Familial Gastric Cancers

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ABSTRACT

Although the majority of gastric carcinomas are sporadic, approximately 10% show familial aggregation, and a hereditary cause is determined in 1%–3% cases. Of these, hereditary diffuse gastric cancer is the most recognized predisposition syndrome. Although rare, the less commonly known syndromes also confer a markedly increased risk for development of gastric cancer. Identification and characterization of these syndromes require a multidisciplinary effort involving oncologists, surgeons, genetic counselors, biologists, and pathologists. This article reviews the molecular genetics, clinical and pathologic features, surveillance guidelines, and preventive measures of common and less common hereditary gastric cancer predisposition syndromes. The Oncologist 2015; 20:1365–1377

Implications for Practice: Although the majority of gastric adenocarcinomas are sporadic with many of those related to chronic Helicobacter pylori infection, approximately 10% of the cases show familial aggregation, and a specific hereditary cause is determined in 1%–3% cases. This review describes the molecular genetics, clinical and pathologic features, surveillance guidelines, and preventive measures of common and less common hereditary gastric cancer predisposition syndromes. Ultimately, a better understanding of the biology of these conditions should allow early identification and intervention as part of a multidisciplinary approach involving oncologists, surgeons, genetic counselors, and pathologists.

INTRODUCTION

Family history is a well-recognized risk factor for gastric cancer, with the most famous example of hereditary transmission of gastric carcinoma being the family of Napoleon Bonaparte. Napoleon had five first degree relatives affected by gastric carcinoma, affecting three consecutive generations [1].

The term “familial gastric cancer” has been used to describe families with 2 first- or second-degree relatives with gastric cancer before the age of 50 years or 3 first- or second-degree relatives with gastric cancer independent of age [2]. Clustering of gastric cancer can be seen in such families in approximately 10% of cases. However, a gene defect can be determined in only 1%–3% of cases [3, 4]. A better understanding of the biology of these predisposition syndromes would allow early identification and intervention and improve life expectancy.

Familial gastric cancer syndromes can be classified into two categories: (a) hereditary gastric cancer with polyps and (b) hereditary gastric cancer without polyps. Polyp-associated syndromes may endoscopically present as “polyposis,” with polyps carpeting the wall of the stomach. Histologically, like sporadic cancer, hereditary neoplasms can be broadly classified as intestinal, diffuse, or mixed. In this review, we discuss the features of hereditary gastric cancers, with a focus on molecular genetics, pathologic features, surveillance guidelines, and preventive measures.

HEREDITARY GASTRIC CANCER ASSOCIATED WITH POLYPS

Familial Adenomatous Polyposis/Attenuated Familial Adenomatous Polyposis

Overview and Inclusion Criteria

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder. The presence of gastric polyps is a known manifestation of FAP, with a reported incidence varying from 51% [5] to 88% [6]. The incidence of gastric polyps in attenuated FAP has been reported to be even higher (93%) in a series of 16 patients [7]. The pediatric population is affected, with gastric polyps reported in 81% of syndromic children, 31% of them harboring dysplasia [8]. The risk of gastric carcinoma in FAP varies geographically. A high risk has been reported in Japan (4.5%–13.6%) [9] but has not been confirmed in the West, where the risk of gastric carcinoma is low (0.6%–4.2%) [10, 11]. Overall, it has been estimated that Korean and Japanese FAP patients are 7–10 times more likely to develop gastric cancer than their counterparts in other parts of the world.

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It is worth noting that although neither gastric polyps nor carcinoma is a defining feature of FAP or attenuated FAP in the West, gastric cancer is considered an extracolonic manifestation of FAP in the East. Another criterion establishing FAP is the presence of more than 100 adenomatous colorectal polyps. If the number is less than 100, a diagnosis of attenuated FAP (AFAP) may be suggested if (a) there are at least 2 family members with 10–99 adenomas at age greater than 30 years or (b) an individual with 10–99 adenomas at age greater than 30 years and 1 first-degree relative with colorectal cancer (CRC) and few adenomas [14]. Other features of FAP or AFAP include extraintestinal abnormalities (e.g., congenital hypertrophy of retinal pigment epithelium, osteomas, epidermoid cysts, desmoid tumor, adrenal adenoma, or thyroid carcinoma, hepatoblastoma, and brain tumors) [13].

Molecular Genetics

The FAP and AFAP syndromes are autosomal dominant disorders with a high penetrance [15] and are caused by heterozygous mutation in the adenomatous polyposis coli (APC) tumor suppressor gene on Chr 5q21. Several mechanisms of germline inactivation of APC have been described, most of which (>90%) lead to truncation of APC protein [16]. These mutations have been detected in approximately 67% of FAP patients and include cases of both point mutations/substitutions (43% cases) and insertion deletions (indels) (57%). Although no mutational hotspots have been identified for point mutations, 97% of the indels were found in exon 15 [16].

The clinical phenotype and severity are determined not only by the loss of function of the APC gene and type of second hit (somatic mutation), but also by the position of the germline mutations [17]. For example, mutations toward the 5’ and the 3’ ends (codons 1,982–1,983) have been associated with profuse gastric fundic gland polyposis [18]. Somatic mutations involving codon 1,554–1,556 also have been reported in 51% of FAP-associated familial gastric polyposis (FGP) and 50% of gastric adenomas (GAs). Finally, because of a higher risk of upper gastrointestinal polyposis, one group has suggested more aggressive upper gastrointestinal screening in patients with mutations in codons 1,099–1,694 [5]. However, no difference has been observed between gastric or duodenal location of the polyps and mutation sites [19]. With regard to the subtype, mutations in exons 10–15H (codon 564–1,465) have been seen with a significantly higher frequency in GAs yet are undetected in FGP cases [20]. Finally, a few studies have reported mutational variation in dysplastic and malignant FAP-associated gastric polyps, with rare KRAS mutations in codon 12 seen in FGP harboring low grade [21] and mutations in exon 4 of the FAP gene reported in gastric polyposis and early-onset gastric carcinoma in AFAP patients [22].

Clinical Features and Pathology

The age of onset of gastric manifestations is variable. Although gastric adenocarcinomas typically develop long after colorectomy (often greater than 20 years) [23], FGP has been detected as early as 8 years of age [24], and gastric carcinoma as early as 11 years of age [5]. The types of benign gastric lesions detected include FGP (reported in 26% [25] to 85% [6] of FAP cases), GAs (reported in 2% [25] to 41% [5]), and, rarely, hyperplastic polyps [26] and pyloric adenomas [27]. Although FGP are limited to the body/fundus, GAs are commonly present at the junction of the body/antrum [26]. In fact, when GAs are detected in the body/fundus, they are commonly associated with adenomatous change in FGP. Another feature associated with syndromic FGP is their multiplicity, endoscopically presenting as gastric polyposis (arbitrarily defined as >20 polyps) [26]. Instead, adenomas tend to be less likely multiple [28] and are generally flat or sessile [29], making the endoscopic identification more challenging.

Syndromic FGP have a higher incidence of harboring incipient dysplasia (25% [30] to 44% [31]) than sporadic FGP (~1%) [30], and low grade dysplasia is observed more commonly than high grade. The risk of developing dysplasia is directly proportional to the size of the polyp and the presence of antral gastritis [6]. The risk of carcinoma is low. Reported gastric adenocarcinomas are of the World Health Organization tubular type (Lauren intestinal type) [23, 32]. Multicentric or metachronous lesions have been described [23]. Gastric cancers can also arise in the absence of precursor lesions [33].

Surveillance and Clinical Management

There are no standard surveillance guidelines for upper endoscopy in FAP patients. However, current data suggest that it should be started at 21–30 years of age [8] and performed at intervals of 3–5 years [34].

Nonsteroidal anti-inflammatory drugs and acid-suppressive therapy have been associated with regression and reduction in the number of gastric polyps [35] and incidence of dysplasia [6]. However, the impact of this on the development of malignancy and overall survival is not known. In severe polyposis causing symptoms, surgical intervention may be considered to control the disease [36].

MUTYH-Associated Polyposis

Overview and Inclusion Criteria

Unlike other polyposis syndromes, MUTYH-associated polyposis (MAP) [37] is an autosomal recessive polyposis syndrome. The diagnosis can be established only after exclusion of FAP syndrome by demonstrating an absence of APC mutation. It has been estimated that the prevalence in MUTYH is 1 in 40,000 and 1 in 20,000 (clinical and subclinical carriers) [38]. Gastric involvement (i.e., polyps and carcinoma) is uncommon, but the incidence of duodenal involvement (especially duodenal carcinoma) is comparable to FAP [39]. Affected individuals are also predisposed to developing colorectal, breast, ovary, skin and sebaceous, and bladder carcinomas [39].

A diagnosis is established only after confirmation of MUTYH mutation [40] in a suspected individual on the basis
of the following criteria: (a) family history of CRC with an autosomal recessive mode of inheritance, (b) >100 colon polyps in the absence of germline APC mutation, (c) 10–100 colon polyps (including adenomas and hyperplastic type), (d) 1–10 colon adenomas in an individual younger than 10 years of age, or (e) CRC with a specific somatic KRAS mutation (c.34G→T) in codon 12.

**Molecular Genetics**

MAP is caused by biallelic mutations in MUTYH (mutY homolog [Escherichia coli]) gene, located at Chr locus 1p34.3-p32.1 [40], which plays an important role in DNA base-excision repair. MUTYH is a DNA glycosylase that excises the misincorporated bases as a result of DNA damage caused by ionizing radiation or chemical oxidants [41]. Biallelic mutations result in the formation of truncated protein [42]. Interestingly, ethnic clustering of mutational hotspots is reported. For example, a higher frequency of biallelic loss at p.Y179C and p.G396D is seen in Caucasians but has not been noted in other populations. This can likely be explained by founder mutation resulting in selective overexpression of a mutational hotspot [43].

**Clinical and Pathologic Features (Including Associated Other Neoplastic Lesions)**

Gastric polyps are noted in 11% of cases, diagnosed at a median age of 49 years (range, 14–67 years). These include both adenomas and fundic gland polyps [39]. The risk of gastric cancer is low, seen in 2% of cases diagnosed at a median age of 38 years (range, 17–48 years). However, the incidence of duodenal cancer is significantly increased (occurring in approximately 17% of cases) [39].

**Surveillance and Clinical Management**

Surveillance guidelines for families with MUTYH germline mutations recommend that upper endoscopy be performed starting between the ages of 30 and 35 years and then subsequently at intervals of 3–5 years. The onset of colonoscopy surveillance has been recommended to be initiated at an earlier age (25–30 years) and repeated more frequently (every 1–2 years). Others have recommended initiation of upper gastrointestinal screening at 25 years of age, to be repeated at 30 years and then subsequently every 2 years if the results are normal [44]. Screening and testing minors is not recommended because of low risk.

**Peutz-Jeghers Syndrome**

**Overview and Inclusion Criteria**

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by multiple gastrointestinal hamartomatous polyps (most commonly jejunal) and melanocytic macules [45]. Estimated incidence is approximately 1 in 200,000 [46] live births. It is estimated that PJS patients have a relative lifetime risk of 89% for developing cancer and are predisposed to developing neoplasms of the gut, pancreas, breast, uterus, cervix, testis, ovary, and lung [47].

A diagnosis of classic PJS can be established if two of the following features are present: (a) small bowel polyposis; (b) hyperpigmentation of lips, buccal mucosa, and digits (which usually fades by puberty); and (c) positive family history, along with histologically confirmed hamartomatous polyps [48]. The detection of the STK11 mutation is not a prerequisite, because mutations are identified in only 70% of cases [49].

**Molecular Genetics**

Germline mutations of tumor suppressor gene STK11 (serine threonine kinase 1, also known as liver kinase B1, LKB1) located on Chr 19p13.3 are seen in 70% of individuals with PJS [50, 51]. Additional genetic alterations (LOH of 17p and 18q) are present in subsequent adenocarcinomas [49], indicating that STK11 may be an “initiator” mutation regulating the development of hamartomas and that secondary somatic “driver” mutations underlie the progression to adenocarcinoma [52]. However, it has been proposed that the proliferating stroma, instead of the epithelial component, is responsible for induction of malignancy by a phenomenon called “landscaper effect.” This has been proven in other hamartomatous polyps in which a clonal genetic abnormality is present only in the stroma and not in the epithelium [53]. However, in PJS polyps, allelic imbalance at the LKM1 locus has been detected in the epithelial component, supporting a hamartoma-adenoma-carcinoma model [54].

It has been suggested that the site and type of STK11 gene mutations are predictors of development of gastric polyps and malignancies; individuals with truncating mutations or no mutations develop an earlier onset of gastric polyps in comparison with those with missense mutations [55]. Notably, mutations in the ATP binding and catalysis area of the gene result in a nonmalignant clinical phenotype, whereas mutations in the substrate recognition area are associated with malignancies [56].

Surveillance guidelines for families with MUTYH germline mutations recommend that upper endoscopy be performed starting between the ages of 30 and 35 years and then subsequently at intervals of 3–5 years. The onset of colonoscopy surveillance has been recommended to be initiated at an earlier age (25–30 years) and repeated more frequently (every 1–2 years).
annual screening [62]. Because of the rarity of cases, detailed histologic studies are lacking. However, in the few reported cases, the histologic pattern has been intestinal type gastric adenocarcinoma [60].

**Surveillance and Clinical Management**
Because gastric polyps develop at a young age, endoscopic surveillance should be initiated early, with baseline endoscopy at the age of 8 years; henceforth, the screening interval may be tailored based on the findings of the first endoscopy. If polyposis is detected, screening should be performed at 2–3-year intervals; if no polyps are seen, it is suggested that screening be reinitiated at 18 years of age. More rigorous screening (every 1–2 years) should be performed after the age of 50 years [48]. Screening colonoscopy has been recommended starting at 20–25 years of age and performed at intervals of 2–5 years.

**Prevention and Treatment**
Because mammalian target of rapamycin (mTOR) is the final downstream effector of LKB1 inactivation, rapamycin (mTOR inhibitor) could be tested as a potential therapeutic agent [63]. Other drugs that have been suggested to decrease polyp burden include COX2 inhibition and metformin [64, 65].

**Juvenile Polyposis Syndrome/Hereditary Hemorrhagic Telangiectasia**

**Overview and Inclusion Criteria**
Juvenile polyposis syndrome (JPS) is an autosomal dominant disorder associated with the development of multiple polyps throughout the entire gastrointestinal tract. The incidence of JPS is 1 in 16,000 to 1 in 100,000 [48].

The inclusion criteria are (a) more than five juvenile polyps in the colon or rectum, (b) juvenile polyps throughout the gastrointestinal tract, or (c) more than one juvenile polyp with a family history of juvenile polyps [66]. However, individuals with mutations in SMAD4 or BMPR1A may exhibit a mixed polyposis phenotype similar to individuals with hereditary mixed polyposis syndrome (HMPS). Hence, JPS and HMPS are regarded, at least in part, as allelic entities [67].

**Molecular Genetics**
JPS is caused by mutations in several genes, most commonly SMAD4 (MADH4 or DPC4) on Chr 18q21.1 (20% of the cases) and in BMPRS1 on Chr 10q22.23 (20%–25% of the cases) [68–70]. Severe gastric polyposis has been associated with mutations in SMAD4, but not with BMPR1A mutations [70].

Germline mutations in PTEN (which controls function of the PI3K/AKT signaling pathway) and possibly ENG genes have been described [70, 71]. Of note, ENG encodes for endoglin, which is a transforming growth factor-β protein, which when mutated is responsible for hereditary hemorrhagic telangiectasia (HHT). Besides the common signaling pathway, there is also morphologic overlap in the phenotypic expression of these two conditions, and consequently, it is suggested that all HHT patients be screened for gastric polyposis [70].

**Clinical and Pathologic Features (Including Associated Other Neoplastic Lesions)**

Gastric polyps are commonly diagnosed in adults (median age of 41 years), whereas colorectal polyps are detected earlier in life (median age of 16 years) [70]. Polyposis may also develop, resulting in obstructive symptoms and hypergastrinemia [72]. The polyps may be associated with gastromegaly, severe anemia, hematemeses, and protein-losing enteropathy [73]. In such cases, the clinical presentation overlaps with Ménétrier disease. Interestingly, mutations in SMAD4 have also been detected in some cases of Ménétrier disease, and because the pathogenesis of both diseases involves dysregulation of transforming growth factor-β signaling pathway, some authors have suggested that Ménétrier disease could represent a variant of JPS in which another etiology (e.g., cytomegalovirus or Helicobacter pylori) would result in the expression of the clinical phenotype [74].

JPS polyps are pedunculated and present a smooth surface, ranging in size from 5 to 50 mm. Although JPS polyps are classically hamartomatous, they may exhibit morphologic heterogeneity, hence the term “mixed polyposis” referring to the hyperplastic, fundic gland, or inflammatory pseudopolyp phenotypes [75]. Gastric adenocarcinoma has been reported in up to 21% of gastric polyps [76]. Similar to polyps, SMAD4 mutations have been reported, but not BMPR1A mutations. Phenotypically, the gastric carcinomas were both intestinal and diffuse type [75].

**Surveillance and Clinical Management**
Upper and lower endoscopy have been recommended to be initiated in midteens or when symptoms begin, whichever is earlier, and repeated every 3 years if no polyps are found [48]. Annual screening is recommended if one to a few polyps are detected, which may be followed by screening every 3 years after no polyps are found. Gastrectomy is recommended for symptomatic patients with many polyps or gastric polyposis [76].

**Familial Gastric Polyposis**

**Overview and Inclusion Criteria**
Familial gastric polyposis is a rare autosomal dominant syndrome reported essentially only in Portuguese families, characterized by the development of a gastric hyperplastic polyposis, a high incidence of gastric carcinoma, and cutaneous psoriasis [77]. It is unclear whether the association with cutaneous psoriasis represents two distinct disorders or pleiotropic manifestations of one syndrome. Given the rarity of this syndrome, no tested inclusion criteria have been established.

**Clinical and Pathology Features (Including Associated Other Neoplastic Lesions)**

Gastric manifestations are seen in young patients, with polyposis involving the entire gastric wall. The polyps acquire a striking villous configuration and display exuberant globoid features. The epithelium is made up of either prominent foveolar hyperplasia or hyperplastic polyps with or without cytologic atypia [78]. No adenomas or fundic gland polyps are
seen [77]. Poorly cohesive gastric adenocarcinoma has been observed arising from the dysplastic foveolar epithelium.

**Molecular Genetics**
The syndrome is inherited as an autosomal dominant trait with incomplete penetrance with reported healthy carriers [79].

**Clinical Management, Surveillance, and Prevention**
No data are available on surveillance and prevention at this time.

**Gastric Adenocarcinoma and Proximal Polyposis Syndrome**

**Overview and Inclusion Criteria**
Gastric adenocarcinoma and proximal polyposis syndrome (GAPPS) is a recently described syndrome with increased risk of gastric carcinoma, characterized by multiple FGP s, with areas of multifocal dysplasia and subsequent development of carcinoma. The diagnosis can be established only after exclusion of other polyposis syndromes [80, 81].

The following diagnostic criteria have been recommended: (a) > 100 gastric polyps in the index case or over 30 polyps in a first-degree relative of a known case, (b) polyps restricted to the body and fundus of the stomach, (c) absence of colorectal or duodenal polyposis, (d) morphologically confirmed FGP s with areas of dysplasia or carcinoma, and (d) autosomal dominant inheritance.

**Molecular Genetics**
The etiology of this autosomal dominant disorder with incomplete penetrance is yet undetermined; however, coding mutations in APC, MUTYH, CDH1, SMAD4, BMPR1A, STK11, and PTEN have been excluded.

**Clinical and Pathologic Features (Including Associated Other Neoplastic Lesions)**
In the two series reported to date, the gastric manifestations were evident as early as 10 years of age, and gastric carcinoma was seen at 33 years of age. It appears to be more common in females.

Extensive polyposis is seen in the body and fundus with sparing of the lesser curvature. The polyps are small (< 10 mm in size) and resemble sporadic FGP s. In fact, it is recommended that endoscopic biopsies be repeated after the patient is off proton pump inhibitor therapy to exclude sporadic FGP s. The polyps are associated with areas of dysplasia and mixed morphology, with combined adenomatous and hyperplastic polyplike areas noted. Gastric carcinomas have been detected in 12.7% of patients and have all been gland-forming.

Although some patients were diagnosed with a few colorectal adenomas, none had colonic polyposis or colorectal carcinoma. Finally, as in sporadic FGP s, an inverse relationship has been seen between *H. pylori* infection and gastric manifestations of GAPPS.

**Surveillance and Clinical Management**
Management ought to be decided on a case-by-case basis, taking into consideration the risk of gastric cancer in the individual family. The presence of gastric polyposis presents difficulties with endoscopic surveillance, and patients may opt for total gastrectomy. Supporting this approach is the report of young patients (33 and 48 years of age), relatives of the proband, who despite endoscopic surveillance and biopsies developed and subsequently died of metastatic gastric carcinoma [81].

**Familial Gastric Cancer Syndromes Without Polypos**
As a result of increased application of genomic analysis, a better understanding of molecular anomalies associated with gastric cancer has emerged. Among these, hereditary diffuse gastric cancer syndrome has been the focus of significant research since the 1998 identification of the E-cadherin protein by Guilford et al. [82]. In addition, identification of genes for other nonpolyposis syndromes predisposing to gastric carcinoma is discussed below (Table 1).

**Hereditary Diffuse Gastric Cancer**

**Overview and Inclusion Criteria**
Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer predisposition syndrome characterized by an increased risk of diffuse gastric cancer and breast carcinoma [83]. The prevalence in the general population is less than 0.1 per 100,000 and less than 1% among individuals with gastric cancer [84]. The lifetime risk of developing gastric carcinoma in male carriers is 70% (95% confidence interval [CI], 59%–80%) and 56% for female carriers (95% CI, 44%–69%). Similarly, the risk for lobular breast carcinoma, initially reported at 60% in female carriers, has been noted subsequently to vary from 39% [85] to 52% [86].

The 1999 guidelines proposed that a diagnosis of HDGC could be established in families with (a) ≥ 2 documented cases of diffuse gastric cancer in first and second degree relatives with at least one diagnosed < 50 years of age or (b) ≥ 3 documented cases of diffuse gastric cancer in first and second degree relatives regardless of the age of onset [87]. In 2010, the guidelines were updated to expand the spectrum of clinical and pathologic findings triggering genetic testing for *CDH1* mutations; that is, (a) pathologic confirmation of diffuse type gastric carcinoma now required only in 1 family member, (b) individuals with diffuse type gastric cancer diagnosed < 40 years of age (even without a family history), (c) addition of lobular breast carcinoma to the prior guidelines, and (d) detection of in situ signet ring cells and/or pagetoid spread of signet ring cells adjacent to diffuse type gastric cancer. Finally, testing for large genomic rearrangements of *CDH1* was recommended in addition to direct sequencing [88]. The latest guidelines propose merging the first two criteria into a new criteria: ≥ 2 documented cases of gastric carcinoma (at least one confirmed diffuse gastric cancer) in first and second degree relatives, irrespective of age [89]. Some have proposed that the criteria laid out by the first workshop be called “Clinical HDGC” and that the expanded criteria be referred to as “Probable HDGC” [2]. A recent study suggested that a personal or family history of 2 histologically proven lobular breast cancers before age 50, after exclusion of a germline mutation in *BRCA1* or *BRCA2*, should be added to the criteria for *CDH1* gene testing [90].
Testing is also recommended in individuals with family history of cleft lip/palate and diffuse gastric carcinoma [89].

### Molecular Genetics

HDGC syndrome is caused by heterozygous mutation in the calcium-dependent adhesion protein (CDH1, Uromodulin) gene located on Chr 16q22.1 [78], inherited as an autosomal dominant disorder with an incomplete clinical penetrance [88]. CDH1 is a tumor suppressor gene encoded by 16 exons [91], but no mutational hotspots are identified, unlike sporadic discohensive gastric carcinoma [82]. CDH1 gene testing should be performed for the entire open reading frame, including intron-exon boundary and copy number analysis [89]. Recognized mutations include frameshift mutations, insertions, and deletions that are not determined [89, 92]. CDH1 mutations we previously reported to 19% after application of CDH1 mutation-positive individuals who decide to decline surgery, which is seen in 20% of HDGC families; other mutations to 1% are a result of in-frame deletions and germline-promoter methylation [84]. These mutations lead to an altered or absent expression of E-cadherin protein, which plays an important role in cell polarity and intercellular adhesion. Notably, CDH1 mutations were previously reported to be detected in approximately 45% of HDGC individuals; however, a recent study reports a decrease in the frequency of CDH1 mutations to 19% after application of the new criteria [89, 92].

Several mechanisms have been proposed for inactivation of the second allele (the second hit), including promoter hypermethylation (which may explain the absence of loss of heterozygosity of the CDH1 allele) [93], intragenic deletions of the wild allele, and, less commonly, somatic mutations in CDH1 [94]. Germline mutations in CTNNA1 gene have been identified in a family of individuals meeting the criteria for HDGC; however, there is insufficient information regarding the penetrance at this point [89].

### Clinical and Pathologic Features

Gastric carcinoma has been seen as early as 14 years of age and as late as 85 years [4]. The topographic distribution of HDGCs varies. Several series have shown clustering of signet ring cell carcinomas in the cardia and proximal stomach, especially in oxyntic type mucosa [95]; however, families from New Zealand were reported to have early onset carcinomas clustered in the distal stomach and antral-body transitional zone [96]. Currently, there are no apparent genetic alterations explaining the differences. Nevertheless, it has been suggested that the confirmation of uneven topographic distribution may increase the diagnostic yield during surveillance [95].

Surveillance biopsies and prophylactic gastrectomies of CDH1 patients have allowed recognition of early stages of diffuse type gastric carcinoma. Microscopic foci of invasive signet ring cells develop just underneath the surface mucosal epithelium, with preservation of the overall architecture of the tissue. Alternatively, individual tumor cells may display a pagetoid spread underneath the preserved epithelium of pits and foveolae but still within the basement membrane. Immunohistochemically, the neoplastic cells show reduced expression or absence of E-cadherin protein (Table 2).

### Surveillance and Clinical Management

Carriers are advised to consider prophylactic gastrectomy after obtaining a baseline endoscopy to exclude the presence of macroscopic lesions. Prophylactic gastrectomies exhibit close to 100% histologic penetrance, unlike “clinical penetrance,” which is seen in ~80% of HDGC cases [88].

It is advised that endoscopic surveillance performed annually be offered to young individuals (~<20 years), to mutation-positive individuals who decide to decline surgery, and to those with mutations of uncertain significance. Multiple biopsies are recommended, including sampling of any endoscopically visible lesion and at least 5 random biopsies from the 6 anatomical zones (cardia, fundus, body, antrum, transitional zone, and prepyloric area, a total of 30 biopsies) [88, 89]. It has

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### Table 1. Gastric cancer predisposing polyposis and nonpolyposis syndromes with characteristic molecular and cytogenetic features

| Syndromes                                | Genes       | Cases associated with mutation, % | Inheritance      | Gastric cancer risk, % |
|------------------------------------------|-------------|----------------------------------|------------------|-----------------------|
| Hereditary diffuse gastric cancer syndrome | CDH1        | 45                               | Autosomal dominant | 56–70                |
| Gastric adenocarcinoma and proximal polyposis syndrome | Implicated gene unknown | Not determined                  | Autosomal dominant | Not determined        |
| Hereditary nonpolyposis colon cancer      | MLH1, MSH2, MSH6, PMS2 | MSH2, ~60; MLH1, ~30; PMS2, ~10 | Autosomal dominant | 2–30                 |
| Peutz-Jeghers syndrome                    | STK11       | 70                               | Autosomal dominant | 29                   |
| Juvenile polyposis                        | SMAD4, BMPR1A | SMAD, 4–20; BMPR1A, 20–25 | Autosomal dominant | 21                   |
| Familial breast cancer                    | BRCA1, BRCA2 | ~99                             | Autosomal recessive | Very low             |
| Li-Fraumeni syndrome                      | TP53        | 70                               | Autosomal dominant | 3.1–4.9              |
| Familial adenomatous polyposis            | APC         | ~90                             | Autosomal dominant | 2.1–4.2              |
| MYH-associated polyposis                  | MYH         | ~99                             | Autosomal recessive | Very low             |

*The rare familial intestinal gastric cancer, ataxia telangiectasia, and xeroderma pigmentosum are not included in this table.*
been estimated that to achieve a 90% detection rate of at least one neoplastic focus on biopsy, theoretically, approximately 1,768 biopsies (range 50–5,832) will be required [97].

**Prevention and Treatment**

Prophylactic gastrectomy (now reported as “risk-reduction gastrectomy,” given the high prevalence of microscopic carcinoma) [89] is the treatment of choice for carriers of pathogenic (truncating) CDH1 mutations. Endoscopic surveillance is an option offered to carriers of pathogenic mutations who opt not to have gastrectomy, individuals carrying mutations of undetermined significance, and individuals with a strong family history of gastric carcinoma but who test negative for CDH1 mutations [98]. The decision to perform genetic testing must be based on the earliest age of cancer onset in the family, but it is recommended that screening be initiated in the late teens or early twenties [97].

In women, annual mammography and breast magnetic resonance imaging are recommended after the age of 35 years. There are insufficient data for consideration of prophylactic mastectomy [84].

The prognosis of individuals undergoing prophylactic gastrectomy is excellent [84]. The surgical procedure includes total gastrectomy with end-to-side Roux-en-Y esophagojejunostomy.

**Hereditary Nonpolyposis Colorectal Cancer**

**Overview and Inclusion Criteria**

Hereditary nonpolyposis colorectal cancer (HNPCC) is the most common form of inherited CRC syndrome, accounting for 2%–4% of all CRC. It is caused by mutations in DNA repair genes resulting in errors in repetitive DNA sequences throughout the genome (microsatellite instability [MSI]) [99]. The syndrome has been subdivided into (a) Lynch syndrome I, predisposing primarily to colonic carcinoma, and (b) Lynch syndrome II, predisposing to other neoplasms in addition to CRC, including those arising in the endometrium, stomach, pancreaticobiliary tract, prostate, and genitourinary tract. Muir-Torre syndrome (MTS) is a variant characterized by HNPCC-related tumors and sebaceous neoplasms.

The lifetime risk for developing gastric cancer varies geographically. It is in fact the most frequent extracolonic carcinoma in countries with a high prevalence of sporadic gastric carcinoma, with a lifetime risk of 30% in Korea [100] and 44.4% in China [101], whereas it is reported at 2.1% in the Netherlands [102]. Only three cases have been reported in association with MTS [103, 104].

Two sets of criteria are used to establish a diagnosis of HNPCC: (a) Amsterdam criteria and (b) Bethesda criteria. Gastric carcinoma is not a defining criterion for HNPCC in either

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**Table 2. Clinicopathologic features and management of polyposis-associated gastric cancer predisposing syndromes**

| Feature                        | Characteristic | FAP | MAP | PJS | JPS | Familial gastric polyposis | GAPPS |
|-------------------------------|----------------|-----|-----|-----|-----|--------------------------|-------|
| Gastric adenocarcinoma        |                |     |     |     |     | Diffuse type             | Young |
| Gastric polyps                | Age            | 8 years | 14 years | 16 years (median) | 41 years (median) | Hyperplastic polyps with vilous configuration and exuberant globoid features | Young |
|                               |                |       |     |     |     | FGPs with mixed morphology including adenomatous areas and hyperplastic poly-poly areas |       |
| Endoscopic surveillance       | Initiative     | 21–30 years | 30–35 years | 8 years | Midteens or when symptoms begin, whichever is earlier | Determined on a case-by-case basis |       |
|                               | Interval       | 3–5 years | 3–5 years | Tailored based on the findings of the first endoscopy | 3 years if no polyps; annual screening if one to a few polyps are detected |       |       |
| Medical treatment             | NSAIDS, acid-suppressive therapy |          | mTOR inhibitors, COX2 inhibitors, and metformin | mTOR inhibitors | — | — |       |
| Surgical management           | In severe polyposis | — | — | In symptomatic patients with numerous polyps or gastric polyposis | — | In severe polyposis | — |

*Lauren classification.

| Abbreviations: = no data; FAP, familial adenomatous polyposis; FGP, familial gastric polyposis; GA, gastric adenoma; GAPPS, gastric adenocarcinoma and proximal polyposis syndrome; JPS, juvenile polyposis syndrome; MAP, MUTYH-associated polyposis; mTOR, mammalian target of rapamycin; NSAID, nonsteroidal anti-inflammatory drug; PJS, Peutz-Jeghers syndrome. |
classification. The 1999 revision of the Amsterdam criteria is characterized by the inclusion of extracolonic carcinomas such as endometrial, small bowel, uterine, or renal pelvis in at least 3 relatives with CRC meeting these criteria: (a) 1 relative should be a first degree relative of the other 2, (b) CRC or HNPCC-related carcinoma affects 2 successive generations, and (c) at least 1 carcinoma should be before the age of 50 years. Histopathologic verification and exclusion of a diagnosis of FAP are cardinal [99].

The Bethesda criteria provide a more complete list of all clinical presentations of HNPCC. The 2002 revision includes additional features of MSI tumors. The criteria include: (a) CRC diagnosed in an individual younger than 50 years of age; (b) presence of synchronous or metachronous colorectal or other HNPCC-related tumors, irrespective of age; (c) CRC with MSI-H histology diagnosed at <60 years of age; (d) individuals with CRC with at least 1 first-degree relative with CRC or HNPCC-related tumor, diagnosed at <50 years of age; (e) individuals with CRC with at least 2 first- or second-degree relatives with CRC or HNPCC-related tumor, irrespective of age. If an individual meets the above criteria, they are referred for molecular and immunohistochemical testing for MSI, because some individuals may meet the clinical criteria but are microsatellite stable on testing, an exclusionary characteristic [99].

Molecular Genetics

The most common defect is seen in \( MSH2 \), which accounts for \( \sim 60\% \) of HNPCC cases (also known as HNPCC1), and \( MLH1 \) accounts for \( \sim 30\% \) of the cases (also known as HNPCC2). Mutations in \( PMS2 \), \( MSH6 \), \( TGFBR2 \), and \( MLH3 \) account for the remaining 10% of the cases. Epigenetic silencing of \( MSH2 \) caused by deletions in upstream \( EPCAM \) gene results in another variant [105]. It is unclear whether there is a significant variation in the incidence of gastric carcinoma between \( MSH2 \) and \( MLH1 \) mutated HNPCC cases; conflicting reports have described higher incidences clustering in one subtype versus the other (T33, T34) [106, 107]. Some phenotypic variations are observed, especially between HNPCC1 (\( MSH2 \) mutated) and other HNPCC types [105, 108].

Clinical and Pathologic Features

It is noteworthy that the original report of HNPCC by Warthin in 1913 presented a family with clustering gastric carcinoma [109]. The cumulative incidence of gastric carcinoma in HNPCC is 13% by 70 years of age [107]. Compared with sporadic tumors, 52% of gastric carcinomas (GCAs) in HNPCC are diagnosed in individuals younger than 50 years (90% of sporadic GCAs are diagnosed after the age of 55 years) [106]. The carcinomas are reported to have an intestinal phenotype [110] (Table 3).

Clinical Management: Surveillance, Prevention, and Treatment

There are no consensus guidelines regarding upper gastrointestinal screening in individuals with HNPCC. Some authors recommend screening in individuals for whom a family history of gastric cancer is present or in countries with a higher incidence [111, 112]. Also, based on the clustering of gastric cancer seen in families with \( MSH2 \) mutations, it has been proposed that screening should be implemented in this subset of families [106]. Eradication of \( H. pylori \) in HNPCC patients may reduce the risk of gastric carcinoma [111]. Routine testing by immunohistochemistry is recommended for screening all colorectal carcinomas in major academic centers and can detect up to 95% of MMR related CRCs [113]. There are no current screening guidelines at this time for identification and screening of MSI-H gastric carcinoma by immunohistochemical testing.

Familial Intestinal Gastric Cancer

Overview and Inclusion Criteria

Familial intestinal gastric cancer (FIGC) is a poorly characterized genetic predisposition for gastric cancer of intestinal phenotype and lacking \( CDH1 \) mutation [88].

The recommended criteria vary geographically and are based on the local incidence of gastric cancer [114]. Guidelines analogous to the Amsterdam criteria for colorectal carcinoma have been used in countries with high incidence. In countries with low incidence, FIGC has been defined as intestinal gastric cancer in 2 or more first- or second-degree relatives, with at least one diagnosis by age 50 or 3 cases or more in first- or second-degree relatives, independent of age.

Molecular Genetics

The mode of inheritance is autosomal dominant, but the genetic factors involved are unclear. These tumors do not exhibit mutations in \( TP53 \), DNA mismatch repair genes, or \( CDH1 \) [115]. However, epigenetic methylation of \( CDH1 \) is reported in approximately 17% of cases, and loss of heterozygosity is reported in 9.4% of cases [114].

Clinical and Pathologic Features (Including Associated Other Neoplastic Lesions)

According to a Japanese study, after applying the Amsterdam criteria to a large cohort of 3,632 families with gastric carcinoma, only 31 (0.9%) met the criteria for FIGC. Gastric carcinoma was seen in 28.6% of individuals before the age of 50.

Clinical Management, Surveillance, Prevention, and Treatment

Based on the experience of the optical endoscopic interval surveillance of gastric cancer, particularly among patients with a family history, Corso et al. [116] suggest a yearly endoscopic examination starting at the age of 60.

Li-Fraumeni Syndrome

Overview and Inclusion Criteria

Li-Fraumeni syndrome (LFS) is an autosomal dominant inherited cancer syndrome characterized by an increased risk of developing sarcomas (index tumors), breast carcinoma, leukemias, and other neoplasms in children and young adults [117]. In contrast to other inherited cancer syndromes, the carriers do not exhibit site-specific tumors but present with multiple primary tumors of divergent phenotype. Gastric carcinoma is detected in 1.8% [118] to 4.9% [119] of LFS carriers. Overall, it is reported that 22.6% of LFS families have at least one member with gastric carcinoma [119].
Table 3. Clinicopathologic features and management of non-polyposis-associated gastric cancer predisposing syndromes

| Feature                        | Characteristic | HDGC  | HNPPC | FIGC  | LFS  | BRCA  |
|--------------------------------|----------------|-------|-------|-------|------|-------|
| Gastric adenocarcinoma         | Age<sup>a</sup> | 14 years | —     | <50 years: 28.6% | 12 years | <50 years: 100% |
|                               | Histologic type<sup>b</sup> | Diffuse type | Intestinal type | Intestinal type (70%) and diffuse type (30%) | No screening guidelines | No screening guidelines, targeted early screening in families with at least one family member with gastric cancer |
| Endoscopic surveillance Initiation | Late teens or early 20s<sup>c</sup> | Targeted screening in families with MSH2 mutations | No screening guidelines | |

<sup>a</sup>Age of onset.<br>
<sup>b</sup>Lauren classification.<br>
<sup>c</sup>See text for surveillance interval.

Abbreviations: —, no data; BRCA, breast cancer susceptibility gene; FIGC, familial intestinal gastric cancer; HDGC, hereditary diffuse gastric cancer; HNPPC, hereditary nonpolyposis colorectal cancer; LFS, Li-Fraumeni syndrome.

Classic LFS is defined as a proband diagnosed with the following criteria: (a) sarcoma before 45 years of age, (b) a first-degree relative with cancer before this same age, and (c) another first- or second-degree relative in the lineage with any cancer before this age or sarcoma at any age [120]. Neoplasms that are more commonly seen, besides sarcomas, include breast carcinomas, brain tumors, and adrenal cortical carcinomas. Gastric carcinoma is a less common malignancy [121].

**Molecular Genetics**

LFS is caused by heterozygous mutations in the *TP53* gene on Chr 17p13.1, with germline mutations in *TP53* present in ~70% of patients [120, 122]. Mutations in gastric carcinoma cases generally have been reported to be predominantly in exons 5–8 (of the 11-exon gene), compromising the DNA-binding domain [123–126]. However, another group has reported mutations in exons 4–10 with no genotype-phenotype correlation [119]. A very high penetrance is seen, with cancer risk approaching 100% in females and ~73% in males [120].

**Clinical and Pathologic Features**

Gastric carcinoma has been reported in a child as young as 12 years of age [127]. However, the mean age at diagnosis of gastric carcinoma is 36 years (range, 24–74 years), with most patients under 50 years of age (e.g., 19% <30 years, 24% <40 years, and 57% <50 years), which is significantly younger compared with the mean age of sporadic gastric cancer in the SEER data set (71 years) [119]. Most of the tumors have been located in the proximal stomach (~50%) compared with the antrum (~30%) and fundus (~10%), and approximately 70% display an intestinal phenotype [119].

**Surveillance and Clinical Management**

Phenotypic diversity among carriers complicates the formulation of effective screening strategies. The National Comprehensive Cancer Network has proposed surveillance guidelines that include screening for breast and colorectal neoplasms [128]. However, it has been suggested that periodic screening gastroscopy of LFS carriers with at least one family member affected by gastric cancer should be considered. Given the early onset of gastric carcinoma, the screening should be initiated at an early age [119].

**BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer**

**Overview and Inclusion Criteria**

The clinical criteria for genetic testing include: 3 or more breast and/or ovarian cancer cases, at least one before the age of 50 years; 2 breast cancer cases before the age of 40 years; male breast cancer and ovarian cancer or early onset female breast cancer; Ashkenazi Jew with breast cancer before the age of 60 years; young onset bilateral breast cancer; and breast and ovarian cancer in the same patient. Certain histologic features may trigger genetic testing, such as breast medullary carcinoma and triple negative phenotype of breast carcinoma in women younger than 50 [129].

In addition, melanoma as well as gastric and pancreatic carcinomas have been associated with BRCA1 and BRCA2 syndromes [130–132]. Gastric cancer has been reported to be one of the most frequent cancers in the families of probands with BRCA mutations in one study, and its incidence before the age of 70 years is twice as common in these patients compared with the general population [133, 134]. The association of gastric carcinoma is reported to be stronger with *BRCA2* than *BRCA1*, with an increased relative risk of gastric cancer in *BRCA2* mutation carriers (2.59; 95% CI = 1.46–4.61) [131]. The frequency of gastric carcinoma is 5 times higher than the general population particularly in Ashkenazi Jews with *BRCA2* mutations (5.7%) [132]. It appears from some studies [135] that the presence of a family history of gastric cancer doubled the probability/risk of *BRCA1/2* carrier (23.8% vs. 11.8%), which would suggest that testing for *BRCA* mutations ought to be performed in all patients with a suggestive history.

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**Molecular Genetics**

BRCA1 and BRCA2 are autosomal recessive syndromes caused by mutations in *BRCA1* located on Chr 17q.21.31 or *BRCA2* on 13q.13.1. BRCA2 syndrome has a lower level of penetrance.
than BRCA1 syndrome [136]. Certain mutations have been seen to result in clustering of gastric carcinoma in BRCA families. These include BRCA1 mutation at c.3,936 C→T, which results in a stop codon at 1,273, resulting in more deleterious effects [137]. Mutation in BRCA2 at 6174delT also has been reported in a higher frequency of gastric carcinoma [132]. Notably, the most common mechanism of BRCA1 inactivation in sporadic gastric carcinoma is microsatellite instability or loss of heterozygosity rather than point mutations as seen in hereditary cases [131, 137, 138].

Clinical and Pathologic Features
All BRCA-related gastric carcinomas were diagnosed under the age of 55 years (range, 27–54 years) in a Polish study [139]. No reports are available studying the histopathologic features of BRCA syndrome-associated gastric carcinoma; however, sporadic carcinoma with BRCA mutations have been reported to be associated with diffuse phenotype, higher tumor grades, and advanced clinical stage [140].

Prevention, Treatment, Clinical Management, and Surveillance
Screening guidelines are not available for surveillance of gastric carcinoma in BRCA carriers [129].

Other Genomic Instability Syndromes With Reported Predisposition to Gastric Cancer: Ataxia Telangiectasia and Xeroderma Pigmentosum

Overview and Inclusion Criteria of Ataxia Telangiectasia
Ataxia telangiectasia is an autosomal recessive disorder characterized by cerebellar ataxia, multiple telangiectasia, immune defects, and multiple primary carcinomas [141]. The clinical diagnosis is straightforward, with the presence of oculocutaneous telangiectasia qualifying for the diagnosis. The presence of neoplasia is not required for the diagnosis [141].

Molecular Genetics
The syndrome is caused by extensive DNA damage as a result of the inherent susceptibility of DNA to radiation secondary to mutations in the DNA repair gene, ataxia telangiectasia-mutated on Chr 11q22.3. Mutations are frequently seen in 10 exons and 2 cDNA fragments (38.5%).

Clinical and Pathologic Features
There have been 10 reports of gastric carcinoma, all detected in the first or second decade of life (range, 14–26 years) and at an advanced stage [142]. It has been postulated that gastritis developing in the setting of the immunodeficiency reported in these patients predisposes to carcinoma [143]. A varied histopathologic spectrum of adenocarcinomas has been reported, including mucinous adenocarcinomas, adenocarcinoma not otherwise specified, and signet ring cell carcinoma.

Surveillance
A systematic screening program involving upper gastrointestinal endoscopy could be considered in any patient over the age of 10 years with nonspecific gastrointestinal manifestations [143].

Overview and Inclusion Criteria of Xeroderma Pigmentosum
Xeroderma pigmentosum carriers are predisposed to developing a high incidence of cutaneous carcinomas in exposed areas and ocular neoplasms. Carriers are at greater than 10,000-fold increased risk of neoplasms [144]. The diagnosis can be established based on family history and a constellation of clinical findings including (a) extreme sun sensitivity, (b) ocular, and (c) neurologic manifestations [145].

Molecular Genetics
The XPS phenotype may be caused by mutation in one of the eight alleles of the XPS gene, which codes for a protein that plays a significant role in global genome nucleotide excision repair as a result of ultraviolet radiation or chemical carcinogens [105, 146, 147]. Certain single nucleotide polymorphisms in the XP gene have been seen with a higher frequency in sporadic gastric carcinomas and have been proposed to be useful markers for identifying high-risk individuals [148].

Clinical and Pathologic Features
Of interest, there is only a single morphologic evaluation of gastric carcinoma in a 3-year-old patient with poorly cohesive adenocarcinoma and widespread metastasis [149].

Surveillance and Clinical Management
XPS patients receive prevention for skin, ocular, and neurologic manifestations, but there are no guidelines for surveillance of gastric carcinoma [145].

Conclusion
Despite better understanding and control over known risk factors, gastric adenocarcinoma remains one of the most common cancers worldwide. Recently, awareness of familial gastric cancer syndromic predisposition has been emphasized, because though these syndromes are uncommon, they bear major management implications for the patients and their families. This review, while providing concise information regarding the molecular and histopathologic characteristics of these syndromes, also aimed to offer updated management guidelines, including follow-up and surveillance.

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