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Review article

Hereditary gastrointestinal carcinomas and their precursors: An algorithm for genetic testing

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ABSTRACT

Recognition of hereditary forms of gastrointestinal cancer is of great importance for patients and their families and pathologists play a crucial role in this. This review recapitulates the clinical, pathological and molecular aspects of Hereditary Diffuse Gastric Cancer and Gastric Adenocarcinoma and Proximal Polyposis of the Stomach, as well as hereditary colorectal cancer syndromes such as Lynch syndrome and gastrointestinal polyposis syndromes (including Familial Adenomatous Polyposis, Peutz-Jeghers syndrome and Juvenile Polyposis syndrome). Histopathological clues to recognize hereditary forms of gastrointestinal cancer and possible ancillary studies that can support an underlying syndrome and guide genetic testing are discussed.

Introduction

Gastric cancer (GC) and colorectal cancer (CRC) are the third and fourth leading cause of cancer-related death worldwide, respectively. Each affect nearly 1 million individuals every year.[1] Although most GCs and CRCs are sporadic, between 20% and 30% appear familial and a hereditary cause is determined in 1–3% and 3–6%, respectively.[2–4]

Hereditary Diffuse Gastric Cancer (HDGC) and gastric adenocarcinoma proximal polyposis syndrome (GAPPS) are the main hereditary GC syndromes. Other tumors can be classified using Laurén's system[5] which defines familial intestinal-type GC (FIGC), familial diffuse GC (FDGC) or simply familial GC (FGC). Most hereditary CRC cases are caused by germline mutations or epimutations in the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* for non-polyposis cases (Lynch syndrome), and in *APC* and *MUTYH* for adenomatous colonic polyposis (Familial Adenomatous Polyposis (FAP) and MUTYH-Associated Polyposis (MAP)). In addition, several hamartomatous polyposis syndromes exist, including juvenile polyposis syndrome (JPS; *SMAD4* or *BMPR1A* germline mutation), Peutz-Jeghers syndrome (PJS; *STK11* germline mutation), and Cowden/PTEN hamartoma syndrome (CS; *PTEN* germline mutation). Some of these syndromes confer increased risk for extra colonic malignancies, including GC. In this regard, GAPPS is recognized as a variant of FAP.[6,7] Lastly, serrated polyposis is a clinically defined syndrome characterized by multiple serrated polyps in the colorectum and an increased CRC risk, but the genetics are not fully elucidated.[4]

In this review, clinical, pathological and molecular features, genetic testing and management recommendations of the main hereditary GC and CRC syndromes (Table 1) are discussed.

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Table 1
Clinical criteria, histopathological features, recommended screening and molecular alterations of hereditary gastric and colorectal cancer syndromes.

	Clinical criteria	Histopathological findings	Recommended genetic testing	Molecular genetics
Hereditary Diffuse Gastric Cancer (HDGC)	Two or more patients with gastric cancer at any age, one confirmed diffuse gastric cancer Individuals with diffuse gastric cancer before the age of 40 Families with diagnoses of both diffuse gastric cancer and lobular breast cancer (one diagnosis before the age of 50)	Diffuse gastric cancer and precursor lesions (*in situ* signet ring cell carcinoma, pagetoid spread of signet ring cells) Lobular breast cancer	*CDH1* mutational analysis Search for large *CDH1* rearrangements *CTNNA1* mutational analysis	First hit: germline *CDH1* mutations (small frameshit insertions and deletions, splice-site, missense and nonsense), large rearrangements, germline promoter methylation Second hit: promoter hypermethylation, loss of heterozygosity, intragenic deletions
Lynch syndrome	**Revised Bethesda criteria**[59] CRC diagnosed < 50 years old Presence of synchronous, metachronous colorectal or other Lynch associated tumors regardless of age CRC with MSI high histology in a patient < 60 years old CRC in ≥ 1 1st degree relatives with a Lynch related tumor; 1 of the cancers diagnosed < 50 years old CRC in ≥ 2 1st or 2nd degree relatives with Lynch-related tumors, regardless of age	Colon carcinoma, often with mucinous, poor or medullary differentiation and tumor infiltrating lymphocytes Few adenomas Extra-gastrointestinal tumors (see text)	Loss of expression of one of the MMR genes Microsatellite analysis Absence of *MLH1* promoter hypermethylation and absence of *BRAF* V600E mutation	Germline mutation in one of the MMR genes *MLH1, MSH2, MSH6* or *PMS2*.
Familial adenomatous polyposis (FAP)	**WHO criteria** ≥100 colorectal adenomatous polyps Germline disease-causing mutation of the *APC* gene Any colorectal adenoma in a young patient with a family history of FAP	Numerous colonic adenomas undistinguishable from sporadic adenomas Single crypt adenoma (unicryptal or oligocryptal dysplasia) Fundic gland polyps in stomach Adenomas in small intestine (principally duodenum) Extra-gastrointestinal tumors (e.g. intra-abdominal desmoid fibromatosis, osteoma of the mandible, multiple epidermoid cysts)	*APC* mutational analysis. Consider *MUTYH* mutational analysis in case of attenuated FAP	Germline *APC* mutation in one allele and somatic second hit inactivation of *APC*
Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)	Gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis More than 100 polyps carpeting the proximal stomach in the index case or > 30 polyps in a first-degree relative Predominantly fundic gland polyps, some having regions of dysplasia (or a family member with either dysplastic fundic gland polyps or gastric adenocarcinoma) Autosomal dominant pattern of inheritance Exclusion of another gastric polyposis syndrome and use of proton-pump inhibitors	Fundic gland polyposis of the stomach with areas of dysplasia Hyperplastic polyps of the stomach Adenomatous polyps of the stomach Mixed polyps with FGP-like, adenomatous and hyperplastic features	*APC* promoter 1B mutational analysis	Germline point mutation *APC* promoter 1B Haploinsufficiency mechanism for fundic gland polyposis; second hit mechanism for gastric adenocarcinoma
Peutz-Jeghers syndrome (PJS)	**WHO criteria** ≥3 hamartomatous polyps ≥1 hamartomatous polyp with a positive family history Mucocutaneous melanosis with a positive family history Mucocutaneous melanosis and ≥1 hamartomatous polyp	Gastrointestinal hamartomas (mainly in small intestine) with a villous architecture and smooth muscle proliferation. Rarely dysplastic.	Genetic testing for *LKB1/STK11*	Germline mutation in *LKB1/STK11*
Juvenile polyposis syndrome (JPS)	**WHO criteria** > 3-5 juvenile polyps in the colon at one time Juvenile polyps throughout GI tract ≥1 juvenile polyp with a positive family history	Well circumscribed hamartomatous polyps in GI tract (mostly in colorectum and stomach) with cystically dilated glands, eroded surface and mixed inflammatory infiltrate. Dysplasia can be present, may be difficult to discern from inflammatory atypia.	Sequence analysis for *BMPR1A* and *SMAD4* (mostly point mutations and small deletions)	50-60% have a mutation in *SMAD4* or *BMPR1A* Co deletion of *BMPR1A* and *PTEN* is associated with severe form of JPS (JPS of infancy)
Cowden syndrome (CS)			Genetic testing for *PTEN*	Germline mutation in *PTEN*

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