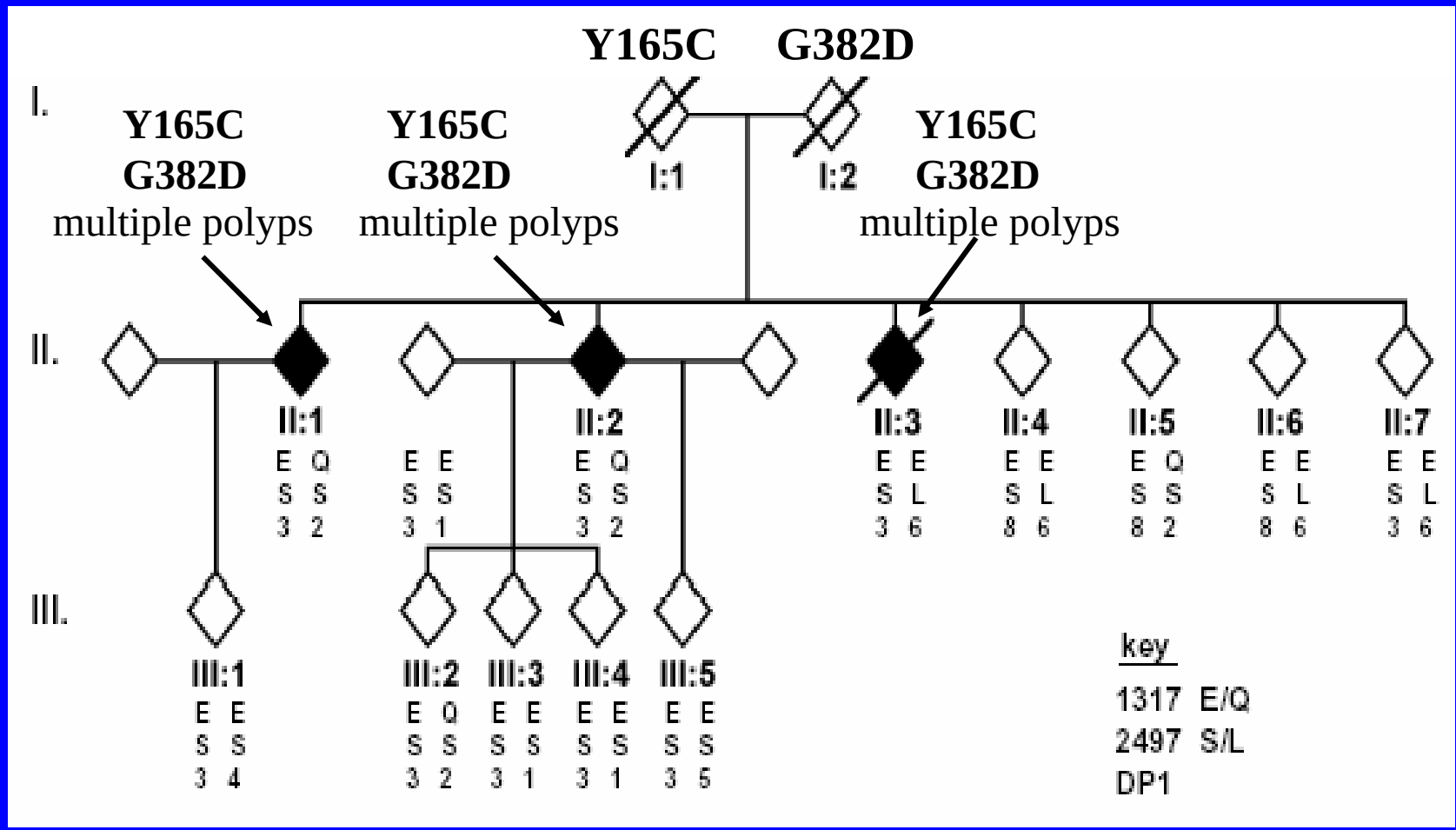
aspartic acid

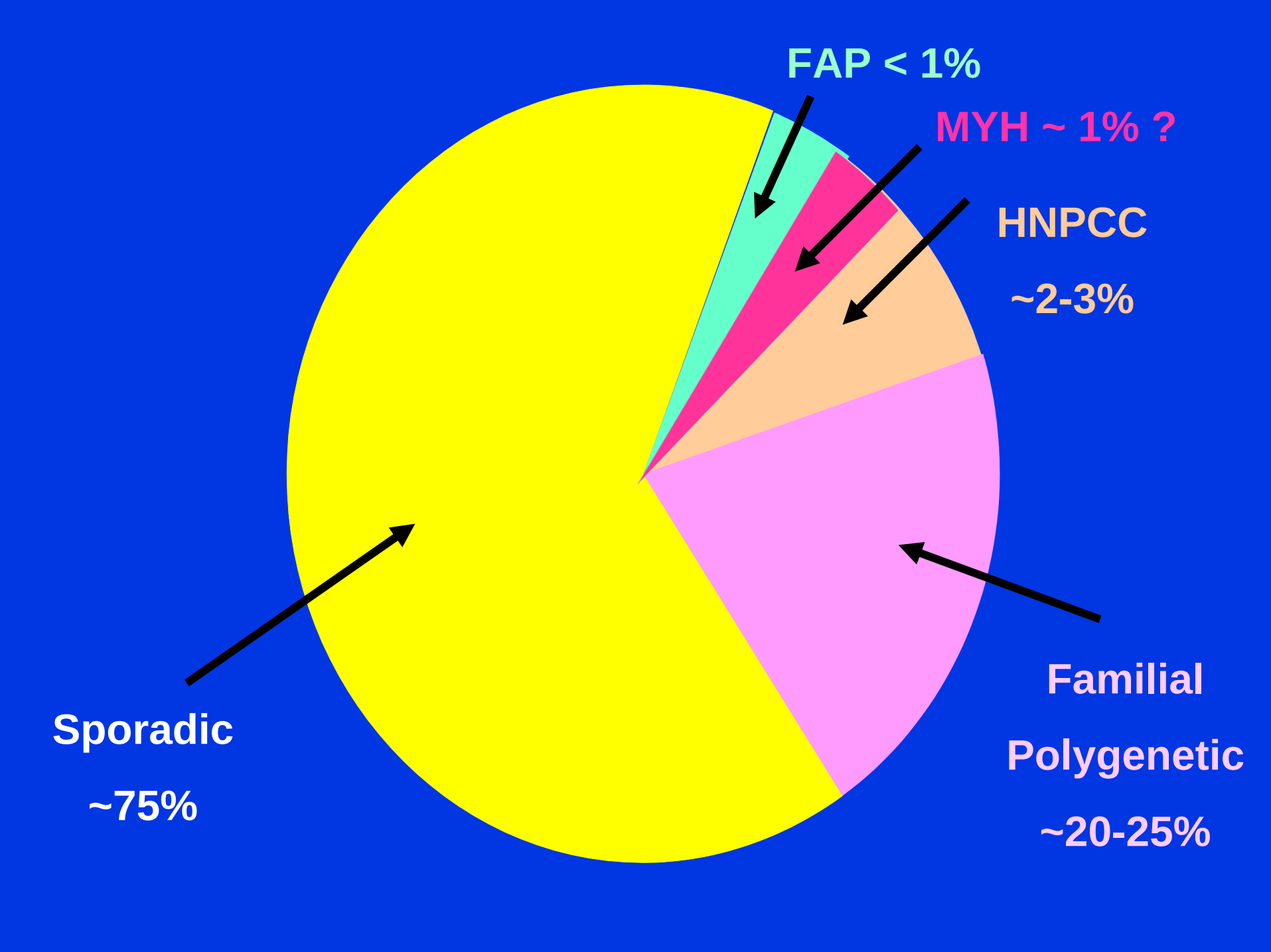
Exon 13 (codon 382)…ctcaGATCTGC…

Frequency of each ~ 1/100 in Caucasians

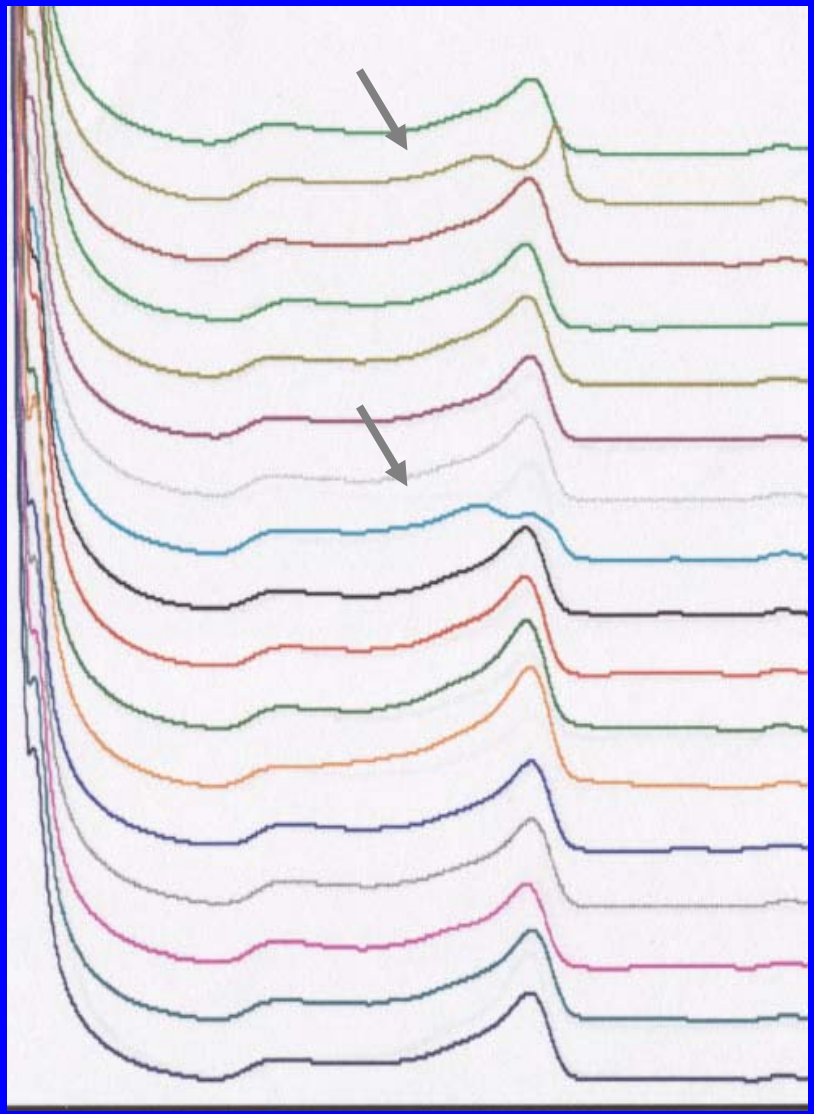
MYH Associated Polyposis (MAP)

Autosomal Recessive Colorectal Cancer

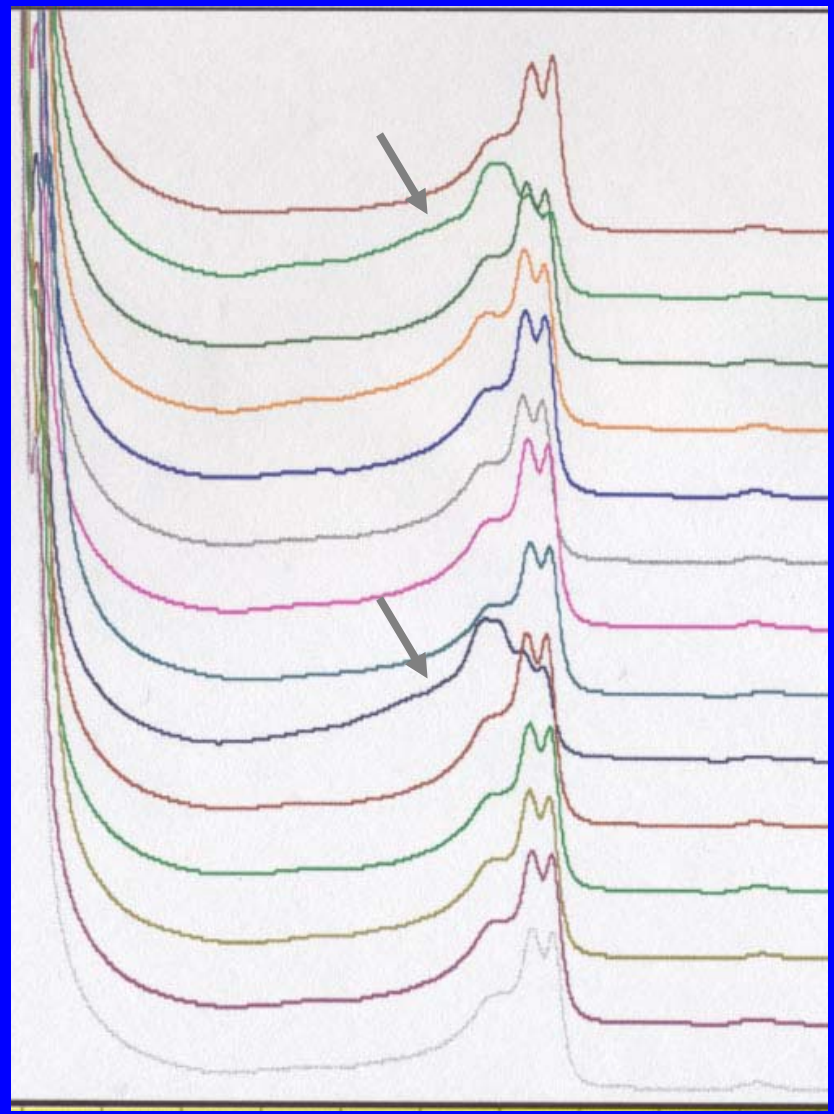



FAP < 1%
MYH ~ 1% ?
HNPCC
~2-3%
Sporadic
~75%
Familial
Polygenetic
~20-25%

Y165C Wave



G382D Wave



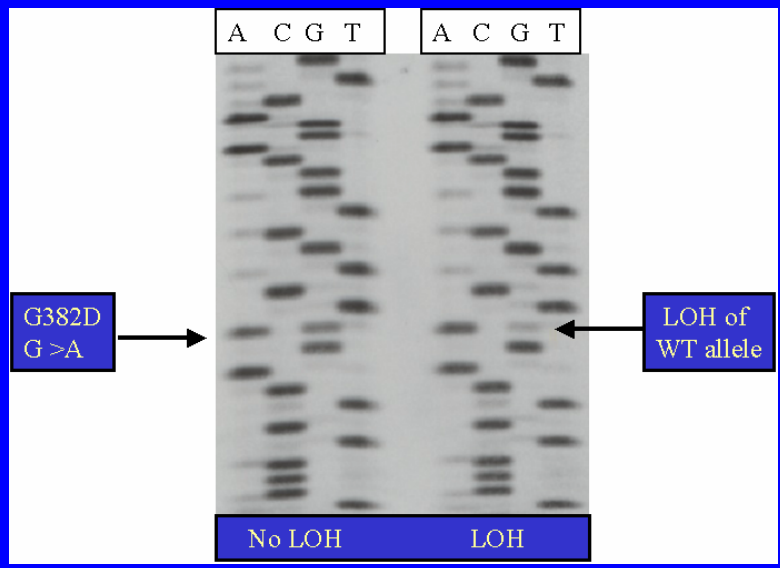
Results

Genotype	Cases N=1238	Controls N=1255	Odds Ratio (95% CI)
Total Carriers	41	21	2.0 (1.2-3.4)
Monoallelic Carriers	29	21	1.4 (0.8-2.5)
Y165C/- Hets	8	4	2.1 (0.6-6.8)
G382D/- Hets	21	17	1.3 (0.7-2.4)
Biallelic Carriers	12	0	
Y165C/Y165C Homos	2	0	
G382D/G382D Homos	4	0	
Y165C/- and G382D/-	3	0	
Y165C/- and Y90X/-	1	0	
Y165C/- and 891+3A->C/-	1	0	
G382D/- and 891+3A->C/-	1	0	
No Y165C or G382D mutation	1197	1234	

Other Findings

- 9/29 monoallelic carriers had multiple adenomas
- 7/12 biallelic carriers had multiple adenomas

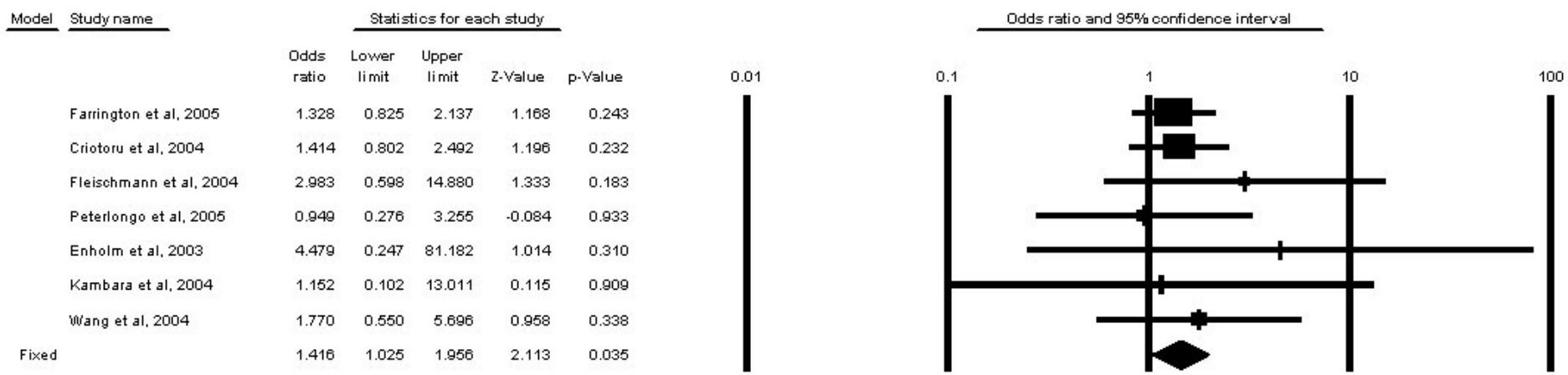
- 1p loss of heterozygosity
  - 47% tumors from monoallelic carriers
  - 20% tumors from biallelic carriers



- Increased frequency of other cancers (lung and breast) in families of carriers

What about the Hets?

Study	Freq in cases* (%)	Freq in controls* (%)
Farrington et al., 2005	45/2205 (2.0%)	28/1822 (1.5%)
Croitoru et al., 2004	29/1226 (2.4%)	21/1255 (1.7%)
Fleischmann et al., 2004	6/356 (1.7%)	2/354 (0.6%)
Peterlongo et al., 2005	4/553 (0.7%)	7/918 (0.8%)
Enholm et al., 2003	5/1038 (0.5%)	0/424 (0.0%)
Kambara et al, 2004	2/92 (2.1%)	1/53 (1.9%)
Wang et al., 2004	10/442 (2.3%)	4/313 (1.3%)



Colorectal cancer in 300 untyped 1st-degree relatives of 39 Ontario probands with a MYH mutation

Ascertainment of proband	Proband's MYH genotype	Observed colorectal cancer cases	Expected colorectal cancer cases*	Standardised incidence ratio
'High' or 'intermediate' risk	Biallelic	10	2.0	5.0 (2.6-9.3)
	Monoallelic	5	1.0	5.2 (2.1-12.5)
'Low' risk	Biallelic	5	1.7	3.0 (1.2-7.3)
	Monoallelic	2	0.4	4.5 (1.1-18.1)

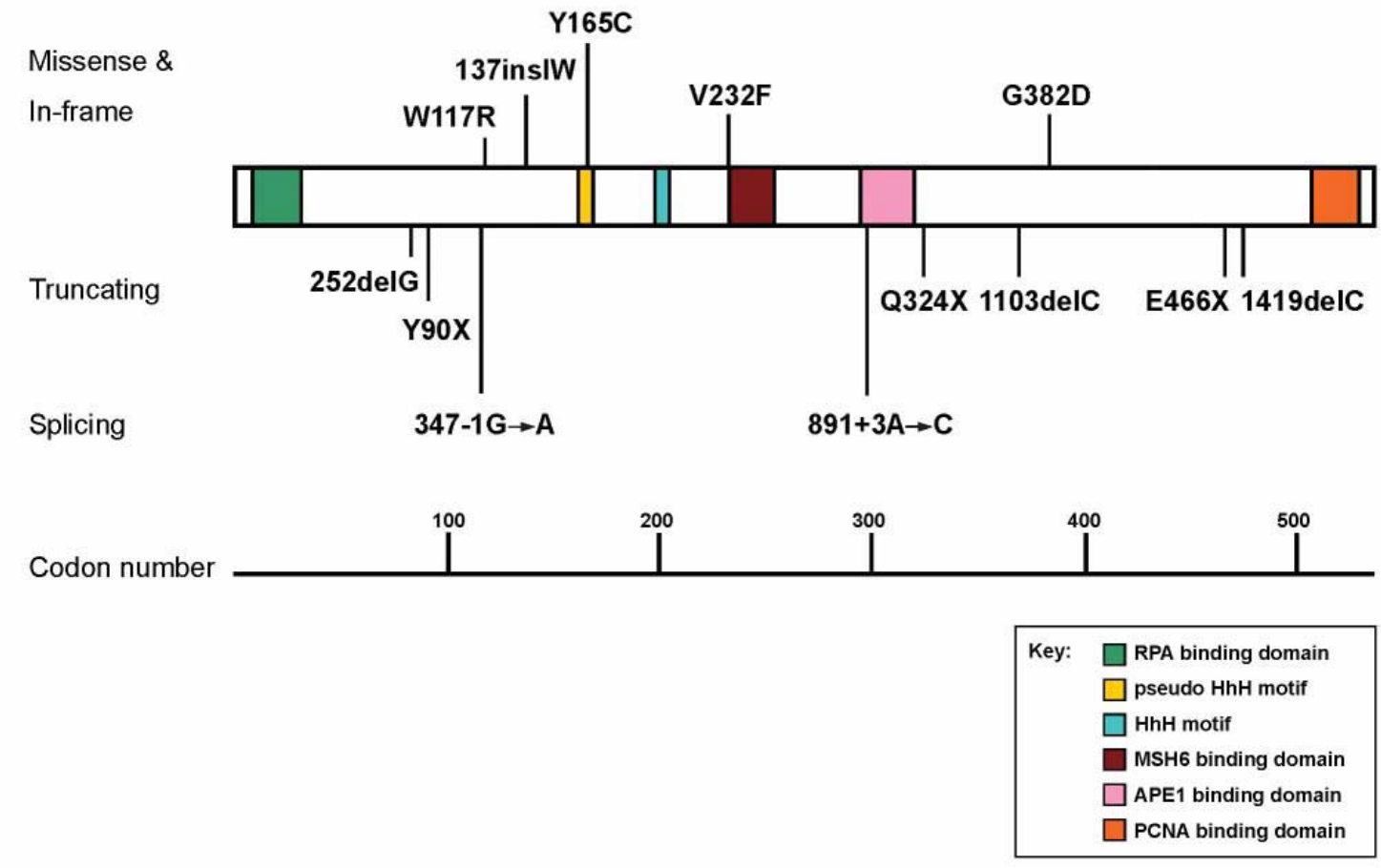
*age and sex-specific incidences

Colorectal cancer risk in *MYH* carriers.

Genotype	Hazard ratio (compared to population risk)*	Significance	Cumulative risk to age 70 years
Monoallelic	2.9 (1.2-7.0)	P=0.02	8% (4%-19%)
Biallelic	53 (14-200)	P<0.0001	80% (35%-100%)

* Estimated using modified segregation analysis, weighting for ascertainment & allowing for background familial aggregation

More MYH Mutations !



Colon CFR-wide Studies of MYH and Colorectal Cancer - Objectives

1) To measure the contribution of *MYH* mutations to CRC, using two **case-control** study populations;

   A) population-based cases from: Ontario, Newfoundland, Australia, Seattle, compared with **population-based controls**, and

   B) population-based cases from all CFRCCS sites: Ontario, Newfoundland, Australia, Seattle, Mayo clinic, Hawaii, and USC, compared with **sibling controls** of the same cases.

2) To determine the cumulative risk of developing CRC (**penetrance**), using kin of affected population-based cases from all CFRCCS registries.

3) To study **functional consequences** of effects of specific known and novel MYH mutations on BER.

4) To characterize **somatic molecular changes** (chromosome 1p loss of heterozygosity (LOH), APC gene mutations, and K-ras gene mutations) in CRCs from affected MYH mutation carriers.

Colon CFR-wide MYH Genotyping

To December 2005

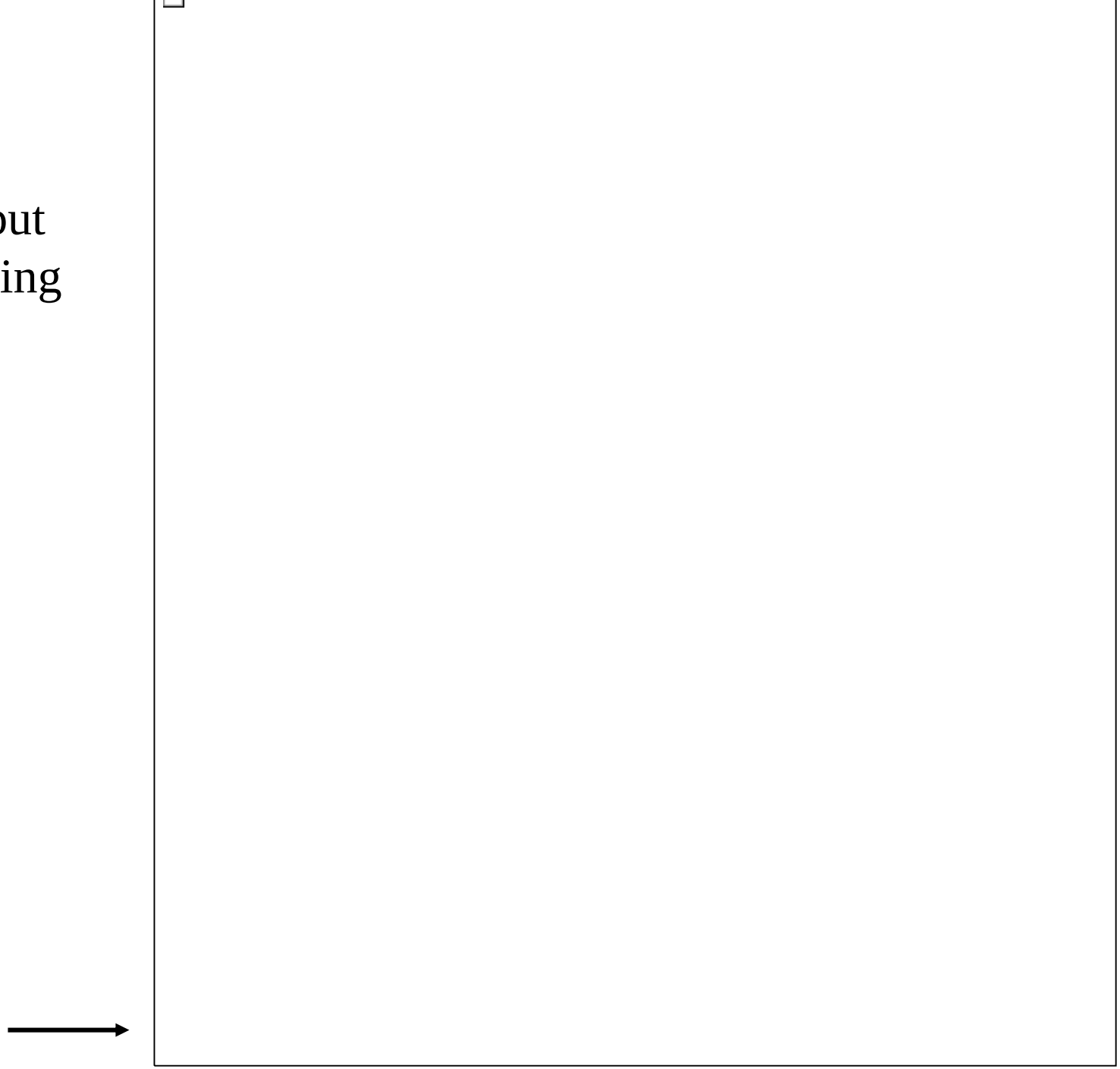
12 MYH mutations

2802 controls

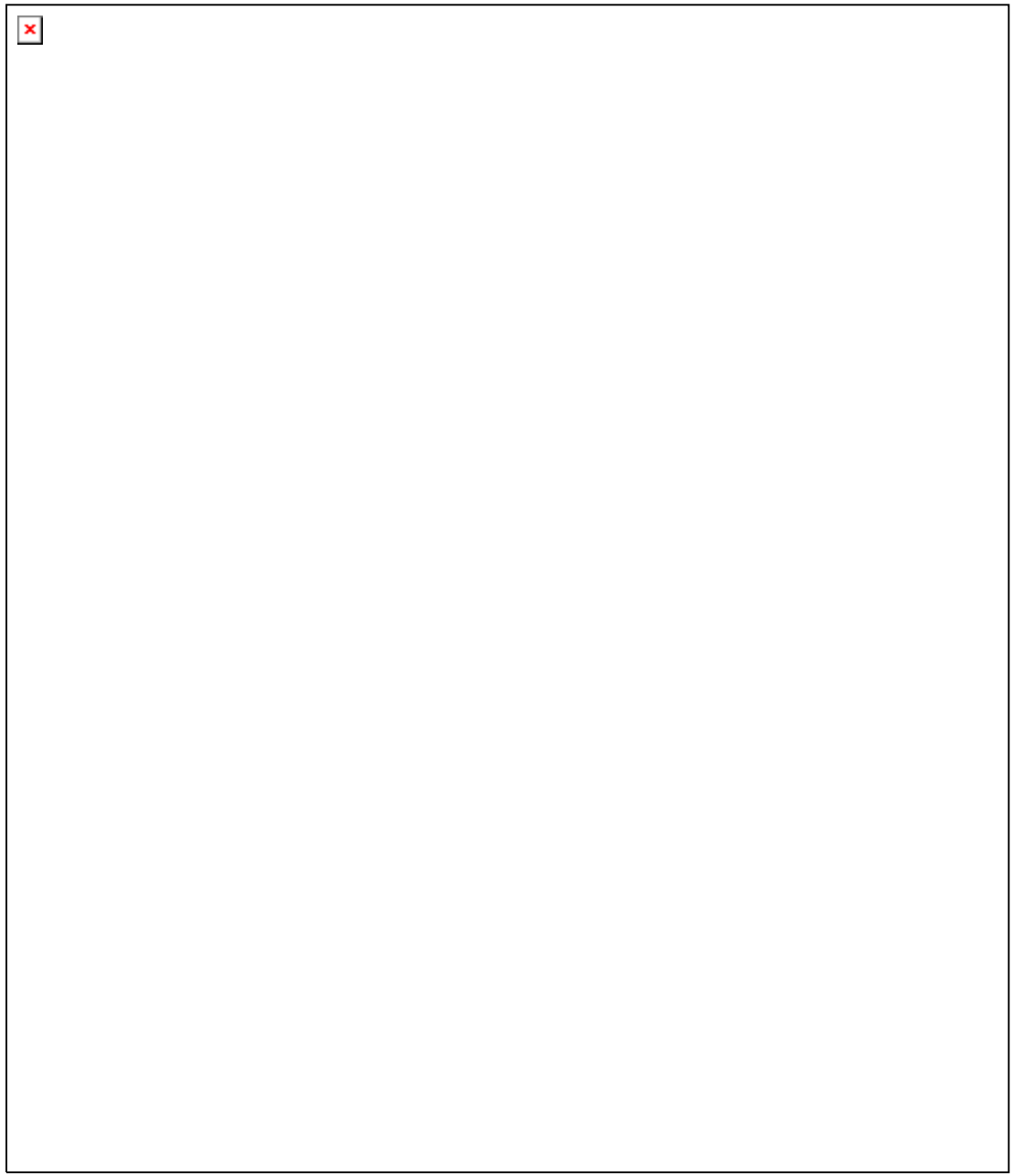
4169 cases

~ 98% successful genotypes

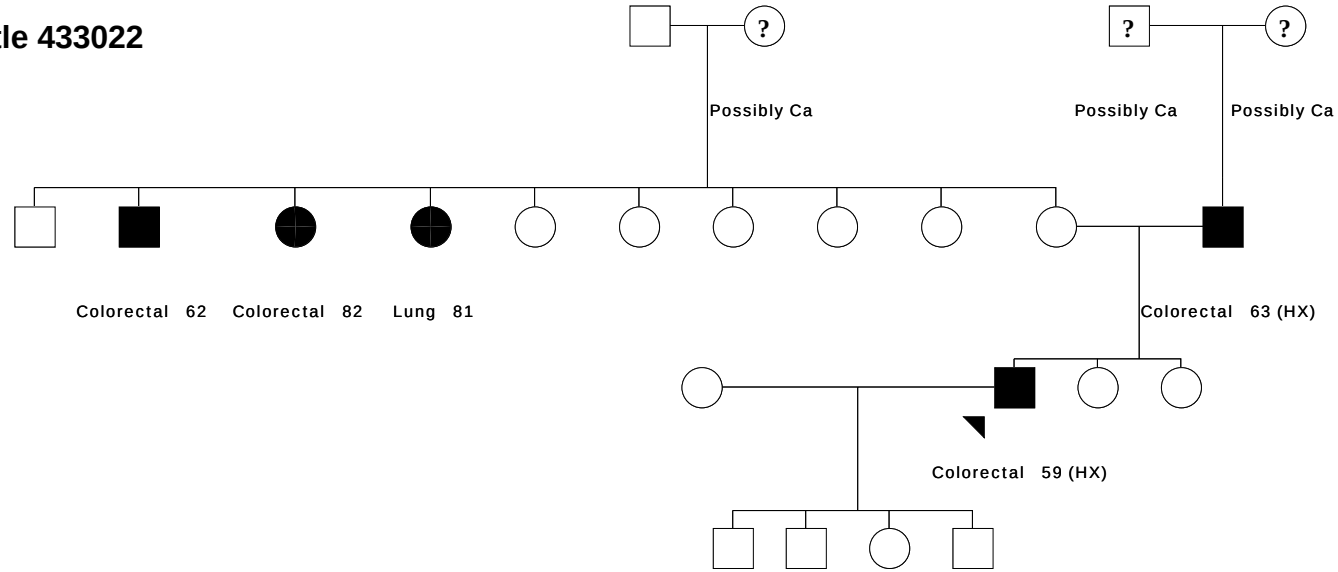
High Throughput
MYH Genotyping
(OFCCR)



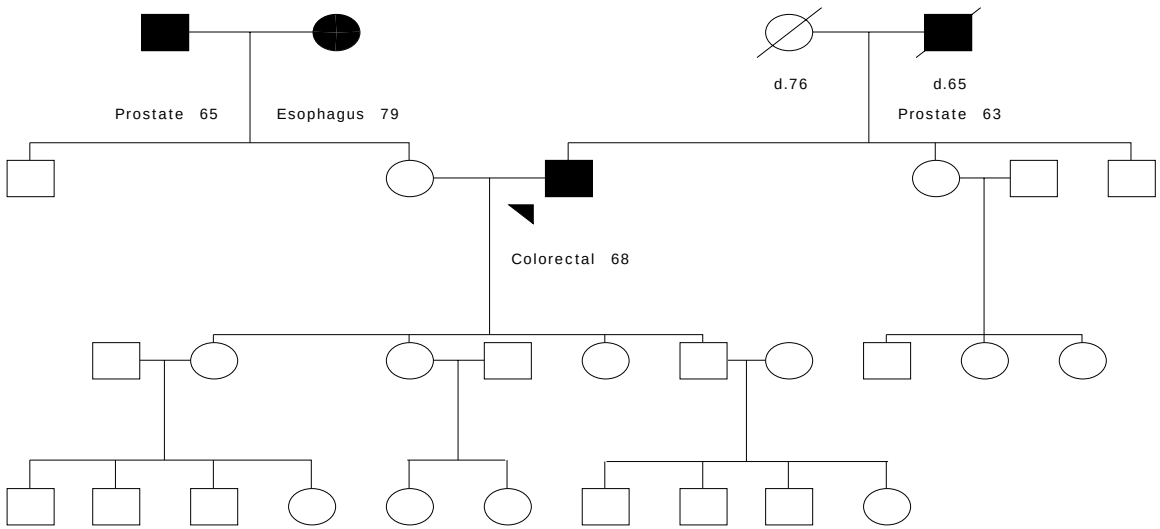
Seattle CFR



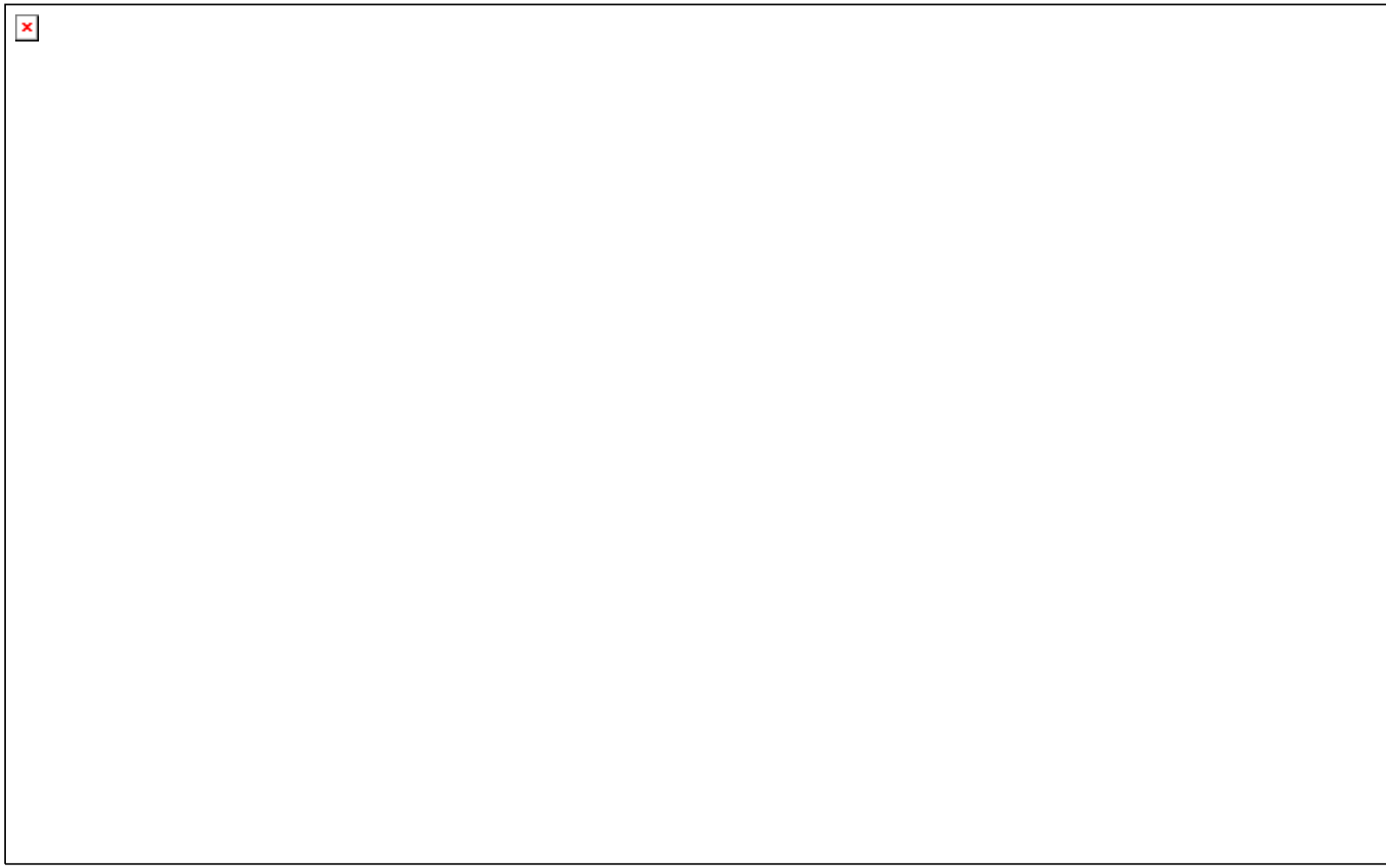
Seattle 433022



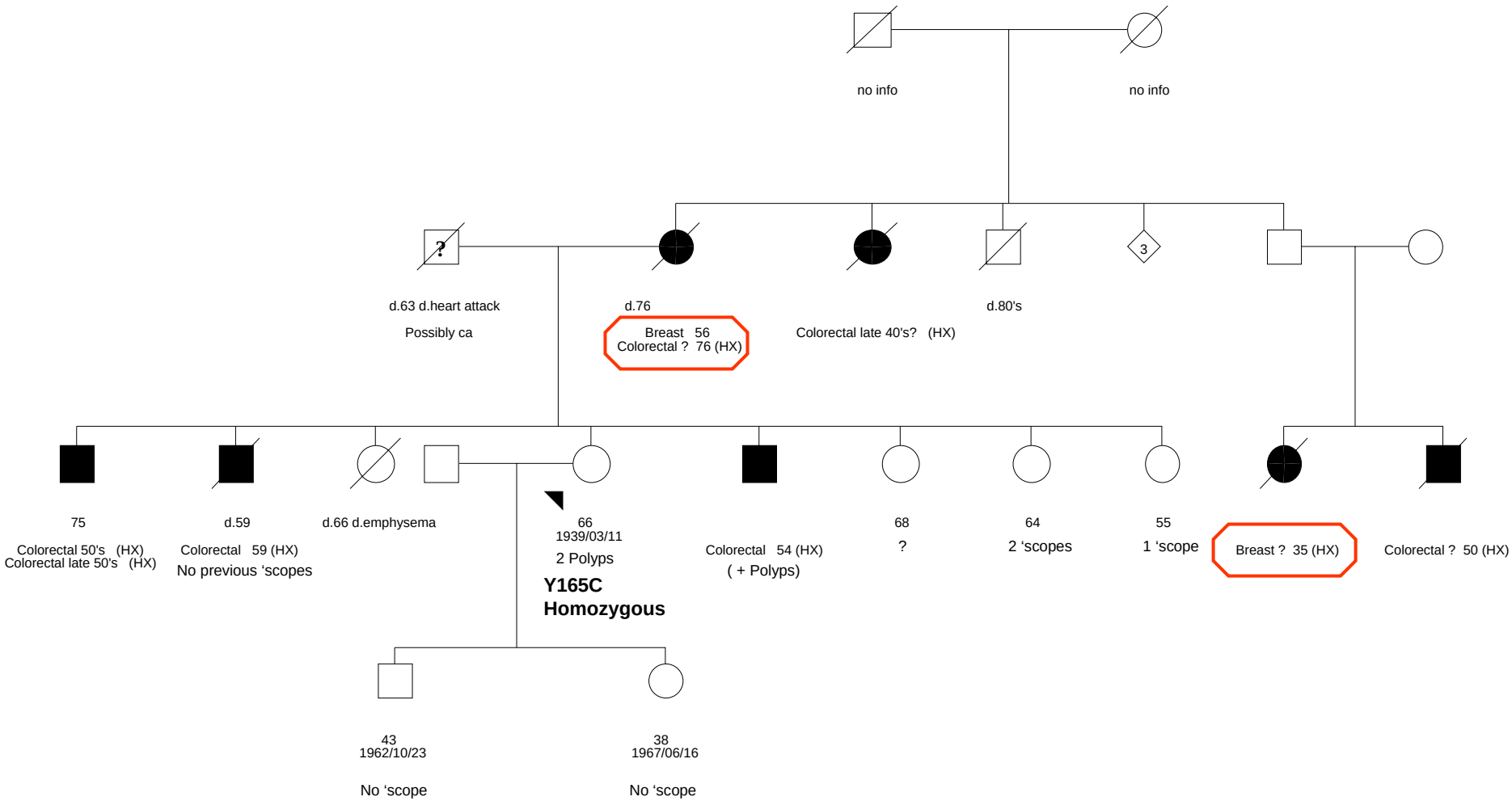
Seattle 429598



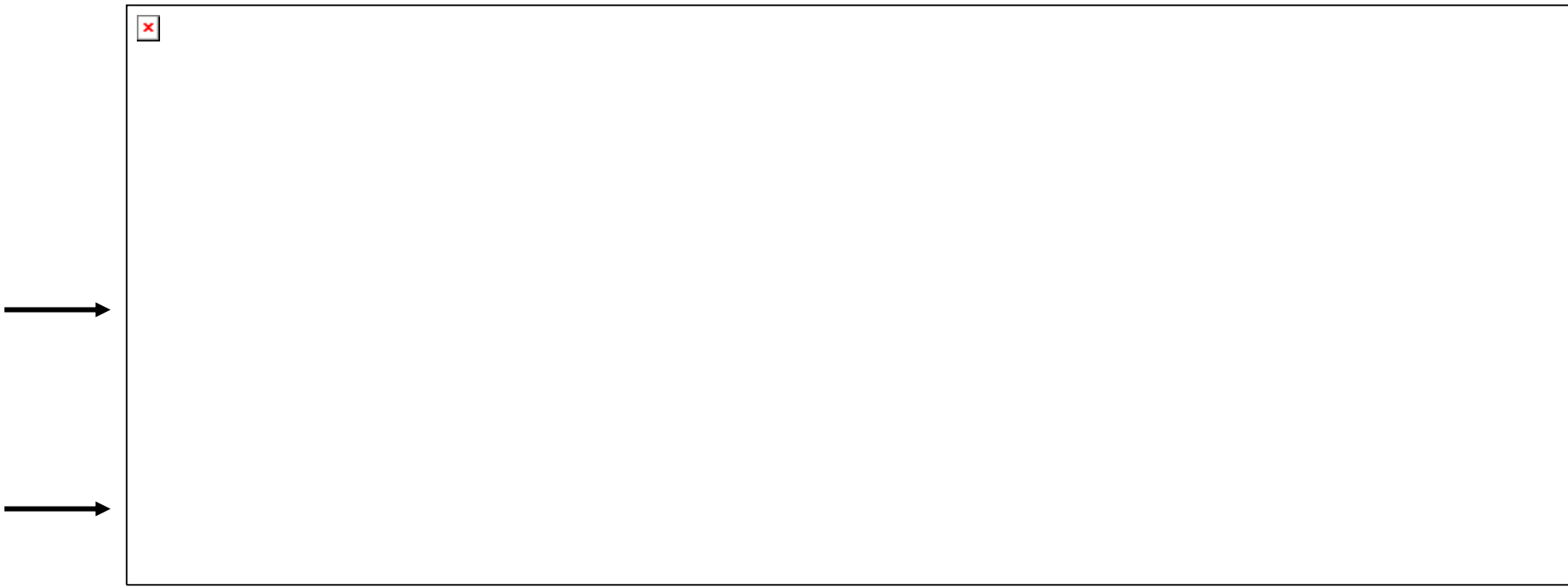
Ontario CFR



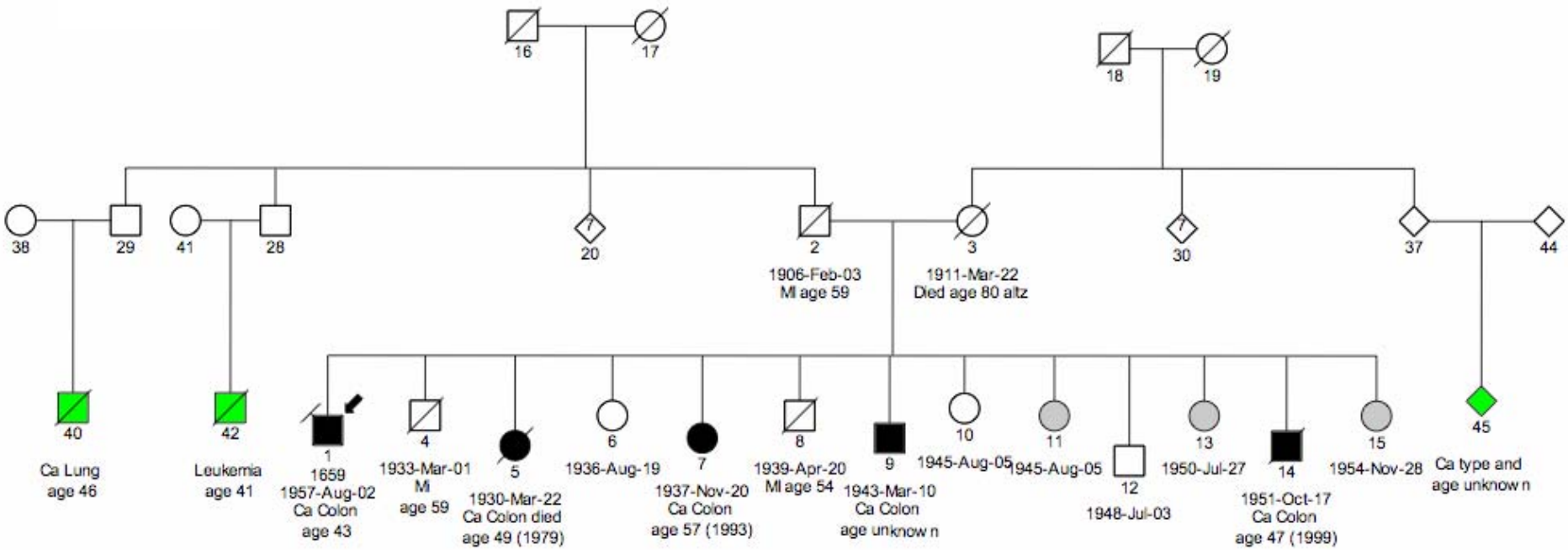
Ontario 36020683 - Control



Seattle CFR

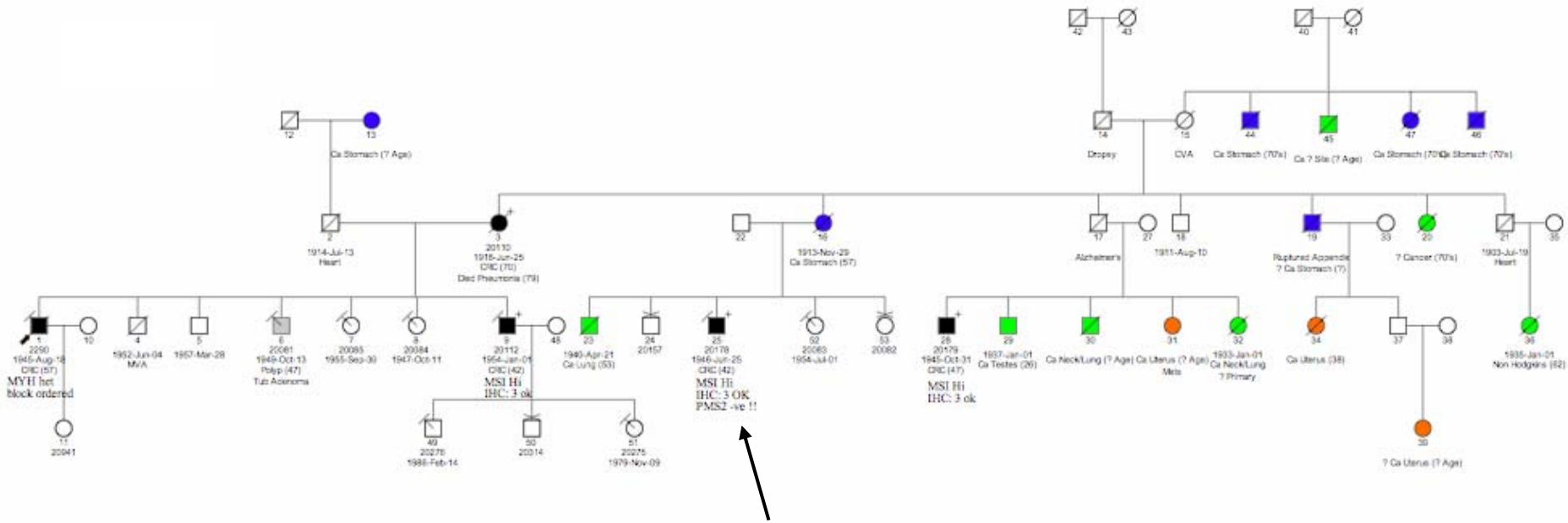


Newfoundland 1659

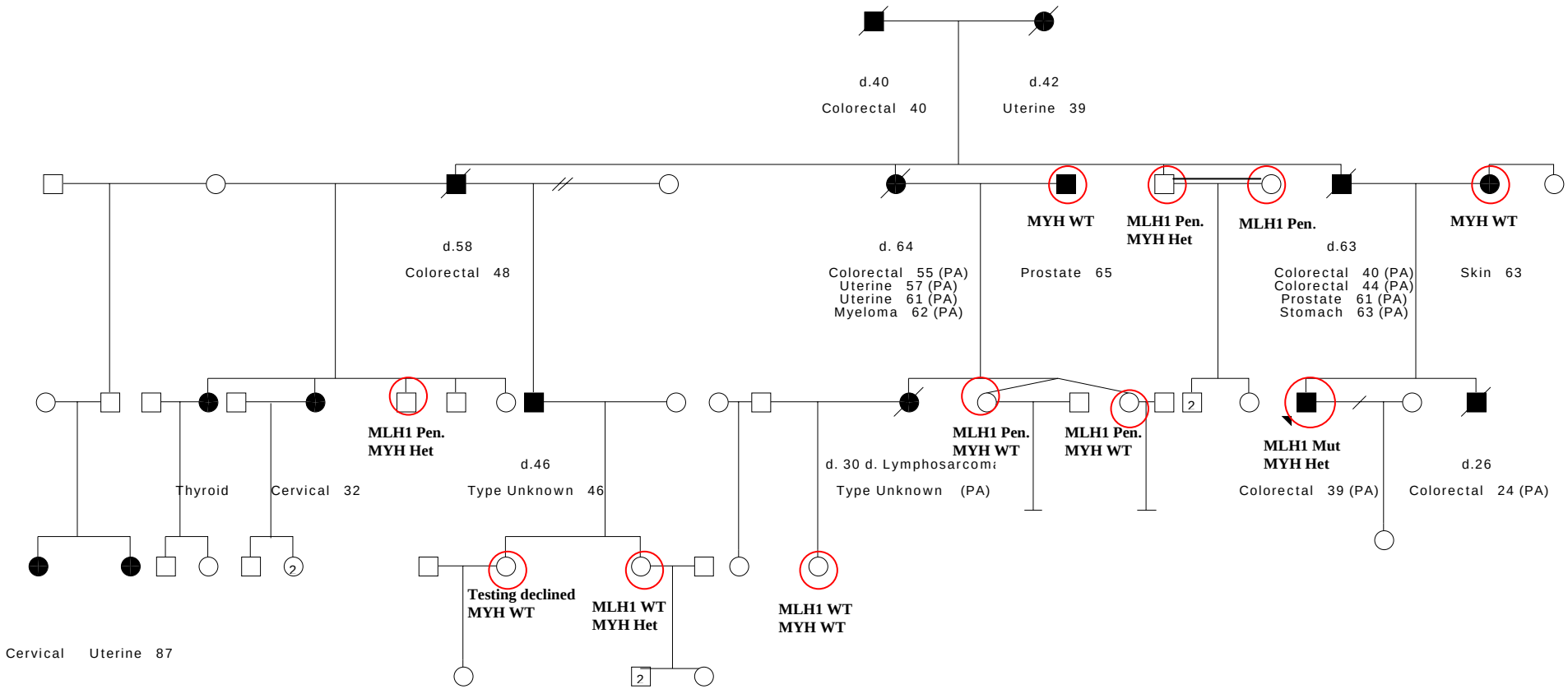


MYH G382D
homozygote

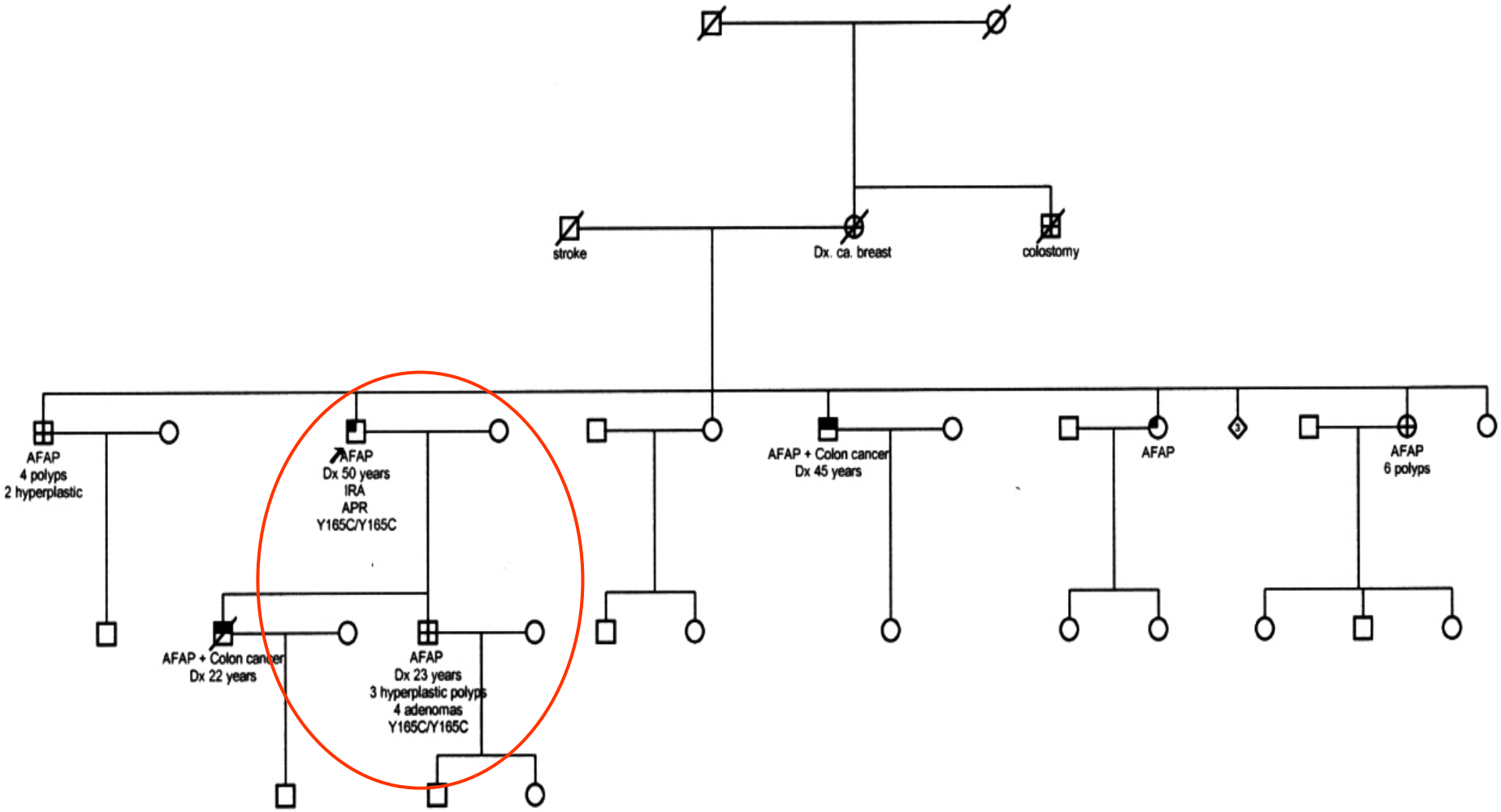
Newfoundland 2290



HNPCC & MYH G382D



How did it happen?



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