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Review article

Hereditary diffuse gastric cancer: translation of *CDH1* germline mutations into clinical practice

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Abstract
Hereditary diffuse gastric cancer (HDGC) is the only known cancer syndrome that is dominated by gastric adenocarcinoma. HDGC is caused by germline mutation of the *CDH1* gene that encodes the cell adhesion protein E-cadherin. Mutation carriers have a more than 70% lifetime risk of developing DGC and an elevated risk of lobular breast cancer. Intestinal-type gastric cancer is not part of the syndrome. Clinical management of HDGC involves predictive genetic testing beginning at or near 16 years of age. It is recommended that mutation carriers undergo prophylactic gastrectomy after about 20 years of age. Anatomical mapping has demonstrated that mutation carriers develop multifocal stage T1a signet ring cell carcinomas, with up to several hundred foci being observed in single stomachs. These foci develop following the somatic inactivation of the second *CDH1* allele by mechanisms that include DNA promoter hypermethylation.

Key words E-cadherin · Hereditary diffuse gastric cancer

Introduction

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer syndrome caused by germline mutation of the gene (*CDH1*) for the cell-to-cell adhesion protein, E-cadherin [1, 2]. The syndrome is dominated by highly penetrant diffuse-type gastric cancer [3] and an elevated risk of lobular breast cancer. The more differentiated intestinal type of gastric cancer [2, 4] is not associated with HDGC. Several other cancers, including colorectal and prostate, have been observed in *CDH1* mutation carriers, but these cancers do not occur at a rate significantly higher than the background levels observed in the wider population [5].

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Genetics of HDGC

Mutations

Approximately 100 germline mutations in the *CDH1* gene have now been published (Table 1). Although there are no major mutational hotspots (Fig. 1), some mutations, including 1003C>T [6–9], 1901C>T [7, 10, 11], and 1137G>A [7, 11, 12], have been observed in several unrelated families. A founder mutation (2398delC), confirmed by haplotype analysis, has been observed in four families from Newfoundland [7]. The most common types of mutation are small insertions or deletions (35% of the published mutations in Table 1). The other mutations are spread between missense (28%), nonsense (16%), splice site (16%), and large exonic deletions (5%) [13]. In addition to these major mutations, two regulatory sequence variants, –160C–>A [14] and the intron 2 variant 163+37235G>A [15] have been associated with an elevated risk of DGC, although these polymorphisms are rarely associated with a strong familial clustering.

No correlations between phenotype and the location or type of germline *CDH1* mutation have been made. In particular, there is no obvious correlation between genotype and the presence of lobular breast cancer in HDGC families [16]. In contrast, somatic *CDH1* mutations in sporadic DGC are predominantly splice site mutations resulting in exon skipping — particularly of exons 8–9, whereas most *CDH1* mutations identified in sporadic lobular breast cancer result in premature stop codons [17, 18].

Although germline *CDH1* mutations are found in all ethnic groups, they are surprisingly rare in countries with high rates of sporadic gastric cancer, including Japan and Korea. The reasons for this uneven

Table 1. Germline *CDH1* mutations identified in hereditary diffuse gastric cancer (HDGC) families

CDH1 mutation	Intron/exon	Type of mutation	*CDH1* mutation	Intron/exon	Type of mutation
del exon 1–2 [37]	Exon 1–>2	Large deletion	1391delTC [11]	Exon 10	Deletion
del exon 1–2 [37]	Exon 1–>2	Large deletion	1460T>C [58]	Exon 10	Missense
del 5′ UTR-exon 1 [37]	UTR–>exon 1	Large deletion	1466insC [59]	Exon 10	Insertion
2T>C[a]	Exon 1	Missense/ initiation codon	1472insA [60]	Exon 10	Insertion
3G>C [6]	Exon 1	Nonsense	1476delAG [40]	Exon 10	Deletion
41delT [61]	Exon 1	Deletion	1488del7 [2]	Exon 10	Deletion
45insT [60]	Exon 1	Insertion	1507C>T, cited in [7]	Exon 10	Nonsense
46insTGC[a]	Exon 1	Insertion	ND [62]	Exon 10	Nonsense
49–2A>C [11]	Intron 1	Splice site	1565+1G>A [16]	Intron 10	Splice site
49–2A>G [63]	Intron 1	Splice site	1565+1G>T [64]	Intron 10	Splice site
53delC [64]	Exon 2	Deletion	1565+2insT [29]	Intron 10	Insertion/ splice site
59G>A [63]	Exon 2	Nonsense	1588insC [2]	Exon 11	Insertion
70G>T [2]	Exon 2	Nonsense	1610delC [65]	Exon 11	Deletion
185G>T [66]	Exon 3	Missense	1619insG [67]	Exon 11	Insertion
187C>T [68]	Exon 3	Nonsense	1682insA [7]	Exon 11	Insertion
190C>T [2]	Exon 3	Nonsense	1710delT [64]	Exon 11	Deletion
283C>T [69]	Exon 3	Nonsense	1711insG [68]	Exon 11	Insertion
353C>G [11]	Exon 3	Missense	1711+5G>A [40]	Intron 11	Splice site
372delC [70]	Exon 3	Deletion	1774G>A, cited in [7]	Exon 12	Missense
377delC, cited in [7]	Exon 3	Deletion	1779insC [40]	Exon 12	Insertion
382delC [40]	Exon 3	Deletion	1792C>T [68]	Exon 12	Nonsense
515C>G, cited in [7]	Exon 4	Missense?	1795A>T, cited in [7]	Exon 12	Missense
517insA [71]	Exon 4	Insertion	1849G>A, cited in [7]	Exon 12	Missense
531+2T>A, cited in [7]	Intron 4	Splice site	1876T>A, cited in [7]	Exon 12	Missense
532–18C>T, cited in [7]	Intron 4	Splice site?	1901C>T [7, 10, 11]	Exon 12	Missense
586G>T [2]	Exon 5	Nonsense	1913G>A [7] [72]	Exon 12	Nonsense
641T>C [73]	Exon 5	Missense	2061delTG [40]	Exon 13	Deletion
687+1G>A [40]	Intron 5	Splice site	2064delTG [29]	Exon 13	Deletion
715 G>A [11]	Exon 6	Missense	2095C>T [1]	Exon 13	Nonsense
731A>G [58]	Exon 6	Missense	2161C>G [6]	Exon 13	Splice site
753insG[a]	Exon 6	Insertion	Del exon 14–16 [13]	Exon 14–>16	Large deletion
808T>G, cited in [7]	Exon 6	Missense	2164+5G>A [7]	Exon 14	Missense/ splice site
832G>A [60]	Exon 6	Splice site	2195G>A [40]	Exon 14	Missense
833–2A>G [29]	Intron 6	Splice site	2245C>T [7]	Exon 14	Missense
892G>A [40]	Exon 7	Missense	2269G>A [74]	Exon 14	Missense
1003C>T [6], [8, 9]	Exon 7	Nonsense	2275G>T [75]	Exon 14	Nonsense
1008G>T [1]	Exon 7	Missense/ splice site	2276delG [6]	Exon 14	Deletion
1018A>G [60]	Exon 8	Missense	2287G>T[a]	Exon 14	Nonsense
1023T>G[a]	Exon 8	Nonsense	2295+5G>A [64]	Intron 14	Splice site
1062delG [6]	Exon 8	Deletion	2310delC [40]	Exon 15	Deletion
1064insT [40]	Exon 8	Insertion	2343A>T [7]	Exon 15	Missense
1107delC [11]	Exon 8	Nonsense	2381insC [1]	Exon 15	Insertion
1118C>T [76]	Exon 8	Missense	2392G>A cited in [7]	Exon 15	Missense
1134del8ins5 [40]	Exon 8	Deletion and insertion	2395delC [29]	Exon 15	Deletion
1137G>A [7, 11], [12]	Exon 8	Splice site	2396C>G [67]	Exon 15	Missense
1137+1G>A [2]	Intron 8	Splice site	2398delC [7]	Exon 15	Deletion
1212delC [40]	Exon 9	Deletion	2399delG [77]	Exon 15	Deletion
1225C>T [40]	Exon 9	Missense	2440–6C>G [11]	Intron 15	Splice site
1243A>C [78]	Exon 9	Missense	2494G>A [79]	Exon 16	Missense
1285C>T [6]	Exon 9	Missense	Del exon 16 [13]	Exon 16	Large deletion
1302_1303insA, 1306_1307delTT [49]	Exon 9	Deletion and Insertion			

Question marks signify uncertainty about the biological significance of the variation
[a] H. More, University of Otago; unpublished results (2009)

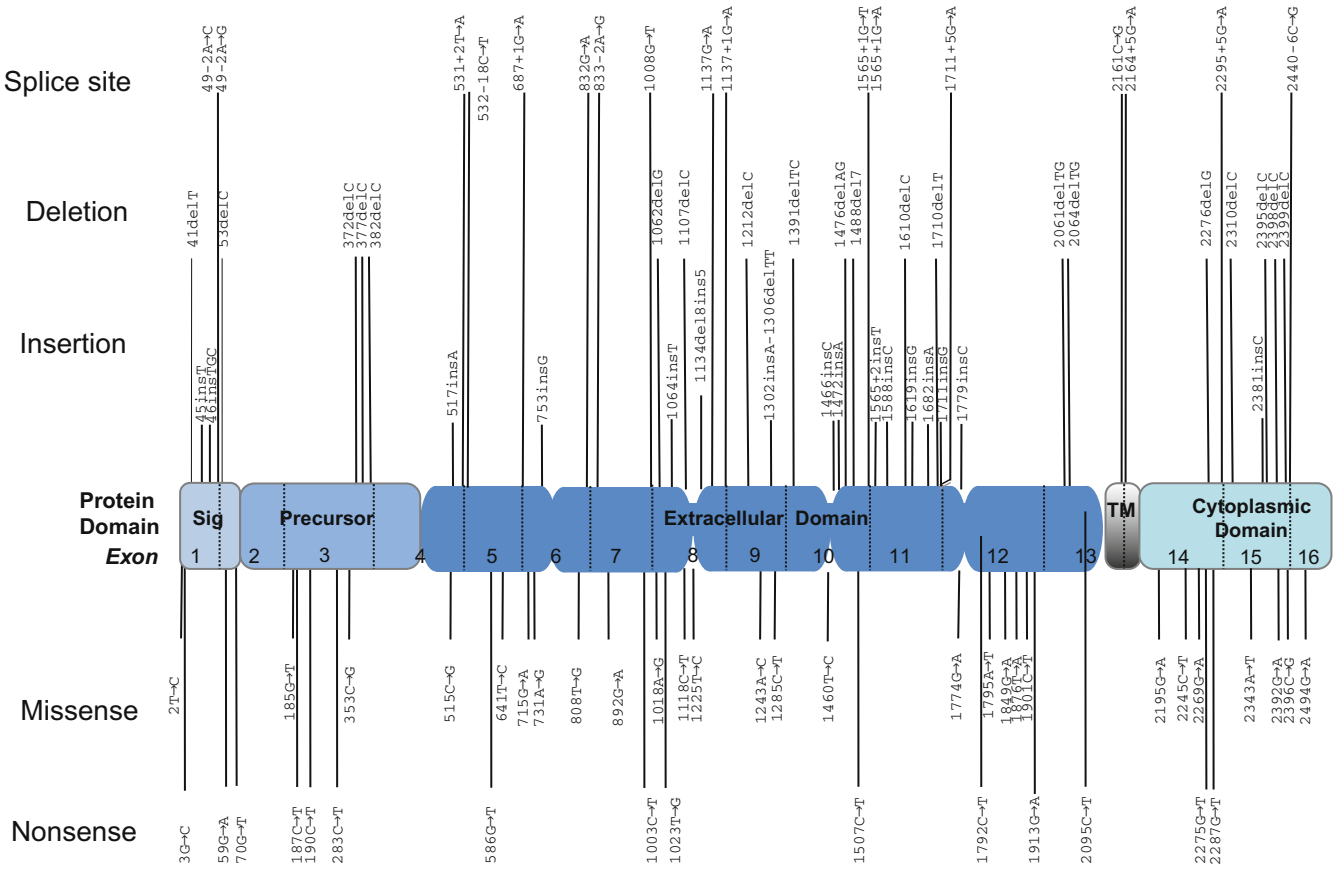

Fig. 1. The location and subclassification of germline *CDH1* mutations identified in hereditary diffuse gastric cancer (HDGC) families. The locations of the protein's signal peptide (*Sig*), precursor sequence, extracellular domains, transmembrane domain (*TM*), and cytoplasmic domain are illustrated by the *shaded segments*

distribution are not known. One possibility may relate to the influence of different genetic backgrounds on the viability of embryos which carry one inactivated *CDH1* allele.

Penetrance

A study of the incidence of advanced gastric cancer in 11 different HDGC kindred showed the penetrance of *CDH1* mutations to be incomplete, but relatively high. The cumulative risk of advanced gastric carcinoma by 80 years of age was 67% in men and 83% in women, with a mean age at diagnosis of 40 years (range, 14–85 years) [5]. There is no evidence for mutations in the *CDH1* coding sequence causing an attenuated form of HDGC analogous to attenuated familial adenomatous polyposis (FAP)[19], although polymorphisms in regulatory sequences such as –160C>A and 163+37235G>A (intron 2) that cause an increase in "sporadic" gastric cancer risk can be considered low-penetrance variants.

Pathology of HDGC

HDGC patients typically present with diffuse-type gastric cancer [3] with signet ring cells and, at late stage, linitis plastica. Advanced hereditary and sporadic DGC are indistinguishable. Anatomical mapping of complete gastrectomy specimens has shown that early-stage HDGC is characterized by the presence of multiple foci of stage T1a signet ring cell carcinoma (SRCC) confined to the superficial lamina propria, and with no nodal metastases [20–22]. The foci are submucosal and are not readily identified by gastroscopy (Fig. 2). The majority of foci appear relatively indolent; mitoses are observed less frequently than in the surrounding nonmalignant mucosa, and staining with β-catenin [23] and the proliferation marker Ki-67 [24] is weak. In addition to these abundant T1a SRCCs, in situ SRCC and the pagetoid spread of signet ring cells below the preserved epithelium of glands and foveolae are occasionally observed [23]. The relationship between the in situ and T1a foci remains to be determined.

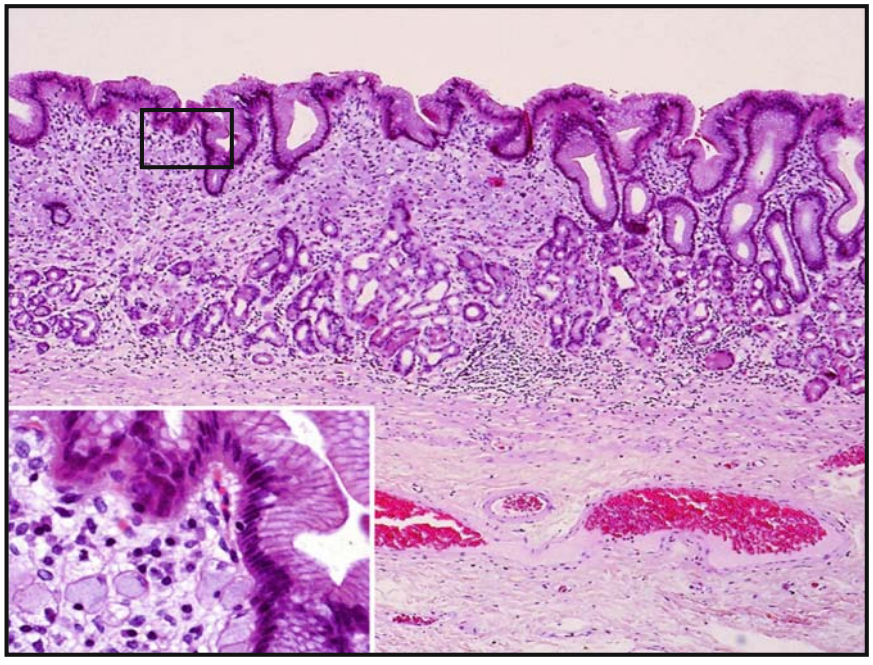

Fig. 2. Stage T1a signet ring cell carcinoma (SRCC) from a *CDH1* germline mutation carrier. The 9-mm focus (*occupying the left two-thirds of the frame*) occupies the full thickness of the mucosa under an intact epithelium (H&E, ×40). The *inset* frame shows signet ring cells in the lamina propria (×400). Adapted from Charlton et al. [22] with permission

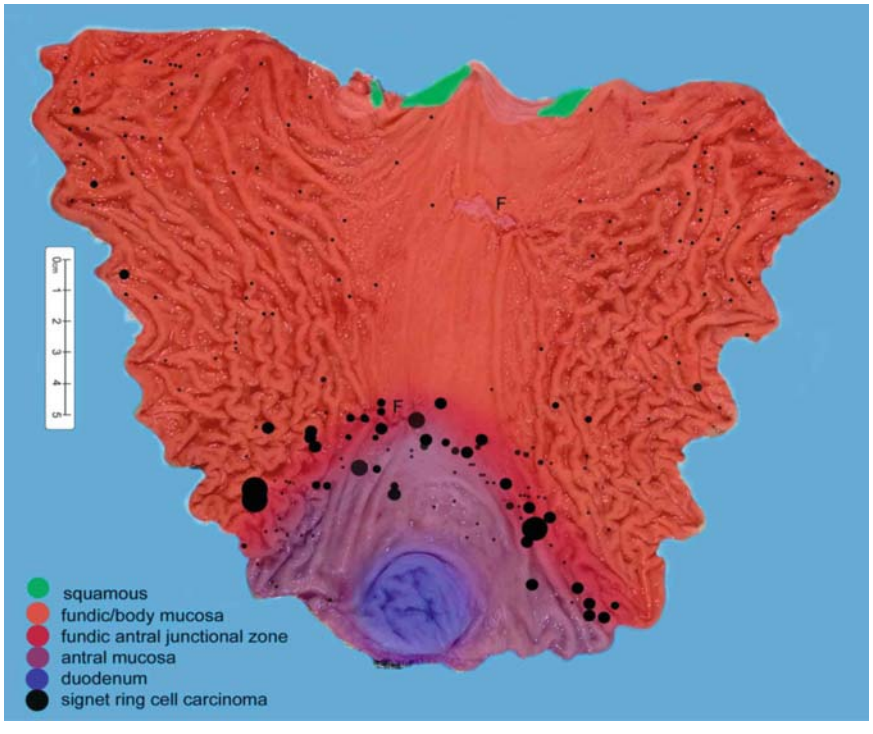

Fig. 3. Anatomical map of stomach showing size and location of foci of SRCC and mucosal zones in a 28-year-old male *CDH1* germline mutation carrier. The foci are to scale, except for foci of less than 1 mm, which are shown as 1 mm for visibility. This patient had 214 foci, with a strong clustering in the transition zone between the antrum and body. Adapted from Charlton et al. [22] with permission

In some, but not all, cases, the distribution of foci shows antral sparing and a marked increase in density and size within the transition zone between the antrum and body [22] (Fig. 3). Transition zone enrichment has been observed previously in canine and murine gastric cancer models: dogs administered with the carcinogen N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) develop SRCCs exclusively in the antral mucosa immediately adjacent to the transition zone [25], and mice which have been exposed to N-nitroso-N-butylurea [26], or have genetic disruption of *Bmpr1a* or *Smad4*, also develop tumors enriched at the gastrointestinal transition zones [27, 28].

There is wide variation in the number of foci both within and between HDGC kindred [23, 29]. Foci are particularly abundant in a New Zealand series (*CDH1*

mutation 1008G > T), where up to 487 T1a foci have been observed in a single stomach (mean, 102; median, 42) [30]. This contrasts with medians of less than 20 for the other three published series [23, 29, 31]. No correlation between patient age and number of foci has been observed. The absence of a positive correlation between age and number of foci may be explained by patients with large numbers of foci having a higher risk of developing advanced disease and therefore being under-represented in the older age groups. Alternatively, the absence of an accumulation in the number of foci over time may indicate: (i) that foci develop in a stochastic manner during a restricted developmental period, or (ii) that they can develop throughout life (perhaps following environmental insult) but often fail to persist. A similar lack of correlation between age and number of polyps has been observed in FAP families [19].

Immunofluorescence studies using gastric differentiation markers and the proliferation marker Ki67 are consistent with the T1a SRCC in HDGC patients developing from the upper isthmus of the neck region of the gastric gland [24, 32]. The neck region is believed to be the location of the gastric stem and progenitor cells [33]. Following initiation, the SRCCs appear to express mucin markers characteristic of differentiated surface pit cells and migrate towards the luminal surface [24, 32]. A comparable pattern of SRCC development has been described previously in human sporadic SRCC [34] and in a canine gastric cancer model [25]. The early SRCCs also produce pepsinogen, the precursor of the zymogen pepsin, in an unpolarized manner [35]. These cells may secrete sufficient pepsinogen from the basolateral surface to cause focal perforation of the basement membrane. Focal degradation of type IV collagen α chains has been observed previously in other subtypes of minimally invasive gastric intramucosal neoplastic lesions [36].

The initiation of HDGC

Cancers begin to develop in *CDH1* germline mutation carriers when the second copy of the *CDH1* gene is somatically inactivated or downregulated. The most common mechanism of downregulation is promoter hypermethylation, occurring in at least 50% of HDGC T1a SRCCs [32]. Loss of heterozygosity (LOH) has been reported in 12.5% (2/16) of advanced HDGC tumors [37], although its contribution to the early T1a SRCC may be less. It is not yet known whether the second hit is a purely stochastic event or if it can be attributed to environmental or physiological pressures. For example, mild nonatrophic gastritis is a common observation in the stomachs of HDGC patients, but it is not yet known if it is a contributing factor to disease initiation.

In the *Drosophila pIIa* cell, the loss of E-cadherin results in disruption of the correct alignment of the mitotic spindle, leading to daughter cells being deposited outside the normal epithelial plane [38]. Similarly, in mammalian Madin-Darby canine kidney (MDCK) cells, E-cadherin has been conclusively shown to act as a spatial cue for spindle orientation [39]. By analogy, we hypothesize that the loss of E-cadherin by the gastric/stem progenitor cells results in abnormal orientation of the mitotic spindle and the occasional division of cells out of the epithelial plane [35]. Deposition of a daughter stem cell in the lamina propria would be predicted to result in the generation of T1a SRCC. These very early SRCC foci are likely to remain relatively indolent until additional genetic damage enables prolonged survival and a capacity for invasion.

Clinical management

Criteria for CDH1 *mutation testing*

The original criteria for screening gastric cancer families for HDGC required confirmed DGC in a minimum of two first- or second-degree relatives, provided one is aged under 50 years, or three confirmed cases at any age [4]. Approximately 30% of families meeting these original criteria carried a predisposing *CDH1* mutation, although few mutations have been found in families without a case of DGC in an individual aged under 50 years. This observation, combined with the frequent impracticality of confirming histotype in more than one family member, has led to new testing criteria, consisting of a minimum of two first- or second-degree relatives with gastric cancer, provided one is aged under 50 years and one is confirmed as having diffuse type [40]; 48% of families meeting these criteria harbor germline *CDH1* mutations [40]. Fewer than 5% of individuals with DGC under 50 years of age and with no family history of gastric or breast cancer carry germline *CDH1* mutations, although this figure is likely to vary markedly between populations with different rates of sporadic gastric cancer [6]. The incidence of *CDH1* mutation carriers is presumably greater for isolated cases in individuals aged under 35 years [6].

Prophylactic total gastrectomy

Currently prophylactic total gastrectomy remains the only option to eliminate an inherited risk of gastric cancer. The reported mortality associated with total gastrectomy ranges from 0% to 6% [41, 42], although many patients in these published series have been

elderly. The mortality for young, healthy HDGC patients is likely to be less than 1% [43] in high-volume medical centers. The long-term morbidity after total gastrectomy is 100% and is related to alteration of eating habits, dumping syndrome, diarrhea, and weight loss. There is usually a 10% to 15% decrease in body weight, which is principally a decrease in body fat [42, 44]. Dumping syndrome (a combination of gastrointestinal and cardiovascular symptoms after eating) of varying severity occurs in all patients post gastrectomy; however, most patients get relief with specific dietary measures [45]. For this and other reasons, perioperative input from a specialist dietician is particularly important.

Surveillance endoscopy

Surveillance in HDGC is controversial because diffuse-type gastric cancer is notoriously difficult to detect at gastroscopy. Even advanced-stage DGC can be missed at gastroscopy as it can infiltrate beneath an intact epithelium. The clues to the presence of linitis plastica may be very subtle, such as the absence of the normal distensibility of the stomach. Despite these limitations, there is a need for gastroscopic surveillance for mutation carriers who: (i) decline prophylactic surgery, (ii) are younger than the age at which prophylactic surgery is recommended (approximately 20 years of age [43]), and (iii) prior to prophylactic surgery in newly diagnosed carriers.

Surveillance endoscopy should be carried out annually using a white light, high definition endoscope, ideally in a center with a special interest in HDGC. Sufficient time needs to be allowed to enable both the careful inspection of the mucosa on inflation and deflation and the taking of biopsies of all suspicious lesions, including any pale areas with a defined margin [46, 47]. Chromoendoscopy with Congo red/methylene blue has been used successfully to facilitate the detection of "pale lesions" [47]; however, this technique has been discontinued due to concerns over the toxicity of Congo red.

Minimum age for genetic testing and interventions in HDGC

The general consensus is that genetic testing should be offered at or near the age of consent (16/18 years). The decision when to test a given individual must consider: (i) the emotional and physical health of the individual and his/her family and (ii) the earliest age of cancer onset in HDGC families from the local population. For example, in New Zealand, the median age of DGC onset is 33 years of age [43], but the youngest case occurred in a 14-year-old boy [1]. As a consequence, it is recommended that genetic testing in New Zealand should begin at 16 years of age, but occasionally 1–2 years before, on a case-by-case basis.

The risk of advanced HDGC has been estimated to be less than 1% at age 20 years [5]. Consequently, prophylactic gastrectomy is not favored in mutation carriers under 20 years of age, because the risk of death from gastric cancer is approximately the same as the mortality associated with prophylactic total gastrectomy. It is therefore recommended that annual surveillance endoscopy be carried out on known mutation carriers in their teenage years.

Surgical management

The surgical approach described in most published HDGC gastrectomy series has essentially been the same, i.e.. total gastrectomy with a Roux-en-Y esophagojejunostomy reconstruction without construction of a jejunal pouch reservoir [43]. While there is some evidence that a jejunal pouch leads to improved food intake and weight gain in the early postoperative months, the long-term benefits have been marginal [42]. An interposition loop to restore duodenal transit has not been used routinely, as evidence suggests minimal clinical benefit and potentially increased risk [42]. Although most HDGC gastrectomies performed to date have used the open technique, there have been two recent reports of successful laparoscopic total gastrectomy for *CDH1* mutation carriers [48, 49].

As in surgery for sporadic gastric cancer, practice varies with respect to D1 versus D2 lymph node dissection. In support of a preference for D1 dissection in prophylactic cases, no nodal metastases have yet been reported in early HDGC [20–22, 43]. To date, the series from Auckland, New Zealand (Middlemore and Auckland City Hospitals) is the only series of gastrectomy in HDGC patients with surveillance-detected carcinoma. The standard approach at this center has been a D2 dissection with preservation of spleen and pancreas. The New Zealand preference for a modified D2 dissection is based on several factors. Firstly, DGC is difficult to detect, let alone reliably stage, and D2 dissection is the standard approach in sporadic gastric cancer in these hospitals. Secondly, provided spleen and pancreas are preserved, a D2 dissection is not considered to increase the mortality risk of the operation, yet has the benefit of full lymph node staging. In gastrectomies with prophylactic intent, the International Gastric Cancer Linkage Consortium's (IGCLC) consensus has been for D1 dissection [4].

For both prophylactic and screen-detected cases, it is essential to ensure the complete resection of the entire gastric mucosa. Determining the exact location of the squamocolumnar junction relative to the anatomical

gastroesophageal junction (GEJ) is hindered by the lack of a palpable or visible serosal surface marking. The practice in New Zealand has been to transect the esophagus 3–4 cm above the anatomical GEJ and visually confirm an intact cuff of squamous esophageal mucosa via an incision at the apex of the fundus [43]. If an intact cuff of squamous esophagus is not present, the esophagus is transected 1 cm more proximally and re-inspected. This approach using visual inspection is based on the premise that a macroscopic margin is preferable to a microscopic margin. Management of the gastroduodenal junction is easier as the palpable pyloric sphincter provides a reliable indication of the mucosal transition. An intact rim of duodenal mucosa can be confirmed through an incision along the greater curve, proximal to the pylorus [43].

Prognosis and follow up post-gastrectomy

Survival data from early gastric cancer (EGC) series provide an indication of the likely prognosis for HDGC. Five-year survival is more than 90% in almost all Western and Japanese EGC series and with T1a lesions has approached 95% in several case series [50]. The general clinical perception is that SRCC and DGC have a worse prognosis than intestinal-type gastric cancer [51]. However, stage-for-stage, survival from gastric SRCC is similar to [52] or if early, significantly better than that from other types [53–55]. This is illustrated by a large South Korean series that compared early gastric SRCCs with early nonSRC cancers: 5-year survival was 94% and 92%, respectively, and 10-year survival was 90% and 79% [53]. Consequently, if HDGC foci are limited to the gastric mucosa, prognosis is likely to be excellent following total gastrectomy. However, it remains possible that gastrectomies curative for gastric disease will unmask an additional risk of carcinoma at other sites in HDGC patients. This situation has been observed in FAP, where prophylactic colectomy has dramatically decreased deaths from colorectal carcinoma, but duodenal carcinoma now occurs with a cumulative incidence of 4.5% by age 57 years [56]. Although experience with HDGC is only ten years old and numbers are limited, there is as yet no suggestion of this additional risk being present.

Nutritional aspects

Total gastrectomy results in lifelong vitamin B12 deficiency and predisposes to iron malabsorption and deficiency. Roux-en-Y reconstruction means food bypasses the duodenum and a variable length of proximal jejunum, which are the major sites for calcium, vitamin D, iron, and folate absorption. Decreased intestinal transit time is thought to cause fat malabsorption in most patients, reducing the absorption of vitamins A, D, E, and K. The increased risk of osteoporosis, osteomalacia, and malnutrition post-gastrectomy is well described in gastric cancer patients, usually aged 60–70 years [44]; however, there is a paucity of data on the risk of these conditions in patients undergoing gastrectomy at a younger age.

Future perspectives

The role endoscopic surveillance plays in the management of HDGC is complicated by the observation that multiple small foci of T1a SRCC have been identified in practically all *CDH1* germline mutation carriers examined, including those in their teenage years [47]. Although these foci are relatively indolent, they can progress rapidly and unpredictably to advanced disease. There is an urgent need for improved endoscopic techniques for the detection of submucosal foci, coupled with histological or immunological markers which can pinpoint those that are more likely to progress. Because an epithelial-mesenchymal transition (EMT) may be correlated with the switch from indolence to aggression [24], EMT markers may constitute one class of putative "risk" markers.

Finally, the critical role that DNA methylation plays in the initiation of the early-stage T1a tumors suggests that DNA demethylating agents such as 5-aza-2′-deoxycytidine, which has been FDA-approved for the treatment of myelodysplastic syndrome, may provide one avenue for the chemoprevention and treatment of the early mucosa-confined SRCCs observed in HDGC. Although the toxicity of DNA demethylating agents would limit their long-term use, the prevention of new DNA methylation events could be achieved through the inhibition of other epigenetic events which may precede promoter hypermethylation, such as histone modification. It is notable that in an in vitro breast cancer model system, *CDH1* is first downregulated by histone deacetylation after exposure to exogenous signals, with DNA methylation only occurring subsequent to deacetylation [57]. Histone deacetylase inhibitors such as suberoylanilide hydroxamic acid (SAHA) and, in particular, the well-tolerated anticonvulsant valproic acid, should be further investigated in this context.

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