HEREDITARY ASPECTS OF GASTRIC CANCER

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NO CONFLICTS OF INTEREST TO DECLARE
### Stomach Cancer Statistics

<table>
<thead>
<tr>
<th>Category</th>
<th>Statistic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fifth most common cancer type worldwide</td>
<td>1 Million</td>
<td>new cases each year globally</td>
</tr>
<tr>
<td>1 in 111 men and women will be diagnosed in their lifetime</td>
<td>1-3%</td>
<td>stomach cancers are related to inherited cancer syndromes</td>
</tr>
<tr>
<td>80%</td>
<td>risk in hereditary cases</td>
<td></td>
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<tr>
<td>4%</td>
<td>5-year survival rate for Stage IV stomach cancer patients</td>
<td></td>
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<tr>
<td></td>
<td>Hereditary Diffuse Gastric Cancer (HDGC) increases risk for diffuse gastric cancer (80% risk by age 80) and lobular breast cancer (42% risk for women by age 80)</td>
<td>Overall 5-year survival rate is 29.3%</td>
</tr>
</tbody>
</table>
Gastric cancer in hereditary cancer syndromes

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Genetic alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch syndrome (HNPCC)</td>
<td>MMR</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK1</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>SMAD4 or BMPR1A</td>
</tr>
</tbody>
</table>
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
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

- Genetic susceptibility (germline alterations)
- Molecular Pathology (somatic alterations)
- Clinical features
- Pathology
Genetic susceptibility
(germline alterations)
HDGC: summary of germline mechanisms

**1998/2002**

- **CDH1** mutations 25%
- CDH1 negative 75%

**Screening of CDH1 coding mutations adopted worldwide**

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

**2018**

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

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

- **CTNNA1** encoding alpha-catenin as an HDGC-causing gene in a small fraction of families
- **MAP3K6**
- TP53
- BRCA2
- MYD88
- ATM
- SDHB
- STK11
- PALB2
- MSR1
- FBXO24 + DOT11L + INSR

**Screening of CDH1 deletions adopted worldwide**

**Consolidation of CTNNA1 encoding alpha-catenin as an HDGC-causing gene in a small fraction of families**

**Awaiting approval for inclusion in HDGC genetic screening by the IGCLC**

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*References*

- 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 IJ 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
<table>
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<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 and familial intestinal gastric cancer</td>
<td><strong>CDH1</strong></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><strong>CTNNA1</strong></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>

van der Post RS & Carneiro F; Surg Pathol Clin. 2017
Absent expression of E-cadherin

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

“1st HIT”
- Mutation

“2nd HIT”
- Promoter methylation
- LOH
- “Second” mutation
- More than one

Molecular Pathology
(Somatic alterations)

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

Oliveira et al; Lancet Oncology 16(2):e60-70, 2015
Intramucosal signet-ring cell (diffuse) carcinoma
Hereditary Diffuse Gastric Cancer (HDGC)
Familial gastric cancer: genetic susceptibility, pathology, and implications for management

Oliveira et al, Lancet Oncology 16(2):e60-70, 2015
In situ SRCC

Intramucosal carcinoma (T1a)

Consultation case
Endoscopic biopsies

• HDGC
• Same family
• Same CDH1 mutation
• Different morphology

Gullo I et al; Gastrointest Endosc. 2018
Indolent phenotype
pT1a (early) HDGC

Aggressive phenotype
pT>1 (advanced) HDGC

Gullo I et al; Gastrointest Endosc. 2018
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
Guidelines for management

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)

Register for clinical research studies
Heightened cancer screening

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

Gastric endoscopic surveillance with Cambridge protocol

Risk reducing gastrectomy

Biopsy negative

Biopsy with SRCC

Or uncertain variant

If refuse or delay surgery due to comorbidity

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)
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**
- 1° - Risk reduction gastrectomy (indicated)
- 2° - Surveillance with gastroscopy and multiple biopsing (controversial)

**Lobular breast cancer**
- 1° - Bilateral surveillance from age 30 with MRI and surgery to remove early lesions (indicated)
- 2° - 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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  Caldas and the IGCLC, JMG 1999  
  Oliveira C et al, Lancet Oncol 2015
Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS): a new autosomal dominant syndrome.

Genetic cause recently identified...
GAPPS (Gastric Adenocarcinoma and Proximal Polyposis of the Stomach)
GAPPS (Gastric Adenocarcinoma and Proximal Polyposis of the Stomach)
Even more recently, another GAPPS family in Europe

**GAPPS** (Gastric Adenocarcinoma and Proximal Polyposis of the Stomach)

**Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) – a rare recently described gastric polyposis syndrome – report of a case**

**GAPPS – eine seltene, 2012 erstmals beschriebene Magenpolyposise – ein Fallbericht**

Authors:
Andrea Beer¹, Berthold Streubel¹, Reza Asari², Clemens Dejaco³, Georg Oberhuber¹

Repak R et al: Gastrointestinal Endoscopy DOI: 10.1016/j.gie.2016.06.023
**Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)**

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Histopathological findings</th>
<th>Recommended genetic testing</th>
<th>Molecular genetics</th>
</tr>
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<tbody>
<tr>
<td>• Gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis</td>
<td>• Fundic gland polyposis of the stomach with areas of dysplasia</td>
<td>• APC promoter 1B mutational analysis</td>
<td>• Germline point mutation APC promoter 1B</td>
</tr>
</tbody>
</table>
| • More than 100 polyps carpeting the proximal stomach in the index case or >30 polyps in a first-degree relative | • Hyperplastic polyps of the stomach
• Predominantly fundic gland polyps, some having regions of dysplasia (or a family member with either dysplastic fundic gland polyps or gastric adenocarcinoma) | • Adenomatous polyps of the stomach
• Mixed polyps with FGP-like, adenomatous and hyperplastic features | • Haploinsufficiency mechanism for fundic gland polyposis; second hit mechanism for gastric adenocarcinoma |
| • Predominantly fundic gland polyps, some having regions of dysplasia (or a family member with either dysplastic fundic gland polyps or gastric adenocarcinoma) | • Fundic gland polyposis of the stomach with areas of dysplasia | • APC promoter 1B mutational analysis | • Germline point mutation APC promoter 1B |
| • Autosomal dominant pattern of inheritance | • Hyperplastic polyps of the stomach
• Adenomatous polyps of the stomach
• Mixed polyps with FGP-like, adenomatous and hyperplastic features | • APC promoter 1B mutational analysis | • Haploinsufficiency mechanism for fundic gland polyposis; second hit mechanism for gastric adenocarcinoma |
| • Exclusion of another gastric polyposis syndrome and use of proton-pump inhibitors | • Fundic gland polyposis of the stomach with areas of dysplasia | • APC promoter 1B mutational analysis | • Germline point mutation APC promoter 1B |

- **Clinical criteria**
- **Histopathological findings**
- **Recommended genetic testing**
- **Molecular genetics**
Table 2
Characteristics of gastric polyposis syndromes

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<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 polyps</td>
<td>Colorectum, thyroid, duodenum, adrenal gland, small bowel, brain</td>
<td>Colorectal and duodenal polyposis</td>
</tr>
</tbody>
</table>
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)
**Integrated Molecular Pathology**  
(Integromics framework)

- Molecular pathology (spacial & temporal heterogeneity)
- Genomics, epigenomics, proteogenomics, ...
- Clinical phenotype

- Better understanding
- Translation to clinics

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Thanks for your attention