HEREDITARY GASTRIC CANCER

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DISCLOSURE OF INTEREST

No conflicts of interest to declare
Genetic tumour syndromes of the digestive system

15.0: Genetic tumour syndromes of the digestive system: Introduction

15.1: Genetics

15.1.1: Genetic tumour syndromes of the digestive system
  15.1.1.1: GAPPS and other fundic gland polyposes
  15.1.1.2: Hereditary diffuse gastric cancer
  15.1.1.3: Lynch syndrome
  15.1.1.4: Familial adenomatous polyposis 1
  15.1.1.5: Other adenomatous polyposes
  15.1.1.6: Serrated polyposis
  15.1.1.7: Familial pancreatic cancer
  15.1.1.8: Juvenile polyposis syndrome
  15.1.1.9: Peutz-Jeghers syndrome
  15.1.1.10: Cowden syndrome
  15.1.1.11: Other genetic tumour syndromes
Review article

Hereditary gastrointestinal carcinomas and their precursors: An algorithm for genetic testing

Clothaire P.E. Spoto\textsuperscript{a,1}, Irene Gullo\textsuperscript{b,1}, Fatima Carneiro\textsuperscript{b}, Elizabeth A. Montgomery\textsuperscript{c}, Lodewijk A.A. Brosens\textsuperscript{a,6}

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Emerging Concepts in Gastric Neoplasia
Heritable Gastric Cancers and Polyposis Disorders

Rachel S. van der Post, MD\textsuperscript{a,6,*}, Fátima Carneiro, MD, PhD\textsuperscript{b,c,d,e}
FAMILIAL/HEREDITARY GASTRIC CANCER
– THREE MAIN SYNDROMES –

• **Hereditary Diffuse Gastric Cancer**
  
  **HDGC - CDH1** germline mutations mainly
  
  Guilford P et al, Nat Genetics 1998

• **Gastric Adenocarcinoma and Proximal Polyposis of the Stomach**
  
  **GAPPS - APC** promoter germline mutations
  
  Worthley et al, Gut 2012

• **Familial Intestinal Gastric Cancer**
  
  **FIGC - NO CAUSE** identified to date
  
MAORI KINDRED

E-cadherin gene (CDH1) *germline mutations

Hereditary Diffuse Gastric Cancer (HDGC)

*Gene map locus: 16q22.1 (MIM ID +192090)

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Tis</th>
<th>T1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosa</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>Muscularis mucosa</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>Submucosa</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
</tbody>
</table>

**In situ carcinoma**

**Pagetoid spread**

**T1a intramucosal signet-ring cell**

**HEREDITARY DIFFUSE GASTRIC CANCER**

WHO Classification of Tumours - 5th Edition

Digestive System Tumours

Edited by the WHO Classification of Tumours Editorial Board

HEREDITARY – *CDH1* germline mutations
Clinically actionable variants (P, LP) are shown in the top; VUS, LB, and B variants are shown in the bottom. TM = transmembrane domain.
**CDH1 INACTIVATION MECHANISM IN HDGC FAMILIES WITH CLINICAL UTILITY**

- **1998/2002**
  - CTNNA1 (~10 families)
  - PALB2 (very rare)
  - TP53 (very rare)
  - BRCA2 (very rare)
  - ATM (rare; controversial)
  - MAP3K6 (rare; controversial)
  - STK11 (very, very rare)
  - MYD88 (very rare; controversial)

- **2018**
  - Screening of CDH1 deletions adopted worldwide
  - Targeted DNAseq and Exome seq in hundreds of probands identified few new candidate genes

**Screening of CDH1 deletions**

- CDH1 negative 60%
- CDH1 deletions 4%
- CDH1 mutations 56%
- Other mutations 6%

**IGCLC criteria validation**

Guilford et al., Nat Genet 1998
Gayther et al, Cancer Res 1999
Oliveira et al, Hum Mutat 2002
Oliveira C et al, EJC 2004
Oliveira C et al, HMG 2009
Pinheiro H et al, HMG 2010
Pinheiro H et al, HMG 2012
Majewsky U et al, J Pathol 2013
Hansford S et al, JAMA Oncol 2015
Vogelaar IP et al, Fam Cancer 2015
Donner I et al, Fam Cancer 2015
Oliveira et al, Lancet Oncol 2015
Vogelaar IP et al, EJHG 2017
Weren RDA et al, JMG 2018
Sahasrabudhe et al, Gastroenterology. 2017
Fewings E et al, Lancet Gastroenterol Hepatol. 2018
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene Mutation</th>
<th>Mode of Inheritance</th>
<th>Gastric Cancer Lifetime Risk</th>
<th>Histology</th>
<th>Associated Malignancies</th>
<th>Important Histologic Clues</th>
<th>Important Clinical Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary diffuse gastric cancer associated with ( CDH1 ) germline mutation</td>
<td>( CDH1 )</td>
<td>Autosomal dominant</td>
<td>70%–80%</td>
<td>Diffuse</td>
<td>Lobular breast cancer</td>
<td>Mucosal foci Abnormal E-cadherin immunostaining</td>
<td>Familial clustering, lobular breast cancer, young age of diagnosis, cleft lip/palate</td>
</tr>
<tr>
<td>Hereditary diffuse gastric cancer associated with ( CTNNA1 ) germline mutation</td>
<td>( CTNNA1 )</td>
<td>Autosomal dominant</td>
<td>Unknown</td>
<td>Diffuse</td>
<td>None</td>
<td>Abnormal a-E-catenin immunostaining</td>
<td>Familial clustering and/or young age of diagnosis</td>
</tr>
<tr>
<td>Familial intestinal gastric cancer</td>
<td>None</td>
<td>Autosomal dominant</td>
<td>Unknown</td>
<td>Intestinal</td>
<td>None</td>
<td>Unknown</td>
<td>Familial clustering of without polyposis</td>
</tr>
</tbody>
</table>
Familial gastric cancer: genetic susceptibility, pathology, and implications for management

Oliveira et al, Lancet Oncology 16(2):e60-70, 2015
Familial gastric cancer: genetic susceptibility, pathology, and implications for management

Primary Tumor

- Promoter Hypermethylation

- Loss of Heterozygosity (LOH)

- LOH & Promoter Hypermethylation
- Promoter Hypermethylation

- LOH & Promoter Hypermethylation

- Somatic Mutation

- Somatic Mutation & Promoter Hypermethylation

Oliveira et al; Lancet Oncology 16(2):e60-70, 2015
HDGC – CLINICAL MANAGEMENT AND STRATEGIES

1. Identification of patients and families at risk of developing HDGC that fulfil HDGC clinical criteria and may exhibit other HDGC-related features (CL/P or LBC)

2. Genetic testing to identify the causative germline defect

3. Integration in a program for risk assessment and risk reduction measures

CDH1 germline mutation carriers

- Diffuse gastric cancer
  1º - Risk reduction gastrectomy (indicated)
  2º - Surveillance with gastroscopy and multiple biopsing (controversial)

- Lobular breast cancer
  1º - Bilateral surveillance from age 30 with MRI and surgery to remove early lesions (indicated)
  2º - Prophylactic mastectomy (controversial)

Caldas & The IGCLC et al, J Med Genet 1999
Fitzgerald R & IGCLC, J Med Genet 2010
van der Post R & IGCLC, J Med Genet 2015

Abstract
Around 10-20% of gastric cancer patients have relatives with a diagnosis of GC and in 1-3% of patients a genetic cause can be confirmed. Histopathologically, GC is classified into intestinal-type, with glandular growth, and diffuse-type with poorly cohesive growth pattern often with signet ring cells. Familial or hereditary GC is classified into hereditary diffuse GC (HDGC), familial intestinal GC (FIGC) and polyposis forms. This review focuses on recent research findings and new concepts of hereditary GC.

KEYWORDS: E-Cadherin; Hereditary diffuse gastric cancer; Stomach
ESMO CLINICAL GUIDELINES FOR HEREDITARY GI CANCERS

Key message: This ESMO Clinical Practice Guidelines provide updated recommendations on the management of Hereditary gastrointestinal cancers (diagnosis, treatment and follow-up).

These guidelines summarize the evidence-based data on hereditary colorectal cancer (CRC), gastric cancer (GC) and pancreatic cancer (PC) and provide useful clinical recommendations for identification and management of patients with hereditary gastrointestinal cancers.
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  **GAPPS** - **APC** promoter germline mutations
  
  Worthley et al, Gut 2012

• **Familial Intestinal Gastric Cancer**
  
  **FIGC** - **No cause** identified to date
  
  Caldas and the IGCLC, JMG 1999  
  Oliveira C et al, Lancet Oncol 2015
GASTRIC ADENOCARCINOMA AND PROXIMAL POLYPOSI
OF THE STOMACH (GAPPS): A NEW AUTOSOMAL DOMINANT SYNDROME.

Worthley et al; Gut 61:774-779, 2012
Mutations were excluded in the following genes:

- APC
- MUTYH
- CDH1
- SMAD4
- BMPR1A
- STK11
- PTEN
Point Mutations in Exon 1B of APC Reveal Gastric Adenocarcinoma and Proximal Polyposis of the Stomach as a Familial Adenomatous Polyposis Variant


The American Journal of Human Genetics (2016), http://dx.doi.org/10.1016/j.ajhg.2016.03.001
APC: Genotype – Phenotype correlations

- **Severe FAP**: (the colon is the main target)
- **Attenuated FAP**: (colon & stomach are the targets)
- **GAPPS**: (the stomach is the single target)
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene Mutation</th>
<th>Mode of Inheritance</th>
<th>Associated Gastric Polyps</th>
<th>Estimates of Gastric Cancer Lifetime Risk</th>
<th>Histology Gastric Cancer</th>
<th>Important Histologic Clues</th>
<th>Locations of Associated Other Malignancies</th>
<th>Important Clinical Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric adenocarcinoma with proximal polyposis</td>
<td>Point mutations in Exon 1B of APC</td>
<td>Autosomal dominant</td>
<td>Fundic gland polyps, few hyperplastic polyps and adenomas</td>
<td>Increased</td>
<td>Intestinal and mixed</td>
<td>Fundic gland polyposis with antral sparing</td>
<td>None</td>
<td>Gastric polyposis without colorectal polyposis and without use of acid-suppression therapy</td>
</tr>
<tr>
<td>Attenuated familial adenomatous polyposis</td>
<td>APC</td>
<td>Autosomal dominant</td>
<td>Predominantly fundic gland polyps, foveolar adenomas, and pyloric gland adenomas</td>
<td>Not increased</td>
<td>Intestinal</td>
<td>Fundic gland polyposis</td>
<td>Colorectum, thyroid, duodenum, adrenal gland, small bowel, brain</td>
<td>Colorectal and duodenal polyposis</td>
</tr>
</tbody>
</table>
GAPPS (Gastric Adenocarcinoma and Proximal Polyposis of the Stomach)

The first European family with gastric adenocarcinoma and proximal polyposis of the stomach: case report and review of the literature

Short title: First case of GAPPS in Europe

Repak R et al: Gastrointestinal Endoscopy DOI: 10.1016/j.gie.2016.06.023

Foretová L, et al: GAPPS - Gastric Adenocarcinoma and Proximal Polyposis of the Stomach Syndrome in 8 Families
First report of an Asian family with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) revealed with the germline mutation of the APC exon 1B promoter region

Yasuhiro Mitsui¹ · Reiko Yokoyama¹ · Shota Fujimoto¹ · Kaizo Kagemoto¹ · Shinji Kitamura¹ · Koichi Okamoto¹ · Naoki Muguruma¹ · Yoshimi Bando² · Hidetaka Eguchi³ · Yasushi Okazaki³ · Hideyuki Ishida⁴ · Tetsuji Takayama¹

Received: 28 March 2018 / Accepted: 29 June 2018
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<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>WHO 2019</th>
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<tbody>
<tr>
<td><strong>Essential criteria</strong></td>
<td></td>
</tr>
<tr>
<td>1. Phenotypic features:</td>
<td></td>
</tr>
<tr>
<td>- Proximal (body and fundus) gastric polyposis with antral sparing. No evidence of colorectal or duodenal polyposis*</td>
<td></td>
</tr>
<tr>
<td>- &gt;100 polyps carpeting the proximal stomach in the index case or &gt;30 polyps in a first-degree relative of another case</td>
<td></td>
</tr>
<tr>
<td>- Predominantly fundic gland polyps (FGP) and/or fundic gland-like polyps</td>
<td></td>
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<tr>
<td>2. Proband or family member with either dysplastic FGPs or gastric adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>3. Mutation in the chr5: 112,043,220–12,043,224 region of promoter 1B of APC**,***</td>
<td></td>
</tr>
<tr>
<td><strong>Supportive criteria</strong> (families in whom genetic testing could be considered)</td>
<td></td>
</tr>
<tr>
<td>1. Family history (autosomal dominant pattern of inheritance)</td>
<td></td>
</tr>
<tr>
<td>2. Spectrum of other histological lesions: hyper-proliferative aberrant pits (HPAPs), hyperplastic polyps, gastric type adenomas</td>
<td></td>
</tr>
</tbody>
</table>

*Exclusions include other heritable gastric polyposis syndromes and use of PPIs. In patients on PPIs it is recommended to repeat the endoscopy off therapy

** The point mutations that segregate with GAPPS (c.-191T>C, c.-192A>G and c.-195A>C) are all positioned within the Ying Yang 1(YY1) binding motif of the APC gene.

*** FAP has also been caused by these mutations. Although criteria for GAPPS means there is no colorectal polyposis, testing for 1b promoter variants should still be considered for patients with FAP that are APC negative - especially if they also have FGPs.
Genetic tumour syndromes of the digestive system

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15.1.1.10: Cowden syndrome
15.1.1.11: Other genetic tumour syndromes
**DIAGNOSTIC ALGORITHM FOR ADENOMATOUS POLYPOSIS**
(FAP and Lynch syndrome Excluded)

- CMMRD, constitutional mismatch repair deficiency;
- MAP, MUTYH-associated polyposis;
- NAP, NTHL1-associated polyposis;
- PPAP, polymerase proofreading–associated polyposis;

...
Genotype or Phenotype – What matters most in hereditary GI cancer syndromes?

↓

BOTH
Thanks for your attention
CRITERIA FOR FAMILIAL GASTRIC CANCER

**CDH1 testing criteria in hereditary diffuse gastric cancer (HDGC updated 2015 criteria)** [1]

**Full criteria**
- Two or more documented cases of GC at any age in first- or second-degree relatives, with at least one confirmed DGC; or
- Personal history of DGC before the age of 40 years; or
- Personal or family history (first- or second-degree relatives) of DGC and lobular breast cancer, one diagnosed before the age of 50 years; or

**Supporting criteria**
- Families with bilateral or multiple cases of lobular breast cancer before the age of 50 years; or
- Families with clustering of DGC and cleft lip/cleft palate and; or
- Any patient that is diagnosed with *in situ* signet ring cells and/ or pagetoid spread of signet ring cells.

**Familial intestinal-type gastric cancer (FIGC)** [7]

- Two or more documented cases of intestinal gastric cancer (IGC) in first- or second-degree relatives, with at least one being diagnosed before the age of 50 years; or
- Three or more cases of IGC in first- or second-degree relatives, independent of age of diagnosis

**Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)** [8, 9]

**Essential criteria**
1. Phenotypic features: Gastric polyps restricted to the body and fundus with antral sparing; no evidence of colorectal or duodenal polyposis; > 100 polyps carpeting the proximal stomach in the index case or > 30 polyps in a first-degree relative of another case; Predominantly fundic gland (-like) polyps (exclusions include other heritable gastric polyposis syndromes and use of PPIs)
2. Proband or family member with dysplastic FGPs or gastric adenocarcinoma
3. Mutation in the chromosome 5 region of promoter 1B of APC

**Supportive criteria**
- 4. An autosomal dominant pattern of inheritance
- 5. Spectrum of other histological lesions: hyperproliferative aberrant pits (HPAPs), hyperplastic polyps, gastric type adenomas