FAP, MAP, and PPAP

Marco Novelli

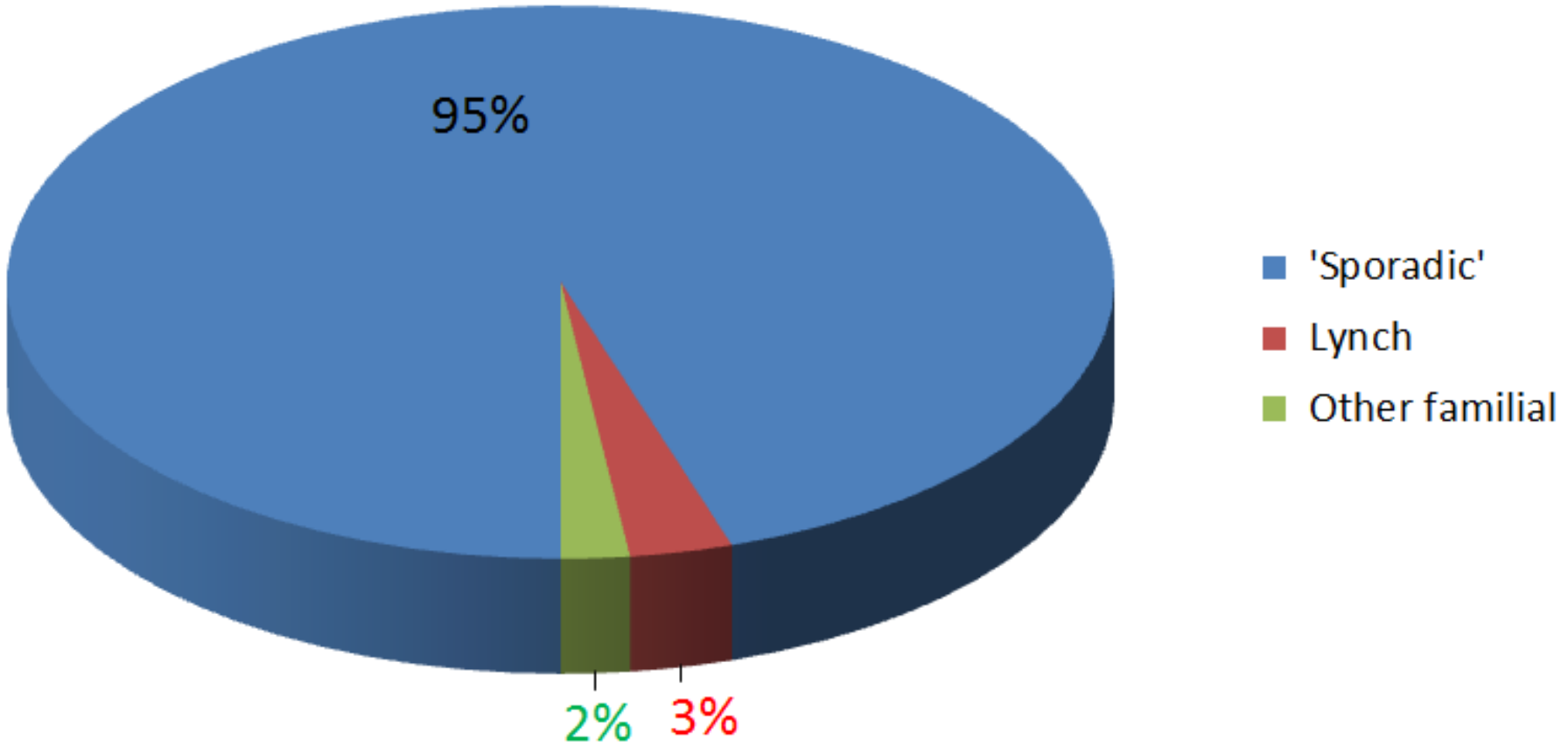
FAP, MAP, NAP and PPAP

Marco Novelli

Overview

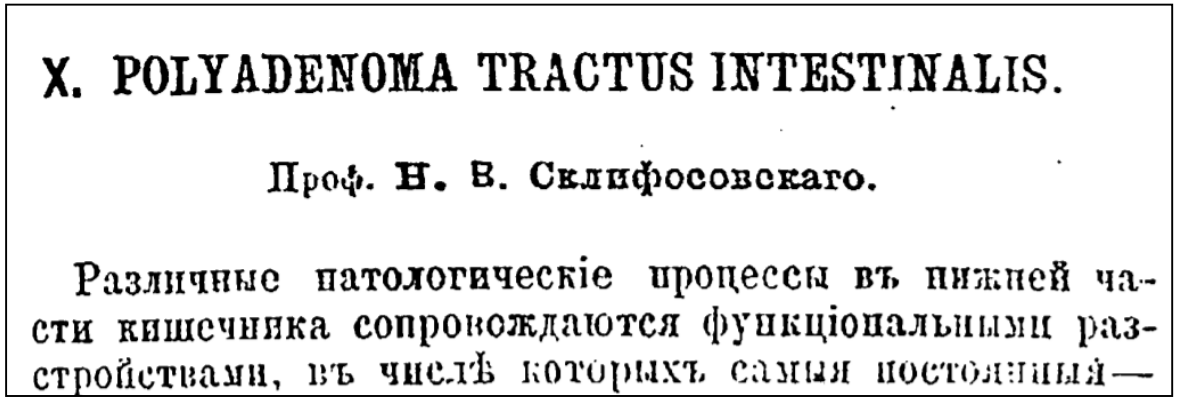
- History of polyposis
- Familial adenomatous polyposis
- MYH-associated polyposis
- NTLH1-associated polyposis
- Other polyposis syndromes

Colorectal cancer



History of polyposis

- First description of colorectal polyposis:
  - Menzel 1721, Berlin
- first histologically verified case of adenomatous polyposis:
  - Sklifasowski 1881, Russia



X. POLYADENOMA TRACTUS INTESTINALIS.

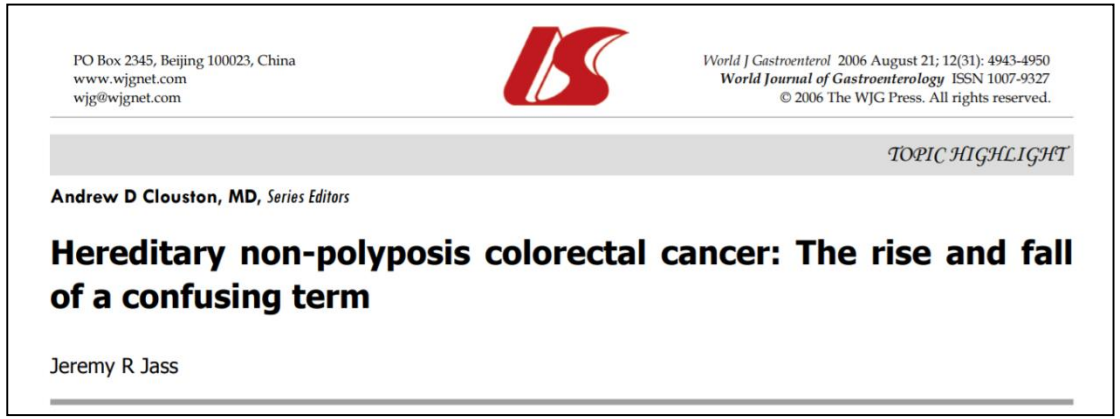
Проф. Н. В. Склифосовскаго.

Различные патологическіе процессы въ нижней части кишечника сопровождаются функціональными разстройствами, въ числѣ которыхъ самыя постоянныя—

- 1882 Cripps termed ‘‘disseminated polypus of the rectum’’ – inherited predisposition.

Lynch syndrome

- “Cancer family syndrome" Lynch 1966.
  - Lynch syndrome 1
  - Lynch syndrome 2
- Lynch named the condition ‘Hereditary Non-Polyposis Colorectal Carcinoma’ (HNPCC), 1985.
- Jass 2006 – terminology HNPCC should be phased out.



PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

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World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

Andrew D Clouston, MD, *Series Editors*

Hereditary non-polyposis colorectal cancer: The rise and fall of a confusing term

Jeremy R Jass

Hereditary CRC Syndromes

- Familial adenomatous polyposis – 1881
- Peutz–Jeghers syndrome – 1921
- Juvenile polyposis – 1939
- Gardner’s syndrome - 1951
- Turcot syndrome – 1959
- Cowden’s syndrome – 1963
- Lynch syndrome (HNPCC) -1966 (1985)
- Muir–Torre syndrome - 1967-8
- Hyperplastic polyposis -1980

Hereditary CRC Syndromes

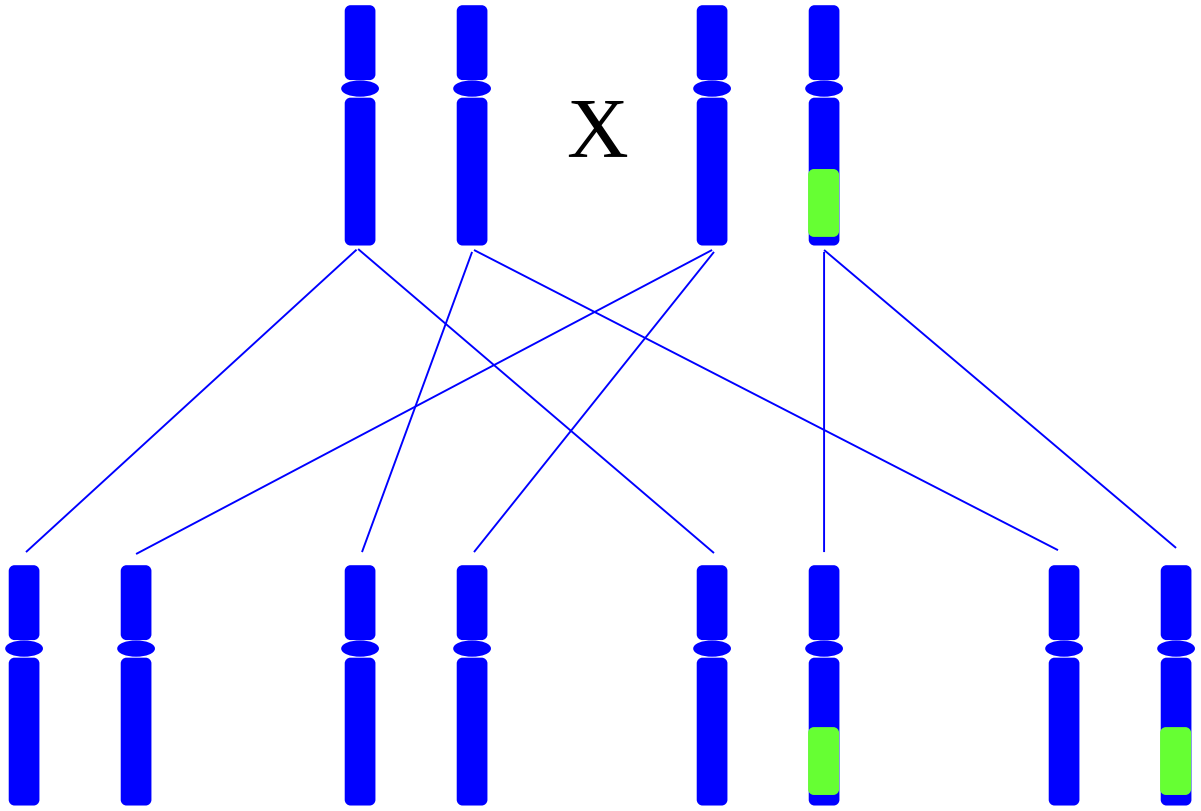
- Familial adenomatous polyposis – 1881
- Peutz–Jeghers syndrome – 1921
- Juvenile polyposis – 1939
- ~~Gardner's syndrome – 1951~~
- ~~Turcot syndrome – 1959~~
- Cowden's syndrome – 1963
- Lynch syndrome ~~(HNPCC)~~ -1966 (1985)
- ~~Muir–Torre syndrome – 1967~~ -8
- ~~Hyperplastic~~ Serrated polyposis -1980

Hereditary CRC Syndromes

- Lynch syndrome
- Familial adenomatous polyposis
- MYH-associated polyposis
- NTHL1-associated polyposis
- Serrated polyposis
- Hereditary mixed polyposis
- Polymerase proof reading-associated polyposis
- Peutz-Jeghers syndrome
- Juvenile polyposis
- PTEN hamartoma syndromes (Cowden’s)
- Constitutional mismatch repair deficiency

Mendelian inheritance

Mendelian Autosomal Dominant Inheritance



50%

Normal

50%

Affected

Autosomal Dominant Inheritance

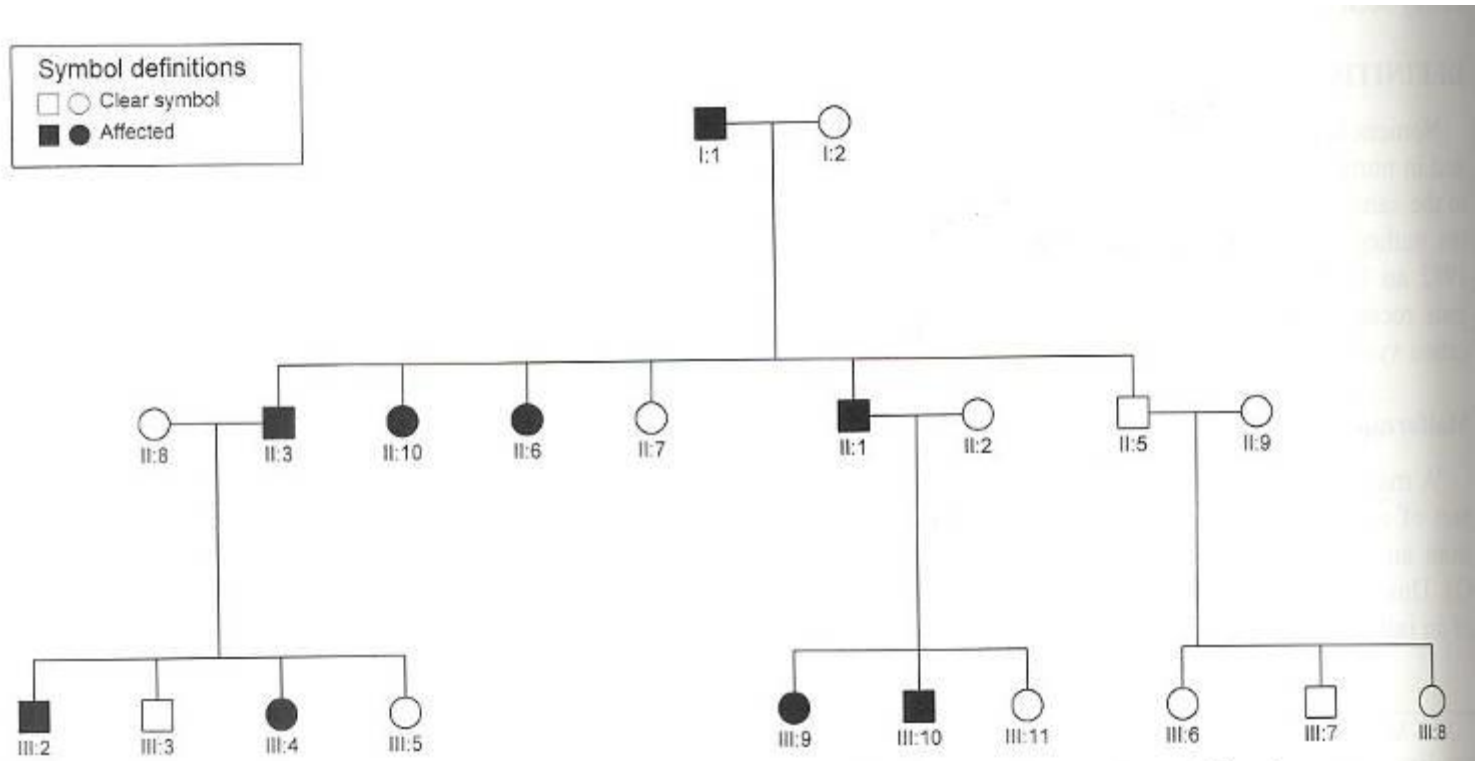
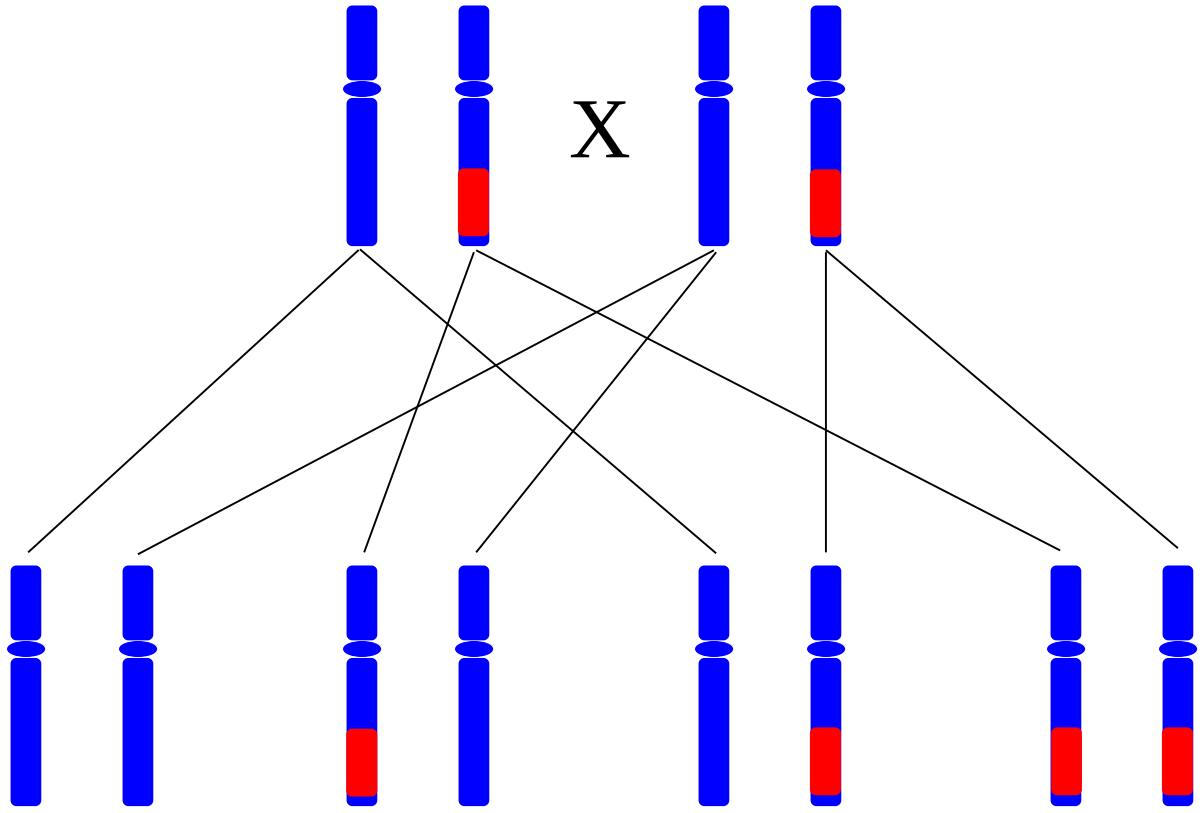


FIG. 89-1. Autosomal-dominant inheritance. Vertical pattern of trait expression; males and females are equally affected.

Mendelian Autosomal Recessive Inheritance



Autosomal Recessive Inheritance

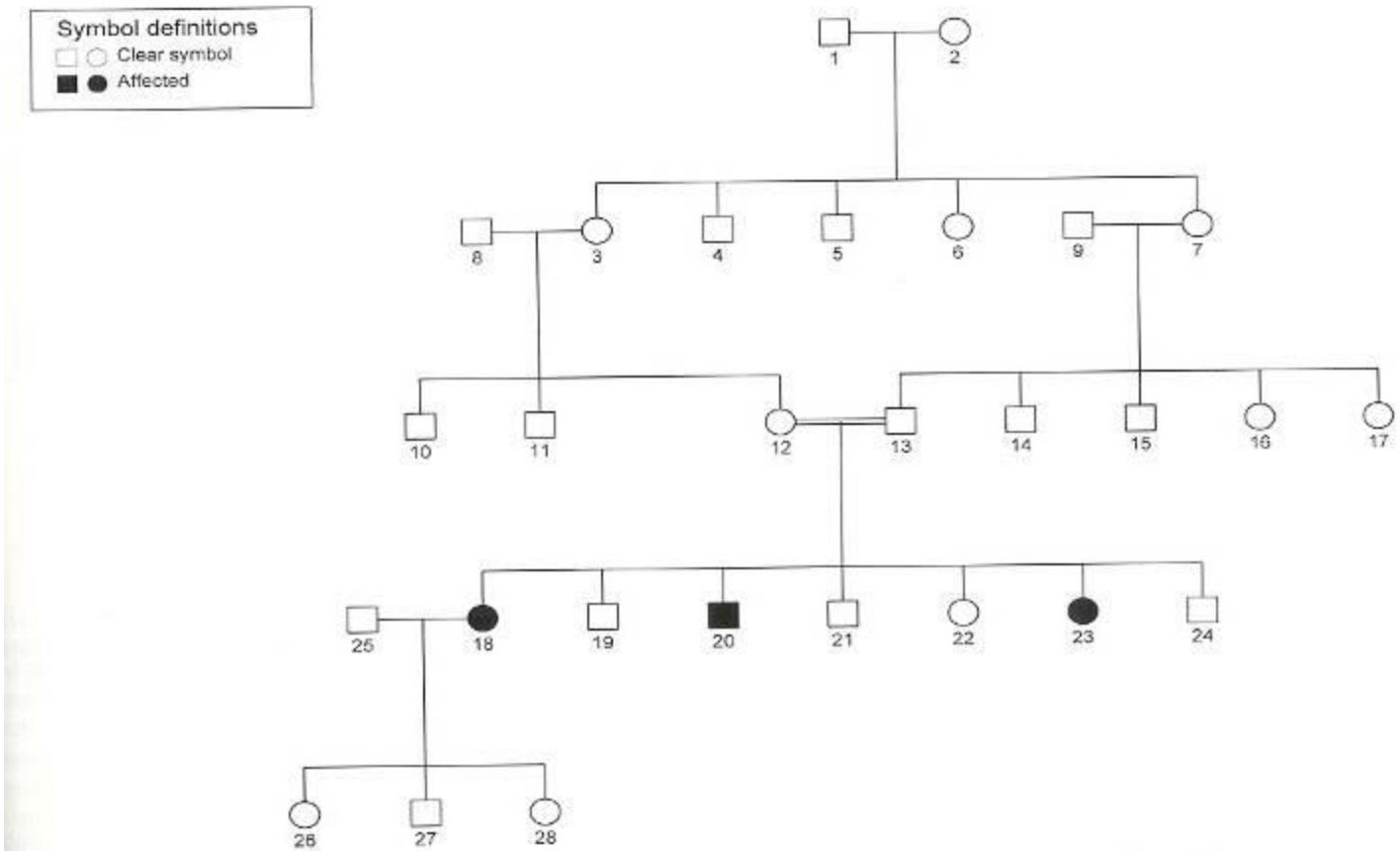
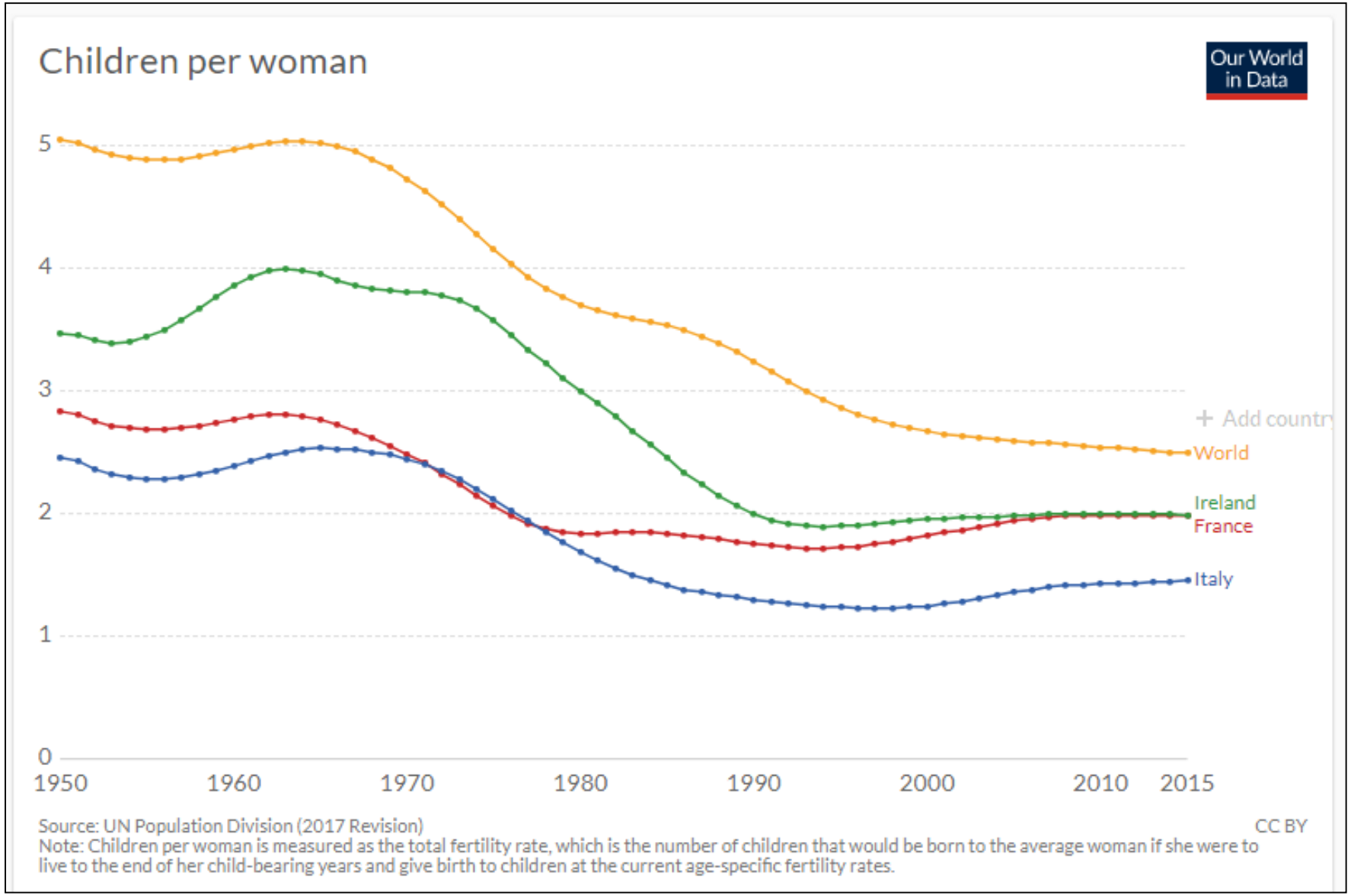
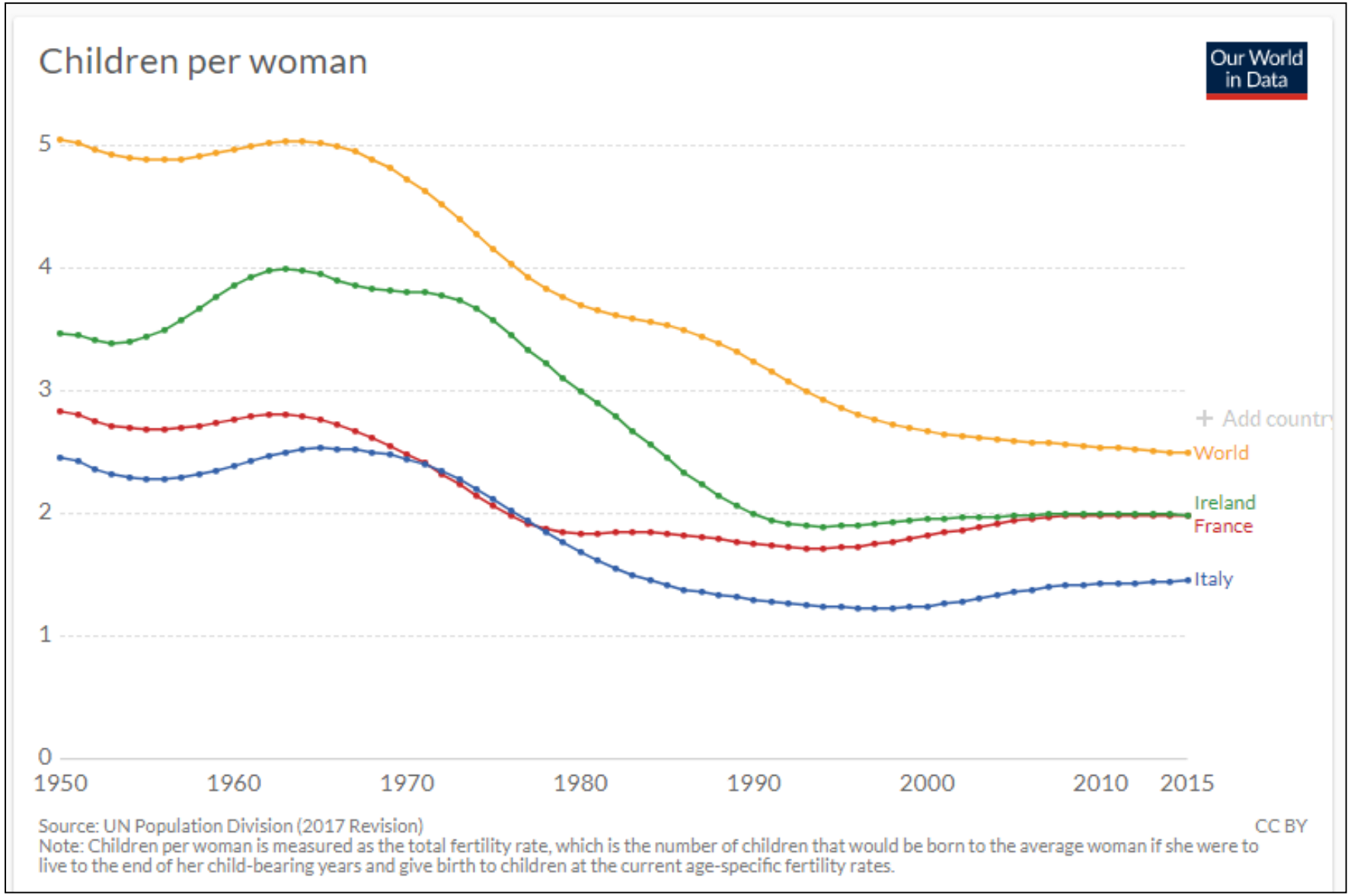


FIG. 89-2. Autosomal recessive inheritance. Horizontal pattern of trait expression. Parental consanguinity is often present in families with autosomal recessive disorders.

Historical reduction in family size



Historical reduction in family size



→ Unlikely to be a family history in recessively inherited syndromes

Hereditary CRC Syndromes

- Lynch syndrome
- Familial adenomatous polyposis
- MYH-associated polyposis
- NTHL1-associated polyposis
- Serrated polyposis
- Hereditary mixed polyposis
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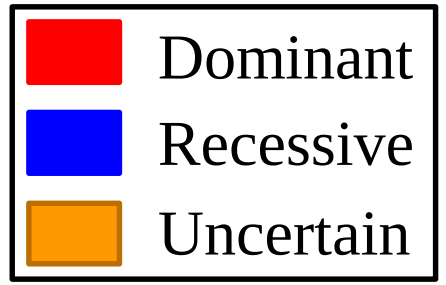
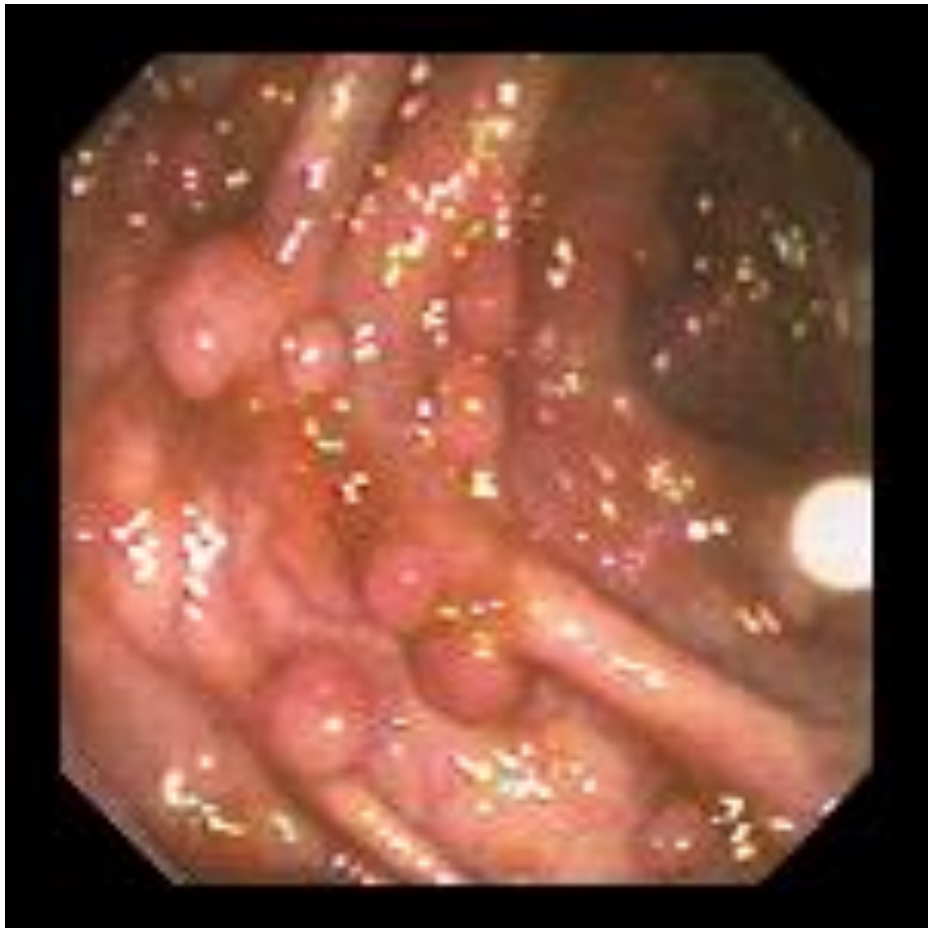


Familial adenomatous polyposis (FAP)



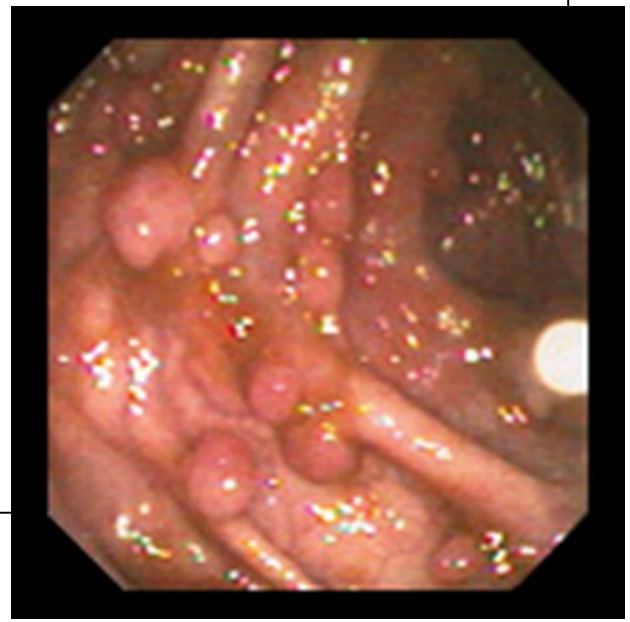
> 100 colorectal polyps


cm 1 2 3 4

Familial adenomatous polyposis

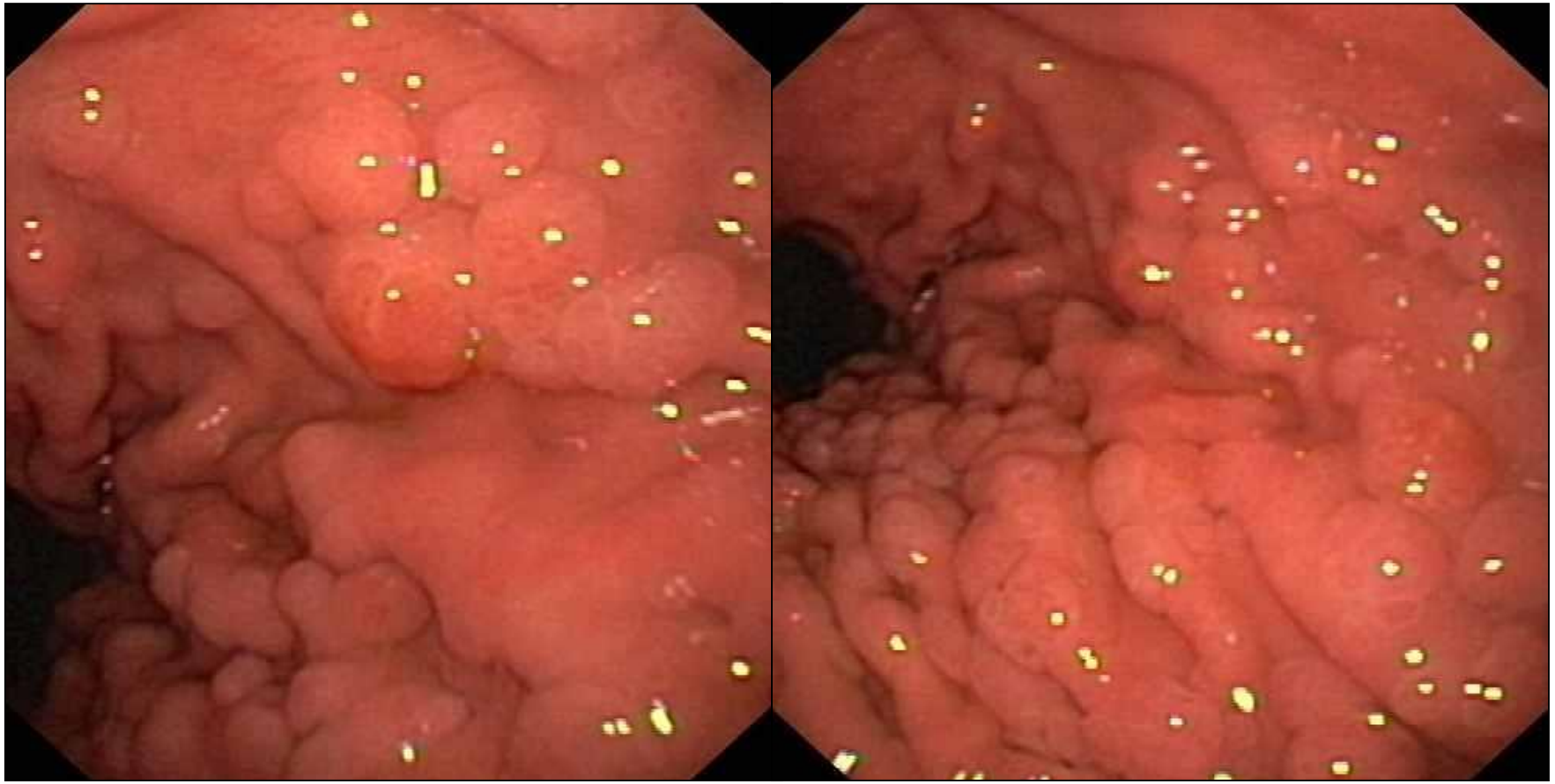
- Due to a germline mutation in the APC gene (5q22)
- > 100 adenomatous polyps predominantly in large intestine (typically 1000s).
- Colorectal adenocarcinomas < 40 years old

  (10-15 years after appearance of polyps).
- Adenomas in small intestine and stomach.
- Extra-intestinal manifestations.
- Commonest cause death now duodenal carcinoma and desmoids.



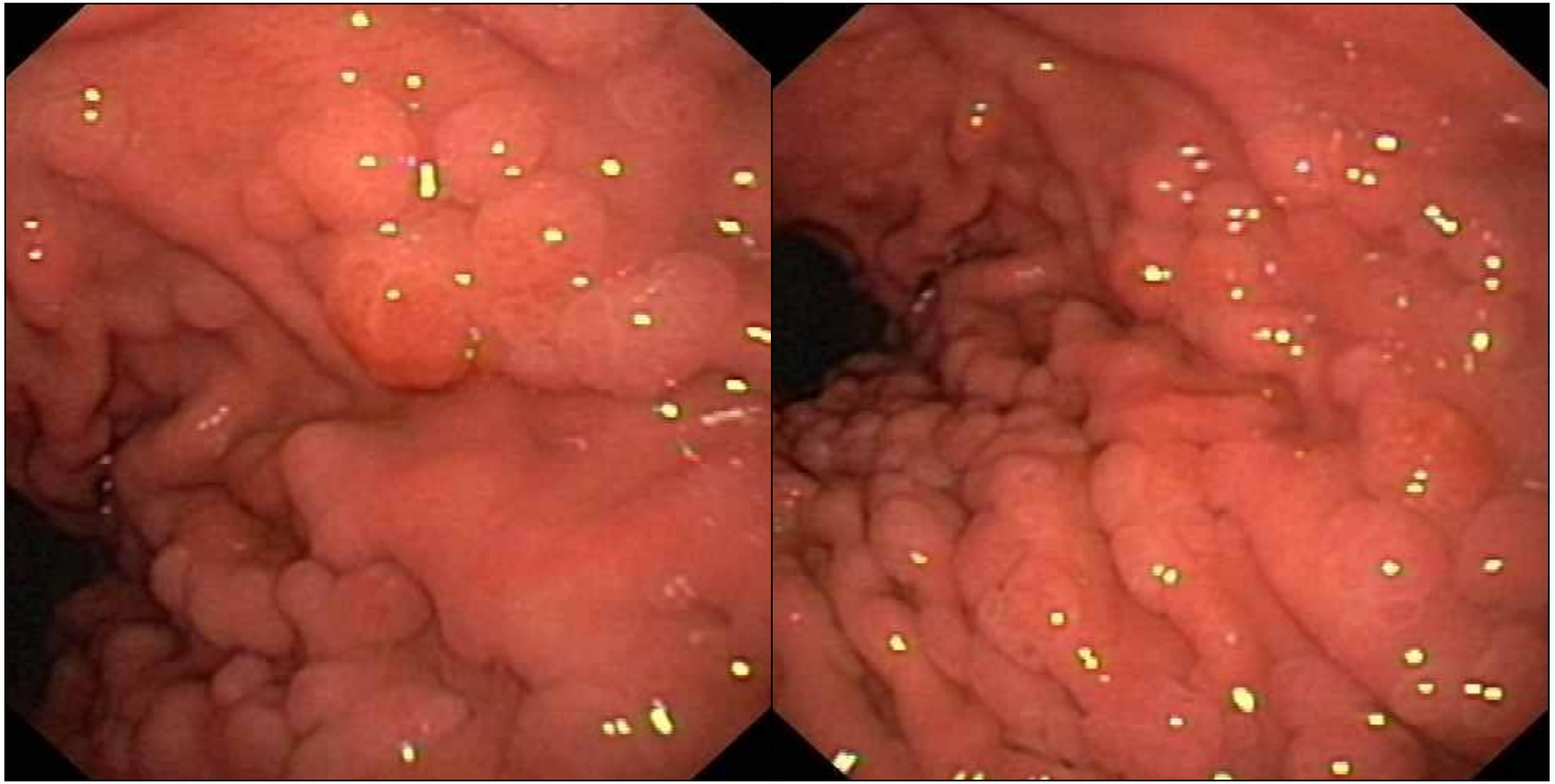
Extra-intestinal manifestations of FAP

- Gastric fundic gland polyps.
- CHRPEs.
- Sebaceous cysts.
- Osteomas (jaw).
- Desmoid tumours.
- Papillary carcinoma of thyroid (Cribriform-morular variant).
- Hepatoblastoma.
- Brain tumours (Glioblastoma M).



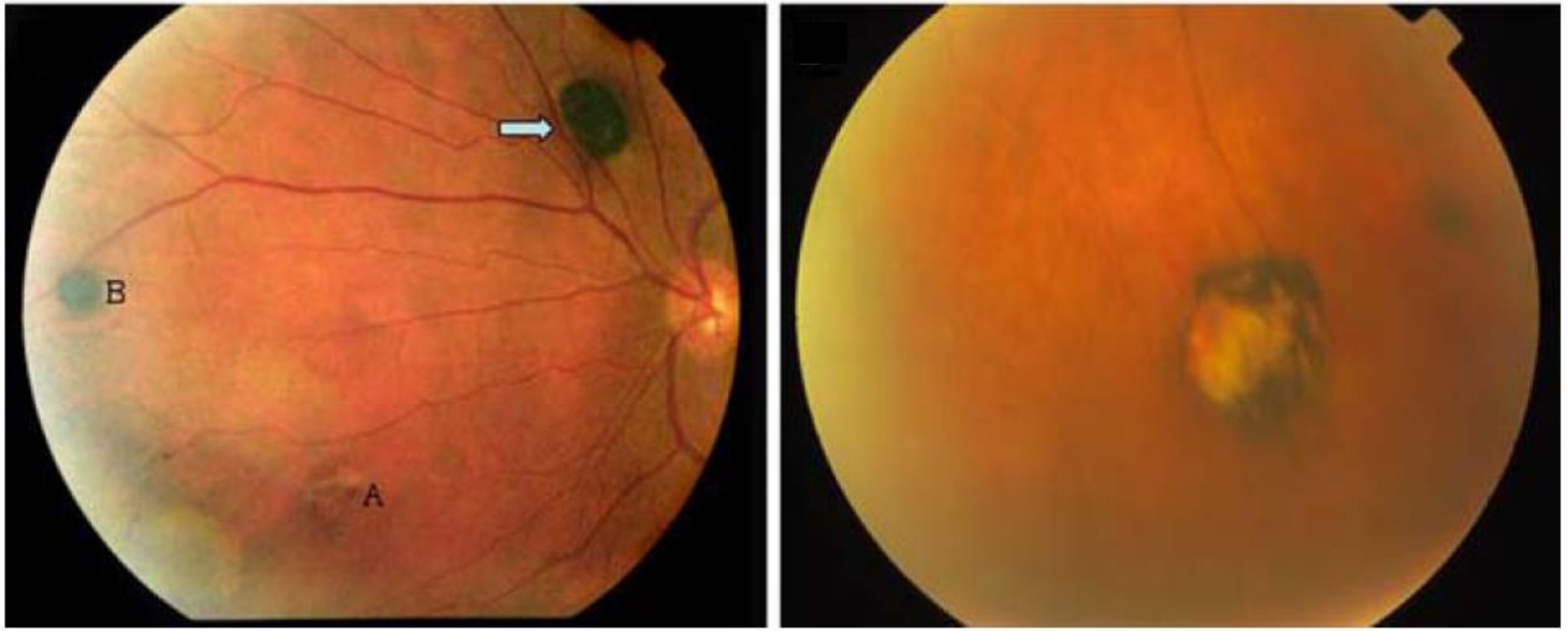
Fundic gland polyps :

- 0.8 –2% normal population.
- 12.5 – 84% FAP patients



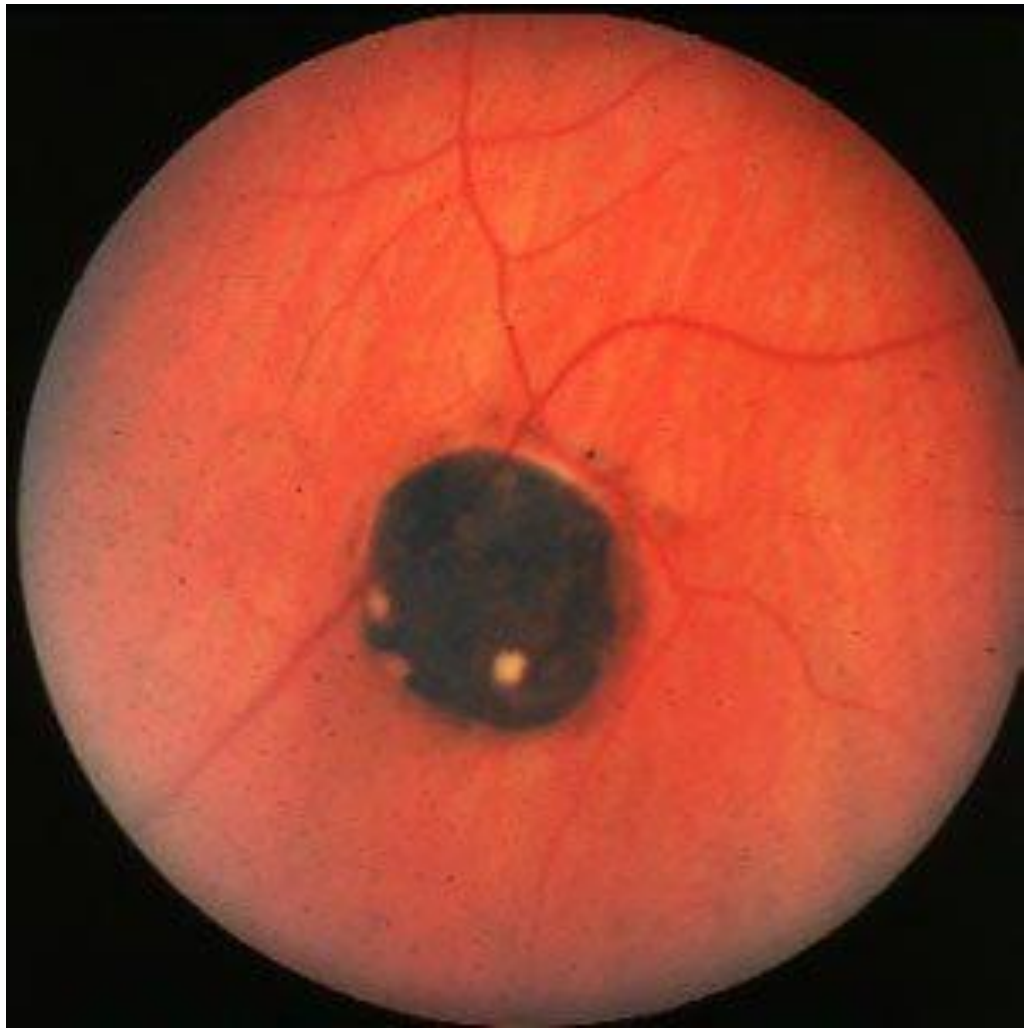
Fundic gland polyps :

- ~~0.8 – 2% normal population.~~ **Common with PPIs**
- 12.5 – 84% FAP patients

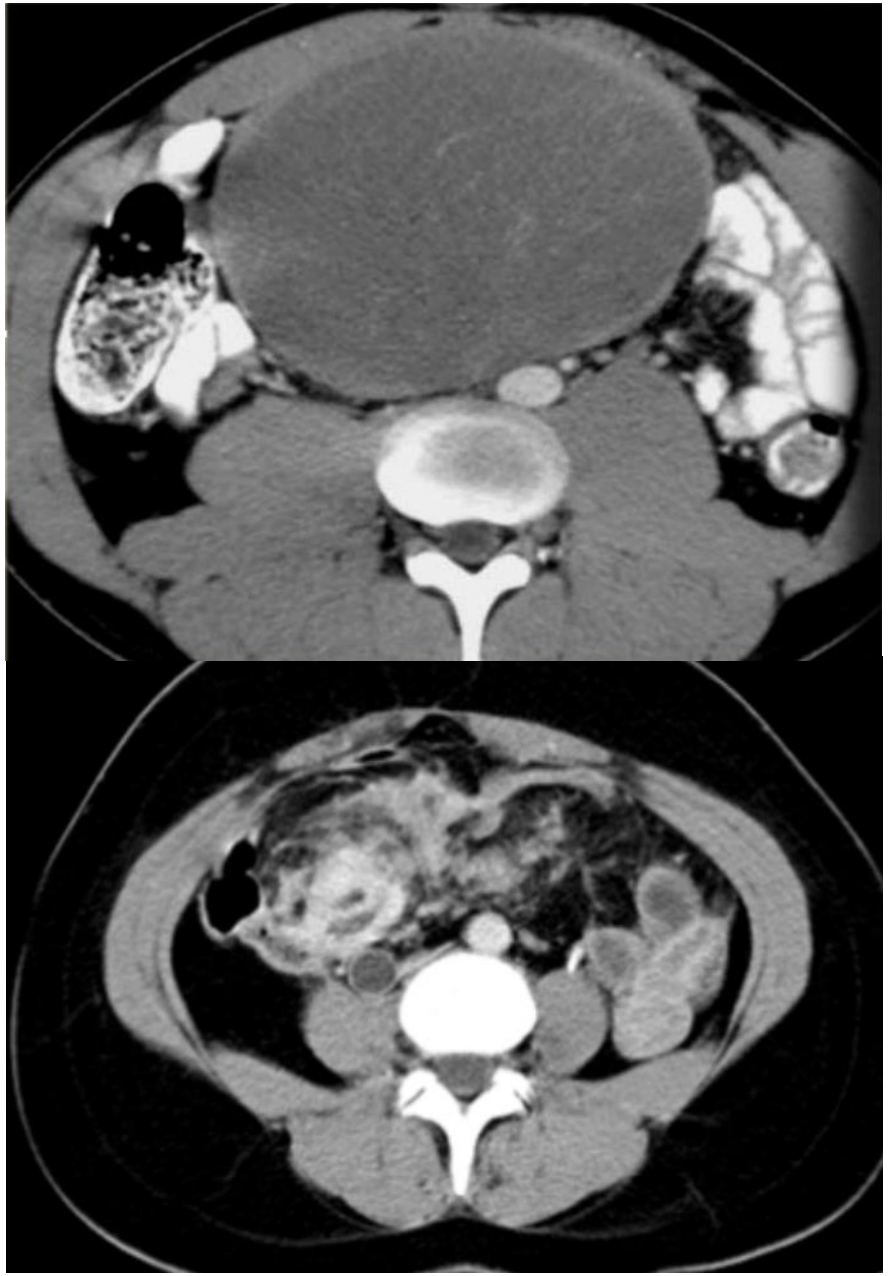


Congenital Hyperpigmentation of the Retinal Pigment Epithelium (CHRPE).

- Normal population 5% (0.3 – 40%)
- FAP 66-92%

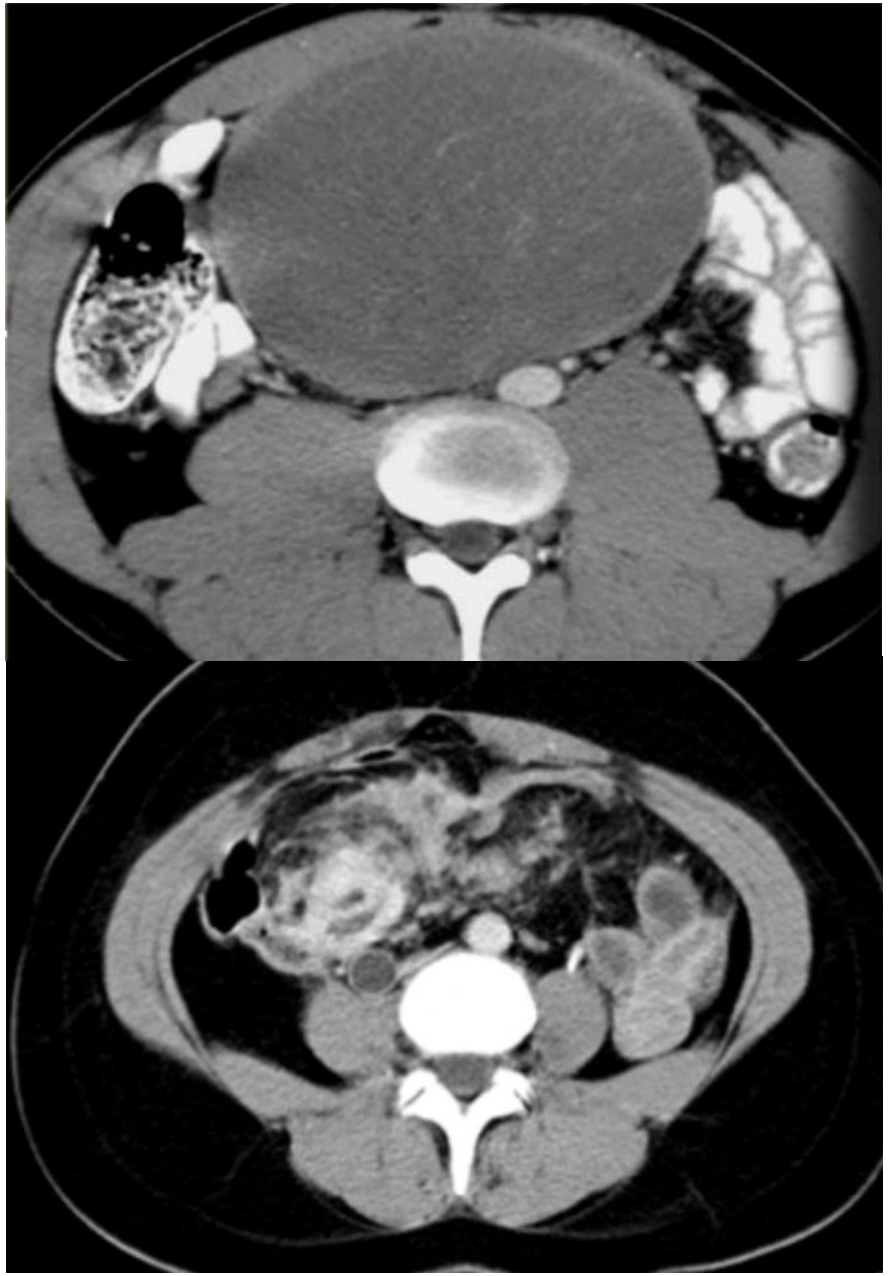


CHRPE in FAP are typically bilateral with a de-pigmented halo.



Desmoid tumours

- Rare tumours 2-4/million per annum.
- 10 - 30% incidence in FAP.
- 7.5% of desmoids occur on a background of FAP.
- Sporadic tumours have a somatic mutation in CTNNB1 (β catenin).



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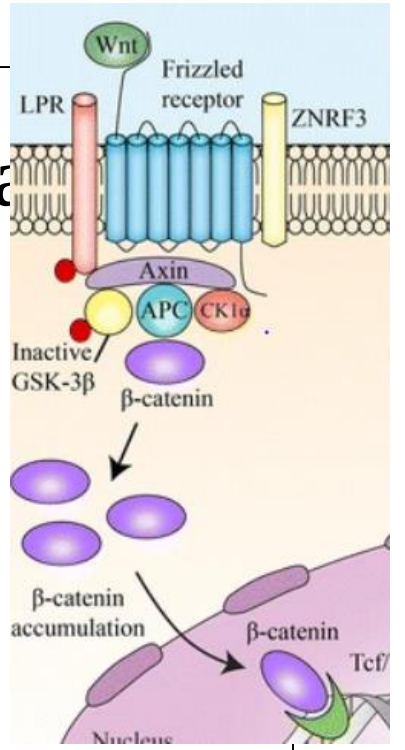
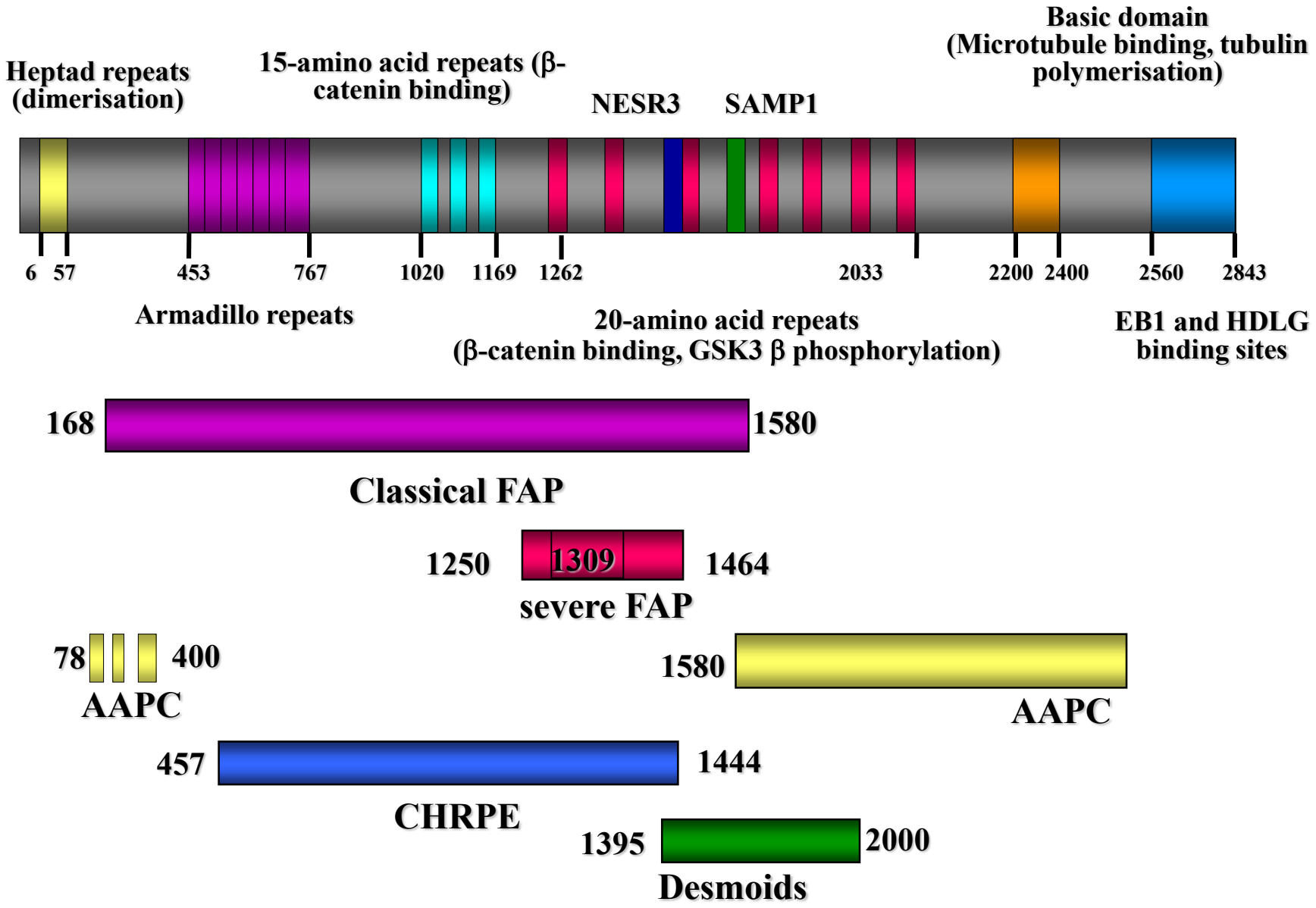


APC protein domains and FAP phenotype association with (truncating) germline mutation position



Attenuated FAP

- Typically less than 100 adenomas in colon.
- Mean 25 adenomas (0 - 470).
- Concentrated in proximal colon.
- Some extra-colonic manifestations.
- Colorectal carcinoma in 70% by 80 years of age.

MUTYH-Associated Polyposis

MYH-Associated Polyposis

MAP

Discovery of MYH-associated polyposis

- Family with multiple adenomas and CRC
- No known pathogenic APC or MMR germline mutation
- 3 affected sibs - 11 tumours
  - 15/18 somatic APC mutations G:C>T:A

→ Suggested mutations from oxidative DNA damage.

Al-Tassan *et al* Nat Genet 30:227-232, 2002

Oxidative damage of DNA

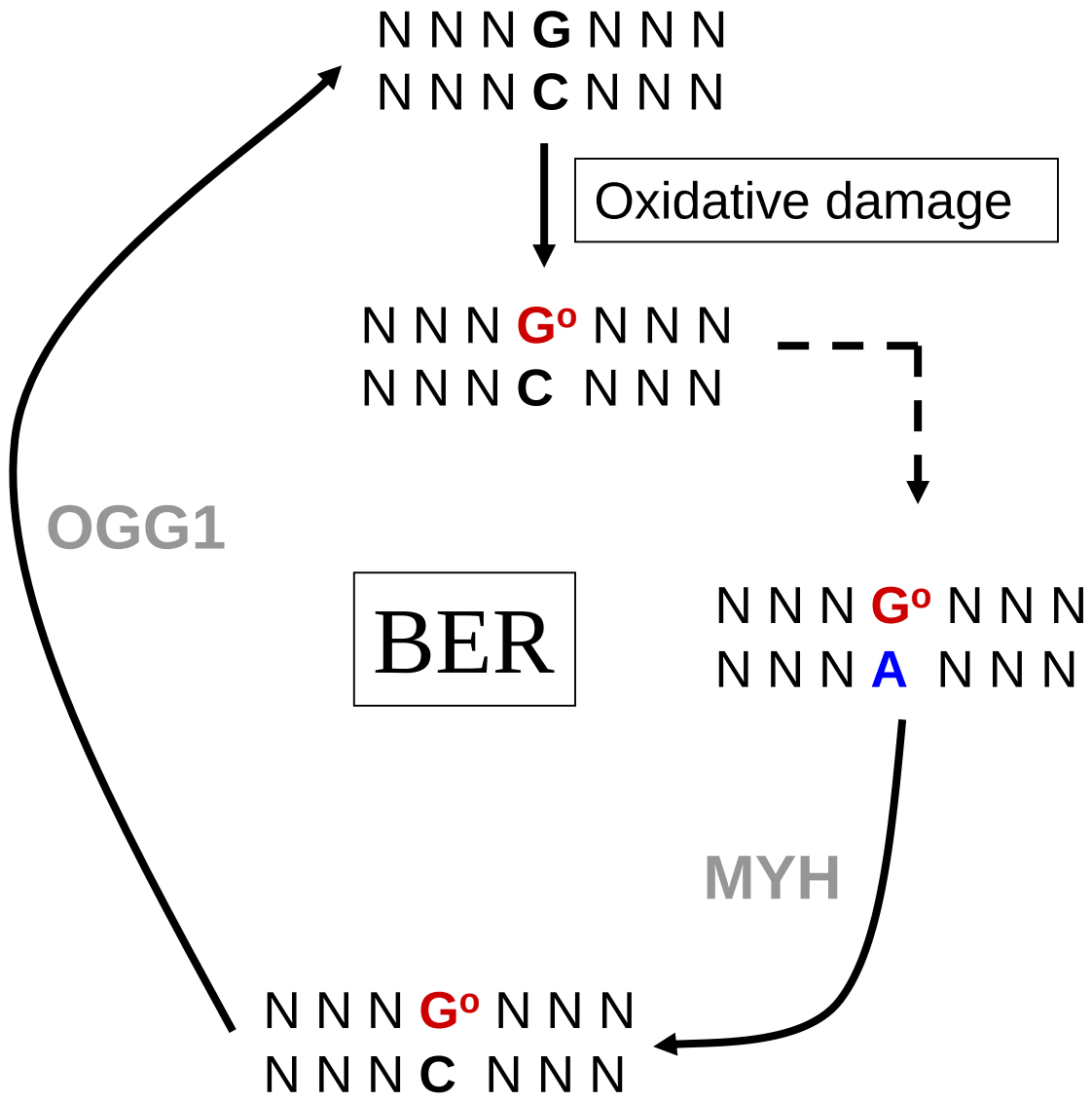
- Oxidative damage - 10^4 lesions/cell/day.
- 8-oxo-G most deleterious.
- 8-oxo-G mis-pairs with adenine residues

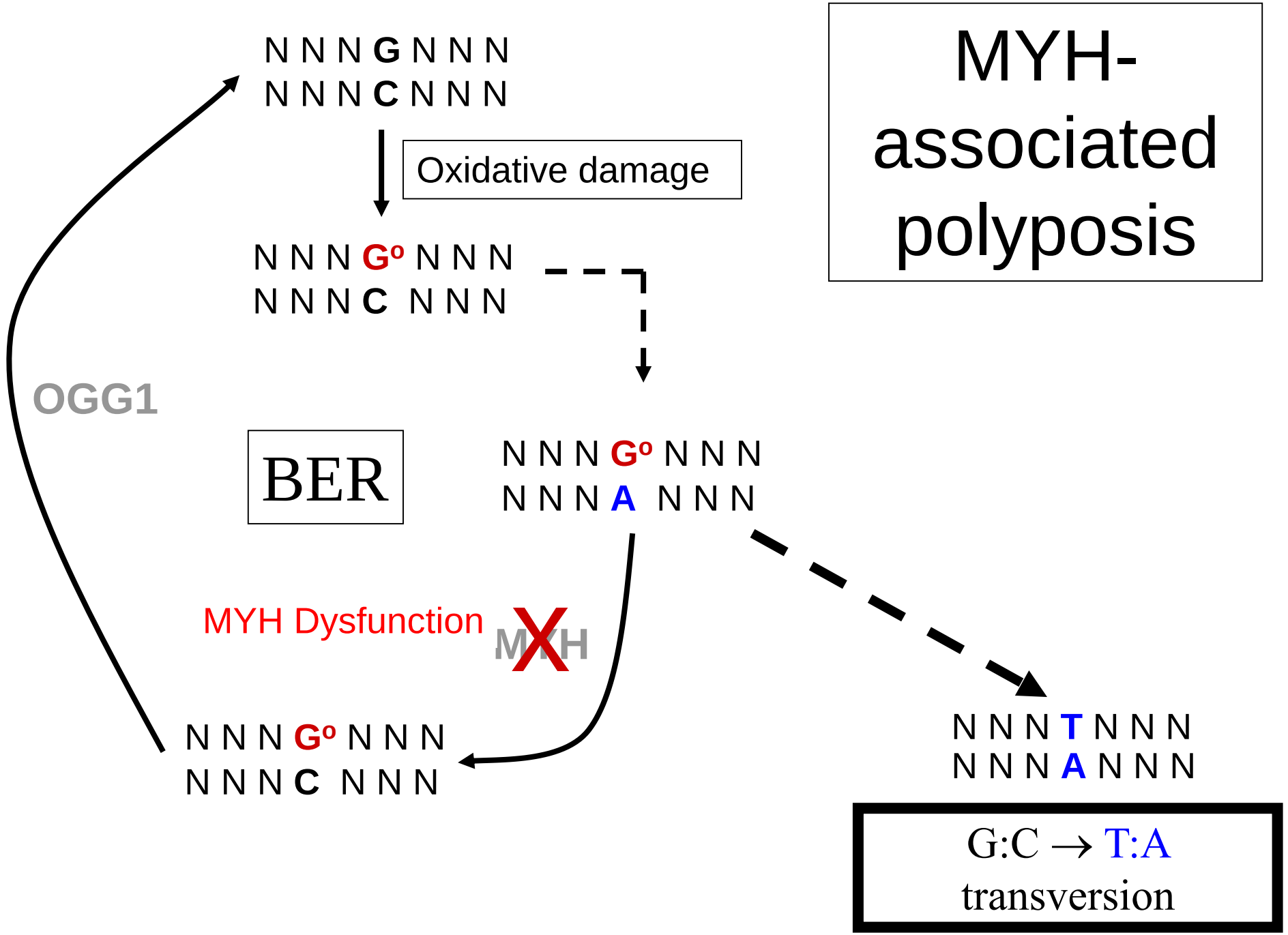
Normal G:C Damaged **G^o**:A

G:C $\rightarrow$ T:A mutation

- Role of MYH is to excise mispaired adenines (Base excision repair BER).

Base Excision Repair




MYH-associated polyposis
N N N G N N N
N N N C N N N
Oxidative damage
N N N Go N N N
N N N C N N N
OGG1
BER
N N N Go N N N
N N N A N N N
MYH Dysfunction
MYH
N N N Go N N N
N N N C N N N
N N N T N N N
N N N A N N N
G:C → T:A
transversion

MYH-associated polyposis

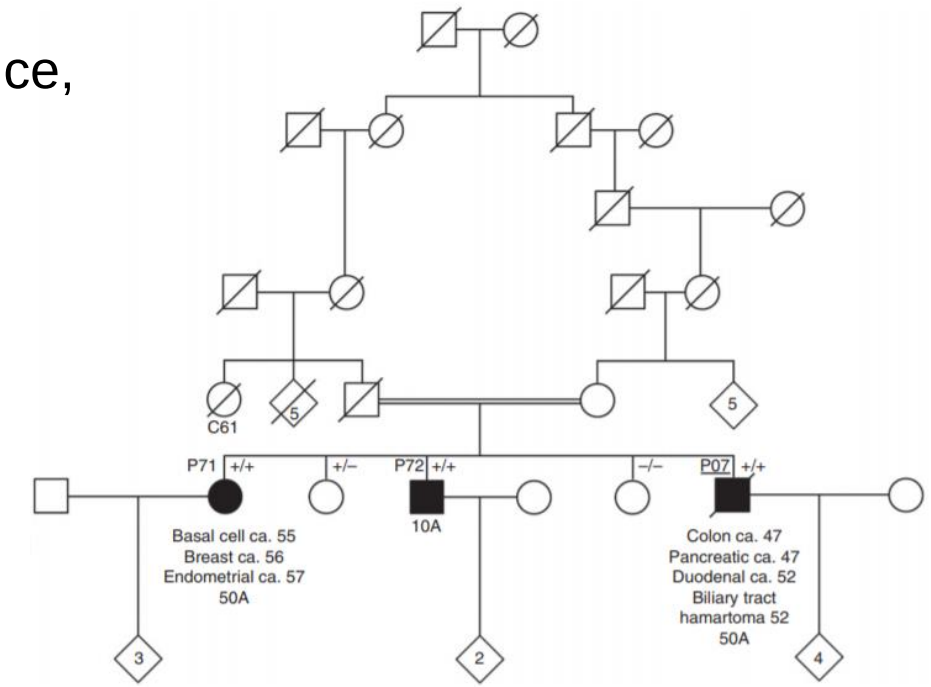
- Autosomal recessive inheritance.
- Penetrance approaching 100%.
- Clinically similar to attenuated FAP.
  - Typically <100 polyps
    (but may show classical FAP phenotype).
  - Some extra colonic manifestations.
  - May also have serrated polyps
- Extracolonic tumours
  - Duodenal, urinary tract, ovarian and ? breast carcinomas.
  - Sebaceous skin tumours,
  - Desmoid tumours (case report).

MYH-associated Polyposis

- Due to biallelic mutations in MYH gene.
- Thought that there is a gradual accumulation oxidative damage causing tumorigenesis
  - *APC* $\rightarrow$ classical adenomas
  - *KRAS* $\rightarrow$ serrated polyps
- Mean age cancer diagnosis 50 years old.
- Up to 30% of European patients with > 15 - 100 adenomas carry biallelic MYH mutations.

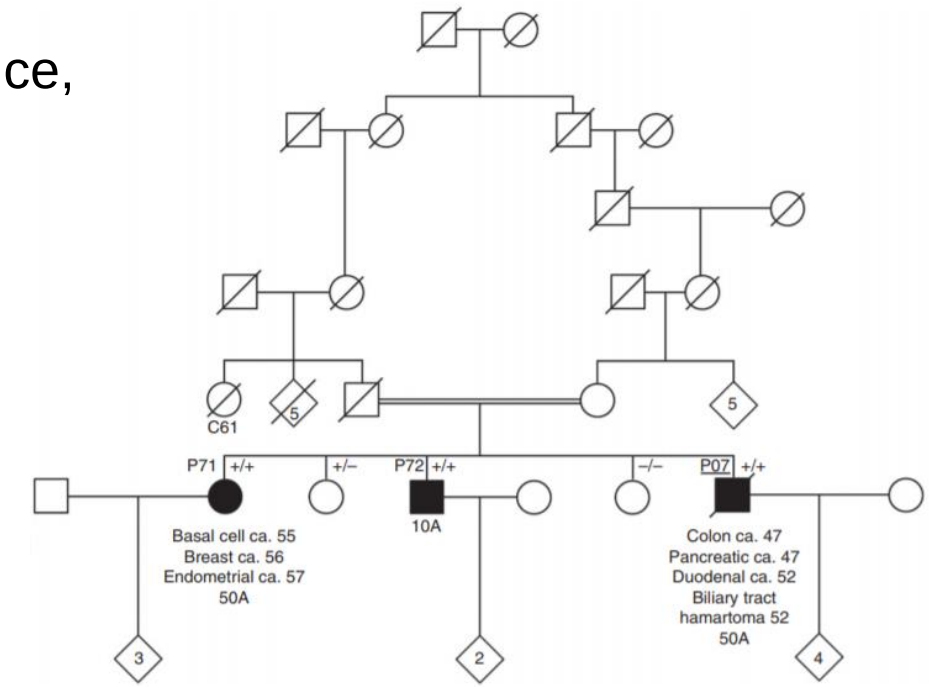
NTHL1-associated polyposis

- NTHL1 is a base excision repair gene (like MYH).
- Broader spectrum of mutations than MAP but more C:G>T:A (MAP C:G>A:T).
- Autosomal recessive inheritance, high penetrance.
- Probably 1/5 as common as MAP.
- Spectrum of tumour types:
  - colorectal carcinoma
  - endometrial carcinoma
  - duodenal carcinoma
  - skin (BCC)
  - others?

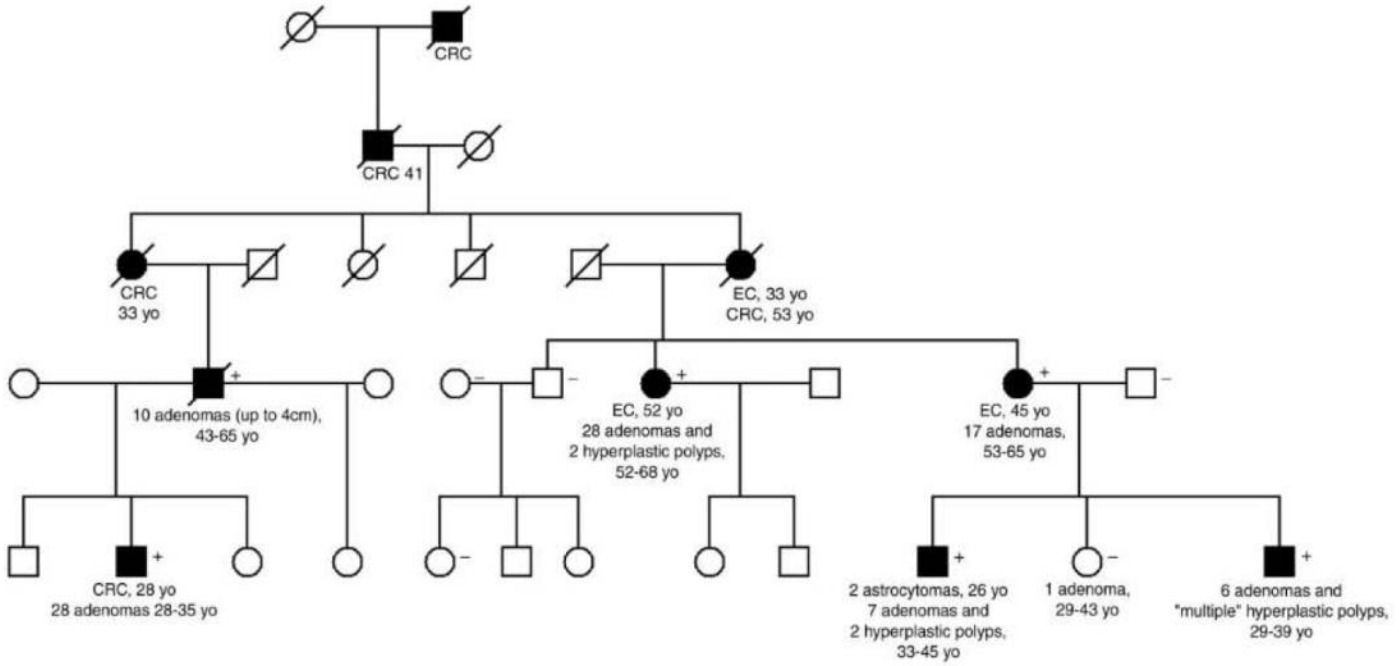


NTHL1-associated tumour syndrome

- NTHL1 is a base excision repair gene (like MYH).
- Broader spectrum of mutations than MAP but more C:G>T:A (MAP C:G>A:T).
- Autosomal recessive inheritance, high penetrance.
- Probably 1/5 as common as MAP.
- Spectrum of tumour types:
  - colorectal carcinoma
  - endometrial carcinoma
  - duodenal carcinoma
  - skin (BCC)
  - bladder, breast, others?



Polymerase Proofreading-associated polyposis (PPAP)



- Germline POLE and POLD1 mutations.
- Major catalytic and proofreading subunits of the Polϵ and Polδ enzyme complexes
- Mutations impair proofreading → hyper mutation

Polymerase Proofreading-associated polyposis (PPAP)

- Autosomal dominant with high penetrance.
- Multiple colorectal adenomas (3 - 10s).
- Early-onset CRC (mean age 36) - may be synchronous, often lymphocyte rich.
- POLD1 - Endometrial adenocarcinomas, breast carcinoma and brain tumours.
- POLE – Endometrial, small bowel, ovarian, pancreatic and brain tumours.
- Tumours microsatellite stable but have multiple point mutations.
- POLE can also be mutated in sporadic CRC (<2%).

Briggs S, Tomlinson I. Germline and somatic polymerase ϵ and δ mutations define a new class of hypermutated colorectal and endometrial cancers. J Pathol. 2013 Jun;230(2):148-53.

Congenital Mismatch Repair Deficiency (Childhood cancer syndrome)

- "Autosomal recessive" Lynch syndrome.
- Biallelic mutations in PMS2, MSH2, MSH6 or MLH1 (compound or homozygous).
- Phenotype:
  - Café-au-lait spots (NF1 type features).
  - **Adenomatous polyposis** and colorectal cancers.
  - Brain tumours (Gliomas, PNETs, meduloblastomas).
  - Haematological malignancies (leukaemias and diffuse large B cell lymphoma).
- Accounts for some cases of Turcot syndome.

Congenital Mismatch Repair Deficiency

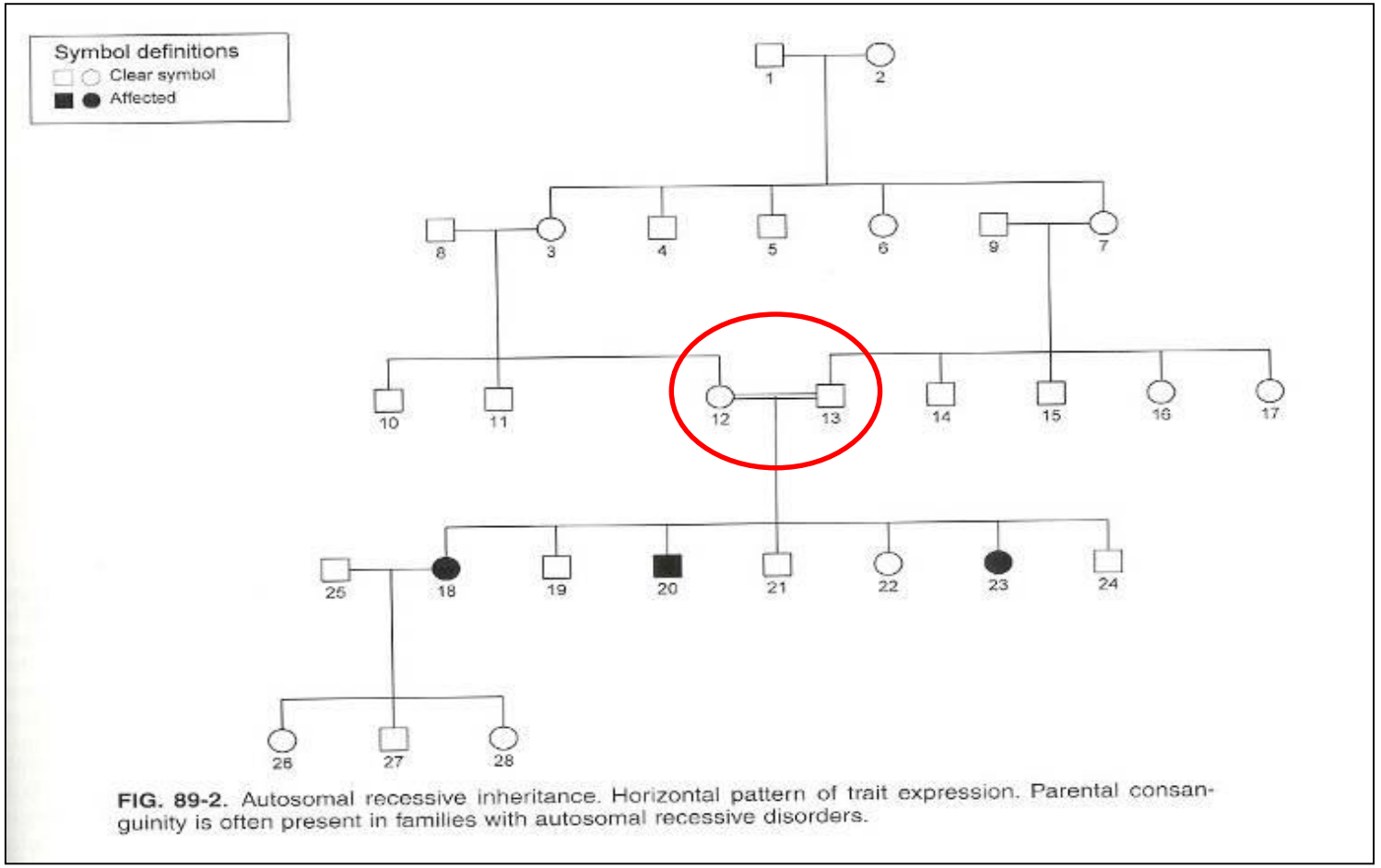
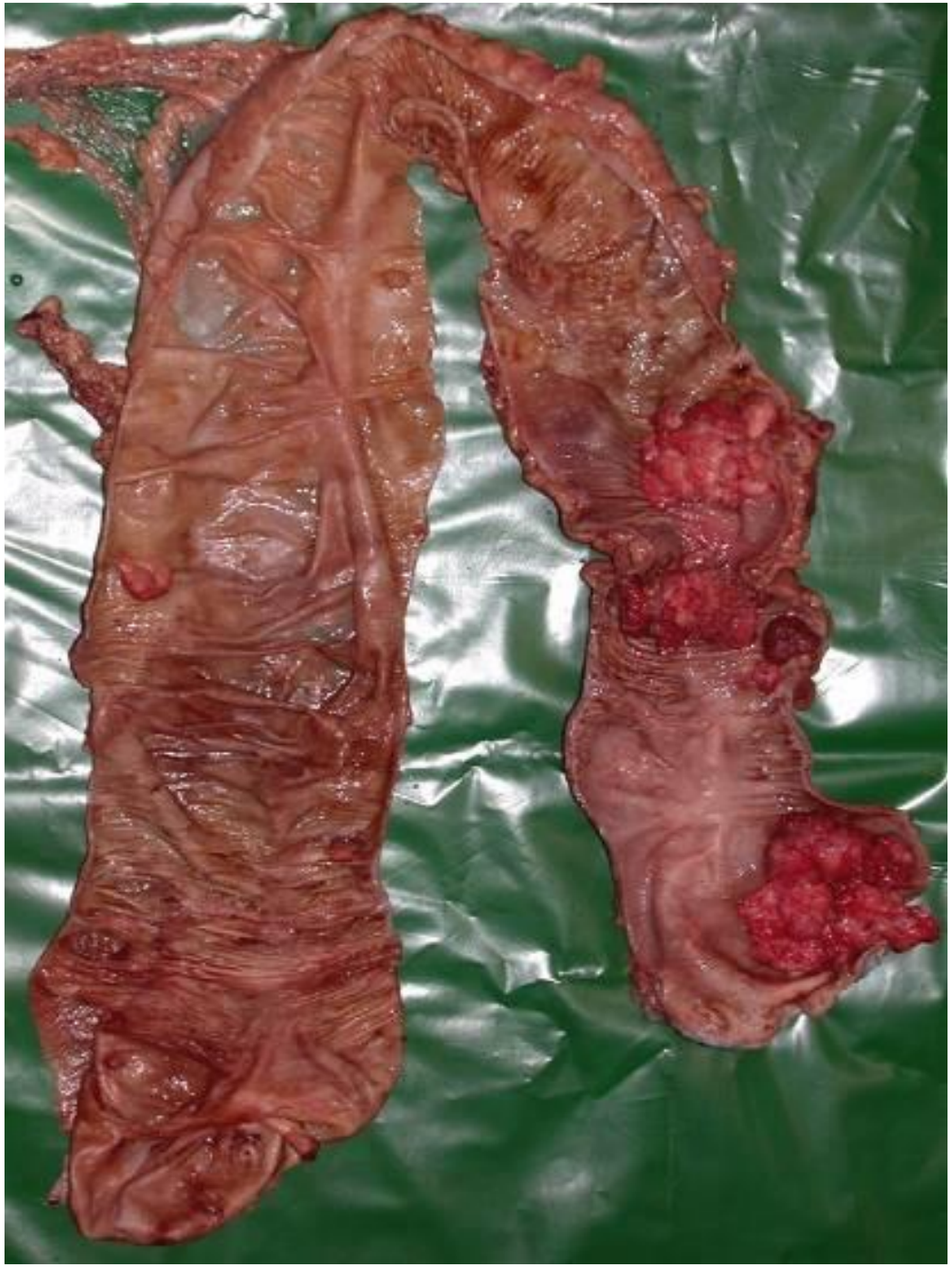


FIG. 89-2. Autosomal recessive inheritance. Horizontal pattern of trait expression. Parental consanguinity is often present in families with autosomal recessive disorders.

- Most commonly seen in asian and arabic populations where consanginous marriages are common



Congenital Mismatch Repair Deficiency

- Café-au-lait spots.
- Adenomatous polyposis and colorectal carcinomas.
- High grade brain tumours.
- Haematological malignancies.

Serrated polyposis

Table 2. World Health Organization diagnostic criteria for the diagnosis of serrated polyposis syndrome (SPS)

Any one of the following	
(1)	At least five serrated polyps proximal to the sigmoid colon, two of which are >10 mm in diameter
(2)	Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS
(3)	Greater than 20 serrated polyps of any size distributed throughout the colon

- Genetics, natural history and phenotype of this syndrome remain poorly characterised.
- Family history CRC in 40-60%
- ?50% chance of developing colorectal carcinoma.
- 26% of carcinomas synchronous/metachronous.

Serrated polyposis

- Polyp spectrum
  - Hyperplastic polyps.
  - Sessile serrated lesions.
  - Traditional serrated adenomas.
  - Conventional adenomas.

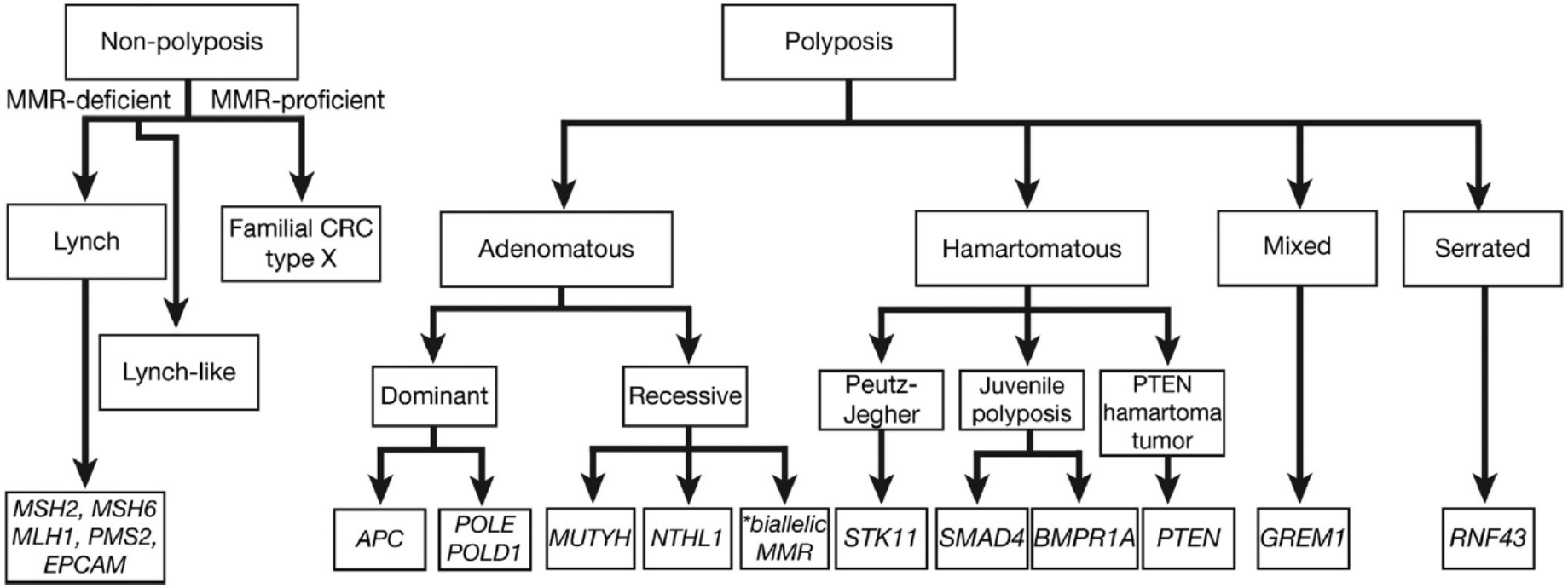
Serrated polyposis

- Polyp spectrum
  - Hyperplastic polyps.
  - Sessile serrated lesions.
  - Traditional serrated adenomas.
  - Conventional adenomas.

→ **PHENOTYPIC OVERLAP WITH MAP**

LEARNING POINTS

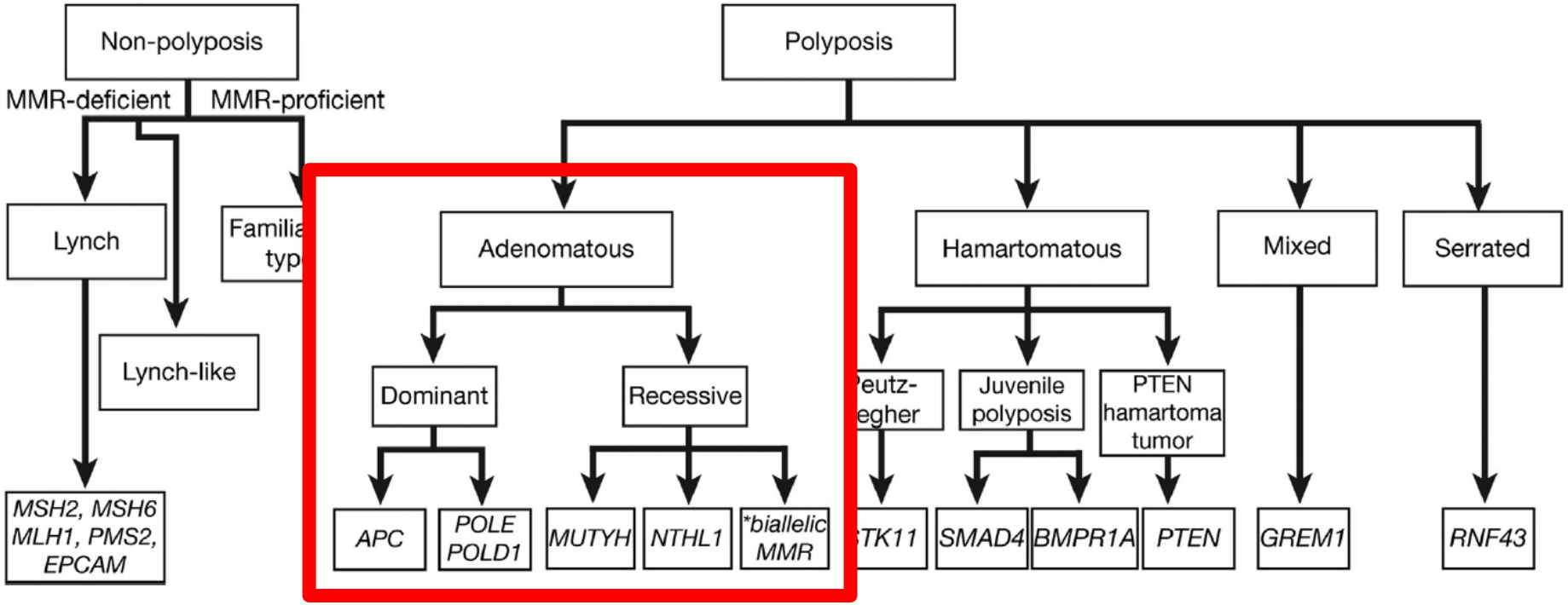
- Adenomatous polyposis syndromes rare (?1% CRC).
- Classical FAP autosomal dominant inheritance but several new syndromes autosomal recessive.
  - MAP + NAP and Constitutional mismatch repair deficiency.
- Two pathways to colorectal carcinogenesis:
  - Genomic instability via p53
  - Hypermutation – MMR, BER, DNA polymerase malfunction.
- Every increasing spectrum of extra-intestinal malignancies.
- MAP and Serrated polyposis may show phenotypic overlap
  - Serrated polyps and adenomas



Recent Discoveries in the Genetics of Familial Colorectal Cancer and Polyposis

Laura Valle

Clinical Gastroenterology and Hepatology 2017;15:809–819



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Thank you for your attention