Familial gastric cancer: genetic susceptibility, pathology, and implications for management

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Familial gastric cancer comprises at least three major syndromes: hereditary diffuse gastric cancer, gastric adenocarcinoma and proximal polyposis of the stomach, and familial intestinal gastric cancer. The risk of development of gastric cancer is high in families affected b-y these syndromes, but only hereditary diffuse gastric cancer is genetically explained (caused by germline alterations of *CDH1*, which encodes E-cadherin). Gastric cancer is also associated with a range of several cancer-associated syndromes with known genetic causes, such as Lynch, Li-Fraumeni, Peutz-Jeghers, hereditary breast–ovarian cancer syndromes, familial adenomatous polyposis, and juvenile polyposis. We present contemporary knowledge on the genetics, pathogenesis, and clinical features of familial gastric cancer, and discuss research and technological developments, which together are expected to open avenues for new genetic testing approaches and novel therapeutic strategies.

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Introduction

Gastric cancer affects nearly 1 million individuals every year, 70–85% of whom die within 5 years of diagnosis, making it the third most lethal cancer worldwide.[1] The high mortality associated with gastric cancer (nearly 800 000 deaths per year) is mainly a result of late diagnosis, and limited therapeutic options. The two major subtypes—diffuse and intestinal[2]—are characterised by distinct epidemiological, morphological, and molecular features. Although most gastric cancers are sporadic, aggregation within families occurs in roughly 10% of cases. In regions where the incidence of gastric cancer is low, most familial cases are probably due to heritable pathogenic mutations that increase risk from birth.[3,4] Truly hereditary cases are thought to account for 1–3% of the global burden of gastric cancer and comprise at least three main syndromes: hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC). A genetic basis has been found in only around 40% of families affected by HDGC. The identification of inherited factors among individuals with family histories of gastric cancer is therefore a crucial step for early diagnosis and disease management.

In this Review, we discuss the available knowledge on hereditary gastric cancer and cancer-associated syndromes from which gastric cancer can arise, with the aim of clarifying questions relevant for the translation of basic research into clinical practice.

Hereditary gastric cancer syndromes

The recognition of familial aggregation (eg, high occurrence in siblings or offspring) is the first step towards the identification of a disease with a genetic component and is clinically useful. Family history, histological classification, and age at onset of disease (<45 years) are used to guide genetic testing and clinical surveillance in the context of a particular gastric cancer hereditary syndrome. The advent of new, fast, and inexpensive massive parallel sequencing technologies is expected to improve the identification of novel causative genetic events, which will affect genetic testing and the management of families with a high frequency of gastric cancers.

HDGC was the first of the hereditary gastric cancer syndromes to be recognised, initiated by inherited causative mutations in the E-cadherin gene (*CDH1*).[5] Mutations in the alpha-E-catenin gene (*CTNNA1*) have been identified as an additional genetic cause of HDGC (table 1).[6] Several patients with early-onset diffuse-type gastric cancers with no apparent family history have been found to be carriers of *CDH1* germline mutations, which supports the role of *CDH1* germline deficiency in disease initiation and helped to identify de-novo HDGC families.[7,8] In HDGC families, lobular breast cancer is the second most frequent type of neoplasia.[9] Although colorectal cancer also arises as part of the tumour spectrum, whether the risk in HDGC families is higher than that in the general population remains unclear.[9] Congenital malformations, such as cleft lip or cleft palate, occur in some *CDH1*-mutation-driven HDGC families,[10] but are not a defining clinical characteristic because of their rarity. However, clinicians should collect information about them when counselling at-risk families.[11]

According to published data, the penetrance of diffuse gastric cancer in mutation carriers reaches more than 80% in both men and women by 80 years of age, and the probability of women developing lobular breast cancer is 60%.[9] The combined risk of gastric cancer and breast cancer in women has been calculated to be 90% at 80 years.[12] Efforts are being made to calculate the penetrance of gastric cancer in a larger number of HDGC *CDH1* mutant families.

GAPPS was identified in 2012, and is characterised by the autosomal dominant transmission of fundic gland polyposis (including dysplastic lesions or intestinal-type gastric adenocarcinoma, or both) that are restricted to the proximal stomach with no evidence of colorectal or duodenal polyposis or other hereditary gastrointestinal cancer syndromes (table 1).[13] It is characterised by incomplete penetrance, and some elderly obligate carriers have

	Clinical criteria	Genetic screening	Alterations described
Hereditary diffuse gastric cancer	Two or more cases of gastric cancer, one confirmed case of diffuse gastric cancer in someone younger than 50 years; Three or more confirmed diffuse gastric cancer cases in first-degree or second-degree relatives, independent of age of onset; Diffuse gastric cancer before age 40 years without a family history; Personal or family history of diffuse gastric cancer and lobular breast cancer, one of which must be diagnosed before age 50 years	Sequencing of *CDH1* coding sequences; Multiplex ligation-dependent probe amplification (large *CDH1* rearrangements); Sequencing of *CTNNA1* coding sequences	Mutations throughout the *CDH1* gene and deletions mainly implicating flanking untranslated regions; One germline truncating mutation in *CTNNA1*
Gastric adenocarcinoma and proximal polyposis of the stomach	Gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis; More than 100 polyps carpeting the proximal stomach in the index case or more than 30 polyps in a first-degree relative of another case; Mainly fundic gastric polyps, some with regions of dysplasia (or a family member with either dysplastic fundic gastric polyps or gastric adenocarcinoma); Autosomal dominant pattern of inheritance; Exclusions include other heritable gastric polyposis syndromes and use of proton-pump inhibitors*	No screening available	No inherited inherited mutations so far
Familial intestinal gastric cancer	Two or more cases of gastric cancer in first-degree or second-degree relatives, with at least one confirmed case of intestinal histology in someone younger than 50 years; Three or more confirmed cases of intestinal gastric cancer in first-degree or second-degree relatives, independent of age	No screening available	No inherited inherited mutations so far

*Proton-pump inhibitors can induce a phenotype similar to that of gastric adenocarcinoma and proximal polyposis of the stomach. Patients taking these drugs should undergo a repeat endoscopy off-therapy to confirm diagnosis of gastric adenocarcinoma and proximal polyposis of the stomach.

Table 1: **Clinical criteria, recommended screening, and inherited alterations of familial gastric cancer syndromes**

normal endoscopies. The genetic cause has yet to be identified.[13,14]

FIGC is characterised mainly by intestinal gastric cancer (table 1). An autosomal dominant inheritance pattern has been noted in many families with intestinal-type gastric cancer.[15] In practical terms, FIGC should be thought of as a potential diagnosis when histopathological reports refer to intestinal-type adenocarcinoma segregating within families without gastric polyposis. The genetic cause is unknown, and only a few recommendations have been advanced for the clinical management of patients at risk of FIGC.[16]

Associations with other hereditary cancer syndromes

Gastric cancer has been identified as part of the tumour spectrum in several other hereditary cancer syndromes, and thus the risk of it should be taken into account in patients with these syndromes. Lynch syndrome is a highly penetrant colorectal cancer syndrome bearing a molecular phenotype of microsatellite instability that is caused by mutations in one of the mismatch repair genes *MLH1, MSH2, MSH6, PMS1, PMS2,* or *EPCAM*.[17] The frequency of gastric cancer in carriers of Lynch syndrome mutations has been estimated at 1·6%, and intestinal-type disease is the main histotype.[18] The risk of development of gastric cancer was 4·8% in patients with germline defects of *MLH1* and 9% in those with germline defects of *MSH2*. Surveillance with oesophagogastroduodenoscopy is necessary in patients with Lynch syndrome who carry mutations in mismatch repair genes.[18]

Li-Fraumeni syndrome encompasses several tumour types that develop generally before 45 years of age because of inherited *TP53* mutations,[19,20] including early-onset gastric cancer. The frequency of gastric cancer in families carrying *TP53* mutations ranges from 1·8% to 4·9%.[21,22] 40% of families with *TP53* mutations present with at least one gastric cancer (mean age 43 years, median age 36; age range 24–74 years), with an excess of early onset gastric cancers.[22] These data support periodic screening with oesophagogastroduodenoscopy in young carriers of *TP53* germline mutations, and particularly in Li-Fraumeni syndrome families in which at least one case of gastric cancer has been reported.[22] Data for the histological type of gastric cancer are insufficient to associate a particular histotype with Li-Fraumeni syndrome. Importantly, gastric cancer can occur in Li-Fraumeni syndrome families without *TP53* mutations (two of 73 families studied), suggesting that incidence could be independent from the presence of germline *TP53* mutation.[21]

Familial adenomatous polyposis is caused by *APC* germline mutations and is characterised by the development of more than 100 colonic and rectal adenomas and early development of colorectal cancer.[23,24] Roughly 8% of patients have attenuated disease, in which fewer adenomas are present and disease onset is later.[24] Adenomas also develop in the upper gastrointestinal tract, especially in the duodenum, and, if untreated, can progress to malignant disease in roughly 5% of cases.[24] A grading system was developed for duodenal polyps in familial adenomatous polyposis for assessment of disease severity.[25] In the stomach, gastric fundic gland polyps and adenomas in the antrum