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Review

# Hereditary diffuse gastric cancer – An overview

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ABSTRACT

The incidence of gastric cancer varies by up to ten fold throughout the world, and the geographic distribution of hereditary cases is not well explored. Familial clustering is seen in 10% of cases, and approximately 3% of all gastric cancers develop due to hereditary diffuse gastric cancer (HDGC). In this review, the characteristics of HDGC are presented according to molecular particularities, geographic distribution, and other parameters. Based on our experience and the data from the literature, we discuss the possibility of applying a mutation signature (spectrum) study and adductomic approaches to a comparative carcinogenesis of HDGC. We also provide a comprehensive, up-to-date review of genetic counseling and criteria for screening and surveillance of eligible families.



**Contents**



## 1. Introduction

### 1.1. Historical data

The first case of hereditary gastric cancer was described in the family of Napoleon Bonaparte; six members of his family (a grandfather, his father, one brother, and three sisters) died as a result of gastric cancer (GC). Another famous family with a similar pedigree, with documents kept at the Ca' Maitino museum in Bergamo, Italy, was that of Pope John XXIII (19th–20th centuries). In this family there were seven cases of intestinal type GC in two consecutive generations; Pope John XXIII himself died as a result of a perforated GC diagnosed as stage cT4bN3a [1].

The first family with hereditary diffuse gastric cancer (HDGC) was described in 1964, and molecular confirmed in 1998, in a large Maori kindred from New Zealand; 28 of the 98 members of this family presented GC [1–3]. In the next years (1998–2010), 95 other families with HDGC were identified around the world [1,4–6].

## 2. Diagnosis of HDGC–eligible families

Hereditary gastric cancer was reported to be diagnosed in about 1% of all GCs, and 10% of cases diagnosed at ages below 50 years old seem to show familial clustering [2,7,8]. In Poland, the family risk in first-degree relatives was reported to be about three-to

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four-fold higher than in control cohorts, independent of the type of gene mutations, with the risk being present for both intestinal and diffuse-type carcinomas [9].

HDGC is the only known inherited type of GC that is produced by germline point or small frameshift mutations of the *CDH1* (E-cadherin) gene, mapping the chromosome 16q22.1, which has been detected in 25–50% of families that meet the strict clinicopathologic criteria [2,5,7–11]. The lifetime risk of occurrence of HDGC in *CDH1* mutation carriers is estimated to be about 67% for males and 83% for females by the age of 80 years [2,6]. In most countries, the median age at HDGC diagnosis is estimated to be 33–40 years old; the youngest patient reported in the literature was 14 years old at diagnosis, and the oldest was 82 years old [2,6]. Below 20 years old, the lifetime risk of developing HDGC is believed to be less than 1%, although few families have benefited from intensive follow-up [2,6,12,13]. In New Zealand, the median age of occurrence of HDGC is lower than in the rest of the world, with most cases being diagnosed at about 15–17 years old [5].

It remains unclear whether intestinal type GC and the *CDH1* wild type can have a positive or a negative genetic predisposition, although an autosomal dominant inheritance pattern is assumed [2]. In an E-cadherin–positive intestinal type adenocarcinoma of the gastroesophageal junction diagnosed in a 40-year-old male patient in our department, genome sequencing was done by using blood from the patient and his 18-year-old healthy son; however, no genetic disorders, including *p53* and *CDH1* genes, were identified (Yamada H et al., personal communication). Further studies are necessary to confirm that genetic predisposition does not occur in intestinal type early-onset gastric carcinoma.

Along with genetic mutations, environmental factors also influence the genesis of GC, although the geographic differences worldwide have not yet been elucidated. At present, diffuse GC is considered as HDGC based on any one of the following criteria proposed by the International Gastric Cancer Linkage Consortium (IGCLC) in 1999 and revised in 2010 [1,2,4–6,14]:

1. One diffuse GC diagnosed before the age of 40 years in a patient without familial history;
2. Two or more documented cases of diffuse GC in first- or second-degree relatives, with at least one diagnosed before the age of 50 years, or
3. Three or more cases of documented diffuse GC in first- or second-degree relatives, independent of age of onset.

New criteria are intended to be introduced for borderline families, with a lower risk for HDGC.

## 3. Diagnosis of HDGC: Histologic and molecular particularities

Microscopically, HDGC is an early-onset diffuse/poorly cohesive or signet ring cell carcinoma. In early stages, several biopsies taken from the stomach have shown multiple intramucosal PAS-positive foci of signet ring cells [5,7,12,15]. These are usually confined to the superficial mucosa, at the proliferative zone or the upper gastric neck, and present hyperchromatic and depolarised nuclei [5,12,15]. These cells are covered by an intact surface epithelium, which makes their identification difficult even for an ill-advised pathologist [2,15]. There are reportedly 4 to 318 foci (with a median of 20–25) in each gastrectomy specimen sized between 0.1 and 10 mm in diameter; the low Ki-67 proliferation index and absence of epithelial–mesenchymal transition prove the longtime indolent behavior of these foci [8,15,16]. The next steps involve the deep mucosal layer, with the tumor cells partially or totally transformed in poorly differentiated carcinoma cells that achieve epithelial–mesenchymal transition [2,15], invading the submucosa and, subsequently, the muscularis, subserosa, and serosa. These findings are not reported to present geographic differences, being related to the *CDH1* mutation; however, our preliminary unpublished data, based on a comparison of cases from Poland, Romania, and Japan, prove that some geographic differences do exist. In the last year, in our department from Romania has observed an increasing number of cases with multiple intramucosal foci (about 20 per case) and of relapses in poorly cohesive carcinomas, including non-hereditary cases without *CDH1* mutations and early cancers. This increased number of multifocal carcinomas has an important clinical impact on surgical intervention because, if such increase is real, total gastrectomy should be done even in tumors located in the antral area. Compared with Romanian patients, although the number of diffuse-type GC was higher in Poland, the multifocal aspect was present only in a few cases (Gurzu S et al., personal communication). Among the Japanese patients, the multifocal intramucosal signet ring cells were very frequently observed, probably because of the efficient national screening programs (Sugimura H et al., ***personal communication).

Immunohistochemically, the tumor cells are negative or focally positive for E-cadherin, indicating that a diminished expression of E-cadherin is sufficient for the initiation of gastric carcinogenesis [2]. Moreover, the Ki-67 proliferation index is not significantly increased, even in advanced stages of HDGCs [17]. This finding might prove that E-cadherin down-regulation could initiate early-onset gastric carcinogenesis but that additional factors, such as maspin nuclear expression, are necessary for the progression of intramucosal clusters of signet ring cells [15].

The other immunohistochemical markers whose expressions seem to be diminished in HDGC are β-catenin and γ-catenin, which are linked to the E-cadherin and cell adhesion function through α-catenin [2,18,19]. Reduced expression of junctional proteins, such as β-actin, p120, and Lin-7, has also been described [15]. On the other hand, vimentin expression was found to become positive, indicating activation of the c-Src kinase and subsequent epithelial–mesenchymal transition [15].

Table 1 shows the geographic particularities of the molecular profile of HDGC based on our experience and the literature data [2,5–9,12,13,15–28].

## 4. Genetic counseling and criteria for surveillance

Annual endoscopic screening remains the gold standard of surveillance for HGDC because the specific diagnostic criteria for its detection are not well known. In cases without hereditary history in a three-generation family pedigree, starting the screening program at the age of 40 is recommended, whereas familial screening should begin at the age of 16 or 18 years, depending on the geographic area and the age limit for informed consent, respectively [2,5–7].

Endoscopic screening (non-*CDH1* mutation carriers) and surveillance (*CDH1* mutation carriers) of early-stage carcinomas should be done by an experienced gastroenterologist because these cases are macroscopically characterized by an intact mucosa covering, which makes them difficult to identify; thus, early cancers are usually associated with negative results in endoscopic screening [2,12,19]. In advanced stages, gastric mucosa can also show a normal appearance in white light gastroscopy or can be seen as a pale or white area that can escape endoscopic detection. A better view can be obtained by using mucolytics, such as acetylcysteine, but a careful examination of the gastric mucosa for at least 30 min, with insufflation and desufflation, is recommended [5,7,12]. Enhanced colors can be obtained in chromoendoscopy by using either Congo red, which is suspected to have a borderline carcinogenic effect,