Other Syndromes and Genes Associated with Gastric Cancer Predisposition

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Abstract

Gastric cancer is the fifth most common type of cancer and the fourth leading cause of cancer-related death; nevertheless, genetic predisposition to this malignancy is still widely unexplored.

Besides hereditary diffuse gastric cancer (HDGC), associated with germline *CDH1* and *CTNNA1* pathogenic variants, other genetic syndromes characterized by high risk to develop gastric cancer have been described, encompassing gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), associated with germline genetic variants in the *APC* promoter, and familial intestinal gastric cancer (FIGC), still lacking a clear genetic cause.

Moreover, gastric cancer risk is associated with pathogenic variants in genes involved in DNA mismatch repair, such as *MLH1* and *MSH2* (Lynch syndrome), apoptosis, including *TP53* (Li-Fraumeni syndrome) and double-strand break

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repair, such as *BRCA1*/*BRCA2* and *PALB2* (hereditary breast and ovarian cancer syndrome).

Furthermore, gastric cancer can be a manifestation of gastrointestinal polyposis syndromes, such as those associated with *APC* (familial adenomatous polyposis), *MUTYH* (MUTYH-associated polyposis), *BMPR1A*/*SMAD4* (juvenile polyposis syndrome), *STK11* (Peutz-Jeghers syndrome), and *PTEN* (Cowden syndrome) genes.

Recent advances in molecular techniques, such as next-generation sequencing, led to the identification of many new genes involved in the predisposition to gastric cancer, some of which are low or moderate penetrant that predispose to other syndromes.

Consequently, in patients with early onset gastric cancer and/or strong gastric cancer family history, the use of multigene panel testing should be considered in cancer risk assessment, including different surveillance recommendations for each syndrome.

7.1 Introduction

Familial predisposition to gastric cancer (GC) has been categorized into three main syndromes with primary predisposition to the stomach: (1) hereditary diffuse gastric cancer (HDGC), (2) familial intestinal gastric cancer (FIGC), and (3) gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). While tumor burden and main genetic causality are established for HDGC (*CDH1*, *CTNNA1*) and GAPPS (*APC*), FIGC remains genetically unexplained and understudied. Nevertheless, other genes that predispose for other cancer syndromes encompass GC within their tumor spectrum: (1) *MLH1*, *MSH2*, *MSH6*, and *PMS2* (Lynch syndrome, LS, or hereditary nonpolyposis colorectal cancer, HNPCC), (2) *TP53* (Li-Fraumeni syndrome, LFS), (3) *BRCA1*, *BRCA2*, and *PALB2* (hereditary breast and ovarian cancer, HBOC), (4) *APC* (familial adenomatous polyposis, FAP), (5) *MUTYH* (MUTYH-associated polyposis, MAP), (6) *BMPR1A* and *SMAD4* (juvenile polyposis syndrome, JPS), (7) *STK11* (Peutz-Jeghers syndrome, PJS), and (8) *PTEN* (PTEN Hamartoma Tumor syndrome, PHTS) (Table 7.1) [1].

7.2 HDGC

Pathogenic or likely pathogenic variants in *CDH1* predispose to HDGC, an autosomal dominant syndrome characterized by diffuse gastric cancer (DGC) and lobular breast cancer (LBC) [2].

In recent years, next-generation sequencing (NGS) approaches have evolved exponentially, leading to the identification of new genes in HDGC. In 2013, the first germline truncating variant in *CTNNA1*, encoding the α-E-catenin protein, was described in an HDGC family [3]. To date, and after multiple HDGC families being

Table 7.1 Hereditary syndromes associated with GC

Syndrome	Gene	GC risk (%)	References
GAPPS	*APC (promoter 1B)*	IGC 13%	[18]
FIGC	Probably polygenic	Variable	[19]
LS	*MLH1*	IGC 5–10%	[20–24]
	MSH2	IGC 9%	[23, 24]
	MSH6	IGC ≤1%–7.9%	[23–26]
	PMS2	Low	[23, 24]
	EPCAM	Low	[24, 27]
LFS	*TP53*	IGC or DGC 2–5%	[28, 29]
HBOC	*BRCA1/BRCA2*	IGC 2%	[29, 30]
FAP	*APC*	IGC 4–7% (Asian population), low (Western population)	[24, 31]
MAP	*MUTYH*	IGC 2–5%	[24, 32]
PJS	*STK11*	IGC 29%	[24, 33]
JPS	*SMAD4/BMPR1A*	IGC or DGC 10–30%	[24, 34]
CS	*PTEN*	Low	[29, 35]

IGC: intestinal-type gastric cancer
DGC: diffuse-type gastric cancer

identified to carry *CTNNA1* truncating variants, *CTNNA1* remains the only gene, besides *CDH1*, clearly associated with the HDGC syndrome [4, 5]. Germline mutations in *MAP3K6* and *MYD88* have also been reported in HDGC families [6, 7]; however, the specific role of these genes remains unclear and their involvement in GC predisposition is still questionable [4]. In 2015, a targeted analysis with a panel of 55 cancer-related genes performed on 144 *CDH1*-negative cases found candidate mutations in 16 probands (11%), including high and moderate penetrance mutations in *CTNNA1*, *BRCA2*, *STK11*, *SDHB*, *PRSS1*, *ATM*, *MSR1*, and *PALB2* [8]. Very recently, a whole exome analysis on 54 *CDH1*-negative GC patients did not identify obvious candidates for GC predisposition [9], while, a gene panel-based analysis of 333 HDGC and non-HDGC cases identified 11 mutation carriers of *PALB2*, *BRCA1*, and *RAD51C*, which are genes involved in DNA homologous recombination (HR) [10]. A recent meta-analysis, performed on NGS published data, identified a list of genes carrying deleterious variants in families meeting the 2020 HDGC clinical criteria [11]. Pathogenic or likely pathogenic variants were found in candidate genes involved in DNA damage response pathways [11], encompassing *ATM* [12, 13], *BRCA1* [13], *BRCA2* [8, 13], *PALB2* [8, 10, 13, 14], *RAD51C* [10], and *ATR* [14]. In fact, *PALB2* and *ATM* were the most frequently mutated genes in the HDGC setting [11]. The former has been extensively associated with breast cancer predisposition [15], while the latter has been associated with both breast and gastric cancer susceptibility [16, 17]. Interestingly, *PALB2* loss of function variants have been shown to be enriched in the HDGC setting, compared to the general population [14]. While *PALB2* association with HDGC holds promise, *ATM* pleiotropy prevents a clear association with this disease.

7.3 GAPPS

In 2012, GAPPS, was described as an autosomal dominant syndrome [18]. The key clinical features of GAPPS include fundic gland polyposis (FGP) of the stomach with occasional hyperplastic and adenomatous polyps, focal foveolar-type dysplasia, hyperproliferative aberrant pits and development of adenomas with gastric type dysplasia or intestinal-/mixed-type gastric adenocarcinoma [18, 36, 37]. Current diagnostic criteria are depicted in Table 7.2 [36, 38].

In 2016, linkage analysis on six selected families mapped the gene to the 5q22 chromosomal region. Through Sanger sequencing, point mutations in *APC* promoter 1B, that co-segregated with the disease in all three families, were identified [38, 39]. Therefore, GAPPS is considered a part of a broad phenotypic spectrum of inherited polyposis associated with *APC* germline defects, but with tropism to the stomach (see paragraph "Familial Adenomatous Polyposis"). Since then, 12 additional families were found to harbor *APC* promoter 1B single nucleotide variants (SNVs) [40–43]. Two SNVs were found co-segregating within a family with severer phenotype, but their individual contribution remains unclear [38].

GAPPS phenotypes are diverse among individuals, in the number of polyps, from 30 to hundreds and GC age of onset ranging from 23 to 75 years of age [18, 43]. In fact, third-generation individuals display a much severer phenotype than first-generation obligated carriers [18]. Altogether, these observations suggest incomplete penetrance of *APC* promoter 1B SNVs that may be aggravated by environmental factors and moderate/low penetrance variants. Risk to develop intestinal- or mixed-type GC is 13% (Table 7.1) [18].

Surveillance of GAPPS families includes endoscopic surveillance with biopsies and prophylactic gastrectomy, due to a rapid malignant progression of FGP [18, 40, 43].

Table 7.2 GAPPS clinical criteria for genetic testing

Clinical criteria		Genetic screening
Essential criteria	Body and fundus gastric polyps	*APC* promoter 1B SNVs
	No evidence of colorectal or duodenal polyposis	
	>100 proximal stomach polyps or >30 polyps in a first degree relative GAPPS diagnosed patient	
	Predominantly fundic gland polyposis, which may have dysplasia	
	Relative with dysplastic FGPs or GC	
Supportive criteria	Autosomal dominant inheritance pattern	
	Presence of hyperproliferative aberrant pits, hyperplastic polyps, and gastric-type adenomas	

7.4 FIGC

FIGC is the HDGC counterpart that predisposes to intestinal-type gastric cancer (IGC). Current clinical criteria have been defined by the international gastric cancer linkage consortium (IGCLC) in 1999, depending on the GC incidence in the population and are depicted in Table 7.3 [44, 45]. Countries with a high GC incidence, such as Japan and Portugal, should use criteria analogous to those proposed for Lynch syndrome [46], while in countries with a low GC incidence, including USA and UK, FIGC selection criteria are more restrictive.

To date, no germline defects have been found to be recurrently associated with FIGC predisposition, which currently has unknown age of onset, tumor spectrum, and penetrance. Thus, clinical criteria have not been updated or validated since firstly described in 1999 [44]. Recently, the average IGC age of onset in FIGC families was found to be 10 years earlier than observed for the sporadic setting [19]. At the somatic level, *TP53*, *BRCA2*, *ATM*, *FOXF1*, *FHIT*, *SDHB*, *MSH6*, *CTNNA1*, and *PXN* were found mutated at higher frequencies in tumors from FIGC patients than in sporadic IGC, which also correlates with increased MSI frequency. The FIGC tumor spectrum is broad and predisposes to IGC, but also to colorectal and breast cancer, at lower frequencies [19]. A recent meta-analysis found *BRCA2* as the most frequently mutated gene in the germline DNA of FIGC probands, reaching 17% [11], a frequency that was similar to that of *BRCA2* somatic variants in sporadic IGC (9%) and higher than that of sporadic DGC (5%) [47].

Carvalho and colleagues [19] hint toward FIGC as a polygenic syndrome, since germline defects in major genes were not found in a large FIGC cohort. These authors also proposed redefinition of clinical criteria for FIGC to at least 2 GC cases diagnosed at any age, with one histologically confirmed as IGC [19].

Considering the number of genes that can be involved in this disease, the lifetime GC risk is not easy to determine due to the high genetic variability (Table 7.1).

Current surveillance is evaluated and applied on a case-by-case basis, yet recommendations include endoscopy in first-degree relatives, 10 years earlier than the earliest IGC age of onset [48], or gastroduodenoscopy at 40 years of age or 5 years earlier than the youngest IGC diagnosed in the family [49]. Eradication of *H. pylori* infection is recommended in FIGC families, due to its high frequency in this setting [49].

Table 7.3 FIGC clinical criteria

Clinical criteria		Genetic screening
High GC incidence countries	At least three relatives with IGC, one first-degree of the other two	Unknown germline cause
	At least two successive generations affected	
	GC diagnosed <50 years of age in at least one relative	
Low GC incidence countries	At least two first/second-degree relatives with IGC, one diagnosed <50 years of age	
	At least three relatives with IGC at any age	

7.5 Non-polyposis Syndromes

7.5.1 Lynch Syndrome

Lynch syndrome (LS) predisposes to colorectal and endometrial cancers and follow an autosomal dominant inheritance pattern [50]. LS is caused by pathogenic variants in *MLH1*, *MSH2*, *MSH6*, and *PMS2*, that encode the DNA mismatch repair (MMR) proteins [51], or by large deletions of the *EPCAM* gene, located upstream of *MSH2* [52]. MMR proteins work in a coordinated mode to repair the DNA mismatches that arise during DNA replication and recombination [53].

LS patients also have an increased risk of developing other tumors [54, 55], encompassing a lifetime risk to develop gastric cancer, estimated to be 1–10%, according to the altered gene (Table 7.1).

Regarding GC surveillance, LS patients with an *MLH1*/*MSH2* pathogenic variant, a family history of GC, and other risk factors should undergo upper endoscopy every 3–5 years beginning at age 40 [24].

Moreover, patients with LS, who have a deficiency of the MMR system (dMMR), can benefit from chemoprevention based on the daily use of aspirin [56] and, in case MSI cancers develop, may be treated with anti-PD-1/PD-L1 therapy [57, 58].

7.5.2 Li-Fraumeni Syndrome

The *TP53* gene is located on chromosome 17p13.1 and encodes the p53 protein, a tumor suppressor that responds to different cellular stresses to regulate expression of target genes, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair, or metabolism changes [59]. Due to its crucial function in maintaining the genomic stability, p53 has been defined as "the guardian of the genome" and, indeed, *TP53* somatic alterations are present in approximately 50% of sporadic tumors [60], conferring to p53 an important role as a biomarker for the diagnosis, tumor progression, poor prognosis, and reduced sensitivity for anticancer drugs [61].

Germline pathogenic variants in the *TP53* gene are associated with Li-Fraumeni syndrome (LFS), a rare autosomal dominant disorder characterized by a high predisposition to several types of cancer, such as brain tumors, breast cancer, sarcomas, acute leukemia, and adrenocortical tumors [28, 62–71].

The lifetime risk of GC for patients with LFS, although not consensual, has been estimated to be 2–5% (Table 7.1) [28, 72, 73].

Given the risk of developing gastrointestinal cancers, the guidelines suggest that LFS patients should undergo upper endoscopy and colonoscopy every 2–5 years starting from age 25 years [29]. Moreover, in children, the recommendations are to perform clinical examination and abdominal ultrasound every 6 months, annual whole-body MRI, and brain MRI from the first year of life, if the *TP53* variant is known to be associated with childhood cancers. In adults, the surveillance should include every year clinical examination, whole-body MRI, breast MRI in females from 20 until 65 years, and brain MRI until 50 years [63].

7.5.3 BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer

The *BRCA1* gene, located on chromosome 17q21.31, encodes a nuclear protein involved in DNA repair, cell cycle checkpoint control, and maintenance of genomic stability forming a large multi-subunit protein complex known as BRCA1-associated genome surveillance complex (BASC) [74–77].

The *BRCA2* gene is located on chromosome 13q13.1 and encodes a nuclear protein involved in repairing damaged DNA, recruiting the recombinase RAD51 to the DNA double-strand breaks (DSBs) through the formation of a BRCA1-PALB2-BRCA2 complex [74, 75, 78, 79].

Germline pathogenic variants in *BRCA1* and *BRCA2* genes are associated with the hereditary breast and ovarian cancer (HBOC) syndrome [80], characterized by a high risk of developing breast and ovarian cancer in females [81–83], breast and prostate cancer in males [84–87] and pancreatic cancer in both sexes [88–90].

Further, *BRCA1* pathogenic variants have been associated with an increased risk of colon cancer [91] and *BRCA2* pathogenic variants have been associated with uveal melanoma [92, 93].

Recently, pathogenic variants in *BRCA1/2* and other genes involved in breast/ovarian cancer predisposition have been associated with an increased GC risk [8, 10, 12–14]. The IGC risk is estimated to be 2% in *BRCA1/2* pathogenic variant carriers (Table 7.1) [30], however prevention should be evaluated on the basis of family history [24].

Moreover, the discovery of the therapeutic potential of inhibitors of the poly adenosine-diphosphate ribose polymerase (PARP) in carriers of germline/somatic *BRCA1/2* pathogenic variants with ovarian, breast, prostate, and pancreatic cancers led to a revolution in the treatment of these tumors [94–100]. PARP inhibitors have shown their efficacy also in patients with pathogenic variants in genes involved in the HR pathway [101–104]. These results pave the way for the future use of PARP inhibitors in all tumors with a deficiency of the HR system, independently of the germline or somatic nature of the alteration, including GC [105].

7.6 Polyposis Syndromes

7.6.1 Familial Adenomatous Polyposis

The APC protein is a tumor suppressor that acts as a Wnt signaling antagonist, and regulates transcriptional activation, cell migration and apoptosis [106]. Pathogenic or likely pathogenic alterations in the *APC* gene (chromosome 5q22.2) predispose to familial adenomatous polyposis (FAP) [107, 108]. This autosomal dominant syndrome is characterized by polyposis and carcinomas in the gastrointestinal tract, as well as, extra-gastrointestinal carcinomas, such as thyroid [34]. While classical FAP predisposes to hundreds to thousands of colonic and rectal polyps that may develop into colorectal carcinoma, attenuated FAP (AFAP) displays a much milder

phenotype [34, 109]. Families with AFAP present fewer and latter-onset of both polyps and carcinomas, as well as cancer-decreased risk [110]. The phenotype severity is dependent on the mutation location within the *APC* gene [111], as above mentioned for GAPPS with unique predisposition to the stomach [38].

FAP and AFAP also predispose to gastric polyps in >60% and 93% of patients, respectively [112]. However, gastric adenocarcinoma risk ranges between 4% and 7% in the Asian population, with no increased risk for the western population (Table 7.1) [24, 31]. In fact, FGP and focal low-grade dysplasia in the stomach commonly do not undergo malignant transformation [113, 114]. Nevertheless, increased risk is observed in the presence of FGP stomach carpeting, polyps larger than 20 mm, tubular adenomas, high-grade dysplasia polyps, pyloric gland adenomas, and in specific geographical areas [31, 115, 116]. According to these high-risk features and family history, specialized surveillance or gastrectomy may be recommended [24].

7.6.2 MUTYH-Associated Polyposis

The *MUTYH* gene is located on chromosome 1p34.1 and encodes the MutY DNA glycosylase, involved in oxidative DNA damage repair and, if unrepaired, apoptosis signaling [117].

MUTYH-associated polyposis (MAP) distinguishes from (A)FAP by presenting a recessive inheritance pattern with reduced risk for colonic and duodenal adenomas (fewer than 100) and carcinomas (5%). Thus, biallelic pathogenic or likely pathogenic variants in *MUTYH* (chromosome 1p34.1) predispose to MAP [118]. Risk to develop IGC ranges from 2% for females to 4% for males (Table 7.1) [32].

Current surveillance measurements include upper endoscopy and side viewing duodenoscopy every 3 months to 4 years beginning at age 30–35 years with subsequent follow-up based on initial findings [24, 119, 120].

7.6.3 Juvenile Polyposis Syndrome

The *BMPR1A* gene, located on chromosome 10q23.2, encodes the bone morphogenetic protein receptor type IA, a transmembrane serine/threonine kinase that binds members of the TGF-β superfamily and plays a role in signal transduction, apoptosis and cell differentiation [121].

The *SMAD4* gene (chromosome 18q21.2) encodes a member of the Smad family of signal transduction proteins that are activated by transmembrane serine-threonine receptor kinases in response to TGF-β and bone morphogenetic protein signaling pathways. *SMAD4* is a transcription factor that acts as a tumor suppressor and inhibits epithelial cell proliferation [122].

Germline pathogenic variants in *BMPR1A* and *SMAD4* genes are associated with juvenile polyposis syndrome (JPS), an autosomal dominant disorder, that

predisposes to hamartomatous polyps in the gastrointestinal tract, specifically in the stomach, small intestine, colon, and rectum [123].

The majority of juvenile polyps are benign, however can undergo malignant transformation. Lifetime estimates of developing gastrointestinal cancers in families with JPS range from 11% to 86%, with variability by region, time period included, and associated gene [124–128]. In fact, approximately 15% of JPS individuals develop cancer [127, 129]. While, the GC incidence is approximately around 10–30% in JPS patients with gastric polyps (Table 7.1) [130, 131], the risk of colorectal cancer ranges between 17% and 22% by 35 years of age and approaches 68% by 60 years of age [132]. In JPS context, small bowel and pancreatic cancers have also been reported [133–137]. Individuals with *SMAD4*-related JPS are more likely to have a personal or family history of upper gastrointestinal polyps than individuals with a *BMPR1A* pathogenic variant. The gastric phenotype in individuals with a *SMAD4* pathogenic variant tends to be more aggressive with significant polyposis, anemia, and a higher GC risk [125, 127, 128].

According to the clinical practice guidelines for JPS, the gastric surveillance recommended for individuals with a *BMPR1A* or *SMAD4* pathogenic variant includes colonoscopy and upper endoscopy every 3 years beginning at age 15 or earlier if symptomatic. If polyps are found, after polyp treatment an annual screening is recommended until no polyps are found, followed by a screening every 3 years [24, 138, 139].

7.6.4 Peutz-Jeghers Syndrome

The *STK11* gene (formerly *LKB1*) is located on chromosome 19p13.3 and encodes a serine/threonine kinase that acts as a tumor suppressor, regulating energy metabolism and cell polarity [140].

Germline pathogenic variants in the *STK11* gene are associated with Peutz-Jeghers syndrome (PJS), an autosomal dominant syndrome. PJS is characterized by melanocytic macules of the lips, buccal mucosa and digits, multiple gastrointestinal hamartomatous polyps, and an increased risk for different tumors, encompassing colorectal, gastric, pancreatic, breast, and ovarian cancers [141].

In *STK11* pathogenic variant carriers, the lifetime GC risk is estimated to be 29% (Table 7.1) [33, 34, 142, 143]. For this reason, the clinical guidelines suggest that PJS patients should undergo upper endoscopy with polypectomy every 2–3 years, starting at the age of 18; shorter intervals may be indicated based on polyp size, number, and pathology [24].

7.6.5 PTEN Hamartoma Tumor Syndrome

The *PTEN* gene (chromosome 10q23.31) encodes a phosphatase which antagonizes the PI3K signaling pathway and negatively regulates the MAPK pathway [144].

Germline pathogenic variants in *PTEN* are associated with the PTEN hamartoma tumor syndrome (PHTS) that includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, PTEN-related Proteus syndrome, and PTEN-related proteus-like syndrome [145].

Cowden syndrome (CS) is an autosomal dominant disorder that predisposes to benign hamartomas and increased lifetime risk of breast, thyroid, uterine, colorectal, and other cancers, including stomach [145–147]. Upper or lower gastrointestinal polyps occur in more than 90% of individuals with a *PTEN* pathogenic variant [148]. In the stomach, the most common findings are hyperplastic polyps, hamartomas, and ganglioneuromas [149–151].

Cowden syndrome does not have increased risk of gastric malignancy (Table 7.1); however, complications of benign neoplasm can occur [35]. Indeed, some CS patients have symptoms including hemorrhage, obstruction, and pain [35]. According to the guidelines, PHTS patients should undergo upper and lower endoscopy with removal of polyps beginning at age 35 years with frequency dependent on degree of polyposis identified [145].

7.7 Conclusions

GC is one of the most common and deadly tumors and, among risk factors for the development of this cancer, genetic predisposition plays an important role.

Besides HDGC, associated with *CDH1* and *CTNNA1* pathogenic variants, other genetic syndromes characterized by high risk to develop GC have been described: GAPPS, associated with genetic variants in the *APC* promoter, and FIGC, still lacking a clear genetic cause.

In addition to these three syndromes, genes including *TP53*, *BRCA1/2*, and MMR genes, whose variants are associated with other cancer genetic syndromes, also include an increased risk for GC (Table 7.1).

Moreover, genes associated with the development of gastrointestinal polyps, such as *APC*, *MUTYH*, *BMPR1A*, *SMAD4*, *STK1*, and *PTEN* may also evolve in GC (Table 7.1).

The evidence of GC risk associated with these syndromes and the availability of recommendations for the management of variant carriers suggest that these genes should be included in a gene panel for the identification of patients at risk of developing GC.

In summary, new genes are constantly emerging from NGS studies, showing that GC predisposition is distributed over several genes, with only a small portion of genes being recurrently mutated.

These findings address the choice of wide panels, including the genes involved in the main cancer syndromes. This creates new diagnostic opportunities but also increases the risk of an incorrect genetic diagnosis [152]. Importantly, the identification of a pathogenic germline variant can not only guide the choice of the best chemoprevention and prophylactic surgeries but also the choice of novel targeted therapies, toward personalized medicine based on the genetic characteristics of each patient.

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