



Polipi multipli del colon: è una poliposi adenomatosa familiare?

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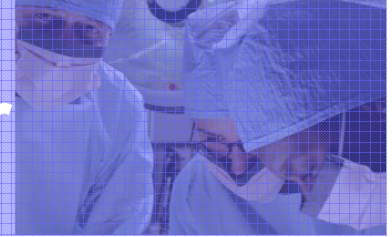
U.O. Chirurgia Generale 1

A.O. Spedali Civili Brescia

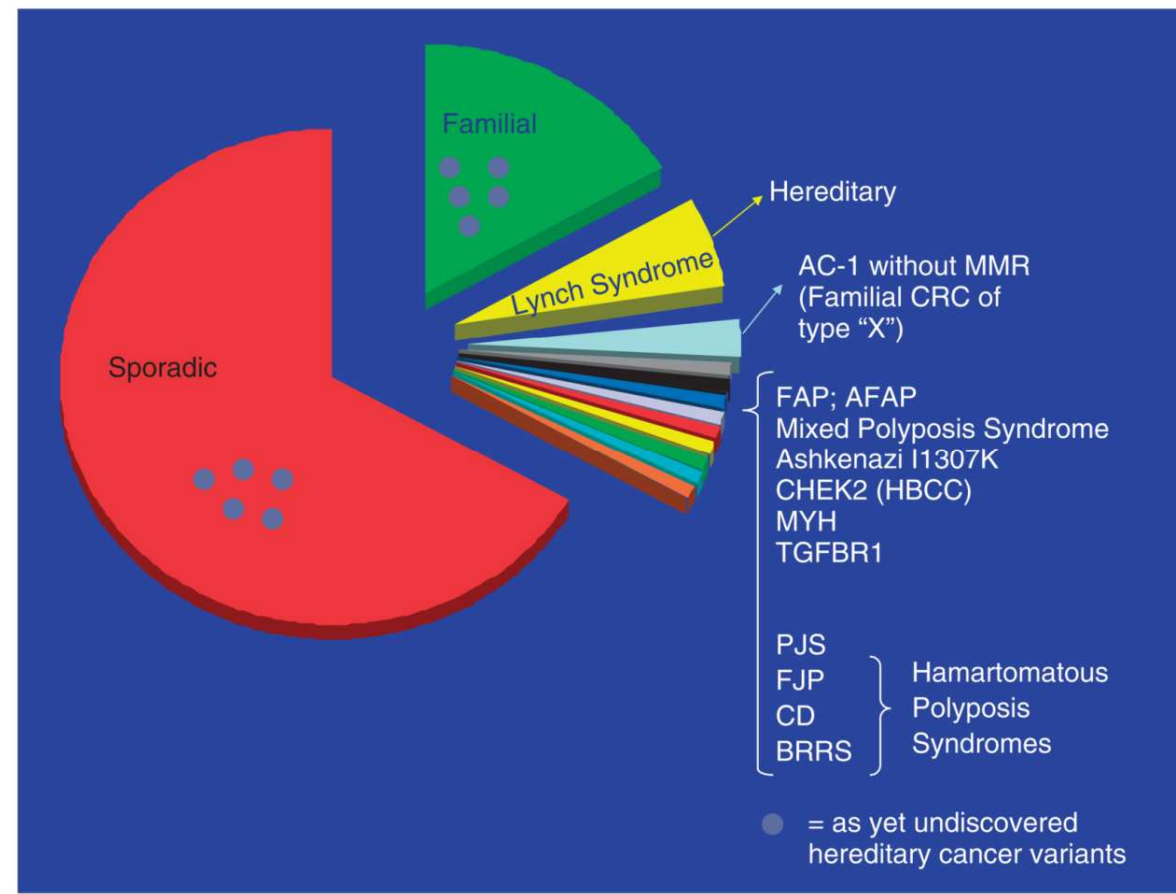
Cattedra di Chirurgia Generale

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Hereditary Colorectal Cancer



Kindred and twin studies estimated that approximately 30% of all CRC cases are an inherited form of the disease.



Hereditary Colorectal Cancer Management

The ultimate goal of Registry-based management

<i>Registry</i>	<i>CRC rate probands</i>	<i>CRC rate call-up</i>
St.Mark's Hospital	66%	9%
Denmark	69%	2%
Brescia	74%	4%

Polyps & hereditary colorectal cancer



The classical histology-based polyposis classification:

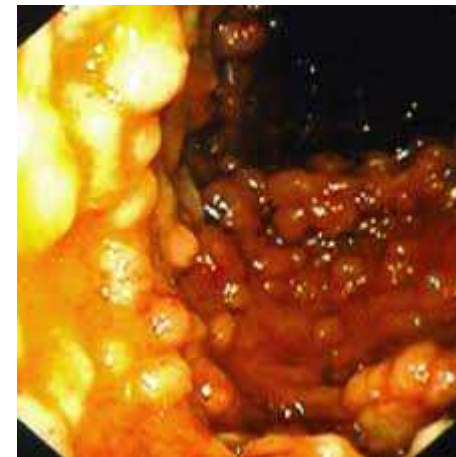
- No polyposis Lynch Syndrome (LS) or Hereditary Non-Polyposis Colorectal Cancer (HNPCC)
- Adenomatous polyposis Familial Adenomatous Polyposis (FAP)
Attenuated FAP (AFAP)
and variants (Gardner, Turcot, etc.)
MutYH-Associated Polyposis (MAP)
- Non-adenomatous polyposis Peutz Jeghers Syndrome (PJS)
Cronkite-Canada Syndrome
Juvenile Polyposis
Cowden Disease
Bannayan-Ruvalcaba-Riley Syndrome
Gorlin-Goltz Syndrome
Neurofibromatosis type VIII
Etc.

Familial Adenomatous Polyposis



Main features

- FAP is the 2nd-most common inherited CRC
- Prevalence of 1 in 10,000 individuals.
- Hundreds to thousands of colonic adenomas beginning in early adolescence, and inevitable CRC in untreated individuals.
- The average age of CRC diagnosis if untreated is 39 years; 7% develop CRC by age 21 and 95% by age 50.



Polypses & hereditary colorectal cancer



The evolving gene-based classification:

- MMR genes Lynch Syndrome (LS)
Familial Colorectal Cancer Type X
- APC gene Familial Adenomatous Polyposis (FAP)
and variants
- MutYH gene MutYH-Associated Polyposis (MAP)
- STK11-LBK gene Peutz Jeghers Syndrome (PJS) and variants
- SMAD4, BMPR1A genes Juvenile Polyposis (JP) and variants
- PTEN gene Cowden Disease and variants

Attenuated Familial Adenomatous Polyposis

Main features

- Attenuated FAP is a less-severe form of the disease
- An average of approximately 25-30 colonic **adenomatous polyps (range, 10–100)**
- An average 69% lifetime risk of CRC
- Polyp and CRC development at a later age
- Tendency to develop proximal colonic neoplasms (or to develop less rectal adenomas)



MutYH-Associated Polyposis (MAP)



Main features

- **MAP mimics attenuated FAP**, including a propensity for proximal colonic neoplasms.
- MAP is characterized by the presence of adenomatous polyposis of the colorectum and an increased risk of CRC.
- Colonic polyposis typically occurs by the time patients reach their 40s, although polyps and cancer can occur at earlier ages.
- Adenomatous polyps predominate in MAP, however, unlike attenuated FAP, **hyperplastic polyps and sessile serrated polyps** are common.

Boparai KS, Dekker E, Van Eeden S, et al. Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. *Gastroenterology* 2008;135:2014–2018.

Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS. Clinical implications of the colorectal cancer risk associated with MUTYH mutation. *J Clin Oncol* 2009;27:3975–3980.

Attenuated Adenomatous Polyposis



Risk of extracolonic features

Malignant features

Duodenum/periampullary

Stomach

Pancreas

Thyroid

Liver (hepatoblastoma)

CNS (medulloblastoma)

FAP (Lifetime Cancer Risk)

Yes (4–12%)

Yes (1%)

Yes (2%)

Yes (1–2%)

Yes (1–2%)

Yes (1%)

MAP

Yes (?)

?

-

-

-

-

Non-malignant features

Gastric fundic gland

CHRPE

Epidermoid cysts

Skull and mandible osteomas

Dental abnormalities

Desmoid tumors

Yes

Yes

Yes

Yes

Yes

Yes

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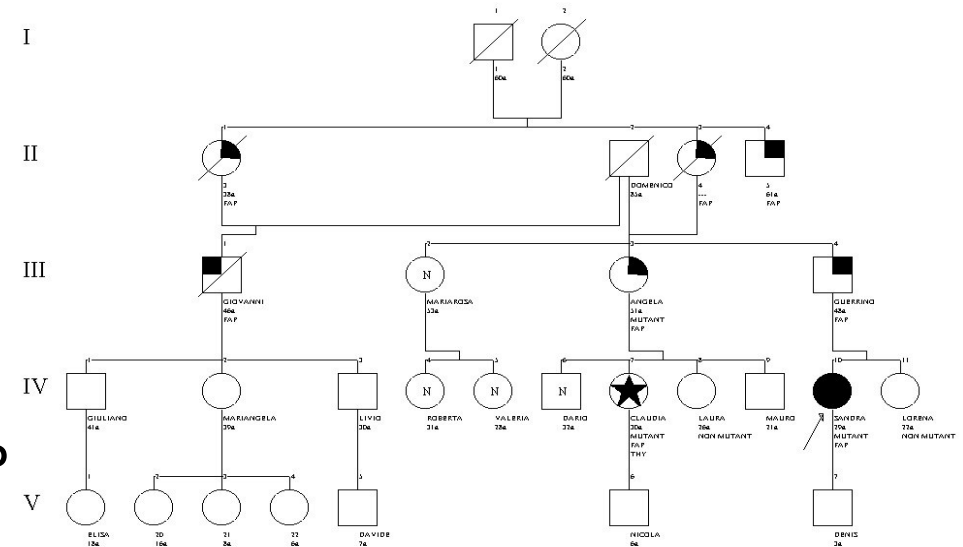
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Familial Adenomatous Polyposis

Genetics

- Pattern of inheritance of **FAP** and attenuated FAP is **autosomal dominant**.
- New or de novo *APC* mutations are responsible for $\approx 25\%$ of FAP cases.
- Pattern of inheritance of **MAP** is **autosomal recessive**.



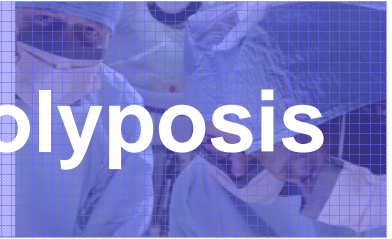
Attenuated Adenomatous Polyposis



Diagnosis

- **Attenuated FAP** is suspected when 10, but 100 adenomas, are found in a person older than 25 years of age.
- The presence of extracolonic lesions can also contribute to the initial diagnosis.
- The identification of **APC mutations** in a proband confirms the diagnosis, allowing precise identification of other relatives who are at risk.
- Genetic testing on **MutYH gene** is warranted in individuals with 10 colorectal adenomas but without an identifiable mutation in *APC*.

Attenuated Familial Adenomatous Polyposis



Management

- Individuals who are at risk for, or have a genetic diagnosis of, FAP should be examined by colonoscopy beginning at age 12 years.
- Once adenomatous polyps emerge (or from 20 years of age), an annual surveillance colonoscopy is recommended.
- Prophylactic colectomy with an ileorectal anastomosis is recommended in the majority of patients.
- In patients with few adenomas repeated colonoscopies with polypectomy may be appropriate, if managed by experts.

Knudsen AL, Bulow S, Tomlinson I et al. Attenuated familial adenomatous polyposis: results from an international collaborative study. *Colorectal Dis* 2010; 12:e243-e249.

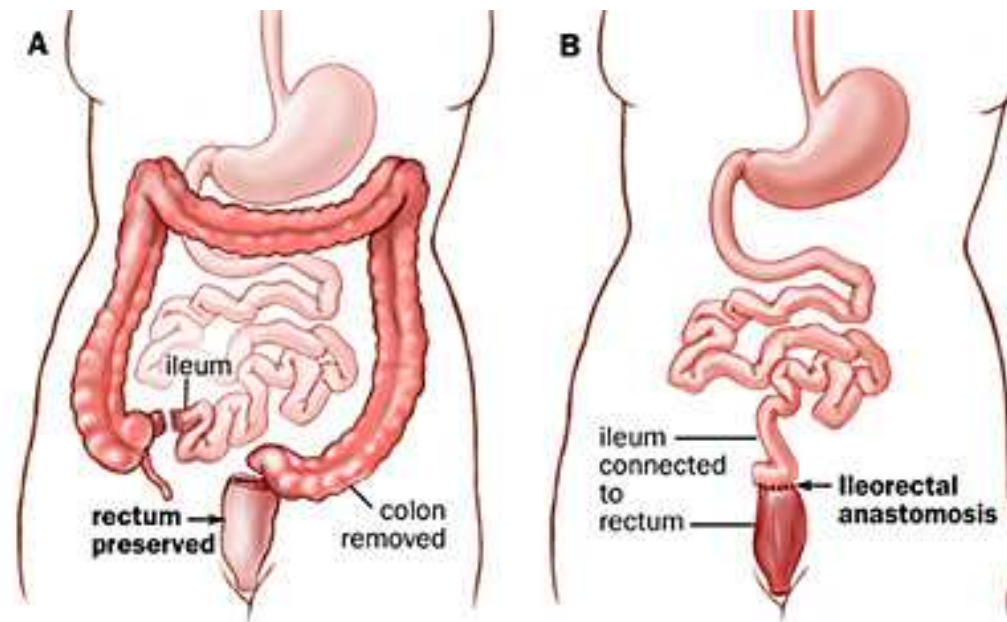
Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS. Clinical implications of the colorectal cancer risk associated with MUTYH mutation. *J Clin Oncol* 2009;27:3975–3980.

MutYH-Associated Polyposis (MAP)



Surgery

- Subtotal colectomy is advised for patients who develop colon cancer and should also be considered when colonoscopic management becomes problematic or when polyps become large or exhibit high-grade dysplasia.



Nascimbeni R, Pucciarelli S, Di Lorenzo D, et al.
Rectum-sparing surgery may be appropriate for biallelic MutYH-associated polyposis.
Dis Colon Rectum 2010;53:1670-1675.

Brescia Hereditary Colorectal Cancer Registry



Suspect of Hereditary Syndrome

Registry Consultation

Appropriate Testing

Specific diagnosis

Proband surveillance (+ Treatment)

Family testing & surveillance (+ Treatment)

Patient & pedigree
database

Tissue & blood bank
Lab credentializing

Administrative work up
RB0050-RB0040

Family meetings
Psychologic support

Brescia Hereditary Colorectal Cancer Registry



Genetic work-up at Brescia Registry

Phenotype	Molecular/gene testing	Confirmed diagnosis
Adenomatous polyposis	APC, MYH gene testing	F.A.P
		M.A.P.
Amsterdam or Bethesda criteria	Microsatellite instability, MMR proteins IHC, BRAF V600E, MLH1-promoter hypermethylation, MLH1,MSH2,MSH6 gene testing	Lynch syndrome
		Familial CRC type X
Amartomatous polyps	STK11 gene testing	Peutz-Jeghers Syndrome

Brescia Hereditary Colorectal Cancer Registry



GISPAC members

- Anatomia Patologica (AP2)
 - Biologia Molecolare (AP1)
 - Endoscopia Digestiva
 - Gastroenterologia
 - Genetica (Lab.Biotecnologie)
 - Oncologia Medica
 - Radiologia
- Dr Villanacci
Dr Vermi, Dr.ssa Medicina, Prof Facchetti
Dr Moneghini, Prof Cestari
Dr Lanzarotto, Dr.ssa Ricci, Prof Lanzini
Dr Di Lorenzo, Prof Caimi
Dr Ferrari
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