Hereditary Gastric Cancer Syndromes

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ACCME/Disclosures

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Dr. Fatima Carneiro declares she has no conflict(s) of interest to disclose.
Gastric cancer in familial/hereditary cancer syndromes

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Genetic alterations</th>
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<tbody>
<tr>
<td>• Lynch syndrome (HNPCC)</td>
<td>MMR</td>
</tr>
<tr>
<td>• Li-Fraumeni syndrome</td>
<td>TP53</td>
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<td>• Peutz-Jeghers syndrome</td>
<td>STK1</td>
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<td>• Familial adenomatous polyposis</td>
<td>APC</td>
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</table>
Several polyposis syndromes may affect the stomach

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

Similar morphological features
Gastric cancer

Sporadic cancer (90%)

Familial cancer (10%)
- Familial Gastric Cancer (FGC)
- Familial Intestinal Gastric Cancer (FIGC)
- Familial Diffuse Gastric Cancer (FDGC)

Hereditary cancer (1-3%)
Maori kindred

E-cadherin gene (CDH1) *germline mutations

Hereditary Diffuse Gastric Cancer (HDGC)


*Gene map locus: 16q22.1 (MIM ID +192090)
E-cadherin & gastric cancer
(sporadic and hereditary)

1998/9
- Familial gastric cancer: overview and guidelines for management. (IGCLC)

2001
- Second hit E-cadherin gene (CDH1) inactivation (promoter methylation) in sporadic diffuse gastric carcinoma

2003
- Functional analyses of E-cadherin (CDH1) germline missense mutations
- Prophylactic gastrectomies in asymptomatic carriers of germ-line E-cadherin mutations

2004
- Model of development of HDGC

2005
- First Portuguese family with HDGC

2006
- Cleft lip/palate and CDH1 mutations in families with HDGC

2007
- E-cadherin repressors in gastric cancer
- Novel germline CDH1 mutations
- Experimental model in Drosophila

2008
- Second hit of CDH1 inactivation
NMD mRNA surveillance downregulates aberrant CDH1 transcripts

2009
- Novel germline CDH1 mutations

2010/11/12/13/14/15
- E-cadherin repressors in gastric cancer
- Prophylactic gastrectomies in asymptomatic carriers of germ-line E-cadherin mutations

References:
- Histopathology 35: 477, 1999
- Lab Invest 79: 459, 1999
- Oncogene 20: 1525, 2001
- Hum Mutat 19:510, 2002
- J Pathol 203: 681, 2004
- Virchows Arch 446: 18, 2005
- Clin Cancer Res 11:5401, 2005
- Hum Mutat15:1704, 2006
- Hum Mutat 28:203, 2007
- J Pathol 211:507, 2007
- Oncogene 27: 4255, 2008
- Gastroenterology 136:2137, 2009
- Cell Mol Life Sci, 2011
4-3 Hereditary Diffuse Gastric Cancer

Fátima Carneiro
Amanda Charlton
David Huntsman

- Genetic susceptibility (germline alterations)
- Molecular Pathology (somatic alterations)
- Clinical features
- Pathology
Genetic susceptibility
(germline alterations)

HEREDITARY - CDH1 germline mutations

[Diagram showing various mutations and frequency of CDH1 alterations]

Frequency of CDH1 alterations

0.8
5.0
30.0
19.2
25.0
19.2

Type of CDH1 alteration

Promoter methylation
Large deletion
Small frameshift
Nonsense
Splice-site
In-frame insertion
Missense
Flow chart for management of individuals at risk.
More recently...

An α-E-catenin (CTNNA1) mutation in hereditary diffuse gastric cancer

Ian J Majewski1,†, Irma Kluijt2,†, Annemieke Cats3, Thomas S Scerri8, Daphne de Jong4, Roelof JC Kluin5, Samantha Hansford11, Frans BL Hogervorst2, Astrid J Bosma1, Ingrid Hofland7, Marcel Winter7, David Huntsman11, Jos Jonkers6, Melanie Bahlo8,9,10, René Bernards1,∗

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Even more recently...

Original Investigation

Hereditary Diffuse Gastric Cancer Syndrome

CDH1 Mutations and Beyond

cases, candidate mutations were identified in 16 of 144 probands (11%), including mutations within genes of high and moderate penetrance: CTNNA1, BRCA2, STK11, SDHB, PRSS1, ATM, MSR1, and PALB2.
Genetic susceptibility
(germline alterations)

- CDH1 negative: 49%
- CDH1 mutations: 30%
- CDH1 deletions: 4%
- CDH1 methylation: 1%
- Other genes: 6%

Currently, ongoing sequencing of the full 100kb CDH1 locus in 90 HDGC patients.

Oliveira C et al, Hum Mol Genet, 2009
Absent expression of E-cadherin

Somatic inactivation of the wild allele in the tumour
CDH1 gene alterations in gastric carcinoma

"1st HIT"  "2nd HIT"

Mutation

- Promoter methylation
- LOH
- "Second" mutation
- More than one

Grady et al. Nat Genet 26:16, 2000
Familial gastric cancer: genetic susceptibility, pathology, and implications for management

Carla Oliveira*, Hugo Pinheiro*, Joana Figueiredo, Raquel Seruca, Fátima Carneiro
Familial gastric cancer: overview and guidelines for management
(International Gastric Cancer Linkage Consortium)

Familial gastric cancer: overview and guidelines for management
(International Gastric Cancer Linkage Consortium)

Carriers of germline E-cadherin truncating mutations

Intensive screening
Prophylactic gastrectomy

New Zealand

Europe & North America

Caldas C et al; Eur J Genet 36: 873, 1999
Penetrance

The cumulative risk of DGC for CDH1 mutation carriers by age 80 years is reported to be 70% for men and 56% for women. Furthermore, the cumulative risk of LBC for women with a CDH1 mutation is estimated to be 42% by 80 years.

There is currently no evidence that the risk of other cancer types in individuals with a CDH1 mutation is significantly increased.

Established criteria
- 2 GC cases regardless of age, at least one confirmed DGC
- One case of DGC <40
- Personal or family history of DGC and LBC, one diagnosed <50

Families in whom testing could be considered
- Bilateral LBC or family history of 2 or more cases of LBC <50
- A personal or family history of cleft lip/palate in a patient with DGC
- In situ signet ring cells and/or pagetoid spread of signet ring cells

*Including 1st and 2nd degree relatives

CDH1 genetic testing from age of informed consent (including MLPA)

- Or uncertain variant
  - Register for clinical research studies
  - Heightened cancer screening

- Multidisciplinary team management
  - Clinical and molecular geneticist
  - Gastroenterologist
  - Surgeon
  - Dietician
  - Pathologist

If refuse or delay surgery due to comorbidity

Gastric endoscopic surveillance with Cambridge protocol

- Biopsy negative
- Biopsy with SRCC

Risk reducing gastrectomy

- Close nutritional follow-up
- Screening for lobular breast cancer from age 30 yrs
- Screening for colon cancer in pedigrees with colon cancer from aged 40 yrs (or 10 yrs younger than affected cases)
Intramucosal signet-ring cell (diffuse) carcinoma
**In situ** (signet ring cell) carcinoma

Pagetoid spread of signet ring cells:
Two-layer structure: an inner layer composed of benign mucous cells and an outer layer of signet ring cells.

Table:

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Tis</th>
<th>T1a</th>
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<tbody>
<tr>
<td>Mucosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscular</td>
<td></td>
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</tr>
</tbody>
</table>

Submucosa

Carneiro F, Charlton A, Huntsman D
Familial gastric cancer: genetic susceptibility, pathology, and implications for management

Carla Oliveira*, Hugo Pinheiro*, Joana Figueiredo, Raquel Seruca, Fátima Carneiro

**In situ carcinoma**

**Pagetoid spread of signet ring cells**

**Intramucosal signet ring cell carcinoma**
Hereditary Diffuse Gastric Carcinoma
Endoscopic biopsies
Differential diagnosis
The GAPPS syndrome...
(A new hereditary gastric cancer syndrome)

Proximal polyposis of the stomach

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

L Worthley,1 K D Phillips,2 N Wayte,3 K A Schrader,4 S Healey,5 P Kaurah,4 A Shukes,6 F Grimpen,7 A Clouston,7 D Moore,6 D Cullen,9 D Ormone,9 D Mounkley,10 X Wen,11 N Lindor,11 F Carneiro,11 D G Huntsman,4 G Chenevix-Trench,2 G K Suthers2,12

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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 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 the syndrome, including the predominant dysplastic fundic gland polypl 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 MYH-associated polyposis (MAP), generalised juvenile polyposis syndrome (GJP), Peutz-Jeghers syndrome (PJS) and Cowden syndrome. However, GAPPS are relatively rare in MAP, an autosomal recessive disorder, and GJP and PJS are often characterised by the presence of specific hamartomatous (rather than purely dysplastic fundic gland) polype.

Sporadic FGPs are usually innocuous, but syndromic FGPs can progress to dysplasia and gastric adenocarcinoma. 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.
Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS): a new autosomal dominant syndrome.

Genetic cause recently identified...

Worthley et al; Gut 61:774-779, 2012
Proximal polyposis of the stomach:

- Fundic gland polyps (predominant)
- Hyperplastic (rare)
- Adenomatous (rare)
Dysplasia in fundic gland polyps
Gastric Adenocarcinoma and Proximal Polyposis of the Stomach
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 recommended to repeat the endoscopy off therapy.

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

- **APC**
- **MUTYH**
- **CDH1**
- **SMAD4**
- **BMPR1A**
- **STK11**
- **PTEN**
Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS): a new autosomal dominant syndrome

The genetic defect is now identified

Mutations in a promoter of APC cause a syndrome of gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) without colorectal involvement

Georgia Chenevix-Trench, Jun Li, Sue Healey, Haran Sivakumaran, Juliet French, Stacey Edwards, Katia Nones, Nic Waddell, Pavel Pichurin, Peter Hulick, Kelly J. Hamman, Joshua J. Waterfall, David Huntsman, Paul Meltzer, Deb Neklason, David Goldgar, Fatima Carneiro, Cathy Kiraly-Borri, Lyn Schofield, Dan Worthley, Noralane Lindor, Graeme Suthers and Intan Schrader
Hereditary gastric cancer
(1-3% of the burden of stomach cancer)

Hereditary Diffuse Gastric Cancer
HDGC
(CDH1, CTNNA1 and other genes)

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS)
HIGC
(APC gene)
Carla Oliveira
Gianpaolo Suriano
José Carlos Machado
Céu Figueiredo
Paulo Ferreira
Rita Mateus
Rachid Karam
Herculano Moreira
Manuel Cardoso de Oliveira
Fátima Carneiro
Raquel Seruca
Manuel Sobrinho-Simões

Hospitais da Universidade de Coimbra

Augusta Cipriano
Mário Rui Silva
Thanks for your attention