Familial Gastric Cancer: Genetics, Diagnosis, and Management

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KEYWORDS

• Familial gastric cancer • Hereditary diffuse gastric cancer
• E-cadherin • Prophylactic gastrectomy

An army marches on its stomach.
—Napoleon Bonaparte 1769–1821

The Bonapartes are probably the most notorious reported gastric cancer family. However, recent analysis of Napoleon's family history and pathology records challenges the assumption of inherited predisposition.[1] Two hundred years ago, the practice of medicine largely rested on the arts of taking an accurate history and sharp clinical observation. Today, despite the explosion in molecular and genetic knowledge, this is still the case and a meticulous family history remains a cornerstone of diagnosis in familial cancer.

Although hereditary diffuse gastric cancer (HDGC) is relatively rare, sporadic, gastric cancer, it is the fourth most common cancer worldwide. In 1998, germline mutations in the E-cadherin gene (*CDH1*) were first described in three gastric cancer families from New Zealand.[2] In the year after this discovery, different *CDH1* mutations were identified in other gastric cancer families from around the world, culminating in the definition of the first and, to date, only inherited cancer syndrome dominated by gastric cancer, HDGC.[3] Despite extensive mutation searching in other candidate genes, no further mutations have been found in families in which gastric cancer predominates.

Parry Guilford and colleagues[2] identified the mutant *CDH1* gene, in part, because the pedigree of the index family (a large Maori family known as Family A) was well

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documented, permitting an accurate genetic linkage analysis. Forty years before this, in 1964, Dr Ted Jones, a young resident doctor at Tauranga Hospital had published the tragic story of multiple deaths in very young family members from a diffuse type of stomach cancer.[4] In 1965, Pekka Lauren,[5] of the eponymous Lauren Classification, published his seminal work on the different morphologic types of gastric cancer.

Lauren described the distinction between stomach cancers that form glands (eg, cancers of the colonic intestine), which he called the "intestinal type," and the "diffuse type" in which discohesive malignant cells invade in single files, sheets, or nests of cells without forming a discrete mass. Epithelial-cadherin is a cell-to-cell adhesion molecule that is a central component of the adherens junction. The difference in E-cadherin expression between gastric cancer histotypes was first demonstrated immunohistochemically by Shimoyama and Hirohashi[6] in 1991. Their study showed that in diffuse gastric cancer (DGC) E-cadherin expression was occasionally absent, but more often reduced or abnormal. Subsequently, Becker and colleagues[7] supported this by demonstrating that *CDH1* mutations are restricted to sporadic gastric cancers with diffuse morphology.

Later work demonstrated that inactivating E-cadherin mutations are exclusively observed in the diffuse component of mixed gastric carcinomas.[8] In a commentary on this paper and other literature, Chan and Wong[9] highlighted that loss of E-cadherin provides a "plausible explanation" for the divergent morphologic phenotype in lobular versus ductal breast cancer and DGC versus intestinal gastric cancer (IGC). In Newfoundland, Canada, a germline *CDH1* mutation was detected in another very large family; however, they were originally identified as a breast cancer family.[10]

This article focuses on the diagnosis and management of familial gastric cancer, particularly HDGC. First, existing consensus guidelines are discussed and then the pathology and genetics of HDGC are reviewed. Second, patient management is covered, including surveillance gastroscopy, prophylactic total gastrectomy, and management of the risk of breast cancer.

CONSENSUS GUIDELINES

In 1999, the first guidelines on diagnosis and management of familial gastric cancer were published by the International Gastric Cancer Linkage Consortium (IGCLC).[11] In New Zealand, because of the particularly young age at which HDGC patients have died, guidelines were needed on the youngest age at which genetic testing, surveillance gastroscopy and prophylactic gastrectomy are recommended. In response, at the 2004 meeting of The New Zealand Familial Gastric Cancer Group (scientists, clinicians, and allied health professionals[12]) consensus guidelines were established based on collective clinical experience managing these families and the literature. At that time, there were 45 HDGC families reported worldwide, 10 from New Zealand.

In the initial 5 years after *CDH1* mutations were described, several key papers were published on genetic counseling,[13] the cumulative risk of gastric and breast carcinoma,[14] prophylactic gastrectomy,[15–17] early gastric pathology,[18–20] and surveillance chromogastroscopy.[21]

In 2008, at the seventh workshop of the IGCLC, updated consensus guidelines were generated.[22] Management algorithms have been formulated highlighting the salient management decisions.[22,23] Now, there are well over 100 HDGC families reported in the literature. The information from the published pedigrees of the first 87 families reported (up to 2008) is summarized in **Table 1** including mutation details, number of gastric and breast cancers, known histotypes, age at diagnosis, and cancers at other sites.