Hereditary Gastric Cancer Syndromes
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
  15.1.1.3: Lynch syndrome
  15.1.1.4: Familial adenomatous polyposis 1
  15.1.1.1: GAPPS and other fundic gland polyposes
  15.1.1.5: Other adenomatous polyposes
  15.1.1.6: Serrated polyposis
  15.1.1.2: Hereditary diffuse gastric cancer
  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
Hereditary gastrointestinal carcinomas and their precursors: An algorithm for genetic testing

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Emerging Concepts in Gastric Neoplasia
Heritable Gastric Cancers and Polyposis Disorders

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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

  Caldas and the IGCLC, JMG 1999
  Oliveira C et al, Lancet Oncol 2015
Maori kindred

E-cadherin gene (CDH1) *germline mutations

Hereditary Diffuse Gastric Cancer (HDGC)


*Gene map locus: 16q22.1 (MIM ID +192090)
4-3 Hereditary Diffuse Gastric Cancer

Fátima Carneiro
Amanda Charlton
David Huntsman

Mucosa
Muscularis mucosa
Submucosa

TNM stage

Tis
T1a

In situ carcinoma
Pagetoid spread
T1a intramucosal signet-ring cell
HEREDITARY – CDH1 germline mutations

Genetic susceptibility
(germline alterations)
E-cadherin schematic representation demonstrating its major domains in relation to the 50 pilot variants curated by an Expert Panel.

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

- CDH1 Mutations 25%
- CDH1 negative 75%

IGCLC criteria validation

- CDH1 negative 60%
- CDH1 mutations 36%
- CDH1 deletions 4%

Screening of CDH1 deletions adopted worldwide

- Negative 53%
- CDH1 mutations 36%
- Other gene mutations 6%
- CDH1 deletions 4%
- CDH1 promoter methylation 1%

2018

Targeted DNAseq and Exome seq in hundreds of probands identified few new candidate genes

- 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)
### Table 1
Characteristics of hereditary diffuse gastric cancer and familial intestinal gastric cancer

<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 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 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

Carla Oliveira, Hugo Pinheiro, Joana Figueiredo, Rogelio Saruga, Filtrina Carneiro
Familial gastric cancer: genetic susceptibility, pathology, and implications for management

Oliveira et al; Lancet Oncology 16(2):e60-70, 2015

van der Post RS¹, Oliveira C²,³,⁴, Guilford P⁵, Carneiro F⁶,⁷,⁸.

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
### Box 1. Criteria familial GC

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

**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 yrs; or
- Personal or family history (first- or second-degree relatives) of DGC and lobular breast cancer, one diagnosed before the age of 50 yrs; or

**Supporting criteria**

- Families with bilateral or multiple cases of lobular breast cancer before the age of 50 yrs; 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)**

- 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 yrs; or
- Three or more cases of IGC in first- or second-degree relatives, independent of age of diagnosis.
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
   - CDH1 mutations/deletions
   - CTNNA1 mutations
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
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  Worthley et al, Gut 2012

• **Familial Intestinal Gastric Cancer**
  
  **FIGC - No cause** identified to date
  
Gastric Adenocarcinoma and Proximal Polyposis 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 \textit{APC} Reveal Gastric Adenocarcinoma and Proximal Polyposis of the Stomach as a Familial Adenomatous Polyposis Variant

Jun Li,1, Sue L. Woods,2, Sue Healey,1 Jonathan Beesley,1 Xiaqing Chen,1 Jason S. Lee,1 Haran Sivakumaran,1 Nicci Wayte,1 Katie Nones,1 Joshua J. Waterfall,1 John Pearson,1,2 Anne-Marie Patch,3 Janine Senz,9 Manuel A. Ferreira,3 Pardeep Kaurah,6 Robertson Mackenzie,7 Alireza Heravi-Moussavi,8 Samantha Hansford,5 Tamsin R.M. Lannagan,2 Amanda B. Spurdle,4 Peter T. Simpson,8,10 Leonard da Silva,9,10 Sunil R. Lakhani,9,10,11 Andrew D. Clouston,12,13 Mark Bettington,10,13,14 Florian Grimpen,15 Rita A. Busuttil,16,17,18 Natasha Di Costanzo,16 Alex Boussioutas,16,17,18,19 Marie Jeanjean,20 George Chong,21 Aurélie Fabre,22,23,24 Sylviane Olschwang,22,23,24 Geoffrey J. Faulkner,25 Evangelos Bellos,1,26 Lachlan Coin,3 Kevin Rioux,27 Oliver E. Bathe,28,29 Xiaogang Wen,30,31 Hilary C. Martin,32 Deborah W. Neklason,33 Sean R. Davis,3 Robert L. Walker,5 Kathleen A. Calzone,3 Itzhak Avital,34 Theo Heller,35 Christopher Koh,35 Marbin Pineda,3 Udo Rudloff,36 Martha Quezado,37 Pavel N. Pichurin,38 Peter J. Hulick,39 Scott M. Weissman,40 Anna Newlin,39 Wendy S. Rubinstein,41 Jone E. Sampson,42 Kelly Hamman,42 David Goldgar,33 Nicola Poplawski,44,46 Kerry Phillips,44,45 Lynn Schofield,46 Jacqueline Armstrong,44 Cathy Kiraly-Borri,46 Graeme K. Suthers,46 David G. Huntsman,7,47 William D. Foulkes,20,48 Fatima Carneiro,30,49 Noralane M. Lindor,50 Stacey L. Edwards,1 Juliet D. French,1 Nicola Waddell,1,4 Paul S. Meltzer,4 Daniel L. Worthley,2 Kasmintan A. Schrader,6,7 and Georgia Chenevix-Trench,1,4

The genetic defect is now identified

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)

Pro 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
<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</td>
<td>Point mutations in Exon</td>
<td>Autosomal dominant</td>
<td>Fundic gland polyps, few hyperplastic polyps and adenomas</td>
<td>Increased</td>
<td>Intestinal</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>polyposis</td>
<td>1B of APC</td>
<td></td>
<td></td>
<td></td>
<td>and mixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attenuated familial adenomatous</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 polyps</td>
<td>Colorectum, thyroid, duodenum, adrenal gland, small bowel, brain</td>
<td>Colorectal and duodenal polyposis</td>
</tr>
<tr>
<td>polyposis</td>
<td></td>
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</tr>
</tbody>
</table>
Mixed gastric carcinoma

More recently, another GAPPS family in Europe

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

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

IGCC- Prague 2019:
8 families from Czech Republic
<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>WHO 2019</th>
</tr>
</thead>
<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</td>
<td></td>
</tr>
<tr>
<td>polyposis with antral sparing. No</td>
<td></td>
</tr>
<tr>
<td>evidence of colorectal or duodenal</td>
<td></td>
</tr>
<tr>
<td>polyposis*</td>
<td></td>
</tr>
<tr>
<td>- &gt;100 polyps carpeting the proximal</td>
<td></td>
</tr>
<tr>
<td>stomach in the index case or &gt;30</td>
<td></td>
</tr>
<tr>
<td>polyps in a first-degree relative of</td>
<td></td>
</tr>
<tr>
<td>another case</td>
<td></td>
</tr>
<tr>
<td>- Predominantly fundic gland polyps</td>
<td></td>
</tr>
<tr>
<td>(FGP) and/or fundic gland-like</td>
<td></td>
</tr>
<tr>
<td>polyps</td>
<td></td>
</tr>
<tr>
<td>2. Proband or family member with either</td>
<td></td>
</tr>
<tr>
<td>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></td>
<td></td>
</tr>
<tr>
<td>(families in whom genetic testing could</td>
<td></td>
</tr>
<tr>
<td>be considered)</td>
<td></td>
</tr>
<tr>
<td>1. Family history (autosomal dominant</td>
<td></td>
</tr>
<tr>
<td>pattern of inheritance)</td>
<td></td>
</tr>
<tr>
<td>2. Spectrum of other histological</td>
<td></td>
</tr>
<tr>
<td>lesions: hyper-proliferative aberrant</td>
<td></td>
</tr>
<tr>
<td>pits (HPAPs), hyperplastic polyps,</td>
<td></td>
</tr>
<tr>
<td>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.
Hereditary Gastric Cancer Syndromes

Genotype or Phenotype – What matters most?

\[ \downarrow \]

BOTH
Thanks for your attention