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Hereditary Diffuse Gastric Cancer

Synonym: HDGC

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Summary

Clinical characteristics

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant susceptibility for diffuse gastric cancer, a poorly differentiated adenocarcinoma that infiltrates into the stomach wall causing thickening of the wall (*linitis plastica*) without forming a distinct mass. Diffuse gastric cancer is also referred to as signet ring carcinoma or isolated cell-type carcinoma. The average age of onset of HDGC is 38 years (range: 14-69 years). The majority of the cancers in individuals with a *CDH1* pathogenic variant occur before age 40 years. The estimated cumulative risk of gastric cancer by age 80 years is 70% for men and 56% for women. Women are also at a 42% risk for lobular breast cancer.

Diagnosis/testing

A diagnosis of HDGC is established in a proband with:

- Diffuse gastric cancer (DGC) and a family history of one or more first- or second-degree relatives with GC; OR
- A personal and/or family history of DGC diagnosed before age 40 years; OR
- A personal and/or family history of DGC and LBC, one diagnosed before age 50 years.

If clinical features and family history are inconclusive, identification of a heterozygous germline *CDH1* pathogenic variant by molecular genetic testing confirms the diagnosis and allows for family studies.

Management

Treatment of manifestations: Ideally, management of individuals who have a *CDH1* cancer-predisposing variant is either intense surveillance for early detection and treatment of gastric cancer or prophylactic total gastrectomy. Care by a multidisciplinary team comprising those with expertise in medical genetics, gastric surgery,

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gastroenterology, pathology, and nutrition is recommended. For women, referral to a high-risk breast cancer clinic is recommended; prophylactic mastectomy may be considered.

Surveillance: To date, the optimal management of individuals at risk for a cancer-predisposing variant has been controversial because of the unproven value of surveillance regimes and the potential morbidity and mortality from prophylactic gastrectomy.

Pregnancy management: Women who have undergone prophylactic total gastrectomy (PTG) and are pregnant should be followed closely by their physician and a dietician who is aware of the situation.

Genetic counseling

Hereditary diffuse gastric cancer is inherited in an autosomal dominant manner. The vast majority of individuals with a pathogenic variant predisposing to diffuse gastric cancer have inherited it from one parent. *De novo* pathogenic variants have been reported. Each child of a proband has a 50% risk of inheriting the cancer-predisposing variant. Prenatal testing for pregnancies at increased risk is possible if the pathogenic variant in the family is known; however, requests for prenatal testing for conditions that (like HDGC) do not affect intellect and have some treatment available are not common.

Diagnosis

Suggestive Findings

According to the latest International Gastric Cancer Linkage Consortium (IGCLC) consensus guidelines [van der Post et al 2015] (see full text), hereditary diffuse gastric cancer (HDGC) **should be suspected** in a proband with ANY of the following:

- A diagnosis of gastric cancer and a family history of one or more individuals with gastric cancer, in which one affected individual has confirmed diffuse gastric cancer (DGC)
- A diagnosis of DGC occurring before age 40 years, regardless of family history
- A personal and/or family history of DGC and lobular breast cancer (LBC), with at least one individual diagnosed with one of these cancers before age 50 years

In addition, molecular genetic testing should be considered in a proband with any of the following:

- A diagnosis of DGC and pathologically confirmed in situ signet ring cells and/or pagetoid spread of signet ring cells adjacent to DGC
- A diagnosis of DGC and a family history of two first- or second-degree relatives with DGC or LBC
- A diagnosis of DGC and a personal or family history of cleft lip/palate

Establishing the Diagnosis

A clinical diagnosis of HDGC **is established** in a proband with diffuse gastric cancer confirmed on endoscopic biopsy AND one of the following:

- A family history of one or more first- or second-degree relatives with gastric cancer
- A personal and/or family history of one individual with DGC diagnosed before age 40 years
- A personal and/or family history of DGC and LBC, one diagnosed before age 50 years

If clinical features and family history are inconclusive, identification of a heterozygous pathogenic (or likely pathogenic) variant in *CDH1* by molecular genetic testing (see Table 1) confirms the diagnosis and allows for family studies. Therefore, molecular testing is recommended in all individuals with one of the Suggestive Findings and in individuals with a clinical diagnosis of HDGC.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *CDH1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *CDH1* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **A multigene panel** that includes *CDH1* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Hereditary Diffuse Gastric Cancer

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CDH1	Sequence analysis [3]	30%-50% [4]
	Gene-targeted deletion/duplication analysis [5]	4% [6]
Unknown [7]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Oliveira et al [2006], Kaurah et al [2007]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. 6.5% of individuals with HDGC who do not have a pathogenic variant identified on sequence analysis [Oliveira et al 2009]
7. Since 50%-70% of families with HDGC reported to date have no identifiable *CDH1* germline pathogenic variant, it is likely that some of these families may have pathogenic variants in other unidentified HDGC-susceptibility genes. Although candidate genes have been analyzed, no pathogenic variants have been identified.

Clinical Characteristics

Clinical Description

Age of onset. The average age of onset of hereditary diffuse gastric cancer (HDGC) is 38 years (range: 14-69 years). The majority of the gastric cancers occur before age 40 years. The age of onset is variable both between

and within families [Gayther et al 1998, Guilford et al 1998]. For age-related risks of developing cancer, see Penetrance.

Symptoms are nonspecific in the early stages of the disease and consequently tend to be dismissed both by affected individuals and by physicians. By the time specific symptoms appear, affected individuals are in an advanced stage of the disease [Wanebo et al 1993]. Symptoms in the late stage may include abdominal pain, nausea, vomiting, dysphagia, postprandial fullness, loss of appetite, and weight loss. Late in the course of stomach cancer, a palpable mass may be present.

Tumor spread or metastasis may lead to an enlarged liver, jaundice, ascites, skin nodules, and fractures.

Other cancers reported in family members include:

- **Lobular breast cancer (LBC).** Females with a *CDH1* germline pathogenic variant are at an increased lifetime risk (42% [95% confidence interval: 23%-68%]) for LBC [Hansford et al 2015]. The average age of onset for breast cancer is 53 years [Pharoah et al 2001].

  In a study of 318 women who had a personal and family history of LBC but no family history of DGC, Schrader et al [2011] found that 1.3% had a *CDH1* germline pathogenic variant.

- **Colorectal cancer** [Richards et al 1999, Oliveira et al 2002, Brooks-Wilson et al 2004]. There is no direct evidence that colorectal cancer is part of the spectrum of cancers associated with *CDH1* germline pathogenic variants. Therefore, these families need to be counseled accordingly on a case-by-case basis. In families where there is a clustering of colon cancer and a *CDH1* pathogenic variant, it is imperative to obtain as much clinical and pathologic information as possible on all individuals who have colon cancer.

Survival. When sporadic (i.e., non-hereditary) diffuse gastric cancer is detected early (i.e., before it has invaded the stomach wall), the five-year survival rate can be greater than 90%. The five-year survival rate drops below 30% when the diagnosis is made at a late stage [Stiekema et al 2013].

If gastric cancer is detected early and resected, the five-year survival rate is 90%. Because early detection of DGC is difficult, survival of individuals with *CDH1* pathogenic variants is believed to be the same as in individuals with sporadic DGC. Therefore, in individuals with a *CDH1* germline pathogenic variant, clinical management options include prophylactic gastrectomy and an intensive regimen of endoscopic surveillance.

Apart from the two of 17 individuals who had prophylactic gastrectomy and previous *Helicobacter pylori* infection on serologic testing [Blair et al 2006], there is no evidence of increased rates of *H pylori* infection associated with the microscopic DGCs in the prophylactic gastrectomy specimens of individuals with a germline *CDH1* pathogenic variant.

Pathology. In DGC, loss of the E-cadherin protein causes the individual tumor cells to grow and invade neighboring structures. The individual malignant cells infiltrate and spread under histologically normal-looking mucosa causing widespread thickening and rigidity of the gastric wall, a phenomenon known as *linitis plastica* [McColl 2006]. No tumor mass is formed, unlike that of the intestinal type. The malignant cells have a distinctive signet ring appearance, which is caused by an accumulation of intracellular mucin that pushes the nucleus to one side. A clearly defined preneoplastic lesion is not seen in DGC. A progression model for DGC developed from studying prophylactic total gastrectomy (PTG) specimens from individuals with a germline *CDH1* pathogenic variant describes isolated neoplastic signet ring cells at the base of the glands and pagetoid spread of signet ring cells below the preserved epithelium of glands/foveolae into the stroma [Carneiro et al 2004].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported to date.

Penetrance

The penetrance of HDGC is incomplete. A recent study that included 75 families with germline *CDH1* pathogenic variants found that by age 80 years, the cumulative incidence of gastric cancer was 70% (95% CI, 59%-80%) for males and 56% (95% CI, 44%-69%) for females, and the risk of breast cancer for females was 42% (95% CI, 23%-68%) [Hansford et al 2015].

Prevalence

The worldwide incidence of gastric cancer has been falling steadily since the 1970s with the phenomenon being most noticeable in developed countries [GLOBOCAN]. Given that the incidence of gastric cancer varies by geographic region, the percentage of individuals with gastric cancer who have a germline *CDH1* pathogenic variant identified ranges from 1% to 3% [Corso et al 2012].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CDH1*.

The loss of E-cadherin protein expression in sporadic diffuse gastric and lobular breast tumors is associated with somatic *CDH1* single-nucleotide variants, loss of heterozygosity, and promoter hypermethylation in the tumors [Becker et al 1994, Oda et al 1994, Day et al 1999, Anastasiadis & Reynolds 2000, Tamura et al 2000, Kallakury et al 2001, Machado et al 2001].

Differential Diagnosis

An estimated 5%-10% of all gastric cancer is thought to be familial [Zanghieri et al 1990, La Vecchia et al 1992]. Familial gastric cancer is both clinically and genetically heterogeneous.

Intestinal-type gastric cancer (IGC) arises from a precursor lesion, intestinal metaplasia, which forms a large protruded, ulcerated, or infiltrative lesion in the stomach. Histologically IGC is composed of tubular or glandular formations of variable differentiation that resemble adenocarcinomas of the intestinal tract. In contrast to diffuse gastric cancer (DGC), E-cadherin is present. IGC is more common than DGC, although the incidence of IGC appears to be declining [Ajani et al 2010]. Risk factors for IGC include chronic gastric mucosal infection with *H pylori* [Uemura et al 2001, Suerbaum & Michetti 2002]; smoking; a diet high in nitrites, salt, and smoked or pickled foods and low in fruit and vegetables; age; and male sex. Variants in *TNF* and *IFNGR1* can significantly increase the risk for gastric cancer, particularly in those infected with virulent strains of *H pylori* [Canedo et al 2008].

Other Cancer Predisposition Syndromes

Gastric cancer is seen in several other autosomal dominant cancer predisposition syndromes, including Lynch syndrome (hereditary non-polyposis colorectal cancer), Li-Fraumeni syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome, and Cowden syndrome (one of the *PTEN* hamartoma tumor syndrome phenotypes).

Lynch syndrome, which is associated with germline pathogenic variants in mismatch repair genes or *EPCAM*, predisposes heterozygotes to colorectal and other cancers. Gastric cancer is the third most common cancer in these individuals. IGC is the predominant subtype in Lynch syndrome [Lynch et al 2005, Capelle et al 2010]. Microsatellite instability (MSI) was observed in approximately 15% of gastric cancers from individuals in Florence, Italy, an area with high gastric cancer risk [D'Errico et al 2009]. Gastric cancers with high MSI tend to occur in the antrum of the stomach, be of the intestinal type, and have better survival rates [Falchetti et al 2008].

Familial adenomatous polyposis (FAP) is caused by germline pathogenic variants in *APC*. Gastric cancer has been seen in 0.6% of persons with FAP in Western populations [Jagelman et al 1988]. The incidence of gastric cancer is significantly higher in individuals with FAP in the East Asian population [Yamaguchi et al 2016].

Li-Fraumeni syndrome (LFS). Cancers in LFS are caused by pathogenic variants in *TP53*. *CHEK2* and *CDKN2A*, which are genes in the *TP53* pathway, may be LFS candidate genes; however, further confirmation of this is needed [Olivier et al 2003, Malkin 2011]. Both DGC and IGC are observed [Keller et al 2004, Oliveira et al 2004].

***BRCA1* and *BRCA2* hereditary breast and ovarian cancer.** Increased risk for gastric cancer has been associated with pathogenic variants in *BRCA1* [Brose et al 2002, Friedenson 2005] and *BRCA2* [Breast Cancer Linkage Consortium 1999, Risch et al 2001]. Gastric cancer occurs in 5.7% of families with the *BRCA2* 6174delT pathogenic variant [Figer et al 2001]. Jakubowska et al [2002] found that in 7% of individuals with gastric cancer a *BRCA2* pathogenic variant may be the underlying genetic cause, although the histopathology of the gastric cancer was not reported. Testing by multigene panels has identified *BRCA1* and *BRCA2* pathogenic variants in a number of individuals with diffuse gastric cancer and a family history of breast cancer [Hansford et al 2015, Sahasrabudhe et al 2017, Slavin et al 2017].

Carney triad (OMIM 604287). A rare gastric lesion, gastric gastrointestinal stromal tumor, previously known as gastric epitheliod leiomyosarcoma, is found in individuals with Carney triad [Carney et al 1977].

Carney-Stratakis syndrome (OMIM 606864). Gastric stromal sarcomas were observed in 12 individuals with this disorder who had paraganglioma, gastric stromal sarcoma, or both [Carney & Stratakis 2002]. Germline pathogenic variants in *SDHB*, *SDHC*, and *SDHD* are causative [Pasini et al 2008]. Inheritance is autosomal dominant.

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is a recently identified autosomal dominant fundic gastric polyposis syndrome with areas of dysplasia or intestinal-type gastric adenocarcinoma that are restricted to the proximal stomach. Affected individuals are at increased risk for gastric cancer, but there is no evidence of colorectal or duodenal polyposis [Worthley et al 2012]. Heterozygous germline pathogenic variants in the promoter 1B of *APC* are causative [Li et al 2016, Repak et al 2016, Beer et al 2017].

Management

The IGCLC has updated consensus guidelines for clinical management of individuals with a *CDH1* pathogenic variant [van der Post et al 2015] (see full text and Figure 1 therein).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hereditary diffuse gastric cancer, the following evaluations are recommended:

- Baseline endoscopy to look for macroscopic tumor [van der Post et al 2015]
- Evaluation of *CDH1* heterozygotes for *H pylori* infection given its ability to induce promoter hypermethylation of *CDH1* and its role in gastric cancer carcinogenesis
- Clinical breast examination and mammography in females
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Care by a multidisciplinary team comprising those with expertise in clinical genetics, gastric surgery, gastroenterology, pathology, and nutrition is recommended. See Fitzgerald et al [2010] (full text) and van der Post et al [2015] (full text).

Diffuse gastric cancer

- Total gastrectomy is recommended [Fitzgerald et al 2010, van der Post et al 2015]. Studies have shown that surgery alone is less than satisfactory, with cure rates approaching only 40%.
- Adjuvant therapy. Three large, randomized controlled trials showed the survival benefit of adjuvant therapy over surgery alone [Macdonald et al 2000, Cunningham et al 2006, Sakuramoto et al 2007]. Numerous randomized clinical trials have failed to show consistent survival benefits from adjuvant radiation therapy or chemotherapy alone in the treatment of gastric cancer.
- *H pylori* infection (if present) is treated in the standard manner.

Lobular breast cancer. The treatment of breast cancer in individuals with *CDH1*-related breast cancer is similar to that in sporadic forms of lobular breast cancer (National Comprehensive Cancer Network Guidelines).

Prevention of Primary Manifestations

Heterozygotes for a Germline *CDH1* Pathogenic Variant

Diffuse gastric cancer. Prophylactic total gastrectomy (PTG) is recommended rather than endoscopic surveillance due to the observation of early gastric cancers in PTG samples from individuals with a germline *CDH1* pathogenic variant [Norton et al 2007]. PTG involves D-2 dissection and Roux-en-Y esophagojejunostomy and obtaining proximal margins to ensure removal of the gastric mucosa [Norton et al 2007]. A multidisciplinary team including a surgeon, gastroenterologist, and dietician should provide preoperative and postoperative care for an individual undergoing PTG. The multidisciplinary team members can counsel candidates for PTG on the risks and benefits of the surgery. In making the decision to undergo PTG, the affected individual and treating physicians should consider the following:

- In a young, healthy individual, the risk of mortality with PTG in an experienced surgeon's hands is less than 1% [Lynch et al 2005].
- The morbidity from PTG is 100% [Worster et al 2014, Muir et al 2016]. All individuals have immediate as well as long-term complications including rapid intestinal transit, dumping syndrome, diarrhea, eating habit alterations, and weight loss [Caldas et al 1999, Lewis et al 2001]. The risk for malabsorption increases, including an increased incidence of osteoporosis, osteomalacia, and malnutrition.
- Gastric cancer is associated with age-specific risks: due to nutritional implications, PTG is not generally recommended until the individual's growth period is complete. In families with early-onset gastric cancer, PTG should be considered on a case-by-case basis [Blair et al 2006]. In these individuals, regular endoscopic screening may be begun prior to the consideration of PTG.
- Individuals with a *CDH1* pathogenic variant are at risk for extragastric cancers (e.g., lobular breast cancer, colorectal cancer) and should follow screening recommendations for these cancers.

Breast cancer. Referral to a high-risk breast clinic is recommended. Prophylactic mastectomy may be considered in women heterozygous for a *CDH1* germline pathogenic variant. The authors are aware of a very limited number of women who have undergone prophylactic mastectomy for this reason [Brandberg et al 2008].

Prevention of Secondary Complications

A multidisciplinary team including a surgeon, gastroenterologist, and dietician should provide postoperative care for an individual undergoing PTG (see Prevention of Primary Manifestations).

Surveillance

See Fitzgerald et al [2010] (full text) and van der Post et al [2015] (full text).

Gastric Cancer

The optimal surveillance of individuals with a *CDH1* germline pathogenic variant is controversial because of the unproven benefit of screening.

Endoscopy permits direct inspection and biopsy of suspicious areas; however, diffuse gastric cancer is difficult to detect at an early, treatable stage because the lesions tend to spread in the submucosa rather than as exophytic masses. The submucosal lesions are difficult to identify; an additional challenge is sampling bias in a macroscopically normal-appearing gastric mucosa. Therefore, diffuse gastric cancer is often not detected until it reaches an advanced, incurable stage.

At-risk individuals who are not ready to undergo PTG should be screened using the Cambridge protocol [Barber et al 2008]:

- Detailed 30-minute upper endoscopy every six to 12 months with multiple random biopsies and biopsies of subtle lesions
- Screening beginning five to ten years prior to the earliest cancer diagnosis in the family

Mi et al [2018] evaluated the utility of endoscopic surveillance in individuals with an identified *CDH1* pathogenic variant who were delaying PTG and a group with clinically diagnosed HDGC but no identified *CDH1* pathogenic variant. The authors used autofluorescence imaging and narrow-band imaging with random biopsies; surveillance was performed by the same group of specialists on all individuals. Individuals with a *CDH1* pathogenic variant were found to have a high yield of signet ring cell carcinoma foci on their first endoscopy (63.6%) compared to the latter group (9.7%), underscoring the importance of baseline endoscopy in perhaps staging invasive disease before gastrectomy in individuals with a *CDH1* pathogenic variant.

Several other screening modalities for diffuse gastric cancer are being tested.

Chromoendoscopy, using indigo-carmine staining, has been shown to improve the detection rate of early gastric cancer [Stepp et al 1998, Fennerty 1999]. Charlton et al [2004] studied six stomachs removed prophylactically after macroscopically normal gastric endoscopies. A pH-sensitive Congo red dye followed by pentagastric stimulation revealed signet ring foci that were five times more prevalent in the transitional zone of the distal stomach, a finding in contrast with other studies [Carneiro et al 2004]. The transitional zone occupies less than 10% of the stomach and lacks gastric-secreting G cells. The authors suggest that chromoendoscopy using Congo red dye and pentagastric stimulation may highlight this area during endoscopy and thus increase the chances of detecting cancer foci. Further research is needed to evaluate this possibility.

The same group of investigators reported a year later on a follow up of 99 surveillance endoscopies over five years [Shaw et al 2005]:

- 69 of 99 (70%) endoscopies were normal.
- 23 lesions with signet ring cell cancer were identified in ten individuals.
- The Congo red/methylene blue dye detected foci between 4 and 10 mm, not less than 4 mm.

Note: Congo red is no longer available for this use due to concerns over toxicity of the dye.

Hüneburg et al [2016] performed endoscopic detection on seven individuals with *CDH1* pathogenic variants by using high-resolution white light endoscopy and pan gastric chromoendoscopy with indigo carmine combined with targeted and random biopsies. All individuals were scheduled for this presurgical procedure. Using the Cambridge protocol, only a single focus of signet ring cell cancer (14%) was detected during the random biopsies. Given the small numbers in these series and the conflicting results, these findings need to be evaluated in more individuals with a *CDH1* pathogenic variant.

Endoscopic ultrasound examination is important in the detection and staging of gastrointestinal cancers [Pfau & Chak 2002], but is not believed to be useful in detecting precursor lesions [Fitzgerald & Caldas 2004].

Other tools in use include PET scan [van Kouwen et al 2004], endoscopic ultrasound, stool for guaiac, abdominal CT, and multiple random stomach biopsies [Barber et al 2008]. However, none of these reliably detects DGC, as demonstrated by the finding – one week after a number of these screening investigations were performed – of multiple small cancer foci in six of six gastrectomy specimens from individuals who were heterozygous for a *CDH1* pathogenic variant [Norton et al 2007].

Lobular Breast Cancer (LBC)

Currently the data on women with germline *CDH1* pathogenic variants and lobular breast cancer are insufficient to determine the best screening strategies. Recommendations for LBC risk management in *CDH1* heterozygotes or at-risk women are based on recommendations for women with a *BRCA1* or *BRCA2* germline pathogenic variant (see *BRCA1* and *BRCA2* Hereditary Breast and Ovarian Cancer) including:

- Monthly breast self-examinations starting at age 20
- Clinical breast examinations every six months starting at age 30
- Referral to a high-risk breast-screening program if possible. Given the low sensitivity of detecting lobular breast cancer by mammography, bilateral breast MRI examination should be performed in females with a *CDH1* pathogenic variant. Annual breast MRI examination starting at age 30 in women with a *CDH1* pathogenic variant is recommended.

Colon Cancer

Although evidence is insufficient to conclude that colon cancer is a manifestation of HDGC, it is prudent to recommend colonoscopy every three to five years beginning at age 40 years or ten years prior to the youngest age at diagnosis of colon cancer in families in which both DGC and colon cancer have occurred [Fitzgerald et al 2010, van der Post et al 2015].

Evaluation of Relatives at Risk

It is appropriate to offer molecular genetic testing to at-risk relatives if the *CDH1* pathogenic variant is identified in an affected family member so that morbidity and mortality can be reduced by early diagnosis and treatment.

See Genetic Counseling, **Predictive testing in minors** for discussion of issues related to testing of this population and issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Evidence shows that pregnancy after PTG can have healthy and normal outcomes. Kaurah et al [2010] discussed six healthy pregnancies and infants born to four women after total gastrectomy. However, it is important that pregnant women who have undergone PTG be followed closely by their physician and a dietician who is aware of their situation.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The

following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hereditary diffuse gastric cancer (HDGC) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The majority of individuals with *CDH1*-related HDGC inherited the *CDH1* pathogenic variant from a parent. Because of reduced penetrance, the parent from whom the pathogenic variant was inherited may not have developed cancer.
- Alternatively, a proband with HDGC may have the disorder as the result of a *de novo* pathogenic variant. Shah et al [2012] described the first conclusive case of a *de novo CDH1* germline pathogenic variant in a family with HDGC.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* germline pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- Note: Although most individuals diagnosed with HDGC have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or reduced penetrance.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected and/or has a *CDH1* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
- The sibs of a proband with clinically unaffected parents are still at increased risk for HDGC because of the possibility of reduced penetrance in a parent.
- If the pathogenic variant cannot be detected in the DNA of either parent and biparental inheritance at the *CDH1* locus is proven by haplotype inheritance, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of a proband is at a 50% risk of inheriting the cancer-predisposing variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected or has a *CDH1* pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without

molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling - for health professionals (part of PDQ®, National Cancer Institute).

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *CDH1* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.
- In 50%-70% of families with HDGC, cancer susceptibility is caused by unknown genetic factors; thus, predictive testing is not possible in these families.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years). Genetic testing in individuals younger than age 18 years has always been a controversial issue. Since there have been reports of individuals younger than age 18 years who are diagnosed with HDGC [Guilford et al 1998], it has been suggested that genetic testing in individuals younger than age 18 years may be beneficial [Caldas et al 1999, Fitzgerald et al 2010]. Kodish [1999] proposed the application of the following rule to the testing of minors: genetic testing should be permitted at an age no earlier than the age of first possible onset of cancer. He states that this rule tries to maximize the benefits to the child while minimizing the risks. Overall, a request from parents for testing of asymptomatic at-risk individuals younger than age 18 years requires sensitive and understanding (though rigorous) counseling for both the parents and the child. The IGCLC has agreed that genetic testing of at-risk individuals at age 16 years can be considered if the age of onset in the family is early [Fitzgerald et al 2010].

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *CDH1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Cancer Institute (NCI)**
  6116 Executive Boulevard
  Suite 300
  Bethesda MD 20892-8322
  Phone: 800-422-6237 (toll-free)
  Email: cancergovstaff@mail.nih.gov
  Stomach (Gastric) Cancer
- **No Stomach For Cancer**
  Phone: 608-692-5141
  Email: support@nostomachforcancer.org
  www.nostomachforcancer.org
- **American Cancer Society**
  Phone: 800-227-2345
  www.cancer.org
- **CancerCare**
  Phone: 800-813-4673
  Email: info@cancercare.org
  www.cancercare.org
- **International Society for Gastrointestinal Hereditary Tumours (InSiGHT)**
  www.insight-group.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hereditary Diffuse Gastric Cancer: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CDH1	16q22.1	Cadherin-1	CDH1 @ LOVD	CDH1	CDH1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Hereditary Diffuse Gastric Cancer (View All in OMIM)

137215	DIFFUSE GASTRIC AND LOBULAR BREAST CANCER SYNDROME; DGLBC
192090	CADHERIN 1; CDH1

Molecular Pathogenesis

E-cadherin is a transmembrane protein that is predominantly expressed at the basolateral membrane of epithelial cells, where it exerts cell-cell adhesion and invasion-suppression functions [Nagar et al 1996].

E-cadherin is one member of the cadherin family of molecules, all of which are transmembrane glycoproteins mediating calcium-dependent cell-cell adhesion [Takeichi 1991, Berx et al 1995]. E-cadherin is critical for establishing and maintaining polarized and differentiated epithelia during development [Keller 2002]. It also plays important roles in signal transduction, differentiation, gene expression, cell motility, and inflammation. The activity of E-cadherin in cell adhesion is dependent on its association with the actin cytoskeleton via undercoat proteins called catenins (α-, β-, and γ-) [Jou et al 1995, Kallakury et al 2001].

A role for E-cadherin in tumor development is well established [Wijnhoven et al 2000] because many human carcinomas (e.g., skin, lung, breast, urologic, gastric, colon, pancreatic, ovarian) exhibit reduced E-cadherin expression relative to their normal cellular counterparts [Giroldi et al 2000, Karayiannakis et al 2001, Tsanou et al 2008, Ch'ng & Tan 2009, Kuner et al 2009]. Loss of E-cadherin expression is seen in most diffuse gastric cancers and in lobular breast cancers; expression is usually maintained in intestinal gastric cancers and ductal breast cancers [Hirohashi 2000].

Cells deficient in E-cadherin lose their ability to adhere to each other and consequently become invasive and metastasize [Birchmeier 1995, Perl et al 1998]. The causal effect of E-cadherin loss or dysregulation in tumorigenesis has been demonstrated using carcinoma cell lines and transgenic models [Hsu et al 2000]. Examination of in situ diffuse gastric cancer lesions from a prophylactic total gastrectomy specimen have shown this loss of E-cadherin to be an early initialing event that leads to invasion [Humar et al 2007].

Loss of heterozygosity is a common phenomenon seen in association with loss of expression of tumor suppressor genes [Knudson 1971]. The tumor suppressor function of E-cadherin is supported through evidence of the loss of expression of the other *CDH1* allele [Grady et al 2000, Barber et al 2008, Oliveira et al 2009].

Gene structure. *CDH1* comprises 16 exons that span 100 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. To date, more than 155 germline pathogenic variants have been reported in families with hereditary diffuse gastric cancer [Gayther et al 1998, Guilford et al 1998, Richards et al 1999, Yoon et al 1999, Dussaulx-Garin et al 2001, Humar et al 2002, Jonsson et al 2002, Oliveira et al 2002, Brooks-Wilson et al 2004, Keller et al 2004, Suriano et al 2005, Frebourg et al 2006, Rodriguez-Sanjuan et al 2006, Kaurah et al 2007, Masciari et al 2007, More et al 2007, Roviello et al 2007, Van Domselaar et al 2007, Oliveira et al 2009, Ghaffari et al 2010, Mayrbaeurl et al 2010].

The pathogenic variants are primarily truncating, usually through frameshift variants, exon/intron splice site variants, and single-nucleotide variants [Gayther et al 1998, Guilford et al 1998, Richards et al 1999, Humar et al 2002, Oliveira et al 2002, Brooks-Wilson et al 2004].

Pathogenic missense variants have also been identified in some families [Shinmura et al 1999, Yoon et al 1999, Oliveira et al 2002, Brooks-Wilson et al 2004]. The pathogenicity of missense variants can be investigated through in vitro analysis, although only on a research basis [Suriano et al 2003].

Large deletions make up approximately 4% of these variants [Oliveira et al 2009, Yamada et al 2014].

The pathogenic variants are distributed throughout the gene. However, there are reports of the same pathogenic variant being found in several unrelated families [Hansford et al 2015].

A founder variant has been seen in four families from Newfoundland, Canada [Kaurah et al 2007]. The pathogenic variant NM_004360.3:c.2398delC (p.Arg800AlafsTer16) was confirmed by haplotype analysis in these families.

Germline pathogenic variants have been identified in several ethnic groups; germline variants appear to be rare in countries in which the rates of sporadic gastric cancer are high [Hansford et al 2015]. The reason is not

known; it may be postulated that the differences in genetic backgrounds of the various ethnicities may have different effects on the viability of embryos with mutated heterozygous germline *CDH1* pathogenic variants.

Normal gene product. The longest transcript, NM_004360.3, is 4.5 kb and is translated into a 135-kd precursor polypeptide of E-cadherin. This in turn is rapidly processed to the mature 120-kd form. The mature E-cadherin protein contains three domains: the extracellular domain encoded by exons 4-13, the transmembrane domain encoded by parts of exons 13 and 14, and the highly conserved cytoplasmic domain encoded by the rest of exon 14 to exon 16.

- The large extracellular domain (N-terminal) is made up of five tandem cadherin repeats each containing about 110 amino acid residues [Oliveira et al 2003, Bryant & Stow 2004]. The extracellular domain homodimerizes with E-cadherin expressed in neighboring epithelial cells in a Ca^{2+}-dependent manner, thus enabling cell-cell adhesion at the zonula adherens junctions of the homotypic neighboring cells.
- The cytoplasmic domain (C-terminal) interacts with the cytoskeleton actin filaments through α-, β-, and γ-catenins and $p120^{ctn}$ catenins in regulating the intracellular signaling pathways. β-catenin attaches to the C-terminal region of E-cadherin and then to α-catenin, which then binds to the F-actin microfilaments of the cytoskeleton. $p120^{ctn}$ binds to a juxtamembrane site of E-cadherin cytoplasmic tail [Bryant & Stow 2004]. p120 also provides complex stability [Weis & Nelson 2006].

E-cadherin expression is controlled through a complex transcriptional regulation system.

- Several transcriptional repressors such as Snail, Slug, Twist, Sip-1/ZEB-2, dEF1/ZEB-1, and E12/E47 bind to the E-box motifs in the *CDH1* promoter [Conacci-Sorrell et al 2003, Nelson & Nusse 2004, Gloushankova 2008].
- Intron 2 of *CDH1* has been implicated in the normal expression of the gene. Intron 2, which accounts for the majority of the noncoding intronic sequences of *CDH1*, contains conserved *cis*-regulatory elements. Stemmler et al [2005] performed a study in which deletion of murine genomic intron 2 led to inactivation of the gene during early embryonic development.

Abnormal gene product. See Molecular Pathogenesis.

Chapter Notes

Revision History

- 22 March 2018 (sw) Comprehensive update posted live
- 31 July 2014 (me) Comprehensive update posted live
- 21 June 2011 (me) Comprehensive update posted live
- 31 August 2006 (pk) Revision: prenatal diagnosis clinically available
- 13 December 2004 (me) Comprehensive update posted live
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- 5 April 2002 (pk) Original submission

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