Early genetic counseling and detection of CDH1 mutation in asymptomatic carriers improves survival in diffuse gastric cancer

M Moslim, B Heald, C Tu, C Burke, RM Walsh
Digestive Disease and Surgery Institute
Sanford R Weiss MD Center for Hereditary Colorectal Neoplasia
Cleveland Clinic, Cleveland, Ohio
Introduction

- Hereditary diffuse gastric cancer (HDGC) associated with E-cadherin (CDH1) germline mutations
- Proliferation of multigene cancer panels
- The implications of CDH1 mutations without a family history of gastric cancer are uncertain
- General availability of genetic counselors is variable to help educate families
  - Independent of surgical team
  - Help entire family understand risks and aid decision making
Original Maori Family Pedigree
CDH-1: E-cadherin
van der Post, J Med Genet, 2015

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 variant of uncertain significance

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

If refuse or delay surgery due to morbidity

Repeat annually

Biopsy negative

Biopsy with signet ring cell carcinoma

Gastric endoscopic surveillance with Cambridge protocol

Prophylactic gastrectomy

Post-gastrectomy
- Close nutritional follow-up
- Screening for LBC from age 30 years
- Screening for colon cancer in families presenting with colon cancer from aged 40 years (or 10 years younger than affected cases)

Register for clinical research studies
Gastric cancer screening
Hypothesis

- Detection and counseling of patients with CDH1 mutations in kindred without family history of HDGC can impact survival
Methods

• Review of patient registry who underwent genetic counseling for CDH1 mutation between February 2011 and August 2017

• Majority of patients were referred to Genomic Medicine Institute due to red flags:
  • Young age of gastric cancer
  • Multiple malignancies
  • Multiple family members with cancer
Methods

- Patients with a known family history of CDH1 mutation → tested for the specific mutation
- All the other patients (unsuspected for CDH1 mutation) → 28-gene hereditary gene panel
- Patients diagnosed with CDH1 mutation were referred for surgical consultation
Results: Demographics

• A total of 21 patients with CDH1 mutation were identified:
  • Median age of 40 (IQR 31-57) years
  • Equal gender distribution

• Eleven patients (52%) with unknown-risk had CGH1 mutation by multigene hereditary cancer panel
Results: Gene Testing

The indications for *CDH1* genetic screening

- Family history of HDGC: 48%
- Young onset of personal or family history of breast cancer: 33%
- Metastatic gastric cancer at young age: 14%
- Testicular cancer: 5%
Results:

Clinical Outcomes:

- 9 patients underwent total gastrectomy with Roux-en-Y esophagojejunostomy (43%)
- 5 referred to palliative care due to metastatic gastric cancer (24%)
- 3 deferred surgery (14%)
- 2 undergoing endoscopic surveillance (9.5%)
- 2 underwent surgery at outside hospital (9.5%)
## Results: Surgery vs Palliative

<table>
<thead>
<tr>
<th></th>
<th>Gastrectomy Group (n=9)</th>
<th>Palliative Group (n=5)</th>
</tr>
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<tbody>
<tr>
<td><strong>Gender (male)</strong></td>
<td>3 (33.3%)</td>
<td>5 (100%)</td>
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<td><strong>Age (yr) - Median [IQR]</strong></td>
<td>32.3 [22.6-47]</td>
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<td>2 (22.2%)</td>
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</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>8 (88.9%)</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>5 (100%)</td>
</tr>
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</table>
Results: Outcomes

• The gastrectomy group:
  • No recurrence
  • No metastases
  • No mortality

• All the palliative patients expired with a median of 11 (IQR 7-12) months from diagnosis
Results: Outcomes

Comparison between:

• Known-risk group:
  • Surgical and palliative patients who had personal or family history of HDGC

• Unknown-risk group:
  • Surgical and palliative patients who were detected on multigene hereditary cancer panels
## Results: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Known-risk Group (n=7)</th>
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<th>p value</th>
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<tr>
<td><strong>Age (yr) - Median [IQR]</strong></td>
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<td>3 (42.9%)</td>
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<tr>
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Limitation

- Retrospective design
- Small numbers of participants → Cannot obtain statistical significance
- Potential referral bias, which underestimate CDH1 mutation prevalence
Summary

- CDH1 mutation associated HDGC is a biologically aggressive variant of gastric cancer
- CDH1 detected on multigene panels have high penetrance and late cancer detection
- Referral by genetic counselors for consideration of gastrectomy is appropriate
- Surgery involves prophylactic and curative total gastrectomy
- Cure is achieved in asymptomatic patients
- Terminal disease with fatal outcome is expected in symptomatic patients
Conclusion

• Recommendation guidelines for treatment of CDH1 mutation should include total gastrectomy in 3rd decade for patients with family history of diffuse gastric cancer and those detected by multigene panels

• Genetic Counselors have an important educational role in patient understanding of disease and prognosis
• Thank you James Church!
• Thoughts and prayers for New Zealand
Hereditary Diffuse Gastric Cancer

R. Mathew Walsh, M.D.
Professor and Chairman
Department of General Surgery
Rich Family Distinguished Chair
Cleveland Clinic

Cleveland Clinic
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Introduction

Statement from FDA Commissioner Scott Gottlieb, M.D., on implementation of agency’s streamlined development and review pathway for consumer tests that evaluate genetic health risks

For Immediate Release

November 6, 2017
Hypothesis

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# Patients
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• Genetic Counselors have an important educational role in patient understanding of disease and prognosis
Case

- WC: 38y/o male
- Paternal aunt passed away from gastric cancer; paternal GM had breast cancer at age 53
- Works in healthcare; took 23andme test with ? positive results
- Underwent 34 gene panel; revealing a likely pathogenic mutation, c.715G>A (p.Gly239Arg), in CDH1.
CDH-1: E-cadherin

Benign epithelial tumour (adenoma) → Loss of E-cadherin-mediated cell-cell adhesion → Malignant invasive tumour (carcinoma) → Metastasis

Christofori, Trends Biochem. Sci., 1999
Benign epithelial tumour (adenoma) → Loss of E-cadherin-mediated cell–cell adhesion → Malignant invasive tumour (carcinoma) → Metastatic tumour cells

Christofori, Trends Biochem, 1999
Loss of heterozygosity
Loss of heterozygosity and promoter hypermethylation
Promoter hypermethylation

Somatic mutation
Somatic mutation and promoter hypermethylation
<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Male</th>
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<th>Female</th>
<th>RR</th>
<th>Female</th>
<th>RR</th>
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<tbody>
<tr>
<td>10-29</td>
<td>4 (0-13)</td>
<td>1937</td>
<td>2 (0-9)</td>
<td>1068</td>
<td>0(0-1)</td>
<td></td>
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<tr>
<td>30-39</td>
<td>10 (3-26)</td>
<td>526</td>
<td>17 (9-32)</td>
<td>2813</td>
<td>3(1-6)</td>
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<tr>
<td>40-49</td>
<td>25 (12-50)</td>
<td>309</td>
<td>25 (13-47)</td>
<td>392</td>
<td>11 (9-14)</td>
<td></td>
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<tr>
<td>50-59</td>
<td>32 (14-64)</td>
<td>42</td>
<td>33 (16-63)</td>
<td>149</td>
<td>21(16-26)</td>
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<tr>
<td>60-69</td>
<td>48(24-80)</td>
<td>35</td>
<td>41 (19-74)</td>
<td>47</td>
<td>32 (26-39)</td>
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<tr>
<td>70-79+</td>
<td>70(40-94)</td>
<td>35</td>
<td>56 (27-90)</td>
<td>47</td>
<td>42 (35-51)</td>
<td></td>
</tr>
</tbody>
</table>

**Breast Cancer**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>RR</th>
</tr>
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<tbody>
<tr>
<td>10-49</td>
<td>7.7</td>
</tr>
<tr>
<td>50+</td>
<td>7.4</td>
</tr>
</tbody>
</table>
Case

- Patient refused referral for gastrectomy

- Underwent Screening EGD:
  A number of pale patches were found in the entire examined stomach. Biopsies were taken with a cold forceps for histology

- Pathology:
  Pale patch, stomach, biopsy (B) - Signet ring cell carcinoma, at least intramucosal
Signet Ring Cells

Fitzgerald, J. Med. Genet, 2010
Comparative Study of Endoscopic Surveillance in HDGC According to CDH1 Mutation Status

- Prospectively enrolled patients with hereditary gastric cancer:
- Either: CDH-1+; refusing prophylactic gastrectomy (n=54)
- or with no pathogenic variant detected (n=31)
- Underwent strict surveillance endoscopy yearly:
- Targeted biopsy specimens were taken from identified lesions, and 5 random biopsy specimens each were taken of the prepylorus, antrum, transitional zone, body, fundus, and cardia segments.
Foci of Gastric Cancer
## Sensitivity, specificity, positive predictive value, and negative predictive value of targeted lesions

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
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<tbody>
<tr>
<td>Polyp</td>
<td>2.8</td>
<td>65.7</td>
<td>2.2</td>
<td>71.0</td>
</tr>
<tr>
<td>Pale areas</td>
<td>27.8</td>
<td>36.5</td>
<td>10.3</td>
<td>65.8</td>
</tr>
<tr>
<td>Erosions</td>
<td>11.1</td>
<td>81.3</td>
<td>14.8</td>
<td>75.8</td>
</tr>
<tr>
<td>Nodular</td>
<td>2.8</td>
<td>92.0</td>
<td>9.1</td>
<td>81.9</td>
</tr>
<tr>
<td>Random Sampling</td>
<td>75.0</td>
<td>N/A</td>
<td>N/A</td>
<td>94.8</td>
</tr>
</tbody>
</table>

Mi, Gastrointest. Endosc., 2018
In CDH1+ patients, most findings of SRCC were made at the first endoscopy (21/33, 63.6%), at which the likelihood of positive findings was 38.9% (21/54).

SRCC foci was 36 of 85 (42.4%). Yield was significantly greater in those with a CDH1 mutation (61.1% compared with 9.7% in CDH1-NPVD patients, \( P < .0005 \)).
Case

- Recommended to undergo total gastrectomy with Dr. Walsh.

- Pathology:
  - Stomach, total gastrectomy (B) - Multifocal intramucosal signet ring
  - cell carcinoma, consistent with the diffuse hereditary gastric cancer
  - Twenty one lymph nodes, negative for malignancy (0/21)
EARLY GENETIC COUNSELING AND DETECTION OF CDH1 MUTATION IN ASYMPTOMATIC CARRIERS IMPROVES SURVIVAL IN HEREDITARY DIFFUSE GASTRIC CANCER

M. M. Islam*, Brandon Head, Carol A. Burke, R. Matthew Walsh
Cleveland Clinic Foundation, University Heights, OH

BACKGROUND: Hereditary diffuse gastric cancer (HDGC) is associated with E-cadherin (CDH1) germline mutations. There is an increasing trend of detecting CDH1 mutations with multi-gene cancer panels. The implications of CDH1 mutations in those without a family history of gastric cancer are uncertain.

METHODS: A registry of patients who underwent genetic counseling for CDH1 mutation was queried between February 2011 and August 2017.

RESULTS: Twenty-one patients with CDH1 mutation were identified. Most indications for CDH1 genetic screening were family history of HDGC (48%) and young onset of personal or family history of breast cancer (39%). Unsuspected CDH1 mutations were detected in 52% undergoing multi-gene cancer panels. Eight patients underwent total gastrectomy, five had metastatic gastric cancer at presentation and referred to palliative care (table). Five are waiting for or had surgery at an outside hospital and three refused surgery. Patients who underwent gastrectomy at our institute had a median age of 31 years and were predominantly females (75%). Four patients (50%) were known to have gastric cancer based on preoperative screening endoscopy utilizing Cambridge surveillance protocol. Seven (87%) were asymptomatic at diagnosis and had diffuse type (signet-ring) gastric cancer with poor differentiation on final pathology (stage IA). Three out of four patients (75%) who underwent prophylactic gastrectomy had gastric cancer on final pathology. The most common location of cancer was in the fundus (82.5%). Median follow-up is 10.3 months with no recurrence, metastases or mortality. The metastatic disease group (n=6) consists of symptomatic males with a median age of 40 years. All died with a median of 11 months from diagnosis. Unsuspected CDH1 carriers were older (median 44 versus 24 years) and more likely to have both metastatic disease and mortality (56% versus 29%) compared to patients with family or personal history of HDGC.

CONCLUSIONS: CDH1 mutations associated HDGC are a biologically aggressive variant of gastric cancer. Curative total gastrectomy is achieved in asymptomatic patients, however symptomatic patients were found to have terminal disease with fatal outcome. Unsuspected CDH1 carriers are becoming increasingly diagnosed on multi-gene panels which at a minimum warrant genetic counseling and aggressive screening endoscopic examinations.
Table: Comparison between the surgical and palliative groups.

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<tr>
<td>Preoperative BMI (kg/m²)</td>
<td>27.1 [25.6-29.4]</td>
<td>27.6 [25-28.2]</td>
</tr>
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<td>5 (100%)</td>
</tr>
<tr>
<td>Preoperative LGD</td>
<td>1 (12.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Preoperative EGD</td>
<td>6 (75%)</td>
<td>5 (100%)</td>
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Case

- Uncle of WC recommended to undergo genetic testing
- MC: 56 y/o M: Heterozygous CDH-1 mutation found.
- SRCs found on EGD, underwent total gastrectomy
### Cancer Foci

<table>
<thead>
<tr>
<th>Case</th>
<th>SCI</th>
<th>IMC</th>
<th>SMC</th>
<th>Σ</th>
<th>Max. Size (mm)</th>
<th>Bx</th>
<th>LN</th>
<th>Group: Stage (AJCC 2010)</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>3.3</td>
<td>Neg.</td>
<td>0/13</td>
<td>IA: pT1a pN0 cM0</td>
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<td>2</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>7</td>
<td>0.6</td>
<td>Neg.</td>
<td>0/13</td>
<td>IA: pT1a pN0 cM0</td>
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<tr>
<td>3</td>
<td>10</td>
<td>122</td>
<td>4*</td>
<td>136</td>
<td>4.0</td>
<td>Pos.</td>
<td>0/16</td>
<td>IA: pT1b pN0 cM0</td>
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<td>4</td>
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<td>7</td>
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<td>11</td>
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<td>5</td>
<td>8</td>
<td>0</td>
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<td>8</td>
<td>0.1</td>
<td>Neg.</td>
<td>0/9</td>
<td>0: pTis pN0 cM0</td>
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<td>6</td>
<td>4</td>
<td>18</td>
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<td>0/16</td>
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<td>1</td>
<td>7</td>
<td>0</td>
<td>8</td>
<td>0.3</td>
<td>Neg.</td>
<td>0/13</td>
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<tr>
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<td>12</td>
<td>7</td>
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<td>19</td>
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<td>39</td>
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<td>47</td>
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*The 4 submucosal foci were continuous with intramucosal foci (Fig. 5).
IMC indicates intramucosal adenocarcinoma; LN, lymph node; neg., negative; pos., positive; SCI, signet ring cell carcinoma in situ; SMC, submucosal adenocarcinoma.

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### Entire Stomach

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<th>Detection Rate</th>
<th>No. Biopsies</th>
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### Fundus

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