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Hereditary diffuse gastric cancer: What the clinician should know

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Abstract

Hereditary diffuse gastric cancer (HDGC) is an inherited autosomal dominant syndrome with a penetrance of up to 80% affecting diverse geographic populations. While it has been shown to be caused mainly by germline alterations in the E-cadherin gene (*CDH1*), problematically, the genetic diagnosis remains unknown in up to 60% of patients. Given the important knowledge gaps regarding the syndrome, asymptomatic carriers of *CDH1* mutations are advised for a prophylactic total gastrectomy. Intensive annual endoscopic surveillance is the alternative for carriers who decline gastrectomy. As HDGCs have a prolonged indolent phase, this provides a window of opportunity for surveillance and treatment. Recent findings of other gene defects in *CTNNA1* and *MAP3K6*, as well as further characterization of *CDH1* mutations and their pathogenicity will change the way HDGC patients are counselled for screening, surveillance and treatment. This review will bring the reader up to date with these changes and discuss future directions for research; namely more accurate risk stratification and surveillance methods to improve clinical care of HDGC patients.

Key words: Hereditary diffuse gastric cancer; *CDH1*; *CTNNA1*; *MAP3K6*; Gastrectomy

Core tip: While the incidence of hereditary diffuse gastric cancer remains low, it is an important clinical entity to recognize due to its high pathogenicity and penetrance. The International Gastric Cancer Linkage Consortium has outlined *CDH1* testing criteria and developed clinical utility gene cards to help clinicians manage such patients. Significant progress has been made in recent years and in future, testing of other genes is likely for *CDH1*-negative families. The mainstay of treatment for asymptomatic carriers of *CDH1* pathogenic mutations remains prophylactic total gastrectomy. Future research should focus on better risk stratification and surveillance methods.

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INTRODUCTION

Gastric cancer (GC) is currently the fourth most common cancer and the second leading cause of cancer associated death worldwide[1]. Based on the Lauren classification, at least two main histological types of GC have been identified: intestinal and diffuse[2]. Both histological types have different clinical features and molecular mechanisms[3-8]. Hereditary GCs account for only 1%-3% of GC cases[9], but are important for clinicians to identify as potentially curative interventions are available. One well-characterized syndrome is Hereditary diffuse gastric cancer (HDGC), which was attributed to germline mutations of the E-cadherin gene (*CDH1*) in 1998[10]. The International Gastric Cancer Linkage Consortium (IGCLC) has since established the latest set of clinical criteria in 2010 (listed in Table 1) to guide genetic screening[11].

Only about 40% of probands meeting the 2010 criteria carry *CDH1* germline alterations (often point or small frameshift mutations)[9,12]. Of the remaining 60%, a small percentage is due to *CDH1* deletions not detected by conventional DNA sequencing. More intriguingly, mutations in other genes like *CTNNA1*[13], *MAP3K6*[14], *INSR*, *FBXO24* and *DOT1L*[15] are starting to be identified. However, pathogenicity and penetrance of many newer mutations remain unanswered, creating management dilemmas. These non-*CDH1* mutations published thus far have been summarized in Table 2. Most studies are small and will require validation in consortium-led efforts for us to better understand the longitudinal impact.

CLINICAL HISTORY

Presentation

Similar to other gastric carcinomas, patients with HDGC are often asymptomatic in the early stages and tend to present late with symptoms such as weight loss, abdominal pain, nausea, anorexia, dysphagia, melaena and early satiety. The median age at diagnosis is 38 years, with the range varying greatly from 14-82 years[10,16].

Majority of HDGCs are inherited in an autosomal dominant pattern. It exhibits high penetrance and invasive disease often manifests before age 40. Therefore, one should have a high clinical suspicion when a family history reveals two or more cases of gastric cancer in first or second degree relatives, especially with one case diagnosed before age 50. The lifetime cumulative risk for diffuse GC reaches > 80% in men and women by age 80 years[11].

Other features seen in HDGC familes

There is an association of HDGC with lobular breast cancer (LBC) and it can be the presentating pathology[17]. Data based on 11 HDGC families, estimated the cumulative risk for LBC for female *CDH1* mutation carriers to be 39% (95%CI: 12%-84%) by 80 years of age[18]. Thus, personal or family history of multiple LBCs at a young age should also prompt CDH1 screening even if there is no HDGC. There have also been case reports of colorectal, prostate and ovarian carcinomas in HDGC families although these are rare and of uncertain significance[19-22]. Interestingly, cleft-lip, with or without cleft-palate malformations have been reported in several HDGC families, some of whom have specific *CDH1* splice site mutations[23,24].

Table 1 Clinical criteria for *CDH1* genetic testing (adapted from Fitzgerald *et al*[11])

⩾ 2 diffuse GC cases in 1st or 2nd degree relatives with one < 50 yr of age
⩾ 3 diffuse GC cases in 1st or 2nd degree relatives independent of age
Diffuse GC < 40 yr of age, without a family history
Personal or family history of diffuse GC and lobular breast cancer with one < 50 yr of age

GC: Gastric cancer.

Other relevant hereditary cancer syndromes

It should be remembered that GC can develop in the setting of other hereditary cancer syndromes aside from HDGC. One example would be Lynch syndrome which more often presents with intestinal-type gastric cancers and also has a high lifetime risk of colorectal and endometrial cancer. Other examples include Familial adenomatous polyposis, Li-Fraumeni syndrome, Peutz-Jegher's syndrome (PJS) and Juvenile Polyposis Syndrome (JPS) (Table 3). The lifetime risk of GC in these syndromes varies considerably but is generally lower than that in HDGC.

PATHOPHYSIOLOGY

Genetic susceptibility

E-cadherin is a cell adhesion protein that is required for development, cell differentiation and maintenance of epithelial architecture[6]. Since the E-cadherin gene *CDH1* was identified as a genetic basis for HDGC in 1998, more than 120 *CDH1* germline mutations have been published[25]. The most common germline alterations are small frameshifts, splice-site and nonsense mutations[9]. Of note, only two *de novo* mutations have been reported to date[26,27].

However, newer HDGC-susceptibility genes have been identified (Table 2). In 2012, an alpha-E-catenin (*CTNNA1)* germline truncating mutation was been found in a large Dutch HDGC pedigree[14] although the evidence presented was not definitive given a number of carriers remained cancer-free and other studies have failed to replicate findings[28]. At time of writing, *MAP3K6*[15], *INSR*, *FBXO24* and *DOT1L*[16] have also identified as candidate genes although they remain reports from single families. The insulin receptor (*INSR)* gene mutation is of special interest given insulin signaling has been reported to affect tumour cell invasion capability by modulating E-cadherin

Table 2 Summary of non-*CDH1* germline mutations in hereditary diffuse gastric cancer

Gene	Mutation	Location	Mutation type	Ethnicity	Ref.	Study type	Frequency	Remarks
CTNNA1	c.76delGA	Chr 5: 138117693	Nonsense	No data	[13]	Family study	1/1 family	Results in a framshift after Arg27 (p.Arg27Thr.fs*17)
MAP3K6	c.598G>T	Chr 1: 27690792	Missense	Canada	[14]	Family study and case series	1/1 family 1/115 cases	Likely pathogenic
MAP3K6	c.620T>G	Chr 1: 27690770	Missense	No data	[14]		No data	
MAP3K6	c.2837C>T	Chr 1: 27684750	Silent	No data	[14]		No data	Single nucleotide variant also in Canadian family, likely pathogenic
MAP3K6	c.2872C>A	Chr 1: 27684715	Missense	No data	[14]		No data	
MAP3K6	c.2544delC	Chr 1: 27685238 - 27685239	Nonsense	Portugese	[14]		1/115 cases	
INSR	c.3937 G>A	Chr 19: 7117279	Missense	Finland	[15]	Family study	1/1 family	
FBXO24	c.242G>C	Chr 7: 100187900	Missense	Finland	[15]		1/1 family	
DOT1L	c.3437C>T	Chr 19: 2223326	Missense	Finland	[15]		1/1 family	

Table 3 Comparison of hereditary cancer syndromes

Condition	Genetic pathology	Lifetime risk of gastric cancer	Histological subtype	Other clinical features
Hereditary diffuse gastric cancer	*CDH1* germline and other gene mutations	80%	Diffuse	Association with lobular breast cancer and cleft-lip malformations
Lynch syndrome	Mutations in mismatch repair genes	4.8% in *MLH1* carrier 9% in *MLH2* carrier[58]	Mainly intestinal-type	Lifetime risk of colon cancer 31%-38%, endometrial cancer 34% and ovarian cancer 20%[59]
Familial adenomatous polyposis	*APC* germline mutations	Population risk[60]	No data	Malignant extraintestinal tumours rare < 3% (thyroid, pancreas, medulloblastoma)[61]
Li-Fraumeni syndrome	*TP53* mutations	[1]4.9%[62]	No predominant subtype	Associated with wide range of early-onset cancers. Includes haematological and solid organ cancers: sarcomas, breast, brain, adrenal and lung cancers
Peutz-Jegher's syndrome	*STK11* mutations	29%[63]	No data	Characteristic mucocutaneous pigmentation commonly around mouth and nose High cumulative lifetime risk of any cancer (85%), most commonly colorectal (50%)[58]
Juvenile polyposis syndrome	*SMAD4* or *BMPR1A* mutations	[1]21%[64]	No data	Also at increased

[1]Frequency based on cross-sectional sample rather than lifetime risk from cohort study.

glycosylation[29] and is known to play a role in a variety of cancers[30]. There has also been a reported possibility of an association of early onset gastric cancer with *IL12RB1* mutation carriers[31] although this is mainly of the intestinal-type.

Somatic events

Guilford *et al*[10] has suggested HDGC develops from multiple foci of signet ring cell carcinomas (SRCC) in mutation carriers before 30 years of age. These SRCC, which have been termed "early HDGC"[32], develop after loss of the second *CDH1* allele *via* a 2nd-hit mechanism[33-36]. The same patient may present with distinct 2nd hit mechanisms in different lesions. Promoter methylation is the most common 2nd-hit mechanism in primary HDGC tumours although loss of heterozygosity was found to be the most prevalent in lymph node metastases[37].

Interestingly, other studies are starting to look at oncogenic pathways involved in metastatic progression in HDGC and have found one such candidate driver in a transforming growth factor beta receptor 2 loss-of-function mutation[38].

MANAGEMENT

Diagnosis

The identification of germline mutations in families fulfilling the criteria for HDGC relies on information from pathology reports from at least one proband. A report by Hebbard *et al*[39] on 23 patients who underwent prophylactic total gastrectomy showed 21 of them had evidence of diffuse/signet-ring carcinoma on final standardized pathological evaluation which was not picked up by preoperative endoscopic screening. Thus, for adequate pathological sampling, IGCLC recommends targeting any endoscopically visible lesions as well as random sampling of six biopsies for each of the following anatomical zones: antrum, transitional zone, body, fundus, cardia. This would give a minimum of 30 biopsies[11].

Treatment

Probands often present with advanced stage GC and

treatment consists of palliative chemotherapy (often taxanes, platinum agents or irinotecan), targeted radiotherapy and bypass surgery. While research looks into E-cadherin pathway regulators to increase chemosensitivity to epidermal growth factor receptor inhibitors and cytotoxics[40-42], there are currently no specific targeted therapies for diffuse GCs although there is an ongoing Phase I clinical trial studying everolimus in combination with chemotherapy[43].

As personalized therapy becomes increasingly prominent in cancer care, management of patients with HDGC should involve a multidisciplinary team of geneticists, surgeons and pathologists to address the following aspects of care: (1) genetic counselling and screening for both *CDH1* positive and negative patients. This should include a three-generation family pedigree, analysis of *CDH1*/other candidate gene mutation and translation into lifetime risks of diffuse GC and LBC[11]; and (2) discussion of prophylactic gastrectomy *vs* surveillance.

Guidelines for the clinical management of *CDH1* mutation carriers have been reviewed by the IGCLC (2010) and are outlined in clinical utility cards for HDGC[44]. Figure 1 summarises the management algorithm.

CDH1 missense mutation carriers

It is suggested that these individuals go on to have their mutations assessed for pathogenicity *via* functional *in-vitro* testing (aggregation and invasion assays) and *in-silico* models that have been developed[45]. These techniques have found a significant number of pathogenic missense variants and should be carried out by molecular diagnostic laboratories with appropriate expertise.

CDH1-negative individuals

Mutation screening in the research setting of HDGC families without *CDH1* mutations can be considered. Approaches needed would include high density single-nucleotide polymorphism (SNP) genotyping, non-parametric and parametric linkage analysis, whole exome sequencing as well as aforementioned pathogenicity assessments[14,15].

Surveillance

There is currently no reliable screening test for early diagnosis of diffuse GCs in mutation carriers. While IGCLC guidelines suggest annual endoscopic surveillance in specific settings, it should be known that direct visualization with endoscopy tends to detect lesions late in the disease process[46] and multiple random endoscopic samples often returns false negatives[39]. Other screening methods like chromoendoscopy and positron emission tomography have not been deemed to be consistently effective[47,48].

Prophylactic gastrectomy

Due to the lack of reliably sensitive surveillance methods, prophylactic total gastrectomy should be considered in the early 20s and is usually advised before age 40 for those carrying *CDH1* mutations. Some authors suggest consideration of gastrectomies in *CDH1* mutation carriers at an age 5 years younger than the youngest family member who developed gastric cancer[49].

There are currently no recommendations with regards to prophylactic gastrectomy in *CDH1*-negative individuals. Prospective studies evaluating prophylactic gastrectomy in HDGC have offered the surgery only to *CDH1* positive individuals[50], while a systematic retrospective review of 28 articles on prophylactic gastrectomy found a small sample of 11 *CDH1*-negative individuals who had undergone the gastrectomy before *CDH1* testing all had negative histopathology results for cancer[51].

Patients may refuse or decide to postpone the procedure due to young age, fertility concerns or fear of surgical complications. Fortunately, there have been reports of successful pregnancies post-prophylactic gastrectomy[52] and the youngest known carrier to date to undergo gastrectomy was 16 years of age[53].

ONGOING CHALLENGES

Risk stratification for CDH1-negative individuals

A significant proportion of HDGC families are likely to be *CDH1* negative. Further study to identify other genetic causes is needed before their risk and therefore management measures such as prophylactic gastrectomy can be assessed. As more cases of HDGC are identified, two lines of study are especially valuable. First, pathogenicity and penetrance of new germline mutations need to be documented to improve genetic counselling and decision-making. This is especially so for missense mutations. Second, prophylactic gastrectomy specimens provide material to identify molecular mechanisms that may predict progression from SRCC lesions to HDGC. In particular, elucidating epigenetic mechanisms, such as analysis of hypermethylation of cell cycle or DNA repair genes[54-57], may provide useful insights into possible environmental or pharmaceutical chemoprevention strategies.

Surveillance methods

Better surveillance methods could reduce morbidity by picking up target lesions earlier such that they are amenable to endoscopic therapies. While detection of diffuse GCs has proven difficult and surveillance frequency remains challenging, one paradigm to guide further research would be to assume that microfoci of SRCC will be present in all adult mutation carriers. Thus, rather than trying to detect all microfoci, the aim of surveillance should be geared towards detecting "high risk" SRCC. While this will require further elucidation of mechanisms of carcinogensis, it is plausible to imagine current surveillance methods, combined with genetic data, as a reliable alternative to prophylactic total

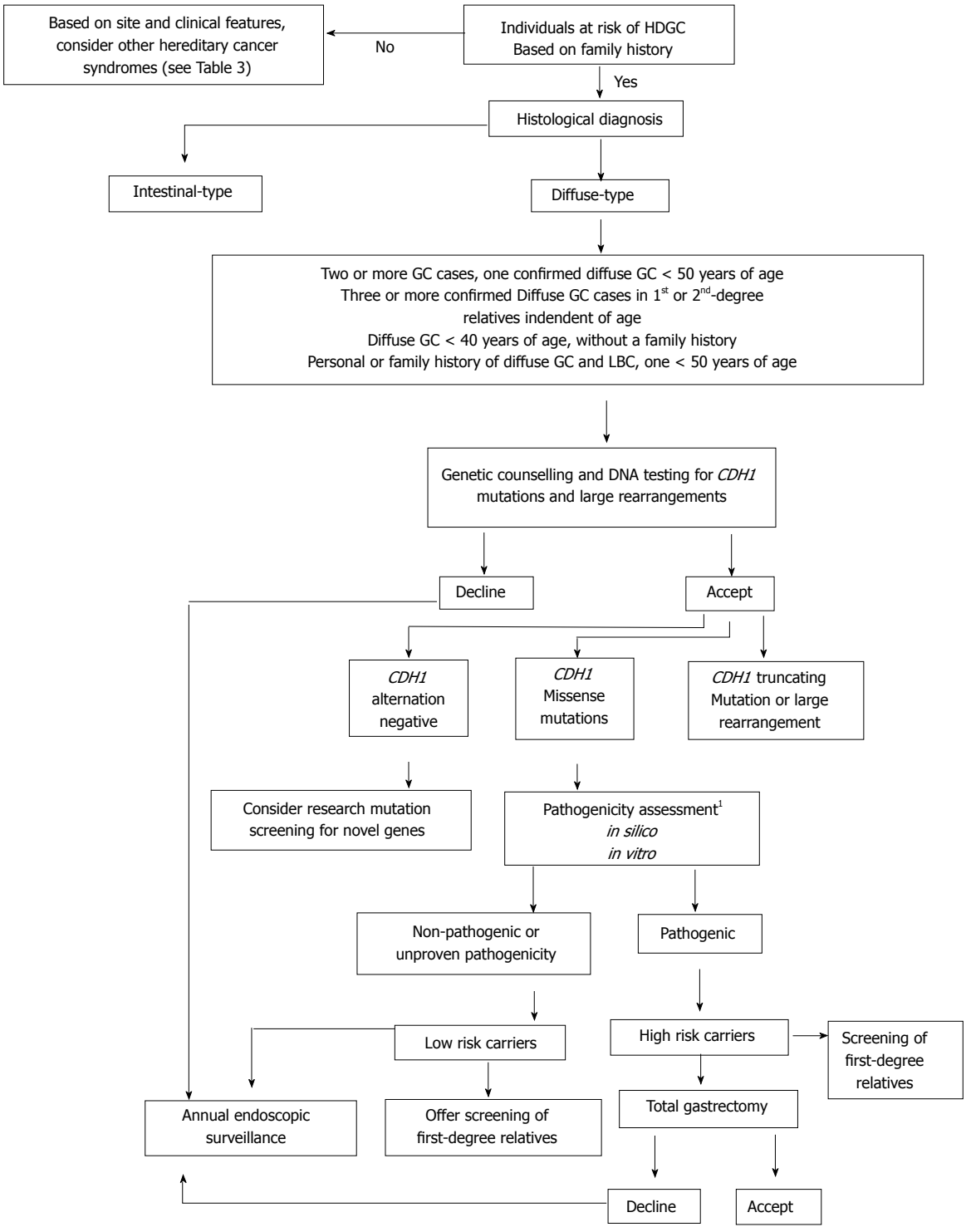

Figure 1 Clinical management of individuals suspected to have hereditary diffuse gastric cancer. Adapted from Pinheiro *et al*[9]. [1]Analyses recommended include: mutation frequency in healthy control population, co-segregation of mutation within pedigree, recurrence of mutation in independent families, in-silico predictions and *in vitro* functional assays[45,65-68].

gastrectomy.

CONCLUSION

While the incidence of HDGC remains low, it is an important clinical entity to recognize because of its high pathogenicity and penetrance. The IGCLC 2010 has outlined *CDH1* testing criteria and developed clinical utility gene cards to help clinicians manage such patients. Significant progress has been made in recent years and in future, testing of other genes is likely for *CDH1*-negative families. The mainstay of treatment for asymptomatic carriers of *CDH1* pathogenic mutations remains prophylactic total gastrectomy. However, it is hoped future research will lead to better risk stratification and surveillance methods to improve clinical

care for patients in terms of screening, prevention and treatment.

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