

## The Role of E-Cadherin in Hereditary Diffuse Gastric Cancer: A Systematic Review

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### Abstract

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. It is likely that 20-40% of individuals with HDGC have a CDH1 mutation. The result of such mutations is the loss of E-cadherin protein function. The absence of E-cadherin, mainly, leads to inability of cells to act as a tumor suppressor. CDH1 mutations have also been associated with lobular breast cancer, prostate cancer and colorectal cancer. Familial patterns have been identified with an array of allelic variants, but there is more to be uncovered about the genetic foundation of the disease.

**Keywords:** CDH1; E-Cadherin; Gastric Cancer; HDGC; Linitis Plastica

### Introduction

#### 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, with a range of 14-69 years. Most of the hereditary diffuse gastric cancers in individuals with a CDH1 pathogenic variant occur prior to the age 40 years. There is an indication that 20-40% of individuals with HDGC have a CDH1 mutation. The estimated cumulative risk of gastric cancer by the age of 80 is estimated as 80% for both sexes. Women also share a 39%-52% risk for lobular breast cancer, when men have the same risk for prostate cancer. CDH1 has been correlated with a slight increase in colorectal cancer [1].

#### Pathophysiology: The Majority of Gastric Cancer

Ooi et al identified a deregulation of three oncogenic pathways in the vast majority (>70%) of gastric cancers: the proliferation/stem cell, NF-kappa $\beta$ , and Wnt/beta-catenin pathways [2]. Their study suggests that interactions between these pathways may play a potent role in influencing disease behaviour and subsequently in patient survival [3]. The intestinal type of non-cardia gastric cancer is altogether thought to arise from *Helicobacter pylori* infection, which initiates a sequence that progresses from chronic non-atrophic gastritis to atrophic gastritis, then intestinal metaplasia, and finally dysplasia. This progression is known as Correa's cascade. In a population-based cohort study, Swedish researchers came to the conclusion that after a 2-year latency, patients with precancerous gastric lesions were at higher risk for gastric cancer than the general Swedish population, and that risk rised steadily with progression through Correa's cascade. The researchers estimated that the 20-year gastric cancer risk in patients with particular gastroscopy findings was as follows [2]:

- Normal mucosa - One in 256
- Gastritis - One in 85

- Atrophic gastritis - One in 50
- Intestinal metaplasia - One in 39
- Dysplasia - One in 19

**Genetic Counselling**

Hereditary diffuse gastric cancer is inherited in an autosomal dominant manner. The majority of individuals with a pathogenic variant predisposing to diffuse gastric cancer have inherited it from one parent. De novo mutation has been reported. Each child of a proband has a 50% risk of inheriting the cancer-predisposing variant. In families with a known pathogenic variant, prenatal testing for pregnancies at increased risk is possible; however, requests for prenatal testing for conditions which (like HDGC) do not affect intellect and do not have any available treatment strategies are not usual [1].

**Methods**

**Molecular Genetics**

Data are compiled from the following standard references: gene from HGNC; chromosome locus, locus name, critical region, complementation group from OMIM; protein from UniProt (Table A).

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

**Table A:** Hereditary Diffuse Gastric Cancer: Genes and Databases.

**Discussion**

**Molecular Genetic 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 [4]. E-cadherin is one member of the cadherin family of molecules, all of which are transmembrane glycoproteins mediating calcium-dependent cell-cell adhesion [5]. E-cadherin is critical for establishing and maintaining polarized and differentiated epithelia during development [6]. 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 ( $\alpha$ -,  $\beta$ -, and  $\gamma$ -) [7]. A role for E-cadherin in tumor development is well established 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 [8-13].

Loss of E-cadherin expression has been spotted mostly in diffuse gastric cancers and in lobular breast cancers; expression is commonly maintained in intestinal gastric cancers and ductal breast cancers [14]. Cells deficient in E-cadherin lose their ability to adhere to each other and consequently become invasive and metastasize. The causal effect of E-cadherin loss or dysregulation in tumorigenesis has been demonstrated using carcinoma cell lines and transgenic models. This loss of E-cadherin expression has been shown to be an early event through the examination of in situ DGC lesions from a prophylactic total gastrectomy specimen. This loss of E-cadherin reveals that it is an early initialising event which contributes to invasion [15]. Loss of heterozygosity is a common phenomenon seen connected to a loss of expression of tumor suppressor genes [16]. Evidence of the loss of expression of the other CDH1 allele support the tumor suppressor function of E-cadherin [17-19].

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

**Pathogenic allelic variants:** To date, more than 100 germline pathogenic variants have been reported in families with HDGC [15,19-36].

The pathogenic variants are primarily truncating, usually through frameshift variants, exon/intron splice site variants, or single nucleotide variants [15,19,20,23,25,31]. In addition to previous findings, pathogenic missense variants have been identified in some families [19,20,36]. The pathogenicity of missense variants can be investigated through in vitro analysis, but this cannot be performed out of a research basis [34]. Large exonic deletions make up approximately 4% of these variants [19]. No “hot spots” have been identified; the pathogenic variants have been distributed throughout the gene. Nevertheless, reports declare that the same pathogenic variant has been detected in several unrelated families:

- NM\_004360.3:c.1003C>T in exon 7 [22,26,34].
- 1137G>A splicing variant in exon 8 [22,30].
- NM\_004360.3:c.1901C>T in exon 12 [22,30,34].

A founder mutation has been seen in four families from Newfoundland, Canada [22]. The pathogenic variant 2398delC 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 GC are high. We don’t know the reason yet; it may be postulated that the diversity in genetic backgrounds of the various ethnicities may play different key roles on the viability of embryos that already carry one mutated germline CDH1 allele. 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. The mature E-cadherin protein consists of 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 [37,38]. The extracellular domain homodimerizes with E-cadherin expressed in neighboring epithelial cells in a  $\text{Ca}_{2+}$ -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  $\alpha$ -,  $\beta$ -, and  $\gamma$ -catenins and p120ctn catenins in regulating the intracellular signaling pathways.  $\beta$ -catenin attaches to the C-terminal region of E-cadherin and then to  $\alpha$ -catenin, which then binds to the F-actin microfilaments of the cytoskeleton. p120ctn binds to a juxtamembrane site of E-cadherin cytoplasmic tail [37]. p120 also provides complex stability [39].
- E-cadherin expression is under the suspicion of 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 [40,41].
- Intron 2 of CDH1 has been implicated in the normal expression of the gene. Intron 2, which accounts for the majority of the non-coding intronic sequences of CDH1, contains conserved cis-regulatory elements. Stemmler et al performed a study in which deletion of murine genomic intron 2 led to inactivation of the gene at the early stages of embryonic development [42-45].

## Conclusion

In 20-40% of individuals with HDGC there is a CDH1 mutation. CDH1 mutations have also been associated with lobular breast cancer, prostate cancer and colorectal cancer. The result of such mutations is the loss of E-cadherin protein function. The absence of E-cadherin, mostly, results in the inability of cells to act as a tumor suppressor. Familial patterns have been identified with an array of allelic variants, but there is more to be uncovered about the genetic foundation of the disease.

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