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Genetics of Young Onset Colorectal Cancer

Esha Baichoo **Lisa A Boardman***
Department of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Abstract

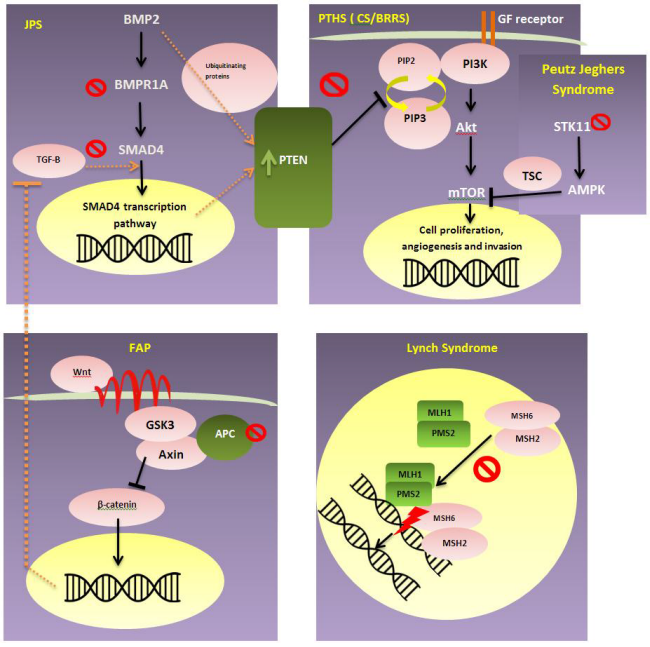
In the United States, more than 150, 000 cases of colorectal cancers are diagnosed annually, making colorectal cancers a major cause of morbidity and mortality. Hereditary colorectal cancers are thought to account for up to 30% of the total number, 5% of which have a known genetic background. Colorectal cancers occurring at ages less than 50 are considered young-onset and are thought to make up 2% to 8% of all cases. They are often a hallmark of a hereditary cancer predisposition. This review covers both the major and the less common hereditary syndromes associated with young-onset colorectal cancers and provide a brief overview of current genetic testing guidelines in place.

Keywords: Young-onset colon cancer; Genetic colon cancer; Colonic polyposis

Abbreviations: CRC: Colorectal Cancer; LS: Lynch Syndrome; MSI: Microsatellite Instability; FAP: Familial Adenomatous Polyposis; AFAP: Attenuated Familial Adenomatous Polyposis; CMMRD: Constitutional DNA Mismatch Repair Deficiency; MAP: MutYH Associated Polyposis; PTHS: PTEN Hamartoma Syndromes; PJS: Peutz-Jeghers Syndrome; JPS: Juvenile Polyposis Syndrome; CS: Cowden Syndrome; BRRS: Bannayan-Riley-Ruvalcaba Syndrome; SPS: Serrated Polyposis Syndrome; HMPS: Hereditary Mixed Polyposis Syndrome

Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality and is the second cause of cancer deaths worldwide (http://www.cancer.org/research/cancerfactsstatistics/index). In the United States alone, more than 150, 000 cases are diagnosed annually and the projected deaths from CRC in 2013 is estimated to be 50, 830 [1]. Although most cases of CRC are sporadic, up to 30% of CRC cases are thought to have a familial component, of which only 5% have a well-characterized genetic basis. Hereditary CRC are often multi-generational, with a young age at onset. The widely accepted definition of young-onset CRC is an age at diagnosis less than, or equal to, 50 years, although a cut-off of 45 years has been suggested. Young-onset CRCs are thought to make up between 2%-8% of all CRC cases [2]. While the rates of cancers among adults older than 50 are on the decline, the incidence of young-onset CRC is increasing [3]. Between 1992 and 2005, the rate of increase of young-onset CRC was 1.5%/year for men and 1.6%/year for women [4]. In 20 to 39 year olds, CRC remains the third leading cause of malignancy-associated deaths [1]. Interestingly, while young-onset CRC are often diagnosed at an advanced stage, they do not necessarily carry a poorer prognosis when compared stage to stage with older CRC cases, and might even fare better [5,6]. While a genetic basis is thought to underlie young-onset CRC, it is not necessarily true for all cases. Young-onset CRC in inflammatory bowel disease (IBD) illustrates such a case since the etiological basis for the malignancy is thought to lie more in chronic inflammation and epigenetic changes than in genetic mutation per second.



JPS: Juvenile Polyposis Syndrome; PJS: Peutz-Jeghers Syndrome; Cowden Syndrome: CS; BRRS: Bannayan-Riley-Ruvalcaba Syndrome; FAP: Familial Adenomatous Polyposis; LS: Lynch Syndrome.

Figure I: Different genetic pathways and the site of mutations in common genetic colorectal cancer syndromes. The overlap in genetic pathways is shown, particularly for hamartomatous polyposis syndromes (Peutz-Jeghers Syndrome, Juvenile Polyposis Syndrome, Cowden syndrome and Bannayan-Riley-Ruvalcaba Syndrome). Also shown is the indirect, downstream effect of the mutated APC gene on the TFG-β/SMAD4 pathway.

Lynch Syndrome

Overview

Lynch syndrome (LS), eponymous for hereditary non-polyposis

***Corresponding author:** Lisa A Boardman, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA, Tel: 507-266-4338; Fax: 507-266-0350; E-mail: boardman.lisa@mayo.edu

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Condition	Prevalence	Average age at CRC diagnosis	Gene involved	Mode of inherit ance	Lifetime CRC risk	Colonic manifestation
LS	1:440	44-45	MLH1, MSH2, PMS2 MSH6	AD	50-80%	Proximal predilection of CRCs
CMMRD	-	16	As LS	AD	100%	Similar to LS. Adenomatous polyps sometimes seen
FAP	1:10,000	39	APC	AD	100%	>100 adenomatous polyps with an average age of onset of 16
AFAP	-	56	APC	AD	80%	Similar to FAP; usually < 100 polyps with a later age of onset
MAP	-	45-56	MutYH	AR	Biallelic: 80% Monoallelic:?	10-100 adenomatous polyps. Serrated and hyperplastic polyps possible. CRCs mostly proximal
PJS	1:29,000 to 1:120,000	43	STK11	AD	39%; 3% at 40 5% at 50	Hamartomatous polyps
JPS	1:16,000 to 1:100,000	42	SMAD4 BMPR1A ENG	AD	40-50%; 17-22% at 35 68% at 60	5-200 juvenile hamartomatous polyps, with an average age of onset of 20
CS	1:200,00 to 1:250,000	<50?	PTEN	AD	9-16%	Hamartomatous polyps
BRRS	-	Pediatric onset?	PTEN	AD	Similar to CS	Hamartomatous polyps, younger age at onset than CS
SPS	1: 3000	63; <50 possible	BRAF	AD/AR ?	?	Serrated polyps
HMPS	-	48	15q13-14?	AD	?	1-15polyps:classic, serrated, tubular; hyperplastic; juvenile; mixed juvenile-adenomatous or hyperplastic adenomatous

LS: Lynch Syndrome; CMMRD: Constitutional DNA Mismatch Repair Deficiency; FAP: Familial Adenomatous Polyposis; AFAP: Attenuated Familial Adenomatous Polyposis; MAP: MutYH-Associated Polyposis; PJS: Peutz-Jeghers Syndrome; JPS: Juvenile Polyposis Syndrome; CS: Cowden Syndrome; BRRS: Bannayan-Riley-Ruvalcaba Syndrome; SPS: Serrated Polyposis Syndrome; HMPS: Hereditary Mixed Polyposis Syndrome.

Table 1: Inherited genetic colorectal cancer syndromes, with a breakdown of their prevalence, mode of inheritance, age at onset, colorectal cancer risk and colonic features.

colorectal cancer (HNPCC), is the most common form of hereditary colorectal cancer (CRC). It is estimated that LS makes up 2-5% of all CRC cases [7]. The prevalence is estimated at 1 in 440 [8]. Germline mutations in four DNA mismatch repair gene (MMR) are causative of LS and are inherited in an autosomal dominant fashion [9]. MMR gene mutations confer an estimated 50-80% lifetime risk of CR development [10,11]. CRC in LS arise from an accelerated adenoma to carcinoma progression, taking as little as two to three years for malignant transformation, compared to eight to ten in sporadic CRC [12]. LS-associated CRC is diagnosed on average between 40-45 years of age, a full decade earlier than sporadic CRC (mean age at diagnosis 60-65). CRC in LS is most likely proximal, often with numerous synchronous and metachronous lesions [13]. Surprisingly, LS-associated CRC appear to have a lower stage at diagnosis than sporadic CRC and when matched for stage, also have a better prognosis, despite their poorly-differentiated histology [14]. LS predisposes to a wide range of cancers, including endometrial, gastric, small bowel, hepatobiliary and urinary tract, ovarian and CNS tumors [15].

A strong, multigenerational family history often prompts the diagnostic workup of LS, using the Amsterdam criteria (AC) I and II. AC I criteria encompass the hereditary features of this syndrome in non-FAP patients and include: (1) at least three relatives with histologically-confirmed CRC, one of whom should be a first-degree relative to the other two; (2) at least two successive generations affected; and (3) CRC diagnosed in at least one case arising under 50 years of age. AC II allows inclusion of extracolonic cancers associated with LS in the place of CRC. However more than 50% of families with LS fail to meet either AC I or II and the Bethesda guidelines were developed to increase detection of LS kindreds and to outline criteria for the consideration of genetic evaluation for LS [16]. Despite the more comprehensive nature of the Bethesda guidelines, only 15-20% of patients meeting Bethesda criteria but not AC I or II will have mutation(s) in the MMR gene(s) [13].

Genetics

LS are caused by germline mutations in one of four DNA MMR genes (MMR), *MLH1*, *MSH2*, *PMS2* and *MSH6*. These DNA MMR genes maintain genomic stability by correcting nucleotide mismatches that occur during DNA replication. Microsatellites are mono, di, and tri-nucleotide repeats spread throughout the genome and these nucleotide repeats may be amplified when the DNA MMR system is inactivated, leading to microsatellite instability (MSI). MSI occurs in individuals with LS when a second somatic mutation in the affected tissue inactivates the function of DNA MMR. MSI measured in the tumor represents an increased number of mono-, di-, or tri-nucleotide repeats in the tumor compared to the normal tissue. MSI is subclassified by the number of microsatellite markers showing instability. Tumors expressing MSI in two or more markers from the recommended panel by the National Cancer Institute (BAT26, BAT25, D5S346, D2S123 and D17S250) are termed MSI-high while those with only one marker are termed MSI-low. MS-stable or MSS tumors have no microsatellite instability. MSI itself may occur in genes important

to cell cycle and growth regulation, creating a mutator phenotype that may result in cancer. MSI is a feature of LS-associated cancers and is present in 85-90% of LS associated CRC. Somatic hypermethylation of the MLH1 promoter region may inactivate *MLH1* and accounts for as many as 15-25% MSI-positive sporadic CRC [9]. Up to 90% of all LS cases have been attributed to germline mutations in *MLH1* or *MSH2*, but this may be an overestimate since mutations in *MLH6* and *PMS2* may have a more attenuated phenotype and thus be underdiagnosed [13,17]. On universal screening of 1,066 CRC, 23 cases were diagnosed with LS, with 13% and 9% attributable to an *MSH6* or a *PMS2* mutation respectively [18]. Moreover, there appears to be geographic difference in MMR mutations. For example, in Finland, *MLH1* mutations accounted for 83% of the mutations, with *MSH2* mutations only accounting for 3% [19].

Germline epithelial cell adhesion molecule (*EPCAM*) gene mutations have been linked to a minority of MSH2-deficient, MSI LS cases lacking a detectable *MSH2* mutation [20,21]. These mutations involve deletions at the 3' end of *EPCAM*, leading to promoter hypermethylation and the epigenetic silencing of the downstream *MSH2* gene. *EPCAM* mutations are thought to account for 6.3% of all LS cases [22]. Individuals with *EPCAM* mutations have the same cumulative risk for CRC as those with *MSH2* mutations: 75% vs. 77% by age 70 [21].

Genotype-phenotype correlations have been reported. A study comparing the genotype-phenotype relationship of *MLH1* and *MSH2* mutations concluded that *MLH1* mutation carriers had an increased CRC risk, while *MSH2* mutations carriers had an increased risk for endometrial cancer and multiple LS-related cancers [23]. The age of onset of CRCs between *MLH1* and *MSH2* mutation carriers were the same, with 80% being diagnosed before 50 [23].

Tumors that result from MSH6 mutations are MSI-low and are more likely to arise in the distal, rather than proximal colon [24]. *MSH6* mutation carriers have a much lower cumulative risk for CRC (12%) by 70 years of age than both *MLH1* (41%) and *MSH2* (48%) mutation carriers [25].

Genetic testing

Genetic testing for LS should be considered in patients with a strong, multigenerational family history or in those presenting with young-onset CRCs. Patients with LS-associated extracolonic cancers or multiple cancers should also be considered for testing. Several methods are available to assist in the clinical diagnosis of LS, including tumor testing by way of immunohistochemistry (IHC) or MSI testing, molecular analysis and mutation prediction models. Testing may be initiated after an extensive, revealing family history but it is more cost-effective to use the Bethesda criteria to first determine individuals who require testing. The most commonly used diagnostic methods are the MSI and/or IHC analysis of CRC tissue. LS typically have MSI-high tumors, making this form of analysis very sensitive [26,27]. *MLH1* and *MSH2* may be tested first, owing to their increased prevalence, but strategies vary widely regarding the order of testing using IHC, notably on whether to test the two most common DNA MMR proteins first or to perform IHC and/or MSI testing for all four proteins from the start. Of note, these techniques do not perform equally well for all mutation types and MMR proteins.

For example, missense germline *MSH6* mutations often yield false negative results with IHC.

MSH6 tumors are also MSI-low, contributing to their under-diagnosis [28]. Currently, IHC is available for all 4 MMR proteins, as well as for the distal portion of the *EPCAM* gene. IHC results subsequently direct germline sequencing for the specific gene(s) implicated.

Alternatively, germline analysis using full gene sequencing and southern blot analysis from DNA obtained from peripheral blood samples may be used to diagnose LS in family members and CRC patients [26]. Identifying disease-causing mutations can be difficult, particularly in the case of missense mutations which are not traditionally considered pathogenic, and it can be challenging to discriminate missense mutations of the polymorphic variant type from those causing disease. Several databases are in place to serve as points of references, including the International Society for Gastrointestinal Hereditary Tumors (InSIGHT), which maintains a collection of published and unpublished mutations reported in LS and the MMR gene

Unclassified Variants Database which focuses specifically on missense mutations [29,30]. Genetic prediction models, including PREMM 1,2,6 (Prediction Model for MLH1, MSH2 and MSH6 Gene Mutations), using computer softwares are highly efficient means of diagnosing LS in patients without cancer or in those without an available cancer specimen for testing [31-34]. If prediction models point towards a pathogenic mutation, gene-specific analysis can then be performed. In the future, widespread use of whole exome or genome sequencing may supplant the need for the cascade of tumor testing with IHC and MSI and targeted sequencing.

Familial Colorectal Cancer X

Overview

This syndrome warrants special mention in this review. Although not typically thought of as predisposing to young-onset CRC, the hereditability of the syndrome does not preclude the occurrence of CRC in younger individuals, and as such, a high degree of suspicion should be maintained. Of the families fulfilling the AC I, only about 60% have a detectable MMR mutation [35]. In 2005, Lindor et al. coined the term Familial Colorectal Cancer Type X (FCCTX) to describe this subset of patient [36]. FCCTX appears to have an autosomal dominant pattern of inheritance, although the genetic basis for the disease is as yet unclear [36]. FCCTX patients have a lower risk for CRC than those with LS, with a standardized incidence rate (SIR) of 2.3 compared to 6.1 in LS and present at a later age, 61 vs. 49 years [36]. In addition, the localization of the CRC is more commonly observed on the left, as compared to the preponderance of right-sided tumors in LS [23]. FCCTX tumors are MSS and have not been found to be associated with an increased risk for LS related extracolonic cancers [26].

Biallelic Mutation of MMR genes- Constitutional DNA Mismatch Repair Deficiency Syndrome

Overview

Constitutional DNA mismatch repair deficiency (CMMRD) is the result of germline biallelic mutations in DNA MMR genes. CMMRD predisposes to a much earlier age of onset of CRC than LS with an average age of 16 years (range 8-35 years) at CRC diagnosis [37-40]. Since the first report of homozygous MMR mutation in 1999, familial cases have been described and the constellation of observed malignancies have been termed constitutional mismatch repair disorder (CMMRD) [37,41]. CMMRD typically manifests in the first decade as a spectrum of malignancies, particularly hematological and central nervous system cancers and with café au lait spots (CALS) reminiscent of neurofibromatosis type 1 (NF-1) [41]. LS-associated malignancies,

notably, CRC and small bowel adenocarcinomas may follow the initial malignancies [42]. Adenomatous polyps are also frequently discovered, often at the time of CRC diagnosis [43].

Genetics

CMMRD is inherited through biallelic deleterious mutations in MMR genes. The specific gene mutated appears to affect the phenotype in CMMRD. LS-associated cancers, including CRC, are more prevalent in biallelic *MSH6* or *PMS2* mutations than in biallelic *MLH1* or *MSH2* deletions. Patients with *MSH6* and *PMS2* biallelic deletions were also observed to have an increased survival rate from their first malignancy and were subsequently more likely to suffer from a second malignancy [42]. This could explain the preponderance of *PMS2* mutations in CMMRD described in literature.

Genetic testing

There is currently no standard predictive testing for CMMRD. It is recommended that patients testing negative for *APC* and *MutYH* mutations benefit from testing for biallelic MMR mutation [44,45]. This subset of patients traditionally received the diagnosis of 'probable de novo FAP' but the differential should be broadened to include CMMRD. This inclusion has a significant impact in CRC prevention, as parents of confirmed CMMRD patients are heterozygous for an MMR mutation, necessitating the same CRC screening as LS [46]. In contrast, de novo FAP children do not necessarily have mutation-carrying parents. Similarly, CMMRD siblings have a 50% chance of a heterozygous MMR mutation and a 25% chance of being biallelic mutation carriers.

FAP

Overview

Familial adenomatous polyposis (FAP) is the second most common hereditary CRC syndrome, accounting for less than 1% of all CRC cases. The estimated prevalence is 1 in 10, 000. The clinical presentation is classically that of hundreds to thousands of adenomatous polyps throughout the colon and rectum [26]. The age of onset of adenomas is variable but by age 30, an estimated 90% of mutation carriers present with FAP [47]. Extracolonic manifestations include duodenal adenoma, gastric polyps, desmoid tumors, dental osteomas, soft tissue tumors and extra-intestinal cancers [26]. This heritable syndrome is autosomal dominant for a germline mutation of the adenomatous polyposis coli (*APC*) gene. De novo mutations of the *APC* gene have been described and may account for up to 30% of cases, particularly in those with no history of CRC in the family [26]. The germline *APC* gene mutation carries an exceedingly strong penetrance, with an estimated 100% cancer risk by a median age of 39, if left without medical follow-up or treatment [48,49]. Very young onset of CRCs can also occur, with 7% developing CRCs by age 21 [27]. Attenuated FAP (AFAP) is a less severe form of the disease, generally occurring at a later age, with fewer polyps on average, typically 20-30 (range 2-100) [50]. AFAP has a later onset of CRC, with a mean age at diagnosis of 56 [51].

As with FAP-related CRC, AFAP CRC arises from the classic adenoma-carcinoma pathway, a result of germline *APC* mutation, coupled with somatic mutation of a second normal copy of APC, leading to inactivation of APC function and decreased or null APC protein. These CRC are thus characterized by early chromosomal aberrations and a chromosomal instability phenotype [52].

Genetics of FAP

Germline mutations in the *APC* gene cause FAP and are inherited in an autosomal dominant fashion. *APC* functions as a tumor suppressor gene and is part of the Wnt pathway. Loss of function leads to uncontrolled epithelial proliferation and, consequently, neoplastic degeneration in the colorectal tract. The penetrance of the *APC* gene appears to be mutation-type dependent. The germ-line mutation seen in the classic form of the syndrome approaches a penetrance of a 100% and is by far the most common mutation detected in carriers [13]. However, the 11307K *APC* polymorphism, particularly prevalent amongst Ashkenazi Jews, approaches a low to moderate penetrance of 10 to 20% [53,54]. As such, more than a thousand variants of *APC* mutations have been described that produce a dysfunctional, truncated protein, a result of frameshift mutations or premature stop codons [55]. Individuals with AFAP have mutation arising from *APC* mutations at the 5' or 3' ends of the gene or in certain areas of exon 9 [56]. AFAP is also inherited in an autosomal dominant manner. An estimated 80% and more of the FAP patients have a detectable mutation and only 10-30% in the case of AFAP [26]. In the remaining patients, a mutation in the MUYH gene should be considered [57-59].

Genetic testing

A strong family history or a patient presenting with polyposis or young-onset CRC warrant testing for FAP. The affected individual undergoes genetic evaluation through full gene sequencing and southern blot analysis for *APC* mutations. Family members of confirmed FAP patients should also be offered genetic testing. If a patient with a classic polyposis phenotype tests negative for *APC*, *MUTYH* mutations should be tested for. It is estimated that up to 30% of *APC*-negative classic polyposis patients are caused by biallelic *MUTYH* mutations [60].

MutYH-associated polyposis

Overview

MutYH-associated polyposis (MAP) was first described in 2002, in a family suffering from adenomatous polyposis despite testing negative for a germline APC mutation [61]. Mutations in the human analog of Escherichia coli muty gene, *MYH (MYH)* was described as causative of MAP. MAP shares phenotypic features with AFAP, presenting with adenomatous polyps usually diagnosed between 40-60 years, with a mean age of 45 [62-64]. Hyperplastic and serrated polyps have also been described [65]. Initially thought to be a classic polyposis syndrome, MAP can be phenotypically diverse, with some patients presenting with CRC without polyps [66]. Both biallelic and monoallelic mutations have been detected in MAP.

Bilallelic mutations have been suggested to carry an estimated risk of CRC of 80% [67]. In a large, systematic population-based study, Farrington et al showed that biallelic *MYH* mutations imparted a 93-fold genotype related risk (GRR) of CRC, with a 100% penetration by 60 years of age [68] .The study failed to find a statistically significant GRR for young-onset CRC attributable to monoallelic mutations and suggest that monoallelic *MYH* mutations confer an increased CRC risk in those above 55 years of age. In a subsequent meta-analysis, the pooled estimated odds ratio (OR) for monoallelic mutations was reported as being 1.23 (95% CI 0.96-1.58), which was not a statistically significant excess of CRC risk as compared to controls [69]. However, in the largest cohort of monoallelic mutation carriers to date, the authors report that monoallelic carriers with a positive family history of CRCs have a two-fold increase in risk of CRC (standardized incidence ratio: 2.04,95% confidence interval, CI 1.56–2.70) [70]. The risk attributed to monoallelic mutations remains controversial.

MAP-related CRCs show a predilection for the right side and are more likely to have synchronous lesions and a precocious age at diagnosis [66]. Very young onset (less than 30 years of age) CRCs in

MAP have also been reported [57,62,63]. About 50% of patients have CRC at time of MAP diagnosis [71]. Biallelic mutations also predispose to extracolonic cancers, including duodenal, ovarian, bladder and skin cancers [72].

Genetics

MYH encodes a DNA glycosylase participating in base-repair excision, with the principal function of protecting genomic information from reactive oxidative stress. Loss of *MYH* leaves DNA vulnerable to 7,8-dihydro-8-oxo-2'deoxyguanosine (8-oxoG), a highly deleterious by-product of oxidative DNA damage. 8-oxoG mispairs with adenine residues, leading to a high frequency of G:C to T:A transversions [73]. These transversions result in a nonsense or splice site mutations in *APC* and *KRAS* genes, setting the stage for uncontrolled cellular proliferation [55,74]. The acquired *APC* mutation in MAP explains the phenotypic similarities with FAP.

In 2003, Sampson et al identified 111 patients with classic polyposis who lacked a clear dominant inheritance pattern or detectable *APC* mutations. Analysis showed that 25 of those patients had biallelic *MYH* mutations, suggesting an autosomal recessive mode of transmission [62]. Geographic and ethnic variations have been suggested in *MYH* mutations [62,75]. In Caucasians, the most frequently reported mutations are Y165C and G383D, accounting for approximately 80% of cases [71] [76]. In contrast, in Asian populations Y165C and G383D are not expressed significantly. Japanese populations show an increased expression of R246C and IVs10-2A>G [77].

Genetic testing

Due to the phenotypic similarity between MAP and FAP/FAP, recommendations have been made that genetic testing for *MYH* mutations be performed on all polyposis patients without a clear pattern of inheritance and no detectable *APC* mutations [62]. Patients without polyposis testing negative for MMR mutations should also benefit from *MYH* testing, as the differential is extended to include the non-polyposis phenotype of MAP. Genetic testing first screens for the two most common variants found in individuals of Western European ancestry, Y165C and G382D. If a mutation is detected, the opposite allele is also tested. In the case of patients of non-Western European ancestry or if both variants test negative and a strong clinical suspicion of MAP remains, other less frequent variants are tested. Siblings of biallelic carriers have the highest risk (25%) of carrying biallelic mutations and should also be offered genetic testing.

Hamartomatous Polyposis Syndromes

Intestinal hamartomatous syndromes form a subset of rare inherited CRC syndromes with a differential diagnosis including Peutz Jeghers syndrome, juvenile polyposis syndromes (JPS), hereditary mixed polyposis syndrome (HMPS) and PTEN hamartomatous tumor syndrome. These syndromes are inherited in an autosomal dominant fashion and confer an increased risk of young-onset CRC.

Peutz Jeghers Syndrome (PJS)

Overview

PJS is a rare autosomal dominant syndrome with incidence ranging from 1 in 29,000 to 1 in 120,000 births [78]. Males and females are affected equally. PJS arises from germline mutations in the serine threonine kinase gene (*STK11*), located in the short arm of chromosome 19, in the 13.3 region [78]. *STK11* is a tumor suppressor, playing key roles in cell cycle regulation and apoptosis [79]. PJS is characterized by a constellation of gastrointestinal polyps, mucocutaneous pigmentation and an increased risk for malignancies. The hamartomatous polyps are most frequently found in the small intestine but may occur elsewhere in the gastrointestinal tract, with up to 30% found in the stomach and colon [26].

Extraintestinal polyps have also been found in the renal pelvis, bronchus, gall bladder, nasal passages, urinary bladder, and ureters [80]. PJS predisposes to an increased risk of intestinal and extraintestinal malignancies. Published data suggests a 9.9 fold increased relative risk (RR) of cancer, with the RR being highest for gastrointestinal cancers (RR=151) and breast cancers (RR=20.3) [81]. PJS confers an increased risk of cancers in younger individuals.

According to a large systematic review of 1,644 PJS patients, CRC was the most common PJS-associated malignancy, with a mean age at diagnosis of 43 years [82]. Lim et al ascribes the overall risk of malignancy at age 20, 40, 60 and 70 as 1%, 19%, 63% and 81% respectively, based on a cohort of 240 PJS patients with a detectable *STK11* mutation [83]. The cumulative risk for CRC is 3% at 40 years and 5% at 50 years [84].

The diagnosis of PJS remains largely clinical, with the finding of the characteristic mucocutaneous pigmentations, and backed by a family history of PJS. Detection of *STK11* confirms the diagnosis. As part of a European consensus [85], clinical diagnosis of PJS may be made when any one of the following is present:

- Two or more histologically confirmed PJS-type hamartomatous polyps
- Any number of PJS-type polyps detected in one individual who has a family history of PJS in a close relative(s)
- Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in a close relative(s)
- Any number of PJS-type polyps in an individual who also has characteristic mucocutaneous pigmentation.

Genetics of PJS

Mutations in *STK11* (previously known as *LKB1*) have been identified as causative of Peutz- Jeghers syndrome (PJS) [79]. An estimated 70% of PJS patients have a detectable *STK11* gene mutation [26]. Over 230 mutations of the *STK11* gene have been described so far, with small deletions and insertions being the most common [78]. Large deletions of individual exons or entire genes have also been described [86]. The existence of other genetic loci predisposing to PJS has been suggested, especially in those patients without a detectable *STK11* mutation, but there have been no clear descriptions of those loci so far [87,88]. Of note, in a study including 25 *STK11* mutation-negative PJS patients, one patient was found to be heterozygous for an *MYH* mutation, suggesting a possible genetic overlap [89].

Genotype-phenotype information from *STK11* mutations remains scant. A study of 297 PJS individuals suggests that neither the type nor the site of the *STK11* mutation influences the overall cancer risk [83]. Subsequent reports that mutations at exon 3 or 6 increased cancer risk surfaced but have not been replicated [83,90]. While cancer risk appears to remain unchanged with the type of mutation, age of symptom onset and severity appear to be mutation-type dependent. Patients testing negative for *STK11* mutations or those with truncated mutations had an earlier age at first-polyp diagnosis than those with missense mutations [91]. Salloch et al. similarly found that patients with truncating mutations had a greater polyp burden, underwent polypectomy earlier and had an overall increased number of surgical interventions [92].

Genetic testing

Although detection of *STK11* confirms a diagnosis of PJS, not all patients carry a detectable mutation, with numbers varying from 30 to 82% in literature [87]. Approximately 50% of patients with a negative family history have a detectable *STK11* mutation [93]. However, the rates of de novo gene mutations remain unknown. PJS is inherited in an autosomal dominant fashion therefore offsprings of an affected parent have a 50% chance of an *STK11* mutation. If the disease-causing mutation is identified, first degree relatives may be tested and prenatal genetic testing of at risk pregnancies may be offered. A negative test does not exclude the risk of PJS and cancer screenings remains advisable.

Juvenile Polyposis Syndrome (JPS)

Overview

Juvenile polyposis syndrome is characterized by the appearance of multiple juvenile polyps throughout the digestive tract and carries an increased lifetime risk of CRC. The risk of CRC is estimated to be 17-22% by age 35, approaching 68% by 60, the median age of CRC diagnosis being 42 [94]. JPS patients are also predisposed to young-onset gastric and small bowel cancers [26]. The incidence of JPS is estimated to be between 1 in 16 000 and 1 in 100,000 persons per year [95]. The term 'juvenile polyps' refers to the type of polyp reminiscent of the inflammatory hamartomatous polyp seen in childhood, rather than the age of onset. Histologically, the polyps are characterized by an edematous lamina propria, hyperplasia of mucous glands and retention cysts [96]. Most individuals develop polyps by 20 years of age, but JPS can be phenotypically-diverse, with some patients developing polyps in their third or fourth decades. Similarly, the number of polyps discovered varies, with an estimated range of 5-200 [96]. Solitary polyps may be discovered in up to 2% of the pediatric population but seldom bear dysplastic changes and do not have an increased risk in malignancy [97].

A significant number of the polyps (80%) in JPS are found within the colon, but can arise anywhere within the digestive tract [78]. The diagnosis of JPS according to the WHO is as follows: 1) more than five juvenile polyps in the colon or rectum, 2) juvenile polyps throughout the intestinal tract, or 3) any number of polyps in a patient with a family history of JPS. JPS shares similar clinical features as other colonic hamartomatous polyp syndromes, such as Cowden Syndrome (CS), Bannayan-Riley-Ruvalcaba (BRRS), PJS and HMPS, and may be misdiagnosed.

Genetics

JPS is inherited in an autosomal dominant fashion and germline mutations in three genes-

SMAD4 (mothers against decapentaplegic, drosophilia, homolog of, 4), *BMPR1A* (Bone Morphogenic Protein Receptor 1A) and *ENG* [98,99]. These genes are involved in the TGF-B pathway, mediating inhibitory growth signals from the cell surface to the nucleus. Mutations in those genes cause uncontrolled cellular proliferation. A 'landscaper mechanism' has been suggested to explain the cancer progression in juvenile polyposis, whereby the abundant stroma in JPS favored an abnormal environment that disrupts the TGF-B pathway. This theory arose from the observation that hamartomatous polyps in JPS had the tendency to develop into serrated or villous-type polyps, both associated with dysplastic changes [100]. The effect of *BMPR1A* knock-out on mice digestive epithelium and the consequent expression of a JPS-like phenotype seem to support this theory [101]. *BMPR1A* is confined to the mesenchyme, suggesting that the polyp stroma plays a critical role in carcinogenesis.

Not all JPS patients carry a detectable mutation, with the percentage varying in available literature. In an early study looking at *SMAD4* mutations, 40% of the patients had a mutation [98]. Subsequent studies report a range of numbers, from 20 to 40% [102,103]. *BMPR1A* mutations are detected in about 20-25 % of patients [104]. *ENG* mutations have been reported in cases of very early onset JPS [99,105]. A *PTEN* mutation on chromosome 10q23 has also been described in a subset of JPS patients, although these results have not been validated since [106,107]. Of note, phenotypically-similar cases of CS or Bannayan- Ruvalcaba-Riley syndrome, both associated with *PTEN* mutation, may be misdiagnosed for JPS. Moreover, *PTEN* mutation may contribute to severe infantile JPS, where large deletions in chromosome 10q involving both the *BMPR1A* and *PTEN* genes have been detected [108].

There is some genotype-phenotype correlation in JPS. *SMAD4* mutations are more often associated with gastric polyps and subsequently to an increased risk of gastric adenocarcinoma [103]. Patients with mutated *SMAD4* also suffer from polyps in the entire digestive tract, in contrast, to BMPR1A mutation, with polyps limited to the anorectal region [78]. JPS occurring in conjunction with hemorrhagic hereditary telangiectasis (JPS/HHT) is seen in 15-22% of patients with *SMAD4* mutations [109]. Mutations in the *ENG* are also known to predispose to JPS/HHT [99]. Overall, patients with a detectable germline gene mutation have a more severe phenotype, with an increased cancer risk and a higher frequency of positive family history [78]. The low combined rate of detectable mutations in JPS observed so far and the varying results point towards heterogeneity in inheritance. Furthermore, complex interactions between the *PTEN* and *BMPR1A* genes have been described, with a resulting additive effect [110]. Juvenile polyposis may also be sporadic [111].

Genetic testing

Clues suggesting a hereditary colonic polyposis condition generally alert to the need for genetic testing. These include, but are not limited to, 1) at least ten adenomas in the colon, 2) at least 3 hamartomatous polyps or 3) at least 1 juvenile polyp [112]. A positive family history is strongly suggestive, but may not be apparent in some patients. Specific phenotypic manifestations may help narrow the gene to be tested. Patients showing signs of HHT should be considered for *SMAD4* testing [113]. Family members may benefit from genetic testing once the disease-causing mutation is known.

PTEN Hamartoma Syndromes

The PTEN hamartoma syndromes (PTHS) are a group of rare disorders caused by germline mutations of the *PTEN* (phosphatase and tensin homolog) gene. Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS) are the two most frequently described disorders and are thought to confer an increased risk for CRC. It has been suggested that they are part of a spectrum of the same disease, with an age-related penetrance [114]. PTHS is inherited in an autosomal dominant fashion, with an estimated 80% penetrance [49].

Cowden syndrome

Overview: Cowden Syndrome (CS), alternatively known as Cowden's Disease or Multiple Hamartoma Disease, is an autosomal dominant disorder first documented in 1963 by Lloyd and Denis [115]. It is part of the PTHS and is phenotypically diverse, presenting with macrocephaly, CNS lesions, multiple hamartomata and an increased

risk of both benign and malignant tumors. The incidence of CS is estimated to be between 1 in 200,000 to 250,000 [116]. However, the actual prevalence is likely higher, as many of the features of CS are commonly found within the general population, leaving CS grossly underdiagnosed. CS is characterized by multi-organ hamartomata, mostly manifesting in the gastrointestinal tract (71% of patients) and the skin and mucous membranes. Mucocutaneous hamartomata are almost pathognomonic of CS, with patients presenting with trichilemmomas (hamartomata of the hair follicle infundibulum) and also with papillomatous papules and acral and plantar keratoses {Hobert, 2009 #666]. The esophagus and colon are the most frequently affected gastrointestinal regions. Polyp prevalence in CS varies and numbers as high as 93% have been reported [117,118]. CS has variable polyp histology- adenomatous, inflammatory, hyperplastic, lymphoid, ganglioneuromatous and leiomyomatous polyps have all been reported [119]. CS polyps have the distinct characteristic of containing neural elements. Patients with CS also have a known predisposition to thyroid, breast and endometrial cancers [120]. The dogma was one that traditionally excluded any CRC risk in CS patients and has since been proven wrong.

There have been, however, very few studies published assessing the CRC risk in CS. A study of Japanese CS patients reported a 9% risk of CRC {Kato, 2000 #673}. A recent review of cases reported that CS patient had a 16% (95% confidence interval (CI) 8%-24%) lifetime risk of CRC while a separate study predicts a 9% (CI 3.8%-14.1%) lifetime risk of CRC [121,122]. A cohort of 127 patients with *PTEN* mutations studied by Heald et al. reported 62 patients with colorectal polyps and nine with CRC (13%), all under the age of 50 [118]. These findings suggest a predisposition to young onset CRC in CS.

The International Cowden Consortium for Cowden Syndrome has set forth diagnostic guidelines for CS, with symptoms divided into major and minor criteria. The diagnostic guidelines were formulated from a review of early published reports and have been criticized as having an inherent selection bias. Age-related penetrance was not factored in within the diagnostic guidelines, leading to misdiagnosis or delayed diagnosis [114]. The guidelines set forth also misrepresent the malignant potential of the GI hamartomatous polyps which are classified under minor criteria, leading to a gross underestimation of the importance of CRC screening. Pilarski et al. propose a revised set of diagnostic criteria to address, among others, the risk of CRC in CS. They propose adding CRC as a minor criterion in the diagnostic work up while promoting hamartomatous polyps to a major criterion [123].

Genetics: CS syndrome is inherited in an autosomal dominant fashion. A mutation of the *PTEN* gene on chromosome 10q22-23 is associated with the syndrome. *PTEN* is a dual-specificity phosphatase and acts as a tumor suppressor gene, negatively regulating the PI3K/AKT/mTOR pathway to cause arrest in G1 phase and apoptosis. *PTEN* also antagonizes the effects of multiple oncoproteins acting through the PI3K kinase. Germline mutations in *PTEN* mostly result in an absent, truncated or dysfunctional protein. Missense *PTEN* mutations are thought to be universally deleterious, exerting as 'dominant negatives'. Impairment of *PTEN* function results in unopposed AKT1 phosphorylation leading to continuous cell replication and an inability to undergo apoptosis [124]. Additionally, the lack of phosphastase activity from the missense mutations causes dysregulation of the mitogen-activated protein kinase pathway (MAPK) and, consequently, abnormal cell survival [124]. The percentage of detected *PTEN* mutations among CS patients is disputed, with earlier studies attributing the mutation to up to 85% of reported cases [125,126]. Recent reports from larger cohorts indicate more conservative numbers, between 30-35% [127,128]. These differences may be explained by the diagnostic criteria used. Earlier studies relied strictly on the Consortium Criteria for CS, with most cases diagnosed through obvious phenotypes. Moreover, the patients studied were part of the original series that eventually led to the identification of *PTEN* as the causative gene in CS.

Bannayan-Ruvalcaba-Riley Syndrome

Overview

BRRS is phenotypically similar to CS, with the addition of pigmented macules of the penis, lipomas and psychomotor retardation [129]. BRRS is a congenital disorder with an early-onset of symptoms, contrasting to the adult manifestation of CS. There are no standard diagnostic criteria for BRSS currently in place, with the diagnosis relying heavily on the presence of cardinal features of the syndrome: macrocephaly, lipomas, intestinal hamartomas and pigmented macules on the penis. BRRS and CS have been suggested to be part of a spectrum of the same disorder with age-related penetrance [114-130]. Families with both CS and BRRS have been reported, lending credence to this theory. Furthermore, the rate of detectable germline *PTEN* mutations in BRSS has been estimated at 60%, supporting the evidence that BRSS is allelic to CS [127]. The cancer risk in *BRSS* is thought to be equal to CS [118].

Genetics

Mutations on chromosome 10 were found to underlie BRRS in 1997 and were subsequently linked to the *PTEN* [131]. BRRS has since been incorporated within the PTHS spectrum, with an autosomal dominant inheritance. While CS patients suffer from mutations in the promoter region of *PTEN*, patients with BRRS commonly have large deletions, often in the entire gene [78].

Genetic testing

Genetic testing in PTHS is dictated by diagnostic guidelines. Due to the autosomal dominant inheritance, children of an affected parent have a 50% chance of having a *PTEN* mutation and subsequently developing PTHS [124]. Genetic testing before the age of 18 may be appropriate given the early-onset symptoms in BRRS [124]. If the disease-causing mutation is identified, prenatal testing for high risk pregnancies is feasible. In families with a detectable *PTEN* mutation, a clinical diagnosis based on pathognomonic features may suffice.

Hereditary Mixed Polyposis Syndrome (HMPS)

Overview

Hereditary mixed polyposis syndrome (HMPS) is a very rare syndrome characterized by numerous polyps of variable histology reminiscent of juvenile, serrated or hyperplastic polyps and sometimes of single polyps with mixed histological features [96,132]. The polyps are found exclusively in the colon and usually range from 1-15 [132]. JPS and HMPS may sometimes be hard to distinguish as a result. HMPS confers an increased risk for CRC, although the exact magnitude is still unclear. The average age at CRC is 48, making HMPS a young-onset CRC syndrome [132].

Genetics

The genetic locus for HMPS, *CRAC1*, was originally mapped to chromosome 6q, but was later found to be on chromosome 15q13-q21 [133,134]. The underlying genetic basis was recently characterized as a heterozygous duplication on chromosome 15q13-q21 upstream of *GREM1*, a gene involved in the *BMP* pathway, possibly explaining

the phenotypic overlap with JPS [135]. So far, *GREM1* mutations have only been detected in Ashkenazi Jews who appear to share a common ancestry [135].

Genetic testing

There are currently no guidelines in place for the genetic testing of HMPS.

Serrated Polyposis Syndrome (SPS)

Overview

Serrated polyposis syndrome is a rare syndrome characterized by multiple serrated polyps in the large intestine. Data from a large population-based screening suggest a prevalence of 1 in 3000 [136]. The revised WHO criteria for SPS diagnosis requires at least one of the following criteria be met: 1) 5 or more serrated polyps proximal to the sigmoid colon, 2 at least 10 mm in diameter; (2) any number of serrated polyps occurring proximal to the sigmoid colon in an individual with a first-degree relative with SPS; and (3) 20 serrated polyps or more of any size distributed throughout the colon [137]. SPS confers an increased risk of CRC, with up to 15- 20% of all CRC possibly arising from the serrated pathway, a shift from the adenoma to carcinoma paradigm [49,137]. A genetic basis for SPS has not been discovered but existing evidence points to a hereditary mode of transmission. Data in support of this argument show that first degree relatives (FDR) of SPS patients have a 5 fold increase risk in CRC, prompting screening recommendations to include FDR [138]. The cumulative risk for CRC in SPS is unclear. Likewise, the age of onset of CRC in SPS is disputed. A recent multi-site study reports the average age of CRC diagnosis in SPS patients as 48 [139]. The authors also find a highly increased risk to FDR if the index case is diagnosed under the age of 50.

Genetics

A mode of inheritance for SPS has not been described, although both autosomal dominant and autosomal recessive have been suggested [140]. Molecular analyses of the neoplastic polyps have shown mutations in the BRAF oncogene leading to CpG island methylator phenotype (CIMP+) with possible MSI [141]. *PTEN* mutations have also been described in SPS cases [99].

Genetic testing

The genetic basis for SPS remains unclear and consequently, no formal genetic testing protocols are in place. In patients with proven SPS, FDR may be offered colonoscopic screening, given the high risk of CRC [138].

Genetic Susceptibility Loci in Young Onset Colorectal Cancer

Although about 35% of CRC are thought to have a genetic background, only 5% of hereditary CRC have an identifiable gene mutation [142]. Rare, high-penetrance gene mutations have been widely described as in the case for LS and FAP. However, according to the common disease-common variant theory, multiple common genetic variants may account for the remaining hereditary cases, with a low to moderate effect on CRC susceptibility [143,144].

Several genome wide association studies (GWAS) have identified low-penetrance susceptibility loci on chromosome arms 8q, 10p,11q,14q, 15q, 16q, 18q, 19q and 20p [145-147]. Some of those variants may be associated with familial features. However studies are in disagreement on the exact risk of CRC conferred by the susceptibility loci, suggesting possible geographic and population factors accounting for the differences observed between the studies. The low-penetrance genetic susceptibility loci are thought to account for 6% of all CRC [144]. Tenesa et al. identified susceptibility loci using single nucleotide polymorphisms (SNP) markers and determined that the individual OR was very low, from 1.10 to 1.26 but also suggest that the loci have an additive effect. For example, co-inheritance of SNPs on chromosomes 8q24, 11q23 and 18q21 were found to have an OR of 2.6 for CRC [146]. Gilraldez et al. reported an increased frequency of low-penetrance susceptibility loci in patients with a positive family history for young-onset CRC, suggesting heritability [148]. The authors also found a differential distribution in variants 10p14, 11q23.1 and 15q13.3 between the early onset (<50) cases when compared to the later onset (>65) cases, suggesting an important role of susceptibility loci in predisposition to young -onset CRC. The cumulative risk conferred by susceptibility loci on CRC remains unclear, especially in the younger population.

References

1. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. CA Cancer J Clin 63: 11-30.
2. Boyle P, Ferlay J (2005) Cancer incidence and mortality in Europe, 2004. Ann Oncol 16: 481-488.
3. Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, et al. (2010) Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 116: 544-573.
4. Siegel, R.L., A. Jemal, E.M. (2009) Ward, Increase in incidence of colorectal cancer among young men and women in the United States. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 18: 1695-16958.
5. Quah HM, Joseph R, Schrag D, Shia J, Guillem JG, et al. (2007) Young age influences treatment but not outcome of colon cancer. Ann Surg Oncol 14: 2759-2765.
6. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, et al. (2004) Do young colon cancer patients have worse outcomes? World J Surg 28: 558-562.
7. Aarnio M (2012) Clinicopathological features and management of cancers in lynch syndrome. Patholog Res Int 2012: 350309.
8. Chen S, Wang W, Lee S, Nafa K, Lee J, et al. (2006) Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA 296: 1479-1487.
9. Peltomäki P (2003) Role of DNA mismatch repair defects in the pathogenesis of human cancer. J Clin Oncol 21: 1174-1179.
10. Grady WM, Carethers JM (2008) Genomic and epigenetic instability in colorectal cancer pathogenesis. Gastroenterology 135: 1079-1099.
11. Stoffel E, Mukherjee B, Raymond VM, Tayob N, Kastrinos F, et al. (2009) Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. Gastroenterology 137: 1621-1627.
12. Vasen HF, Nagengast FM, Khan PM (1995) Interval cancers in hereditary non-polyposis colorectal cancer (Lynch syndrome) Lancet 345: 1183-1184.
13. Lynch HT, de la Chapelle A (2003) Hereditary colorectal cancer. N Engl J Med 348: 919-932.
14. Watson P, Lin KM, Rodriguez-Bigas MA, Smyrk T, Lemon S, et al. (1998) Colorectal carcinoma survival among hereditary nonpolyposis colorectal carcinoma family members. Cancer 83: 259-266.
15. Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, et al. (1999) Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 81: 214-218.
16. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, et al. (2004) Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. Journal of the National Cancer Institute 96: 261-268.
17. Miyaki M, Konishi M, Tanaka K, Kikuchi-Yanoshita R, Muraoka M, et al. (1997) Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. Nat Genet 17: 271-272.

18. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, et al. (2005) Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 352: 1851-1860.

19. Nyström-Lahti M, Wu Y, Moisio AL, Hofstra RM, Osinga J, et al. (1996) DNA mismatch repair gene mutations in 55 kindreds with verified or putative hereditary non-polyposis colorectal cancer. Hum Mol Genet 5: 763-769.

20. Ligtenberg MJ, Kuiper RP, Chan TL, Goossens M, Hebeda KM, et al. (2009) Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. Nat Genet 41: 112-117.

21. Kempers MJ, Kuiper RP, Ockeloen CW, Chappuis PO, Hutter P, et al. (2011) Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. Lancet Oncol 12: 49-55.

22. Niessen RC, Hofstra RM, Westers H, Ligtenberg MJ, Kooi K, et al. (2009) Germline hypermethylation of MLH1 and EPCAM deletions are a frequent cause of Lynch syndrome. Genes Chromosomes Cancer 48: 737-744.

23. Pérez-Cabornero L, Infante M, Velasco E, Lastra E, Miner C, et al. (2013) Genotype-phenotype correlation in MMR mutation-positive families with Lynch syndrome. Int J Colorectal Dis 28: 1195-1201.

24. Berends MJ, Wu Y, Sijmons RH, Mensink RG, van der Sluis T, et al. (2002) Molecular and clinical characteristics of MSH6 variants: an analysis of 25 index carriers of a germline variant. Am J Hum Genet 70: 26-37.

25. Bonadona V, Bonaïti B, Olschwang S, Grandjouan S, Huiart L, et al. (2011) Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 305: 2304-2310.

26. Kastrinos F, Syngal S (2011) Inherited colorectal cancer syndromes. Cancer J 17: 405-415.

27. Jasperson KW, Tuohy TM, Neklason DW, Burt RW (2010) Hereditary and familial colon cancer. Gastroenterology 138: 2044-2058.

28. Ying Wu, Berends MJW, Mensink RGJ, Kempinga C, Sijmons RH, et al. (1999) Association of hereditary nonpolyposis colorectal cancerâ€ related tumors displaying low microsatellite instability with MSH6 germline mutations. American journal of human genetics 65: 1291-1298.

29. Peltomäki P, Vasen H (2004) Mutations associated with HNPCC predisposition -- Update of ICG-HNPCC/INSiGHT mutation database. Dis Markers 20: 269-276.

30. Ou J, Niessen RC, Vonk J, Westers H, Hofstra RM, et al. (2008) A database to support the interpretation of human mismatch repair gene variants. Hum Mutat 29: 1337-1341.

31. Kastrinos F, Steyerberg EW, Mercado R, Balmaña J, Holter S, et al. (2011) The PREMM(1,2,6) model predicts risk of MLH1, MSH2, and MSH6 germline mutations based on cancer history. Gastroenterology 140: 73-81.

32. Green RC, Parfrey PS, Woods MO, Younghusband HB (2009) Prediction of Lynch syndrome in consecutive patients with colorectal cancer. J Natl Cancer Inst 101: 331-340.

33. Pouchet CJ, Wong N, Chong G, Sheehan MJ, Schneider G, et al. (2009) A comparison of models used to predict MLH1, MSH2 and MSH6 mutation carriers. Ann Oncol 20: 681-688.

34. Monzon JG, Cremin C, Armstrong L, Nuk J, Young S, et al. (2010) Validation of predictive models for germline mutations in DNA mismatch repair genes in colorectal cancer. Int J Cancer 126: 930-939.

35. de Jong AE, Puijenbroek Mv, Hendriks Y (2004) Microsatellite instability, immunohistochemistry, and additional PMS2 staining in suspected hereditary nonpolyposis colorectal cancer. Clinical cancer research: an official journal of the American Association for Cancer Research, 10: 972-980.

36. Lindor NM, Rabe K, Petersen GM, Haile R, Casey G, et al. (2005) Lower cancer incidence in Amsterdam I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA: the journal of the American Medical Association, 293: 1979-1985.

37. Gallinger S, Aronson M, Shayan K, Ratcliffe EM, Gerstle JT, et al. (2004) Gastrointestinal cancers and neurofibromatosis type 1 features in children with a germline homozygous MLH1 mutation. Gastroenterology 126: 576-585.

38. Jackson CC, Holter S, Pollett A, Clendenning M, Chou S, et al. (2008) Café-au-lait macules and pediatric malignancy caused by biallelic mutations in the DNA mismatch repair (MMR) gene PMS2. Pediatr Blood Cancer 50: 1268-1270.

39. Trimbath JD, Petersen GM, Erdman SH, Ferre M, Luce MC, et al. (2001) Café-au-lait spots and early onset colorectal neoplasia: a variant of HNPCC? Fam Cancer 1: 101-105.

40. Wimmer K, Etzler J (2008) Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg? Hum Genet 124: 105-122.

41. Bandipalliam, P. (2005) Syndrome of early onset colon cancers, hematologic malignancies & features of neurofibromatosis in HNPCC families with homozygous mismatch repair gene mutations. Familial cancer 4: 323-333.

42. Wimmer K, Kratz CP (2010) Constitutional mismatch repair-deficiency syndrome. Haematologica 95: 699-701.

43. Durno CA, Aronson M, Tabori U, Malkin D, Gallinger S, et al. (2012) Oncologic surveillance for subjects with biallelic mismatch repair gene mutations: 10 year follow-up of a kindred. Pediatr Blood Cancer 59: 652-656.

44. Jerkic S, Rosewich H, Scharf JG, Perske C, Füzesi L, et al. (2005) Colorectal cancer in two pre-teenage siblings with familial adenomatous polyposis. Eur J Pediatr 164: 306-310.

45. Durno CA, Holter S, Sherman PM, Gallinger S (2010) The gastrointestinal phenotype of germline biallelic mismatch repair gene mutations. Am J Gastroenterol 105: 2449-2456.

46. Lindor NM, Petersen GM, Hadley DW, Kinney AY, Miesfeldt S, et al. (2006) Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 296: 1507-1517.

47. Galiatsatos P, Foulkes WD (2006) Familial adenomatous polyposis. Am J Gastroenterol 101: 385-398.

48. Cruz-Correa M, Giardiello FM (2003) Familial adenomatous polyposis. Gastrointest Endosc 58: 885-894.

49. Patel SG, Ahnen DJ (2012) Familial colon cancer syndromes: an update of a rapidly evolving field. Curr Gastroenterol Rep 14: 428-438.

50. Burt RW, Leppert MF, Slattery ML, Samowitz WS, Spirio LN, et al. (2004) Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. Gastroenterology 127: 444-451.

51. Half E, Bercovich D, Rozen P (2009) Familial adenomatous polyposis. Orphanet J Rare Dis 4: 22.

52. Bläker H, Scholten M, Sutter C, Otto HF, Penzel R (2003) Somatic mutations in familial adenomatous polyps. Nuclear translocation of beta-catenin requires more than biallelic APC inactivation. Am J Clin Pathol 120: 418-423.

53. Lynch HT, Smyrk T, Lynch J, Lanspa S, McGinn T, et al. (1996) Genetic counseling in an extended attenauted familial adenomatous polyposis kindred. Am J Gastroenterol 91: 455-459.

54. Brensinger JD, Laken SJ, Luce MC, Powell SM, Vance GH, et al. (1998) Variable phenotype of familial adenomatous polyposis in pedigrees with 3' mutation in the APC gene. Gut 43: 548-552.

55. Out AA, Tops CM, Nielsen M, Weiss MM, van Minderhout IJ, et al. (2010) Leiden Open Variation Database of the MUTYH gene. Hum Mutat 31: 1205-1215.

56. Knudsen AL, Bisgaard ML, Bülow S (2003) Attenuated familial adenomatous polyposis (AFAP). A review of the literature. Fam Cancer 2: 43-55.

57. Aretz S, Uhlhaas S, Goergens H, Siberg K, Vogel M, et al. (2006) MUTYH-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. Int J Cancer 119: 807-814.

58. Armstrong JG, Davies DR, Guy SP, Frayling IM, Evans DG (1997) APC mutations in familial adenomatous polyposis families in the Northwest of England. Hum Mutat 10: 376-380.

59. Renkonen ET, Nieminen P, Abdel-Rahman WM, Moisio AL, Järvelä I, et al. (2005) Adenomatous polyposis families that screen APC mutationâ€ negative by conventional methods are genetically heterogeneous. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 23: 5651-5659.

60. Fleischmann C, Peto J, Cheadle J, Shah B, Sampson J, et al. (2004) Comprehensive analysis of the contribution of germline MYH variation to early-onset colorectal cancer. Int J Cancer 109: 554-558.

61. Al-Tassan N, Chmiel NH, Maynard J, Fleming N, Livingston AL, et al. (2002) Inherited variants of MYH associated with somatic G:C-->T:A mutations in colorectal tumors. Nat Genet 30: 227-232.

62. Sampson JR, Dolwani S, Jones S, Eccles D, Ellis A, et al. (2003) Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of MYH. Lancet 362: 39-41.

63. Nielsen M, Franken PF, Reinards TH, Weiss MM, Wagner A, et al. (2005) Multiplicity in polyp count and extracolonic manifestations in 40 Dutch patients with MYH associated polyposis coli (MAP). J Med Genet 42: e54.

64. Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS (2009) Clinical implications of the colorectal cancer risk associated with MUTYH mutation. J Clin Oncol 27: 3975-3980.

65. Boparai KS, Dekker E, Van Eeden S, Polak MM, Bartelsman JF, et al. (2008) Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. Gastroenterology 135: 2014-2018.

66. Cleary SP, Cotterchio M, Jenkins MA, Kim H, Bristow R, et al. (2009) Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study. Gastroenterology 136: 1251-1260.

67. Jenkins MA, Croitoru ME, Monga N, Cleary SP, Cotterchio M, et al. (2006) Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a populationâ€ based case family study. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 15: 312-314.

68. Farrington SM, Tenesa A, Barnetson R, Wiltshire A, Prendergast J, et al. (2005) Germline susceptibility to colorectal cancer due to base-excision repair gene defects. Am J Hum Genet 77: 112-119.

69. Webb EL, Rudd MF, Houlston RS (2006) Colorectal cancer risk in monoallelic carriers of MYH variants. Am J Hum Genet 79: 768-771.

70. Win AK, Cleary SP, Dowty JG, Baron JA, Young JP, et al. (2011) Cancer risks for monoallelic MUTYH mutation carriers with a family history of colorectal cancer. Int J Cancer 129: 2256-2262.

71. Lindor NM (2009) Hereditary colorectal cancer: MYH-associated polyposis and other newly identified disorders. Best Pract Res Clin Gastroenterol 23: 75-87.

72. Vogt S, Jones N, Christian D, Engel C, Nielsen M, et al. (2009) Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology 137: 1976-1985.

73. Yamaguchi S, Ogata H, Katsumata D, Nakajima M, Fujii T, et al. (2013) MUTYH-associated colorectal cancer and adenomatous polyposis. Surg Today.

74. Tao H, Shinmura K, Hanaoka T, Natsukawa S, Shaura K, et al. (2004) A novel splice-site variant of the base excision repair gene MYH is associated with production of an aberrant mRNA transcript encoding a truncated MYH protein not localized in the nucleus. Carcinogenesis 25: 1859-1866.

75. Yanaru-Fujisawa R, Matsumoto T, Ushijima Y, Esaki M, Hirahashi M, et al. (2008) Genomic and functional analyses of MUTYH in Japanese patients with adenomatous polyposis. Clin Genet 73: 545-553.

76. Sieber OM, Lipton L, Crabtree M, Heinimann K, Fidalgo P, et al. (2003) Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N Engl J Med 348: 791-799.

77. Miyaki M, Iijima T, Yamaguchi T, Hishima T, Tamura K, et al. (2005) Germline mutations of the MYH gene in Japanese patients with multiple colorectal adenomas. Mutat Res 578: 430-433.

78. Stojcev Z, Borun P, Hermann J, Krokowicz P, Cichy W, et al. (2013) Hamartomatous polyposis syndromes. Hered Cancer Clin Pract 11: 4.

79. Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, et al. (1998) A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature 391: 184-187.

80. Giardiello FM, Trimbath JD (2006) Trimbath, Peutz Jeghers syndrome and management recommendations. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association, 4: 408-415.

81. Boardman LA, Thibodeau SN, Schaid DJ, Lindor NM, McDonnell SK, et al. (1998) Increased risk for cancer in patients with the Peutz Jeghers syndrome. Annals of internal medicine 128: 896-899.

82. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, et al. (2010) High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol 105: 1258-1264.

83. Lim W, Olschwang S, Keller JJ, Westerman AM, Menko FH, et al. (2004) Relative frequency and morphology of cancers in STK11 mutation carriers. Gastroenterology 126: 1788-1794.

84. Mehenni H, Resta N, Park JG, Miyaki M, Guanti G, et al. (2006) Cancer risks in LKB1 germline mutation carriers. Gut 55: 984-990.

85. Beggs AD, Latchford AR, Vasen HF, Moslein G, Alonso A, et al. (2010) Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut 59: 975-986.

86. Volikos E, Robinson J, Aittomäki K, Mecklin JP, Järvinen H, et al. (2006) LKB1 exonic and whole gene deletions are a common cause of Peutz-Jeghers syndrome. J Med Genet 43: e18.

87. Olschwang S, Boisson C, Thomas G (2001) Peutz-Jeghers families unlinked to STK11/LKB1 gene mutations are highly predisposed to primitive biliary adenocarcinoma. J Med Genet 38: 356-360.

88. Boardman LA, Couch FJ, Burgart LJ, Schwartz D, Berry R, et al. (2000) Genetic heterogeneity in Peutz-Jeghers syndrome. Hum Mutat 16: 23-30.

89. Alhopuro P, Phichith D, Tuupanen S, Sammalkorpi H, Nybondas M, et al. (2008) Unregulated smooth-muscle myosin in human intestinal neoplasia. Proc Natl Acad Sci U S A 105: 5513-5518.

90. Mehenni H, Resta N, Guanti G, Mota-Vieira L, Lerner A, et al. (2007) Molecular and clinical characteristics in 46 families affected with Peutz-Jeghers syndrome. Dig Dis Sci 52: 1924-1933.

91. Amos CI, Keitheri-Cheteri MB, Sabripour M, Wei C, McGarrity TJ, et al. (2004) Genotype-phenotype correlations in Peutz-Jeghers syndrome. J Med Genet 41: 327-333.

92. Salloch H, Reinacher-Schick A, Schulmann K, Pox C, Willert J, et al. (2010) Truncating mutations in Peutz-Jeghers syndrome are associated with more polyps, surgical interventions and cancers. Int J Colorectal Dis 25: 97-107.

93. Ylikorkala A, Avizienyte E, Tomlinson IP, Tiainen M, Roth S, et al. (1999) Mutations and impaired function of LKB1 in familial and non familial Peutz Jeghers syndrome and a sporadic testicular cancer. Human molecular genetics 8: 45-51.

94. Jass JR, Williams CB, Bussey HJ, Morson BC (1988) Juvenile polyposis--a precancerous condition. Histopathology 13: 619-630.

95. Burt RW, Bishop DT, Lynch HT, Rozen P, Winawer SJ (1990) Risk and surveillance of individuals with heritable factors for colorectal cancer. WHO Collaborating Centre for the Prevention of Colorectal Cancer. Bull World Health Organ 68: 655-665.

96. Jass JR (2008) Colorectal polyposes: from phenotype to diagnosis. Pathol Res Pract 204: 431-447.

97. Attard TM, Young RJ (2006) Young, Diagnosis and management of gastrointestinal polyps: pediatric considerations. Gastroenterology nursing: the official journal of the Society of Gastroenterology Nurses and Associates 29: 23-24.

98. Howe JR, Roth S, Ringold JC, Summers RW, Järvinen HJ, et al. (1998) Mutations in the SMAD4/DPC4 gene in juvenile polyposis. Science 280: 1086-1088.

99. Sweet K, Willis J, Zhou XP, Gallione C, Sawada T, et al. (2005) Molecular classification of patients with unexplained hamartomatous and hyperplastic polyposis. JAMA 294: 2465-2473.

100. Kinzler KW, Vogelstein B (1998) Landscaping the cancer terrain. Science 280: 1036-1037.

101. Haramis AP, Begthel H, van den Born M, van Es J, Jonkheer S, et al. (2004) De novo crypt formation and juvenile polyposis on BMP inhibition in mouse intestine. Science 303: 1684-1686.

102. Pyatt RE, Pilarski R, Prior TW (2006) Mutation screening in juvenile polyposis syndrome. J Mol Diagn 8: 84-88.

103. Calva-Cerqueira D, Chinnathambi S, Pechman B, Bair J, Larsen-Haidle J, et al. (2009) The rate of germline mutations and large deletions of SMAD4 and BMPR1A in juvenile polyposis. Clin Genet 75: 79-85.

104. Sayed MG, Ahmed AF, Ringold JR, Anderson ME, Bair JL, et al. (2002) Germline SMAD4 or BMPR1A mutations and phenotype of juvenile polyposis. Ann Surg Oncol 9: 901-906.

105. van Hattem WA, Brosens LA, de Leng WW, Morsink FH, Lens S, et al. (2008) Large genomic deletions of SMAD4, BMPR1A and PTEN in juvenile polyposis. Gut 57: 623-627.

106. Lynch ED, Ostermeyer EA, Lee MK, Arena JF, Ji H, et al. (1997) Inherited mutations in PTEN that are associated with breast cancer, cowden disease, and juvenile polyposis. Am J Hum Genet 61: 1254-1260.

107. Marsh DJ, Roth S, Lunetta KL, Hemminki A, Dahia PL, et al. (1997) Exclusion of PTEN and 10q22-24 as the susceptibility locus for juvenile polyposis syndrome. Cancer Res 57: 5017-5021.

108. Septer S, Zhang L, Lawson CE, Cocjin J, Attard T, et al. (2013) Aggressive juvenile polyposis in children with chromosome 10q23 deletion. World J Gastroenterol 19: 2286-2292.

109. Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, et al. (2004) A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). Lancet 363: 852-859.

110. Delnatte C, Sanlaville D, Mougenot JF, Stoppa-Lyonnet D (2006) Contiguous gene deletion within chromosome arm 10q is associated with juvenile polyposis of infancy, reflecting cooperation between the BMPR1A and PTEN tumor suppressor genes. American journal of human genetics 78: 1066-1074.

111. Rustgi AK (2007) The genetics of hereditary colon cancer. Genes Dev 21: 2525-2538.

112. Jasperson KW (2012) Genetic testing by cancer site: colon (polyposis syndromes). Cancer J 18: 328-333.

113. Brosens LA, Langeveld D, van Hattem WA, Giardiello FM, Offerhaus GJ (2011) Juvenile polyposis syndrome. World J Gastroenterol 17: 4839-4844.

114. Lachlan KL (2013) Cowden syndrome and the PTEN hamartoma tumor syndrome: how to define rare genetic syndromes. J Natl Cancer Inst 105: 1595-1597.

115. LLOYD KM 2nd, DENNIS M (1963) Cowden's disease. A possible new symptom complex with multiple system involvement. Ann Intern Med 58: 136-142.

116. Nelen MR, Kremer H, Konings IB, Schoute F, van Essen AJ, et al. (1999) Novel PTEN mutations in patients with Cowden disease: absence of clear genotype-phenotype correlations. Eur J Hum Genet 7: 267-273.

117. Marra G, Armelao F, Vecchio FM, Percesepe A, Anti M (1994) Cowden's disease with extensive gastrointestinal polyposis. J Clin Gastroenterol 18: 42-47.

118. Heald B, Mester J, Rybicki L, Orloff MS, Burke CA, et al. (2010) Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. Gastroenterology 139: 1927-1933.

119. Carlson GJ, Nivatvongs S, Snover DC (1984) Colorectal polyps in Cowden's disease (multiple hamartoma syndrome). Am J Surg Pathol 8: 763-770.

120. Patnaik MM, Raza SS, Khambatta S, Stanich PP, Goetz MP (2010) Oncophenotypic review and clinical correlates of phosphatase and tensin homolog on chromosome 10 hamartoma tumor syndrome. J Clin Oncol 28: e767-768.

121. Riegert-Johnson DL, Gleeson FC, Roberts M, Tholen K, Youngborg L, et al. (2010) Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients. Hered Cancer Clin Pract 8: 6.

122. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, et al. (2012) Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 18: 400-407.

123. Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, et al. (2013) Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. J Natl Cancer Inst 105: 1607-1616.

124. Eng C (2003) PTEN: one gene, many syndromes. Hum Mutat 22: 183-198.

125. Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, et al. (1997) Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet 16: 64-67.

126. Marsh DJ, Coulon V, Lunetta KL, Rocca-Serra P, Dahia PL, et al. (1998) Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. Hum Mol Genet 7: 507-515.

127. Pilarski R, Stephens JA, Noss R, Fisher JL, Prior TW (2011) Predicting PTEN mutations: an evaluation of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. J Med Genet 48: 505-512.

128. Tan MH, Mester J, Peterson C, Yang Y, Chen JL, et al. (2011) A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. Am J Hum Genet 88: 42-56.

129. Bannayan GA (1971) Lipomatosis, angiomatosis, and macrencephalia. A previously undescribed congenital syndrome. Arch Pathol 92: 1-5.

130. Marsh DJ, Kum JB, Lunetta KL, Bennett MJ, Gorlin RJ, et al. (1999) PTEN mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome. Hum Mol Genet 8: 1461-1472.

131. Zigman AF, Lavine JE, Jones MC, Boland CR, Carethers JM (1997) Localization of the Bannayan-Riley-Ruvalcaba syndrome gene to chromosome 10q23. Gastroenterology 113: 1433-1437.

132. Whitelaw SC, Murday VA, Tomlinson IP, Thomas HJ, Cottrell S, et al. (1997) Clinical and molecular features of the hereditary mixed polyposis syndrome. Gastroenterology 112: 327-334.

133. Thomas HJ, Whitelaw SC, Cottrell SE, Murday VA, Tomlinson IP, et al. (1996) Genetic mapping of hereditary mixed polyposis syndrome to chromosome 6q. Am J Hum Genet 58: 770-776.

134. Jaeger EE, Woodford-Richens KL, Lockett M, Rowan AJ, Sawyer EJ, et al. (2003) An ancestral Ashkenazi haplotype at the HMPS/CRAC1 locus on 15q13-q14 is associated with hereditary mixed polyposis syndrome. Am J Hum Genet 72: 1261-1267.

135. Jaeger E, Leedham S, Lewis A, Segditsas S, Becker M, et al. (2012) Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist GREM1. Nat Genet 44: 699-703.

136. Lockett, MJ, Atkin WS (2001) Hyperplastic polyposis (HPP): Prevalence and cancer risk. Gastroenterology 120: 742.

137. Lanspa SJ, Ahnen DJ, Lynch HT (2012) Serrated polyposis: the last (or only the latest?) frontier of familial polyposis? Am J Gastroenterol 107: 779-781.

138. Boparai KS, Reitsma JB, Lemmens V, van Os TA, Mathus-Vliegen EM, et al. (2010) Increased colorectal cancer risk in first-degree relatives of patients with hyperplastic polyposis syndrome. Gut 59: 1222-1225.

139. Win AK, Walters RJ, Buchanan DD, Jenkins MA, Sweet K, et al. (2012) Cancer risks for relatives of patients with serrated polyposis. Am J Gastroenterol 107: 770-778.

140. Young J, Jass JR (2006) The case for a genetic predisposition to serrated neoplasia in the colorectum: hypothesis and review of the literature. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 15: 1778-1784.

141. Guarinos C, Sánchez-Fortún C, Rodríguez-Soler M, Alenda C, Payá A, et al. (2012) Serrated polyposis syndrome: molecular, pathological and clinical aspects. World J Gastroenterol 18: 2452-2461.

142. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, et al. (2000) Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 343: 78-85.

143. Hosking FJ, Dobbins SE, Houlston RS (2011) Genome-wide association studies for detecting cancer susceptibility. Br Med Bull 97: 27-46.

144. Tenesa A, Dunlop MG (2009) New insights into the aetiology of colorectal cancer from genome-wide association studies. Nat Rev Genet 10: 353-358.

145. Jaeger E, Webb E, Howarth K, Carvajal-Carmona L, Rowan A, et al. (2008) Common genetic variants at the CRAC1 (HMPS) locus on chromosome 15q13.3 influence colorectal cancer risk. Nat Genet 40: 26-28.

146. Tenesa A, Farrington SM, Prendergast JG, Porteous ME, Walker M, et al. (2008) Genome-wide association scan identifies a colorectal cancer susceptibility locus on 11q23 and replicates risk loci at 8q24 and 18q21. Nat Genet 40: 631-637.

147. Houlston RS, Webb E, Broderick P, Pittman AM, Di Bernardo MC, et al. (2008) Meta-analysis of genome-wide association data identifies four new susceptibility loci for colorectal cancer. Nat Genet 40: 1426-1435.

148. Giráldez MD, López-Dóriga A, Bujanda L, Abulí A, Bessa X, et al. (2012) Susceptibility genetic variants associated with early-onset colorectal cancer. Carcinogenesis 33: 613-619.