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Gastrointestinal tract cancers: Genetics, heritability and germ line mutations (Review)

XIAO-PENG LV

Xuzhou Central Hospital, Xuzhou Clinical School of Xuzhou Medical College, The Affiliated Xuzhou Hospital of Medical College of Southeast University, Xuzhou, Jiangsu 221009, P.R. China

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Abstract. Gastrointestinal (GI) tract cancers that arise due to genetic mutations affect a large number of individuals worldwide. Even though many of the GI tract cancers arise sporadically, few of these GI tract cancers harboring a hereditary predisposition are now recognized and well characterized. These include Cowden syndrome, *MUTYH*-associated polyposis, hereditary pancreatic cancer, Lynch syndrome, Peutz-Jeghers syndrome, familial adenomatous polyposis (FAP), attenuated FAP, serrated polyposis syndrome, and hereditary gastric cancer. Molecular characterization of the genes that are involved in these syndromes was useful in the development of genetic testing for diagnosis and also facilitated understanding of the genetic basis of GI cancers. Current knowledge on the genetics of GI cancers with emphasis on heritability and germ line mutations forms the basis of the present review.

Contents

1. Introduction

Cancers arising within the gastrointestinal (GI) tract are genetic disorders caused by the sequential accumulation of alterations in genes that control the growth, differentiation, and DNA repair (1). Although the majority of cases appear to arise sporadically, a small percentage of GI cancers have an apparent hereditary component, as evidenced by the well-characterized genetic syndromes and the family history associated with the high risk of these syndromes (2). Nearly 5% of inherited cases are due to highly penetrant mutations with well characterized clinical presentations (3). An additional 20-25% of cases are estimated to have an associated hereditary component, which has not yet been established (4). Many of the GI tract cancers appear to be due to mutations in single genes and these types of cancer are less penetrant but occur more frequently as compared to the cancers seen in combination with well-characterized syndromes (1). Examples for single gene mutations include common single-nucleotide polymorphisms (SNPs) in genes that are involved in the control of metabolism or which are regulated by environmental factors (4). Mutations in multiple susceptibility loci can also lead to these cancers by inducing additive effects (2). Identification of individuals who are at risk for GI tract cancer, and the development of methods for better diagnosis and prevention of cancer and therapeutic approaches is dependent on proper understanding of the molecular basis and genetics of GI tract cancers (3).

The present review addresses the genetics of the currently well-characterized hereditary cancers of GI tract. In this review we focus on the genetics of hereditary GI cancers, which are primarily that of a type of colorectal cancer (CRC) syndromes and also briefly discuss some aspects of pancreatic, and stomach cancers.

2. Hereditary CRC syndromes

Clinical, pathological, and genetic features form the basis for identifying and classifying the CRC syndromes. Pathophysiological conditions that lead to adenomatous polyps include familial adenomatous polyposis (FAP), attenuated FAP (AFAP), MUTYH-associated polyposis (MAP) and Lynch syndrome. Hamartomatous polyps are the primary lesions in Peutz-Jeghers syndrome (PJS) and juvenile polyposis syndrome (JPS) (5). Serrated polyposis syndrome (SPS) is unique situation as it poses much higher cancer risk and therefore this syndrome needs to be identified separately from other conditions. Except for MAP, all these abovementioned conditions are inherited autosomal dominant disorders. MAP

Correspondence to: Dr Xiao-Peng Lv, Xuzhou Central Hospital, Xuzhou Clinical School of Xuzhou Medical College, The Affiliated Xuzhou Hospital of Medical College of Southeast University, 199 Jiefang South Road, Xuzhou, Jiangsu 221009, P.R. China
E-mail: rqxjdymui8201@163.com

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Table I. Mode of inheritance of non-polyposis syndrome as well as the associated genes, lifetime risk of cancer development and non-malignant features.

Syndrome	Inheritance	Gene	Sites	Lifetime risk (%)	Non-malignant features
Lynch syndrome	Autosomal dominant	*hMLH1*	Colon	50-80	Physical or non-malignant features, with the exception of keratoacanthomas and sebaceous adenomas/carcinomas, are rare
		hMLH2	Endometrium	40-60	
		hMLH6	Stomach	11-19	
		hPMS2	Ovary	9-12	
		EpCAM	Hepatobiliary tract	2-7	
		EpCAM	Upper urinary tract	4-5	
			Pancreas	3-4	
			Small bowel	1-4	
			CNS	1-3	

hMLH, human mutL homolog; hPMS2, human postmeiotic segregation 2; CNS, central nervous system.

is autosomal recessive, whereas, SPS is rarely inherited. There are many similarities between the phenotypes of AFAP and MAP, which are associated with varying numbers of adenomas, and these also resemble the phenotypes of Lynch syndrome, sporadic polyps, and other polyposis syndromes, often causing some confusion (6). Despite the clinical similarities between these syndromes, each of them has unique genetic aetiologies and cancer risks, and also specific clinical features.

3. CRC syndromes with adenomatous polyps

Conditions that express adenomatous polyps are seen only in a few of the inherited GI cancer predisposition syndromes, such as Lynch syndrome, FAP, AFAP, and MAP. The chances of developing colon cancer and tumors elsewhere are quite high in these syndromes (7) and non-malignant manifestations seen in these syndromes contribute to elevated morbidity and mortality.

Lynch syndrome. Lynch syndrome or hereditary non-polyposis colon cancer is one of the main causes for up to 5% of all CRC (8-10). Individuals with Lynch syndrome have an 80% risk for CRC (4). The syndrome is also associated with an increased risk of developing malignancies at extra-colonic sites such as endometrium, stomach, ovary, small bowel, pancreas, ureter, renal pelvis, hepatobiliary tract, and brain (11-14). Among these sites, cancer arising within endometrium is the second most common malignancy in Lynch syndrome with a lifetime risk between 40 and 60% (Table I), which is similar to or even higher than the estimated risk for CRC in women with Lynch syndrome. However, endometrial cancer often occurs before CRC in these women (8,15,16). Approximately 2% of all endometrial cancers likely arise due to Lynch syndrome (17).

An important feature of Lynch syndrome is that there is an early onset of cancer as compared to the general population (13,18). Thus, while in the general population, CRC has an onset at 65 years and endometrial cancer at 60 years, these onset ages are much lower in people with Lynch syndrome, at 44 and 48 years, respectively, for these two types of cancer (14,19-21). Lynch syndrome is also characterized by the occurrence of synchronous (multiple primary cancers occurring simultaneously) and metachronous (multiple cancers occurring at intervals) tumors (22,23). Synchronous and metachronous cancers occur to different extents in individuals with Lynch syndrome (50% incidence) as compared to those with sporadic CRC (20% incidence) (14,24). Furthermore, the right or proximal colon are frequent sites for CRC in Lynch syndrome patients, whereas in individuals with sporadic CRC, there is relatively higher incidence of sigmoid/distal carcinomas (9,13,14,25). Crohn's-like reactions, tumor-infiltrating lymphocytes, signet ring cells and mucinous adenocarcinoma are some of the main pathologic features of CRC associated with Lynch syndrome. These pathological features, which are often considered as red flags for Lynch syndrome, are less common in sporadic CRC (14,21,22,26). A high level of microsatellite instability (MSI-H), which is a feature of carcinogenic process when there is defective DNA mismatch, is also a characteristic of Lynch syndrome. Studies show that MSI-H-bearing colon cancers have better overall prognosis unlike the colon cancers without MSI (27).

Germline mutations in mismatch repair (MMR) genes, which are a special class of tumor suppressor genes that are responsible for correcting DNA errors that occur during replication, lead to the pathogenesis of Lynch syndrome (23). Genes recognized to be associated with Lynch syndrome include human mutL homolog 1 (*hMLH1*) at 3p21.3, human mutS homolog 2 (*hMSH2*) at 2p21-p22, *hMSH3* at 5q11-q12, *hMSH6* at 2p16 human postmeiotic segregation 1 (*hPMS1*) at 2q31-q33, and *hPMS2* at 7q22 (22). Almost 90% of the cases with Lynch syndrome arise due to mutations in *hMLH1* and *hMSH2*, whereas a small number of cases (10%) are thought to be due to mutations in *hMSH6* and only on rare occasions mutations in *hPMS2* are evident (28-31). Mutations in these genes show predominantly autosomal dominant inheritance with close to 80% penetrance for CRC and a 25% risk for metachronous CRC (14). These numbers are relatively lower for endometrial cancer (60% penetrance) as well as for other cancers (<20%). Observed phenotypic variations show dependency on the specific gene mutation. Thus, there is a slightly increased incidence of endometrial cancer in families with *hMSH6* mutations who also show a moderately lower incidence of CRC compared with families harboring *hMLH1*

Table II. Frequencies of tumors in patients with Lynch syndrome.

	h*MSH6*		h*MLH1*/*MSH2*	
Tumors	n	%	n	%
All primary tumors	144	-	859	-
Colorectal cancer	61	42.4	563	65.5
Endometrial cancer	9	6.3	43	5.0
Ovarian cancer	4	2.8	12	1.4
Stomach cancer	10	6.9	37	4.3
Breast cancer	8	5.6	17	2.0
Lung cancer	7	4.9	5	0.6
Prostate cancer	4	2-8	6	0-7
Cancer of renal pelvis and ureter	0	0	13	1.5

MSH6, mutS homolog 6; MLH1, mutL homolog 1; MSH2, mutS homolog 2.

Table III. Penetrance as HR and cumulative risk to 70 years of age for cancer based on gender.

Cancer	Gender	HR (95% CI)	Risk, % (95% CI)
CRC	Male	5-2 (2.8-9.7)	20 (11-34)
	Female	5-2 (2.8-9.7)	15 (8-26)
Endometrial	Female	7-5 (2.8-20.0)	15 (6-35)
	Male	2.5 (0.4-16.2)	6 (1-33)
Less frequent Lynch cancers	Female	2.5 (0.5-12.6)	6 (1-25)
	Male	0.9 (0.3-2.3)	24 (10-51)
Other cancers	Female	1.5 (0.8-3.1)	27 (15-48)
	Male	-	25 (16-48)
Any Lynch syndrome-associated cancer	Female	-	32 (21-53)

CRC, colorectal cancer; HR, hazard ratio; CI, confluence interval.

and *hMSH2* mutations (Table II) (32). However, *hPMS2* mutation carriers display very different risk, which is 15-20% risk for CRC, 15% for endometrial cancer, and 25-32% for any Lynch syndrome-associated cancer (Table III) (29,33). In comparison to other MMR genes, these risks are much lower.

FAP. FAP is the second most common inherited CRC syndrome and accounts for approximately 1% of all CRC. It is characterized by the emergence of hundreds to thousands of adenomatous polyps throughout the colorectum, usually beginning in late childhood or adolescence. If untreated, individuals with FAP in adolescence inevitably develop CRC by the age of 40 years. Therefore, the penetrance of this syndrome is 100%. Even though polyps may appear as early as 16 years of age, diagnosis of CRC may be delayed until 36 years of age (34). Development of CRC is observed in approximately 7% of patients by 21 years of age whereas 95% develop CRC by age 50.

Other types of cancer associated with FAP are duodenal cancer, thyroid cancer, medulloblastoma, bile duct cancer, and childhood hepatoblastoma (Table IV). Benign neoplasms associated with FAP are upper GI polyps, desmoids tumors, sebaceous and epidermoid cysts, osteomas, supernumerary teeth, and congenital hypertrophy of the retinal pigment epithelium (CHRPE) (35). Although desmoids tumors are classified as benign, they occur in approximately 10% of FAP patients and can result in major medical complications, including death (36). Indeed, complications from desmoid tumors are one of the leading causes of death in individuals with FAP who have had a prophylactic colectomy (37).

FAP arises as a consequence of a germline heterozygous mutation in the adenomatous polyposis coli (*APC*) gene, a tumor suppressor gene located on chromosome 5q21. Individuals who carry a germline pathogenic mutation in the *APC* gene eventually develop FAP. Despite being a rare disease, FAP has been considered as a good model for hereditary cancers and mutations in *APC* gene are a good example of the molecular pathogenesis of neoplasia (38). Indeed, as is the case for other tumor suppressor genes, *APC* gene inactivation occurs only after both alleles have been damaged due to mutations. In FAP, one allele is inherited in a mutated form. Adenoma formation is initiated when the second allele is damaged or lost by somatic event. Inasmuch as significant number of adenomas likely develop within 15-40 years, it is quite possible that initiation of tumorigenesis can be triggered with just two hits. However, considering that only a small number of these adenomas progress to cancer, the presence of several additional mutations is probably necessary for this tumorigenesis (39,40).

Autosomal dominant inheritance of APC mutation is common in many cases of FAP, even though few cases (15-20%) appear to display *de novo* APC mutation. Patients with these types of mutations therefore do not present with a family history of the disease, but appear to have somatic mosaicism (36,37). Acquired *APC* mutations are often seen in sporadic colorectal carcinomas and recent studies suggest that nearly 66% of all CRCs harbor the mutated *APC* gene. Over 800 APC germline mutations have been reported (39) with the vast majority associated with FAP being truncating or nonsense mutations, and typically insertion or deletion, leading to altered reading frame (40,41).

The *APC* gene also has another mutation, APC 11307K, which appears mostly in individuals of Ashkenazi Jewish descent (42). The APC 11307K mutation is an indirect causative factor for CRC, through the formation of a weak spot in the *APC* gene, which is critical to the development of CRC (42). The APC 11307K mutation is autosomal dominantly inherited and people with this mutation generally develop cancer around the age of 60 years (43,44). The lifetime risk of CRC development in individuals with APC 11307K gene mutation is much less than the risk associated with the other hereditary CRC syndromes, and is estimated to be 10-20% (45,46).

AFAP. AFAP is a variant of FAP and is also characterized by polyposis. However, in AFAP, the total number of polyps is

Table IV. Mode of inheritance of adenomatous polyposis syndromes as well as gene, lifetime risk of cancer development and non-malignant features associated with these syndromes.

Syndrome	Inheritance	Gene	Sites	Lifetime risk (%)	Non-malignant features
FAP	Autosomal dominant	*APC*	Colon	100	100-1000 of colorectal adenomas
			Duodenum/periampullary	4-12	Gastric fundic gland and duodenal
			Stomach	<1	Adenomatous polyposis
			Pancreas	2	CHRPE, epidermoid cysts, osteomas
			Thyroid	1-2	Dental abnormalities
			Liver (hepatoblastoma)	1-2	Desmoids tumors
			CNS (medulloblastoma)	<1	
AFAP	Autosomal dominant	*APC*	Colon	70	<100 colonic adenomas (0-100)
			Duodenum/periampullary	4-12	Upper GI polyposis similar to FAP
			Thyroid	1-2	Other non-malignant features are rare in AFAP
MAP	Autosomal recessive	*MUTYH*	Colon	80	Colonic phenotype similar to AFAP
			Duodenum	4	Duodenal polyposis

FAP, familial adenomatous polyposis; AFAP, attenuated familial adenomatous polyposis; MAP, MUTYH-associated polyposis; CNS, central nervous system; CHRPE, congenital hypertrophy of the retinal pigment epithelium; APC, adenomatous polyposis coli; GI, gastrointestinal.

<100 (Table IV), and the polyps have a tendency to develop on the right side of the colon (22). Furthermore, the penetrance of AFAP appears to be lower than that of FAP, and AFAP patients have a delayed development of CRC, by approximately 12 years, compared to those with classic FAP (36).

AFAP may also result from splice-site mutations, which cause in-frame deletions of APC ORF (open reading frame) in a small number of patients and in most cases, genes with these mutations encode near full-length protein, providing an intuitive explanation for the weak attenuated phenotype. On the other hand, mutations in the 5' region of the *APC* gene, upstream of codon 157, appear to cause most cases of AFAP. How these mutations which potentially lead to truncation of the APC contribute to the development of cancer remains to be determined. This paradox may be explained by the fact that translation is reinitiated at an in-frame ATG, at codon 184, when a mutation upstream of codon 169 causes truncation and such internal initiation is facilitated by an internal ribosome entry site. The resulting protein is devoid of regions containing amino acid sequences required for homodimerization and nuclear export, suggesting that these functions are probably not crucial for APC function. The hypomorphic nature of the truncated APC may be the cause for the lower number of polyps.

MAP. Unlike the other polyposis syndromes, which show an autosomal dominant pattern, MAP shows autosomal recessive inheritance and is possibly restricted to single generation. There are multiple colonic polyps in MAP patients and often it is difficult to distinguish MAP from classical AFAP (43). It has been suggested that MAP is the real AFAP (44). MAP is now known to be associated with CHRPE, osteomas, duodenal adenomas, anomalies, and gastric fundic gland polyps, as well as desmoids tumors, which are considered to be hallmarks of FAP (47). There may be up to 500 colorectal polyps in MAP and these polyps tend to be mostly small tubular or tubulovillous adenomas with mild dysplasia and there may also be hyperplastic polyps. Even though adenomas seem to show a right colonic predisposition, tumorigenesis can occur throughout colorectum. At the time of diagnosis, which is generally at approximately 45 years of age, the number of adenomas is <100 in many MAP patients and by approximately 50 years of age these patients develop CRC (45-49).

MAP is caused by bi-allelic mutations in the *MUTYH* gene, which encodes a base excision repair protein and loss of this protein compromises base excision repair and results in CG-AT transversions in several genes, including *APC* and *KRAS* (43,50,51). While germline *MUTYH* mutations appear to be potential causes for polyps and cancer predisposition, somatic *MUTYH* mutations may not have a significant role in the pathogenesis of colon cancer (52,53). There is approximately 80% lifetime CRC risk for *MUTYH* mutation carriers (Table IV). The two most common *MUTYH* mutations are missense mutations Y179V and G396D (earlier labeled as Y165V and G382D, respectively), and occur in more than 80% of individuals of European ancestry with MAP (43,50,52,54-56). Other population-specific *MUTYH* mutations have been found (53). Nearly 90% of MAP patients in western populations have at least one of these mutations (53).

In 8-13% of patients with >100 adenomas, even though disease causing APC mutations are absent, bi-allelic *MUTYH* mutations are found and these mutations are also seen in 16-40% of patients without any FAP but with 15-99 colonic adenomas (50,54,55,57-59). Occurrence of bi-allelic mutations in patients with few to no polyps and early-onset CRC, as well as in CRC-negative individuals but having <10 adenomas,

Table V. Mode of inheritance of hamartomatous polyposis syndromes as well as gene, lifetime risk of cancer development and non-malignant features associated with these syndromes.

Syndrome	Inheritance	Gene	Sites	Lifetime risk (%)	Non-malignant features
PJS	Autosomal dominant	*STK11*	Breast	54	Mucocutaneous pigmentations
			Colon	39	Gastrointestinal hamartomatous (Peutz-Jegher) polyps
			Pancreas	11-36	
			Stomach	29	
			Ovary	21	
			Lung	15	
			Small bowel	13	
			Uterine/cervix	9	
			Testicle	<1	
JPS	Autosomal dominant	SMAD4	Colon	39	Gastrointestinal hamartomatous (juvenile) polyps
		BMPR1A	Stomach, pancreas, and small bowel	21	Features of HHT congenital defects

PJS, Peutz-Jeghers syndrome; JPS, juvenile polyposis syndrome; HHT, hereditary hemorrhagic telangiectasia.

is rare (60). The presence of MAP is frequent in individuals having 20-90 adenomas (53,61).

Polymerase proofreading-associated polyposis. A new type of polyposis syndrome that is associated with polymerase proofreading, which shows a phenotype including an early onset of colorectal and endometrial cancers along with oligo-adenomatous polyposis, is described in a few families (62). The disease appears to have a high penetrance. Two germline mutations *POLE* p.Leu424Val and *POLD1* p.Ser478Asn were identified in individuals with this syndrome. The two pathogenic mutations are characterized by a dominant pattern of inheritance and associated with a high risk of multiple colorectal adenomas, large adenomas, early-onset CRC and multiple CRCs. *POLD1* mutations are also associated with increased risk of endometrial cancer in female carriers (62,63).

Most of the germline mutations identified that *POLE* and *POLD1* polymerases are situated in the proofreading (exonuclease) domain of these enzymes, indicating that these mutant polymerases are unable to proofread and repair DNA replication errors (62,64-66). In MSI-positive colorectal and endometrial tumors certain mutations in the non-exonuclease domain of these polymerases and these mutations were found to be passenger mutations (66).

4. Hamartomatous polyposis syndromes

Among the hamartomatous polyposis conditions, which confer elevated risk for CRC and other malignancies, JPS and PJS seem to be more important (67), as compared to many other rare hamartomatous polyposis syndromes, such as Cowden syndrome (CS), which pose little risk for CRC.

PJS. PJS patients have multiple hamartomatous polyps, through the GI tract as well as mucocutaneous melanocytic macules. This type of hyperpigmentation is found mostly near the eyes or on the buccal mucosa, nose, or axilla. Other characteristics include small flat, brown, or dark blue spots in the peribuccal area and across the vermillion border of the lips (68). The elevated pigmentation is normally seen in childhood but disappears by adulthood.

The characteristic GI lesions are small bowel, histologically distinctive hamartomatous polyps (69). Gastric and colonic Peutz-Jeghers polyps are found in ~25 and 30% of cases, respectively. There is ~87% lifetime risk of cancer and close to 70% risk specifically for GI tract cancer in people with PJS (65). In these patients the risk for pancreatic cancer is 11-36%. Other types of cancer are observed (Table V) and nearly 50% of patients with PJS succumbed to cancer by age 57 years. PJS is inherited in an autosomal-dominant manner with variable penetrance. It arises from mutations of the *STK11* gene on chromosome 19p13.3.

JPS. JPS is an autosomal-dominantly inherited syndrome and patients with JPS have multiple juvenile polyps in many parts of the GI tract including, colorectum, stomach, jejunum, ileum, and duodenum (67,70-73). Size of the polyps ranges from 5 to 50 mm, and these polyps are spherical and either single or multi-lobulated, with surface erosion. Patients with JPS show symptoms of bleeding, diarrhea, abdominal pain, intussusceptions and rectal prolapse. Because of the overlap with hereditary hemorrhagic telangiectasia (HHT) and arteriovenous shunting, sometimes digital clubbing has been noted in these patients (71).

JPS occurs as a result of mutations of the *SMAD4* gene or the *BMPR1A* gene (73-77). Up to 60% of individuals with

clinically defined JPS are now found to exhibit mutations of the *SMAD4* or *BMPR1A* genes (78). Germline mutations in these genes have been identified in ~40% of JPS patients (79,80). JPS patients with mutations in the *SMAD4* gene usually have a family history of upper GI polyposis and are predisposed to developing large gastric polyps (79,81). Patients with *BMPR1A* mutations have a smaller number of gastric polyps compared to patients with *SMAD4A* (79,81,82). A large proportion of JPS patients with *SMAD4* mutations have a 39% lifetime CRC risk, and develop GI juvenile polyps, while JPS patients with *BMPR1A* have a 21% lifetime risk of extra-colonic cancers and develop an HHT (Table V), a dominant disorder characterized by epistaxis, visceral arteriovenous malformations and telangiectasias (83). In two JPS patients, who did not show any symptoms of hemorrhagic telangiectasia, rare germline mutations in the *ENG* gene, which confers susceptibility to HHT, have been observed (84). It has been suggested that some patients with *PTEN* mutations, who have been misclassified as PJS patients, most likely belong to the *PTEN* hamartoma tumor group (85,86). In these patients, microdeletions at the chromosomal region 10q22-q23, which includes both *PTEN* and *BMPR1A* genes, has been reported (87).

CS. CS is associated with a wide range of clinical phenotypes that include orocutaneous lesions. These lesions include palmoplantar keratosis, oral mucosal papillomatosis, and facial trichlemmomas. The patients are at risk of developing cancers of the breast and thyroid. Adenocarcinoma of the uterus may also be associated with the syndrome (88). The majority of patients with CS have polyps throughout the colon (89,90). Hamartomatous polyps are the most common histologic polyps (89). Other polyp types include, juvenile polyps, ganglioneuromas, adenomas, and inflammatory polyps, and less commonly leiomyomas, lipomas, and lymphoid polyps (89-93).

Several investigations report the frequent occurrence of multiple hamartomatous polyps in the stomach, duodenum, and small bowel (67,89,94). The presence of gastric and colon cancers has been reported in some CS patients. CS is caused by germline mutations in the *PTEN* gene, which is a dual-specific phosphatase associated with the negative regulation of the *AKT* signaling (95-99).

SPS. SPS is a rare condition with characteristically large and multiple polyps of the colon, with an enhanced risk of CRC. Patients with SPS are a heterogeneous group with different disease phenotypes, which are probably caused by different genetic alterations (100). There are three different subgroups of SPS phenotypes: i) A right-sided phenotype with large sessile serrated adenomas along with an early-onset CRC with *BRAF* mutation; ii) a left-sided phenotype displaying a high number of small polyps showing *KRAS* mutation; and iii) a mixed phenotype with the characteristics of phenotypes 1 and 2 (100,101). Nearly 80% of patients with SPS display regular colonic adenomas, which are a common occurrence in CRC-affected individuals with SPS (102,103).

Recessive and dominant inheritance patterns have been suggested for the SPS transmittance (104-106). Serrated polyps were observed in patients with bi-allelic mutations in the *MUTYH*, *PTEN*, *SMAD4*, and *BMPR1A* genes or with duplication in the *GREM1* gene (107,108). Therefore, these genes were suggested to be altered in individuals with SPS (109). However, the fact that a history of adenomas was reported by 3 patients who meet criteria for SPS in a series of 17 bi-allelic *MUTYH* mutation carriers, and by one bi-allelic MUTYH mutation carrier among 126 patients with SPS, is indicative of some overlap in the presentation of MAP and SPS.

HPC. Despite the fact that there is a genetic risk of pancreatic cancer, the basis for this inheritance is poorly defined. One of the well characterized risk factors for the development of pancreatic cancer is the hereditary chronic recurrent pancreatitis, which has an early onset in life. Both hereditary pancreatitis and age are cumulative factors elevate the relative risk for pancreatic cancer significantly up to 50-fold. Of note, this cumulative risk is found to be higher by as much as 75%, if there is paternal inheritance for pancreatitis. It has been demonstrated that either mutations in *PRSS1* gene or a history of pancreatitis have the potential to confer a 5% risk for tumorigenesis in the same family members (3). Mutations in *SPINK1* and *CFTR* genes, which have been linked to hereditary pancreatitis, may also be associated with elevated risk of pancreatic cancer.

Evidence suggests that germline mutations in *BRCA2* gene, which is one of the genes associated with hereditary breast and ovarian cancer, might be the cause of up to 10% of pancreatic cancer cases (110,111). The 6174de1T *BRCA2* mutation, which is found in nearly 1% of individuals of Ashkenazi Jewish ancestry, likely explains the relatively higher incidence of pancreatic cancer in these people.

A clear genetic correlation between pancreatic cancer and familial melanoma has been described. Thus, patients with a mutation in *CDKN2A* have an elevated risk of both melanoma and pancreatic cancer (112). Whole genome sequencing or linkage analysis of familial pancreatic cancer kindred, have identified palladin (*PALLD*), *ATM*, and *PALB2* genes, which enhance the risk of pancreatic cancer development (113-116). Apparently, previously known genetic mutations are causative for only 20% of familial clustering of pancreatic cancer. Therefore, in most cases, the responsible hereditary factors that are responsible for the increased number of pancreatic cancer cases in these kindred have not been identified.

Hereditary gastric cancer. Hereditary diffuse gastric cancer (HDGC) is also inherited in an autosomal dominant manner and develops into a poorly differentiated diffuse gastric adenocarcinoma (117). Clinical presentation of patients generally occurs around 40 years of age with linitis plastica, without a defined gastric tumor. The cumulative risk for the development of gastric cancer by 80 years of age is relatively high in women (83%) compared to men (67%). Even though no specific area of the stomach is targeted by tumor development, a diffuse area with up to 160 independent foci of tumor have been identified at prophylactic gastrectomy.

Germline mutations in the *CDH1* gene, encoding the transmembrane protein E-cadherin, were found to be the cause of HDGC, with a penetrance of 70-80% (118). Risk of developing diffuse gastric cancer and lobular breast cancer is enhanced by heterozygous germline mutations in the *CDH1* gene. Not all

families fulfilling these criteria have mutations in CDH1, indicating that other genes may also be involved in diffuse gastric cancer predisposition. Germline mutations in *CTNNA1* gene were described in three families that presented with diffuse gastric cancer (119).

A family history of gastric cancer in the absence of *CDH1* mutation, is known as the familial gastric cancer syndrome and can arise due to other inherited cancer predisposition syndromes such FAP and Li-Fraumeni syndrome (which is due to germline mutations in the *TP53* tumor suppressor gene). Lynch syndrome confers ~13% risk for gastric cancer and inherited germline *BRCA2* mutations also confer a great risk. A specific *BRCA2*, 614del1T, has been reportedly associated with a risk of gastric cancer by ~5.7% (120). It is important to bear in mind that nearly 21% patients with a family history of breast or gastric cancers, have *BRCA2* mutation. *BRCA2* mutations are also noted in 24% of the patients with a family history of ovarian and gastric cancer (121).

5. Conclusion

Several well established hereditary GI cancer syndromes now exist, each with implication for specific cancer risk in GI and other organ systems. Investigation of the causative genetic factors has led to the identification of specific germline mutations for several syndromes. Understanding the effect of these mutations in susceptibility is of great importance for cancer research aimed at developing new therapeutic and preventive strategies. Although there are numerous gaps in current knowledge related to certain hereditary GI cancer syndromes, it is not unreasonable to assume that studies of GI syndromes may continue to lead the field in cancer research.

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