Review Article

Genetics of gastric cancer: what do we know about the genetic risks?

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Abstract: An appreciable number of patients with gastric cancer have an underlying hereditary cancer susceptibility syndrome as the cause of their gastric cancer, particularly those with early onset gastric cancer or a family history of gastric or other cancers. Pathogenic germline variants in specific genes account for the known gastric cancer predisposition syndromes. Germline genetic testing can identify individuals and their family members who carry inherited pathogenic gene variants, and thus have increased risk of developing gastric or other cancers. Ideally, germline pathogenic variants can be identified in family members before the onset of disease, when early detection or prevention strategies can be implemented most effectively to decrease gastric cancer- related morbidity and mortality. This article reviews some of the currently known gastric cancer predisposition syndromes and their associated cancer risks. We also discuss current research and advances in the field of genetic gastric cancer susceptibility.

Keywords: Stomach neoplasms; gastric cancer; cadherins; hereditary nonpolyposis; genetic testing; genetic predisposition to disease

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Introduction

Over the past few years, the annual global rates of new gastric cancer cases and deaths due to gastric cancer have been estimated to be over 1,000,000 and 700,000, respectively (1). Only 31% of individuals diagnosed with gastric cancer are expected to survive 5 years or more (2). However, the identification of a predisposition to gastric cancer enables interventions that may extend survival for patients and/or their family members. Unfortunately, very little is known about an underlying genetic susceptibility for the vast majority of gastric cancer patients.

Only 1% to 3% of gastric cancer patients are thought to have a hereditary form of gastric cancer (3), and tools for assessing genetic gastric cancer risk are limited. However, inherited susceptibility to develop gastric cancer (herein referencing gastric adenocarcinomas) is associated with certain germline genetic syndromes. These syndromes include hereditary diffuse gastric cancer syndrome (HDGC), Peutz-Jeghers syndrome, juvenile polyposis syndrome, Lynch syndrome, Li-Fraumeni syndrome, familial adenomatous polyposis (FAP), and gastric adenocarcinoma

Table 1 Genetic risk associated with pathogenic variants in gastric cancer predisposition genes

Gene (s) disrupted	Syndrome	Gastric cancer risk	Other cancer risk
CDH1	Hereditary diffuse gastric cancer syndrome (HDGC)	Up to 70% (6,7)	Lobular breast (6,7)
STK11	Peutz-Jeghers syndrome	Up to 29% (8)	GI, panc, breast (8)
SMAD4	Juvenile polyposis	Up to 21% (8)	GI (8)
MLH1, *MSH2* (includes *EPCAM* deletions), *MSH6*, *PMS2*	Lynch syndrome	1–13% (8)	GI, ov, ut, urinary tract, other (8)
APC	Familial adenomatous polyposis	<1% (8)	GI, thyroid (8)
APC promoter 1B	Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)	Significantly elevated (5)	Unknown, GI in some families (5)
TP53	Li-Fraumeni syndrome	1–4% (9)	Breast, brain, sarcoma, lung, adrenal cortical, other (9)
Unknown	Familial gastric cancer	Unclear (4)	Unclear (4)

Numbers provided in the parentheses refer to references. GI, gastrointestinal; panc, pancreatic; ov, ovarian; ut, uterine.

and proximal polyposis of the stomach (GAPPS), which is a variant of FAP (4,5) (*Table 1*). Gastric cancer also has been reported in families with other homologous recombination (HR) DNA repair pathway syndromes, due to likely pathogenic or pathogenic variant (10) (henceforth pathogenic variants) in *BRCA2* and *PALB2*, among others (6,11,12).

Germline genetic testing is a clinical tool that enables the identification of cancer predisposition syndromes and/or individuals at high risk for developing gastric cancer. For individuals carrying pathogenic variants, results can lead to earlier gastric cancer detection and/or prevention and decreased gastric cancer-related morbidity and mortality. The purpose of this article is to review the genes and syndromes associated with hereditary gastric cancer and to discuss some of the ongoing research and advances in the field.

Gene-specific risks

Genes with pathogenic variants most clearly associated with gastric cancer predisposition and their associated risks are highlighted in *Table 1*. The absolute lifetime risk for developing gastric cancer in an individual who is a carrier of a pathogenic variant in one of these genes ranges from 1% to 70% (6-9). The patients with the highest risk are those with HDGC syndrome, which is characterized by the development of diffuse, signet ring cell gastric cancers at an early age. The average age of gastric cancer diagnosis in patients with HDGC syndrome is 37 years (7). HDGC syndrome also has been associated with lobular breast cancer development in females (7,13,14). A germline mutation in the E-cadherin gene, *CDH1*, can predispose an individual to HDGC syndrome (15,16).

Testing for *CDH1* germline variants *should be* offered to any individual/family with: (I) two gastric cancer cases in a family with one confirmed as diffuse gastric cancer; (II) early-onset diffuse gastric cancer prior to age 40 years; and/or (III) personal or family history of diffuse gastric cancer and lobular breast cancer with one being diagnosed under the age of 50 years. Beyond the above, consideration for testing can be in the following scenarios: (I) bilateral lobular breast cancer or family history of two or more individuals with lobular breast cancer under age 50; (II) personal or family history of cleft lip/palate in an individual with diffuse gastric cancer; and/or (III) *in situ* signet ring cells and/or pagetoid spread of signet ring cells in pathology specimens (17). However, only 10–50% of HDGC families have a pathogenic *CDH1* variant (6,17,18). Other genes, such as *CTNNA1*, may be associated with forms of HDGC syndrome with an unclear or lower lifetime risk for gastric cancer (lower penetrance) (6,19,20).

All mutated genes referenced in this article cause cancer in families in an autosomal dominant pattern. Autosomal dominant inheritance occurs when a disease-causing gene is located on an autosome (one of the 22 sets of non-sex chromosomes), and the disease is found in those who inherit one copy of the pathogenic variant. Therefore, the cancer predisposition equally affects males and females

and does not generally skip generations. Rarely, gastric cancer predisposition is observed in patients with autosomal recessive disorders like Ataxia-telangiectasia, Xeroderma pigmentosa, or Bloom syndrome (7). These recessive disorders are important, but rare syndromes that are beyond the scope of this review.

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer syndrome, should be suspected in families with colorectal, uterine, and ovarian cancers. Peutz-Jeghers syndrome should be suspected in individuals with a history of gastrointestinal Peutz-Jeghers hamartomatous polyps (8). Likewise, individuals with juvenile polyposis syndrome often present with hamartomatous juvenile polyps. Patients with FAP syndrome often have a strong personal and/or family history of colon polyposis and/or colon cancer. Significant lifetime risks for intestinal type gastric cancer appear to also occur with GAPPS, a variant of FAP; however, the exact level of risk remains to be elucidated (5).

Less clear associations have been suggested for many well-known cancer genes in the DNA repair pathway (e.g., *ATM*, *BRCA2*, *PALB2*). Research to better define risk associations are ongoing (6,12).

Genetic testing and multigene panels

Genetic cancer risk assessment is an interdisciplinary medical standard-of-care practice (21) that utilizes genomic tools to identify individuals and families at increased risk for developing cancer, ideally before the onset of disease, when early detection and prevention strategies can be implemented most effectively. Hereditary breast and ovarian cancer (HBOC) syndrome, caused mainly by germline pathogenic variants in *BRCA1* and *BRCA2*, has been the model cancer syndrome for genetic cancer risk assessment, and suspected HBOC remains the most common cause for clinical referral (22). Personalized management options available for HBOC pathogenic variant carriers include: risk-reducing prophylactic bilateral salpingo-oophorectomy and/or mastectomy, chemoprevention, and precision therapy with PARP inhibitors (13,23). When a cancer predisposition germline pathogenic variant is known in the family, other family members can also be offered precision genetic cancer risk assessment (13).

Similar to HBOC, guidelines have been developed to help physicians determine who may benefit from further risk evaluation for hereditary gastric cancer (*Table 2*). As new genetic associations are better understood, the guidelines evolve, and updates should be actively integrated into patient care by health care professionals.

Multigene panel testing, in which multiple genes are tested at the same time, is the most common type of germline genetic testing currently used in genetic cancer risk assessment. For instance, individuals referred for genetic cancer risk assessment due to their personal or family history of non-syndrome-specific gastric cancer or other cancers would likely undergo evaluation of the genes in listed in *Table 1*. In contrast, individuals referred due to very specific presentations, such as HDGC, may only require germline evaluation of *CDH1* and possibly *CTNNA1* as an initial approach. However, if no pathogenic variants are identified, reflex testing would likely involve at least the evaluation of the remaining genes listed in *Table 1*.

Regardless of the clinical presentation, interpreting the pathogenicity of germline variants identified by genetic testing is often challenging. Given this challenge, the Clinical Genome Resource (ClinGen) has begun assembling Variant Curation Expert Panels to develop and implement rules specifically for some of the genes associated with gastric cancer predisposition (*CDH1*, *TP53*). To date, *CDH1* variant classification guidelines have been published (24) that modify the general gene variant classification offered in 2015 by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) (10). Thus, the panel now provides the genetics community with a tailored framework to assess the pathogenicity of germline *CDH1* variants (24), with the aim of improving our collective ability to perform *CDH1* genetic cancer risk assessment for individuals and their families.

Managing risks

Once an individual is identified with a gastric cancer predisposition, screening or risk-reducing procedures can be initiated for early cancer detection or prevention, respectively. All syndromes listed in *Table 1* have established guidelines recommending upper endoscopy as part of their management (7,8). HDGC is unique given its extremely high-risk of diffuse gastric cancer and limited efficacy of surveillance endoscopy. Management of unaffected *CDH1* pathogenic variant-positive HDGC includes risk-reducing gastrectomy in adulthood, or if gastrectomy is declined, upper endoscopy with random biopsies every 6 to 12 months (7). In one study, the majority of individuals with *CDH1* pathogenic variants who underwent the random biopsy screening protocol (the Cambridge protocol)

Table 2 Patient presentations that warrant further gastric genetic cancer risk assessment

Personal cancer history of gastric cancer (GC) with:
Onset before age 40
Onset before age 50 with a close relative with GC
Onset at any age with two or more close relatives with GC
Breast cancer, with one diagnosed before age 50
Onset at any age and family history of breast cancer, with one close relative diagnosed before age 50
Onset at any age with a family history of juvenile polyps, gastrointestinal polyposis, or Lynch syndrome spectrum cancers (colorectal, endometrial, small bowel, or urothelial)
Family history of GC with:
A close relative with a known pathogenic variant in a gastric cancer susceptibility gene
Onset in a close relative before the age of 40
Onset in two close relatives, with one diagnosed before age 50
Onset in three close relatives independent of age
A close relative with GC and breast cancer, with one diagnosed before the age of 50
A close family member with juvenile polyps or gastrointestinal polyposis

A close relative is defined as a first- or second-degree relative. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer V.2.2018. © 2018 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available (7).

ultimately decided to complete gastrectomy. This occurred most commonly due to: (I) the finding of cryptic diffuse gastric cancer or due to the stress of screening biopsies and the potential to find cancer; (II) the diagnosis or recent death of close family members with gastric cancer, or; (III) siblings having successful risk-reducing gastrectomies (25). Age-adjusted risks are now available through online risk calculators to help patients make informed decisions, particularly if a *CDH1* pathogenic variant is identified later in life (26).

It should be noted that all the genetic syndromes described in *Table 1* have concomitant secondary cancer risks. Therefore, although multiple individuals in the family may present with gastric cancer, family members may also present with other cancers along the syndrome-associated spectrum. Many of these cancers can be screened for and/or prevented by risk-reducing surgeries, such as risk-reducing salpingo-oophorectomy to prevent ovarian cancer in Lynch syndrome pathogenic variant carriers (8), or in the case of HDGC, female high-risk breast cancer screening for the elevated risk for lobular breast cancer (7,13). With regard to more recently associated syndromes with gastric cancer risk, even though the gastric cancer screening/surveillance management recommendations have not been established, important management considerations exist for other associated cancers, such as the breast and ovarian cancer risks conferred by germline *BRCA2* pathogenic variants and the breast cancer risks with germline *PALB2* pathogenic variants (13).

In the United Kingdom and the United States, familial intestinal (non-diffuse adenocarcinoma) type gastric cancer without a known pathogenic variant in the family is defined by having at least two close (first- or second-degree) relatives affected by intestinal gastric cancer before the age of 50 years, or at least three close relatives with intestinal gastric cancer at any age (4,27). In countries with high gastric cancer incidence, like Portugal and Japan, even stricter criteria are applied (4,27). It is particularly difficult to counsel familial intestinal gastric cancer families without a pathogenic variant regarding absolute lifetime gastric cancer risks and screening recommendations as guidelines and strategies are still lacking.

Future directions

There remains a substantial knowledge gap regarding familial gastric cancer. Families affected by gastric cancer may have a yet-to-be-identified pathogenic gene variant, or other heritable or environmental risk factor(s) contributing to the development of gastric cancer. Multiple publications have identified new potential targets for germline gastric cancer susceptibility (6,12), and research is ongoing to better understand the clinical utility and meaning of suspected pathogenic variants in potential candidate genes. Other heritable factors, such as single nucleotide polymorphisms (SNPs), are also being evaluated for clinical utility (28), following the polygenic risk score model implemented to evaluate breast cancer risk (29). Environmental and other non-genetic factors are also being studied (30).

Alternatives to traditional genetic cancer risk assessment and germline genetic testing are now also identifying individuals with previously unknown gastric cancer syndromes. For instance, both somatic tumor sequencing and circulating tumor DNA testing may have the ability to identify incidental germline gastric cancer predisposition variants (31-33).

For gastric cancer due to Lynch syndrome and pathogenic variants within the HR pathway, there is the potential for use of targeted therapeutics that exploit features of the tumor resulting from aberrant DNA repair (23,34).

Conclusions

Gastric cancer risk is inherent in many well-known genetic syndromes. These syndromes are also often associated with risk for non-gastric cancers. Genetic cancer risk assessment can be a powerful tool to identify pathogenic gene variants in families to help understand who in the family is at high risk for gastric cancer. Identification of high-risk individuals can allow for precision cancer screening and potentially risk-reducing gastrectomy to decrease gastric cancer-related morbidity and mortality. Currently, clear genetic cancer risk assessment/germline genetic testing guidelines are lacking for many gastric cancers that do not fit a particular syndromic pattern; particularly in cases of familial intestinal type gastric cancer. Discussion with a genetics professional can inform the determination of appropriate treatment strategies and referrals for genetic cancer risk assessment and/or genetic testing.

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Footnote

Conflict of Interest: R Karam was an employee of Ambry Genetics during the preparation of this manuscript. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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