

## LEADING ARTICLE

## Clinical implications of E-cadherin associated hereditary diffuse gastric cancer

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Approximately 1–3% of gastric cancers arise as a result of inherited gastric cancer predisposition syndromes. These may be of the diffuse or intestinal type. Linkage analysis has recently implicated E-cadherin mutations in an estimated 25% of families with an autosomal dominant predisposition to diffuse type gastric cancers. This subset of gastric cancer has been termed hereditary diffuse gastric cancer (HDGC).

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persons die aged less than 40 years; this is compared with the mean age of death of 60–70 years for sporadic gastric cancers. Furthermore, there appears to be an increased frequency of cancers occurring at other sites such as the breast, colorectum, and prostate in these mutation carriers.<sup>9–11</sup> However, inclusion of other associated cancers into the definition of HDGC is felt to be too premature at the current time.<sup>7</sup>

#### LOCUS AND GENETIC ABNORMALITIES OF CDH1

Analysis of all reported genetic abnormalities in CDH1 found in HDGC reveals that the majority are inactivating mutations (splice site, frameshift, and nonsense) rather than missense. Furthermore, CDH1 germline mutations are evenly distributed along the E-cadherin gene, in contrast with the clustering in exons 7–9 observed in sporadic diffuse gastric cancer.<sup>12</sup> CDH1 is a tumour suppressor gene and hence loss or inactivation of the remaining normal allele is a required initiating event in susceptible individuals with a germline mutation. The “second hit” is normally deletion of the whole gene or silencing of the gene by promoter methylation. Aberrant CDH1 promoter methylation has been demonstrated in three of six HDGC cases with negative E-cadherin expression,<sup>13</sup> in common with a number of non-inherited tumours such as breast, prostate, hepatocellular, and thyroid,<sup>14–16</sup> as well as in sporadic diffuse gastric cancer. A better understanding of the mechanism underlying the “second hit” may be important in order to develop alternative therapeutic approaches to these patients, such as treatment with demethylating agents.<sup>13</sup>

#### GENETIC TESTING AND CLINICAL MANAGEMENT FOR FAMILIES AT RISK FOR HDGC

It is recognised that genetic testing for E-cadherin mutations involves uncertainty about clinical management and disease outcome, and imposes a psychosocial burden on the family member.<sup>7</sup> However, in light of the highly lethal nature of HDGC, which is autosomal dominant with a high degree of penetrance, it is also possible that withholding this information may not be in the best interests of the families concerned. Deliberate and thoughtful counselling and consultation with family members, external counsellors, and advisers is an essential component of genetic testing.

**Abbreviations:** HDGC, hereditary diffuse gastric cancer

The existence of a familial form of gastric cancer has been known about since the 1800s when multiple cases of gastric cancer were noted in the Bonaparte family.<sup>1</sup> It has now been established that approximately 1–3% of gastric cancers arise as a result of inherited gastric cancer predisposition syndromes.<sup>2–5</sup> These may be of the diffuse or intestinal type, and linkage analysis has recently implicated E-cadherin (CDH1) mutations in an estimated 25% of families with an autosomal dominant predisposition to diffuse type gastric cancers (or linitis plastica).<sup>6</sup> This subset of gastric cancer has been termed hereditary diffuse gastric cancer (HDGC).

#### CHARACTERISTICS OF HDGC

In order to qualify for a diagnosis of HDGC, the following criteria have to be met<sup>7–8</sup>:

- (1) two or more documented cases of diffuse gastric cancer in first or second degree relatives, with at least one diagnosed before the age of 50 years; or
- (2) three or more cases of documented diffuse gastric cancer in first or second degree relatives, independent of age of onset.

Preliminary data from these families suggest that the penetrance of CDH-1 gene mutations are high, with an estimated range of 70–80%. In other words, if you carry the abnormal E-cadherin gene you have a 70–80% lifetime risk of developing gastric cancer.<sup>9</sup> This high penetrance is similar to medullary thyroid cancers in MEN2 syndromes and breast cancer in BRCA1 carriers.

The longest follow up data of patients with HDGC comes from Maori kindred which were first described in 1964 and from which Guilford *et al* first identified the germline mutations of CDH1 in 1998.<sup>6</sup> Death from gastric cancer in these families has occurred in individuals as young as 14 years and the majority of affected

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“Genetic testing for E-cadherin mutations involves uncertainty about clinical management and disease outcome, and imposes a psychosocial burden on the family member”

Once a CDH-1 mutation has been identified in an asymptomatic individual, the therapeutic options currently available are either endoscopic surveillance with the aim of identifying an early curable lesion or prophylactic gastrectomy.

Endoscopic gastric cancer surveillance is unproven. The problems associated with this approach include the difficulty in identifying submucosal lesions and sampling bias in a macroscopically normal appearing mucosa. However, if there is a site predilection for intramucosal disease, as suggested by Charlton and colleagues<sup>17</sup> in this issue of *Gut* [see page 814], then it may be possible to perform targeted biopsies. In their series of six cases the signet ring carcinoma foci density was five times greater in the transitional zone than in the body or antral mucosa. This region occupies less than 10% of the gastric mucosal surface and is characterised histopathologically by a lack of gastric secreting G cells. Hence it is not an easily identifiable area endoscopically. However, as discussed by Charlton and colleagues,<sup>17</sup> chromoendoscopy using a pH sensitive dye congo red following stimulation by pentagastrin may help to highlight this area. Further research is needed to determine the frequency of this disease localisation phenomenon and to determine the scientific explanation for it.

With regard to the current clinical recommendations for surveillance, at a recent meeting of the International Gastric Cancer Linkage Consortium (IGCLC, 2003), the consensus was that a thorough 30 minute endoscopy should be performed every six months by a team experienced at diagnosing early gastric cancer. In an effort to improve the diagnostic yield of surveillance endoscopy in the upper gastrointestinal tract, techniques such as chromoendoscopy should be performed and optical endoscopic methods (such as optical coherence tomography, elastic scattering spectroscopy, and autofluorescence) need to be systematically evaluated.<sup>18</sup> Endoscopic ultrasound examination is unlikely to be helpful for detection of these lesions. The question also arises as to the carcinogenic role of coexistent infection with *Helicobacter pylori*. This is an active research area and it is quite possible that *H pylori* infection as well as dietary and other environmental influences may modify the disease risk in susceptible individuals.<sup>19</sup> In the meantime, it would seem sensible to recommend *H pylori* eradication therapy in patients undergoing surveillance endoscopy in order to minimise the risk of other gastric carcinogens. The role of surveillance needs to be systematically evaluated in a similar way to studies of surveillance for gastric cancer in hereditary non-polyposis colorectal cancer.<sup>20</sup>

“The estimated risk reduction of gastric cancer by gastrectomy is significant”

Prophylactic gastrectomy is clearly a huge undertaking and not without significant psychological and clinical effects on the patient. To date, two groups<sup>21–23</sup> have demonstrated that prophylactically resected stomachs from different families all carried multifocal signet ring cancer. Importantly, surveillance using endoscopy (with chromoendoscopy in some cases) and multiple mucosal biopsies had failed to identify intramucosal carcinoma in all of the published cases surveyed. Hence from these limited examples, the estimated risk reduction of gastric cancer by gastrectomy is significant. However, it also follows that since there is an estimated 70% penetrance, a universal policy of prophylactic gastrectomy

would result in 30% of HDGC mutation carriers receiving an unnecessary operation. It is vital that a careful evaluation of all patients undergoing genetic testing and different courses of clinical management is undertaken in order that a better understanding can be gained about the optimum management of these rare families. The questions which need to be addressed are outlined below.

## UNANSWERED QUESTIONS

### Genetic counselling

The age at which genetic testing (and gastrectomy) should be performed is not yet clear from the current evidence, as at least five subjects have been reported to develop this lethal cancer before the age of 18 years.<sup>6–24</sup> However, since the implications of the diagnosis are far reaching, it is the opinion of the authors that genetic screening should be reserved until the patient is able to make informed consent.<sup>25</sup>

### Surveillance endoscopy

As there is currently no proof that surveillance can successfully diagnose early gastric cancer in these patients, it is our view that all patients having surveillance should be seen by endoscopists experienced in the detection of early gastric cancer and entered into a research protocol in order to compare different endoscopic methods. In the future, the development of molecular markers which can be applied to gastric brushings or lavage fluid might be an alternative way to overcome the sampling bias inherent in current random biopsy sampling methods.

### Screening for other cancers

Due to the increased incidence of other cancers in individuals with CDH1 mutations, it needs to be considered whether it is necessary to provide screening for other anatomical sites (for example, for breast<sup>24–26</sup> and colonic cancers<sup>11</sup>). The cumulative risk of breast cancer in these individuals is 39% by age 80 years.<sup>9</sup> However, gastric cancer penetrance is much higher, and a mutation carrier is almost five times more likely to develop gastric cancer than breast cancer. With regard to colon cancer, the combined epidemiological data<sup>27</sup> do not support the fact that E-cadherin alterations predispose to colon cancer in these families. Hence at the current time screening for malignancies other than possibly breast cancer is not recommended. Long term follow up of these patients will determine whether this is the correct strategy.

### Gastrectomy

Data from three large surgical centres suggest that gastrectomy should be performed by centres performing at least 25 gastrectomies per year with a surgical mortality for cancer of <5% (personal communication, Carlos Caldas on behalf of the IGCLC). The optimal type of reconstruction is not yet known and there are very limited data on the physical and psychological outcomes of performing a prophylactic gastrectomy for asymptomatic individuals.<sup>21–28–30</sup>

“The severity and degree of complications in previously healthy young individuals following gastrectomy have not been evaluated”

Long term follow up of gastrectomy patients is required in order to assess their ability to return to work and effects on their quality of life,<sup>7</sup> and to determine whether prophylactic gastrectomy extends life expectancy. For example, although a prophylactic gastrectomy may improve quality life as a result of a reduction in anxiety about stomach cancer, it may worsen because of the side effects associated with the procedure. For example, gastrectomy may result in weight loss, lactose intolerance, fat malabsorption and steatorrhea,

dumping syndrome, bacterial overgrowth, postprandial fullness, and vitamin deficiencies.<sup>29–31</sup> However, the severity and degree of complications in previously healthy young individuals following gastrectomy have not been evaluated.

### HDGC REGISTER AND RESEARCH

In view of the need for longitudinal follow up data and for ongoing research into this condition, families undergoing germline E-cadherin testing should be entered into research protocols for the initial mutational analysis. Patients should also be asked whether they are willing to be entered into a cooperative registry for ongoing research and discovery. For the minority of the population affected by rare inherited cancer syndromes, the challenge is to reduce cancer development once asymptomatic individuals at risk have been identified. Establishment of specialist centres with the necessary research and clinical expertise should enable considerable progress to be made in this important area.

### IMPLICATIONS OF THIS RESEARCH FOR SPORADIC GASTRIC CANCER

Identification of patients with germline CDH1 mutations paves the way for studies to increase our understanding of the mechanisms by which these mutations actually lead to sporadic as well as HDGC. It is perhaps not surprising that E-cadherin has been implicated in HDGC since in 1994 Becker *et al* identified somatic E-cadherin mutations in specimens of sporadic diffuse gastric cancer.<sup>32</sup> Since then somatic CDH1 mutations have been found in 40–83% of sporadic diffuse cancers but not in intestinal type gastric cancers.<sup>33–35</sup> Furthermore, in a series of young gastric cancer probands who did not have a documented family history, two novel missense alterations of CDH-1 together with an intronic variant were found. Using an *in vitro* approach, it was then possible to demonstrate that missense variants may be associated with functional consequences affecting the cell capacity for invasion and metastasis.<sup>36</sup> These missense variants are in contrast with the inactivating truncating mutations found in the majority of HDGC kindreds. In our view, in order to determine the significance of missense mutations in CDH-1 at least four affected members need to be genotyped, in combination with functional and transcript analyses (to look for activation of cryptic splice sites).

With the advent of high throughput genotyping it is now possible to look for genetic polymorphisms (variations in genes which account for the normal variability within a population) in low penetrance genes as well as in high penetrance genes. As low penetrance genetic variants may be common in the population, they may account for a substantial fraction of sporadic cancer cases.<sup>37</sup> The prospect of a polygenic approach to common diseases has generated much attention. The question frequently posed is whether or not molecular testing for common variants can have sufficient power to be of practical use, either for the individual or for defining risk groups in the population at large.

“At the moment, asymptomatic patients with CDH-1 mutations are faced with very stark therapeutic options”

As clinicians, we have the responsibility of care to our patients. At the moment, asymptomatic patients with CDH-1 mutations are faced with very stark therapeutic options. Given that inherited cancer syndromes are rare, it is mandatory that we pool our data and experiences so that we can provide patients with meaningful clinical advice in the future. As these new genetic techniques begin to be applied to sporadic cancers, we have the potential to improve

the burden of upper gastrointestinal cancer for which the current five year mortality is appalling.

### CONTACT INFORMATION

If you would like to know more about the National HDGC Reference Centre which provides information on the latest guidelines and developments in genetic testing, endoscopic surveillance, and prophylactic surgery, please contact Nicola Grehan, Research Nurse to Professor Carlos Caldas, Box 193, University Department of Oncology, Addenbrookes Hospital, Cambridge CB2 2QQ, UK.

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