GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Hereditary Diffuse Gastric Cancer

[*HDGC*]

Pardeep Kaurah, MSc, CCGC
Hereditary Cancer Program
BC Cancer Agency
Vancouver
pkaurah@bccancer.bc.ca

David G Huntsman, MD
Hereditary Cancer Program
BC Cancer Agency
Vancouver
dhuntsma@bccancer.bc.ca

Initial Posting: November 4, 2002.
Last Revision: August 31, 2006.

Summary

Disease characteristics. Hereditary diffuse gastric cancer (HDGC) is the 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 hereditary diffuse gastric cancer is 38 years, with a range of 14-69 years. The majority of the cancers in individuals with *CDH1* mutations occur before the age of 40 years. The estimated cumulative risk of gastric cancer by age 80 years is 67% for men and 83% for women. Women also have a 39% risk for lobular breast cancer.

Diagnosis/testing. The International Gastric Cancer Linkage Consortium defined HDGC as the presence of two or more documented cases of diffuse gastric cancer in first- or second-degree relatives with at least one case diagnosed prior to age 50 years OR three or more documented cases of diffuse gastric cancer in first- or second-degree relatives, regardless of age of onset. *CDH1* is the only gene known to be associated with hereditary diffuse gastric cancer. Sequence analysis of the *CDH1* gene is available on a clinical basis.

Management. Ideally, management of individuals who have a *CDH1* cancer-predisposing mutation is either intense surveillance for early detection and treatment of gastric cancer or prophylactic gastrectomy. However, to date, the optimal management of individuals at risk for a cancer-predisposing mutation has been controversial because of the unproven value of surveillance regimes and the potential morbidity and mortality from prophylactic gastrectomy.

Genetic counseling. Hereditary diffuse gastric cancer is inherited in an autosomal dominant manner. The vast majority of individuals with a mutation predisposing to diffuse gastric cancer have inherited it from one parent. *De novo* mutations have not been reported. Each child of a proband has a 50% risk of inheriting the cancer-predisposing mutation. Prenatal testing is available; however, requests for prenatal testing for conditions such as HDGC that do not affect intellect and have some treatment available are not common.

Diagnosis

Clinical Diagnosis

Revised criteria for consideration of *CDH1* molecular genetic testing in individuals with gastric cancer (GC) and diffuse gastric cancer (DGC) were put forth by Brooks-Wilson et al (2004) based on a study of 42 families with HDGC. These revised criteria replace the criteria previously established by the International Gastric Cancer Linkage Consortium (IGCLC) [Caldas et al 1999]. These criteria are applicable to North America, northern Europe, and other regions of low gastric cancer incidence but are likely too broad for use in regions of high gastric cancer incidence such as Japan and Korea.

The six criteria:

1. Two or more cases of gastric cancer in a family, with at least one diffuse gastric cancer diagnosed before age 50 years
2. Three or more cases of gastric cancer in a family, diagnosed at any age, with at least one documented case of diffuse gastric cancer
3. An individual diagnosed with diffuse gastric cancer before 45 years of age
4. An individual diagnosed with both diffuse gastric cancer and lobular breast cancer (no other criteria met)
5. One family member diagnosed with diffuse gastric cancer and another with lobular breast cancer (no other criteria met)
6. One family member diagnosed with diffuse gastric cancer and another with signet ring colon cancer (no other criteria met)

Note: Criterion 3 may be too inclusive. Lowering the cut-off age for individual cases of diffuse gastric cancer with no other suspicous history to before age 40 is warranted based upon unpublished data [Huntsman DG].

Testing

Pathology. Over 90% of individuals with morphologically verified stomach cancer have adenocarcinoma. The two major histological variants of gastric cancer are: diffuse gastric cancer and intestinal-type gastric cancer [Lauren 1965]. *CDH1* mutations have been found only in diffuse-type gastric cancers [Machado et al 1999, Becker et al 1999, Oliveira et al 2002].

- **Diffuse gastric cancers** are poorly differentiated. Individual cells infiltrate into the stomach wall causing thickening of the wall (*linitis plastica*) without forming a distinct mass. Diffuse, poorly differentiated tumors tend to predominate in younger individuals [Lo et al 1996] and demonstrate a nearly equal sex ratio, compared with a male preponderance in the intestinal form. Individuals with diffuse-type tumors have a poorer prognosis than those with intestinal-type tumors.
- **Intestinal-type gastric cancers** are usually exophytic and often ulcerating. They are associated with intestinal metaplasia of the stomach and *Helicobacter pylori* infection. They occur in the distal stomach more often than the diffuse type.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant*

any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.

Molecular Genetic Testing—Gene. *CDH*, encoding the protein E-cadherin, is the only gene known to be associated with hereditary diffuse gastric cancer [Gayther et al 1998, Guilford et al 1998, Guilford et al 1999, Richards et al 1999, Dussaulx-Garin et al 2001, Humar et al 2002, Oliveira et al 2002, Brooks-Wilson et al 2004]. Mutations in *CDH1* account for approximately one-third of hereditary diffuse gastric cancers.

Other genes. Mutations in other genes may account for susceptibility to HDGC. The following are being considered:

- **Genes causing hereditary nonpolyposis colorecal cancer (HNPCC).** The risk of gastric cancer in HNPCC is believed to be 11-15%. In a study of 55 individuals of Portuguese descent with gastric cancer, two families were noted to have tumors demonstrating microsatellite instability (MSI), although mutations were not found in either *hMLH1* or *hMSH2*.
- ***MET*.** In the first study to associate a *MET* mutation with diffuse gastric cancer, Kim et al (2003) identified a germline pathological missense *MET* mutation in one of 21 Korean families with gastric cancer. In a previous study Lee et al (2000) had identified a missense *MET* mutation in a proband with intestinal gastric cancer; however, family history was not reported. No *MET* mutations were identified in the 18 Indian and European probands studied by Chen et al (2001). Further investigations need to be done to verify the association of *MET* mutations and diffuse gastric cancer.
- ***BRCA2*.** Gastric cancer occurs in 5.7% of families with the *BRCA2* 6174delT mutation [Figer et al 2001]. Jakubowska at al (2002) found that in a subset (7%) of individuals with gastric cancer, a *BRCA2* mutation may be the underlying genetic cause; however, the histopathology of the gastric cancer was not reported. Because the individuals with gastric cancer were deceased, they could not be tested for the mutations found in their families.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Predisposition testing

  Note: Such testing is performed on an affected individual in a family prior to being offered to at-risk family members in order to determine the specific mutation present in the family.
- Prenatal diagnosis (technically available but rarely performed)

  Note: It is the policy of *GeneReviews* to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer (s).

Molecular genetic testing: Clinical method

- **Sequence analysis.** Sequence analysis of all 16 exons of the *CDH1* gene detects mutations in about 30% of individuals with a clinical diagnosis of HDGC.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Rate in Individuals with a Clinical Diagnosis of HDGC	Test Availability
Sequence analysis	Mutations in the *CDH1* coding region	~30%	Clinical Testing

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Note: Clinical management in individuals with missense mutations remains problematic because both extensive family data and functional data are needed in order to predict the pathogenicity of a missense mutation. In the absence of such data, it may not be appropriate to use *CDH1* missense mutation to define risks.

Genetically Related (Allelic) Disorders

In sporadic diffuse gastric cancers and lobular breast cancers, E-cadherin loss in the tumor is associated with point mutations of the *CDH1* gene, loss of heterozygosity, and promoter hypermethylation [Becker et al 1994, Oda et al 1994, Day et al 1999, Anastasiadis et al 2000, Tamura et al 2000, Machado et al 2001, Kallakury et al 2001].

Clinical Description

Natural History

Age of onset. The average age of onset of hereditary diffuse gastric cancer is 38 years, with a range of 14-69 years. The majority of the cancers occur before the age of 40 years. The age of onset is also variable between and within families [Gayther et al 1998, Guilford et al 1998].

Symptoms. Symptoms are nonspecific in the early stages of the disease. Consequently, when present, symptoms tend to be dismissed both by affected individuals and by physicians. By the time that 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. Other cancers reported in family members include:

- Colorectal cancer [Richards et al 1999, Oliveira et al 2002, Brooks-Wilson et al 2004]. In the study by Brooks-Wilson et al (2004), an individual with a histologically defined signet ring cell cancer (SRCC) of the colon was found to harbor a pathological missense mutation. The same group had previously seen a missense mutation in another family with diffuse gastric cancer and SRCC of the colon.
- Lobular breast cancer [Keller et al 1999, Oliveira et al 2002, Brooks-Wilson et al 2004]

Survival. When sporadic (i.e., nonhereditary) diffuse gastric cancer is detected early, i.e., before it has invaded the wall of the stomach, the five-year survival rate can be greater than 90%. The five-year survival rate drops to lower than 20% when the diagnosis is made at a late stage [Karpeh 2001].

As has been shown to be the case in HNPCC [Bertario et al 1999], individuals with HGDC could possibly have a different prognosis stage to stage when compared to individuals with sporadic diffuse gastric cancers.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported to date.

Penetrance

The penetrance of HDGC is incomplete. Based on data from eleven families, Pharoah et al (2001) estimated the cumulative risk of gastric cancer by age 80 years to be 67% for men (95% confidence interval, 39-99 years) and 83% for women (95% confidence interval, 58-99 years). Females were found to have a 39% risk for breast cancer.

Prevalence

Worldwide, the cancer burden of gastric cancer is second only to lung cancer [Parkin et al 2001]. Stomach cancer incidence rates show substantial variation internationally [Parkin et al 2001]. Rates are highest in Japan (80 cases per 100,000) and eastern Asia. Other areas of the world with high incidence of stomach cancer include Eastern Europe and parts of Latin America. Incidence rates are generally lower in Western Europe and the United States (10-40 per 100,000). Although the relative frequencies of gastric cancer subtypes is largely dependent on stringency of diagnosis in North America, approximately 50% of cancers are pure intestinal, 35% are pure diffuse, and 15% have mixed phenotype [Pisani et al 2002]. Although the incidence of gastric cancer is higher in Japan and China, most of the *CDH1* mutations have been found in European populations. There is, however, the possibility of a higher incidence of HDGC in New Zealand Maori families [Humar et al 2002].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

About 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 heterogenous.

Gastric cancer is seen in several other cancer predisposition syndromes, including hereditary nonpolyposis colorectal cancer (HNPCC) [Aarnio et al 1997]; Li-Fraumeni syndrome (LFS) [Varley et al 1995]; familial adenomatous polyposis (FAP); Peutz-Jeghers syndrome [Williams et al 1982]; and Cowden syndrome, one of the *PTEN* hamartoma tumor syndrome phenotypes [Hamby et al 1995].

A rare gastric lesion, gastric leiomyosarcoma, is found in individuals with Carney complex [Carney et al 1977].

Gastric stromal sarcomas were recently identified to be part of a new syndrome [Carney & Stratakis 2002].

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

In evaluating a person suspected of having gastric cancer, the following is appropriate:

- A complete personal medical history

- A complete family history to determine if there are other cases of gastric, breast and or colon cancer in the family
- Endoscopic biopsy to determine pathology of the gastric cancer
- Molecular genetic testing to determine if a germline *CDH1* mutation is present
- After gastrectomy in females, screening for lobular breast cancer

Treatment of Manifestions

Total gastrectomy is recommended if the biopsy shows diffuse-type carcinoma [Chun et al 2001].

Macdonald et al (2000) showed that persons receiving combined chemoradiation therapy had improved disease-free survival and improved overall survival rates. Numerous randomized clinical trials have failed to show consistent survival benefits from adjuvant radiation therapy or chemotherapy alone in the treatment of gastric cancer.

Prevention of Primary Manifestations

The importance of identifying the genetic basis of cancer susceptibility in families with HDGC has been underscored by the recent observation of early gastric cancers in prophylactic gastrectomy samples obtained from ten individuals with germline *CDH1* mutations [Huntsman et al 2001, Chun et al 2001]. These findings suggest that currently prophylactic gastrectomy, rather than endoscopic screening, is the best preventive measure for individuals who have a *CDH1* germline mutation.

Note: The morbidity from prophylactic gastrectomy is high. All individuals have long-term morbidity related to rapid intestinal transit, dumping syndrome, diarrhea, and weight loss [Caldas et al 1999]. In making the decision to undergo prophylactic gastrectomy, the affected individual and his/her physician should consider:

- The age-specific risks of gastric cancer
- The 100% morbidity of gastrectomy, including the 1-2% risk of mortality following the surgery
- The risk of developing extragastric cancers, such as lobular breast cancer and colorectal cancer, and the screening recommendations for these cancers

Surveillance

Gastric cancer. Although it has been proposed that individuals who have a *CDH1* cancer-predisposing mutation undergo routine surveillance for gastric cancer, the optimal management of individuals at risk for a cancer is controversial because of the unproven value of surveillance regimes. In most cases, the cancer is not detected until it reaches an incurable, advanced stage.

- **Endoscopy.** The effectiveness of endoscopy (currently the only method in use) in detecting the early lesions of gastric cancer has not been proven. Endoscopy permits direct inspection and biopsy of suspicious areas, but 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 problems are: (1) difficulty in identifying the submucosal lesions and (2) sampling bias in a macroscopically normal-appearing gastric mucosa [Fitzgerald & Caldas 2004]. It is recommended that individuals at risk who do not wish to have prophylactic gastrectomy undergo a detailed 30-minute endoscopic examination of the gastric mucosa with multiple random biopsies and biopsies of subtle lesions at six- to 12-month intervals [Caldas et al 1999].

- **Chromoendoscopy** , using indigo-carmine staining, has been shown to improve the detection rate of early gastric cancer [Stepp et al 1998, Fennerty 1999]. More recently 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 possiblity.
- **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].

Lobular breast cancer. At-risk women should undergo regular breast screening as determined by their physicians, including a clinical examination every six months and breast self-examinations. Because lobular breast cancer is often difficult to diagnose on clinical examination and mammography, it may also be prudent to refer a woman who has a *CDH1* germline mutation to a high-risk breast cancer screening program and to consider use of MRI, which appears to be more sensitive than mammography in detecting tumors in such women [Schelfout et al 2004; Schelfout, personal communication].

Colon cancer. Although evidence is insufficient to conclude that colon cancer is a manifestation of HDGC, it is prudent to recommend colonoscopy every 12-18 months beginning five to ten years earlier than the youngest age of colon cancer onset in families in which both DGC and colon cancer have occurred.

Other

In Japan, where the prevalence of gastric cancer is high, a mass population screening program allows for successful detection of early disease by endoscopy [Shiratori et al 1985]. In this program, all suspicious findings seen on endoscopy are biopsied and evaluated histologically. Suspicious findings include minute changes in the color of the mucosa, altered vascular pattern, roughened surface, flat lesions, and minor mucosal irregularities.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- The majority of individuals with a *CDH1* mutation predisposing to diffuse gastric cancer have inherited it from one parent. It is possible that the parent from whom the mutation was inherited may not have developed cancer because of incomplete penetrance.
- In addition, a proband with HDGC may have the disorder as the result of a *de novo* gene mutation; however, a *de novo* mutation has not been reported in an individual with HDGC and is probably rare.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include molecular genetic testing.

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 incomplete penetrance.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected and/or has a *CDH1* mutation, the risk to the sibs of inheriting the mtuation is 50%.
- If the disease-causing mutation cannot be detected in the DNA of either parent and biparental inheritance at the CDH1 locus is proven by haplotype inheritance, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. The risk to the sibs of the proband depends on the spontaneous mutation rate of *CDH1* and the probability of germline mosaicism in a parent. No instances of *de novo* mutations or germline mosaicism have been reported, although these remain possibilities.

Offspring of a proband. Each child of a proband has a 50% risk of inheriting the cancer-predisposing mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected or to have a *CDH1* mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Genetic cancer risk assessment and counseling. For comprehensive descriptions of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see:

- Genetic Cancer Risk Assessment and Counseling: Recommendations of the National Society of Genetic Counselors
- Elements of Cancer Genetics Risk Assessment and Counseling (part of PDQ®, National Cancer Institute)

Testing of asymptomatic at-risk adults. Testing of asymptomatic at-risk adults for HDGC is available only after an affected family member has been tested and a *CDH1* disease-causing mutation found. Testing of an asymptomatic at-risk individual is considered predictive testing, not diagnostic testing. Lynch et al (2000) describe the genetic counseling process that they followed with a large kindred with HDGC. Relevant issues that should be discussed with family members seeking predictive testing for HDGC include:

- The genetics of cancer development and HDGC
- The individual's knowledge of HDGC
- The individual's reasons for requesting the test
- The individual's understanding of the risk for having inherited the mutation based on family history of HDGC
- Availability of molecular genetic testing
- Cancer risk if the individual has inherited the mutation
- Recommendations for cancer screening and prophylactic surgery
- The possible social impact of positive and negative test results

In 50-70% of families with HDGC, cancer susceptibility is caused by unknown genetic factors; thus predictive testing is not possible at present.

Testing of asymptomatic at-risk individuals during childhood. Genetic testing in individuals younger than 18 years of age has always been a controversial issue. Since there have been reports of individuals diagnosed with HDGC under the age of 18 years [Carneiro et al 1995, Guilford et al 1998], it has been suggested that genetic testing in individuals younger than 18 years may be beneficial [Caldas et al 1999]. 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 18 years of age requires sensitive and understanding, though rigorous, counseling for both the parents and child.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition is affected, possible nonmedical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation

or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as HDGC that do not affect intellect and have some treatment available are not common. 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. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member. For laboratories offering PGD, see Testing.

Note: It is the policy of *GeneReviews* to include information on prenatal testing and preimplantation genetic diagnosis available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of their use by the author(s), editor(s), or reviewer(s).

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Hereditary Diffuse Gastric Cancer

Gene Symbol	Chromosomal Locus	Protein Name
CDH1	16q22.1	Epithelial-cadherin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Hereditary Diffuse Gastric Cancer

137215	GASTRIC CANCER
192090	CADHERIN 1; CDH1

Table C. Genomic Databases for Hereditary Diffuse Gastric Cancer

Gene Symbol	Entrez Gene	HGMD
CDH1	999 (MIM No. 192090)	CDH1

For a description of the genomic databases listed, click here.

Normal allelic variants: The human E(epithelial)-cadherin gene, called *CDH1* (Cadherin 1), was cloned in 1995 [Berx et al 1995]. The gene consists of 16 exons that span 100 kb.

Pathologic allelic variants: To date, 36 germline mutations have been reported in families with HDGC [Gayther et al 1998, Oliveira et al 2002, Brooks-Wilson et al 2004]. The mutations have mainly been truncating mutations, usually through frameshift mutations, exon/intron splice site mutations, or point mutations [Gayther et al 1998, Guilford et al 1998, Richards et al 1999, Oliveira et al 2002, Humar et al 2002, Brooks-Wilson et al 2004]. No "hot spots" have been identified; the mutations have been scattered throughout the gene. Missense mutations 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 mutations can be determined through in vitro analysis [Suriano et al 2003].

Normal gene product: The 4.5-kb transcript is translated into a 135-kd precursor polypeptide of E-cadherin. This in turn is rapidly processed to the mature 120-kd form. 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]. E-cadherin is critical for establishing and maintaining polarized and differentiated epithelia during development. It plays important roles in signal transduction, differentiation, gene expression, cell motility, and inflammation. The activity of E-cadherin in cell adhesion is dependent upon its association with the actin cytoskeleton via undercoat proteins called catenins (α-, β-, and γ-) [Jou et al 1995, Kallakury et al 2001].

Abnormal gene product: A role for E-cadherin in tumor development is well established [Wijnhoven et al 2000] because many human carcinomas, for example, skin, head and neck, lung, breast, thyroid, gastric, colon, and ovarian, exhibit reduced E-cadherin expression relative to their normal cellular counterparts. Loss of E-cadherin expression is seen in most diffuse gastric cancers and in lobular breast cancers, although expression is usually maintained in intestinal gastric cancers and ductal breast cancers [Hirohashi 2000]. 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]. Evidence supports a role for the E-cadherin/catenin complex both in suppressing invasion and metastasis and in suppressing proliferation [Birchmeier 1995].

In HGDC cases, loss of E-cadherin expression is also associated with a transcriptional down-regulation of the wild-type *CDH1* allele by promoter hypermethylation [Grady et al 2000].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Cancer Institute (NCI)
Stomach (Gastric) Cancer

PMP Pals
PO Box 6484
Salinas CA 93912
Phone: 831-424-4545
Email: pmppals@yahoo.com
www.pmppals.org

AMC Cancer Research Center and Foundation
1600 Pierce Street
Denver CO 80214
Phone: 800-321-1577; 303-233-6501
www.amc.org

American Cancer Society
Provides contact information for regional support.
1599 Clifton Road NE

Atlanta GA 30329
Phone: 800-227-2345
www.cancer.org

CancerCare
275 Seventh Avenue
New York NY 10001
Phone: 800-813-HOPE (800-813-4673); 212-712-8400
Email: info@cancercare.org
www.cancercare.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American Society of Clinical Oncology (2003) Statement on genetic testing for cancer susceptibility

Literature Cited

Aarnio M, Salovaara R, Aaltonen LA, Mecklin JP, Jarvinen HJ. Features of gastric cancer in hereditary non-polyposis colorectal cancer syndrome. Int J Cancer. 1997;74:551–5. [PubMed: 9355980]

Anastasiadis PZ, Reynolds AB. The p120 catenin family: complex roles in adhesion, signaling and cancer. J Cell Sci 113 (Pt. 2000;8):1319–34. [PubMed: 10725216]

Becker KF, Atkinson MJ, Reich U, Becker I, Nekarda H, Siewert JR, Hofler H. E-cadherin gene mutations provide clues to diffuse type gastric carcinomas. Cancer Res. 1994;54:3845–52. [PubMed: 8033105]

Becker KF, Reich U, Schott C, Becker I, Berx G, vanRoy F, Hofler H. Identification of eleven novel tumor-associated E-cadherin mutations. Hum Mutat. 1999;13:171. [PubMed: 10094558]

Bertario L, Russo A, Sala P, Eboli M, Radice P, Presciuttini S, Andreola S, Rodriguez-Bigas MA, Pizzetti P, Spinelli P. Survival of patients with hereditary colorectal cancer: comparison of HNPCC and colorectal cancer in FAP patients with sporadic colorectal cancer. Int J Cancer. 1999;80:183–7. [PubMed: 9935197]

Berx G, Staes K, van Hengel J, Molemans F, Bussemakers MJ, van Bokhoven A, van Roy F. Cloning and characterization of the human invasion suppressor gene E-cadherin (CDH1). Genomics. 1995;26:281–9. [PubMed: 7601454]

Birchmeier W. E-cadherin as a tumor (invasion) suppressor gene. Bioessays. 1995;17:97–9. [PubMed: 7748170]

Brooks-Wilson AR, Kaurah P, Suriano G, Leach S, Senz J, Grehan N, Butterfield YS, Jeyes J, Schinas J, Bacani J, Kelsey M, Ferreira P, MacGillivray B, MacLeod P, Micek M, Ford J, Foulkes W, Australie K, Greenberg C, LaPointe M, Gilpin C, Nikkel S, Gilchrist D, Hughes R, Jackson CE, Monaghan KG, Oliveira MJ, Seruca R, Gallinger S, Caldas C, Huntsman D. Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria. J Med Genet. 2004;41:508–17. [PubMed: 15235021]

Caldas C, Carneiro F, Lynch HT, Yokota J, Wiesner GL, Powell SM, Lewis FR, Huntsman DG, Pharoah PD, Jankowski JA, MacLeod P, Vogelsang H, Keller G, Park KG, Richards FM, Maher ER, Gayther SA, Oliveira C, Grehan N, Wight D, Seruca R, Roviello F, Ponder BA, Jackson CE. Familial gastric cancer: overview and guidelines for management. J Med Genet. 1999;36:873–80. [PubMed: 10593993]

Carneiro F, Huntsman DG, Smyrk TC, Owen DA, Seruca R, Pharoah P, Caldas C, Sobrinho-Simoes M. Model of the early development of diffuse gastric cancer in E-cadherin mutation carriers and its implications for patient screening. J Pathol. 2004;203:681–7. [PubMed: 15141383]

Carney JA, Sheps SG, Go VL, Gordon H. The triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma. N Engl J Med. 1977;296:1517–8. [PubMed: 865533]

Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet. 2002;108:132–9. [PubMed: 11857563]

Charlton A, Blair V, Shaw D, Parry S, Guilford P, Martin IG. Hereditary diffuse gastric cancer: predominance of multiple foci of signet ring cell carcinoma in distal stomach and transitional zone. Gut. 2004;53:814–20. [PubMed: 15138207]

Chen JD, Kearns S, Porter T, Richards FM, Maher ER, Teh BT. MET mutation and familial gastric cancer. J Med Genet. 2001;38:E26. [PubMed: 11483642]

Chun YS, Lindor NM, Smyrk TC, Petersen BT, Burgart LJ, Guilford PJ, Donohue JH. Germline E-cadherin gene mutations: is prophylactic total gastrectomy indicated? Cancer. 2001;92:181–7. [PubMed: 11443625]

Day ML, Zhao X, Vallorosi CJ, Putzi M, Powell CT, Lin C, Day KC. E-cadherin mediates aggregation-dependent survival of prostate and mammary epithelial cells through the retinoblastoma cell cycle control pathway. J Biol Chem. 1999;274:9656–64. [PubMed: 10092652]

Dussaulx-Garin L, Blayau M, Pagenault M, Le Berre-Heresbach N, Raoul JL, Campion JP, David V, Bretagne JF. A new mutation of E-cadherin gene in familial gastric linitis plastica cancer with extra-digestive dissemination. Eur J Gastroenterol Hepatol. 2001;13:711–5. [PubMed: 11434599]

Fennerty MB. Tissue staining (chromoscopy) of the gastrointestinal tract. Can J Gastroenterol. 1999;13:423–9. [PubMed: 10377475]

Figer A, Irmin L, Geva R, Flex D, Sulkes J, Sulkes A, Friedman E. The rate of the 6174delT founder Jewish mutation in BRCA2 in patients with non-colonic gastrointestinal tract tumours in Israel. Br J Cancer. 2001;84:478–81. [PubMed: 11207041]

Fitzgerald RC, Caldas C. Clinical implications of E-cadherin associated hereditary diffuse gastric cancer. Gut. 2004;53:775–8. [PubMed: 15138199]

Gayther SA, Gorringe KL, Ramus SJ, Huntsman D, Roviello F, Grehan N, Machado JC, Pinto E, Seruca R, Halling K, MacLeod P, Powell SM, Jackson CE, Ponder BA, Caldas C. Identification of germ-line E-cadherin mutations in gastric cancer families of European origin. Cancer Res. 1998;58:4086–9. [PubMed: 9751616]

Grady WM, Willis J, Guilford PJ, Dunbier AK, Toro TT, Lynch H, Wiesner G, Ferguson K, Eng C, Park JG, Kim SJ, Markowitz S. Methylation of the CDH1 promoter as the second genetic hit in hereditary diffuse gastric cancer. Nat Genet. 2000;26:16–7. [PubMed: 10973239]

Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, Taite H, Scoular R, Miller A, Reeve AE. E-cadherin germline mutations in familial gastric cancer. Nature. 1998;392:402–5. [PubMed: 9537325]

Guilford PJ, Hopkins JB, Grady WM, Markowitz SD, Willis J, Lynch H, Rajput A, Wiesner GL, Lindor NM, Burgart LJ, Toro TT, Lee D, Limacher JM, Shaw DW, Findlay MP, Reeve AE. E-cadherin germline mutations define an inherited cancer syndrome dominated by diffuse gastric cancer. Hum Mutat. 1999;14:249–55. [PubMed: 10477433]

Hamby LS, Lee EY, Schwartz RW. Parathyroid adenoma and gastric carcinoma as manifestations of Cowden's disease. Surgery. 1995;118:115–7. [PubMed: 7604372]

Hirohashi S. Molecular aspects of adhesion-epigenetic mechanisms for inactivation of the E-Cadherin-mediated cell adhesion system in cancers. Verh Dtsch Ges Pathol. 2000;84:28–32. [PubMed: 11217445]

Hsu MY, Meier FE, Nesbit M, Hsu JY, Van Belle P, Elder DE, Herlyn M. E-cadherin expression in melanoma cells restores keratinocyte-mediated growth control and down-regulates expression of invasion-related adhesion receptors. Am J Pathol. 2000;156:1515–25. [PubMed: 10793063]

Humar B, Toro T, Graziano F, Muller H, Dobbie Z, Kwang-Yang H, Eng C, Hampel H, Gilbert D, Winship I, Parry S, Ward R, Findlay M, Christian A, Tucker M, Tucker K, Merriman T, Guilford P. Novel germline CDH1 mutations in hereditary diffuse gastric cancer families. Hum Mutat. 2002;19:518–25. [PubMed: 11968084]

Huntsman DG, Carneiro F, Lewis FR, MacLeod PM, Hayashi A, Monaghan KG, Maung R, Seruca R, Jackson CE, Caldas C. Early gastric cancer in young, asymptomatic carriers of germ-line E- cadherin mutations. N Engl J Med. 2001;344:1904–9. [PubMed: 11419427]

Jakubowska A, Nej K, Huzarski T, Scott RJ, Lubinski J. BRCA2 gene mutations in families with aggregations of breast and stomach cancers. Br J Cancer. 2002;87:888–91. [PubMed: 12373604]

Jou TS, Stewart DB, Stappert J, Nelson WJ, Marrs JA. Genetic and biochemical dissection of protein linkages in the cadherin- catenin complex. Proc Natl Acad Sci U S A. 1995;92:5067–71. [PubMed: 7761449]

Kallakury BV, Sheehan CE, Winn-Deen E, Oliver J, Fisher HA, Kaufman RP Jr, Ross JS. Decreased expression of catenins (alpha and beta), p120 CTN, and E- cadherin cell adhesion proteins and E-cadherin gene promoter methylation in prostatic adenocarcinomas. Cancer. 2001;92:2786–95. [PubMed: 11753952]

Karpeh MS, Kelsen DP, Tepper JE. Cancer of the stomach. In: Devita VT Jr, Hellman S, Rosenberg SA (eds) Cancer: Principles and Practice of Oncology, 6 ed. Lippincott-Raven Publishers, Philadelphia. 2001

Keller G, Vogelsang H, Becker I, Hutter J, Ott K, Candidus S, Grundei T, Becker KF, Mueller J, Siewert JR, Hofler H. Diffuse type gastric and lobular breast carcinoma in a familial gastric cancer patient with an E-cadherin germline mutation. Am J Pathol. 1999;155:337–42. [PubMed: 10433926]

Kim IJ, Park JH, Kang HC, Shin Y, Lim SB, Ku JL, Yang HK, Lee KU, Park JG. A novel germline mutation in the MET extracellular domain in a Korean patient with the diffuse type of familial gastric cancer. J Med Genet. 2003;40:e97. [PubMed: 12920089]

Kodish ED. Testing children for cancer genes: the rule of earliest onset. J Pediatr. 1999;135:390–5. [PubMed: 10484811]

La Vecchia C, Negri E, Franceschi S, Gentile A. Family history and the risk of stomach and colorectal cancer. Cancer. 1992;70:50–5. [PubMed: 1606546]

Lauren P. The two histological main types of gastric carcinomas: diffuse and so-called intestinal-type carcinoma. Acta Pathol Microbiol Scand. 1965;64:31–49.

Lee JH, Han SU, Cho H, Jennings B, Gerrard B, Dean M, Schmidt L, Zbar B, Vande Woude GF. A novel germ line juxtamembrane Met mutation in human gastric cancer. Oncogene. 2000;19:4947–53. [PubMed: 11042681]

Lo SS, Wu CW, Hsieh MC, Kuo HS, Lui WY, P'Eng FK. Relationship between age and clinical characteristics of patients with gastric cancer. J Gastroenterol Hepatol. 1996;11:511–4. [PubMed: 8792301]

Lynch HT, Grady W, Lynch JF, Tsuchiya KD, Wiesner G, Markowitz SD. E-cadherin mutation-based genetic counseling and hereditary diffuse gastric carcinoma. Cancer Genet Cytogenet. 2000;122:1–6. [PubMed: 11104024]

Machado JC, Oliveira C, Carvalho R, Soares P, Berx G, Caldas C, Seruca R, Carneiro F, Sobrinho-Simoes M. E-cadherin gene (CDH1) promoter methylation as the second hit in sporadic diffuse gastric carcinoma. Oncogene. 2001;20:1525–8. [PubMed: 11313896]

Machado JC, Soares P, Carneiro F, Rocha A, Beck S, Blin N, Berx G, Sobrinho-Simoes M. E-cadherin gene mutations provide a genetic basis for the phenotypic divergence of mixed gastric carcinomas. Lab Invest. 1999;79:459–65. [PubMed: 10211998]

Oda T, Kanai Y, Oyama T, Yoshiura K, Shimoyama Y, Birchmeier W, Sugimura T, Hirohashi S. E-cadherin gene mutations in human gastric carcinoma cell lines. Proc Natl Acad Sci U S A. 1994;91:1858–62. [PubMed: 8127895]

Oliveira C, Bordin MC, Grehan N, Huntsman D, Suriano G, Machado JC, Kiviluoto T, Aaltonen L, Jackson CE, Seruca R, Caldas C. Screening E-cadherin in gastric cancer families reveals germline mutations only in hereditary diffuse gastric cancer kindred. Hum Mutat. 2002;19:510–7. [PubMed: 11968083]

Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer. 2001;94:153–6. [PubMed: 11668491]

Pfau PR, Chak A. Endoscopic ultrasonography. Endoscopy. 2002;34:21–8. [PubMed: 11778127]

Pharoah PD, Guilford P, Caldas C. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology. 2001;121:1348–53. [PubMed: 11729114]

Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. Int J Cancer. 2002;97:72–81. [PubMed: 11774246]

Richards FM, McKee SA, Rajpar MH, Cole TR, Evans DG, Jankowski JA, McKeown C, Sanders DS, Maher ER. Germline E-cadherin gene (CDH1) mutations predispose to familial gastric cancer and colorectal cancer. Hum Mol Genet. 1999;8:607–10. [PubMed: 10072428]

Schelfout K, Van Goethem M, Kersschot E, Verslegers I, Biltjes I, Leyman P, Colpaert C, Thienpont L, Van den Haute J, Gillardin JP, Tjalma W, Buytaert P, De Schepper A. Preoperative breast MRI in patients with invasive lobular breast cancer. Eur Radiol. 2004;14:1209–16. [PubMed: 15024602]

Shinmura K, Kohno T, Takahashi M, Sasaki A, Ochiai A, Guilford P, Hunter A, Reeve AE, Sugimura H, Yamaguchi N, Yokota J. Familial gastric cancer: clinicopathological characteristics, RER phenotype and germline p53 and E-cadherin mutations. Carcinogenesis. 1999;20:1127–31. [PubMed: 10357799]

Shiratori Y, Nakagawa S, Kikuchi A, Ishii M, Ueno M, Miyashita T, Sakurai T, Negami J, Suzuki T, Sato I. Significance of a gastric mass screening survey. Am J Gastroenterol. 1985;80:831–4. [PubMed: 4050756]

Stepp H, Sroka R, Baumgartner R. Fluorescence endoscopy of gastrointestinal diseases: basic principles, techniques, and clinical experience. Endoscopy. 1998;30:379–86. [PubMed: 9689513]

Suriano G, Oliveira C, Ferreira P, Machado JC, Bordin MC, De Wever O, Bruyneel EA, Moguilevsky N, Grehan N, Porter TR, Richards FM, Hruban RH, Roviello F, Huntsman D, Mareel M, Carneiro F, Caldas C, Seruca R. Identification of CDH1 germline missense mutations associated with functional inactivation of the E-cadherin protein in young gastric cancer probands. Hum Mol Genet. 2003;12:575–82. [PubMed: 12588804]

Takeichi M. Cadherin cell adhesion receptors as a morphogenetic regulator. Science. 1991;251:1451–5. [PubMed: 2006419]

Tamura G, Yin J, Wang S, Fleisher AS, Zou T, Abraham JM, Kong D, Smolinski KN, Wilson KT, James SP, Silverberg SG, Nishizuka S, Terashima M, Motoyama T, Meltzer SJ. E-Cadherin gene promoter hypermethylation in primary human gastric carcinomas. J Natl Cancer Inst. 2000;92:569–73. [PubMed: 10749913]

Varley JM, McGown G, Thorncroft M, Tricker KJ, Teare MD, Santibanez-Koref MF, Martin J, Birch JM, Evans DG. An extended Li-Fraumeni kindred with gastric carcinoma and a codon 175 mutation in TP53. J Med Genet. 1995;32:942–5. [PubMed: 8825920]

Wanebo HJ, Kennedy BJ, Chmiel J, Steele G Jr, Winchester D, Osteen R. Cancer of the stomach. A patient care study by the American College of Surgeons. Ann Surg. 1993;218:583–92. [PubMed: 8239772]

Wijnhoven BP, Dinjens WN, Pignatelli M. E-cadherin-catenin cell-cell adhesion complex and human cancer. Br J Surg. 2000;87:992–1005. [PubMed: 10931041]

Williams CB, Goldblatt M, Delaney PV. 'Top and tail endoscopy' and follow-up in Peutz-Jeghers syndrome. Endoscopy. 1982;14:82–4. [PubMed: 7075565]

Yoon KA, Ku JL, Yang HK, Kim WH, Park SY, Park JG. Germline mutations of E-cadherin gene in Korean familial gastric cancer patients. J Hum Genet. 1999;44:177–80. [PubMed: 10319582]

Zanghieri G, Di Gregorio C, Sacchetti C, Fante R, Sassatelli R, Cannizzo G, Carriero A, Ponz de Leon M. Familial occurrence of gastric cancer in the 2-year experience of a population-based registry. Cancer. 1990;66:2047–51. [PubMed: 2224804]

Chapter Notes

Revision History

- 31 August 2006 (pk) Revision: prenatal diagnosis clinically available
- 13 December 2004 (me) Comprehensive update posted to live Web site
- 4 November 2002 (me) Review posted to live Web site
- 5 April 2002 (pk) Original submission