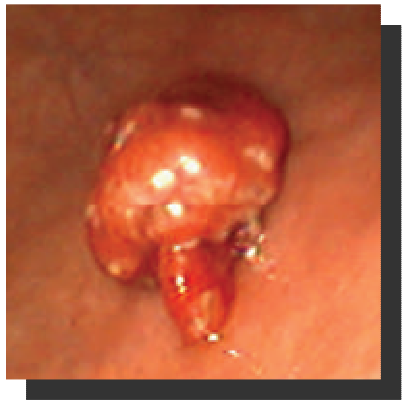
Curso de Patología Digestiva

"Pólipos gástricos"

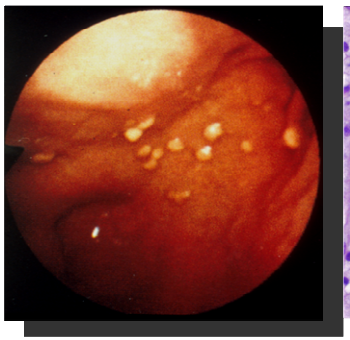
Fátima Carneiro
IPATIMUP
&
Medical Faculty/Centro Hospitalar São João
Porto, Portugal

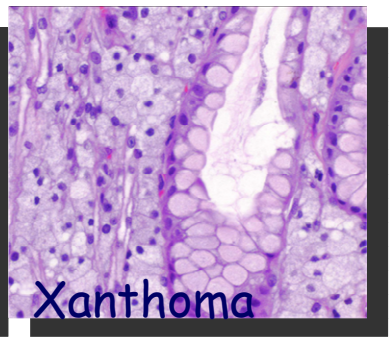


Gastric polyps

- Solitary (sporadic)
- Polyposis syndromes (hereditary)

  - Neoplastic (benign or malignant)
  - Hyperplastic
  - Inflammatory
  - Hamartomatous
  - Heterotopic
  - Miscellaneous





CLASSIFICATION OF GASTRIC POLYPS

Epithelial polyps

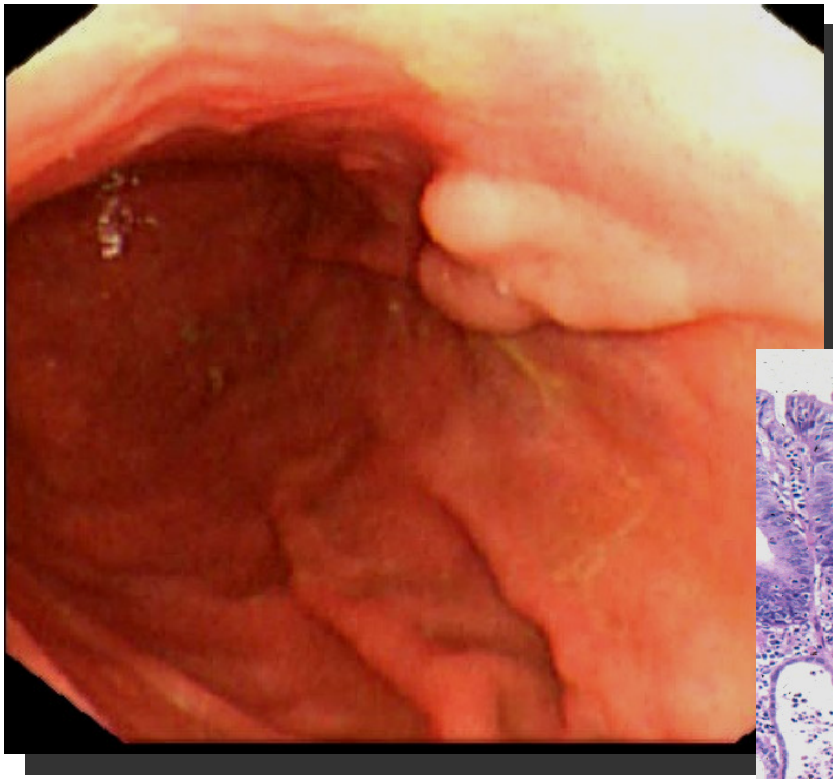
- Fundic gland polyp
- Hyperplastic polyp
- Adenomatous polyp
- Hamartomatous polyps
  - Juvenile polyp
  - Peutz-Jeghers syndrome
  - Cowden syndrome
- Polyposis syndromes (non-hamartomatous)
  - Juvenile polyposis
  - Familial adenomatous polyposis

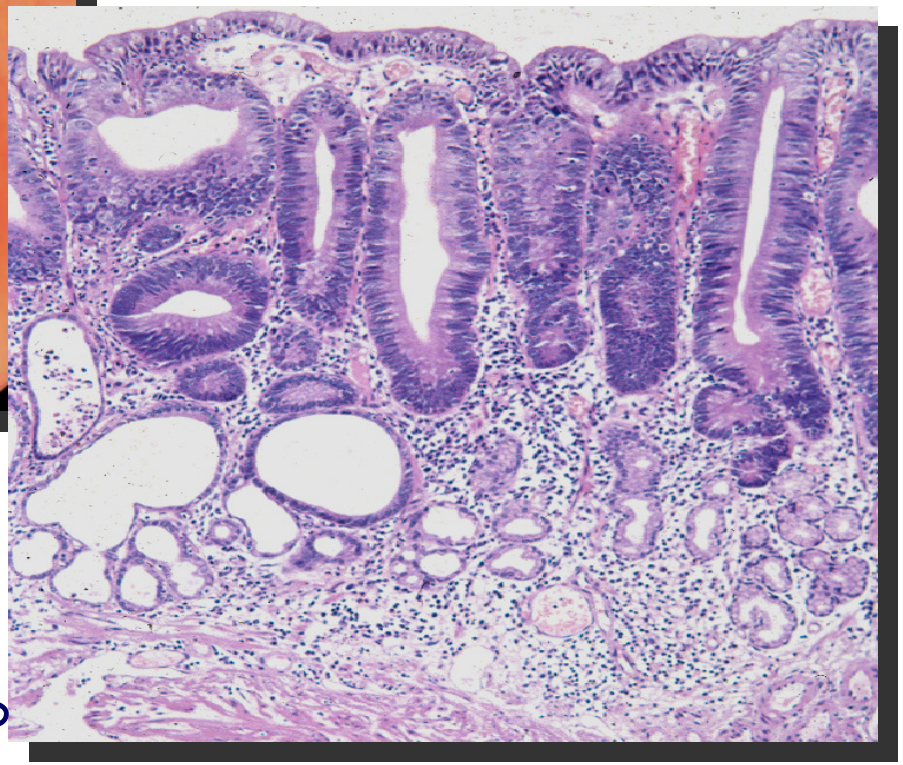
Non-mucosal intramural polyps

- Gastrointestinal stromal tumour
- Leiomyoma
- Inflammatory fibroid polyp
- Fibroma and fibromyoma
- Lipoma
- Ectopic pancreas
- Neurogenic and vascular tumours
- Neuroendocrine tumours (carcinoids)

Goddard AF et al, on behalf of the British Society of Gastroenterology. Gut 2010;59:1270

Adenomatous polyp (adenoma)

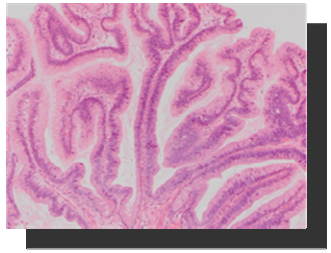




- Usually solitary (82%),
- Located in the antrum,<2cm.
- 0.5–3.75% in western countries
- 9–27% in China and Japan
- Some cases associated with FAP

- Circumscribed lesions, pedunculated or sessile
- Dysplastic epithelium without invasion of the lamina propria.

- Adenomas
  - Intestinal-type
  - Gastric-type adenomas*
    - Foveolar adenoma →
    - Pyloric gland adenoma



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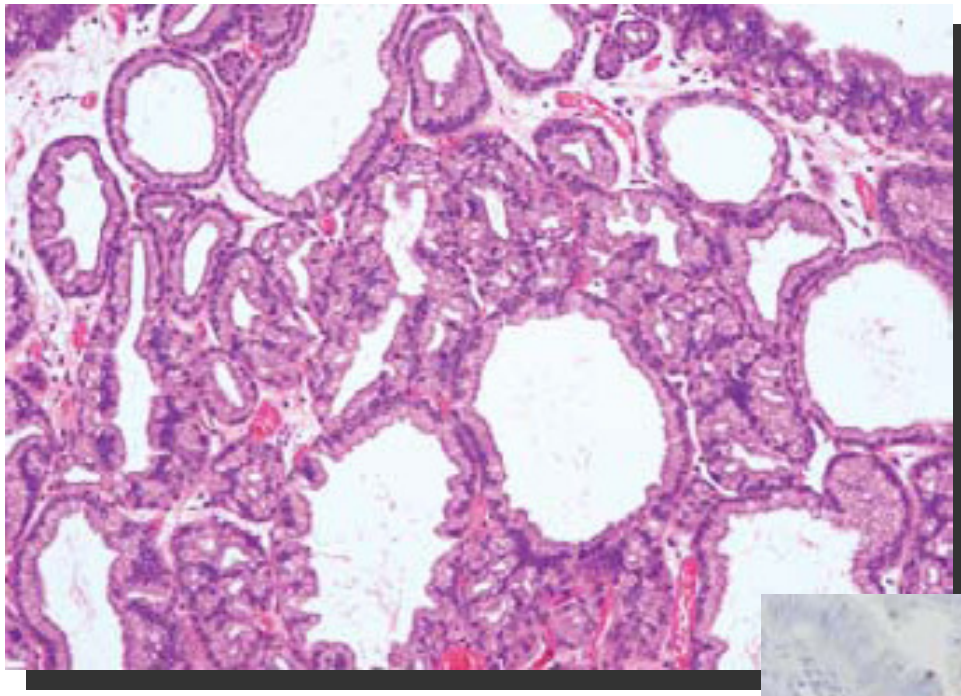
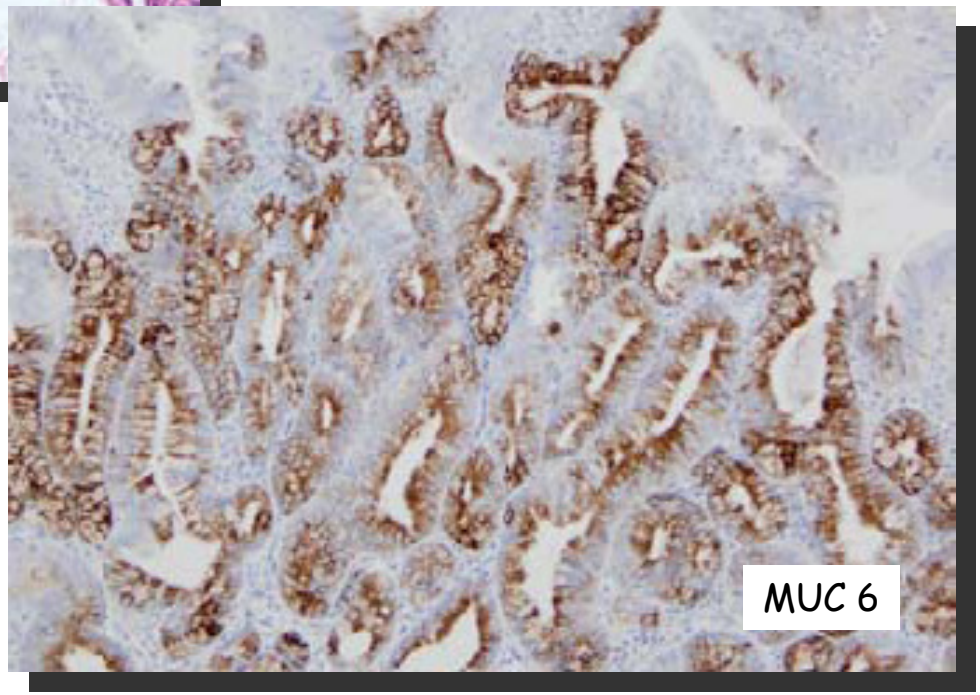
* Few reports of Chief cell proliferation/ hyperplasia/"adenoma"

WHO – 4th Edition, 2010





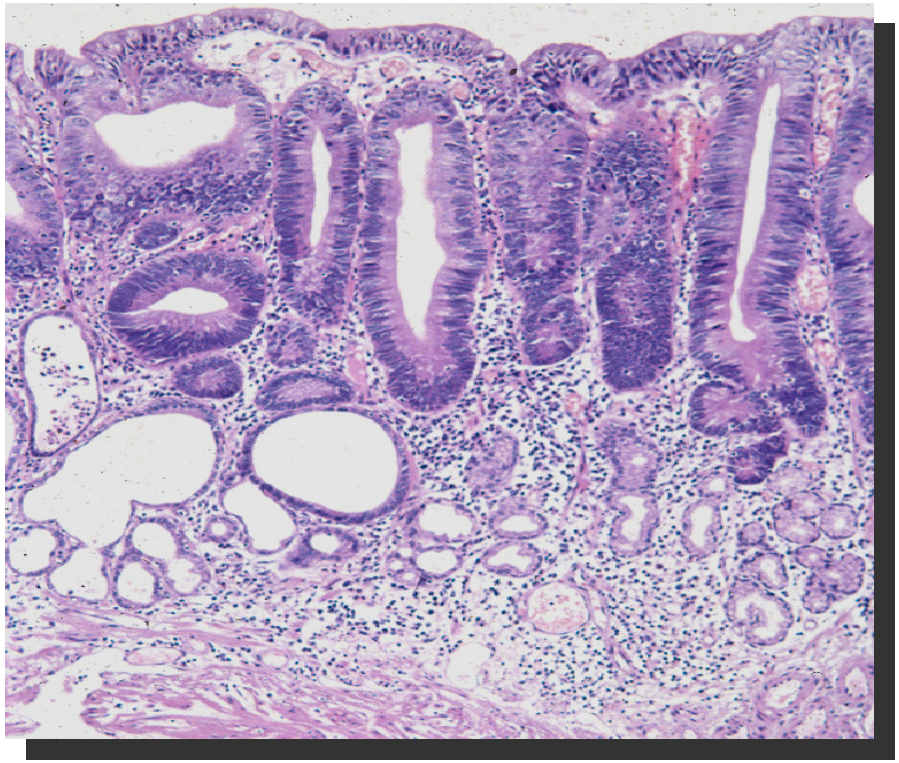
Pyloric gland adenoma

Phenotypic classification

	CD10	MUC2	MUC5AC	MUC6
Intestinal-type	**Positive** (Apical membrane)	**Positive** (Goblet cells)	Negative	Negative
Foveolar adenoma*	Generally negative	Few scattered cells	**Strongly positive**	**Positive** (adenoma cells, deep in the mucosa)
Pyloric gland adenoma	Generally negative	Generally negative	Positive in the foveolae and some pyloric glands	**Strongly positive in pyloric type glands**
Mixed gastric & intestinal type	Negative	Positive	Positive (superficial adenoma cells)	Positive (deep adenoma cells)

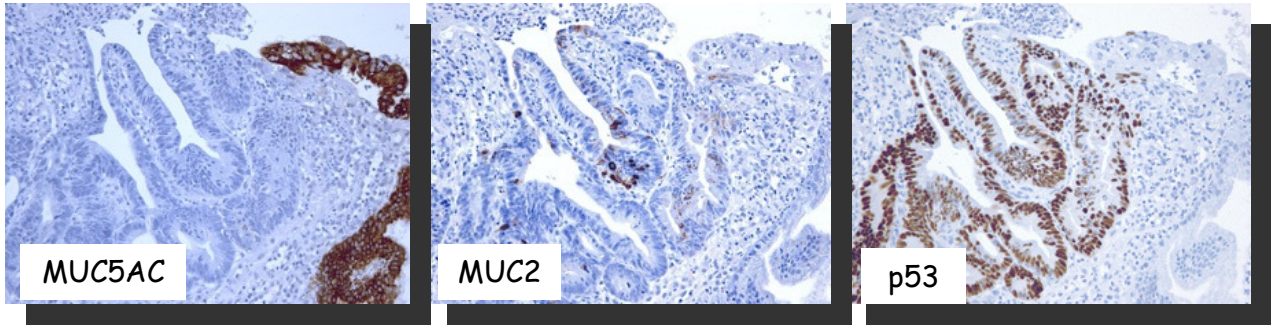
* Increased frequency in FAP

Adenoma



• Circumscribed epithelial lesion, pedunculated or sessile (flat mucosa) with dysplasia

Gastric dysplasia

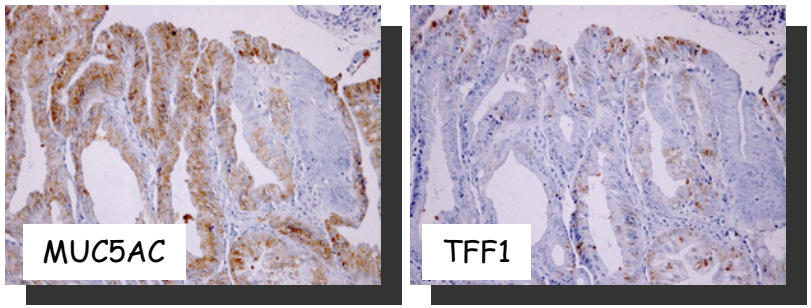


Flat mucosa:

Intestinal phenotype (68%)
Tubular structure (58%)
Expression of p53 (16%)

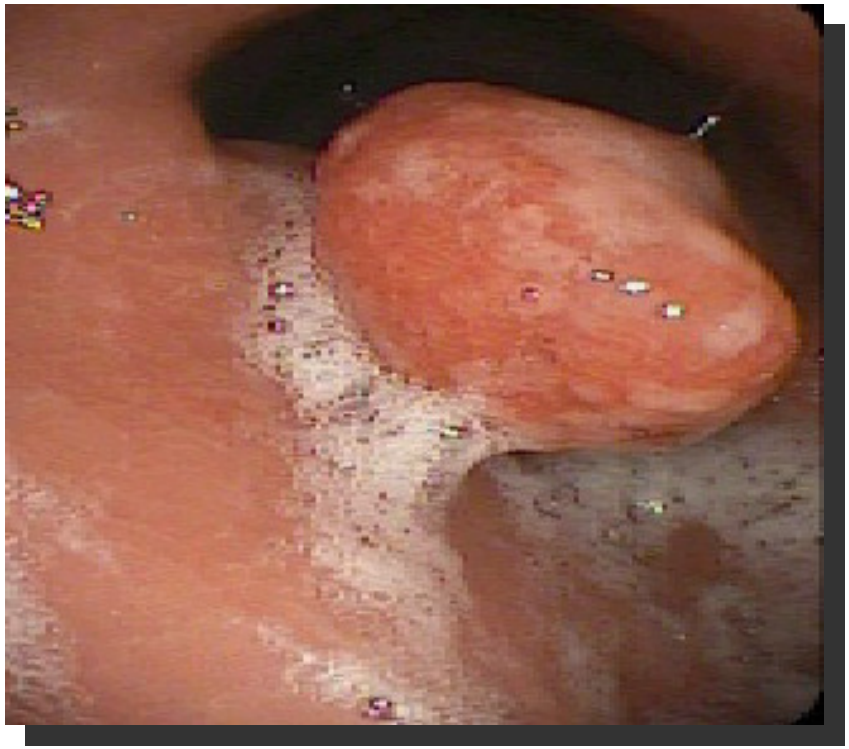
Polypoid lesions:

Gastric phenotype (84%)
Villous & tubullo-vilous structure (57%)
Microsatellite instability (28%)

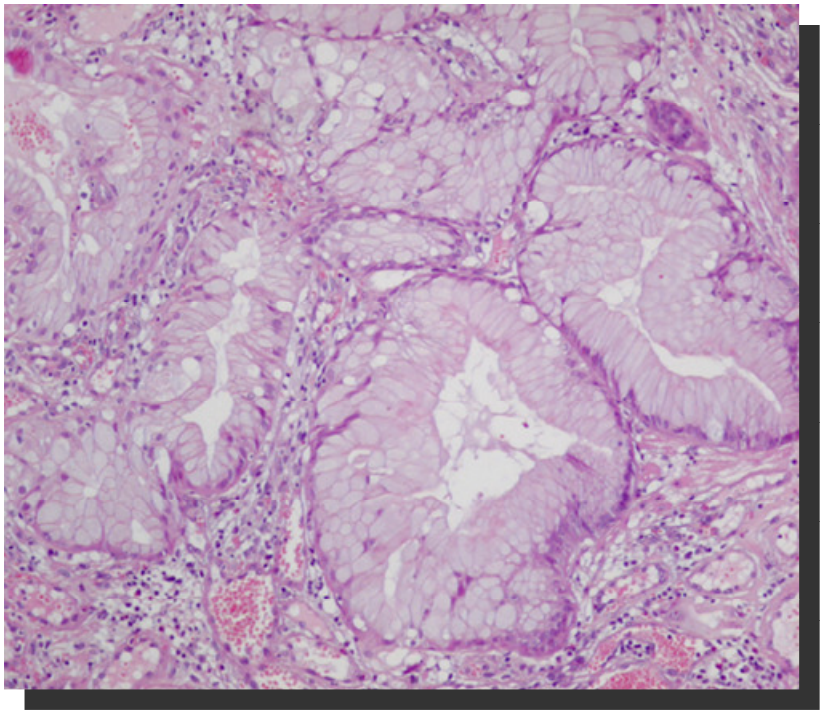


Nogueira *et al;* J Pathol 187: 541, 1999
Machado *et al;* Pathol 190: 437, 2000

Hyperplastic polyp



- Multiple
- Frequently localized in the antrum
- Found also in the "cardia" (GORD)
- 17%-80% of all gastric polyps (wide variation)
- Association with *H.pylori* infection, autoimmune gastritis, bile reflux

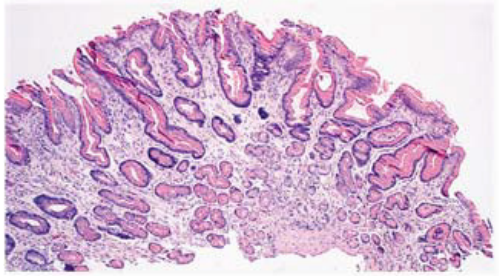


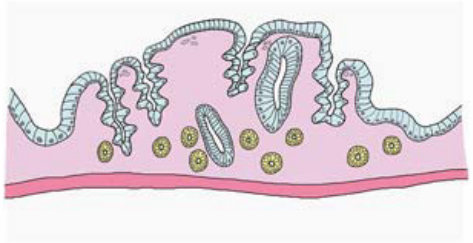
- Elongated, distorted and branching foveolae
- Inflammatory stroma
- DD: Peutz-Jeghers polyp and prolapse polyp (muscle fibres in the stroma)

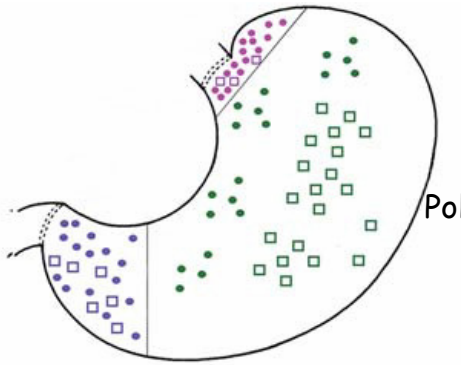
Gastric Hyperplastic Polyps: A Heterogeneous Clinicopathologic Group Including a Distinct Subset Best Categorized as Mucosal Prolapse Polyp

Elvira Gonzalez-Obeso, MD,† Hiroshi Fujita, MD,‡ Vikram Deshpande, MD,§*
Fumihiro Ogawa, MD,†§ Mikhail Lisovsky, MD,‖ Muriel Genevay, MD,¶*
*Krzysztof Grzyb, MD,§# William Brugge, MD,** Jochen K. Lennerz, MD, PhD,§*
Michio Shimizu, MD, †† Amitabh Srivastava, MD,‖ and Gregory Y. Lauwers, MD§

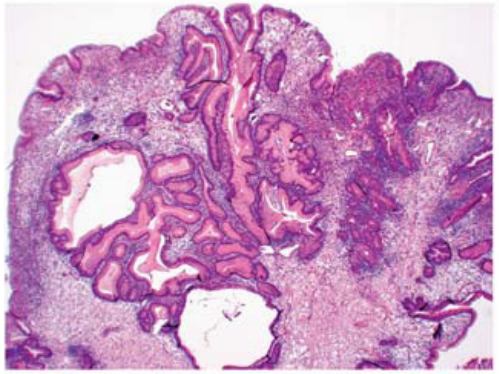
Am J Surg Pathol 2011;35:670–677

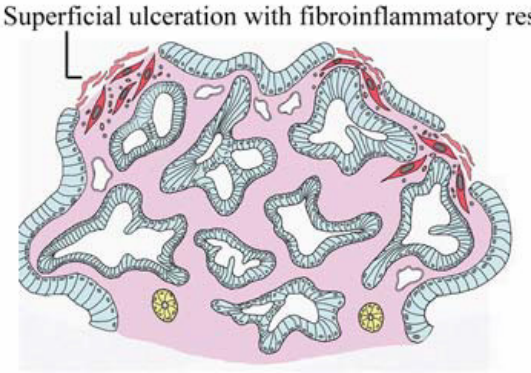


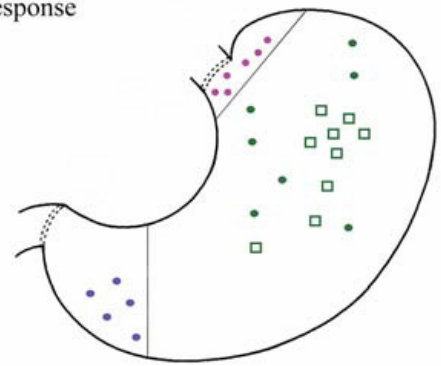




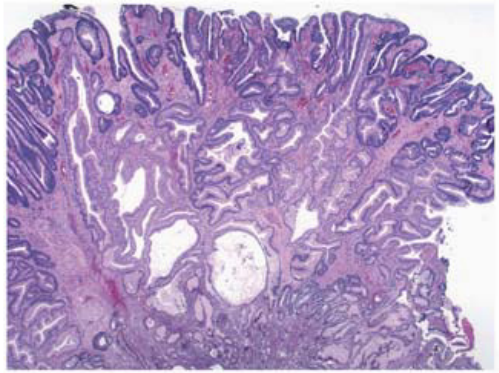
Polypoid foveolar hyperplasia

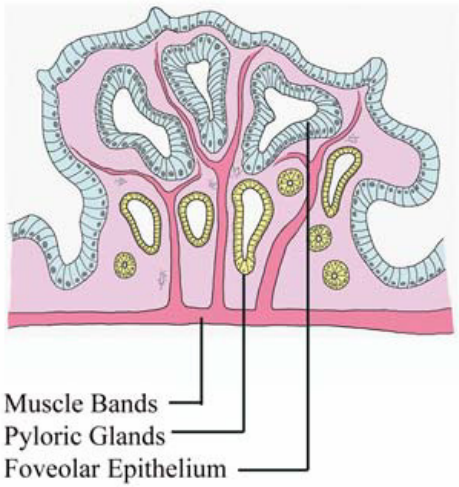


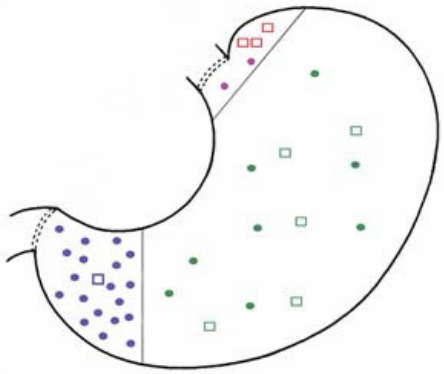




Hyperplastic polyp







Mucosal prolapse polyp

Gonzalez-Obeso E et al. Am J Surg Pathol 2011;35:670

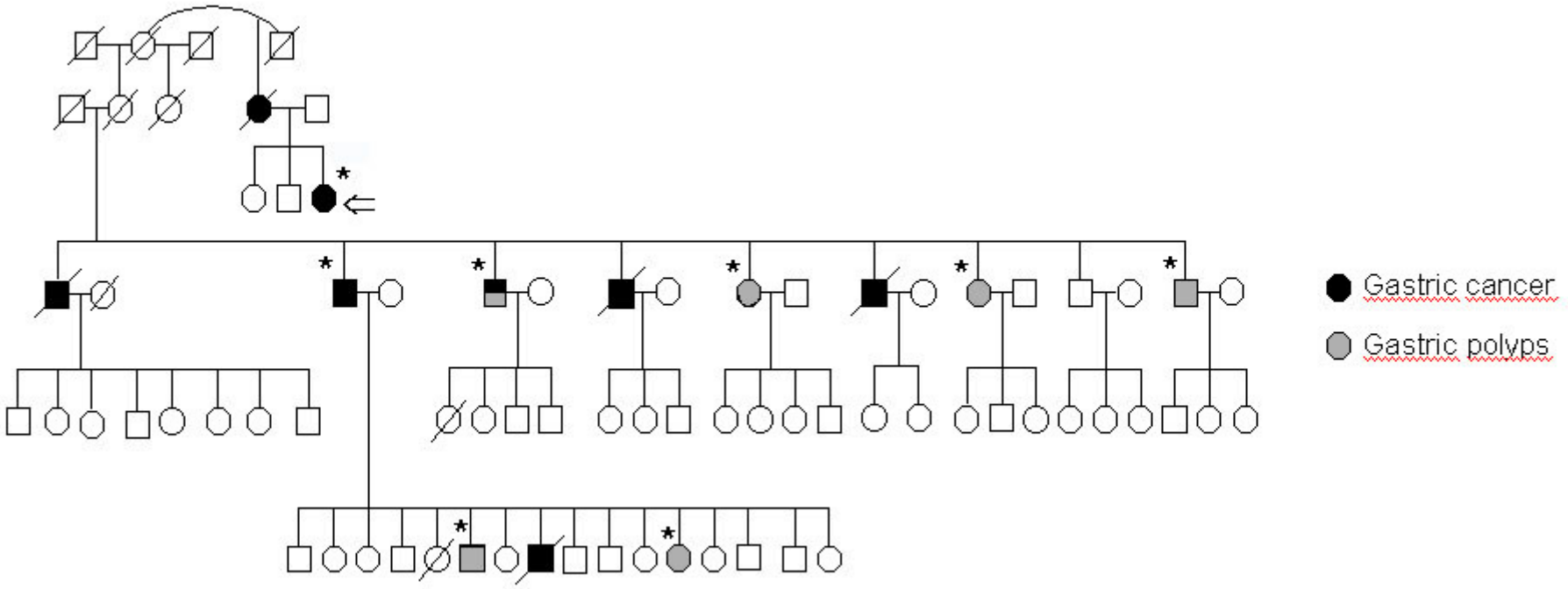
H. Pylori Status of the Patients and Quality of Surrounding Mucosa

Type of Polyp	H. Pylori Infection (%)	Surrounding Mucosa
PFH (n=103)	Positive: 6 (9.5) Negative: 58 (9.5) Unknown: 39	Reactive gastropathy (n=14) Chronic inactive gastritis (n=14) Intestinal metaplasia (n=5) Fundic gland polyp (n=3) Normal (n=9) NA (n=58)
Hyperplastic polyp (n=41)	Positive: 7 (20.5) Negative: 27 (79.5) Unknown: 7	Reactive gastropathy (n=4) Chronic inactive gastritis (n=3) Intestinal metaplasia (n=1) Fundic gland polyp (n=2) NA (n=31)
Mucosal prolapse polyp (n=64)	Positive: 12 (19.7) Negative: 49 (80.3) Unknown: 3	Reactive gastropathy (n=14) Chronic inactive gastritis (n=14) Intestinal metaplasia (n=5) Fundic gland polyp (n=3) Normal (n=9) NA (n=58)

NA indicates not available; PFH, polypoid foveolar hyperplasia

Gonzalez-Obeso E et al. Am J Surg Pathol 2011;35:670

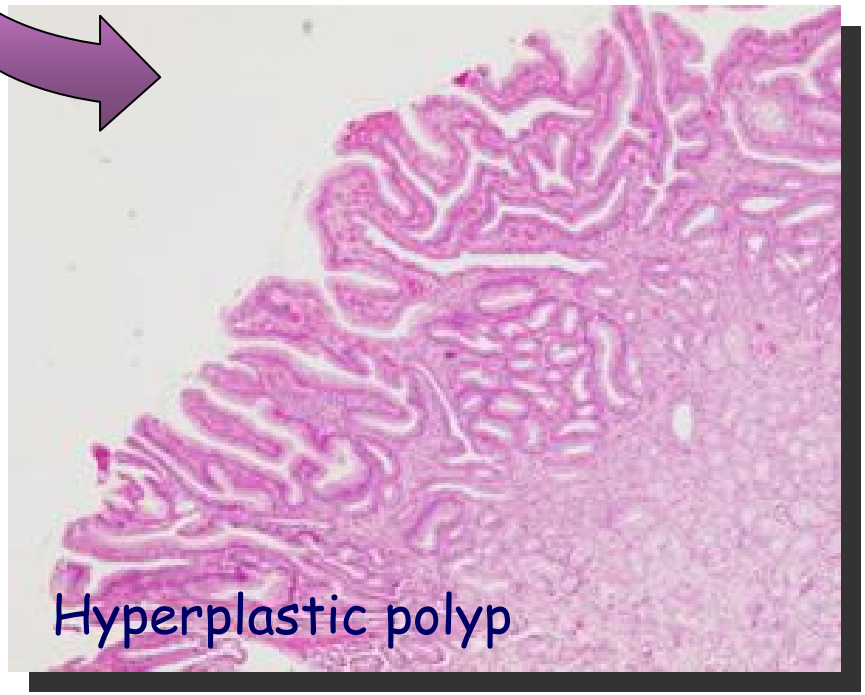
Hyperplastic polyposis and diffuse carcinoma of the stomach

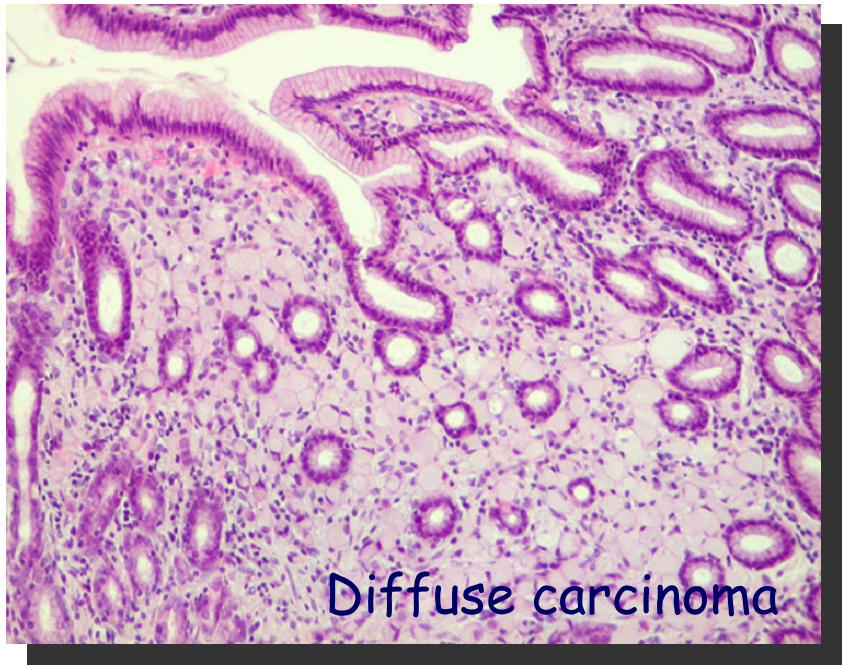


- Portuguese family
- Autosomal dominant inheritance

Seruca *et al.* Cancer Genet Cytogenet 53: 97, 1991
Carneiro *et al.* Cancer 72: 323, 1993

Familial gastric polyposis and carcinoma of the stomach



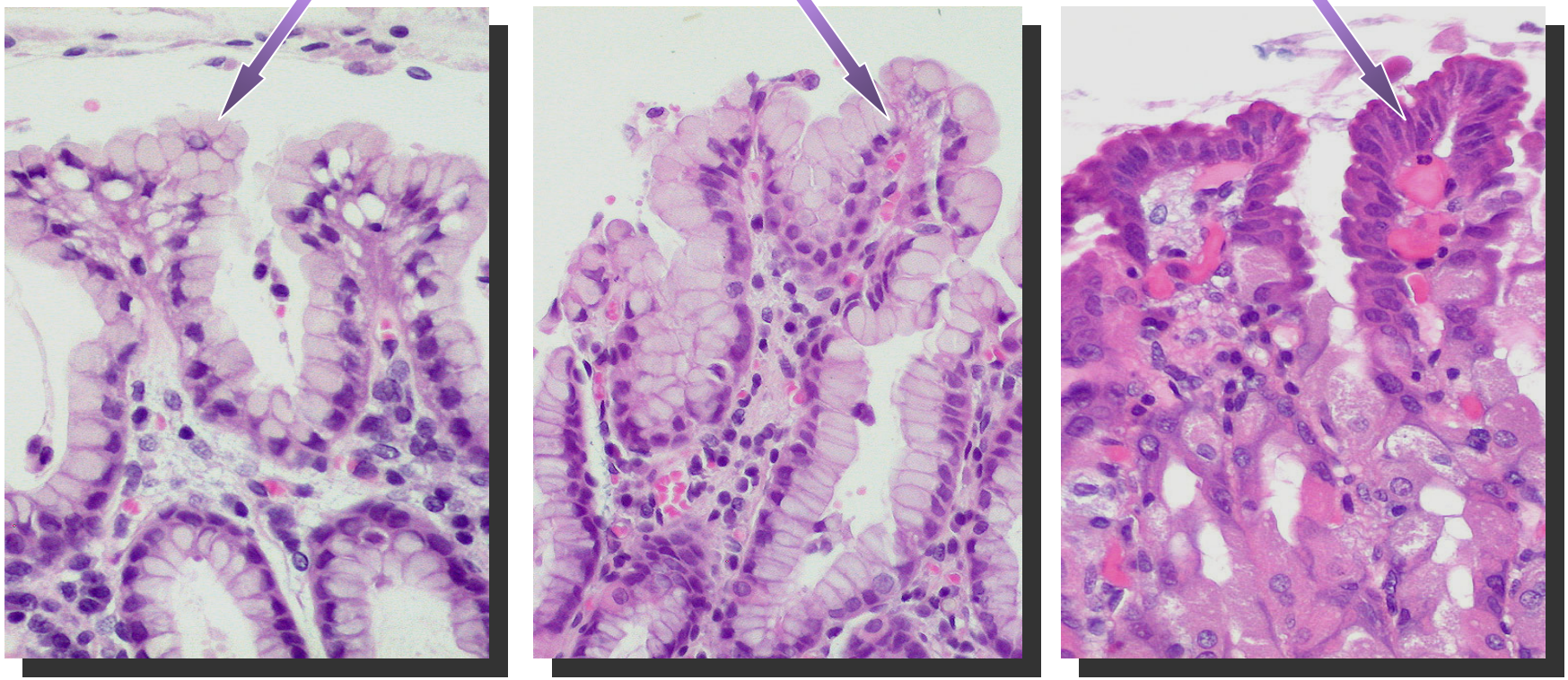


GENETIC DEFECT?
(we have been studying this without success)

In the setting of Hereditary Diffuse Gastric Carcinoma (HDGC)

Foveolar hyperplasia,
tufting and glogoid change

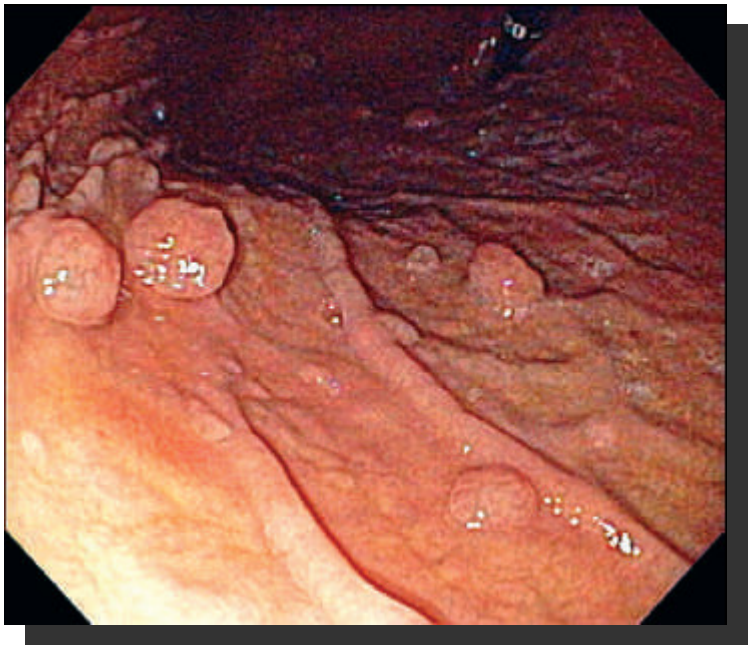
Epithelial atypia

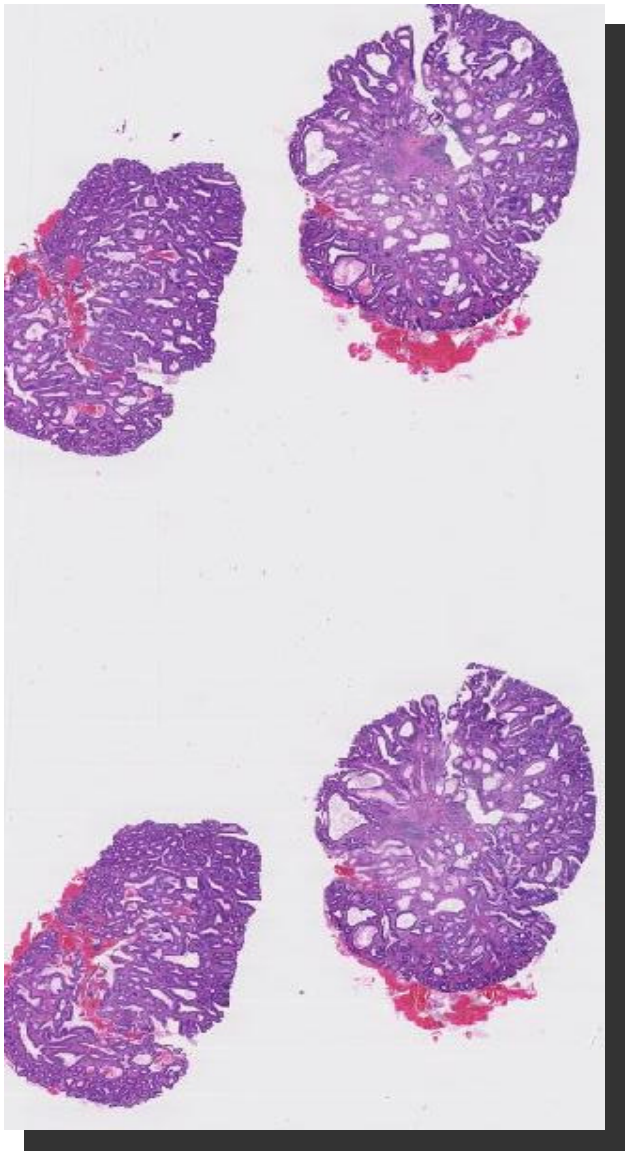


Huntsman D, Carneiro F, Lewis F *et al*
N Engl J Med 344: 1904, 2001

Carneiro F, Huntsman D, Smyrk T *et al*
J Pathol 203:681, 2004

Fundic gland polyps





- Most frequent gastric polyps (75%)
- Prevalence in population (3%-11%)
- Smooth, circumscribed elevations in the body-fundic oxyntic mucosa

- Cystically dilated oxyntic glands; foveolar epithelium at the surface.

The fundic gland polyps and polyposes

- Sporadic, single
- Sporadic, multiple, associated to PPIs
- Familial, in the setting of FAP
- Familial, not associated with FAP

- More recently: GAPPS

FAP: Familial adenomatous polyposis

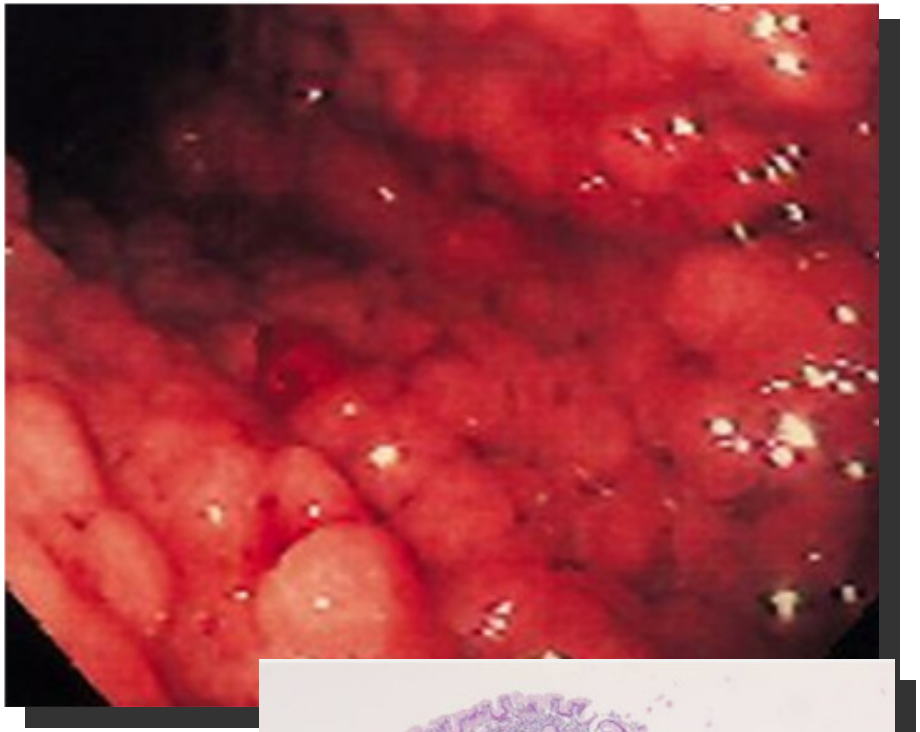
Mutations in the *APC* – β-catenin pathway have been encountered in sporadic and syndromic fundic gland polyps:

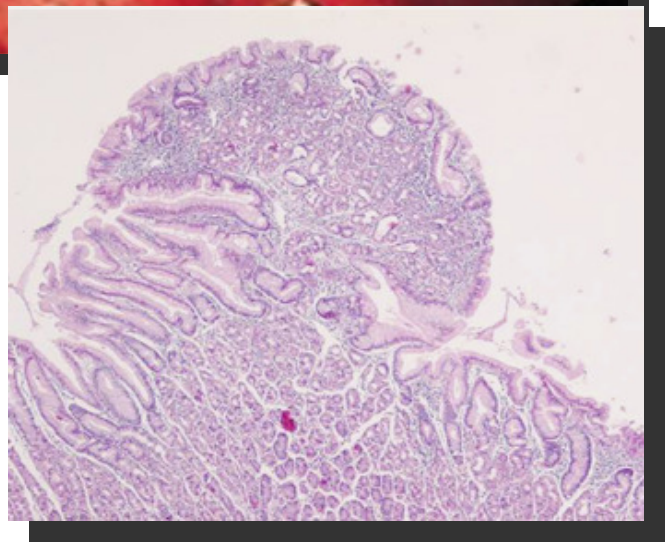
FAP: *APC* germline mutations (90%)
APC somatic mutations (75%)

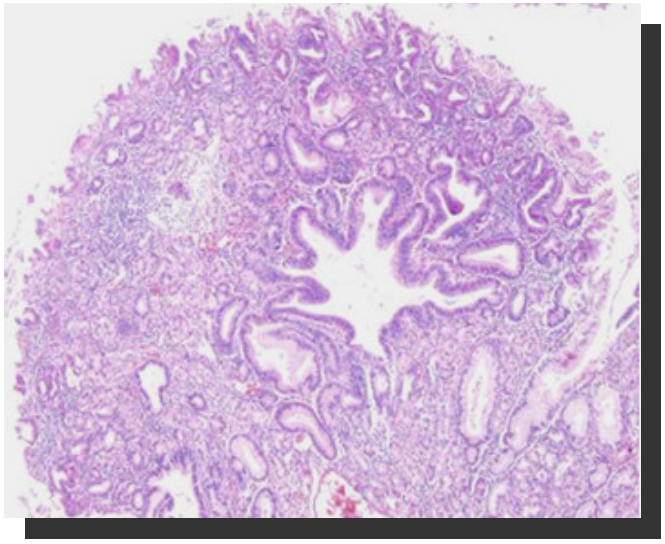
Sporadic FGPs:
Somatic mutations of β-catenin (65% - 90%)
Somatic mutations of *APC* (rare cases)*

* Increased risk of dysplasia

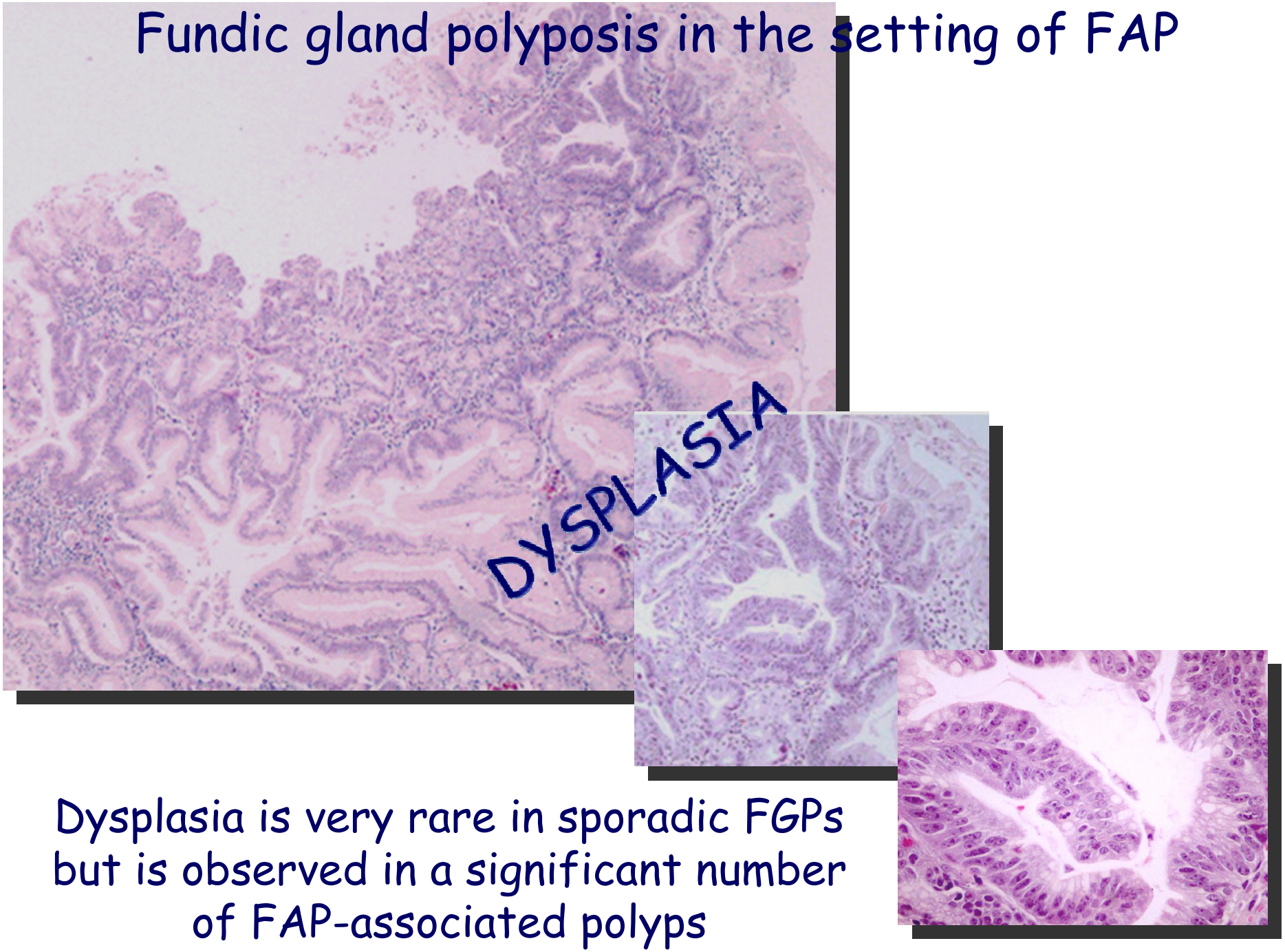
Fundic gland polyposis in the setting of FAP





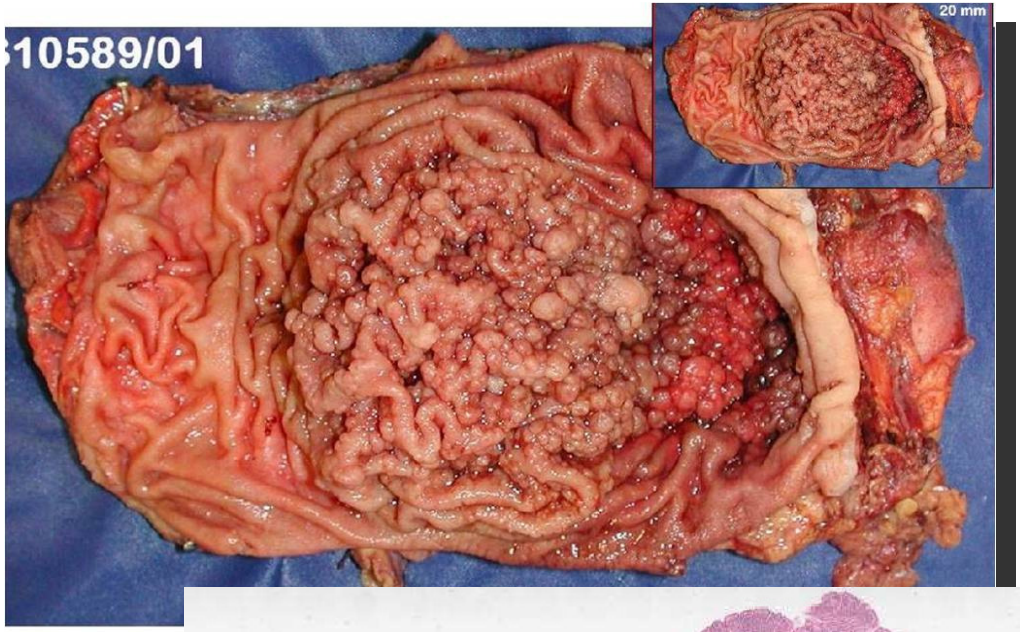


Fundic gland polyposis in the setting of FAP

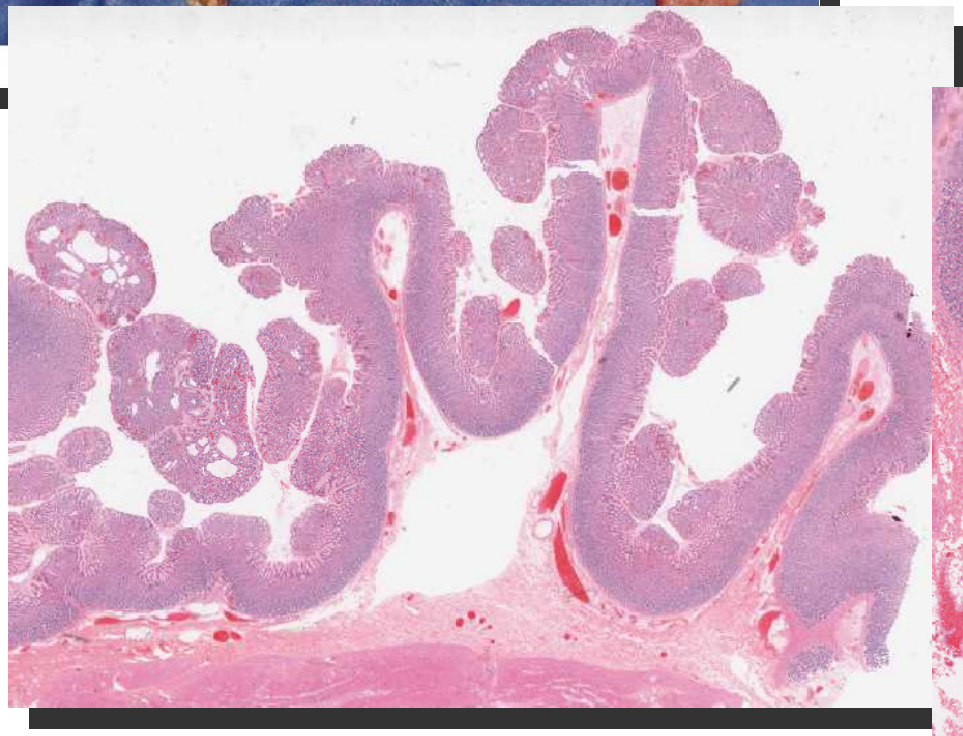


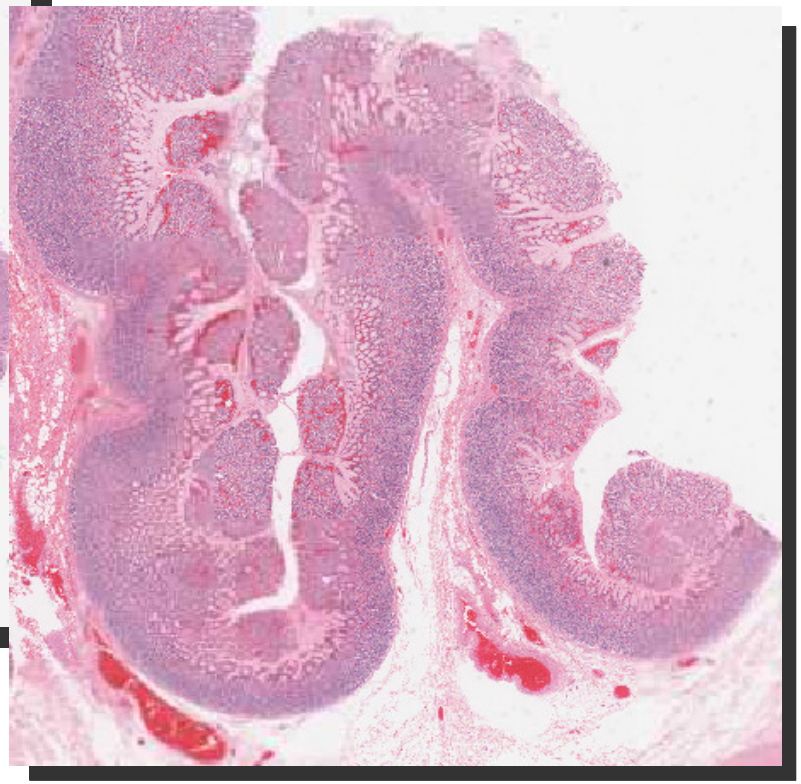
Dysplasia is very rare in sporadic FGPs but is observed in a significant number of FAP-associated polyps

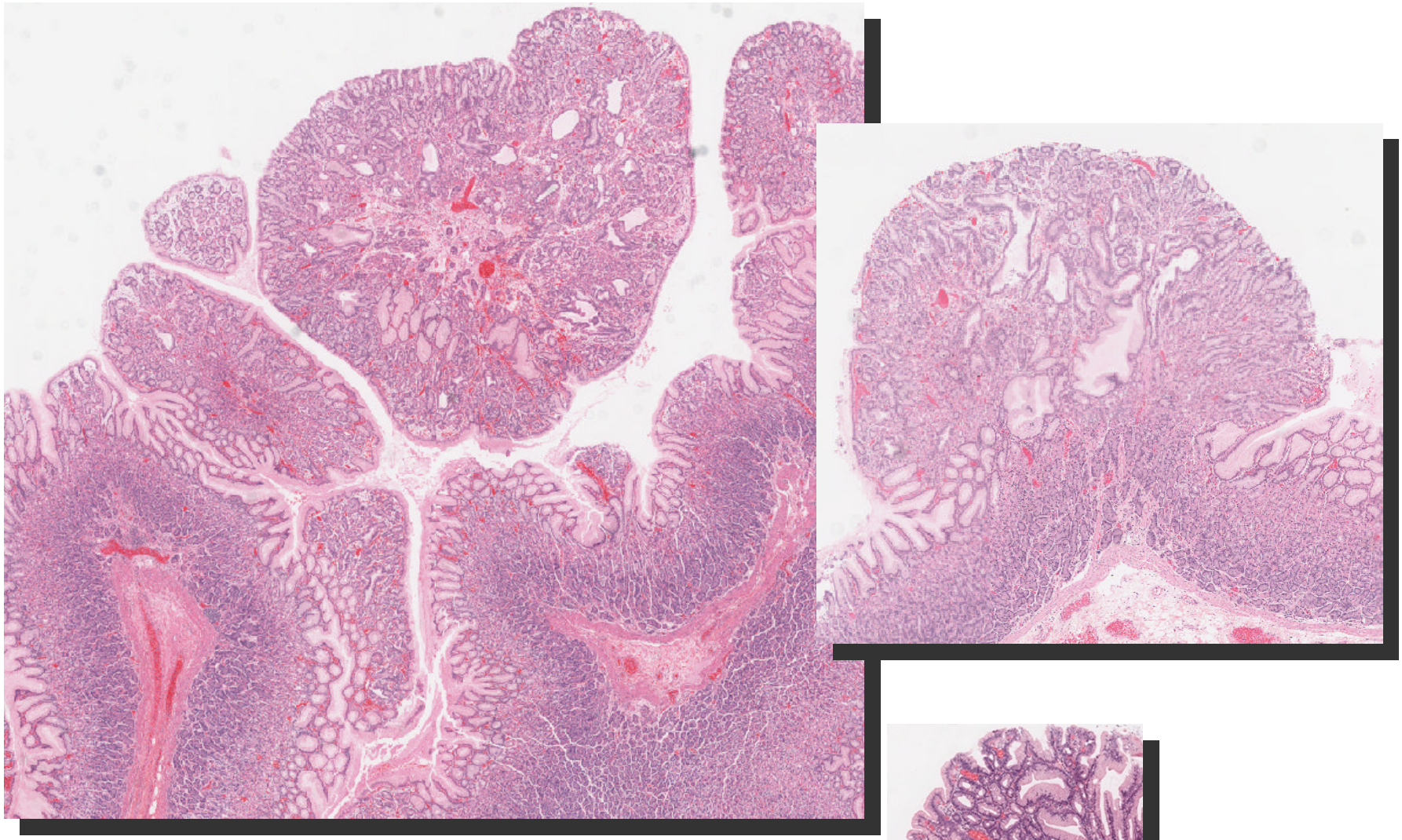
The brand new GAPPS syndrome…



Proximal polyposis of the stomach

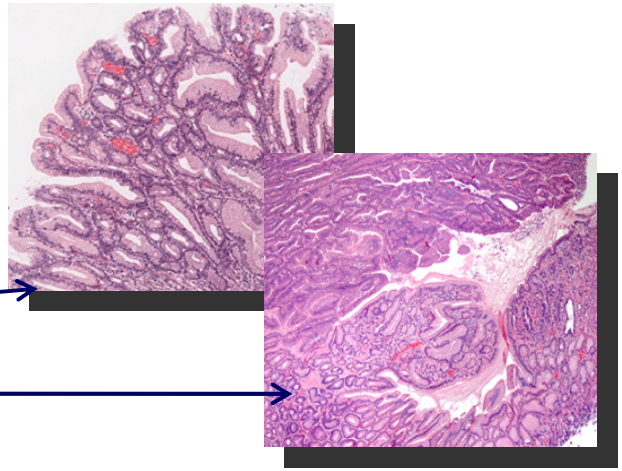


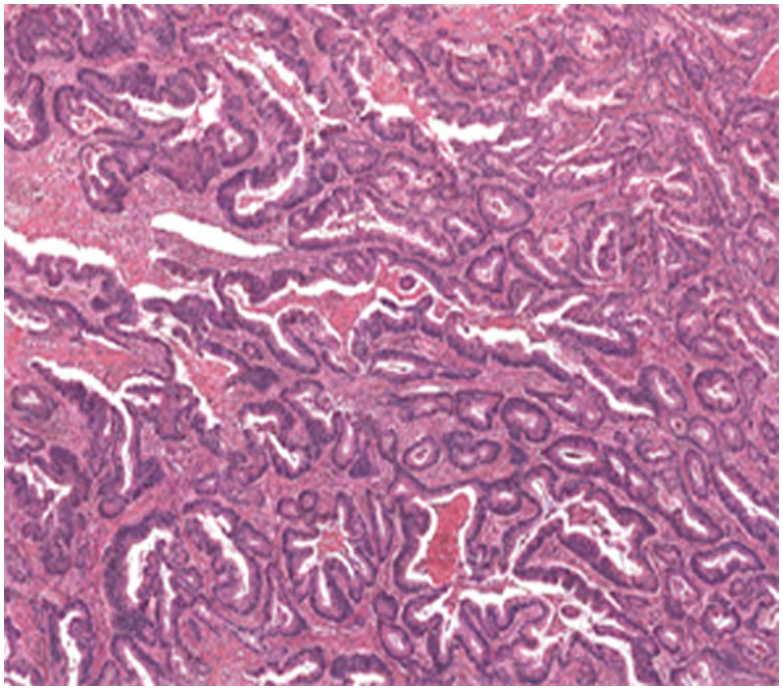


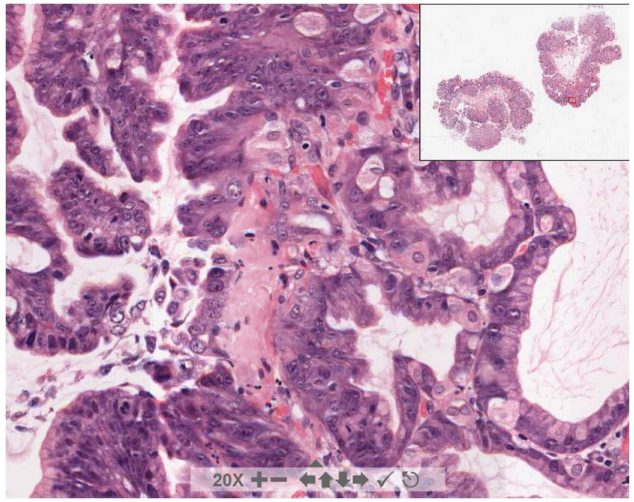


Proximal polyposis of the stomach:

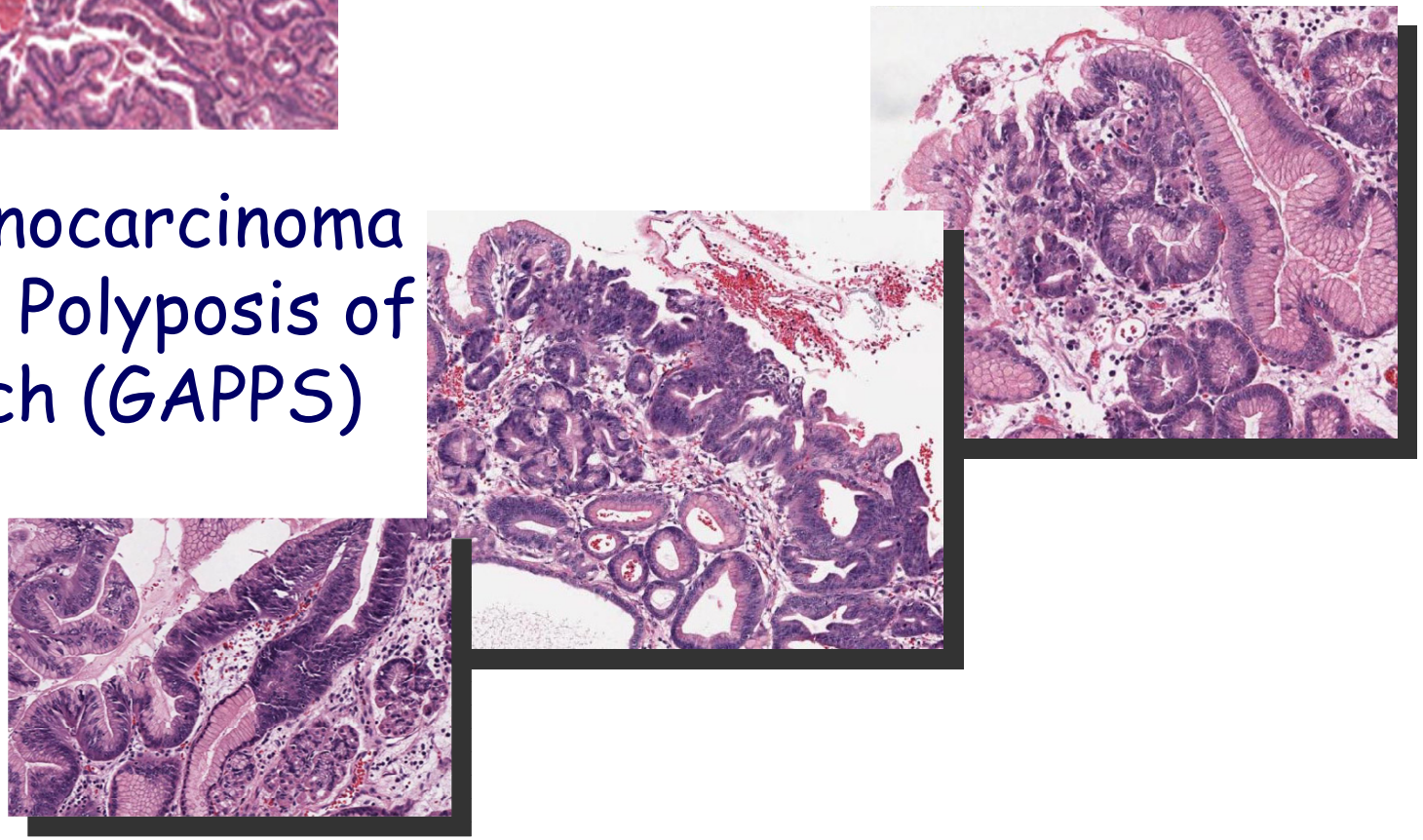
- Fundic gland polyps (predominant)
- Hyperplastic (rare)
- Adenomatous (rare)





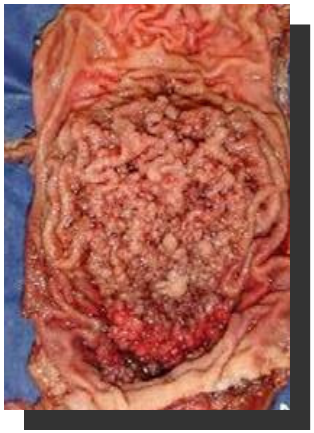


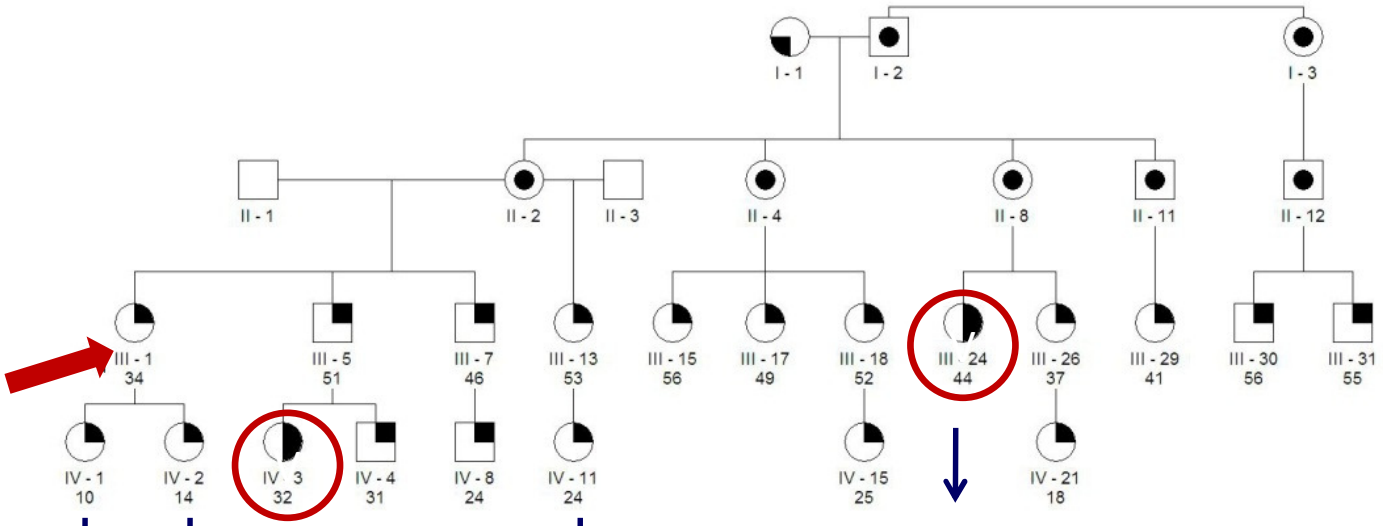
Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS)



Family 1

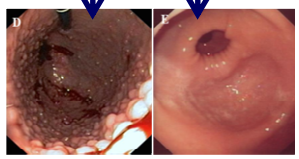
FGP

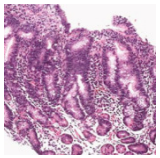




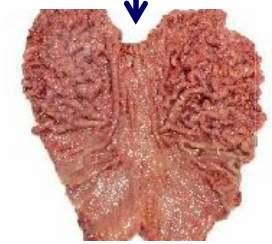
Proband

FGP

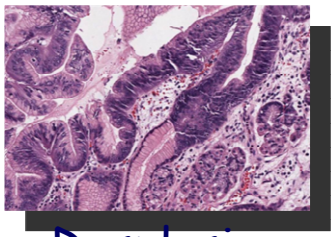




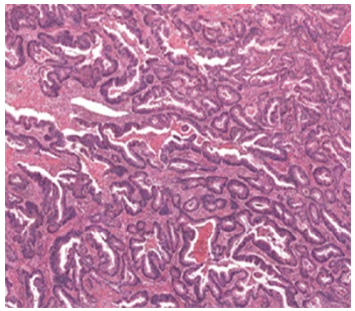
Dysplasia



FGP

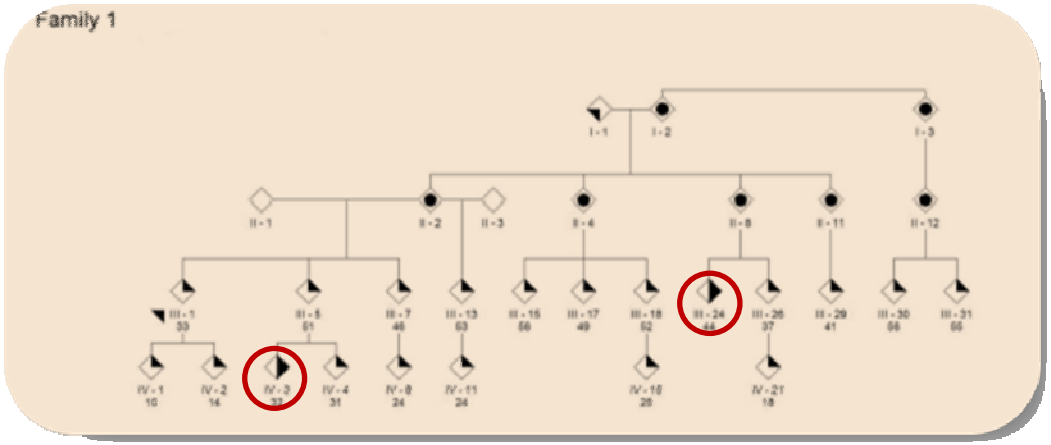


Dysplasia



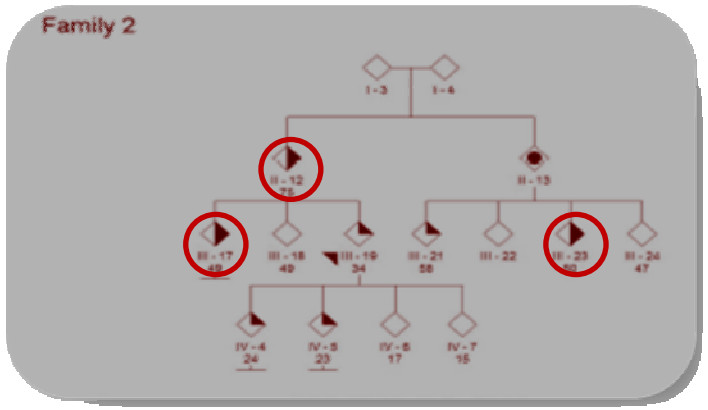
Gastric Adenocarcinoma

FGPs in 20 family members

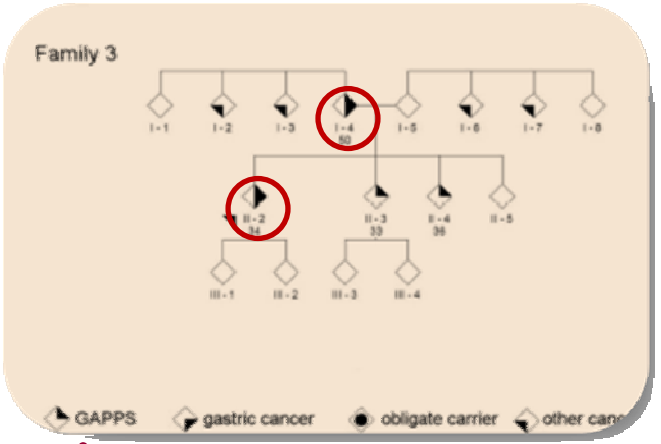


Family 1 – Australian Caucasian
- Fundic gland polyposis
- Two cases of intestinal type adenocarcinoma
- No significant colorectal pathology

Family 2 – Caucasian American
- Fundic gland polyposis
- Three cases of intestinal type adenocarcinoma
- No significant colorectal pathology



Family 3 - Caucasian Canadian
- Fundic gland polyposis
- Two cases of intestinal type adenocarcinoma
- Normal colonoscopies



Autosomal dominant pattern of inheritance.

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome

D L Worthley,[1] K D Phillips,[2] N Wayte,[3] K A Schrader,[4] S Healey,[5] P Kaurah,[4] A Shulkes,[6] F Grimpen,[7] A Clouston,[7] D Moore,[8] D Cullen,[9] D Ormonde,[9] D Mounkley,[10] X Wen,[11] N Lindor,[11] F Carneiro,[11] D G Huntsman,[4] G Chenevix-Trench,[5] G K Suthers[2,12]

[1]Division of Digestive and Liver Diseases, Columbia University, New York, New York, USA
[2]SA Clinical Genetics Service, SA Pathology, South Australia, Australia
[3]School of Medicine, University of Queensland, Queensland, Australia
[4]Hereditary Cancer Program, BC Cancer Agency, British Columbia, Canada
[5]Queensland Institute of Medical Research, Queensland, Australia
[6]Department of Surgery, University of Melbourne, Victoria, Australia
[7]Royal Brisbane and Women's Hospital, Queensland, Australia
[8]Women's and Children's Hospital, South Australia, Australia
[9]St John of God Hospital, Western Australia, Australia
[10]Flinders Medical Centre, South Australia, Australia
[11]Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP) and Medical Faculty/Hospital S. João, Porto, Portugal
[12]

ABSTRACT

Objective The purpose of this study was the clinical and pathological characterisation of a new autosomal dominant gastric polyposis syndrome, gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS).

Methods Case series were examined, documenting GAPPS in three families from Australia, the USA and Canada. The affected families were identified through referral to centralised clinical genetics centres.

Results The report identifies the clinical and pathological features of this syndrome, including the predominant dysplastic fundic gland polyp histology, the exclusive involvement of the gastric body and fundus, the apparent inverse association with current *Helicobacter pylori* infection and the autosomal dominant mode of inheritance.

Conclusions GAPPS is a unique gastric polyposis syndrome with a significant risk of gastric adenocarcinoma. It is characterised by the autosomal dominant transmission of fundic gland polyposis, including areas of dysplasia or intestinal-type gastric adenocarcinoma, restricted to the proximal stomach, and with no evidence of colorectal or duodenal polyposis or other heritable gastrointestinal cancer syndromes.

include *MUTYH*-associated polyposis (MAP), generalised juvenile polyposis syndrome (GJPS), Peutz Jeghers syndrome (PJS) and Cowden syndrome.[5 6] However, FGPs are relatively rare in MAP, an autosomal recessive disorder, and GJPS and PJS are often characterised by the presence of specific hamartomatous (rather than purely dysplastic fundic gland) polyps.[5 6]

Sporadic FGPs are usually innocuous, but syndromic FGPs can progress to dysplasia and gastric adenocarcinoma.[7 9] Therefore, clinicians must distinguish patients with sporadic versus syndromic fundic gland polyposis so that additional scrutiny is provided for the latter without subjecting the majority of patients to needless investigation.

Here we describe a new autosomal dominant syndrome characterised by fundic gland polyposis and gastric cancer. We refer to the syndrome as gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). This report documents the detailed clinical and pathological features of GAPPS in a large Australian family and in two smaller North American families. We propose diagnostic criteria and management strategies for GAPPS and examine potential factors that may contribute to the pathogenesis.

Diagnostic criteria for GAPPS

i)gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis;

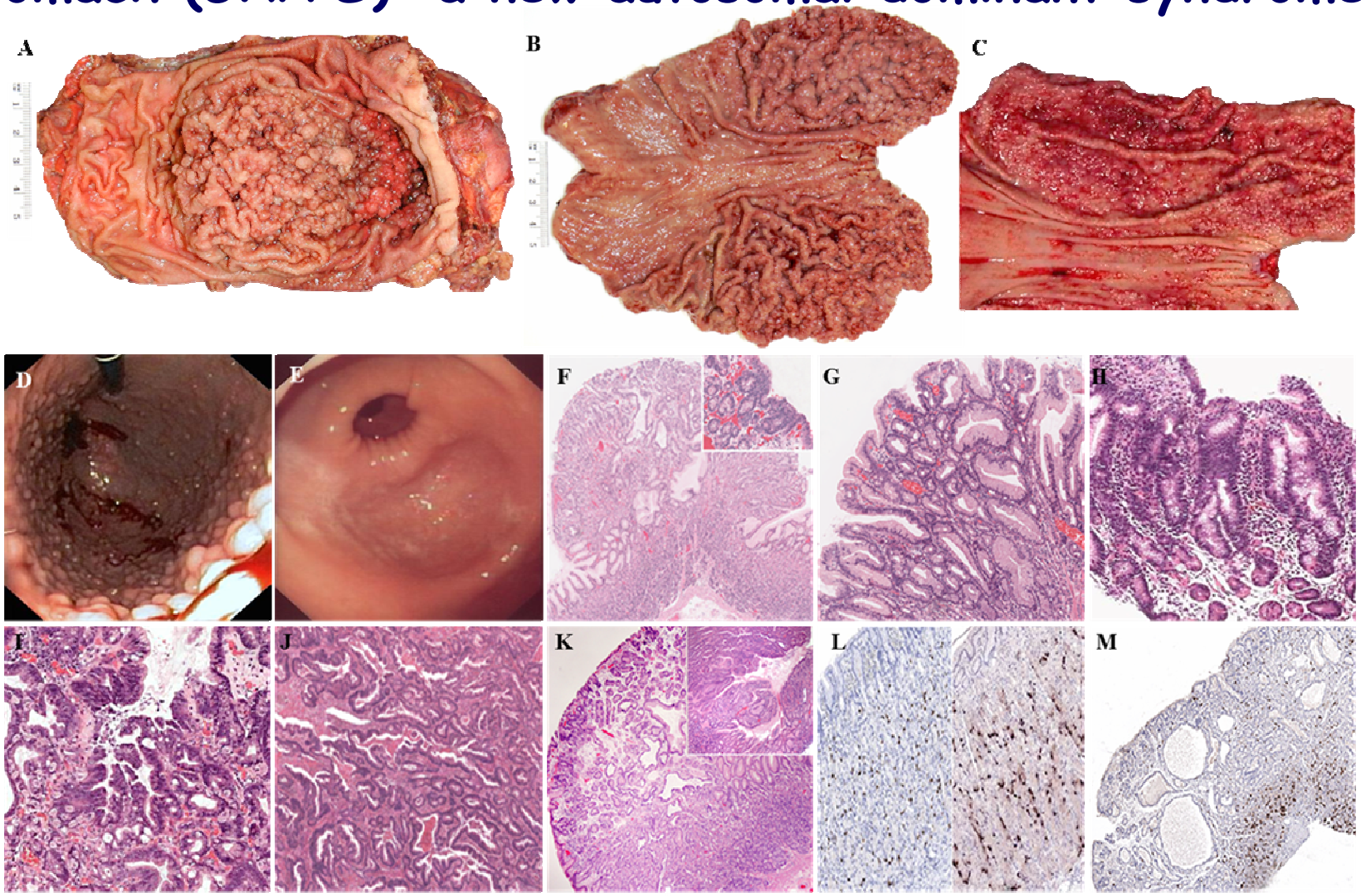
ii) >100 polyps carpeting the proximal stomach in the index case or >30 polyps in a first degree relative of another case;

iii) predominantly FGPs, some having regions of dysplasia (or a family member with either dysplastic FGPs or gastric adenocarcinoma);

iv) an autosomal dominant pattern of inheritance.

Exclusions include other heritable gastric polyposis syndromes and use of PPIs. In patients on PPIs it is

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS): a new autosomal dominant syndrome.



Worthley et al; Gut 61:774-779, 2012

Now in the search of the genetic defect…

Mutations were excluded in the following genes:

- *APC*
- *MUTYH*
- *CDH1*
- *SMAD4*
- *BMPR1A*
- *STK11*
- *PTEN*

Gut Online First, published on October 25, 2011 as 10.1136/gutjnl-2011-301384

LETTER

Familial fundic gland polyposis with gastric cancer

We read with interest the article by Worthley *et al*[1] regarding a new autosomal dominant syndrome characterised by fundic gland polyposis (FGP) and gastric cancer, which was not associated with familial adenomatous polyposis (FAP). We have experienced two similar cases of gastric adenocarcinoma occurring in pedigrees with familial FGP without FAP.

CASE 1

A 56-year-old woman was referred to our institution for further investigation of her multiple gastric polyps. On admission, serology and ^{13}C urea breath test yielded negative results for *Helicobacter pylori*. Upper gastrointestinal endoscopy revealed numerous fundic gland polyps covering the gastric fundus and corpus (figure 1A). In the fundus, there was also a flat and discoloured area circumscribed by polyps (figure 1B). A biopsy from the area revealed well-differentiated adenocarcinoma. No other polyps or adenomas were found in the duodenum. The colonoscopy did not show any colorectal lesions and the CT scan of the chest and abdomen was normal. A total gastrectomy was performed. Macroscopically, there were numerous small polypoid lesions. There was also a discoloured area measuring 6×5.5 cm in the gastric fundus (figure 1C). Histologically, numerous small fundic gland polyps were diffusely distributed (figure 1D). The tumour was a well-differentiated adenocarcinoma focally invading the superficial portion of the submucosa (figure 1E). Since hereditary hamartomatous polyposis was suspected, we performed an upper endoscopy on seven other family members: two sisters, one brother, two daughters, one son and one nephew. As a result, five of the seven subjects had similar gastric FGP (figure 2).

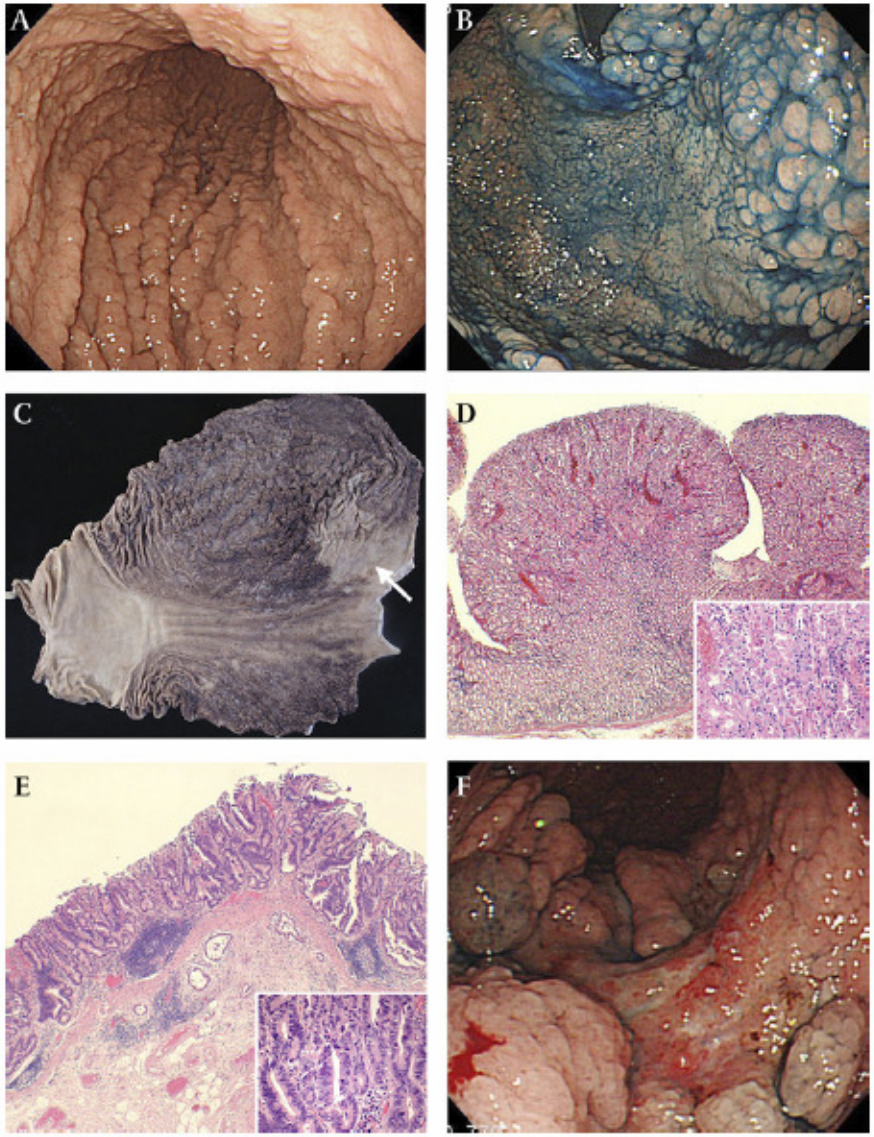


Figure 1 Endoscopic and pathological findings. (A and B) Case 1. Endoscopic images reveal numerous fundic gland polyps in the corpus (A), while a flat area circumscribed by polyps can be seen in the fundus (B). (C) Macroscopic finding of the gastrectomy specimen showing numerous

Autosomal dominant pattern of inheritance for FGP.

Negative for the germline mutation of:

- *APC*
- ß-catenin
- *MADH4*
- *BMPR1A*

GAPPS is an autosomal dominant
gastric cancer syndrome,
genetic cause unknown

"The authors would welcome notification of any families that fulfil the GAPPS criteria so that, through collaboration, the genetic basis of this novel and challenging syndrome can be found"

Worthley et al; Gut 61:774, 2012

Familial gastric cancer

- Sporadic (90%)
- Familial Aggregation (10%)
  - Familial Gastric Cancer (FGC)
  - Familial Intestinal Gastric Cancer (FIGC)
  - Familial Diffuse Gastric Cancer (FDGC)
- Hereditary (1%?)
  - Hereditary Diffuse Gastric Cancer (HDGC)
  - Gastric Adenocarcinoma and Proximal Polyposis of the Stomach – GAPPS (HIGC)

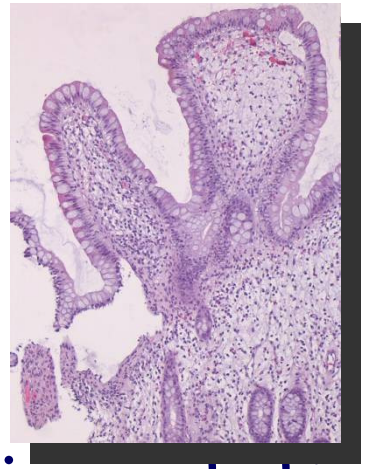
Other polyposis syndromes may affect the stomach and often present with manifestations unrelated to gastric polyps

- Cronkhite-Canada
- Cowden syndrome (*PTEN*)
- Peutz-Jeghers polyposis (*STK11/LKB1*)
- Juvenile polyposis (*SMAD4 or BMPR1A*)

Similar morphological features

Cronkhite-Canada Syndrome

Rare, noninherited GI polyposis (pathogenesis? autoimmune mechanism?)



- Malabsorption, diarrhea, hypoproteinemia, and weight loss
- Ectodermal changes: alopecia, skin pigmentation, onychodstrophy
- Gastric polyps can not be distinguished from hyperplastic polyps, with foveolar hyperplasia, cystic glands, and stromal inflammation

Cowden Disease

Component of PTEN hamartoma syndrome, caused by germline mutations (deletion of #10):

- Bannayan-Riley-Ruvalcaba syndrome
- Proteus syndrome
- Cowden disease:

  Endodermal, mesodermal, and ectodermal alterations with hamartomas in various organs and GI polyps (35%-65%)

.

  Polyps are similar to hyperplastic polyps (cystic glands with papillary infoldings)

  Increased risk for cancer (breast, thyroid, urogenital, stomach)

Peutz-Jeghers syndrome

Autosomal dominant, caused by germline mutations of STK11/LKB1 gene

- The PJ polyps are more frequent in the small intestine (90%), than in the colon (78%) and stomach (74%)

- In the stomach PJ polyps tend to be sessile; polyps display branching bundles of smooth muscle, and the epithelium is frequently dysplastic (DD: hyperplastic polyps)

Solitary PJ gastric polyps have been described

Juvenile Polyposis

Autosomal dominant, caused by germline mutations of SMAD4 or BMPR1A genes (implicated in the TGFβ-signaling pathway)

- Multiple juvenile polyps throughout the GI
- In the stomach PJ polyps tend to localize in the antrum, but occur also in the body/fundus
- Indistinguishable from hyperplastic polyps and only suspected when multiple or associated with juvenile polyps elsewhere in the GI

Morphologic Characterization of Syndromic Gastric Polyps

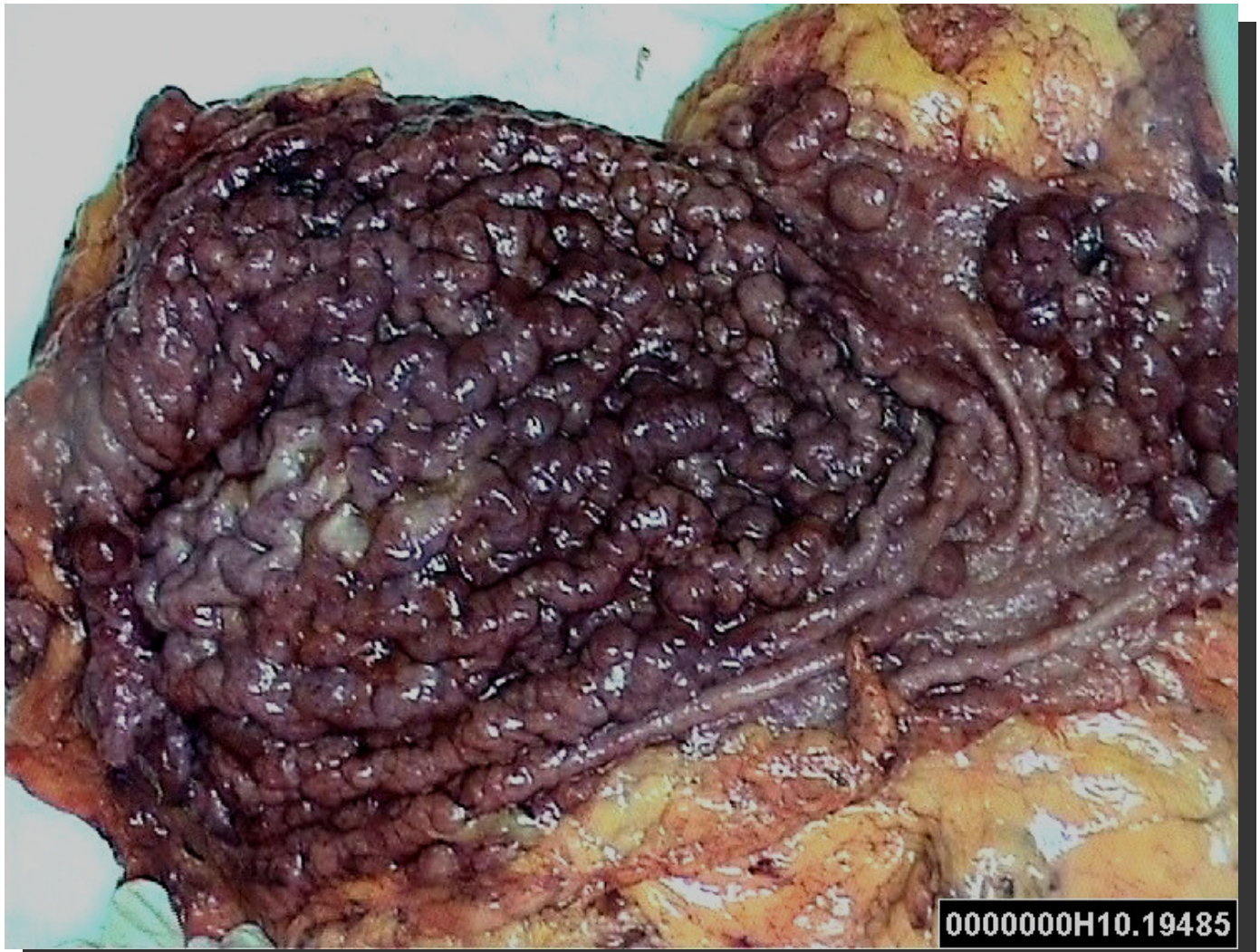
Dora Lam-Himlin, MD, Jason Y. Park, MD, PhD, Toby C. Cornish, MD, PhD, Chanjuan Shi, MD, PhD, and Elizabeth Montgomery, MD

Abstract: The morphology of gastric hamartomatous polyps from patients with juvenile polyposis syndrome (JuvPS) and Peutz-Jeghers' Syndrome (PJS) is poorly characterized. We investigated the histologic features of gastric polyps in patients with established JuvPS or PJS to develop improved histologic criteria to distinguish these from gastric hyperplastic (HP) polyps. The patients with clinically confirmed hamartomatous polyposis syndromes were identified, including 26 patients with JuvPS (both familial and sporadic) and 17 patients with PJS. All gastric polyps (n = 30) from these patients were intermixed with gastric HP polyps from nonsyndromic patients (n = 26) and yielded an accuracy of only 54%. The accuracy did not improve when results were stratified for polyp location but did with biopsy size which were more than equal to10 mm. Whereas these syndromic polyps are readily diagnosed in the small bowel and colon, histologic features to distinguish gastric JuvPS and PJS from gastric HP polyps are unreliable.

Key Words: juvenile polyposis, Peutz-Jeghers' syndrome, Cronkhite-Canada syndrome, gastric polyps, hyperplastic polyps, stomach

(*Am J Surg Pathol* 2010;34:1656–1662)

Whereas JuvPS and PJS are readily diagnosed in the small bowel and colon, histologic features to distinguish them from gastric Hyperplastic polyps (HP) are unreliable.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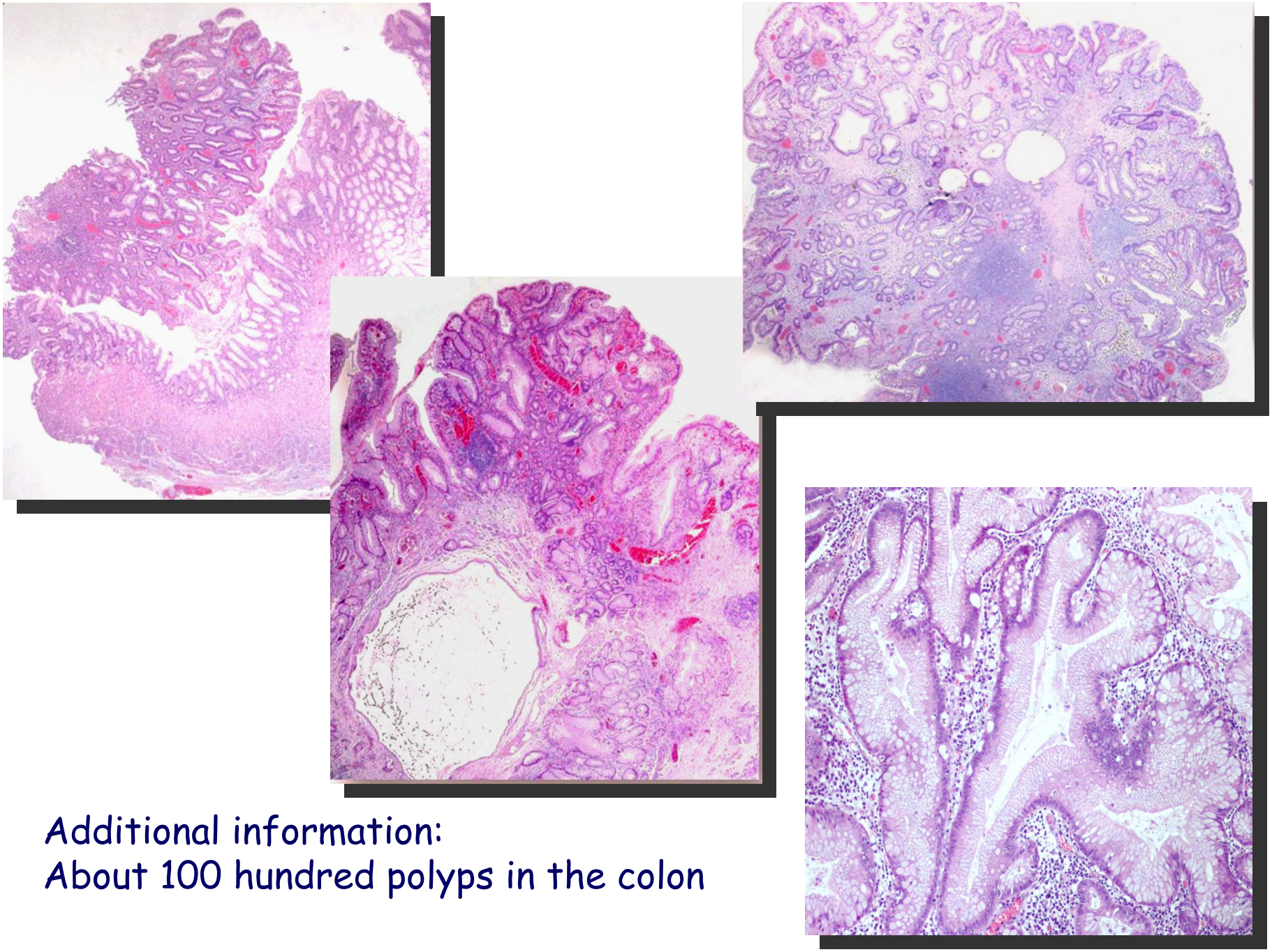
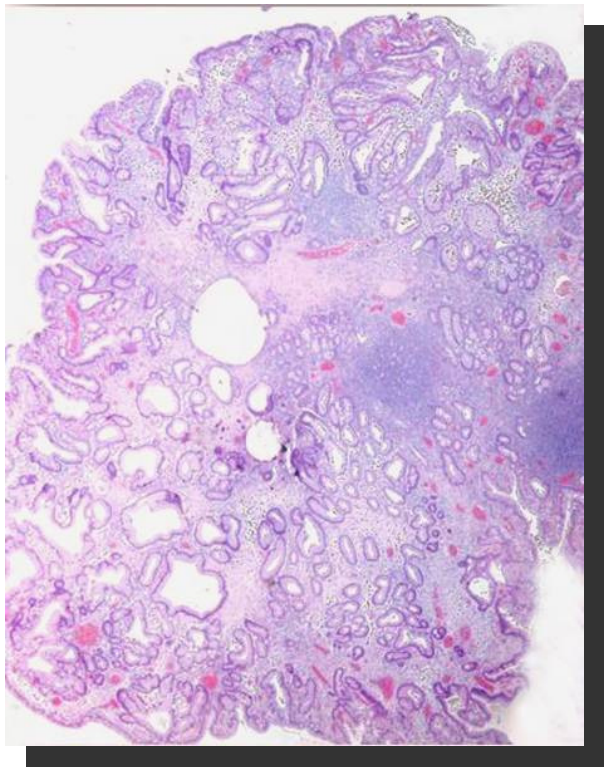
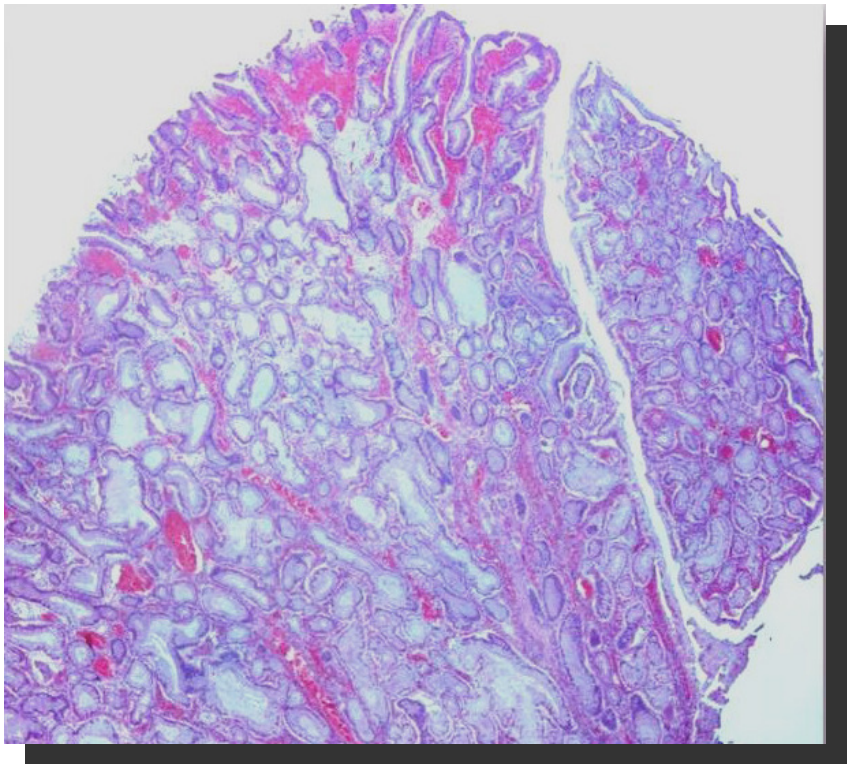


Additional information:
About 100 hundred polyps in the colon

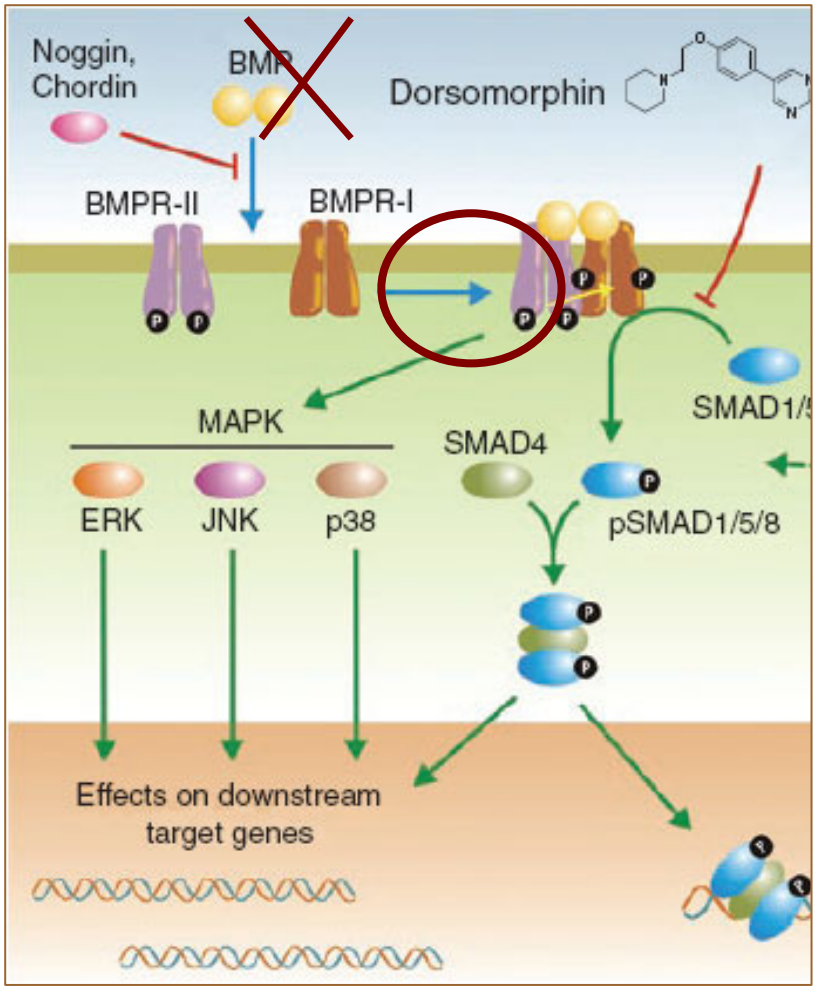
Additional information:
About 100 hundred polyps in the colon



Gastric polyp



Colonic polyp



Juvenile/hyperplastic polyposis (SMAD4)

Juvenile Polyposis

Genes (germline mutations):

- *SMAD4*
- *BMPR1A*

43% (identified by sequencing or MLPA)

- Other not yet described germline mutations?
- Mutations in regulatory regions?
- ENG?

57%

Sub-types:

- Juvenile polyposis *coli*
- Juvenile polyposis of infancy
- Generalized juvenile polyposis
- Massive gastric juvenile polyposis

Thanks for your attention

Save the Date

25th European Congress of Pathology

31 August – 4 September 2013
in Lisbon, Portugal

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